CHAPTER 4.6

Serotonin and Schizophrenia

Boris B. Quednow[*,1], Mark A. Geyer[2] and Adam L. Halberstadt[2]

[1]*University Hospital of Psychiatry, University of Zurich, Switzerland*
[2]*Department of Psychiatry, University of California at San Diego, California*

Abstract: Although the serotonin hypothesis of schizophrenia is one of the oldest neurochemical hypotheses on the pathogenesis of this disease, it is still highly topical. The concept of how the serotonin system is involved in the origin and progress of schizophrenia has considerably changed over the past decades. Therefore, the present work will give an overview about the development and the current directions of the serotonin hypothesis of schizophrenia. In this regard, we will discuss the phenomenology of hallucinogenic drug action, model psychosis and translational research, *post mortem* studies on receptors and transporters, imaging studies, antipsychotic drug action, neuroendocrine challenge studies, platelet and cerebrospinal fluid data, genetic association studies, developmental aspects, and the cross-talk between the glutamate and the serotonin system. In sum, there are several lines of evidence suggesting that the serotonin system plays a major role in the pathogenesis of at least a subpopulation of schizophrenia patients. Further studies are needed to better characterize patients whose psychotic symptoms are suspected to have a serotonergic origin.

Keywords: serotonin, 5-HT, schizophrenia, model psychosis, LSD, psilocybin, atypical antipsychotics, 5-HT_{2A} receptor, platelets, positron emission tomography, single nucleotide polymorphism, developmental disorder, dopamine, glutamate, cognition.

Introduction

The symptoms of schizophrenia can be divided into three major domains: (1) positive symptoms such as hallucinations, perceptual disturbances, delusional phenomena and formal thought disorder; (2) cognitive dysfunction, which includes motivational and executive function deficits; and (3) negative symptoms, including flat affect, poverty of speech, avolition and inappropriate emotional responses (Tamminga and Holcomb, 2005). Presentation of symptoms from these three domains is heterogeneous, making the illness difficult to diagnose and treat. The highest risk period for developing schizophrenia is during young adulthood. Both sexes are equally affected by the disorder, although the age of onset of symptoms is typically younger for men than women (Goldstein *et al.*, 1989; Faraone *et al.*, 1994; Bromet and Fennig, 1999). Although incidence figures vary depending on the diagnostic criteria, schizophrenia affects approximately 1 percent of the general population. Individuals with schizophrenic parents or siblings have an increased risk for developing the illness (8–12 percent). For monozygotic twins, the concordance rate is approximately 50 percent (Holzman and Matthysse, 1990; Gottesman, 1991). The elevated familial incidence of schizophrenia strongly indicates that there is a genetic contribution to the disorder, although the fact that concordance rates for monozygotic twins are lower than 100 percent suggests that environmental factors are also involved. It is therefore likely that a combination of genetic susceptibility and environmental factors is required for the illness to develop (Gottesman, 1991). Linkage studies of schizophrenia have identified several chromosomal regions and candidate genes that are associated with the disorder (reviewed by Harrison and Owen, 2003; Harrison and Weinberger, 2005).

Although there is evidence for enlarged ventricles and decreased cerebral (cortical and hippocampal) volume associated with schizophrenia, there is not a distinct 'diagnostic' neuropathology associated with the disease (reviewed by Harrison, 1999a, 2004; Harrison and Owen, 2003). Misplaced and clustered neurons, particularly in the entorhinal cortex, indicate problems of neuronal migration, and suggest an early developmental anomaly (Jakob and Beckmann, 1986; Arnold *et al.*, 1991; Falkai *et al.*, 2000). Pyramidal neurons in the hippocampus and neocortex have been shown to have smaller cell bodies and fewer dendritic spines and dendritic

[*]Corresponding author
E-mail: quednow@bli.uzh.ch

Christian Müller & Barry Jacobs (Eds.)
Handbook of Behavioral Neurobiology of Serotonin
ISBN 978-0-12-374634-4

DOI: 10.1016/B978-0-12-374634-4.00034-4

arborizations (reviewed by Harrison and Weinberger, 2005). Additionally, decreased presynaptic proteins such as synaptophysin, SNAP-25 and complexin II have been observed in schizophrenia brains (Harrison and Eastwood, 2001; Honer and Young, 2004), as well as decreased density of interneurons (e.g., parvalbumin-immunoreactive cells; Lewis, 2000; Reynolds *et al.*, 2002a). There are also reports of decreases in cell numbers in the thalamus and a decreased number of oligodendrocytes. Neuroimaging data and *post mortem* studies have shown that N-acetylaspartate (NAA), a marker of neuronal integrity, is decreased in first-episode and never-medicated patients (Bertolino and Weinberger, 1999; Nudmamud *et al.*, 2003). Based on these neuropathological changes, investigators have conceptualized schizophrenia as a disease of functional 'dysconnectivity' (Weinberger *et al.*, 1992; Friston and Frith, 1995; McGlashan and Hoffman, 2000), or a 'disorder of the synapse' (Mirnics *et al.*, 2001; Frankle *et al.*, 2003) affecting the machinery of the synapse (Harrison and Eastwood, 2001; Honer and Young, 2004).

Not only structural alterations but also neurochemical changes have been proposed to play a role in the etiopathogenesis of schizophrenia. In the following sections, we give an overview on the serotonin hypothesis of schizophrenia. Although it is one of the oldest neurochemical hypotheses on the pathogenesis of this disease, it is still highly topical, as will be shown in the following sections.

History of the serotonin hypothesis of schizophrenia

The first step in the direction of the idea that the serotonin system may contribute to schizophrenia was probably made by the German psychiatrist Kurt Beringer (1923). He was the first to propose the use of the hallucinogen mescaline as an experimental model of psychosis, despite the fact that he had no knowledge of serotonin receptors or the principles of neurotransmission. Previously, on the eve of World War I, Knauer and Maloney (1913) had already recommended the mescaline self-experience for psychiatrists to gain better insights into the psychotic states of their patients. Subsequently, we have come to understand that mescaline is a selective serotonin-2A (5-HT_{2A}) receptor agonist that played an important role in the development of the transmethylation hypothesis of schizophrenia. In 1943, Albert Hofmann identified the impressive psychotomimetic effects of d-lysergic acid diethylamid (LSD) during an unintentional self-intoxication in his laboratory at Sandoz Pharmaceutical Company (Stoll, 1947). During subsequent repeated self-experiments, Hofmann noted that the necessary dose of LSD to cause psychological effects was very small, strongly suggesting that there must be a receptor or some other specific site of action for the LSD molecule. Mescaline, in contrast, had to be given in hundreds of milligrams to produce psychotomimetic effects that were comparable to the effects of several micrograms of LSD (Stoll, 1947). Hofmann gave LSD to Walter Stoll, a psychiatrist at the University Hospital of Psychiatry Zurich 'Burghölzli', and the son of Hofmann's supervisor Arthur Stoll at Sandoz. The younger Stoll explored the psychopathological effects of LSD in 16 healthy volunteers and found that the LSD effects were strikingly similar to the symptoms of schizophrenia (Stoll, 1947).[1] Subsequently, both Stoll and his colleague Condrau administered LSD to patients with schizophrenia, hoping that the LSD 'shock' may have some therapeutic benefits. They noted that LSD is much less potent in schizophrenia patients than in normal controls, and therefore concluded that a toxic substance similar to LSD may cause schizophrenic psychoses (Stoll, 1947, 1949; Condrau, 1949). With this perception, they paved the way for the transmethylation hypothesis. Moreover, both authors noted that LSD may prove to be a valuable tool to induce psychotic states experimentally in the laboratory.

While searching for a vasoconstrictive substance in platelets, Rapport and colleagues (1948) discovered serotonin; soon thereafter, the structure of serotonin was deduced (Rapport, 1949). Betty Twarog and Page (1953) subsequently demonstrated that serotonin could be found in the mammalian brain. Initially it was thought that serotonin was simply a residue of blood in the brain, but the structural similarities between LSD and serotonin led to the suggestion that serotonin may act directly in the brain (Healy, 2002). Gaddum (1953) quickly determined that the oxytocic effects of serotonin could be antagonized by LSD. As was fashionable at the time among pharmacologists, Gaddum took LSD himself. The intense experience encouraged him to propose that serotonin in the brain may play a role in preserving sanity (Gaddum and Hameed, 1954; Healy, 2002). At the same time, Woolley and Shaw (1953) independently discovered that other centrally acting indoleamines (yohimbine, ergot alkaloids, harmine) also antagonize the vasoconstrictive action of serotonin, and they also concluded that serotonin may play a role in nervous disorders (Woolley and Shaw, 1954). Gaddum and Hameed (1954) and Woolley and Shaw (1954) proposed that serotonin activity might be decreased in the brain of schizophrenia patients. Subsequent evidence indicating that LSD is an agonist rather than an antagonist

[1] Interestingly, Stoll (1947) had already suggested radioactive labeling of LSD to investigate, in animals, which brain regions LSD acts upon.

questioned this hypothesis (Baumeister and Hawkins, 2004). Later, Woolley (1962) revoked his initial suggestion and stated that schizophrenia may result from an excess of brain serotonin.

Shortly before the discoveries of Gaddum, Woolley and Shaw, another serotonin-related hypothesis of schizophrenia had also appeared. As early as 1932, Henk de Jong noted that mescaline is chemically related to epinephrine. He therefore supposed that a disturbance of epinephrine metabolism might lead to the synthesis of a mescaline-like substance that causes catatonia, one of the primary forms of schizophrenia at that time (de Jong, 1932). Twenty years later, Osmond and Smythies (1952) reinvented this idea and proposed the influential transmethylation hypothesis of schizophrenia. Osmond and Smythies observed that an asthmatic patient developed psychotic symptoms after he had taken old (and therefore oxidized) epinephrine during an asthmatic attack. In a self-experiment, Osmond and his director Abram Hoffer then took adrenochrome – a breakdown product of epinephrine, pink in color – and reported that it produced hallucinogenic responses (Healy, 2002). These observations led to their assumption that schizophrenia results from an endogenous neurotoxin that is formed by aberrant metabolic processes during the biosynthesis of catecholamines. The last step of the biosynthesis of epinephrine is methylation of the amino group of norepinephrine. If the phenolic hydroxyl groups were irregularly methylated instead, then a mescaline-like compound would be produced. Later Hoffer, Osmond and Smythies (1991) expanded the transmethylation hypothesis by proposing the possibility of an aberrant endogenous biosynthesis of methylated indolamine hallucinogens such as LSD. In the following years, many researchers tried to find the 'pink spot' of adrenochrome and other suspected endogenous neurotoxins in the brain, blood or urine of schizophrenia patients; however, it was never convincingly found. Moreover, Hoffer and Osmond brought their theory directly to the clinic and treated schizophrenia patients with large doses of nicotinic acid because it acts to trap methyl donors, and thus the aberrant transmethylation of catecholamines or indolamines should be decreased. The authors reported that nicotinic acid alone, as well as in combination with chlorpromazine, had some beneficial effects in the treatment of schizophrenia, but these results could not be replicated in later studies performed by the Canadian Association of Mental Health (Healy, 2002). Although the transmethylation hypothesis still has strong face validity, it fell out of favor after the 1960s for two reasons: first, the schizophrenogenic substances could not be isolated; and secondly, a new influential theory targeting another neurotransmitter commandeered the focus of schizophrenia research. For the time being, the serotonin hypotheses were superseded by the influential dopamine hypothesis of schizophrenia.

The dopamine hypothesis of schizophrenia

Based on the finding of Brodie *et al.* (1955, 1956) that reserpine acutely releases brain serotonin while post-acutely depeleting it, the group of Arvid Carlsson demonstrated that reserpine has the same effect on catecholamines (Bertler *et al.*, 1956). These results suggested that serotonin and catecholamines may play a role in the sedative and motor-depressant effects of reserpine. Carlsson *et al.* (1957) tested this hypothesis by administering the precursors L-dopa and 5-hydroxytryptophan to animals after a pre-treatment with reserpine. Only L-dopa attenuated the behavioral effects of reserpine, whereas 5-hydroxytryptophan had no effect. Subsequently, it was shown that L-dopa increases brain dopamine but not norepinephrine (Carlsson, 1959). These results suggested an important role of dopamine in brain function. In 1963, Carlsson and Lindquist reported that chlorpromazine and haloperidol reduced catecholamine activity through a postsynaptic action (Carlsson and Lindqvist, 1963). Later, van Rossum (1966) explicated that blockade of postsynaptic dopamine receptors is responsible for the behavioral effects of these neuroleptic drugs. The dopamine hypothesis of schizophrenia – which is actually a hypothesis of neuroleptic drug action – was born. For more than three decades, the dopamine hypothesis has dominated biological research on the etiopathogenesis of schizophrenia. The assumption that schizophrenia is caused by a significant disturbance of dopamine transmission (or metabolism) that results in an increase of dopamine function was initially supported by the following data (Bleich *et al.*, 1988):

1. All (admitted) antipsychotic drugs are dopamine-D_2 (D_2) receptor antagonists, and before the advent of 'atypical' antipsychotics 20 years ago it was shown that antipsychotic potency of the neuroleptics was directly correlated with D_2 receptor binding (Meltzer and Stahl, 1976; Seeman, 1987). However, the latter is not true for clozapine, which is still the gold standard of antipsychotic drug action, because it has only a moderate affinity for D_2 receptors but higher affinity for 5-HT_{2A}, 5-HT_{2C}, 5-HT_6 and 5-HT_7 receptors, as well as for D_4, histamine H_1, muscarinic M_1, α_1, and α_2 receptors (Arnt and Skarsfeldt, 1998; Abi-Dargham and Krystal, 2000).
2. Sustained or high-dose exposure to indirect dopamine agonists (e.g., L-dopa, cocaine, amphetamine) may cause psychotic symptoms in healthy subjects that

are similar to those of paranoid schizophrenia (Segal *et al.*, 1981). Moreover, indirect dopamine agonists provoke exacerbation of symptoms in schizophrenia patients. Amphetamine is known to release presynaptic dopamine and norepinephrine, and it was shown that antipsychotics could improve the acute symptoms of amphetamine psychosis (Snyder, 1973; Carlsson, 1988). Nevertheless, psychotic states induced by indirect dopamine agonists mimic only the positive symptoms of schizophrenia; thus, maybe only the positive symptoms might be due to an increased dopaminergic activity (Angrist and Gershon, 1970).

3. *Post-mortem* studies and imaging studies with positron emission tomography (PET) initially indicate an increase of striatal D_2 receptor levels in the brains of schizophrenia patients (Wong *et al.*, 1986; Seeman, 1987). However, up-regulation of D_2 receptor expression could be the result of adaptation to antipsychotic drug treatment rather than a pathological abnormality inherent to schizophrenia, and in fact many *post-mortem* and PET studies could not replicate the finding of increased striatal D_2 receptor density in drug-naïve schizophrenia patients (Harrison, 1999a; Weinberger and Laruelle, 2002). However, there is accumulating evidence for a presynaptic dopaminergic abnormality in schizophrenia, implying disturbances in presynaptic storage, vesicular transport, release, reuptake and metabolic mechanisms in mesolimbic dopamine systems (Laruelle *et al.*, 1999; Weinberger and Laruelle, 2002).

The current view on the role of dopamine in schizophrenia is that subcortical mesolimbic dopamine projections might be hyperactive (causing productive symptoms) and that the mesocortical dopamine projections to the prefrontal cortex (PFC) and the anterior cingulate are hypoactive (causing negative symptoms and cognitive impairment). These two dysfunctions might be linked, as the cortical dopamine system generally inhibits the subcortical dopamine system (Weinberger and Laruelle, 2002).

Addressing the psychopathological heterogeneity of schizophrenia, Timothy Crow (1980a, 1980b) proposed that schizophrenia be divided into two syndromes: type I is characterized by positive symptoms that reflect an increase in striatal dopamine function, and responds well to antipsychotics; while type II is more characterized by negative symptoms, structural brain abnormalities (cortical atrophy and/or ventricular enlargement) and limited response to (typical) antipsychotics. Bleich *et al.* (1988) suggested that the type II syndrome might respond better to serotonin antagonistic compounds, and thus he proposed a dopaminergic and serotonergic form of schizophrenia. This view is supported by the fact that some atypical substances having a strong 5-HT_{2A} receptor antagonistic component may be superior in the treatment of negative symptoms when compared to typical neuroleptics without a strong serotonin antagonistic action (Meltzer, 1999). The fact that amisulpride, a pure D_2/D_3 antagonist, has nevertheless a strong impact on not only positive but also negative symptoms may be due to its unique pharmacokinetic properties (Leucht, 2004).

Phenomenology of hallucinogenic drug action

Effects of hallucinogens in human subjects

Serotonergic hallucinogens produce profound alterations in thought, mood, affect and sensory perception. The effects of these drugs are often characterized by visual illusions and elementary hallucinations, altered sense of time and space, and depersonalization. Hallucinogen-induced Altered States of Consciousness (ASCs) are highly subjective, and are typically assessed using self-reports. Various rating scales have been used to assess the effects of hallucinogens (reviewed by Strassman, 1995). The Addiction Research Center Inventory (Haertzen *et al.*, 1963) is an older instrument that emphasized the unpleasant effects of hallucinogens. The Hallucinogen Rating Scale (HRS) was designed specifically to detect the effects of intravenous N,N-dimethyltryptamine (Strassman *et al.*, 1994), and has now been validated for other hallucinogens (Gouzoulis-Mayfrank *et al.*, 1999). Another rating scale, the Altered States of Consciousness Questionnaire (APZ), was developed by Dittrich to assess various types of ASCs, independent of their etiology (Dittrich, 1998). The original APZ includes three dimensions that have been labeled: Oceanic Boundlessness (OB), Anxious Ego Dissolution (AED) and Visionary Restructuralization (VR). The OB dimension measures states that resemble mystical experiences, the AED dimension reflects 'bad trip'-like experiences, and the VR dimension refers to altered visual perception. An updated version of the APZ, the 5D-ASC, includes two additional dimensions: Reduction of Vigilance (RV) and Auditory Alterations (AA). For a detailed description of the APZ and 5D-ASC core dimensions, see Table 1.

Clinical studies have demonstrated that psilocybin, DMT and mescaline increase scores in the OB, AED and VR dimensions of the APZ (Hermle *et al.*, 1992; Vollenweider *et al.*, 1997a; Dittrich, 1998;

Table 1 Core dimensions of the 5D-ASC (Dittrich, 1998)

Dimension	Symptoms assessed
Oceanic Boundlessness (OB)	*Positive derealization*
	Positive depersonalization
	Altered sense of time
	Positive mood
	Mania-like experience
Anxious Ego Dissolution (AED)	*Anxious derealization*
	Thought disorder
	Delusion
	Fear of loss of control
Visionary Restructuralization (VR)	*Elementary hallucinations*
	Visual pseudohallucinations
	Synesthesia
	Changed meaning of percepts
	Facilitated recollection
	Facilitated imagination
Auditory Alterations (AA)	*Auditory illusions*
	Auditory pseudohallucinations
Reduction of Vigilance (RV)	*Drowsiness*
	Decreased alertness
	Impaired cognitive function

Gouzoulis-Mayfrank *et al.*, 1999). Additional studies have shown that psilocybin produces a dose-dependent increase of scores in the five core dimensions of the 5D-ASC rating scale (Hasler *et al.*, 2004). However, AED and AA scores are increased significantly only after administration of a high dose of psilocybin (0.315 mg/kg, p.o.), and are relatively unaffected by lower doses (0.045–0.215 mg/kg).

A large amount of preclinical evidence indicates that the 5-HT_{2A} receptor mediates most of the behavioral effects of hallucinogens. Pre-treatment with the 5-HT_{2A} antagonist ketanserin blocks the effects of psilocybin on the APZ in human volunteers (Vollenweider *et al.*, 1998), confirming the involvement of the 5-HT_{2A} receptor. According to a recent PET study with [^{18}F]altanserin, the ability of psilocybin to increase 5D-ASC scores is directly correlated with the level of 5-HT_{2A} receptor occupation in the anterior cingulate cortex and medial PFC (Hasler, Quednow, Vollenweider, unpublished data, Figure 1). These findings are consistent with those of an [^{18}F]fluorodeoxyglucose PET study (Vollenweider *et al.*, 1997a), which found that the effects of psilocybin on the APZ are correlated with increases in PFC and anterior cingulate metabolic activity.

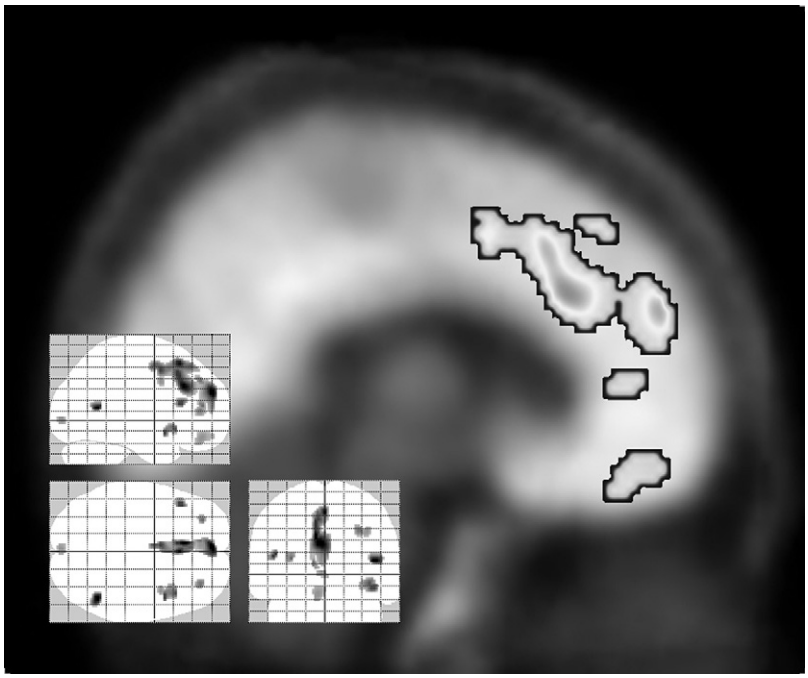

Figure 1 Inverse Correlation of 5D-ASC Global Scale scores and [^{18}F]altanserin apparent distribution volume [DV′]. Results of a voxel based correlation analysis (Δ 5D-ASC global vs ΔDV′, threshold $P < 0.005$, uncorrected) using Statistical Parametric Mapping (SPM2) (Hasler, Quednow, Vollenweider, unpublished data). To see the full color version of this figure, please refer to the color plate in the back of the book. Copies produced via our print on demand service do not contain color plates. If your copy does not have the color plate, please go to this website to view the figure in color www.elsevierdirect.com/companions/9780123746344

Comparison of hallucinogen effects and endogenous psychoses

As noted earlier, Beringer was the first investigator to propose that hallucinogens could be used to produce a 'model psychosis' in healthy humans (Beringer, 1923). Subsequent investigations confirmed that administration of mescaline, psilocybin and LSD induces states that resemble the symptoms of the earliest phases of schizophrenia (Rinkel *et al.*, 1952, 1955; Keeler, 1965; Bowers and Freedman, 1966). Indeed, the loss of control over thought processes that occurs after ingestion of psilocybin (Vollenweider *et al.*, 1997a) closely parallels acute psychotic decompensation (Keeler, 1965; Bowers and Freedman, 1966). Despite these similarities, Hollister (1962) and other clinicians have argued that there are notable differences between the effects of hallucinogens and the symptomatology of schizophrenia, leading them to question whether hallucinogen-induced psychedelic phenomena is a valid model for endogenous psychotic states. For example, Hollister noted that auditory but not visual hallucinations are prominent in schizophrenia, whereas changes of visual perception are a characteristic effect of hallucinogens. However, disturbances in visual perception, including hallucinations and synesthesias, do occur during the acute phase of schizophrenia (McCabe *et al.*, 1972; Freedman and Chapman, 1973). Hollister (1962) also argued that schizophrenics often display social and emotional withdrawal, but this effect is rarely observed after administration of serotonergic hallucinogens. There is evidence, however, that administration of hallucinogens, especially at high doses, can sometimes induce withdrawal and states resembling catatonia (Gouzoulis-Mayfrank *et al.*, 1998a).

In a study conducted by Gouzoulis-Mayfrank and colleagues (1998b), the symptoms of schizophrenia were assessed using the APZ rating scale. The goal of that investigation was to determine, using objective criteria, whether psychotic patients experience hallucinogen-like psychedelic effects. The study compared APZ scores from 50 healthy controls and 93 patients with acute schizophrenia, schizophreniform disorder or schizoaffective disorder. The APZ scores of psychotic patients were found to be significantly higher than those of controls. The study also examined whether the APZ scores correlate with scores on the Brief Psychiatric Rating Scale (BPRS), which measures positive symptoms and general psychopathology. Correlation analysis revealed that the OB subscale of the APZ correlates with BPRS factor 3 (reflecting most of the typical positive symptoms of schizophrenia), whereas the AED subscale correlates with BPRS factor 1 (reflecting anxiety and depression). These findings confirm that patients with acute schizophrenia experience hallucinogen-like effects, indicating that the syndrome induced by hallucinogens is a valid model of acute schizophrenia.

Animal models of hallucinogen effects relevant to schizophrenia

In laboratory animals, serotonergic hallucinogens have been shown to (1) potentiate neophobia (Tilson *et al.*, 1975; Adams and Geyer, 1982, 1985); (2) increase the responsiveness to sensory stimulation (Key, 1964; Geyer *et al.*, 1978; Geyer, 1998); and (3) retard habituation in a variety of input modalities and response output systems (Key, 1964; Geyer *et al.*, 1978; Geyer, 1998; Dulawa and Geyer, 2000; Geyer and Moghaddam, 2002). Given the similarities between the psychedelic state induced by hallucinogens and the symptoms of acute schizophrenia, there has been substantial interest in developing animal models of schizophrenia based on the acute behavioral effects of hallucinogens (Geyer and Vollenweider, 2008). Unfortunately, many of the unconditioned behaviors induced by hallucinogens in animals (e.g., head-twitch response, ear scratch) have no human counterpart, and thus it is not clear how these behaviors relate to the subjective effects of hallucinogens. However, hallucinogens produce effects on habituation and prepulse inhibition (PPI) of startle in animals that are analogous to hallucinogen effects in humans. Based partially on these cross-species similarities, the effects of hallucinogens on habituation and PPI have been proposed as potential behavioral models of schizophrenia (reviewed by Powell and Geyer, 2007). A brief description of these two behavioral models is provided below.

