Review

Psychedelics and schizophrenia

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Research on psychedelics such as lysergic acid diethylamide (LSD) and dissociative drugs such as phencyclidine (PCP) and the symptoms, neurochemical abnormalities and treatment of schizophrenia have converged. The effects of hallucinogenic drugs resemble some of the core symptoms of schizophrenia. Some atypical antipsychotic drugs were identified by their high affinity for serotonin 5-HT_{2A} receptors, which is also the target of LSD-like drugs. Several effects of PCP-like drugs are strongly affected by both 5-HT_{2A} and metabotropic glutamate 2/3 receptor modulation. A serotonin–glutamate receptor complex in cortical pyramidal neurons has been identified that might be the target both of psychedelics and the atypical and glutamate classes of antipsychotic drugs. Recent results on the receptor, signalling and circuit mechanisms underlying the response to psychedelic and antipsychotic drugs might lead to unification of the serotonin and glutamate neurochemical hypotheses of schizophrenia.

Introduction

Schizophrenia is a chronic mental illness affecting nearly 1% of the population [1,2]. Its precise causes are unknown, but epidemiological approaches indicate an increased risk associated with both genetic and environmental factors [3,4]. After the onset of schizophrenia, usually in late adolescence or early adulthood, its severely disabling symptoms usually persist for life. Antipsychotic medications currently available are often only partially successful. Some patients are unresponsive to therapy, and suicide is a leading cause of premature death in schizophrenic patients [5].

Unlike the chronic neurodegenerative diseases Alzheimer's and Parkinson's, schizophrenia lacks both diagnostic neuropathological changes and genetic animal models. For several decades schizophrenia research has focused on neurochemical hypotheses and models, based largely on the pharmacology of antipsychotic medications and of certain drugs of abuse. An interest in dopamine resulted from the observation that early antipsychotic medications such as chlorpromazine and haloperidol shared a capacity to block dopamine D_2 receptors. Furthermore, amphetamines, which increase synaptic dopamine, aggravate schizophrenic symptoms [1]. However, an exclusive emphasis on dopamine and the D_2 receptor is difficult to reconcile with the lack of antipsychotic properties of some potent dopamine D_2 receptor antagonists such as eticlopride. Also, postmortem brain and positron emission tomographic (PET) studies have not consistently found upregulation or higher activity of D_2 receptors. Roles for serotonin and for glutamate in the pathophysiology of schizophrenia have also been proposed [6–8]. Abnormalities of serotonin in schizophrenia were indicated by the finding that second-generation antipsychotics such as clozapine or olanzapine have lower affinity for the D_2 receptor than for the serotonin 5-HT_{2A} receptor. Glutamate has been implicated by the schizophrenia-like state elicited by drugs of abuse that inhibit the *N*-methyl-D-aspartate (NMDA) subtype of the glutamate receptor. Here, we discuss recent findings that provide insight into the related neurochemical mechanisms of psychedelics and of some classes of antipsychotic drugs.

Psychotomimetic drug models of psychosis

Because schizophrenia is a uniquely human disorder, it is difficult to judge the similitude of rodent models that attempt to recapitulate aspects of its behavioural alterations [9]. Animal models derive from the similarity of the human effects of psychotomimetic drugs to the symptoms of schizophrenia. The manifestations of schizophrenia are divided into 'positive' symptoms (e.g. hallucinations, delusions and other thought disorders) and 'negative' symptoms (e.g. social withdrawal, apathy and abnormal emotional responses). The human psychoactive effects of drugs such as phencyclidine (PCP) and lysergic acid diethylamide (LSD) include perceptual disturbances, sensory processing, cognition, changes in brain metabolism and self-representation (see Box 1 for chemical names). Dissociative PCP-like drugs (e.g. ketamine and MK801) are non-competitive antagonists at glutamate NMDA receptors [10], whereas psychedelic drugs such as LSD, mescaline and psilocybin act as agonists at 5-HT_{2A} receptors [11–14]. PCP-like drugs are extensively used as schizophrenia models because of their ability to evoke positive and negative symptoms and cognitive deficits similar to those of the illness [10,15]. To date, the PCP model of psychosis has been proposed to be one of the best pharmacological models to mimic schizophrenic psychosis in healthy volunteers. Interestingly, recent studies indicate that the psychoactive effects of PCP and LSD model different clinical features and/or subtypes of schizophrenia. PCP psychosis reflects more of the negative schizophrenia symptoms together with certain catatonic symptoms, whereas LSD elicits neuropsychological responses that could be a better model for the paranoid type of schizophrenia [16–19]. Psychedelics tend to induce visual perceptual disturbances, whereas schizophrenia is more commonly associated with auditory hallucinations. However, similar to the effects of psychedelics, the symptoms of