Habituation

Repeated presentation of irrelevant stimuli leads to a marked response decrement, a process known as habituation. Habituation is the simplest form of learning, and is necessary for selective attention. Deficits of attention and information-processing are core features of schizophrenia (Braff, 1985; Braff and Geyer, 1990). Patients with schizophrenia are often unable to filter out extraneous stimuli, leading to distractibility, sensory flooding and impaired cognition (McGhie and Chapman, 1961). Several studies have found that schizophrenic patients show deficits of startle reflex habituation, potentially contributing to the sensory overload and disorganized cognitive processes that occur in the disorder (e.g., Geyer and Braff, 1982, 1987; Bolino *et al.*, 1994; Parwani *et al.*, 2000; Ludewig *et al.*, 2003; Quednow *et al.*, 2006). An advantage of using habituation as a behavioral model is that similar

testing procedures can be used to assess habituation in experimental animals and humans. For example, LSD and mescaline have been shown to decrease habituation to startling tactile stimuli in rats (Geyer *et al.*, 1978; Braff and Geyer, 1980), similar to the finding in patients with schizophrenia.

Prepulse inhibition

The PPI paradigm has been multiply applied in order to assess the loss of sensorimotor gating functions in schizophrenia. PPI refers to the fact that weak prestimuli presented at brief intervals (30–500 ms) prior to a startle-eliciting stimulus reduce (or gate) the amplitude of the startle response. Studies have consistently detected robust PPI deficits in schizophrenia patients (see, for example, Braff *et al.*, 1978; Braff and Geyer, 1990; Bolino *et al.*, 1994; Parwani *et al.*, 2000; Ludewig *et al.*, 2003; Quednow *et al.*, 2006). It was proposed that the mechanism underlying PPI regulates sensory input by filtering out irrelevant or distracting stimuli in order to prevent sensory information overflow and to allow for selective and efficient processing of relevant information (Swerdlow and Geyer, 1998). The consistently reported PPI deficits in schizophrenia patients contributed to the view that schizophrenia could be seen as gating- or filter-deficit disorder (Carlsson, 1995). As detailed in Chapter 4.7, hallucinogens such as LSD and DOI also disrupt PPI. Thus, the hallucinogen-treated animals tested in the PPI paradigm exhibit an increased or unfiltered responsiveness to sensory stimuli – that is, they fail to exhibit the gating or inhibition of the response normally produced by the prepulse stimulus. As reviewed elsewhere (Geyer *et al.*, 2001; Swerdlow *et al.*, 2001), this cross-species phenomenon of PPI is very robust, unlearned and ubiquitous. Indeed, depending on the testing parameters used, the hallucinogen psilocybin has been shown to produce PPI deficits in normal human volunteers (Vollenweider *et al.*, 2007). Hence, the ability of hallucinogens to alter PPI has been considered to be a useful model to study the positive symptoms of schizophrenia.

Serotonin receptor and transporter changes *in vivo* and *post-mortem* in schizophrenia

Early *post-mortem* studies with schizophrenia patients revealed that 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) levels were increased in subcortical brain regions such as the putamen, nucleus accumbens and globus pallidus (Crow *et al.*, 1979; Farley *et al.*, 1980), and that 5-HIAA levels are decreased in cortical regions, including cingulate and frontal areas (Winblad *et al.*, 1979). Many subsequent studies investigated altered serotonin receptor and transporter expression in schizophrenia patients *in vivo* and *post-mortem*, especially with radiolabeled compounds. Most of these receptor investigations explored the 5-HT_{1A} or 5-HT_{2A} receptor density, usually with highly divergent results.

5-HT_{1A} receptors

Among the most consistent alterations of 5-HT parameters in schizophrenia, as identified in *post-mortem* studies, is an increase in the density of 5-HT_{1A} receptors in the PFC (Bantick *et al.*, 2001; Weinberger and Laruelle, 2002). Seven of ten studies – using either [^{3}H]8-hydroxy-2,3-(dipropylamino)-tetralin ([^{3}H]8-OH-DPAT) or the more specific compound [^{3}H]WAY-100653 for 5-HT_{1A} receptor binding and audioradiography, and/or analysis of receptor mRNA – have reported a 15–80 percent increase in 5-HT_{1A} receptor levels in the dorsolateral or orbital PFC, whereas other brain regions such as the anterior cingulate cortex and the temporal cortex have shown less consistent results, including possible increases (for review and citations, see Bantick *et al.*, 2001; Gray *et al.*, 2006). Interestingly, the increase in prefrontal 5-HT_{1A} receptor density was not necessarily accompanied by a change in 5-HT_{1A} receptor mRNA (Burnet *et al.*, 1996a). Moreover, the only study that stained for 5-HT_{1A}-like immunoreactivity did not find differences between schizophrenia patients and controls (Cruz *et al.*, 2004). Since receptors located at other cellular locations could not be visualized with the antibody used, changes in the overall density of the 5-HT_{1A} receptor could not be excluded by this study.

In contrast to the consistent findings in *post-mortem* studies, recent investigations of 5-HT_{1A} receptor distribution using [^{11}C]WAY-100653 PET in schizophrenia patients are contradictory. One study reported increased binding only in the medial temporal lobe (Tauscher *et al.*, 2002), another study described decreased binding in the amygdala (Yasuno *et al.*, 2004), whereas two further studies found no alterations in cortical 5-HT_{1A} receptor binding (Bantick *et al.*, 2004; Frankle *et al.*, 2006). Moreover, Bantick *et al.* (2004) found no differences in 5-HT_{1A} receptor binding between clozapine-treated patients, patients medicated with antipsychotics with low 5-HT_{1A} affinity, and healthy human volunteers. The authors concluded that clozapine did not occupy 5-HT_{1A} receptors at clinical doses. With respect to the inconsistencies between PET and *post-mortem* studies, Frankle *et al.* (2006) suggested that the alterations found in *post-mortem* studies cannot be reliably detected in PET studies, which puts into question whether 5-HT_{1A} receptors play a major

role in the pathophysiology of schizophrenia. Due to the fact that schizophrenia patients included in *post-mortem* studies are rarely antipsychotic-naïve, whereas PET studies have mostly assessed in drug-naïve or unmedicated patients, it is likely that the 5-HT_{1A} receptor changes found in the majority of *post-mortem* studies are probably the result of chronic medication with antipsychotics or other psychotropics. However, in two of the *post-mortem* studies, 5-HT_{1A} receptor increases were seen also in drug-free patients (Hashimoto *et al.*, 1991; Sumiyoshi *et al.*, 1996).

In sum, findings with respect to 5-HT_{1A} receptor changes are highly contradictory. Whereas *post-mortem* studies consistently suggest an increase of 5-HT_{1A} receptor especially in the PFC, PET studies did not find changes of prefrontal receptor binding. Effects of chronic antipsychotic medication may contribute to these different results. When schizophrenia patients actually display frontal up-regulation in 5-HT_{1A} receptors, this might reflect an abnormal glutamatergic network because in the neocortex these receptors are mainly located on pyramidal cells (Bantick *et al.*, 2001).

5-HT_{2A} receptors

The 5-HT_{2A} receptor is the most intensively investigated 5-HT receptor in *post-mortem* schizophrenia studies in the last 30 years. Of 18 *post-mortem* studies, 14 reported finding decreased 5-HT_{2A} receptor binding/densities (or decreased 5-HT_{2A} receptor mRNA expression) in cortical areas, especially in the frontal cortex, of schizophrenia patients (for references and details, see Table 2). Two of the studies reported an increase in several brain regions, whereas the two remaining studies did not find 5-HT_{2A} receptor changes. Moreover, only five investigations explored 5-HT_{2A} receptors in the basal ganglia, but just one report suggested increased 5-HT_{2A} levels, whereas the other four studies found no changes. It should be noted that the radioligands that were used in these studies have high affinity for 5-HT_{2A} receptors, but they also label other receptor types. For example, ketanserin additionally labels α-adrenoreceptors, histamine H_1 receptors and vesicular monoamine transporters; LSD binds to 5-HT_{1A}, 5-HT_{1E}, 5-HT_{2C}, 5-HT_6, 5-HT_7 and dopamine-D_1 receptors; whereas spiperone also has high affinity for D_2 receptors (Harrison, 1999b). This lack of specificity must be taken into account when these studies are interpreted.

Legitimately, the question has been raised whether these receptor changes are simply the result of chronic drug treatment, because most of the patients studied were treated with antipsychotics for many years. Indeed, it was shown that long-term treatment with clozapine decreases 5-HT_{2A} receptor binding and mRNA expression in the cingulate and frontal cortex of rats. In contrast, haloperidol did not alter cortical 5-HT_{2A} receptor density or expression in the frontal cortex of rats (Reynolds *et al.*, 1983a; Wilmot and Szczepanik, 1989; O'Dell *et al.*, 1990; Burnet *et al.*, 1996b). Other atypical antipsychotics that are 5-HT_{2A} antagonists may also reduce cortical 5-HT_{2A} receptors when given chronically (Mikuni and Meltzer, 1984; Andree *et al.*, 1986; Padin *et al.*, 2006). However, particularly in the early studies, only a very small number of patients were treated with clozapine or other atypical substances. Additionally, antipsychotic medication may increase rather than decrease 5-HT_{2A} receptor expression (Hernandez and Sokolov, 2000), and many studies also found decreased 5-HT_{2A} receptor densities in unmedicated subjects, or did not detect dose effects of previous antipsychotic drug treatment (Table 2). Thus, the decrease of 5-HT_{2A} receptors especially in the dorsolateral PFC could not be explained only by chronic drug treatment; a pathological process also has to be involved (Dean, 2003).

PET studies applying 5-HT_{2A} receptor tracers to schizophrenia patients show controversial results. Three studies using [^{18}F]septoperone and one study using [^{11}C]*N*-methylspiperone did not show any significant differences in 5-HT_{2A} receptor densities between schizophrenia patients and controls, either with regions-of-interest (ROI)-based or voxel-based analyses (Trichard *et al.*, 1998; Lewis *et al.*, 1999; Okubo *et al.*, 2000; Verhoeff *et al.*, 2000). However, both tracers suffer from a relatively low affinity for 5-HT_{2A} receptors, and thus they have an insufficient signal-to-noise ratio in subcortical areas (Erritzoe *et al.*, 2008). In contrast, one study using [^{18}F]septoperone found decreased frontal 5-HT_{2A} receptor densities in antipsychotic-naïve schizophrenia patients (-16.3 percent; Ngan *et al.*, 2000), while a recently published study using the more selective 5-HT_{2A} antagonist [^{18}F]altanserin could not demonstrate a frontal decrease but rather an increase of 5-HT_{2A} receptors in the caudate in a similar patient sample (Erritzoe *et al.*, 2008). Two further studies investigated 5-HT_{2A} receptor density with [^{18}F]altanserin PET in subjects supposed to be in a prodromal state of schizophrenia and both reported decreased binding of the radio tracer in the PFC (Hurlemann *et al.*, 2005, 2008). In the later study, Hurlemann *et al.* (2008) additionally detected decreased 5-HT_{2A} receptor binding in the right insular cortex, the left amygdala, both hippocampi, the right caudate and the left putamen in never-medicated subjects in a late prodromal stage. Interestingly, a low 5-HT_{2A} receptor density in the right caudate predicted later conversion to full-blown psychosis, a finding that is highly discrepant with the results of Erritzoe *et al.* (2008). Taken together, in contrast to the consistency of the *post-mortem* findings,

Table 2 *Post-mortem* studies investigating 5-HT_{2A} receptor density in schizophrenia (modified and updated according to Harrison, 1999a)

Study	Method[1]	Brain region[2]	Cases/controls	Medicated cases	Main findings
Decrease in cortical binding					
Bennett *et al.* (1979)	HB with [^{3}H]LSD	BA 6, 8–11, 44–47	26/25[3]	18	↓ 40–50%, no effect of medication
Mita *et al.* (1986)	HB with [^{3}H]ketanserin	BA 9	11/9	7	↓ 36%, no effect of medication
Arora and Meltzer (1991)	HB with [^{3}H]spiperone	BA 8/9	11/11	11	↓ 33%, no effect of medication
Laruelle *et al.* (1993a)	HB with [^{3}H]ketanserin	BA 10, 17/18	10/12[4]	6	↓ 21% in BA 10, no effect of medication
Burnet *et al.* (1993b)	a) RA with [^{3}H]ketanserin	BA 17, 22, 46, MTL, AC	13/15	12	↓ 27% in BA 46, ↓ 38% MTL, similar trend in AC
	b) mRNA using ISH				↓ 49–63% in BA 17, 22, 46, AC, ↔ in MTL
Dean and Hayes (1996)	RA with [^{3}H]ketanserin	BA 8, 9, 10	20/20	19	↓ 25–33% in all frontal regions
Gurevich and Joyce (1997)	RA with [^{125}I]LSD	BA 1-3, 4, 6, 8, 9, 31, 32, 40, 44–46, AC, PC	10/12	5	↓ ~60% in BA 6, 24 in drug-free cases, ↓ ~70–90% in all brain regions in medicated cases
Kouzmenko *et al.* (1997)	RA with [^{3}H]ketanserin	BA 9/46	63/62[5]	60	↓ 33%
Dean *et al.* (1998)	RA with [^{3}H]ketanserin	BA 9	55/55	55	↓ 33%
Dean *et al.* (1999a)	RA with [^{3}H]ketanserin	BA 9	19/19	17	↓ 35%
Hernandez and Sokolov (2000)	mRNA using ISH	BA 9	21/14	18	↓ 60% in patients being drug free for $>$ 26 weeks, antipsychotic treatment increased 5-HT2A mRNA
Pralong *et al.* (2000)	a) RA with [^{3}H]ketanserin	BA 22 (planum temporale)	20/20	17	↓ 32%
	b) HB with [^{3}H]ketanserin	BA 22 (planum temporale)	10/10	10	↓ 34% B_{max},↑ 119%, changes in affinity (K_d) but not density (B_{max}) explained by medication effects
Scarr *et al.* (2004)	RA with [^{3}H]ketanserin	MTL (only hippocampus)	20/20	20	↓ ~29–47% across different regions of hippocampus
Matsumoto *et al.* (2005)	RA with [^{3}H]ketanserin	BA 9, MTL	6/6	6	↓ 39% in BA 9, ↔ in MTL
Increase in cortical binding					
Whitaker *et al.* (1981)	HB with [^{3}H]LSD	BA 4, 10, 11	13/8	8	↔, ↑ 55% in unmedicated cases
Joyce *et al.* (1993)	RA with [^{125}I]LSD	BA 4, 9, 21, AC, PC, MTL	8/10	4	↑ ~50–100% only in MTL, BA 21, PC
No changes in cortical binding					
Reynolds *et al.* (1983b)	HB with [^{3}H]ketanserin	BA 10	11/10	11	↔

(*Continued*)

Table 2 (*Continued*)

Study	Method[1]	Brain region[2]	Cases/controls	Medicated cases	Main findings
Dean *et al.* (1996)	HB with [^{3}H]ketanserin	BA 9	20/20	19	↔
Increase in basal ganglia					
Joyce *et al.* (1993)	RA with [^{3}H]ketanserin	Caudate, putamen, NAC	8/10	4	↑ ~30–75%
No changes in basal ganglia					
Mackay *et al.* (1978)	HB with [^{3}H]spiperone	NAC	26/17	?	↔
Owen *et al.* (1981)	HB with [^{3}H]LSD, [^{3}H]5-HT	Caudate, putamen	19/20	?12	↔
Seeman *et al.* (1993)	HB with [^{3}H]ketanserin	Striatum	9/4	6	↔
Matsumoto *et al.* (2005)	RA with [^{3}H]ketanserin	Caudate, putamen	6/6	6	Not significant but strong trend for decrease (↓ 34%)

Notes:
[1] HB, homogenate binding; ISH, *in situ* hybridization; RA, receptor autoradiography.
[2] BA, Brodmann area; BA 4, motor cortex; BA 6, 8, 9, 10, 11, 44–47, prefrontal cortex; BA 17/18, occipital cortex; BA 21, 22, temporal cortex; AC, anterior cingulate cortex; PC, posterior cingulate cortex; MTL, mediotemporal lobe including hippocampus, amygdala, uncus, parahippocampal gyrus, entorhinal cortex; NAC, nucleus accumbens.
[3] Sum of three separate case–control groups. The decrease in [^{3}H]LSD binding was demonstrated in all three comparisons.
[4] Includes six subjects with schizoaffective disorder. Significant differences remained when these subjects were excluded.
[5] Included cases of Burnet *et al.* (1996b) and Dean and Hayes (1996).

the PET results are highly contradictory. Given that the methodological differences between the PET studies are not really obvious, further studies are needed to clarify whether 5-HT_{2A} receptor changes could also be detected with an *in vivo* imaging approach. The new and highly selective 5-HT_{2A} receptor radioligand [^{11}C]MDL 100,907 may be a promising tool to further investigate 5-HT_{2A} receptor alterations in schizophrenia (Ito *et al.*, 1998).

Other serotonin receptors

Other serotonin receptor types have been investigated in *post-mortem* studies: two studies using [^{3}H]GR113808 autoradiography showed that the density of 5-HT_4 receptors is unaltered in either the dorsolateral PFC or the hippocampus of deceased schizophrenia patients when compared to control subjects (Dean *et al.*, 1999b; Scarr *et al.*, 2004). A *post-mortem* study investigating the concentration of 5-HT_3 receptors (which is the only ion channel in the 5-HT receptor family) in the amygdala of schizophrenia patients and controls with [^{3}H]LY278584 autoradiography did not find group differences (Abi-Dargham *et al.*, 1993). The 5-HT_6 receptor density measured with [^{125}I]SB-258585 in the frontal cortex was not changed in 20 schizophrenia patients compared to 17 control subjects (East *et al.*, 2002). Recently, two studies investigated the densities of 5-HT_{1D} and 5-HT_{1F} receptors in the dorsolateral PFC and the hippocampus, respectively, of schizophrenia patients using methiothepin-sensitive and -insensitive [^{3}H]sumatriptane autoradiography (Scarr *et al.*, 2004; Dean *et al.*, 2006). While Scarr *et al.* (2004) reported a decrease of 5-HT_{1F} but unaltered 5-HT_{1D} receptors in the hippocampus, Dean and colleagues did not find any changes in HT_{1F} and 5-HT_{1D} receptors in the dorsolateral PFC of the patients. In the same study, however, Dean *et al.* (2006) found decreased 5-HT_7 receptor levels in dorsolateral PFC of schizophrenia patients using [^{3}H]SB-269970. By contrast, haloperidol treatment increased the number of 5-HT_7 receptors in the cortex of rats (Dean *et al.*, 2006). The authors therefore concluded that 5-HT_7 receptors are possibly involved in the pathological processes of schizophrenia and that appropriate 5-HT_7 receptor levels may be critical for normal cortical development. These recent findings regarding alterations of HT_{1F} and 5-HT_7 receptors in schizophrenia need confirmation by further *post-mortem* and, if possible, PET studies.

Serotonin transporter (SERT)

Serotonin transporters (SERT) are located presynaptically on serotonergic axon terminals and are believed

to serve as an index of serotonergic innervation (Abi-Dargham and Krystal, 2000). Two *post-mortem* studies applying [^{3}H]cyano-imipramine and [^{3}H]paroxetine initially showed that the density of SERT was decreased in the frontal cortex (Joyce *et al.*, 1993; Laruelle *et al.*, 1993a). In the study of Joyce and colleagues (1993), SERT was also decreased in the anterior and posterior cingulate cortex of schizophrenia patients, but increased in the striatum. On the contrary, later studies using radiolabeled serotonin reuptake inhibitors (SRIs), such as [^{3}H]paroxetine, [^{3}H]citalopram or [^{125}I]RTI-55, did not demonstrate any alterations in the SERT density in several brain regions, including the PFC or the cingulate cortex, in schizophrenia patients (Dean *et al.*, 1995, 1999b; Naylor *et al.*, 1996; Gurevich and Joyce, 1997). In fact, three of these studies did not report altered SERT densities but did find a decrease in the affinity of [^{3}H]paroxetine for SERT in hippocampal membranes, whereas the affinity of [^{3}H]paroxetine for SERT binding in the frontal cortex was unaltered (Dean *et al.*, 1995, 1996; Naylor *et al.*, 1996). Gurevich and Joyce (1997) concluded that the initial positive findings were probably confounded by the large number of schizophrenia patients in the samples who committed suicide. The same may be true for the finding of decreased SRI affinity in hippocampal SERT, as Dean and colleagues showed that the effect was more pronounced in schizophrenia patients who committed suicide (Dean *et al.*, 2006).

Examining the expression of SERT mRNA, Hernandez and Sokolov (1997) found a four-fold increase in the level of SERT mRNA in the dorsolateral PFC, but a two-fold decrease in the temporolateral cortex, of schizophrenics. However, since these changes were strongly correlated with previous antipsychotic drug treatment, they cannot be attributed to the illness process.

A SPECT study using [^{123}I]RTI-55 could not detect any differences in SERT concentration in midbrain areas of schizophrenia patients (Laruelle *et al.*, 2000). However, [^{123}I]RTI-55 is not specific for SERT but also labels the dopamine transporter (DAT) (Neumeyer *et al.*, 1991). In addition, [^{123}I]RTI-55 does not permit measurement of SERT availability in regions other than the midbrain (Laruelle *et al.*, 1993b). Recently, Frankle *et al.* (2005) also failed to detect any differences in SERT binding between schizophrenia patients and controls when using the more specific radiotracer [^{11}C]DASB. However, [^{11}C]DASB does not have a good signal-to-noise ratio when assessing regions with low SERT density such as the neocortex (Frankle *et al.*, 2005), complicating a possible detection of group differences in, for example, the frontal cortex. Thus, taking all these findings into account, it is unlikely that SERT plays an important role in the pathophysiology of schizophrenia.

Genetic association studies regarding schizophrenia and serotonin

Given that, to date, more than 1400 association studies searching for potential genetic risk factors have been published with largely inconsistent results, a regularly updated online database ('SzGene') including meta-analyses of all published genetic studies for schizophrenia has recently been established (Allen *et al.*, 2008; www.schizophreniaforum.org). Single nucleotide polymorphisms (SNPs) having genotype data available in at least four independent case–control samples were included in random-effect meta-analyses using allelic contrasts. In the ranking of the meta-analyses showing the strongest effect sizes, two serotonin-related SNPs are currently placed in the top 20 (status 30 September, 2009): the tryptophan hydroxylase 1 (TPH1) A218C polymorphism ranked eleventh (odds ratio (OR) = 1.25), and the 5-HT$_{2A}$ A-1438G polymorphism ranked sixteenth (OR = 1.16). Table 3 displays all serotonin SNPs for which meta-analyses were done. For comparison, the strongest effect so far was shown for the A2897G polymorphism of the disrupted-in-schizophrenia gene 1 (DISC1; OR = 1.80, confidence interval (CI) = 1.2–2.68). The second ranking belongs to the A277C polymorphism of the vesicular monoamine transporter 1 (VMAT1; OR = 1.63, CI = 1.03–2.57). VMAT1 is involved in the intracellular transport of all monoamines including serotonin. The rs6556547 SNP of the GABA-A beta-2 receptor (OR = 0.70, CI = 0.52–0.95), is ranked third. These ORs reported for schizophrenia susceptibility genes are comparable with those found in other genetically complex neuropsychiatric diseases such as Alzheimer's disease (Allen *et al.*, 2008).

TPH1 and TPH2 are rate-limiting enzymes in 5-HT synthesis, but while TPH1 is primarily expressed in peripheral regions such as the pineal gland and enterochromaffin cells of the gut, TPH2 is expressed predominantly in serotonergic neurons of the raphe nuclei (Zhang *et al.*, 2006). Moreover, the TPH1 A779C and A218C SNPs are intronic (non-coding), and alternative mechanisms probably providing gene expression from intronic sequences such as splicing and exon skipping have been ruled out (Shaltiel *et al.*, 2005). For these reasons, the positive associations between the TPH1 A218C polymorphism and schizophrenia were strongly criticized (Reuter *et al.*, 2007). However, in a *post-mortem* study, Zill *et al.* (2007) recently demonstrated the expression of TPH1 mRNA in several brain regions. Therefore, it seems to be largely unclear to date which role TPH1 plays in cerebral function and schizophrenia. Most likely, the intronic TPH1 A218C SNP is in linkage disequilibrium with other functional as yet unidentified gene variations. Variations of the TPH2 gene have not been positively linked to

Table 3 Meta-analyses of association studies between polymorphisms of the serotonin system and schizophrenia*

Gene	Substrate	SNP	Chromosome (location)	Synonymy	Number of studies	Number of patients	Number of controls	Minor allele (% frequency in controls)	Risk allele	Odds ratio (all studies)	95% confidence interval
5-HT1B	Receptor	rs6296 (G861C)	6 (6q13)	Synonymous	4	763	1123	C (38%)	C	0.95	0.75–1.20
5-HT2A	Receptor	rs6311 (A-1438G)	13 (13q14-q21)	Synonymous	8	2678	2964	A (42%)	G	1.16	1.01–1.33
		rs6313 (T102C)	13 (13q14-q21)	Synonymous	46	9369	10076	T (47%)	T	0.96	0.89–1.04
		rs6314 (His452Tyr)	13 (13q14-q21)	Non-synonymous	5	2706	2878	T (9%)	T	0.96	0.79–1.17
5-HT6	Receptor	rs1805054 (C267T)	1 (1p36-p35)	Synonymous	4	530	519	T (25%)	–	1.00	0.73–1.37
SERT	Transporter	5-HTTVNTR	17 (17q11.1-q12)	Synonymous	13	2629	3042	10 (30%)	10	0.90	0.78–1.03
		5-HTTLPR	17 (17q11.1-q12)	Synonymous	23	3861	4998	L (48%)	L	1.03	0.97–1.10
TPH1	Enzyme	rs1800532 (A218C)	11 (11p13.3-p14)	Synonymous	6	1239	1708	A (45%)	C	1.25	1.08–1.44
		rs1799913 (A779C)	11 (11p13.3-p14)	Synonymous	5	653	994	A (48%)	C	0.91	0.78–1.06

Published on the SchizophreniaGene database (www.schizophreniaforum.org/res/sczgene/default.asp, status 30 September 2009.
Meta-analyses were done for SNPs with a minor allele frequency > 1%, and when more than three independent case–control samples were available (Allen *et al.*, 2008).
Abbreviations: SNP, single nucleotide polymorphisms; SERT, serotonin transporter; TPH1, tryptophan hydroxylase 1.

schizophrenia so far (De Luca *et al.*, 2005; Higashi *et al.*, 2007).

The positive association findings regarding the 5-HT_{2A} A-1438G polymorphism once more underscore the significance of this receptor for schizophrenia (Table 3). The A-1438G polymorphism is silent and does not result in an alteration of the amino acid sequence of the 5-HT_{2A} receptor, but is located within the promoter region of the 5-HT_{2A} receptor gene (Spurlock *et al.*, 1998), and thus it has been proposed that the A-1438G polymorphism alters promoter activity and expression of 5-HT_{2A} receptors (Parsons *et al.*, 2004). The 5-HT_{2A} A-1438G and T102G receptor polymorphisms are usually in perfect linkage disequilibrium. We have recently shown that the sensorimotor gating deficits of schizophrenia patients – which are seen as a promising endophenotype of schizophrenia (Gottesman and Gould, 2003) – are strongly modulated by the 5-HT_{2A} A-1438G and T102C receptor SNPs that were completely linked in our sample (Quednow *et al.*, 2008). In accordance with the genetic association studies, carriers of the high-risk G and C alleles displayed diminished sensorimotor gating. We have just replicated this finding in a sample of 94 normal subjects (Quednow *et al.*, 2009). In conclusion, the C allele of the T102C variation and the G allele of the A-1438G variation may cause lower 5-HT_{2A} receptor densities in some brain areas, which may lead to a less flexible serotonin system and worse dopaminergic modulation (Serretti *et al.*, 2007).

The SzGene meta-analyses regarding 5-HT_{1B} G861C, 5-HT_{2A} His452Tyr and 5-HT_6 C267T receptor SNPs, and the well-known SERT polymorphisms, suggest rather weak or no associations with schizophrenia (Table 3).

Currently, there are also some new interesting data coming from single association studies that still have to be replicated. Huang *et al.* (2004) reported an increased frequency of the G allele of the 5-HT_{1A} C-1019G promoter polymorphism in schizophrenia patients. The occurrence of the G allele is associated with enhanced gene expression (Lemonde *et al.*, 2003), which would fit with the *post-mortem* data on increased 5-HT_{1A} receptor levels in the PFC of schizophrenics. However, in a large *post-mortem* autoradiographic study, Huang *et al.* (2004) could not demonstrate differences in 5-HT_{1A} receptor binding between 5-HT_{1A} C-1019G genotypes in suicidal, depressed and healthy subjects. Moreover, significant associations were reported for the 5-HT_{2C} G68C (Segman *et al.*, 2000), a 5-HT_4 haplotype (Suzuki *et al.*, 2003), and several 5-HT_{5A} (Birkett *et al.*, 2000; Iwata *et al.*, 2001;

Dubertret *et al.*, 2004) and two 5-HT_7 receptor polymorphisms (Ikeda *et al.*, 2006). There have also, however, been some negative reports for 5-HT_{2C} G68C (Segman *et al.*, 1997; Semwal *et al.*, 2002) and the 5-HT_7 receptor polymorphisms (Fallin *et al.*, 2005). Further studies are needed to finally assess the sustainability of these initial findings.

Not only schizophrenia itself, but also drug response or risk for developing side effects such as tardive dyskinesia or weight gain, were the subject of pharmacogenetic studies of mutations in the serotonin system (for a comprehensive review, see Arranz and de Leon, 2007). The aim of these studies was the development of genetic predictors for treatment response and side effects to preselect and therefore improve antipsychotic treatment. The functional C-1019G variant of the 5-HT_{1A} receptor was recently demonstrated to influence the response to atypical antipsychotics (Reynolds *et al.*, 2006; Wang *et al.*, 2008; Mossner *et al.*, 2009). These studies have consistently shown that carriers of the C allele show greater improvement, especially in regard to negative symptoms. A number of studies reported significant associations between the linked 5-HT_{2A} A-1438G and T102C receptor SNPs and response to atypical antipsychotics (mostly clozapine), but there are some discrepant results with respect to the risk alleles for non-responding (Arranz *et al.*, 1995, 1998a, 1998b; Joober *et al.*, 1999; Yu *et al.*, 2001; Lane *et al.*, 2002; Hamdani *et al.*, 2005; see also Arranz and de Leon, 2007). In addition, there are several studies reporting that there is no association between the T102C substitution and the therapeutic response to clozapine and other antipsychotics (Masellis *et al.*, 1995; Nothen *et al.*, 1995; Jonsson *et al.*, 1996; Malhotra *et al.*, 1996; Lin *et al.*, 1999). A more consistent picture comes from studies showing an influence of the functional His452Tyr polymorphism of the 5-HT_{2A} receptor on the clozapine response (Arranz *et al.*, 1996; Masellis *et al.*, 1998). Although several other studies failed to detect an association of this SNP and treatment response (Masellis *et al.*, 1995; Nothen *et al.*, 1995; Jonsson *et al.*, 1996; Malhotra *et al.*, 1996; Lin *et al.*, 1999), a recent meta-analysis has shown a relatively strong association of the Tyr variant with poor response to clozapine (Arranz *et al.*, 1998b). Mutations in the promoter (VNTR, T-759C and G-995A) and coding region (Cys23Ser) of the 5-HT_{2C} receptor have also been associated with clozapine response and improvement in negative symptoms (Sodhi *et al.*, 1995; Arranz *et al.*, 2000a; Reynolds *et al.*, 2005). A further study was unable to detect an effect of the Cys23Ser SNP on treatment response (Rietschel *et al.*, 1997). In sum, the contribution of the variants to general drug response is relatively moderate, possibly indicating contribution to specific symptoms or side effects that need further investigation (Arranz and de Leon, 2007). There are also some indices for an association of the 5-HT_6 T-267C receptor variant with the response to treatment with clozapine and risperidone in Chinese patients (Yu *et al.*, 1999; Lane *et al.*, 2004), although this association has not been replicated in US patients (Masellis *et al.*, 2001).

Additionally, SERT polymorphisms have been investigated in respect to drug response but, with the exception of an initial positive finding (Arranz *et al.*, 2000b), all further reports did not find significant associations (Arranz *et al.*, 2000a; Tsai *et al.*, 2000; Kaiser *et al.*, 2001). Through combining the data of gene variants previously associated with clozapine response, Arranz *et al.* (2000b) found that a combination of SNPs in the genes coding for 5-HT_{2A}, 5-HT_{2C}, histamine H_2 receptors and the SERT resulted in the correct prediction of response in 76 percent of cases. However, so far this finding has not replicated (Schumacher *et al.*, 2000).

The findings with respect to the association of 5-HT_{2A} polymorphisms and tardive dyskinesia are controversial (Basile *et al.*, 2001; Segman *et al.*, 2001; Tan *et al.*, 2001; Lattuada *et al.*, 2004; Deshpande *et al.*, 2005; Lerer *et al.*, 2005). The same is true for 5-HT_{2C} polymorphisms (Rietschel *et al.*, 1997; Zhang *et al.*, 2002; Deshpande *et al.*, 2005). Two recent studies reported promising results regarding a possible interaction of the 5-HT_{2A}, 5-HT_{2C} and D_3 receptor genotype with respect to the risk of developing tardive dyskinesia under antipsychotic treatment (Segman *et al.*, 2000; Segman and Lerer, 2002).

The most significant results associated the 5-HT_{2C} T-759C receptor variant with antipsychotic-induced weight gain (Arranz and de Leon, 2007). Although a number of studies failed to replicate this finding (Hong *et al.*, 2001; Basile *et al.*, 2002; Tsai *et al.*, 2002; Theisen *et al.*, 2004), the evidence for a protective effect of the T allele is convincing (Reynolds *et al.*, 2002b, 2003; Buckland *et al.*, 2005; Ellingrod *et al.*, 2005; Miller *et al.*, 2005; Templeman *et al.*, 2005). Given the strength of the reported associations, this could be a discovery with a useful clinical application as a predictor of drug-induced weight gain (Arranz and de Leon, 2007).

In summary, genetic studies imply a critical role of mainly 5-HT_{1A} and 5-HT_{2A} receptors in the pathophysiology of schizophrenia and drug-response to antipsychotics.

Serotonergic mechanisms of atypical antipsychotics

5-HT_{2A} receptor antagonism

For a long time, one of the most important arguments for an involvement of the serotonin system in the etiology of schizophrenia was the serotonergic action of most

of the so-called atypical antipsychotics. Due to clinical experiences with the early antipsychotics, neuropharmacologists initially believed that extrapyramidal side effects (EPS) are an essential part of the antipsychotic effectiveness. The antiquated term 'neuroleptics' ('seize the neuron') still refers to this association (Lidow, 2000). The reason for the positive correlation of antipsychotic effectiveness and EPS is that the antipsychotic potency of the early neuroleptics is proportional to their ability to block striatal D_2 receptors, which is also the cause for EPS (Seeman *et al.*, 1976). As a consequence, D_2 receptor blockade was proposed to be the principal mechanism of action of neuroleptics known until then (Creese *et al.*, 1976), such as the phenothiazines chlorpromazine, perphenazine, fluphenazine and thioridazine, the thioxanthenes thiothixene and flupentixol, and the butyrophenone haloperidol (which is still the most widely used neuroleptic drug). However, the dibenzodiazepine clozapine broke these rules, because its therapeutic effectiveness was not paired with notable EPS. Therefore, clozapine was described as an 'atypical' antipsychotic.[2] Unfortunately, the conditions for atypicality are not well defined. The narrowest definition is that atypical drugs produce lower EPS than typical drugs. However, in the past two decades several further prerequisites have been proposed – that atypical drugs should have (1) a lower capacity to elevate prolactin levels and more strongly ameliorate negative and cognitive symptoms of schizophrenia compared to typical substances; (2) a multi-receptor profile, and higher *in vivo* selectivity for corticolimbic D_2 receptors compared to striatal D_2 receptors; and (3) a higher D_4 receptor affinity, and a serotonergic component or a higher affinity for 5-HT_{2A} receptors than for D_2 receptors (Meltzer, 1991, 1999; Blin, 1999; Lidow, 2000; Seeman, 2002). It becomes clear that, in the end, all these definitions are derived from the multiple mechanisms of action of clozapine, and thus only clozapine itself matches all of these criteria, reducing the concept of atypicality to absurdity.

Although clozapine is still the gold standard regarding antipsychotic effectiveness, it has a not especially rare (0.5–2 percent) and potentially life-threatening side effect: agranulocytosis (Buchanan, 1995). Therefore, scientists have aimed to develop novel antipsychotics having the antipsychotic potency but not the dangerous side effects of clozapine. Given that the superior efficacy of clozapine had been attributed to its high 5-HT_{2A} receptor selectivity relative to the D_2 receptor (Meltzer *et al.*, 1989; Meltzer, 1991), the development of 'balanced' 5-HT_{2A}/D_2 antagonists as potential antipsychotics was initiated in the late 1980s (Abi-Dargham and Krystal, 2000). This approach led to the discovery of novel antipsychotic substances, such as risperidone, olanzapine, quetiapine, ziprasidone and sertindole. All these compounds have higher affinity for the 5-HT_{2A} receptor than for the D_2 receptor, even if none of them shows as high a D_2/5-HT_{2A}-binding ratio as clozapine (only the dibenzoxazepine amoxapine has a higher ratio than clozapine) (Seeman, 2002). As a consequence, Meltzer (1999) proposed that atypical antipsychotics with a high D_2/5-HT_{2A}-binding ratio are more effective against negative symptoms, show a stronger improvement of cognitive functions, and cause less EPS than typical antipsychotics. Several clinical trials have shown that atypical antipsychotics with strong 5-HT_{2A} antagonism – first and foremost clozapine – improve negative symptoms more efficaciously than typical compounds (see, for example, Kane *et al.*, 1988; Marder and Meibach, 1994; Moller *et al.*, 1995; Tollefson and Sanger, 1997). However, meta-analyses revealed rather moderate advantages of atypical antipsychotics in the treatment of negative symptoms (Carman *et al.*, 1995; Leucht *et al.*, 1999, 2009). Some scientists argued that these beneficial effects are only related to the improvement of secondary negative symptoms, which are correlated with the improvement of positive symptoms, depressive symptoms, EPS or environmental deprivation, but that primary negative symptoms (also called as the 'deficit syndrome') are still unaffected by atypicals (Carpenter *et al.*, 1995; Buchanan *et al.*, 1998; Lidow, 2000). Moreover, the view that a 5-HT_{2A} receptor blockade is probably not necessary to improve negative symptoms is supported by large meta-analyses showing that amisulpride – an atypical antipsychotic that is a selective D_2/D_3 receptor antagonist – has a comparable efficacy to clozapine with regard to negative symptoms (Leucht *et al.*, 2002, 2009).

Cognitive dysfunctions constitute core symptoms of schizophrenia, and improvement of cognitive function is highly relevant for functional outcome such as social and occupational functioning (Green, 1996; Liddle, 2000). Many studies have shown that when compared to haloperidol, the atypicals clozapine, risperidone and olanzapine differently improved functioning in several cognitive domains, including semantic memory, verbal learning and memory, sustained attention, and working memory (Kern *et al.*, 1999; Meltzer and McGurk, 1999; Purdon *et al.*, 2000; Bilder *et al.*, 2002). However, most of these clinical trials did not use a control group or did not measure the control groups repeatedly. Meanwhile, recent data suggest that the measured cognitive improvements are only in the range of the expected test–retest enhancement (Goldberg *et al.*, 2007; Quednow and Wagner, unpublished data).

[2] Second- or new-generation antipsychotics, multireceptor antipsychotics, or modern antipsychotics are often used (but not necessarily better) synonyms for atypical antipsychotics. Typical antipsychotics are also termed as classical or first-generation antipsychotics or neuroleptics, respectively.

Additionally, the large ($n = 817$) CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) schizophrenia trial funded by the National Institute of Mental Health (NIMH) has recently shown only small effects of several atypical drugs on neurocognitive composite scores after 2, 6 and 18 months of continued treatment (Keefe *et al.*, 2007). After 2 months, treatment with the atypicals ziprasidone ($z = 0.12$), olanzapine (0.13), quetiapine (0.18) and risperidone (0.26), as well as the typical antipsychotic perphenazine (0.25) (where z is the least-squares mean improvement in the neurocognitive composite score), resulted in only small but significant neurocognitive improvements, with no significant differences between treatment groups. In contrast, after 18 months of treatment, neurocognitive enhancement was significantly greater in the perphenazine group than in the olanzapine and risperidone groups, despite the fact that perphenazine is a stronger D_2 receptor than a 5-HT_{2A} receptor blocker. This is in line with our previous data that treatment with the selective D_2/D_3 blocker amisulpride resulted in greater improvement of all cognitive domains (attention, executive function, working memory and declarative memory) in schizophrenia patients compared to the clozapine-copy olanzapine (Wagner *et al.*, 2005). These data strongly call the following two hypotheses into question: (1) that atypical antipsychotics improve cognitive deficits beyond simple test–retest effects; and (2) that 5-HT_{2A} receptor blockade is necessary for the cognition enhancing effects of atypical substances.

A recent meta-analysis showed that clozapine is still the antipsychotic drug with the lowest risk to produce EPS (measured by the amount of antiparkinsonian medication), followed by sertindole and olanzapine (Leucht *et al.*, 2009). Several suggestions have been made to explain the low probability of EPS under clozapine treatment. The anticholinergic properties, the lack of ability to increase acetylcholine in the striatum, D_1 and D_4 receptor blockade, α_1- or α_2-adrenoreceptor antagonism, and the 5-HT_{2A} receptor antagonism of clozapine have been proposed to reduce the risk of EPS. Data from animal models of schizophrenia as well as clinical data suggest that a high 5-HT_{2A} receptor blockade in combination with a low D_2 receptor blockade may help to avoid EPS, whereas the D_1 receptor did not play a meaningful role (Meltzer, 1999; Roth and Meltzer, 2000). Given that many atypical compounds still induce EPS if higher doses are given, 5-HT_{2A} blockade may not be sufficient for the reduction of EPS in the presence of complete or near-complete D_2 blockade. However, 5-HT_{2A} antagonism may reduce the risk for EPS when D_2 receptors are not completely saturated (Abi-Dargham and Krystal, 2000).

Animal studies first indicated that selective 5-HT_{2A} receptor antagonists lacking a dopaminergic component may have antipsychotic properties (Geyer *et al.*, 2001). The selective 5-HT_{2A} receptor blocker MDL 100,907 was the first compound whose antipsychotic activity was exclusively predicted by preclinical animal models (Varty *et al.*, 1999). In a subsequent clinical trial MDL 100,907 was not sufficiently more effective than haloperidol in the treatment of schizophrenia, although it was more effective than placebo in reducing psychotic symptoms (de Paulis, 2001). Nevertheless, so far there is no efficacious and approved antipsychotic without a dopaminergic mechanism of action. Moreover, the mechanism underlying the therapeutic superiority of clozapine is still unclear. One alternative hypothesis for atypicality focused on the special kinetics of interaction with the D_2 receptor displayed by atypical drugs and, therefore, negating the role of 5-HT_{2A} receptors (Kapur and Seeman, 2001). Data reported in Seeman (2002) are interpreted to suggest that most of the atypical drugs dissociate much faster from D_2 receptors than do typical compounds. The dibenzapines clozapine and quetiapine and the benzamides amisulpride and remoxipride show the fastest dissociation from the D_2 receptor. Seeman (2002) concluded that transient occupation of D_2 receptors allows relatively normal dopamine neurotransmission, which is likely to be a prerequisite for normal prolactin levels, intact cognition and avoidance of EPS. This 'fast-off-D_2' theory was strongly criticized because it applies only to clozapine and quetiapine and is inconsistent with the relatively slow dissociation of several atypicals, including olanzapine, risperidone, ziprasidone and sertindole (Meltzer *et al.*, 2003). However, so far there is no other theory that explains the high antipsychotic efficacy of both clozapine and amisulpride.

Schizophrenia is most likely not a homogeneous entity of an illness, but rather a cluster of diverse schizophreniform diseases with different pathogeneses. Thus, some patients may have more benefit from a serotonergic compound than others. However, to date there are no criteria to safely predict the response to treatment with either antipsychotic.

Role of other 5-HT receptors

Most of the atypical antipsychotics have affinities for multiple 5-HT receptors (Table 4). This section briefly discusses the interaction of antipsychotics with 5-HT_{1A}, 5-HT_{2C}, 5-HT_3, 5-HT_4, 5-HT_6 and 5-HT_7 receptors.

Numerous antipsychotics display activity at human 5-HT_{1A} receptors – aripiprazole, clozapine, quetiapine and ziprasidone display marked affinity and act as agonists or partial agonists, whereas risperidone and sertindole display low affinity and act as antagonists. Moreover, several of the typical compounds, including

haloperidol and chlorpromazine, also exhibit relatively low affinity and antagonistic properties at 5-HT_{1A} receptors (Newman-Tancredi *et al.*, 1998; Shapiro *et al.*, 2003). Thus, a specific 5-HT_{1A} action is likely not necessary for antipsychotic activity. However, a 5-HT_{1A} agonist activity was proposed to enhance memory and cognition in schizophrenia because it was shown that (1) 5-HT_{1A} receptors are concentrated in brain regions thought to mediate several cognitive functions (e.g., hippocampus, thalamus, cingulate cortex and PFC) (Roth *et al.*, 2004), and (2) clozapine increases dopamine release in the PFC via its 5-HT_{1A} agonism (Rollema *et al.*, 1997). In support of this hypothesis, Sumiyoshi and colleagues reported that chronic administration of the selective 5-HT_{1A} receptor agonist tandospirone as a co-therapy with typical antipsychotics enhanced verbal memory and executive functions in schizophrenia patients (Sumiyoshi *et al.*, 2001a, 2001b). In contrast, chronic co-administration of the 5-HT_{1A} receptor partial agonist buspirone with atypical antipsychotics improved psychomotor speed but not memory or executive function in schizophrenia patients (Sumiyoshi *et al.*, 2007). On the other hand, tandospirone exerted negative effects on memory function in demented patients (Yasuno *et al.*, 2003), and the potent 5-HT_{1A} agonist NAE-086 induced hallucinations and nightmares in healthy volunteers after repeated doses (Renyi *et al.*, 2001). Thus, augmentation with a 5-HT_{1A} partial agonist for cognitive enhancement in schizophrenia seems only to be effective in combination with antipsychotics that lack 5-HT_{1A} activity. Contrarily, atypical antipsychotics with a 5-HT_{1A} agonistic action should not be combined with tandospirone or buspirone because this may worsen psychotic symptoms and has no additional effects on cognition (Roth *et al.*, 2004).

In addition, clozapine has higher affinity for the 5-HT_{2C} receptor than for the 5-HT_{2A} receptor. Animal studies first suggested that activation of 5-HT_{2C} receptors is inhibitory, while activation of 5-HT_{2A} receptors is stimulatory (Martin *et al.*, 1997, 1998). This led to the conclusion that 5-HT_{2C} receptor agonists might be antipsychotic (Abi-Dargham and Krystal, 2000). Newer data have shown that 5-HT_{2C} receptor antagonists can directly increase dopamine release in the nucleus accumbens and PFC (Di Matteo *et al.*, 1998), while 5-HT_{2C} receptor agonists markedly decrease dopamine and noradrenalin levels in the frontal cortex of rats (Millan *et al.*, 1998). Administration of the 5-$HT_{2C/2A}$ agonist m-CPP caused deterioration of positive psychotic symptoms in schizophrenia, an effect that could be prevented by the 5-$HT_{2C/2A}$ blocker ritanserin (Abi-Saab *et al.*, 2002). Moreover, ritanserin in combination with risperidone showed significant superiority over risperidone alone in decreasing negative symptoms in schizophrenia patients (Akhondzadeh *et al.*, 2008). These results suggest that 5-HT_{2C} blockade may actually have beneficial effects on positive, negative and cognitive symptoms in schizophrenia (Meltzer *et al.*, 2003). In contrast, earlier work demonstrated that affinity to the 5-HT_{2C} receptor did not distinguish typical from atypical antipsychotics (Roth *et al.*, 1992), and Meltzer *et al.* (2003) concluded that the high 5-HT_{2C} receptor affinity of some atypical substances (e.g., clozapine, olanzapine, sertindole) roughly corresponds with their potential to produce weight gain rather than with potential antipsychotic activity. However, some

Table 4 Affinities of selected antipsychotic drugs for 5-HT receptors expressed as pK_i (the negative logarithm to base 10 of the equilibrium dissociation constant, K_i, in molar concentration units)*

Drug	5-HT_{1A}	5-HT_{1B}	5-HT_{1D}	5-HT_{1E}	5-HT_{1F}	5-HT_{2A}	5-HT_{2B}	5-HT_{2C}	5-HT_{5A}	5-HT_{6}	5-HT_{7}
Aripiprazol	8.2^{ag}	6.1^{ag}	7.2^{ag}			7.5–8.1^{ag}		7.6^{ag}			
Chlorpromazine	6.2^{ant}					8.1^{iag}		7.6–8.2^{ant}		7.7–7.8^{iag}	7.6^{iag}
Clozapine	6.8–6.9^{ag}	6.2^{ag}	6.4^{ag}	6.4^{ag}	6.9^{ag}	7.6–9.0^{iag}	8.0–8.8^{ant}	7.4–8.7^{iag}	6.0–6.5^{ant}	7.8–8.1^{iag}	7.2–7.8^{iag}
Haloperidol	5.7–5.8^{ant}		6.6^{ant}			6.7–7.3^{ant}	5.8–6.4^{ant}				6.3–6.6^{ant}
Olanzapine	5.6–5.8^{ag}	6.3^{ag}	6.2^{ag}	5.7^{ag}	6.5^{ag}	8.6–8.7^{ant}		8.1–8.2^{iag}		8^{iag}	6.5^{ant}
Perphenazine						8.2^{ant}		6.9^{ant}		7.1^{iag}	7.2^{iag}
Quetiapine	6.5–6.6^{ag}		5.7^{ag}	5.9^{ag}	5.6^{ag}	6.4–7.0					
Risperidone	6.4–6.5^{ant}	6.6–7.0^{ant}	7.8 – 8.0^{ant}	5.9^{ant}	5.9^{ant}	9.3–10.0^{iag}		7.5–7.6^{iag}		5.6^{ant}	8.3–8.7^{iag}
Sertindole	6.4–6.6^{ant}	7^{ant}	7.2^{ant}	6.4^{ant}	6.4^{ant}	9.2–9.4^{ant}		9.0–9.2^{iag}			
Ziprasidone	7.9–8.9^{pag}	8.3^{ag}	9^{ag}	6.4^{ag}		8.8–9.5^{ant}		7.9–8.4^{iag}			8.4^{iag}

*Higher values imply a higher affinity. No value is shown if no data were available or if the pK_i was below 3. All data were drawn from the IUPHAR database (Harmar *et al.*, 2009; www.iuphar-db.org).

Abbreviations: ag, agonist; ant, antagonist; pag, partial agonist; iag, inverse agonist.

clinical data did suggest that augmentation with the 5-$HT_{2C/2A}$ antagonists ritanserin and mianserin may have some beneficial effects, especially on negative and cognitive symptoms in schizophrenia (Lieberman *et al.*, 1998; Meltzer *et al.*, 2003; Akhondzadeh *et al.*, 2008).

5-HT_3 receptor antagonists have also been investigated as potential antipsychotics because clozapine has a moderate affinity for this receptor, and preclinical animal studies indicated possible antipsychotic efficacy (Lieberman *et al.*, 1998). Although an open-label and uncontrolled clinical trial demonstrated a moderate antipsychotic activity of the selective 5-HT_3 receptor antagonist ondansetron (DeVeaugh-Geiss *et al.*, 1992), these results could not be replicated in a double-blind study (Gaster and King, 1997). Also, the 5-HT_3 antagonist zacopride was not effective in the treatment of schizophrenia (Newcomer *et al.*, 1992), suggesting that the 5-HT_3 receptor is not a promising drug target in the treatment of schizophrenia.

Given that 5-HT_4 receptors modulate acetylcholine and GABA release, and that 5-HT_4 receptors are found in high densities in the frontal cortex and the hippocampus, it was suggested that modification of 5-HT_4 receptor activity could be helpful in improving cognition in schizophrenia. Several animal studies support this assumption, but studies in healthy human volunteers and schizophrenia patients are lacking so far (Roth *et al.*, 2004; Gray and Roth, 2007). Since atypical antipsychotic drugs are devoid of major 5-HT_4 receptor actions, Roth *et al.* (2004) recommended that a 5-HT_4 partial agonist would be potentially beneficial as add-on therapy for improving cognition in schizophrenia.

On the basis of animal studies, the $5HT_6$ receptor was suggested to be a promising drug target to specifically improve cognition in schizophrenia as well (Meltzer *et al.*, 2003; Roth *et al.*, 2004; Gray and Roth, 2007). The 5-HT_6-selective antagonist SB-271046 is currently undergoing preclinical testing as a cognitive enhancer in schizophrenia (Hatcher *et al.*, 2005; Marcos *et al.*, 2008; Da Silva Costa *et al.*, 2009). However, several typical (e.g., chlorpromazine, fluphenazine) and atypical (e.g., clozapine, olanzapine, ziprasidone and quetiapine) antipsychotics have high affinity for the 5-HT_6 receptor, making it unlikely that addition of a 5-HT_6 antagonistic drug would further improve cognition in schizophrenia patients treated with these antipsychotics (Roth *et al.*, 1994, 2004). Moreover, both 5-HT_6 agonists and antagonists have shown pro-cognitive properties in preclinical animal studies, but an explanation for these paradoxical effects is currently missing (Fone, 2008). Thus, further studies are needed to further understand the role of the 5-HT_6 receptor in the modulation of cognition and to develop 5-HT_6 antagonist compounds for the treatment of cognitive deficits in schizophrenia.

Both clozapine and risperidone, as well as the typical drugs chlorpromazine, fluphenazine and pimozide, have high affinity for the 5-HT_7 receptor (Roth *et al.*, 1994); this suggests that a 5-HT_7 action is not a feature of atypicality (Abi-Dargham and Krystal, 2000). Evidence primarily drawn from knockout studies in mice indicates that the 5-HT_7 receptor plays an important role in hippocampus-dependent functions, including learning and memory (Gray and Roth, 2007). These data warrant further investigation into the potential use of 5-HT_7 receptor antagonist compounds in the treatment of memory dysfunction in schizophrenia (Gray and Roth, 2007).

Antipsychotic drug action and serotonin receptor occupancy

Most of the molecular imaging studies investigating the role of receptor occupancy in antipsychotic activity by PET or SPECT have traditionally focused on the dopamine system. Here it was consistently shown that typical antipsychotics usually produce higher striatal D_2 receptor occupancy rates (>70 percent) than atypical antipsychotics (<70 percent) at mean therapeutic doses (Lieberman *et al.*, 1998; Kasper *et al.*, 1999; Weinberger and Laruelle, 2002). Given that the atypicals clozapine and quetiapine display the lowest rates of D_2 occupancy (20–67 percent) at clinically effective doses and that most of the studies could not demonstrate a linear correlation between striatal D_2 binding and therapeutic efficacy, striatal D_2 receptor occupancy rates alone cannot sufficiently explain antipsychotic activity (Kasper *et al.*, 1999; Weinberger and Laruelle, 2002). On the contrary, several studies consistently found a clear correlation between EPS and striatal D_2 receptor occupancy, indicating a high likelihood of EPS when D_2 occupancy exceeds a threshold of 80 percent (Kasper *et al.*, 1999; Weinberger and Laruelle, 2002; Zipursky *et al.*, 2007). Since at least 50–60 percent D_2 receptor occupancy is required to observe rapid clinical response with typical antipsychotics such as haloperidol, an optimal antipsychotic dose range resulting in 70–80 percent D_2 occupancy was suggested (Nordstrom *et al.*, 1993; Nyberg *et al.*, 1999; Kapur *et al.*, 2000). However, this rule does not apply to clozapine and quetiapine.

In line with the *in vivo* data (see above), most of the atypical drugs display higher 5-HT_{2A} than D_2 occupancy rates when dual-tracer approaches are used (Kapur *et al.*, 1998; Nyberg *et al.*, 1999; Gefvert *et al.*, 2001; Mamo *et al.*, 2004). However, although it was suggested that the predominant 5-HT_{2A} receptor antagonism of atypical drugs protects against EPS (Meltzer, 1999), even atypical substances such as olanzapine or risperidone cause

EPS when given in higher doses that lead to D_2 receptor occupancy of more than 80 percent (Kapur *et al.*, 1998; Nyberg *et al.*, 1999). Thus, occupancy of 5-HT_{2A} receptors does not confer protection against EPS, because the threshold of D_2 receptor occupancy associated with EPS is not markedly reduced for atypical substances with a balanced 5-HT_{2A}/D_2 receptor profile (Weinberger and Laruelle, 2002). Compared to the other atypicals, aripiprazole is an interesting exception regarding D_2, 5-HT_{2A} and 5-HT_{1A} receptor occupancy. A recent study has shown that aripiprazole exhibits very high striatal D_2 occupancy (81–94 percent), lower occupancy of frontal and temporal 5-HT_{2A} receptors (31–84 percent), and even lower occupancy at frontal and temporal 5-HT_{1A} receptors (−2 percent to 44 percent) at doses between 10 and 30 mg in schizophrenia patients. EPS was seen only in two of four subjects with D_2 occupancies exceeding 90 percent (Mamo *et al.*, 2007). In accordance with the study of Bantick *et al.* (2004), who showed that clozapine did not occupy the 5-HT_{1A} receptor at clinical doses, these data do not support an important role of the 5-HT_{1A} receptor regarding antipsychotic activity. In sum, molecular imaging studies do not support the view that the 5-HT_{2A} or 5-HT_{1A} mechanism of several atypical drugs contributes significantly to their clinical superiority.

Serotonergic challenge studies

Given that the release of several hormones, such as cortisol, prolactin and growth hormone (GH), is under monoaminergic control, the neuroendocrine challenge paradigm is suitable to investigate the functional state of central monoaminergic systems. In a hypersensitive system the stimulation of 5-HT receptors will induce augmented hormonal release, whereas in a hypoactive system increased release would be expected. If 5-HT receptors are antagonized, the reverse results are anticipated (Murphy *et al.*, 1986).

Early neuroendocrine challenge studies investigating small samples of schizophrenia patients and employing the 5-HT precursors tryptophan and 5-hydroxytryptophan (5-HTP) reported inconsistent results. Two studies reported an increased prolactin response and a blunted GH release (Cowen *et al.*, 1985; Kolakowska *et al.*, 1987). One study found decreased prolactin responses and decreased GH response only in long-term haloperidol-treated patients, whereas short-term treated patients did not differ from controls in both measures (Hoshino *et al.*, 1985). However, precursor effects are relatively muted because of their ‘upstream’ (and therefore secondary) actions on synaptic function, making these studies hard to interpret (Breier, 1995).

Challenge studies with the serotonin releaser fenfluramine (racemate or d-form) provided some conflicting results as well. Whereas an initial study reported a decreased prolactin release in chronic patients (Lerer *et al.*, 1988), two later studies found prolactin hyperresponsivity in drug-free patients (Abel *et al.*, 1996; Monteleone *et al.*, 1999). However, in a study by Monteleone *et al.* (1999), the elevated prolactin response was restricted to patients who were refractory to typical neuroleptics. In line with that, Mohr *et al.* (1998) reported that a higher prolactin response to d-fenfluramine, and therefore a higher responsiveness of the 5-HT system, was associated with poorer treatment response to haloperidol in unmedicated first-episode patients. Additionally, Sharma *et al.* (1999) found that a higher prolactin response to dl-fenfluramine was correlated with more negative symptoms. These studies also varied with regard to psychotic symptom provocation after fenfluramine: some reported no changes, while others described exacerbation of positive symptoms.

The serotonin and noradrenaline reuptake inhibitor clomipramine, which also acts as a 5-HT_2 receptor antagonist, provoked an increased prolactin response in drug-naïve schizophrenia patients – an effect that was positively correlated with duration of illness and negatively correlated with treatment response (Angelopoulos *et al.*, 2002). However, another study did not find changes in the prolactin release after clomipramine in patients treated with typical antipsychotics (Markianos *et al.*, 2001).

The drug m-chlorophenylpiperazine (mCPP) preferentially acts as a partial agonist at 5-HT_{2C} receptors and as an antagonist at 5-HT_{2A} receptors, but also binds to several other 5-HT receptor subtypes (Kahn and Wetzler, 1991). mCPP increases anxiety, body temperature and plasma levels of prolactin, cortisol, GH and ACTH, but does not provoke psychotic symptoms in healthy human volunteers (Breier, 1995). Schizophrenia patients show either blunted (Iqbal *et al.*, 1991; Maes and Meltzer, 1996) or normal prolactin response to mCPP (Kahn *et al.*, 1992; Krystal *et al.*, 1993). Moreover, mCPP has been reported to exacerbate (Iqbal *et al.*, 1991; Krystal *et al.*, 1993; Abi-Saab *et al.*, 2002), reduce (Kahn *et al.*, 1992) or have no effect on psychotic symptoms (Breier *et al.*, 1993; Owen *et al.*, 1993; Koreen *et al.*, 1997). Clozapine has been reported to block the symptom-worsening and hormone-releasing effects of mCPP; this was attributed to 5-HT_{2C} antagonistic effects of clozapine (Breier *et al.*, 1993; Kahn *et al.*, 1993a; Krystal *et al.*, 1993; Owen *et al.*, 1993). Similar effects were shown for olanzapine (Abi-Saab *et al.*, 2002) and the 5-HT_2 antagonist ritanserin (Scheepers *et al.*, 2001a).

In general, the contradictory results across the different serotonergic challenge studies point to heterogeneity

in central serotonergic sensitivity within different subpopulations of schizophrenia patients. This assumption is also supported by the consistent observation that a hypersensitive 5-HT system is associated with poor treatment response to mostly typical antipsychotics. Serotonergic challenge studies might therefore be useful for tailoring individual antipsychotic pharmacotherapy.

Serotonin metabolites in the cerebrospinal fluid

Many studies have measured monoamine metabolite concentrations in the cerebrospinal fluid (CSF) of schizophrenia patients in order to investigate central 5-HT and dopamine turnover. Most of the early studies did not find changes in the CSF concentration of the major 5-HT metabolite 5-HIAA, but some reported decreased 5-HIAA CSF levels in schizophrenia (for review and references, see Bleich *et al.*, 1991). A more recent meta-analysis and a recent study with a large sample of schizophrenia patients have supported the view that mean 5-HIAA concentrations in the CSF are generally relatively unaltered in schizophrenia patients (Tuckwell and Koziol, 1996; Wieselgren and Lindstrom, 1998). In contrast, another meta-analysis has indicated that CSF levels of the main metabolite of dopamine, homovanillic acid (HVA), are lowered in schizophrenia patients (Tuckwell and Koziol, 1993); this finding was confirmed by a more recent study investigating 90 schizophrenia patients and 47 healthy controls (Wieselgren and Lindstrom, 1998). Studies linking specific characteristics of the illness with 5-HIAA CSF levels have shown that low 5-HIAA concentrations are associated with advanced brain atrophy (Nyback *et al.*, 1983; Potkin *et al.*, 1983; Jennings *et al.*, 1985; Losonczy *et al.*, 1986), more prominent negative symptoms (Pickar *et al.*, 1986; Csernansky *et al.*, 1990), and failure to activate the PFC during the Wisconsin Card Sorting Test (Weinberger *et al.*, 1988). However, all of these measures have been found to be associated with decreased HVA CSF levels as well (Nyback *et al.*, 1983; Potkin *et al.*, 1983; Jennings *et al.*, 1985; Losonczy *et al.*, 1986; Pickar *et al.*, 1986; Csernansky *et al.*, 1990; Weinberger *et al.*, 1988; Scheepers *et al.*, 2001b). However, one of the best replicated findings in biological psychiatry is the strong intercorrelation of monoamine metabolites in the CSF, which possibly could be explained by similar transport mechanisms of all monoamines (Hsiao *et al.*, 1993). This idea has led to the approach of calculating HVA/5-HIAA concentration ratios to investigate the relation of serotonergic and dopaminergic activity in schizophrenia (Hsiao *et al.*, 1993). Lewine *et al.* (1991) demonstrated, for example, that the HVA/5-HIAA ratio was a better predictor of the extent of brain atrophy than HVA or 5-HIAA CSF levels alone (see also Nyback *et al.*, 1983). Additionally, while 5-HIAA and HVA levels alone could not predict treatment outcome, a low HVA/5-HIAA CSF ratio was significantly associated with better response to clozapine and typical antipsychotics in several studies (Pickar *et al.*, 1992; Kahn *et al.*, 1993b; Risch and Lewine, 1993; Szymanski *et al.*, 1993; Lieberman *et al.*, 1994; Risch, 1995). These results suggested that the antipsychotic effect is associated with changing dopamine function relative to 5-HT function, rather than changing dopamine or 5-HT function *per se* (Scheepers *et al.*, 2001b). However, at least two studies failed to find a predictive value of the HVA/5-HIAA CSF ratios regarding treatment response to olanzapine, clozapine or haloperidol treatment (Jacobsen *et al.*, 1997; Scheepers *et al.*, 2001b), while one study reported a worse long-term outcome in patients with a low HVA/5-HIAA CSF ratio (Wieselgren and Lindstrom, 1998). These discrepancies may be explained due to differences in patient populations, duration of treatment, method of analysis or criteria of response.

Surprisingly, several investigations demonstrated that neither typical nor atypical antipsychotics changed 5-HIAA CSF levels in the course of treatment, although many of these substances strongly affect the 5-HT system (van Kammen *et al.*, 1986; Kahn *et al.*, 1994; Jacobsen *et al.*, 1997; Wieselgren and Lindstrom, 1998; Scheepers *et al.*, 2001b). These results put the idea that 5-HIAA CSF concentrations are a valid marker of the central 5-HT turnover somewhat into question. Moreover, it was suggested that 5-HIAA concentrations may not mirror 5-HT metabolism in the whole brain, but rather reflect turnover in specific brain regions such as frontal cortices and the striatum (Scheepers *et al.*, 2001b). On the contrary, typical antipsychotics seemed to consistently elevate HVA CSF levels and HVA/5-HIAA CSF ratios, while atypical substances did not (Hsiao *et al.*, 1993; Kahn *et al.*, 1993b; Wieselgren and Lindstrom, 1998; Scheepers *et al.*, 2001b).

In sum, investigations on 5-HT metabolite levels in the CSF in schizophrenia are hard to interpret because it is not clear what the specific neuronal substrate of 5-HIAA CSF levels is. However, there is some consistency in the data showing that at least a subpopulation of patients display changes in global 5-HT and dopamine turnover, and these patients may respond differentially to antipsychotics than other subpopulations.

Platelet studies

Human blood platelets have been proposed as a peripheral model of central 5-HT function because platelets are neuroectodermal derivatives that share several biochemical

and morphological characteristics with 5-HT synapses (Bleich *et al.*, 1991).

Most of the studies investigating platelet or whole blood 5-HT concentrations in schizophrenia patients found elevated values, although there have also been some contradictory results (for review, see Bleich *et al.*, 1991; Iqbal and van Praag, 1995). The increase in peripheral 5-HT concentrations reported in the early studies was apparently not an artifact of medication, as no *in vivo* effect of antipsychotics on platelet 5-HT could be demonstrated (Bleich *et al.*, 1991). On the contrary, accumulating evidence suggests that treatment with clozapine and other atypical and typical antipsychotics increases 5-HT plasma levels in schizophrenia patients (Joseph *et al.*, 1977; Schulz *et al.*, 1997; Fleischhaker *et al.*, 1998; van der Heijden *et al.*, 2004; Ertugrul *et al.*, 2007). These findings suggest that antipsychotics still have an impact on peripheral 5-HT concentrations, and indicate that medication may have indeed influenced previous results.

The findings regarding platelet 5-HT uptake are less consistent. The numbers of studies reporting reduced or unchanged platelet 5-HT uptake are more or less equal (for review, see Bleich *et al.*, 1991; Iqbal and van Praag, 1995). However, Arora and Meltzer (1983) have convincingly demonstrated that a 2-week treatment with chlorpromazine significantly decreased platelet 5-HT uptake in schizophrenia patients and healthy controls. Thus, previous findings of reduced platelet 5-HT uptake in schizophrenia patients are likely explained by acute or residual antipsychotic treatment effects. Moreover, several studies investigating [^{3}H]imipramine binding sites on platelets, which have been suggested as another measure of 5-HT uptake or transport, predominantly yielded no differences between normals and schizophrenia patients (for review, see Bleich *et al.*, 1991; Iqbal and van Praag, 1995).

Platelet 5-HT_{2A} receptors are identical to brain 5-HT_{2A} receptors in terms of their pharmacological properties (Ostrowitzki *et al.*, 1993). Although Arora and Meltzer (1983) detected an increased number of 5-HT_{2A} receptors on platelets from suicidal schizophrenia patients, a newer study reported increased platelet 5-HT_{2A} receptor density in chronic, medication-free patients with schizophrenia (Arranz *et al.*, 2003). Given that treatment with risperidone strongly increased platelet 5-HT_{2A} receptor density, Arranz *et al.* (2003) concluded that the increased platelet 5-HT_{2A} receptor density in their drug-free sample was a residual drug effect caused by previous antipsychotic treatment. Additionally, these authors reported recently that low baseline platelet 5-HT_{2A} receptor levels may predict clinical response to olanzapine in a group of antipsychotic-naïve schizophrenia patients (Arranz *et al.*, 2007).

The activity of platelet monoamine oxidase (MAO) has also been studied in schizophrenia, demonstrating results similar to platelet 5-HT_{2A} receptor density. Although there are some indications of decreased platelet MAO activity in at least some subgroups of schizophrenia patients (Zureick and Meltzer, 1988), it could not be excluded that this effect is primarily caused by antipsychotic treatment (DeLisi *et al.*, 1981; Ohuoha *et al.*, 1993; Ertugrul *et al.*, 2007).

It should be noted that the changes of serotonergic markers found in platelets are largely in the opposite direction to the alterations that have been found in more centrally relevant 5-HT measures in schizophrenia patients (e.g., decreased 5-HT in CSF and brain tissue vs increased 5-HT in blood and platelets; decreased 5-HT receptors in several brain regions vs increased 5-HT_{2A} receptor density in platelets). In addition, treatment with antipsychotics has also had mostly opposite effects on platelet and brain 5-HT markers, respectively. These facts suggest that platelets are not an ideal model for brain 5-HT function (Roth and Meltzer, 2000).

Neurotrophic role of serotonin in the developmental disorder schizophrenia

As reviewed by Whitaker-Azmitia in Chapter 3.1 of this volume, serotonin plays a major role at several stages of neuroplasticity. During embryogenesis, the serotonin system is one of the first neurotransmitter systems that innervates brain structures and demonstrates functional activity. In this phase, serotonin acts as a growth factor that influences neuronal and glial morphology, and connectivity. Some of these effects are direct, whereas some others are mediated by the interaction with further chemical messengers (such as brain-derived neurotrophic factor (BDNF) or S100β) and other neurotransmitter systems (such as dopamine, GABA and glutamate). However, postnatal serotonin also influences the formation and degradation of synapses and axon terminals, indicating that serotonin is important not only for neuronal development but also for the preservation and maintenance of normal function in the adult brain (see also Sodhi and Sanders-Bush, 2004).

Accumulating evidence from several domains suggests that schizophrenia could be a neurodevelopmental disorder that is – at least in part – caused by aberrant early brain development:

1. Many schizophrenia patients exhibit delayed developmental milestones in childhood, including cognitive, motor and behavioral abnormalities, which indicates abnormal brain function prior to diagnosis of schizophrenia.

2. Obstetric complications and prenatal infections increase the risk for schizophrenia.
3. *Post-mortem* studies have not found indicators for neurodegenerative processes such as gliosis or loss of neurons in the brain of schizophrenia patients.
4. Several anatomical and functional disruptions are associated with exacerbation of schizophrenia in adulthood, and these disruptions can be simulated in developmental animal models (Marenco and Weinberger, 2000; Miyamoto *et al.*, 2003).

As suggested by Murray *et al.* (1992), aberrant developmental processes may play a major role, especially in the congenital subform of schizophrenia that shows a gradual increase in behavioral disturbances until the disorder is diagnosed in adolescence or early adulthood. Maynard and colleagues (2001) have proposed a two-hit hypothesis of schizophrenia. According to their suggestion, a lesion occurring in early neurodevelopment (first hit) and caused by a genetic load or adverse embryonic and perinatal events, in combination with a second hit arising from hormonal events, excitotoxicity, psychosocial stress or oxygen radical formation, may cause schizophrenia.

Immunocytochemical and ultrastructural *post-mortem* studies have demonstrated neurocellular alterations in schizophrenia, such as decreased neuronal size, increased cellular packing density, fewer dendritic spines and synapses, and distortions in neuronal orientation (for review, see Arnold, 1999). The abnormalities in the cytoarchitecture, such as neuronal disarray, heterotopias and malpositioning, indicate disruption of proliferation or migration during the gestational period (Miyamoto *et al.*, 2003). In accordance, it was consistently shown that the expression of reelin, a glycoprotein that regulates neuronal migration, is strongly decreased in schizophrenia patients (Impagnatiello *et al.*, 1998; Guidotti *et al.*, 2000). Moreover, anatomical studies found enlargements of the lateral and third ventricles in conjunction with a decrease in cortical volume, especially within the hippocampal formation and the amygdala; additionally, subcortical structures appear to be reduced in size, including the thalamus and striatum (for review, see Sodhi and Sanders-Bush, 2004). It is unlikely that these macrostructural alterations are simply caused by neurodegenerative processes, because some of them have also been shown at a prodromal state of schizophrenia (Wood *et al.*, 2003; Morey *et al.*, 2005; Jessen *et al.*, 2006), and *post-mortem* studies did not find gliosis and neuronal cell loss. Thus, these anatomical and cytoarchitectual changes are likely to arise during brain maturation.

Several lines of evidence suggest that abnormalities in brain development may contribute to the pathogenesis of schizophrenia in a subset of patients. Moreover, we know that serotonin plays an important role in neurogenesis and neuronal plasticity. However, future studies will have to determine whether genetic or early developmental insults could alter the serotonin system in a manner that leads to sustained neuronal changes during brain development, which consequently induces the symptoms of schizophrenia.

Serotonin–glutamate interactions

NMDA antagonists such as phencyclidine (PCP) and ketamine produce effects in humans that closely mimic the symptoms of schizophrenia (Javitt and Zukin, 1991; Krystal *et al.*, 1994). Microdialysis studies have demonstrated that ketamine and PCP increase glutamate outflow in PFC (Moghaddam *et al.*, 1997; Adams and Moghaddam, 1998). Potentially related to this effect is evidence that increases in glutamatergic activity may contribute to the psychotomimetic and behavioral effects of these drugs. Indeed, diminution of PCP-induced glutamate release by activation of metabotropic glutamate 2/3 ($mGlu_{2/3}$) receptors attenuates the effects of PCP on locomotor activity and stereotypy (Moghaddam and Adams, 1998). Other agents that decrease glutamate release also reduce the behavioral effects of PCP and ketamine (Anand *et al.*, 2000; Idris *et al.*, 2005). In each of these cases the actions of the released glutamate would presumably be on non-NMDA glutamate receptors – AMPA, kainate, or metabotropic – since PCP and ketamine block NMDA receptor functions. The involvement of glutamate release in the psychotomimetic effects of NMDA antagonists is consistent with the hypothesis that dysfunction of glutamatergic systems underlies the psychopathology of schizophrenia (Javitt and Zukin, 1991; Halberstadt, 1995; Jentsch and Roth, 1999).

Electrophysiological evidence demonstrates that LSD and other serotonergic hallucinogens can modulate cellular responses to glutamate (Rahman and Neuman, 1993; Arvanov *et al.*, 1999). Recent studies indicate that hallucinogens increase the release of glutamate in neocortex (Scruggs *et al.*, 2003; Muschamp *et al.*, 2004). Activation of $5\text{-}HT_{2A}$ receptors by 5-HT and the hallucinogen 2,5-dimethoxy-4-iodoamphetamine (DOI) produces an enhancement of the frequency and amplitude of spontaneous excitatory postsynaptic potentials/currents (EPSPs/EPSCs) in most layer V pyramidal cells of PFC (Aghajanian and Marek, 1997; Lambe *et al.*, 2000; Klodzinska *et al.*, 2002; Benneyworth *et al.*, 2007); this effect is mediated by increased glutamate efflux and subsequent activation of AMPA receptors (Zhang and Marek, 2008). There is also evidence that 5-HT- and DOI-induced EPSCs are suppressed by activation of $mGlu_{2/3}$ receptors,

and augmented by $mGlu_{2/3}$ receptor blockade (Marek *et al.*, 2000; Klodzinska *et al.*, 2002; Benneyworth *et al.*, 2007). Although it is generally accepted that 5-HT_{2A} receptor activation increases the terminal release of glutamate in PFC, there has been some controversy regarding the source of these glutamatergic terminals. Based on evidence that lesions of the medial thalamus attenuate 5-HT-induced EPSCs, Marek and colleagues have argued that thalamocortical afferents are involved (Marek *et al.*, 2001). However, Béïque *et al.* (2007) recently identified a subpopulation of pyramidal cells in the deep layers of PFC that are excited by 5-HT_{2A} receptor activation, indicating that the spontaneous EPSCs evoked by 5-HT may be a product of PFC recurrent network activity.

As was found with PCP, the behavioral effects of serotonergic hallucinogens are attenuated by activation of $mGlu_{2/3}$ receptors. The ability of DOI to induce the head-twitch response in mice and rats is suppressed by the selective $mGlu_{2/3}$ agonists LY354740 and LY379268; conversely, the selective $mGlu_{2/3}$ antagonist LY341495 enhances the frequency of DOI-induced head-twitch (Gewirtz and Marek, 2000; Klodzinska *et al.*, 2002). Likewise, the $mGlu_2$ positive allosteric modulator biphenyl-indanone A inhibits the head-twitch response induced by the hallucinogen (−)-2,5-dimethoxy-4-bromoamphetamine (DOB) (Benneyworth *et al.*, 2007). It has also been shown that the discriminative stimulus effects of LSD are potentiated by LY341495 and partially antagonized by LY379268 (Winter *et al.*, 2004). The ability of $mGlu_{2/3}$ receptor ligands to alter the behavioral response to DOI, DOB and LSD indicates that the behavioral effects of hallucinogens are linked to their ability to increase glutamate release.

Taken together, the aforementioned findings demonstrate that NMDA receptor antagonists and serotonergic hallucinogens increase glutamate release, and it has been suggested that the glutamatergic system may represent a common final pathway for their psychotomimetic effects (Vollenweider and Geyer, 2001). This view is consistent with the fact that both ketamine and psilocybin produce metabolic hyperfrontality (Vollenweider *et al.*, 1997a, 1997b), and have somewhat similar effects on perception and cognition (Vollenweider and Geyer, 2001). Additional support for the convergence of serotonergic and glutamatergic systems is derived from the finding that the behavioral effects of hallucinogens are potentiated by co-administration of NMDA antagonists (Dall'Olio *et al.*, 1999; Winter *et al.*, 2000, 2004; Zhang and Marek, 2008). Recently, evidence has emerged that $mGlu_2$ and 5-HT_{2A} receptors are co-localized in cortical neurons, where they may form functional complexes (Gonzalez-Maeso *et al.*, 2008). The existence of a $mGlu_2$/5-HT_{2A} receptor complex is intriguing in light of a recent report that a prodrug for a selective $mGlu_{2/3}$ agonist possesses significant antipsychotic efficacy in schizophrenic patients (Patil *et al.*, 2007).

Conclusions and future directions

As reviewed above, considerable evidence derived from converging methods suggests that schizophrenia patients display abnormalities in serotonergic function. Nevertheless, different approaches intended to measure identical biological markers have frequently produced contradictory results (e.g., autoradiographic *post-mortem* studies vs PET studies). In particular, results from peripheral measures (CSF, platelets, blood, hormone response) have often not matched findings based upon more central parameters of serotonin function (receptor density, brain levels of 5-HT and metabolites). Moreover, it has repeatedly been shown that some alterations of the 5-HT system reported in schizophrenia patients could be explained by chronic treatment with antipsychotic drugs. Despite some methodological reservations and the many contradictory results, there is accumulating evidence that the 5-HT_{1A} and 5-HT_{2A} receptor subtypes play an especially important role in schizophrenia. *Post-mortem* studies and some PET data suggest that schizophrenia patients display an increase of 5-HT_{1A} and a decrease of 5-HT_{2A} receptors, especially in the PFC. Genetic variations of the 5-HT_{2A} receptor (and perhaps also of the 5-HT_{1A} receptor) appear to contribute to the risk of developing schizophrenia and the response to antipsychotic treatment. These genetic variations also appear to be associated with endophenotypic markers of schizophrenia, such as sensorimotor gating. Hallucinogenic 5-HT_{2A} agonists produce some schizophrenia-like symptoms, and also mimic several endophenotypes of schizophrenia. In contrast, the hypothesis that a serotonergic mechanism is necessary for the claimed therapeutic superiority of the so-called atypical antipsychotics is not well supported by the data so far, because a 5-HT antagonistic action seems to be not sufficient for an antipsychotic effect (at least on the level of large and heterogenous populations of schizophrenia patients). Nevertheless, 5-HT_{1A} agonists and 5-HT_{2C} antagonists may have some beneficial effects, particularly on cognition and negative symptoms. Additionally, agents acting at other 5-HT receptor subtypes (5-HT_4, 5-HT_6, 5-HT_7) may have some pro-cognitive effects in schizophrenia patients.

The highly contradictory results regarding serotonergic alterations in schizophrenia might have two origins:

1. Alterations of the serotonin system are not sufficient to explain the full picture of schizophrenia. This view is supported by the fact that other transmitter systems

(e.g., dopamine, GABA, glutamate, acetylcholine) and biochemical substrates (e.g., reelin, BDNF, synaptophysin, SNAP-25 and complexin II) are also affected in schizophrenia patients.

2. Not all but only a subpopulation of the patients within the broad disease cluster schizophrenia display changes in serotonin function. This assumption is supported by several studies showing that some patients better respond to serotonergic antipsychotic drugs than other patients, that some alterations of the 5-HT systems at baseline could predict treatment response, and that serotonergic challenges induce a broad range of reactions ranging from improvement to worsening of symptoms, pointing to substantial heterogeneity of central serotonergic activity.

The 5-HT system is probably only one piece of the enigmatic mosaic of the multifactorial causation of the group of schizophrenia spectrum disorders. Specific polymorphisms within the 5-HT system might influence – for example, the expression of serotonin receptors during neurogenesis – and these changes could have an impact on later brain maturation and 5-HT function. However, only in combination with further neurodevelopmental 'hits' (such as pre- and postnatal infections, stressful events or drug use during pregnancy, obstetric complications, a stressful adolescence or further critical life events) and other genetic variations (DISC1, VMAT1, GRIN2) could the symptom pattern of a schizophreniform disorder arise.

Future studies should devote more attention to the demarcation of subpopulations of schizophrenia patients exhibiting specific changes of the 5-HT system, who could then be successfully treated with specific serotonergic drugs. These subpopulations should be characterized not only by distinct biological markers but also by a more precise psychopathological description. Moreover, the behavioral consequences of genetic variations within the 5-HT system or of pharmacological manipulations of the system might help us to better understand disturbed brain functions of schizophrenia patients. Finally, recent preclinical data suggest that also alterations in the interaction between the serotonin and the glutamate system might have an influence on the development and the symptoms of schizophrenia. These interactions should be further investigated in healthy humans and schizophrenia patients.

Acknowledgements

Mark Geyer and Adam Halberstadt were supported by grants from the National Institute on Drug Abuse (DA002925, DA025412) and the National Institute of Mental Health (MH52885, MH42228) and by the Veterans Affairs VISN 22 Mental Illness Research, Education, and Clinical Center. Boris Quednow was supported by the Deutsche Forschungsgemeinschaft (DFG, grant QU 218/1-1) and by the Nachwuchsförderungskredit of the University of Zurich.

References

Abel, K.M., O'Keane, V. and Murray, R.M. (1996) Enhancement of the prolactin response to d-fenfluramine in drug-naive schizophrenic patients. Br. J. Psychiatry, 168: 57–60.

Abi-Dargham, A. and Krystal, J. (2000) Serotonin receptors as targets of antipsychotic medication. In: Lidow, M.S. (Ed.), Neurotransmitter Receptors in Actions of Antipsychotic Medications. CRC Press LLC, Boca Raton, FL, pp. 79–107.

Abi-Dargham, A., Laruelle, M., Lipska, B., Jaskiw, G.E., Wong, D.T., Robertson, D.W., Weinberger, D.R. and Kleinman, J.E. (1993) Serotonin 5-HT3 receptors in schizophrenia: a postmortem study of the amygdala. Brain Res., 616: 53–57.

Abi-Saab, W., Seibyl, J.P., D'Souza, D.C., Karper, L.P., Gueorgueva, R., Abi-Dargham, A., Wong, M.L., Rajhans, S., Erdos, J.P., Heninger, G.R., Charney, D.S. and Krystal, J.H. (2002) Ritanserin antagonism of m-chlorophenylpiperazine effects in neuroleptic-free schizophrenics patients: support for serotonin-2 receptor modulation of schizophrenia symptoms. Psychopharmacology (Berl.), 162: 55–62.

Adams, L.M. and Geyer, M.A. (1982) LSD-induced alterations of locomotor patterns and exploration in rats. Psychopharmacology (Berl.), 77: 179–185.

Adams, L.M. and Geyer, M.A. (1985) A proposed animal model for hallucinogens based on LSD's effects on patterns of exploration in rats. Behav. Neurosci., 99: 881–900.

Adams, B. and Moghaddam, B. (1998) Corticolimbic dopamine neurotransmission is temporally dissociated from the cognitive and locomotor effects of phencyclidine. J. Neurosci., 18: 5545–5554.

Aghajanian, G.K. and Marek, G.J. (1997) Serotonin induces excitatory postsynaptic potentials in apical dendrites of neocortical pyramidal cells. Neuropharmacology, 36: 589–599.

Akhondzadeh, S., Malek-Hosseini, M., Ghoreishi, A., Raznahan, M. and Rezazadeh, S.A. (2008) Effect of ritanserin, a 5HT2A/2C antagonist, on negative symptoms of schizophrenia: a double-blind randomized placebo-controlled study. Prog. Neuropsychopharmacol. Biol. Psychiatry, 32: 1879–1883.

Allen, N.C., Bagade, S., McQueen, M.B., Ioannidis, J.P., Kavvoura, F.K., Khoury, M.J., Tanzi, R.E. and Bertram, L. (2008) Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: the SzGene database. Nat. Genet., 40: 827–834.

Anand, A., Charney, D.S., Oren, D.A., Berman, R.M., Hu, X.S., Cappiello, A. and Krystal, J.H. (2000) Attenuation of the neuropsychiatric effects of ketamine with lamotrigine: support for hyperglutamatergic effects of N-methyl-D-aspartate receptor antagonists. Arch. Gen. Psychiatry, 57: 270–276.

Andree, T.H., Mikuni, M., Tong, C.Y., Koenig, J.I. and Meltzer, H.Y. (1986) Differential effect of subchronic treatment with various neuroleptic agents on serotonin2 receptors in rat cerebral cortex. J. Neurochem., 46: 191–197.

Angelopoulos, E.K., Markianos, M., Daskalopoulou, E.G., Hatzimanolis, J. and Tzemos, J. (2002) Changes in central serotonergic function as a correlate of duration of illness in paranoid schizophrenia. Psychiatry Res., 110: 9–17.

Angrist, B.M. and Gershon, S. (1970) The phenomenology of experimentally induced amphetamine psychosis – preliminary observations. Biol. Psychiatry, 2: 95–107.

Arnold, S.E. (1999) Neurodevelopmental abnormalities in schizophrenia: insights from neuropathology. Dev. Psychopathol., 11: 439–456.

Arnold, S.E., Hyman, B.T., Van Hoesen, G.W. and Damasio, A.R. (1991) Some cytoarchitectural abnormalities of the entorhinal cortex in schizophrenia. Arch. Gen. Psychiatry, 48: 625–632.

Arnt, J. and Skarsfeldt, T. (1998) Do novel antipsychotics have similar pharmacological characteristics? A review of the evidence. Neuropsychopharmacology, 18: 63–101.

Arora, R.C. and Meltzer, H.Y. (1983) Effects of chlorpromazine on serotonin uptake in blood platelets. Psychiatry Res., 9: 23–28.

Arora, R.C. and Meltzer, H.Y. (1991) Serotonin2 (5-HT2) receptor binding in the frontal cortex of schizophrenic patients. J. Neural Transm. Gen. Sect., 85: 19–29.

Arranz, M., Collier, D., Sodhi, M., Ball, D., Roberts, G., Price, J., Sham, P. and Kerwin, R. (1995) Association between clozapine response and allelic variation in 5-HT2A receptor gene. Lancet, 346: 281–282.

Arranz, M.J., Collier, D.A., Munro, J., Sham, P., Kirov, G., Sodhi, M., Roberts, G., Price, J. and Kerwin, R.W. (1996) Analysis of a structural polymorphism in the 5-HT2A receptor and clinical response to clozapine. Neurosci. Lett., 217: 177–178.

Arranz, M.J. and de Leon, J. (2007) Pharmacogenetics and pharmacogenomics of schizophrenia: a review of last decade of research. Mol. Psychiatry, 12: 707–747.

Arranz, M.J., Munro, J., Owen, M.J., Spurlock, G., Sham, P.C., Zhao, J., Kirov, G., Collier, D.A. and Kerwin, R.W. (1998a) Evidence for association between polymorphisms in the promoter and coding regions of the 5-HT2A receptor gene and response to clozapine. Mol. Psychiatry, 3: 61–66.

Arranz, M.J., Munro, J., Sham, P., Kirov, G., Murray, R.M., Collier, D.A. and Kerwin, R.W. (1998b) Meta-analysis of studies on genetic variation in 5-HT2A receptors and clozapine response. Schizophr Res., 32: 93–99.

Arranz, M.J., Munro, J., Birkett, J., Bolonna, A., Mancama, D., Sodhi, M., Lesch, K.P., Meyer, J.F., Sham, P., Collier, D.A., Murray, R.M. and Kerwin, R.W. (2000a) Pharmacogenetic prediction of clozapine response. Lancet, 355: 1615–1616.

Arranz, M.J., Bolonna, A.A., Munro, J., Curtis, C.J., Collier, D.A. and Kerwin, R.W. (2000b) The serotonin transporter and clozapine response. Mol. Psychiatry, 5: 124–125.

Arranz, B., Rosel, P., Sarro, S., Ramirez, N., Duenas, R., Cano, R., Maria Sanchez, J. and San, L. (2003) Altered platelet serotonin 5-HT2A receptor density but not second messenger inositol trisphosphate levels in drug-free schizophrenic patients. Psychiatry Res., 118: 165–174.

Arranz, B., Rosel, P., San, L., Ramirez, N., Duenas, R.M., Salavert, J., Centeno, M. and del Moral, E. (2007) Low baseline serotonin-2A receptors predict clinical response to olanzapine in first-episode schizophrenia patients. Psychiatry Res., 153: 103–109.

Arvanov, V.L., Liang, X., Russo, A. and Wang, R.Y. (1999) LSD and DOB: Interaction with 5-HT2A receptors to inhibit NMDA receptor-mediated transmission in the rat prefrontal cortex. Eur. J. Neurosci., 11: 3064–3072.

Bantick, R.A., Deakin, J.F. and Grasby, P.M. (2001) The 5-HT1A receptor in schizophrenia: a promising target for novel atypical neuroleptics? J. Psychopharmacol., 15: 37–46.

Bantick, R.A., Montgomery, A.J., Bench, C.J., Choudhry, T., Malek, N., McKenna, P.J., Quested, D.J., Deakin, J.F. and Grasby, P.M. (2004) A positron emission tomography study of the 5-HT1A receptor in schizophrenia and during clozapine treatment. J. Psychopharmacol., 18: 346–354.

Basile, V.S., Ozdemir, V., Masellis, M., Meltzer, H.Y., Lieberman, J.A., Potkin, S.G., Macciardi, F.M., Petronis, A. and Kennedy, J.L. (2001) Lack of association between serotonin-2A receptor gene (HTR2A) polymorphisms and tardive dyskinesia in schizophrenia. Mol. Psychiatry, 6: 230–234.

Basile, V.S., Masellis, M., De Luca, V., Meltzer, H.Y. and Kennedy, J.L. (2002) 759C/T genetic variation of 5HT(2C) receptor and clozapine-induced weight gain. Lancet, 360: 1790–1791.

Baumeister, A.A. and Hawkins, M.F. (2004) The serotonin hypothesis of schizophrenia: a historical case study on the heuristic value of theory in clinical neuroscience. J. Hist. Neurosci., 13: 277–291.

Béïque, J.C., Imad, M., Mladenovic, L., Gingrich, J.A. and Andrade, R. (2007) Mechanism of the 5-hydroxytryptamine 2A receptor-mediated facilitation of synaptic activity in prefrontal cortex. Proc. Natl. Acad. Sci. USA, 104: 9870–9875.

Bennett, J.P. Jr., Enna, S.J., Bylund, D.B., Gillin, J.C., Wyatt, R.J. and Snyder, S.H. (1979) Neurotransmitter receptors in frontal cortex of schizophrenics. Arch. Gen. Psychiatry, 36: 927–934.

Benneyworth, M.A., Xiang, Z., Smith, R.L., Garcia, E.E., Conn, P.J. and Sanders-Bush, E. (2007) A selective positive allosteric modulator of metabotropic glutamate receptor subtype 2 blocks a hallucinogenic drug model of psychosis. Mol. Pharmacol., 72: 477–484.

Beringer, K. (1923) Experimentelle Psychosen durch Mescalin. Z. Ges. Neurol. Psychiatry, 84: 426–433.

Bertler, A., Carlsson, A. and Rosengren, E. (1956) Release by reserpine of catechol amines from rabbits' hearts. Naturwissenschaften, 43: 521.

Bertolino, A. and Weinberger, D.R. (1999) Proton magnetic resonance spectroscopy in schizophrenia. Eur. J. Radiol., 30: 132–141.

Bilder, R.M., Goldman, R.S., Volavka, J., Czobor, P., Hoptman, M., Sheitman, B., Lindenmayer, J.P., Citrome, L., McEvoy, J., Kunz, M., Chakos, M., Cooper, T.B., Horowitz, T.L. and Lieberman, J.A. (2002) Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. Am. J. Psychiatry, 159: 1018–1028.

Birkett, J.T., Arranz, M.J., Munro, J., Osbourn, S., Kerwin, R.W. and Collier, D.A. (2000) Association analysis of the 5-HT5A gene in depression, psychosis and antipsychotic response. Neuroreport, 11: 2017–2020.

Bleich, A., Brown, S.L., Kahn, R. and van Praag, H.M. (1988) The role of serotonin in schizophrenia. Schizophr. Bull., 14: 297–315.

Bleich, A., Brown, S.L. and van Praag, H.M. (1991) A serotonergic theory of schizophrenia. In: Brown, S.L. and van Praag, H.M. (Eds.), The Role of Serotonin in Psychiatric Disorders. Brunner/Mazel, Publishers, New York, NY, pp. 183–214.

Blin, O. (1999) A comparative review of new antipsychotics. Can. J. Psychiatry, 44: 235–244.

Bolino, F., Di Michele, V., Di Cicco, L., Manna, V., Daneluzzo, E. and Casacchia, M. (1994) Sensorimotor gating and habituation

evoked by electro-cutaneous stimulation in schizophrenia. Biol. Psychiatry, 36: 670–679.
Bowers, M.B. Jr. and Freedman, D.X. (1966) 'Psychedelic' experiences in acute psychoses. Arch. Gen. Psychiatry, 15: 240–248.
Braff, D. (1985) Attention, habituation and information processing in psychiatric disorders. In: Micheks, B., Cavenar, J., Brodie, H., Cooper, A., Guze, S. and Judd, L. (Eds.), Psychiatry. Lippincott, Philadelphia, PA, pp. 1–12.
Braff, D.L. and Geyer, M.A. (1980) Acute and chronic LSD effects on rat startle: data supporting an LSD–rat model of schizophrenia. Biol. Psychiatry, 15: 909–916.
Braff, D.L. and Geyer, M.A. (1990) Sensorimotor gating and schizophrenia. Human and animal model studies. Arch. Gen. Psychiatry, 47: 181–188.
Braff, D.L., Stone, C., Callaway, E., Geyer, M., Glick, I. and Bali, L. (1978) Prestimulus effects on human startle reflex in normals and schizophrenics. Psychophysiology, 15: 339–343.
Breier, A. (1995) Serotonin, schizophrenia and antipsychotic drug action. Schizophr. Res., 14: 187–202.
Breier, A., Kirkpatrick, B. and Buchanan, R.W. (1993) Clozapine attenuates meta-chlorophenylpiperazine (mCPP)-induced plasma cortisol increases in schizophrenia. Biol. Psychiatry, 34: 492–494.
Brodie, B.B., Pletscher, A. and Shore, P.A. (1955) Evidence that serotonin has a role in brain function. Science, 122: 968.
Brodie, B.A., Shore, P.A. and Pletscher, A. (1956) Serotonin-releasing activity limited to Rauwolfia alkaloids with tranquilizing action. Science, 123: 992–993.
Bromet, E.J. and Fennig, S. (1999) Epidemiology and natural history of schizophrenia. Biol. Psychiatry, 46: 871–881.
Buchanan, R.W. (1995) Clozapine: efficacy and safety. Schizophr. Bull., 21: 579–591.
Buchanan, R.W., Breier, A., Kirkpatrick, B., Ball, P. and Carpenter, W.T. Jr. (1998) Positive and negative symptom response to clozapine in schizophrenic patients with and without the deficit syndrome. Am. J. Psychiatry, 155: 751–760.
Buckland, P.R., Hoogendoorn, B., Guy, C.A., Smith, S.K., Coleman, S.L. and O'Donovan, M.C. (2005) Low gene expression conferred by association of an allele of the 5-HT2C receptor gene with antipsychotic-induced weight gain. Am. J. Psychiatry, 162: 613–615.
Burnet, P.W., Eastwood, S.L. and Harrison, P.J. (1996a) 5-HT1A and 5-HT2A receptor mRNAs and binding site densities are differentially altered in schizophrenia. Neuropsychopharmacology, 15: 442–455.
Burnet, P.W., Chen, C.P., McGowan, S., Franklin, M. and Harrison, P.J. (1996b) The effects of clozapine and haloperidol on serotonin-1A, -2A and -2C receptor gene expression and serotonin metabolism in the rat forebrain. Neuroscience, 73: 531–540.
Carlsson, A. (1959) The occurrence, distribution and physiological role of catecholamines in the nervous system. Pharmacol. Rev., 11: 490–493.
Carlsson, A. (1988) The current status of the dopamine hypothesis of schizophrenia. Neuropsychopharmacology, 1: 179–186.
Carlsson, A. (1995) Neurocircuitries and neurotransmitter interactions in schizophrenia. Intl. Clin. Psychopharmacol., 10(Suppl. 3): 21–28.
Carlsson, A. and Lindqvist, M. (1963) Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and nor-metanephrine in mouse brain. Acta Pharmacol. Toxicol. (Copenh), 20: 140–144.
Carlsson, A., Lindqvist, M. and Magnusson, T. (1957) 3,4-Dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. Nature, 180: 1200.
Carman, J., Peuskens, J. and Vangeneugden, A. (1995) Risperidone in the treatment of negative symptoms of schizophrenia: a meta-analysis. Intl. Clin. Psychopharmacol., 10: 207–213.
Carpenter, W.T. Jr., Conley, R.R., Buchanan, R.W., Breier, A. and Tamminga, C.A. (1995) Patient response and resource management: another view of clozapine treatment of schizophrenia. Am. J. Psychiatry, 152: 827–832.
Condrau, G. (1949) Klinische Erfahrungen an Geisteskranken mit Lysergsäure-diäthylamid. Acta Psychiatr. Neurol., 24: 9–32.
Cowen, P.J., Gadhvi, H., Gosden, B. and Kolakowska, T. (1985) Responses of prolactin and growth hormone to L-tryptophan infusion: effects in normal subjects and schizophrenic patients receiving neuroleptics. Psychopharmacology (Berl.), 86: 164–169.
Creese, I., Burt, D.R. and Snyder, S.H. (1976) Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. Science, 192: 481–483.
Crow, T.J. (1980a) Molecular pathology of schizophrenia: more than one disease process? Br. Med. J., 280: 66–68.
Crow, T.J. (1980b) Positive and negative schizophrenic symptoms and the role of dopamine. Br. J. Psychiatry, 137: 383–386.
Crow, T.J., Baker, H.F., Cross, A.J., Joseph, M.H., Lofthouse, R., Longden, A., Owen, F., Riley, G.J., Glover, V. and Killpack, W.S. (1979) Monoamine mechanisms in chronic schizophrenia: post-mortem neurochemical findings. Br. J. Psychiatry, 134: 249–256.
Cruz, D.A., Eggan, S.M., Azmitia, E.C. and Lewis, D.A. (2004) Serotonin1A receptors at the axon initial segment of prefrontal pyramidal neurons in schizophrenia. Am. J. Psychiatry, 161: 739–742.
Csernansky, J.G., King, R.J., Faustman, W.O., Moses, J.A. Jr., Poscher, M.E. and Faull, K.F. (1990) 5-HIAA in cerebrospinal fluid and deficit schizophrenic characteristics. Br. J. Psychiatry, 156: 501–507.
Da Silva Costa, V., Duchatelle, P., Boulouard, M. and Dauphin, F. (2009) Selective 5-HT6 receptor blockade improves spatial recognition memory and reverses age-related deficits in spatial recognition memory in the mouse. Neuropsychopharmacology, 34: 488–500.
Dall'Olio, R., Gaggi, R., Bonfante, V. and Gandolfi, O. (1999) The non-competitive NMDA receptor blocker dizocilpine potentiates serotonergic function. Behav. Pharmacol., 10: 63–71.
de Jong, H. (1932) Die experimentelle Katatonie als vielfach vorkommende Reaktionsform des Zentralnervensystems. Z. Ges. Neurol. Psychiatry, 139: 468–499.
De Luca, V., Likhodi, O., Van Tol, H.H., Kennedy, J.L. and Wong, A.H. (2005) Tryptophan hydroxylase 2 gene expression and promoter polymorphisms in bipolar disorder and schizophrenia. Psychopharmacology (Berl.), 183: 378–382.
de Paulis, T. (2001) M-100907 (Aventis). Curr. Opin. Investig. Drugs, 2: 123–132.
Dean, B. (2003) The cortical serotonin2A receptor and the pathology of schizophrenia: a likely accomplice. J. Neurochem., 85: 1–13.

Dean, B. and Hayes, W. (1996) Decreased frontal cortical serotonin2A receptors in schizophrenia. Schizophr. Res., 21: 133–139.

Dean, B., Opeskin, K., Pavey, G., Naylor, L., Hill, C., Keks, N. and Copolov, D.L. (1995) [3H]paroxetine binding is altered in the hippocampus but not the frontal cortex or caudate nucleus from subjects with schizophrenia. J. Neurochem., 64: 1197–1202.

Dean, B., Hayes, W., Opeskin, K., Naylor, L., Pavey, G., Hill, C., Keks, N. and Copolov, D.L. (1996) Serotonin2 receptors and the serotonin transporter in the schizophrenic brain. Behav. Brain Res., 73: 169–175.

Dean, B., Hayes, W., Hill, C. and Copolov, D. (1998) Decreased serotonin2A receptors in Brodmann's area 9 from schizophrenic subjects. A pathological or pharmacological phenomenon? Mol. Chem. Neuropathol., 34: 133–145.

Dean, B., Hussain, T., Hayes, W., Scarr, E., Kitsoulis, S., Hill, C., Opeskin, K. and Copolov, D.L. (1999a) Changes in serotonin2A and GABA(A) receptors in schizophrenia: studies on the human dorsolateral prefrontal cortex. J. Neurochem., 72: 1593–1599.

Dean, B., Tomaskovic-Crook, E., Opeskin, K., Keks, N. and Copolov, D. (1999b) No change in the density of the serotonin1A receptor, the serotonin4 receptor or the serotonin transporter in the dorsolateral prefrontal cortex from subjects with schizophrenia. Neurochem. Intl., 34: 109–115.

Dean, B., Pavey, G., Thomas, D. and Scarr, E. (2006) Cortical serotonin7, 1D and 1F receptors: effects of schizophrenia, suicide and antipsychotic drug treatment. Schizophr. Res., 88: 265–274.

DeLisi, L.E., Wise, C.D., Bridge, T.P., Rosenblatt, J.E., Wagner, R.L., Morihisa, J., Karson, C., Potkin, S.G. and Wyatt, R.J. (1981) A probable neuroleptic effect on platelet monoamine oxidase in chronic schizophrenic patients. Psychiatry Res., 4: 95–107.

Deshpande, S.N., Varma, P.G., Semwal, P., Rao, A.R., Bhatia, T., Nimgaonkar, V.L., Lerer, B. and Thelma, B.K. (2005) II. Serotonin receptor gene polymorphisms and their association with tardive dyskinesia among schizophrenia patients from North India. Psychiatr. Genet., 15: 157–158.

DeVeaugh-Geiss, J., McBain, S., Cooksey, P. and Bell, J.M. (1992) The effects of a novel 5-HT3 anatgonist, ondansetron, in schizophrenia. In: Meltzer, H.Y. (Ed.), Novel Antipsychotic Drugs. Raven Press, New York, NY, pp. 225–232.

Di Matteo, V., Di Giovanni, G., Di Mascio, M. and Esposito, E. (1998) Selective blockade of serotonin2C/2B receptors enhances dopamine release in the rat nucleus accumbens. Neuropharmacology, 37: 265–272.

Dittrich, A. (1998) The standardized psychometric assessment of altered states of consciousness (ASCs) in humans. Pharmacopsychiatry, 31(Suppl 2): 80–84.

Dubertret, C., Hanoun, N., Ades, J., Hamon, M. and Gorwood, P. (2004) Family-based association studies between 5-HT5A receptor gene and schizophrenia. J. Psychiatr. Res., 38: 371–376.

Dulawa, S.C. and Geyer, M.A. (2000) Effects of strain and serotonergic agents on prepulse inhibition and habituation in mice. Neuropharmacology, 39: 2170–2179.

East, S.Z., Burnet, P.W., Leslie, R.A., Roberts, J.C. and Harrison, P.J. (2002) 5-HT6 receptor binding sites in schizophrenia and following antipsychotic drug administration: autoradiographic studies with [125I]SB-258585. Synapse, 45: 191–199.

Ellingrod, V.L., Perry, P.J., Ringold, J.C., Lund, B.C., Bever-Stille, K., Fleming, F., Holman, T.L. and Miller, D. (2005) Weight gain associated with the −759C/T polymorphism of the 5HT2C receptor and olanzapine. Am. J. Med. Genet. B Neuropsychiatr. Genet., 134B: 76–78.

Erritzoe, D., Rasmussen, H., Kristiansen, K.T., Frokjaer, V.G., Haugbol, S., Pinborg, L., Baare, W., Svarer, C., Madsen, J., Lublin, H., Knudsen, G.M. and Glenthoj, B.Y. (2008) Cortical and subcortical 5-HT2A receptor binding in neuroleptic-naive first-episode schizophrenic patients. Neuropsychopharmacology, 33: 2435–2441.

Ertugrul, A., Ucar, G., Basar, K., Demir, B., Yabanoglu, S. and Ulug, B. (2007) Influence of clozapine on platelet serotonin, monoamine oxidase and plasma serotonin levels. Psychiatry Res., 149: 49–57.

Falkai, P., Schneider-Axmann, T. and Honer, W.G. (2000) Entorhinal cortex pre-alpha cell clusters in schizophrenia: quantitative evidence of a developmental abnormality. Biol. Psychiatry, 47: 937–943.

Fallin, M.D., Lasseter, V.K., Avramopoulos, D., Nicodemus, K.K., Wolyniec, P.S., McGrath, J.A., Steel, G., Nestadt, G., Liang, K.Y., Huganir, R.L., Valle, D. and Pulver, A.E. (2005) Bipolar I disorder and schizophrenia: a 440-single-nucleotide polymorphism screen of 64 candidate genes among Ashkenazi Jewish case-parent trios. Am. J. Hum. Genet., 77: 918–936.

Faraone, S.V., Chen, W.J., Goldstein, J.M. and Tsuang, M.T. (1994) Gender differences in age at onset of schizophrenia. Br. J. Psychiatry, 164: 625–629.

Farley, I.J., Shannak, K.S. and Hornykiewicz, O. (1980) Brain monoamine changes in chronic paranoid schizophrenia and their possible relation to increased receptor sensitivity. In: Pepeu, G., Kuhar, M.J. and Enna, S.J. (Eds.), Receptors for Neurotransmitters and Peptides. Raven Press, New York, NY, pp. 427–433.

Fleischhaker, C., Schulz, E. and Remschmidt, H. (1998) Biogenic amines as predictors of response to clozapine treatment in early-onset schizophrenia. J. Psychiatr. Res., 32: 325–333.

Fone, K.C. (2008) An update on the role of the 5-hydroxytryptamine6 receptor in cognitive function. Neuropharmacology, 55: 1015–1022.

Frankle, W.G., Lerma, J. and Laruelle, M. (2003) The synaptic hypothesis of schizophrenia. Neuron, 39: 205–216.

Frankle, W.G., Narendran, R., Huang, Y., Hwang, D.R., Lombardo, I., Cangiano, C., Gil, R., Laruelle, M. and Abi-Dargham, A. (2005) Serotonin transporter availability in patients with schizophrenia: a positron emission tomography imaging study with [11C]DASB. Biol. Psychiatry, 57: 1510–1516.

Frankle, W.G., Lombardo, I., Kegeles, L.S., Slifstein, M., Martin, J.H., Huang, Y., Hwang, D.R., Reich, E., Cangiano, C., Gil, R., Laruelle, M. and Abi-Dargham, A. (2006) Serotonin 1A receptor availability in patients with schizophrenia and schizo-affective disorder: a positron emission tomography imaging study with [11C]WAY 100635. Psychopharmacology (Berl.), 189: 155–164.

Freedman, B. and Chapman, L.J. (1973) Early subjective experience in schizophrenic episodes. J. Abnorm. Psychol., 82: 46–54.

Friston, K.J. and Frith, C.D. (1995) Schizophrenia: a disconnection syndrome? Clin. Neurosci., 3: 89–97.

Gaddum, J.H. (1953) Antagonism between lysergic acid diethylamide and 5-hydroxytryptamine. J. Physiol., 121: 15P.

Gaddum, J.H. and Hameed, K.A. (1954) Drugs which antagonize 5-hydroxytryptamine. Br. J. Pharmacol. Chemother., 9: 240–248.

Gaster, L.M. and King, F.D. (1997) Serotonin 5-HT3 and 5-HT4 receptor antagonists. Med. Res. Rev., 17: 163–214.

Gefvert, O., Lundberg, T., Wieselgren, I.M., Bergstrom, M., Langstrom, B., Wiesel, F. and Lindstrom, L. (2001) D(2) and 5HT(2A) receptor occupancy of different doses of quetiapine in schizophrenia: a PET study. Eur. Neuropsychopharmacol., 11: 105–110.

Gewirtz, J.C. and Marek, G.J. (2000) Behavioral evidence for interactions between a hallucinogenic drug and group II metabotropic glutamate receptors. Neuropsychopharmacology, 23: 569–576.

Geyer, M.A. (1998) Behavioral studies of hallucinogenic drugs in animals: implications for schizophrenia research. Pharmacopsychiatry, 31(Suppl. 2): 73–79.

Geyer, M.A. and Braff, D.L. (1982) Habituation of the Blink reflex in normals and schizophrenic patients. Psychophysiology, 19: 1–6.

Geyer, M.A. and Braff, D.L. (1987) Startle habituation and sensorimotor gating in schizophrenia and related animal models. Schizophr. Bull., 13: 643–668.

Geyer, M. and Moghaddam, B. (2002) Animal models relevant to schizophrenia disorders. In: Davis, K.L., Charney, C., Coyle, J.T. and Nemeroff, C. (Eds.), Neuropsychopharmacology: The Fifth Generation of Progress. Lippincott Williams and Wilkins, Philadelphia PA, pp. 689–701.

Geyer, M.A. and Vollenweider, F.X. (2008) Serotonin research: contributions to understanding psychoses. Trends Pharmacol. Sci., 29: 445–453.

Geyer, M.A., Petersen, L.R., Rose, G.J., Horwitt, D.D., Light, R.K., Adams, L.M., Zook, J.A., Hawkins, R.L. and Mandell, A.J. (1978) The effects of lysergic acid diethylamide and mescaline-derived hallucinogens on sensory-integrative function: tactile startle. J. Pharmacol. Exp. Ther., 207: 837–847.

Geyer, M.A., Krebs-Thomson, K., Braff, D.L. and Swerdlow, N.R. (2001) Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review. Psychopharmacology (Berl.), 156: 117–154.

Goldberg, T.E., Goldman, R.S., Burdick, K.E., Malhotra, A.K., Lencz, T., Patel, R.C., Woerner, M.G., Schooler, N.R., Kane, J.M. and Robinson, D.G. (2007) Cognitive improvement after treatment with second-generation antipsychotic medications in first-episode schizophrenia: is it a practice effect? Arch. Gen. Psychiatry, 64: 1115–1122.

Goldstein, J.M., Tsuang, M.T. and Faraone, S.V. (1989) Gender and schizophrenia: implications for understanding the heterogeneity of the illness. Psychiatry Res., 28: 243–253.

Gonzalez-Maeso, J., Ang, R.L., Yuen, T., Chan, P., Weisstaub, N.V., Lopez-Gimenez, J.F., Zhou, M., Okawa, Y., Callado, L.F., Milligan, G., Gingrich, J.A., Filizola, M., Meana, J.J. and Sealfon, S.C. (2008) Identification of a serotonin/glutamate receptor complex implicated in psychosis. Nature, 452: 93–97.

Gottesman, I. (1991) Schizophrenia Genesis: The Origin of Madness. W. H. Freeman, New York, NY.

Gottesman, I. and Gould, T.D. (2003) The endophenotype concept in psychiatry: etymology and strategic Intentions. Am. J. Psychiatry, 160: 636–645.

Gouzoulis-Mayfrank, E., Hermle, L., Thelen, B. and Sass, H. (1998a) History, rationale and potential of human experimental hallucinogenic drug research in psychiatry. Pharmacopsychiatry, 31(Suppl. 2): 63–68.

Gouzoulis-Mayfrank, E., Habermeyer, E., Hermle, L., Steinmeyer, A.M., Kunert, H.J. and Sass, H. (1998b) Hallucinogenic drug induced states resemble acute endogenous psychoses: Results of an empirical study. Eur. Psychiatry, 13: 399–406.

Gouzoulis-Mayfrank, E., Thelen, B., Habermeyer, E., Kunert, H.J., Kovar, K.A., Lindenblatt, H., Hermle, L., Spitzer, M. and Sass, H. (1999) Psychopathological, neuroendocrine and autonomic effects of 3,4-methylenedioxyethylamphetamine (MDE), psilocybin and d-methamphetamine in healthy volunteers. Results of an experimental double-blind placebo-controlled study. Psychopharmacology (Berl.), 142: 41–50.

Gray, J.A. and Roth, B.L. (2007) Molecular targets for treating cognitive dysfunction in schizophrenia. Schizophr. Bull., 33: 1100–1119.

Gray, L., Scarr, E. and Dean, B. (2006) Serotonin 1a receptor and associated G-protein activation in schizophrenia and bipolar disorder. Psychiatry Res., 143: 111–120.

Green, M.F. (1996) What are the functional consequences of neurocognitive deficits in schizophrenia? Am. J. Psychiatry, 153: 321–330.

Guidotti, A., Pesold, C. and Costa, E. (2000) New neurochemical markers for psychosis: a working hypothesis of their operation. Neurochem. Res., 25: 1207–1218.

Gurevich, E.V. and Joyce, J.N. (1997) Alterations in the cortical serotonergic system in schizophrenia: a postmortem study. Biol. Psychiatry, 42: 529–545.

Haertzen, C.A., Hill, H.E. and Belleville, R.E. (1963) Development of the Addiction Research Center Inventory (ARCI): selection of items that are sensitive to the effects of various drugs. Psychopharmacologia, 4: 155–166.

Halberstadt, A.L. (1995) The phencyclidine–glutamate model of schizophrenia. Clin. Neuropharmacol., 18: 237–249.

Hamdani, N., Bonniere, M., Ades, J., Hamon, M., Boni, C. and Gorwood, P. (2005) Negative symptoms of schizophrenia could explain discrepant data on the association between the 5-HT2A receptor gene and response to antipsychotics. Neurosci. Lett., 377: 69–74.

Harmar, A.J., Hills, R.A., Rosser, E.M., Jones, M., Buneman, O.P., Dunbar, D.R., Greenhill, S.D., Hale, V.A., Sharman, J.L., Bonner, T.I., Catterall, W.A., Davenport, A.P., Delagrange, P., Dollery, C.T., Foord, S.M., Gutman, G.A., Laudet, V., Neubig, R.R., Ohlstein, E.H., Olsen, R.W., Peters, J., Pin, J.P., Ruffolo, R.R., Searls, D.B., Wright, M.W. and Spedding, M. (2009) IUPHAR-DB: the IUPHAR database of G protein-coupled receptors and ion channels. Nucleic Acids Res., 37: D680–D685.

Harrison, P.J. (1999a) The neuropathology of schizophrenia. A critical review of the data and their interpretation. Brain, 122(Pt 4): 593–624.

Harrison, P.J. (1999b) Neurochemical alterations in schizophrenia affecting the putative receptor targets of atypical antipsychotics. Focus on dopamine (D1, D3, D4) and 5-HT2a receptors. Br. J. Psychiatry Suppl.: 12–22.

Harrison, P.J. (2004) The hippocampus in schizophrenia: a review of the neuropathological evidence and its pathophysiological implications. Psychopharmacology (Berl.), 174: 151–162.

Harrison, P.J. and Eastwood, S.L. (2001) Neuropathological studies of synaptic connectivity in the hippocampal formation in schizophrenia. Hippocampus, 11: 508–519.

Harrison, P.J. and Owen, M.J. (2003) Genes for schizophrenia? Recent findings and their pathophysiological implications. Lancet, 361: 417–419.

Harrison, P.J. and Weinberger, D.R. (2005) Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Mol. Psychiatry, 10: 40–68; image 45

Hashimoto, T., Nishino, N., Nakai, H. and Tanaka, C. (1991) Increase in serotonin 5-HT1A receptors in prefrontal and temporal cortices of brains from patients with chronic schizophrenia. Life Sci., 48: 355–363.

Hasler, F., Grimberg, U., Benz, M.A., Huber, T. and Vollenweider, F.X. (2004) Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose–effect study. Psychopharmacology (Berl.), 172: 145–156.

Hatcher, P.D., Brown, V.J., Tait, D.S., Bate, S., Overend, P., Hagan, J.J. and Jones, D.N. (2005) 5-HT6 receptor antagonists improve performance in an attentional set shifting task in rats. Psychopharmacology (Berl.), 181: 253–259.

Healy, D. (2002) The Creation of Psychopharmacology. Harvard University Press, Cambridge, MA.

Hermle, L., Funfgeld, M., Oepen, G., Botsch, H., Borchardt, D., Gouzoulis, E., Fehrenbach, R.A. and Spitzer, M. (1992) Mescaline-induced psychopathological, neuropsychological, and neurometabolic effects in normal subjects: experimental psychosis as a tool for psychiatric research. Biol. Psychiatry, 32: 976–991.

Hernandez, I. and Sokolov, B.P. (1997) Abnormal expression of serotonin transporter mRNA in the frontal and temporal cortex of schizophrenics. Mol. Psychiatry, 2: 57–64.

Hernandez, I. and Sokolov, B.P. (2000) Abnormalities in 5-HT2A receptor mRNA expression in frontal cortex of chronic elderly schizophrenics with varying histories of neuroleptic treatment. J. Neurosci. Res., 59: 218–225.

Higashi, S., Ohnuma, T., Shibata, N., Higashi, M., Matsubara, Y. and Arai, H. (2007) No genetic association between tryptophan hydroxylase 2 gene polymorphisms and Japanese schizophrenia. Psychiatr. Genet., 17: 123.

Hollister, L.E. (1962) Drug-induced psychoses and schizophrenic reactions: a critical comparison. Ann. N.Y. Acad. Sci., 96: 80–92.

Holzman, P. and Matthysse, S. (1990) The genetics of schizophrenia: a review. Psychol. Sci., 1: 279–285.

Honer, W. and Young, C. (2004) Presynaptic proteins and schizophrenia. In: Smythies, J. (Ed.), Disorders of Synaptic Plasticity and Schizophrenia. Elsevier, Amsterdam, pp. 175–201.

Hong, C.J., Lin, C.H., Yu, Y.W., Yang, K.H. and Tsai, S.J. (2001) Genetic variants of the serotonin system and weight change during clozapine treatment. Pharmacogenetics, 11: 265–268.

Hoshino, Y., Kaneko, M., Kumashiro, H. and Tachibana, R. (1985) Endocrinological function in schizophrenic patients under haloperidol treatment: plasma PRL, HGH and 5HT levels after L-5HTP loading. Folia Psychiatr. Neurol. Jpn, 39: 25–31.

Hsiao, J.K., Potter, W.Z., Agren, H., Owen, R.R. and Pickar, D. (1993) Clinical investigation of monoamine neurotransmitter interactions. Psychopharmacology (Berl.), 112: S76–S84.

Huang, Y.Y., Battistuzzi, C., Oquendo, M.A., Harkavy-Friedman, J., Greenhill, L., Zalsman, G., Brodsky, B., Arango, V., Brent, D.A. and Mann, J.J. (2004) Human 5-HT1A receptor C(−1019)G polymorphism and psychopathology. Intl. J. Neuropsychopharmacol., 7: 441–451.

Hurlemann, R., Boy, C., Meyer, P.T., Scherk, H., Wagner, M., Herzog, H., Coenen, H.H., Vogeley, K., Falkai, P., Zilles, K., Maier, W. and Bauer, A. (2005) Decreased prefrontal 5-HT2A receptor binding in subjects at enhanced risk for schizophrenia. Anat. Embryol. (Berl.), 210: 519–523.

Hurlemann, R., Matusch, A., Kuhn, K.U., Berning, J., Elmenhorst, D., Winz, O., Kolsch, H., Zilles, K., Wagner, M., Maier, W. and Bauer, A. (2008) 5-HT2A receptor density is decreased in the at-risk mental state. Psychopharmacology (Berl.), 195: 579–590.

Idris, N.F., Repeto, P., Neill, J.C. and Large, C.H. (2005) Investigation of the effects of lamotrigine and clozapine in improving reversal-learning impairments induced by acute phencyclidine and D-amphetamine in the rat. Psychopharmacology (Berl.), 179: 336–348.

Ikeda, M., Iwata, N., Kitajima, T., Suzuki, T., Yamanouchi, Y., Kinoshita, Y. and Ozaki, N. (2006) Positive association of the serotonin 5-HT7 receptor gene with schizophrenia in a Japanese population. Neuropsychopharmacology, 31: 866–871.

Impagnatiello, F., Guidotti, A.R., Pesold, C., Dwivedi, Y., Caruncho, H., Pisu, M.G., Uzunov, D.P., Smalheiser, N.R., Davis, J.M., Pandey, G.N., Pappas, G.D., Tueting, P., Sharma, R.P. and Costa, E. (1998) A decrease of reelin expression as a putative vulnerability factor in schizophrenia. Proc. Natl. Acad. Sci. USA, 95: 15718–15723.

Iqbal, N. and van Praag, H.M. (1995) The role of serotonin in schizophrenia. Eur. Neuropsychopharmacol., 5(Suppl.): 11–23.

Iqbal, N., Asnis, G.M., Wetzler, S., Kahn, R.S., Kay, S.R. and van Praag, H.M. (1991) The MCPP challenge test in schizophrenia: hormonal and behavioral responses. Biol. Psychiatry, 30: 770–778.

Ito, H., Nyberg, S., Halldin, C., Lundkvist, C. and Farde, L. (1998) PET imaging of central 5-HT2A receptors with carbon-11-MDL 100,907. J. Nucl. Med., 39: 208–214.

Iwata, N., Ozaki, N., Inada, T. and Goldman, D. (2001) Association of a 5-HT(5A) receptor polymorphism, Pro15Ser, to schizophrenia. Mol. Psychiatry, 6: 217–219.

Jacobsen, L.K., Frazier, J.A., Malhotra, A.K., Karoum, F., McKenna, K., Gordon, C.T., Hamburger, S.D., Lenane, M.C., Pickar, D., Potter, W.Z. and Rapoport, J.L. (1997) Cerebrospinal fluid monoamine metabolites in childhood-onset schizophrenia. Am. J. Psychiatry, 154: 69–74.

Jakob, H. and Beckmann, H. (1986) Prenatal developmental disturbances in the limbic allocortex in schizophrenics. J. Neural Transm., 65: 303–326.

Javitt, D.C. and Zukin, S.R. (1991) Recent advances in the phencyclidine model of schizophrenia. Am. J. Psychiatry, 148: 1301–1308.

Jennings, W.S. Jr., Schulz, S.C., Narasimhachari, N., Hamer, R.M. and Friedel, R.O. (1985) Brain ventricular size and CSF monoamine metabolites in an adolescent inpatient population. Psychiatry Res., 16: 87–94.

Jentsch, J.D. and Roth, R.H. (1999) The neuropsychopharmacology of phencyclidine: from NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. Neuropsychopharmacology, 20: 201–225.

Jessen, F., Scherk, H., Traber, F., Theyson, S., Berning, J., Tepest, R., Falkai, P., Schild, H.H., Maier, W., Wagner, M. and Block, W. (2006) Proton magnetic resonance spectroscopy in subjects at risk for schizophrenia. Schizophr. Res., 87: 81–88.

Jonsson, E., Nothen, M.M., Bunzel, R., Propping, P. and Sedvall, G. (1996) 5HT 2a receptor T102C polymorphism and schizophrenia. Lancet, 347: 1831.

Joober, R., Benkelfat, C., Brisebois, K., Toulouse, A., Turecki, G., Lal, S., Bloom, D., Labelle, A., Lalonde, P., Fortin, D., Alda, M., Palmour, R. and Rouleau, G.A. (1999) T102C polymorphism in

the 5HT2A gene and schizophrenia: relation to phenotype and drug response variability. J. Psychiatry Neurosci., 24: 141–146.
Joseph, M.H., Owen, F., Baker, H.F. and Bourne, R.C. (1977) Platelet serotonin concentration and monoamine oxidase activity in unmedicated chronic schizophrenic and in schizo-affective patients. Psychol. Med., 7: 159–162.
Joyce, J.N., Shane, A., Lexow, N., Winokur, A., Casanova, M.F. and Kleinman, J.E. (1993) Serotonin uptake sites and serotonin receptors are altered in the limbic system of schizophrenics. Neuropsychopharmacology, 8: 315–336.
Kahn, R.S. and Wetzler, S. (1991) m-Chlorophenylpiperazine as a probe of serotonin function. Biol. Psychiatry, 30: 1139–1166.
Kahn, R.S., Siever, L.J., Gabriel, S., Amin, F., Stern, R.G., DuMont, K., Apter, S. and Davidson, M. (1992) Serotonin function in schizophrenia: effects of meta-chlorophenylpiperazine in schizophrenic patients and healthy subjects. Psychiatry Res., 43: 1–12.
Kahn, R.S., Davidson, M., Siever, L., Gabriel, S., Apter, S. and Davis, K.L. (1993a) Serotonin function and treatment response to clozapine in schizophrenic patients. Am. J. Psychiatry, 150: 1337–1342.
Kahn, R.S., Davidson, M., Knott, P., Stern, R.G., Apter, S. and Davis, K.L. (1993b) Effect of neuroleptic medication on cerebrospinal fluid monoamine metabolite concentrations in schizophrenia. Serotonin–dopamine interactions as a target for treatment. Arch. Gen. Psychiatry, 50: 599–605.
Kahn, R.S., Davidson, M., Siever, L.J., Sevy, S. and Davis, K.L. (1994) Clozapine treatment and its effect on neuroendocrine responses induced by the serotonin agonist, m-chlorophenylpiperazine. Biol. Psychiatry, 35: 909–912.
Kaiser, R., Tremblay, P.B., Schmider, J., Henneken, M., Dettling, M., Muller-Oerlinghausen, B., Uebelhack, R., Roots, I. and Brockmoller, J. (2001) Serotonin transporter polymorphisms: no association with response to antipsychotic treatment, but associations with the schizoparanoid and residual subtypes of schizophrenia. Mol. Psychiatry, 6: 179–185.
Kane, J., Honigfeld, G., Singer, J. and Meltzer, H. (1988) Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch. Gen. Psychiatry, 45: 789–796.
Kapur, S. and Seeman, P. (2001) Does fast dissociation from the dopamine d(2) receptor explain the action of atypical antipsychotics?: a new hypothesis. Am. J. Psychiatry, 158: 360–369.
Kapur, S., Zipursky, R.B., Remington, G., Jones, C., DaSilva, J., Wilson, A.A. and Houle, S. (1998) 5-HT2 and D2 receptor occupancy of olanzapine in schizophrenia: a PET investigation. Am. J. Psychiatry, 155: 921–928.
Kapur, S., Zipursky, R., Jones, C., Remington, G. and Houle, S. (2000) Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. Am. J. Psychiatry, 157: 514–520.
Kasper, S., Tauscher, J., Kufferle, B., Barnas, C., Pezawas, L. and Quiner, S. (1999) Dopamine- and serotonin-receptors in schizophrenia: results of imaging-studies and implications for pharmacotherapy in schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci., 249(Suppl. 4): 83–89.
Keefe, R.S., Bilder, R.M., Davis, S.M., Harvey, P.D., Palmer, B.W., Gold, J.M., Meltzer, H.Y., Green, M.F., Capuano, G., Stroup, T.S., McEvoy, J.P., Swartz, M.S., Rosenheck, R.A., Perkins, D.O., Davis, C.E., Hsiao, J.K. and Lieberman, J.A. (2007) Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. Arch. Gen. Psychiatry, 64: 633–647.
Keeler, M.H. (1965) Similarity of schizophrenia and the psilocybin syndrome as determined by objective methods. Intl. J. Neuropsychiatry, 1: 630–634.
Kern, R.S., Green, M.F., Marshall, B.D. Jr., Wirshing, W.C., Wirshing, D., McGurk, S.R., Marder, S.R. and Mintz, J. (1999) Risperidone versus haloperidol on secondary memory: can newer medications aid learning? Schizophr. Bull., 25: 223–232.
Key, B.J. (1964) The effect of LSD-25 on the interaction between conditioned and non-conditioned stimuli in a simple avoidance situation. Psychopharmacologia, 6: 319–326.
Klodzinska, A., Bijak, M., Tokarski, K. and Pilc, A. (2002) Group II mGlu receptor agonists inhibit behavioural and electrophysiological effects of DOI in mice. Pharmacol. Biochem. Behav., 73: 327–332.
Knauer, A. and Maloney, W.J.M.A. (1913) A prelimnary note on the psychic action of mescaline, with special reference to the mechanism of visual hallucinations. J. Nerv. Ment. Dis., 40: 425–436.
Kolakowska, T., Cowen, P.J. and Murdock, P. (1987) Endocrine responses to tryptophan infusion in schizophrenic patients treated with neuroleptics. Psychoneuroendocrinology, 12: 193–202.
Koreen, A.R., Lieberman, J.A., Alvir, J. and Chakos, M. (1997) The behavioral effect of m-chlorophenylpiperazine (mCPP) and methylphenidate in first-episode schizophrenia and normal controls. Neuropsychopharmacology, 16: 61–68.
Kouzmenko, A.P., Hayes, W.L., Pereira, A.M., Dean, B., Burnet, P.W. and Harrison, P.J. (1997) 5-HT2A receptor polymorphism and steady state receptor expression in schizophrenia. Lancet, 349: 1815.
Krystal, J.H., Seibyl, J.P., Price, L.H., Woods, S.W., Heninger, G.R., Aghajanian, G.K. and Charney, D.S. (1993) m-Chlorophenylpiperazine effects in neuroleptic-free schizophrenic patients. Evidence implicating serotonergic systems in the positive symptoms of schizophrenia. Arch. Gen. Psychiatry, 50: 624–635.
Krystal, J.H., Karper, L.P., Seibyl, J.P., Freeman, G.K., Delaney, R., Bremner, J.D., Heninger, G.R., Bowers, M.B. Jr. and Charney, D.S. (1994) Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch. Gen. Psychiatry, 51: 199–214.
Lambe, E.K., Goldman-Rakic, P.S. and Aghajanian, G.K. (2000) Serotonin induces EPSCs preferentially in layer V pyramidal neurons of the frontal cortex in the rat. Cereb. Cortex, 10: 974–980.
Lane, H.Y., Chang, Y.C., Chiu, C.C., Chen, M.L., Hsieh, M.H. and Chang, W.H. (2002) Association of risperidone treatment response with a polymorphism in the 5-HT(2A) receptor gene. Am. J. Psychiatry, 159: 1593–1595.
Lane, H.Y., Lin, C.C., Huang, C.H., Chang, Y.C., Hsu, S.K. and Chang, W.H. (2004) Risperidone response and 5-HT6 receptor gene variance: genetic association analysis with adjustment for nongenetic confounders. Schizophr. Res., 67: 63–70.
Laruelle, M., Abi-Dargham, A., Casanova, M.F., Toti, R., Weinberger, D.R. and Kleinman, J.E. (1993a) Selective abnormalities of prefrontal serotonergic receptors in schizophrenia. A postmortem study. Arch. Gen. Psychiatry, 50: 810–818.
Laruelle, M., Baldwin, R.M., Malison, R.T., Zea-Ponce, Y., Zoghbi, S.S., al-Tikriti, M.S., Sybirska, E.H., Zimmermann, R.C., Wisniewski, G., Neumeyer, J.L. et al. (1993b) SPECT imaging of dopamine and serotonin transporters with

[123I]beta-CIT: pharmacological characterization of brain uptake in nonhuman primates. Synapse, 13: 295–309.

Laruelle, M., Abi-Dargham, A., Gil, R., Kegeles, L. and Innis, R. (1999) Increased dopamine transmission in schizophrenia: relationship to illness phases. Biol. Psychiatry, 46: 56–72.

Laruelle, M., Abi-Dargham, A., van Dyck, C., Gil, R., D'Souza, D.C., Krystal, J., Seibyl, J., Baldwin, R. and Innis, R. (2000) Dopamine and serotonin transporters in patients with schizophrenia: an imaging study with [(123)I]beta-CIT. Biol. Psychiatry, 47: 371–379.

Lattuada, E., Cavallaro, R., Serretti, A., Lorenzi, C. and Smeraldi, E. (2004) Tardive dyskinesia and DRD2, DRD3, DRD4, 5-HT2A variants in schizophrenia: an association study with repeated assessment. Intl. J. Neuropsychopharmacol., 7: 489–493.

Lemonde, S., Turecki, G., Bakish, D., Du, L., Hrdina, P.D., Bown, C.D., Sequeira, A., Kushwaha, N., Morris, S.J., Basak, A., Ou, X.M. and Albert, P.R. (2003) Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. J. Neurosci., 23: 8788–8799.

Lerer, B., Ran, A., Blacker, M., Silver, H., Weller, M.P., Drummer, D., Ebstein, B. and Calev, A. (1988) Neuroendocrine responses in chronic schizophrenia. Evidence for serotonergic dysfunction. Schizophr. Res., 1: 405–410.

Lerer, B., Segman, R.H., Tan, E.C., Basile, V.S., Cavallaro, R., Aschauer, H.N., Strous, R., Chong, S.A., Heresco-Levy, U., Verga, M., Scharfetter, J., Meltzer, H.Y., Kennedy, J.L. and Macciardi, F. (2005) Combined analysis of 635 patients confirms an age-related association of the serotonin 2A receptor gene with tardive dyskinesia and specificity for the non-orofacial subtype. Int. J. Neuropsychopharmacol, 8: 411–425.

Leucht, S. (2004) Amisulpride a selective dopamine antagonist and atypical antipsychotic: results of a meta-analysis of randomized controlled trials. Int. J. Neuropsychopharmacol., 7(Suppl 1): S15–S20.

Leucht, S., Pitschel-Walz, G., Abraham, D. and Kissling, W. (1999) Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. Schizophr. Res., 35: 51–68.

Leucht, S., Pitschel-Walz, G., Engel, R.R. and Kissling, W. (2002) Amisulpride, an unusual 'atypical' antipsychotic: a meta-analysis of randomized controlled trials. Am. J. Psychiatry, 159: 180–190.

Leucht, S., Corves, C., Arbter, D., Engel, R.R., Li, C. and Davis, J.M. (2009) Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet, 373: 31–41.

Lewine, R.R., Risch, S.C., Risby, E., Stipetic, M., Jewart, R.D., Eccard, M., Caudle, J. and Pollard, W. (1991) Lateral ventricle–brain ratio and balance between CSF HVA and 5-HIAA in schizophrenia. Am. J. Psychiatry, 148: 1189–1194.

Lewis, D.A. (2000) GABAergic local circuit neurons and prefrontal cortical dysfunction in schizophrenia. Brain Res. Brain Res. Rev., 31: 270–276.

Lewis, R., Kapur, S., Jones, C., DaSilva, J., Brown, G.M., Wilson, A.A., Houle, S. and Zipursky, R.B. (1999) Serotonin 5-HT2 receptors in schizophrenia: a PET study using [18F]setoperone in neuroleptic-naive patients and normal subjects. Am. J. Psychiatry, 156: 72–78.

Liddle, P.F. (2000) Cognitive impairment in schizophrenia: its impact on social functioning. Acta Psychiatr. Scand. Suppl., 400: 11–16.

Lidow, M.S. (2000) General overview of contemporary antipsychotic medications. In: Lidow, M.S. (Ed.), Neurotransmitter Receptors in Actions of Antipsychotic Medications. CRC Press LLC, Boca Raton, FL, pp. 17–29.

Lieberman, J.A., Kane, J.M., Safferman, A.Z., Pollack, S., Howard, A., Szymanski, S., Masiar, S.J., Kronig, M.H., Cooper, T. and Novacenko, H. (1994) Predictors of response to clozapine. J. Clin. Psychiatry, 55(Suppl. B): 126–128.

Lieberman, J.A., Mailman, R.B., Duncan, G., Sikich, L., Chakos, M., Nichols, D.E. and Kraus, J.E. (1998) Serotonergic basis of antipsychotic drug effects in schizophrenia. Biol. Psychiatry, 44: 1099–1117.

Lin, C.H., Tsai, S.J., Yu, Y.W., Song, H.L., Tu, P.C., Sim, C.B., Hsu, C.P., Yang, K.H. and Hong, C.J. (1999) No evidence for association of serotonin-2A receptor variant (102T/C) with schizophrenia or clozapine response in a Chinese population. Neuroreport, 10: 57–60.

Losonczy, M.F., Song, I.S., Mohs, R.C., Small, N.A., Davidson, M., Johns, C.A. and Davis, K.L. (1986) Correlates of lateral ventricular size in chronic schizophrenia, I: behavioral and treatment response measures. Am. J. Psychiatry, 143: 976–981.

Ludewig, K., Geyer, M.A. and Vollenweider, F.X. (2003) Deficits in prepulse inhibition and habituation in never-medicated, first-episode schizophrenia. Biol. Psychiatry, 54: 121–128.

Mackay, A.V., Doble, A., Bird, E.D., Spokes, E.G., Quik, M. and Iversen, L.L. (1978) 3H-Spiperone binding in normal and schizophrenic post-mortem human brain. Life Sci., 23: 527–532.

Maes, M. and Meltzer, H.Y. (1996) Effects of meta-chlorophenylpiperazine on neuroendocrine and behavioral responses in male schizophrenic patients and normal volunteers. Psychiatry Res., 64: 147–159.

Malhotra, A.K., Goldman, D., Ozaki, N., Breier, A., Buchanan, R. and Pickar, D. (1996) Lack of association between polymorphisms in the 5-HT2A receptor gene and the antipsychotic response to clozapine. Am. J. Psychiatry, 153: 1092–1094.

Mamo, D., Kapur, S., Shammi, C.M., Papatheodorou, G., Mann, S., Therrien, F. and Remington, G. (2004) A PET study of dopamine D2 and serotonin 5-HT2 receptor occupancy in patients with schizophrenia treated with therapeutic doses of ziprasidone. Am. J. Psychiatry, 161: 818–825.

Mamo, D., Graff, A., Mizrahi, R., Shammi, C.M., Romeyer, F. and Kapur, S. (2007) Differential effects of aripiprazole on D(2), 5-HT(2), and 5-HT(1A) receptor occupancy in patients with schizophrenia: a triple tracer PET study. Am. J. Psychiatry, 164: 1411–1417.

Marcos, B., Chuang, T.T., Gil-Bea, F.J. and Ramirez, M.J. (2008) Effects of 5-HT6 receptor antagonism and cholinesterase inhibition in models of cognitive impairment in the rat. Br. J. Pharmacol., 155: 434–440.

Marder, S.R. and Meibach, R.C. (1994) Risperidone in the treatment of schizophrenia. Am. J. Psychiatry, 151: 825–835.

Marek, G.J., Wright, R.A., Schoepp, D.D., Monn, J.A. and Aghajanian, G.K. (2000) Physiological antagonism between 5-hydroxytryptamine(2A) and group II metabotropic glutamate receptors in prefrontal cortex. J. Pharmacol. Exp. Ther., 292: 76–87.

Marek, G.J., Wright, R.A., Gewirtz, J.C. and Schoepp, D.D. (2001) A major role for thalamocortical afferents in

serotonergic hallucinogen receptor function in the rat neocortex. Neuroscience, 105: 379–392.
Marenco, S. and Weinberger, D.R. (2000) The neurodevelopmental hypothesis of schizophrenia: following a trail of evidence from cradle to grave. Dev. Psychopathol., 12: 501–527.
Markianos, M., Hatzimanolis, J. and Lykouras, L. (2001) Neuroendocrine serotonergic and dopaminergic responsivity in male schizophrenic patients during treatment with neuroleptics and after switch to risperidone. Psychopharmacology (Berl.), 157: 55–59.
Martin, P., Waters, N., Carlsson, A. and Carlsson, M.L. (1997) The apparent antipsychotic action of the 5-HT2a receptor antagonist M100907 in a mouse model of schizophrenia is counteracted by ritanserin. (Rapid communication.) J. Neural Transm., 104: 561–564.
Martin, P., Waters, N., Schmidt, C.J., Carlsson, A. and Carlsson, M.L. (1998) Rodent data and general hypothesis: antipsychotic action exerted through 5-Ht2A receptor antagonism is dependent on increased serotonergic tone. J. Neural Transm., 105: 365–396.
Masellis, M., Paterson, A.D., Badri, F., Lieberman, J.A., Meltzer, H.Y., Cavazzoni, P. and Kennedy, J.L. (1995) Genetic variation of 5-HT2A receptor and response to clozapine. Lancet, 346: 1108.
Masellis, M., Basile, V., Meltzer, H.Y., Lieberman, J.A., Sevy, S., Macciardi, F.M., Cola, P., Howard, A., Badri, F., Nothen, M.M., Kalow, W. and Kennedy, J.L. (1998) Serotonin subtype 2 receptor genes and clinical response to clozapine in schizophrenia patients. Neuropsychopharmacology, 19: 123–132.
Masellis, M., Basile, V.S., Meltzer, H.Y., Lieberman, J.A., Sevy, S., Goldman, D.A., Hamblin, M.W., Macciardi, F.M. and Kennedy, J.L. (2001) Lack of association between the T→C 267 serotonin 5-HT6 receptor gene (HTR6) polymorphism and prediction of response to clozapine in schizophrenia. Schizophr. Res., 47: 49–58.
Matsumoto, I., Inoue, Y., Iwazaki, T., Pavey, G. and Dean, B. (2005) 5-HT2A and muscarinic receptors in schizophrenia: a postmortem study. Neurosci. Lett., 379: 164–168.
Maynard, T.M., Sikich, L., Lieberman, J.A. and LaMantia, A.S. (2001) Neural development, cell–cell signaling, and the 'two-hit' hypothesis of schizophrenia. Schizophr. Bull., 27: 457–476.
McCabe, M.S., Fowler, R.C., Cadoret, R.J. and Winokur, G. (1972) Symptom differences in schizophrenia with good and poor prognosis. Am. J. Psychiatry, 128: 1239–1243.
McGhie, A. and Chapman, J. (1961) Disorders of attention and perception in early schizophrenia. Br. J. Med. Psychol., 34: 103–116.
McGlashan, T.H. and Hoffman, R.E. (2000) Schizophrenia as a disorder of developmentally reduced synaptic connectivity. Arch. Gen. Psychiatry, 57: 637–648.
Meltzer, H.Y. (1991) The mechanism of action of novel antipsychotic drugs. Schizophr. Bull., 17: 263–287.
Meltzer, H.Y. (1999) The role of serotonin in antipsychotic drug action. Neuropsychopharmacology, 21: 106S–115S.
Meltzer, H.Y. and McGurk, S.R. (1999) The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. Schizophr. Bull., 25: 233–255.
Meltzer, H.Y. and Stahl, S.M. (1976) The dopamine hypothesis of schizophrenia: a review. Schizophr. Bull., 2: 19–76.
Meltzer, H.Y., Bastani, B., Ramirez, L. and Matsubara, S. (1989) Clozapine: new research on efficacy and mechanism of action. Eur. Arch. Psychiatry Neurol. Sci., 238: 332–339.
Meltzer, H.Y., Li, Z., Kaneda, Y. and Ichikawa, J. (2003) Serotonin receptors: their key role in drugs to treat schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry, 27: 1159–1172.
Mikuni, M. and Meltzer, H.Y. (1984) Reduction of serotonin-2 receptors in rat cerebral cortex after subchronic administration of imipramine, chlorpromazine, and the combination thereof. Life Sci., 34: 87–92.
Millan, M.J., Dekeyne, A. and Gobert, A. (1998) Serotonin (5-HT)2C receptors tonically inhibit dopamine (DA) and noradrenaline (NA), but not 5-HT, release in the frontal cortex in vivo. Neuropharmacology, 37: 953–955.
Miller, D.D., Ellingrod, V.L., Holman, T.L., Buckley, P.F. and Arndt, S. (2005) Clozapine-induced weight gain associated with the 5HT2C receptor -759C/T polymorphism. Am. J. Med. Genet. B Neuropsychiatr. Genet., 133B: 97–100.
Mirnics, K., Middleton, F.A., Lewis, D.A. and Levitt, P. (2001) Analysis of complex brain disorders with gene expression microarrays: schizophrenia as a disease of the synapse. Trends Neurosci., 24: 479–486.
Mita, T., Hanada, S., Nishino, N., Kuno, T., Nakai, H., Yamadori, T., Mizoi, Y. and Tanaka, C. (1986) Decreased serotonin S2 and increased dopamine D2 receptors in chronic schizophrenics. Biol. Psychiatry, 21: 1407–1414.
Miyamoto, S., LaMantia, A.S., Duncan, G.E., Sullivan, P., Gilmore, J.H. and Lieberman, J.A. (2003) Recent advances in the neurobiology of schizophrenia. Mol. Interv., 3: 27–39.
Moghaddam, B. and Adams, B.W. (1998) Reversal of phencyclidine effects by a group II metabotropic glutamate receptor agonist in rats. Science, 281: 1349–1352.
Moghaddam, B., Adams, B., Verma, A. and Daly, D. (1997) Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. J. Neurosci., 17: 2921–2927.
Mohr, P., Horacek, J., Motlova, L., Libiger, J. and Czobor, P. (1998) Prolactin response to D-fenfluramine challenge test as a predictor of treatment response to haloperidol in acute schizophrenia. Schizophr. Res., 30: 91–99.
Moller, H.J., Muller, H., Borison, R.L., Schooler, N.R. and Chouinard, G. (1995) A path-analytical approach to differentiate between direct and indirect drug effects on negative symptoms in schizophrenic patients. A re-evaluation of the North American risperidone study. Eur. Arch. Psychiatry Clin. Neurosci., 245: 45–49.
Monteleone, P., Tortorella, A., Borriello, R., Cassandro, P. and Maj, M. (1999) Prolactin hyperresponsiveness to D-fenfluramine in drug-free schizophrenic patients: a placebo-controlled study. Biol. Psychiatry, 45: 1606–1611.
Morey, R.A., Inan, S., Mitchell, T.V., Perkins, D.O., Lieberman, J.A. and Belger, A. (2005) Imaging frontostriatal function in ultra-high-risk, early, and chronic schizophrenia during executive processing. Arch. Gen. Psychiatry, 62: 254–262.
Mossner, R., Schuhmacher, A., Kuhn, K.U., Cvetanovska, G., Rujescu, D., Zill, P., Quednow, B.B., Rietschel, M., Wolwer, W., Gaebel, W., Wagner, M. and Maier, W. (2009) Functional serotonin 1A receptor variant influences treatment response to atypical antipsychotics in schizophrenia. Pharmacogenet. Genomics, 19: 91–94.
Murphy, D.L., Mueller, E.A., Garrick, N.A. and Aulakh, C.S. (1986) Use of serotonergic agents in the clinical assessment of central serotonin function. J. Clin. Psychiatry, 47(Suppl.): 9–15.
Murray, R.M., O'Callaghan, E., Castle, D.J. and Lewis, S.W. (1992) A neurodevelopmental approach to the classification of schizophrenia. Schizophr. Bull., 18: 319–332.

Muschamp, J.W., Regina, M.J., Hull, E.M., Winter, J.C. and Rabin, R.A. (2004) Lysergic acid diethylamide and [-]-2,5-dimethoxy-4-methylamphetamine increase extracellular glutamate in rat prefrontal cortex. Brain Res., 1023: 134–140.

Naylor, L., Dean, B., Opeskin, K., Pavey, G., Hill, C., Keks, N. and Copolov, D. (1996) Changes in the serotonin transporter in the hippocampus of subjects with schizophrenia identified using [3H]paroxetine. J. Neural Transm., 103: 749–757.

Neumeyer, J.L., Wang, S.Y., Milius, R.A., Baldwin, R.M., Zea-Ponce, Y., Hoffer, P.B., Sybirska, E., al-Tikriti, M., Charney, D.S., Malison, R.T. et al. (1991) [123I]-2 beta-carbomethoxy-3 beta-(4-iodophenyl)tropane: high-affinity SPECT radiotracer of monoamine reuptake sites in brain. J. Med. Chem., 34: 3144–3146.

Newcomer, J.W., Faustman, W.O., Zipursky, R.B. and Csernansky, J.G. (1992) Zacopride in schizophrenia: a single-blind serotonin type 3 antagonist trial. Arch. Gen. Psychiatry, 49: 751–752.

Newman-Tancredi, A., Gavaudan, S., Conte, C., Chaput, C., Touzard, M., Verriele, L., Audinot, V. and Millan, M.J. (1998) Agonist and antagonist actions of antipsychotic agents at 5-HT1A receptors: a [35S]GTPgammaS binding study. Eur. J. Pharmacol., 355: 245–256.

Ngan, E.T., Yatham, L.N., Ruth, T.J. and Liddle, P.F. (2000) Decreased serotonin 2A receptor densities in neuroleptic-naive patients with schizophrenia: a PET study using [(18)F]setoperone. Am. J. Psychiatry, 157: 1016–1018.

Nordstrom, A.L., Farde, L., Wiesel, F.A., Forslund, K., Pauli, S., Halldin, C. and Uppfeldt, G. (1993) Central D2-dopamine receptor occupancy in relation to antipsychotic drug effects: a double-blind PET study of schizophrenic patients. Biol. Psychiatry, 33: 227–235.

Nothen, M.M., Rietschel, M., Erdmann, J., Oberlander, H., Moller, H.J., Nober, D. and Propping, P. (1995) Genetic variation of the 5-HT2A receptor and response to clozapine. Lancet, 346: 908–909.

Nudmamud, S., Reynolds, L.M. and Reynolds, G.P. (2003) N-acetylaspartate and N-acetylaspartylglutamate deficits in superior temporal cortex in schizophrenia and bipolar disorder: a postmortem study. Biol. Psychiatry, 53: 1138–1141.

Nyback, H., Berggren, B.M., Hindmarsh, T., Sedvall, G. and Wiesel, F.A. (1983) Cerebroventricular size and cerebrospinal fluid monoamine metabolites in schizophrenic patients and healthy volunteers. Psychiatry Res., 9: 301–308.

Nyberg, S., Eriksson, B., Oxenstierna, G., Halldin, C. and Farde, L. (1999) Suggested minimal effective dose of risperidone based on PET-measured D2 and 5-HT2A receptor occupancy in schizophrenic patients. Am. J. Psychiatry, 156: 869–875.

O'Dell, S.J., La Hoste, G.J., Widmark, C.B., Shapiro, R.M., Potkin, S.G. and Marshall, J.F. (1990) Chronic treatment with clozapine or haloperidol differentially regulates dopamine and serotonin receptors in rat brain. Synapse, 6: 146–153.

Ohuoha, D.C., Hyde, T.M. and Kleinman, J.E. (1993) The role of serotonin in schizophrenia: an overview of the nomenclature, distribution and alterations of serotonin receptors in the central nervous system. Psychopharmacology (Berl.), 112: S5–S15.

Okubo, Y., Suhara, T., Suzuki, K., Kobayashi, K., Inoue, O., Terasaki, O., Someya, Y., Sassa, T., Sudo, Y., Matsushima, E., Iyo, M., Tateno, Y. and Toru, M. (2000) Serotonin 5-HT2 receptors in schizophrenic patients studied by positron emission tomography. Life Sci., 66: 2455–2464.

Osmond, H. and Smythies, J. (1952) Schizophrenia: a new approach. J Ment. Sci., 98: 309–315.

Ostrowitzki, S., Rao, M.L., Redei, J. and Andres, A.H. (1993) Concurrence of cortex and platelet serotonin2 receptor binding characteristics in the individual and the putative regulation by serotonin. J. Neural Transm. Gen. Sect., 93: 27–35.

Owen, F., Cross, A.J., Crow, T.J., Lofthouse, R. and Poulter, M. (1981) Neurotransmitter receptors in brain in schizophrenia. Acta Psychiatr. Scand. Suppl., 291: 20–28.

Owen, R.R. Jr., Gutierrez-Esteinou, R., Hsiao, J., Hadd, K., Benkelfat, C., Lawlor, B.A., Murphy, D.L. and Pickar, D. (1993) Effects of clozapine and fluphenazine treatment on responses to m-chlorophenylpiperazine infusions in schizophrenia. Arch. Gen. Psychiatry, 50: 636–644.

Padin, J.F., Rodriguez, M.A., Dominguez, E., Dopeso-Reyes, I.G., Buceta, M., Cano, E., Sotelo, E., Brea, J., Caruncho, H.J., Isabel Cadavid, M., Castro, M. and Isabel Loza, M. (2006) Parallel regulation by olanzapine of the patterns of expression of 5-HT2A and D3 receptors in rat central nervous system and blood cells. Neuropharmacology, 51: 923–932.

Parsons, M.J., D'Souza, U.M., Arranz, M.J., Kerwin, R.W. and Makoff, A.J. (2004) The −1438A/G polymorphism in the 5-hydroxytryptamine type 2A receptor gene affects promoter activity. Biol. Psychiatry, 56: 406–410.

Parwani, A., Duncan, E.J., Bartlett, E., Madonick, S.H., Efferen, T.R., Rajan, R., Sanfilipo, M., Chappell, P.B., Chakravorty, S., Gonzenbach, S., Ko, G.N. and Rotrosen, J.P. (2000) Impaired prepulse inhibition of acoustic startle in schizophrenia. Biol. Psychiatry, 47: 662–669.

Patil, S.T., Zhang, L., Martenyi, F., Lowe, S.L., Jackson, K.A., Andreev, B.V., Avedisova, A.S., Bardenstein, L.M., Gurovich, I.Y., Morozova, M.A., Mosolov, S.N., Neznanov, N.G., Reznik, A.M., Smulevich, A.B., Tochilov, V.A., Johnson, B.G., Monn, J.A. and Schoepp, D.D. (2007) Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized Phase 2 clinical trial. Nat. Med., 13: 1102–1107.

Pickar, D., Roy, A., Breier, A., Doran, A., Wolkowitz, O., Colison, J. and Agren, H. (1986) Suicide and aggression in schizophrenia. Neurobiologic correlates. Ann. N. Y. Acad. Sci., 487: 189–196.

Pickar, D., Owen, R.R., Litman, R.E., Konicki, E., Gutierrez, R. and Rapaport, M.H. (1992) Clinical and biologic response to clozapine in patients with schizophrenia. Crossover comparison with fluphenazine. Arch. Gen. Psychiatry, 49: 345–353.

Potkin, S.G., Weinberger, D.R., Linnoila, M. and Wyatt, R.J. (1983) Low CSF 5-hydroxyindoleacetic acid in schizophrenic patients with enlarged cerebral ventricles. Am. J. Psychiatry, 140: 21–25.

Powell, S.B. and Geyer, M.A. (2007) Overview of animal models of schizophrenia. Curr. Protoc. Neurosci., Chapter 9, Unit 9 24.

Pralong, D., Tomaskovic-Crook, E., Opeskin, K., Copolov, D. and Dean, B. (2000) Serotonin(2A) receptors are reduced in the planum temporale from subjects with schizophrenia. Schizophr. Res., 44: 35–45.

Purdon, S.E., Jones, B.D., Stip, E., Labelle, A., Addington, D., David, S.R., Breier, A. and Tollefson, G.D. (2000) Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. The Canadian Collaborative Group for research in schizophrenia. Arch. Gen. Psychiatry, 57: 249–258.

Quednow, B.B., Wagner, M., Westheide, J., Beckmann, K., Bliesener, N., Maier, W. and Kuhn, K.U. (2006) Sensorimotor gating and habituation of the startle response in schizophrenic

patients randomly treated with amisulpride or olanzapine. Biol. Psychiatry, 59: 536–545.
Quednow, B.B., Kuhn, K.U., Mossner, R., Schwab, S. G., Schuhmacher, A., Maier, W. and Wagner, M. (2008) Sensorimotor gating of schizophrenia patients is influenced by 5-HT2A receptor polymorphisms. Biol. Psychiatry, 64: 434–437.
Quednow, B.B., Schmechtig, A., Ettinger, U., Petrovsky, N., Collier, D.A., Vollenweider, F.X., Wagner, M. and Kumari, V. (2009) Sensorimotor gating depends on polymorphisms of the serotonin-2A receptor and catechol-O-methyltransferase, but not on neuregulin-1 Arg38Gln genotype: a replication study. Biol. Psychiatry, 66: 614–620.
Rahman, S. and Neuman, R.S. (1993) Activation of 5-HT2 receptors facilitates depolarization of neocortical neurons by N-methyl-D-aspartate. Eur. J. Pharmacol., 231: 347–354.
Rapport, M.M. (1949) Serum vasoconstrictor (serotonin) the presence of creatinine in the complex; a proposed structure of the vasoconstrictor principle. J. Biol. Chem., 180: 961–969.
Rapport, M.M., Green, A.A. and Page, I.H. (1948) Serum vasoconstrictor, serotonin; isolation and characterization. J. Biol. Chem., 176: 1243–1251.
Renyi, L., Evenden, J.L., Fowler, C.J., Jerning, E., Kelder, D., Lake-Bakaar, D., Larsson, L.G., Mohell, N., Sallemark, M. and Ross, S.B. (2001) The pharmacological profile of (R)-3, 4-dihydro-N-isopropyl-3-(N-isopropyl-N-propylamino)-2H-1-benzopyran-5-carboxamide, a selective 5-hydroxytryptamine(1A) receptor agonist. J. Pharmacol. Exp. Ther., 299: 883–893.
Reuter, M., Ott, U., Vaitl, D. and Hennig, J. (2007) Impaired executive control is associated with a variation in the promoter region of the tryptophan hydroxylase 2 gene. J. Cogn. Neurosci., 19: 401–408.
Reynolds, G.P., Garrett, N.J., Rupniak, N., Jenner, P. and Marsden, C.D. (1983a) Chronic clozapine treatment of rats down-regulates cortical 5-HT2 receptors. Eur. J. Pharmacol., 89: 325–326.
Reynolds, G.P., Rossor, M.N. and Iversen, L.L. (1983b) Preliminary studies of human cortical 5-HT2 receptors and their involvement in schizophrenia and neuroleptic drug action. J. Neural Transm. Suppl., 18: 273–277.
Reynolds, G.P., Beasley, C.L. and Zhang, Z.J. (2002a) Understanding the neurotransmitter pathology of schizophrenia: selective deficits of subtypes of cortical GABAergic neurons. J. Neural Transm., 109: 881–889.
Reynolds, G.P., Zhang, Z.J. and Zhang, X.B. (2002b) Association of antipsychotic drug-induced weight gain with a 5-HT2C receptor gene polymorphism. Lancet, 359: 2086–2087.
Reynolds, G.P., Zhang, Z. and Zhang, X. (2003) Polymorphism of the promoter region of the serotonin 5-HT(2C) receptor gene and clozapine-induced weight gain. Am. J. Psychiatry, 160: 677–679.
Reynolds, G.P., Yao, Z., Zhang, X., Sun, J. and Zhang, Z. (2005) Pharmacogenetics of treatment in first-episode schizophrenia: D3 and 5-HT2C receptor polymorphisms separately associate with positive and negative symptom response. Eur. Neuropsychopharmacol., 15: 143–151.
Reynolds, G.P., Arranz, B., Templeman, L.A., Fertuzinhos, S. and San, L. (2006) Effect of 5-HT1A receptor gene polymorphism on negative and depressive symptom response to antipsychotic treatment of drug-naive psychotic patients. Am. J. Psychiatry, 163: 1826–1829.
Rietschel, M., Naber, D., Fimmers, R., Moller, H.J., Propping, P. and Nothen, M.M. (1997) Efficacy and side-effects of clozapine not associated with variation in the 5-HT2C receptor. Neuroreport, 8: 1999–2003.
Rinkel, M., DeShon, H.J., Hyde, R.W. and Solomon, H.C. (1952) Experimental schizophrenia-like symptoms. Am. J. Psychiatry, 108: 572–578.
Rinkel, M., Hyde, R.W., Solomon, H.C. and Hoagland, H. (1955) Experimental psychiatry. II. Clinical and physiochemical observations in experimental psychosis. Am. J. Psychiatry,, 111: 881–895.
Risch, S.C. (1995) Clozapine therapy and increases in homovanillic acid. Arch. Gen. Psychiatry, 52: 244.
Risch, S.C. and Lewine, R.R. (1993) Low cerebrospinal fluid homovanillic acid-5-hydroxyindoleacetic acid ratio predicts clozapine efficacy: a replication. Arch. Gen. Psychiatry, 50: 670.
Rollema, H., Lu, Y., Schmidt, A.W. and Zorn, S.H. (1997) Clozapine increases dopamine release in prefrontal cortex by 5-HT1A receptor activation. Eur. J. Pharmacol., 338: R3–R5.
Roth, B. and Meltzer, H.Y. (2000) The role of serotonin in schizophrenia. In: Bloom, F.E. and Kupfer, D.J. (Eds.), Psychopharmacology: The Fourth Generation of Progress. American College of Neuropsychopharmacology, Nashville, TN, pp. 1215–1228.
Roth, B.L., Ciaranello, R.D. and Meltzer, H.Y. (1992) Binding of typical and atypical antipsychotic agents to transiently expressed 5-HT1C receptors. J. Pharmacol. Exp. Ther., 260: 1361–1365.
Roth, B.L., Craigo, S.C., Choudhary, M.S., Uluer, A., Monsma, F.J. Jr., Shen, Y., Meltzer, H.Y. and Sibley, D.R. (1994) Binding of typical and atypical antipsychotic agents to 5-hydroxytryptamine-6 and 5-hydroxytryptamine-7 receptors. J. Pharmacol. Exp. Ther., 268: 1403–1410.
Roth, B.L., Hanizavareh, S.M. and Blum, A.E. (2004) Serotonin receptors represent highly favorable molecular targets for cognitive enhancement in schizophrenia and other disorders. Psychopharmacology (Berl.), 174: 17–24.
Scarr, E., Pavey, G., Copolov, D. and Dean, B. (2004) Hippocampal 5-hydroxytryptamine receptors: abnormalities in postmortem brain from schizophrenic subjects. Schizophr. Res., 71: 383–392.
Scheepers, F.E., Gespen de Wied, C.C. and Kahn, R.S. (2001a) The effect of olanzapine treatment on m-chlorophenylpiperazine-induced hormone release in schizophrenia. J. Clin. Psychopharmacol., 21: 575–582.
Scheepers, F.E., Gispen-de Wied, C.C., Westenberg, H.G. and Kahn, R.S. (2001b) The effect of olanzapine treatment on monoamine metabolite concentrations in the cerebrospinal fluid of schizophrenic patients. Neuropsychopharmacology, 25: 468–475.
Schulz, E., Fleischhaker, C., Clement, H.W. and Remschmidt, H. (1997) Blood biogenic amines during clozapine treatment of early-onset schizophrenia. J. Neural Transm., 104: 1077–1089.
Schumacher, J., Schulze, T.G., Wienker, T.F., Rietschel, M. and Nothen, M.M. (2000) Pharmacogenetics of the clozapine response. Lancet, 356: 506–507.
Scruggs, J.L., Schmidt, D. and Deutch, A.Y. (2003) The hallucinogen 1-[2,5-dimethoxy-4-iodophenyl]-2-aminopropane (DOI) increases cortical extracellular glutamate levels in rats. Neurosci. Lett., 346: 137–140.
Seeman, P. (1987) Dopamine receptors and the dopamine hypothesis of schizophrenia. Synapse, 1: 133–152.

Seeman, P. (2002) Atypical antipsychotics: mechanism of action. Can. J. Psychiatry, 47: 27–38.

Seeman, P., Lee, T., Chau-Wong, M. and Wong, K. (1976) Antipsychotic drug doses and neuroleptic/dopamine receptors. Nature, 261: 717–719.

Seeman, P., Guan, H.C. and Van Tol, H.H. (1993) Dopamine D4 receptors elevated in schizophrenia. Nature, 365: 441–445.

Segal, D.S., Geyer, M.A. and Schuckit, M.A. (1981) Stimulant-induced psychosis: An evaluation of animal models. In: Youdim, M.B.H., Lovenberg, W., Sharman, D.F. and Lagnado, J.R. (Eds.), Essays in Neurochemistry and Neuropharmacology. John Wiley & Sons, New York, NY, pp. 95–130.

Segman, R.H. and Lerer, B. (2002) Age and the relationship of dopamine D3, serotonin 2C and serotonin 2A receptor genes to abnormal involuntary movements in chronic schizophrenia. Mol. Psychiatry, 7: 137–139.

Segman, R.H., Ebstein, R.P., Heresco-Levy, U., Gorfine, M., Avnon, M., Gur, E., Nemanov, L. and Lerer, B. (1997) Schizophrenia, chronic hospitalization and the 5-HT2C receptor gene. Psychiatr. Genet., 7: 75–78.

Segman, R.H., Heresco-Levy, U., Finkel, B., Inbar, R., Neeman, T., Schlafman, M., Dorevitch, A., Yakir, A., Lerner, A., Goltser, T., Shelevoy, A. and Lerer, B. (2000) Association between the serotonin 2C receptor gene and tardive dyskinesia in chronic schizophrenia: additive contribution of 5-HT2Cser and DRD3gly alleles to susceptibility. Psychopharmacology (Berl.), 152: 408–413.

Segman, R.H., Heresco-Levy, U., Finkel, B., Goltser, T., Shalem, R., Schlafman, M., Dorevitch, A., Yakir, A., Greenberg, D., Lerner, A. and Lerer, B. (2001) Association between the serotonin 2A receptor gene and tardive dyskinesia in chronic schizophrenia. Mol. Psychiatry, 6: 225–229.

Semwal, P., Prasad, S., Varma, P.G., Bhagwat, A.M., Deshpande, S.N. and Thelma, B.K. (2002) Candidate gene polymorphisms among North Indians and their association with schizophrenia in a case–control study. J. Genet., 81: 65–71.

Serretti, A., Drago, A. and De Ronchi, D. (2007) HTR2A gene variants and psychiatric disorders: a review of current literature and selection of SNPs for future studies. Curr. Med. Chem., 14: 2053–2069.

Shaltiel, G., Shamir, A., Agam, G. and Belmaker, R.H. (2005) Only tryptophan hydroxylase (TPH)-2 is relevant to the CNS. Am. J. Med. Genet. B Neuropsychiatr. Genet., 136B: 106.

Shapiro, D.A., Renock, S., Arrington, E., Chiodo, L.A., Liu, L.X., Sibley, D.R., Roth, B.L. and Mailman, R. (2003) Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. Neuropsychopharmacology, 28: 1400–1411.

Sharma, R.P., Singh, V., Janicak, P.G., Javaid, J.I. and Pandey, G.N. (1999) The prolactin response to fenfluramine in schizophrenia is associated with negative symptoms. Schizophr. Res., 39: 85–89.

Snyder, S.H. (1973) Amphetamine psychosis: a 'model' schizophrenia mediated by catecholamines. Am. J. Psychiatry, 130: 61–67.

Sodhi, M.S. and Sanders-Bush, E. (2004) Serotonin and brain development. Intl. Rev. Neurobiol., 59: 111–174.

Sodhi, M.S., Arranz, M.J., Curtis, D., Ball, D.M., Sham, P., Roberts, G.W., Price, J., Collier, D.A. and Kerwin, R.W. (1995) Association between clozapine response and allelic variation in the 5-HT2C receptor gene. Neuroreport, 7: 169–172.

Spurlock, G., Heils, A., Holmans, P., Williams, J., D'Souza, U.M., Cardno, A., Murphy, K.C., Jones, L., Buckland, P.R., McGuffin, P., Lesch, K.P. and Owen, M.J. (1998) A family based association study of T102C polymorphism in 5HT2A and schizophrenia plus identification of new polymorphisms in the promoter. Mol. Psychiatry, 3: 42–49.

Stoll, W.A. (1947) Lysergsäure-diäthylamid, ein Phantastikum aus der Mutterkorngruppe. Schweiz Arch. Neurol. Psychiatr., 60: 279–323.

Stoll, W.A. (1949) Ein neues, in sehr kleinen Mengen wirksames Phantastikum. Schweiz Arch. Neurol. Psychiatr., 64: 483–484.

Strassman, R.J. (1995) Hallucinogenic drugs in psychiatric research and treatment. Perspectives and prospects. J. Nerv. Ment. Dis., 183: 127–138.

Strassman, R.J., Qualls, C.R., Uhlenhuth, E.H. and Kellner, R. (1994) Dose–response study of N,N-dimethyltryptamine in humans. II. Subjective effects and preliminary results of a new rating scale. Arch. Gen. Psychiatry, 51: 98–108.

Sumiyoshi, T., Stockmeier, C.A., Overholser, J.C., Dilley, G.E. and Meltzer, H.Y. (1996) Serotonin1A receptors are increased in postmortem prefrontal cortex in schizophrenia. Brain Res., 708: 209–214.

Sumiyoshi, T., Matsui, M., Nohara, S., Yamashita, I., Kurachi, M., Sumiyoshi, C., Jayathilake, K. and Meltzer, H.Y. (2001a) Enhancement of cognitive performance in schizophrenia by addition of tandospirone to neuroleptic treatment. Am. J. Psychiatry, 158: 1722–1725.

Sumiyoshi, T., Matsui, M., Yamashita, I., Nohara, S., Kurachi, M., Uehara, T., Sumiyoshi, S., Sumiyoshi, C. and Meltzer, H.Y. (2001b) The effect of tandospirone, a serotonin(1A) agonist, on memory function in schizophrenia. Biol. Psychiatry, 49: 861–868.

Sumiyoshi, T., Park, S., Jayathilake, K., Roy, A., Ertugrul, A. and Meltzer, H.Y. (2007) Effect of buspirone, a serotonin1A partial agonist, on cognitive function in schizophrenia: a randomized, double-blind, placebo-controlled study. Schizophr. Res., 95: 158–168.

Suzuki, T., Iwata, N., Kitamura, Y., Kitajima, T., Yamanouchi, Y., Ikeda, M., Nishiyama, T., Kamatani, N. and Ozaki, N. (2003) Association of a haplotype in the serotonin 5-HT4 receptor gene (HTR4) with Japanese schizophrenia. Am. J. Med. Genet. B Neuropsychiatr. Genet., 121B: 7–13.

Swerdlow, N.R. and Geyer, M.A. (1998) Using an animal model of deficient sensorimotor gating to study the pathophysiology and new treatments of schizophrenia. Schizophr. Bull., 24: 285–301.

Swerdlow, N.R., Geyer, M.A. and Braff, D.L. (2001) Neural circuit regulation of prepulse inhibition of startle in the rat: current knowledge and future challenges. Psychopharmacology (Berl.), 156: 194–215.

Szymanski, S., Lieberman, J., Pollack, S., Munne, R., Safferman, A., Kane, J., Kronig, M. and Cooper, T. (1993) The dopamine–serotonin relationship in clozapine response. Psychopharmacology (Berl.), 112: S85–S89.

Tamminga, C.A. and Holcomb, H.H. (2005) Phenotype of schizophrenia: a review and formulation. Mol. Psychiatry, 10: 27–39.

Tan, E.C., Chong, S.A., Mahendran, R., Dong, F. and Tan, C.H. (2001) Susceptibility to neuroleptic-induced tardive dyskinesia and the T102C polymorphism in the serotonin type 2A receptor. Biol. Psychiatry, 50: 144–147.

Tauscher, J., Kapur, S., Verhoeff, N.P., Hussey, D.F., Daskalakis, Z.J., Tauscher-Wisniewski, S., Wilson, A.A., Houle, S., Kasper, S. and Zipursky, R.B. (2002) Brain serotonin 5-HT(1A) receptor

binding in schizophrenia measured by positron emission tomography and [11C]WAY-100635. Arch. Gen. Psychiatry, 59: 514–520.

Templeman, L.A., Reynolds, G.P., Arranz, B. and San, L. (2005) Polymorphisms of the 5-HT2C receptor and leptin genes are associated with antipsychotic drug-induced weight gain in Caucasian subjects with a first-episode psychosis. Pharmacogenet. Genomics, 15: 195–200.

Theisen, F.M., Hinney, A., Bromel, T., Heinzel-Gutenbrunner, M., Martin, M., Krieg, J.C., Remschmidt, H. and Hebebrand, J. (2004) Lack of association between the -759C/T polymorphism of the 5-HT2C receptor gene and clozapine-induced weight gain among German schizophrenic individuals. Psychiatr. Genet., 14: 139–142.

Tilson, H.A., Baker, T.G. and Chamberlain, J.H. (1975) Behavioral and neuropharmacological analysis of amphetamine and 2,5-dimethoxy-4-methylamphetamine in rats. Psychopharmacologia, 44: 229–239.

Tollefson, G.D. and Sanger, T.M. (1997) Negative symptoms: a path analytic approach to a double-blind, placebo- and haloperidol-controlled clinical trial with olanzapine. Am. J. Psychiatry, 154: 466–474.

Trichard, C., Paillere-Martinot, M.L., Attar-Levy, D., Blin, J., Feline, A. and Martinot, J.L. (1998) No serotonin 5-HT2A receptor density abnormality in the cortex of schizophrenic patients studied with PET. Schizophr. Res., 31: 13–17.

Tsai, S.J., Hong, C.J., Yu, Y.W., Lin, C.H., Song, H.L., Lai, H.C. and Yang, K.H. (2000) Association study of a functional serotonin transporter gene polymorphism with schizophrenia, psychopathology and clozapine response. Schizophr. Res., 44: 177–181.

Tsai, S.J., Hong, C.J., Yu, Y.W. and Lin, C.H. (2002) − 759C/T genetic variation of 5HT(2C) receptor and clozapine-induced weight gain. Lancet, 360: 1790.

Tuckwell, H.C. and Koziol, J.A. (1993) A meta-analysis of homovanillic acid concentrations in schizophrenia. Int. J. Neurosci., 73: 109–114.

Tuckwell, H.C. and Koziol, J.A. (1996) On the concentration of 5-hydroxyindoleacetic acid in schizophrenia: a meta-analysis. Psychiatry Res., 59: 239–244.

Twarog, B.M. and Page, I.H. (1953) Serotonin content of some mammalian tissues and urine and a method for its determination. Am. J. Physiol., 175: 157–161.

van der Heijden, F.M., Tuinier, S., Fekkes, D., Sijben, A.E., Kahn, R.S. and Verhoeven, W.M. (2004) Atypical antipsychotics and the relevance of glutamate and serotonin. Eur. Neuropsychopharmacol., 14: 259–265.

van Kammen, D.P., Peters, J. and van Kammen, W.B. (1986) Cerebrospinal fluid studies of monoamine metabolism in schizophrenia. Psychiatr. Clin. North Am., 9: 81–97.

van Rossum, J.M. (1966) The significance of dopamine-receptor blockade for the mechanism of action of neuroleptic drugs. Arch. Int. Pharmacodyn. Ther., 160: 492–494.

Varty, G.B., Bakshi, V.P. and Geyer, M.A. (1999) M100907, a serotonin 5-HT2A receptor antagonist and putative antipsychotic, blocks dizocilpine-induced prepulse inhibition deficits in Sprague-Dawley and Wistar rats. Neuropsychopharmacology, 20: 311–321.

Verhoeff, N.P., Meyer, J.H., Kecojevic, A., Hussey, D., Lewis, R., Tauscher, J., Zipursky, R.B. and Kapur, S. (2000) A voxel-by-voxel analysis of [18F]setoperone PET data shows no substantial serotonin 5-HT(2A) receptor changes in schizophrenia. Psychiatry Res., 99: 123–135.

Vollenweider, F.X. and Geyer, M.A. (2001) A systems model of altered consciousness: integrating natural and drug-induced psychoses. Brain Res. Bull., 56: 495–507.

Vollenweider, F.X., Leenders, K.L., Scharfetter, C., Maguire, P., Stadelmann, O. and Angst, J. (1997a) Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. Neuropsychopharmacology, 16: 357–372.

Vollenweider, F.X., Leenders, K.L., Scharfetter, C., Antonini, A., Maguire, P., Missimer, J. and Angst, J. (1997b) Metabolic hyperfrontality and psychopathology in the ketamine model of psychosis using positron emission tomography (PET) and [18F]fluorodeoxyglucose (FDG). Eur. Neuropsychopharmacol., 7: 9–24.

Vollenweider, F.X., Vollenweider-Scherpenhuyzen, M.F., Babler, A., Vogel, H. and Hell, D. (1998) Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. Neuroreport, 9: 3897–3902.

Vollenweider, F.X., Csomor, P.A., Knappe, B., Geyer, M.A. and Quednow, B.B. (2007) The effects of the preferential 5-HT2A agonist psilocybin on prepulse inhibition of startle in healthy human volunteers depend on interstimulus interval. Neuropsychopharmacology, 32: 1876–1887.

Wagner, M., Quednow, B.B., Westheide, J., Schlaepfer, T.E., Maier, W. and Kuhn, K.U. (2005) Cognitive improvement in schizophrenic patients does not require a serotonergic mechanism: randomized controlled trial of olanzapine vs amisulpride. Neuropsychopharmacology, 30: 381–390.

Wang, L., Fang, C., Zhang, A., Du, J., Yu, L., Ma, J., Feng, G., Xing, Q. and He, L. (2008) The −1019 C/G polymorphism of the 5-HT(1)A receptor gene is associated with negative symptom response to risperidone treatment in schizophrenia patients. J. Psychopharmacol., 22: 904–909.

Weinberger, R.D. and Laruelle, M. (2002) Neurochemical and neuropharmacological imaging in schizophrenia. In: Davis, K.L., Charney, D.S., Coyle, J.T. and Nemeroff, C.B. (Eds.), Neuropsychopharmacology: The Fifth Generation of Progress. Lippincott, Williams and Wilkins, Philadelphia, PA, pp. 833–855.

Weinberger, D.R., Berman, K.F. and Illowsky, B.P. (1988) Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. III. A new cohort and evidence for a monoaminergic mechanism. Arch. Gen. Psychiatry, 45: 609–615.

Weinberger, D.R., Berman, K.F., Suddath, R. and Torrey, E.F. (1992) Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: a magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins. Am. J. Psychiatry, 149: 890–897.

Whitaker, P.M., Crow, T.J. and Ferrier, I.N. (1981) Tritiated LSD binding in frontal cortex in schizophrenia. Arch. Gen. Psychiatry, 38: 278–280.

Wieselgren, I.M. and Lindstrom, L.H. (1998) CSF levels of HVA and 5-HIAA in drug-free schizophrenic patients and healthy controls: a prospective study focused on their predictive value for outcome in schizophrenia. Psychiatry Res., 81: 101–110.

Wilmot, C.A. and Szczepanik, A.M. (1989) Effects of acute and chronic treatments with clozapine and haloperidol on serotonin (5-HT2) and dopamine (D2) receptors in the rat brain. Brain Res., 487: 288–298.

Winblad, B., Bucht, G., Gottfries, C.G. and Roos, B.E. (1979) Monoamines and monoamine metabolites in brains from demented schizophrenics. Acta Psychiatr. Scand., 60: 17–28.

Winter, J.C., Doat, M. and Rabin, R.A. (2000) Potentiation of DOM-induced stimulus control by non-competitive NMDA antagonists: a link between the glutamatergic and serotonergic hypotheses of schizophrenia. Life Sci., 68: 337–344.

Winter, J.C., Eckler, J.R. and Rabin, R.A. (2004) Serotonergic/glutamatergic interactions: the effects of mGlu2/3 receptor ligands in rats trained with LSD and PCP as discriminative stimuli. Psychopharmacology (Berl.), 172: 233–240.

Wong, D.F., Wagner, H.N. Jr., Tune, L.E., Dannals, R.F., Pearlson, G.D., Links, J.M., Tamminga, C.A., Broussolle, E.P., Ravert, H.T., Wilson, A.A., Toung, J.K., Malat, J., Williams, J.A., O'Tuama, L.A., Snyder, S.H., Kuhar, M.J. and Gjedde, A. (1986) Positron emission tomography reveals elevated D2 dopamine receptors in drug-naive schizophrenics. Science, 234: 1558–1563.

Wood, S.J., Berger, G., Velakoulis, D., Phillips, L.J., McGorry, P.D., Yung, A.R., Desmond, P. and Pantelis, C. (2003) Proton magnetic resonance spectroscopy in first episode psychosis and ultra high-risk individuals. Schizophr. Bull., 29: 831–843.

Woolley, D.W. (1962) The Biochemical Bases of Psychosis or the Serotonin Hypothesis about Mental Disease. John Wiley & Sons, New York, NY.

Woolley, D.W. and Shaw, E. (1953) Antimetabolites of serotonin. J. Biol. Chem., 203: 69–79.

Woolley, D.W. and Shaw, E. (1954) Some neurophysiological aspects of serotonin. Br. Med. J., 2: 122–126.

Yasuno, F., Suhara, T., Nakayama, T., Ichimiya, T., Okubo, Y., Takano, A., Ando, T., Inoue, M., Maeda, J. and Suzuki, K. (2003) Inhibitory effect of hippocampal 5-HT1A receptors on human explicit memory. Am. J. Psychiatry, 160: 334–340.

Yasuno, F., Suhara, T., Ichimiya, T., Takano, A., Ando, T. and Okubo, Y. (2004) Decreased 5-HT1A receptor binding in amygdala of schizophrenia. Biol. Psychiatry, 55: 439–444.

Yu, Y.W., Tsai, S.J., Lin, C.H., Hsu, C.P., Yang, K.H. and Hong, C.J. (1999) Serotonin-6 receptor variant (C267T) and clinical response to clozapine. Neuroreport, 10: 1231–1233.

Yu, Y.W., Tsai, S.J., Yang, K.H., Lin, C.H., Chen, M.C. and Hong, C.J. (2001) Evidence for an association between polymorphism in the serotonin-2A receptor variant (102T/C) and increment of N100 amplitude in schizophrenics treated with clozapine. Neuropsychobiology, 43: 79–82.

Zhang, C. and Marek, G.J. (2008) AMPA receptor involvement in 5-hydroxytryptamine2A receptor-mediated pre-frontal cortical excitatory synaptic currents and DOI-induced head shakes. Prog. Neuropsychopharmacol. Biol. Psychiatry, 32: 62–71.

Zhang, X., Beaulieu, J.M., Gainetdinov, R.R. and Caron, M.G. (2006) Functional polymorphisms of the brain serotonin synthesizing enzyme tryptophan hydroxylase-2. Cell. Mol. Life Sci., 63: 6–11.

Zhang, Z.J., Zhang, X.B., Sha, W.W., Zhang, X.B. and Reynolds, G.P. (2002) Association of a polymorphism in the promoter region of the serotonin 5-HT2C receptor gene with tardive dyskinesia in patients with schizophrenia. Mol. Psychiatry, 7: 670–671.

Zill, P., Buttner, A., Eisenmenger, W., Moller, H.J., Ackenheil, M. and Bondy, B. (2007) Analysis of tryptophan hydroxylase I and II mRNA expression in the human brain: a post-mortem study. J. Psychiatr. Res., 41: 168–173.

Zipursky, R.B., Meyer, J.H. and Verhoeff, N.P. (2007) PET and SPECT imaging in psychiatric disorders. Can. J. Psychiatry, 52: 146–157.

Zureick, J.L. and Meltzer, H.Y. (1988) Platelet MAO activity in hallucinating and paranoid schizophrenics: a review and meta-analysis. Biol. Psychiatry, 24: 63–78.