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Box 1. Pharmaceutical agents and their full chemical names

5-HTP: L-5-hydroxytryptophan
DOB: 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane
DOI: 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane
DOM: 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane
LSD: lysergic acid diethylamide
LY314582: [±]-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid
LY341495: 2*S*-2-amino-2-[1*S*,2*S*-2-carboxycyclopropan-1-yl]-3-[xanth-9-yl]propionic acid
LY379268: (–)-2-oxa-4-aminobicyclo [3,1,0]hexane-4,6-dicarboxylic acid
LY404039: (–)-(1*R*,4*S*,5*S*,6*S*)-4-amino-2-sulfonylbicyclo[3.1.0]hexane-4,6-dicarboxylic acid
MK801 (dizocilpine): (5*R*,10*S*)-(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine
PCP (phencyclidine): 1-(1-phenylcyclohexyl)-piperidine

early schizophrenia more often include visual disturbances. As described later, recent work on the neurobiological effects of both LSD-like and PCP-like drugs in animal models provides insight into possible related mechanisms underlying psychosis.

The cortical 5-HT$_{2A}$ receptor mediates the responses induced by LSD-like drugs

5-HT$_{2A}$ receptor knockout mice are insensitive to the behavioural effects of psychedelics [13,14]. This observation is consistent with studies showing that pharmacological inactivation of 5-HT$_{2A}$ receptor signalling blocks the behavioural effects of hallucinogens in a variety of species including humans [18,20]. Some studies indicated that the effects of LSD-like drugs resulted from actions at presynaptic 5-HT$_{2A}$ receptors expressed by thalamocortical neurons [21–23]. However, recent work from several laboratories using different experimental approaches, including a systems pharmacology method termed transcriptome fingerprint [14] (Figure 1), a genetic strategy to express 5-HT$_{2A}$ receptors primarily in mouse cortical neurons [13], electrophysiological recordings in mouse cortical slices [24] and electrolytic lesions in the thalamic nuclei [25,26], identify the 5-HT$_{2A}$ receptor expressed by cortical pyramidal neurons as required and sufficient for the cellular and behavioural responses to psychedelics (Figure 2a). Overall, a preponderance of evidence indicates that the schizophrenia-related psychosis elicited by LSD-like drugs results from the drug complexing with postsynaptic cortical 5-HT$_{2A}$ receptors.

Although the effects of LSD-like drugs require activating the 5-HT$_{2A}$ receptor, closely related non-hallucinogenic chemicals such as lisuride and ergotamine have similar 5-HT$_{2A}$ pharmacology but lack comparable neuropsychological effects. Recent results showing that the pattern of signalling elicited by LSD-like drugs acting at the 5-HT$_{2A}$ receptor on cortical pyramidal neurons differs from that of structurally related non-psychedelic 5-HT$_{2A}$ receptors agonists might resolve this longstanding paradox. Whereas the hallucinogens cause activation of both $G_{q/11}$ and $G_{i/o}$ subtype G proteins, the non-hallucinogens activate only $G_{q/11}$ [14]. These results indicate that the mechanism underlying the differences between hallucinogenic and non-hallucinogenic 5-HT$_{2A}$ receptor agonists are consistent with a pharmacological model termed 'agonist trafficking of receptor signalling'. In this model, the receptor has more than a single 'on' state, each of which can be selected by different activating drugs leading to distinct patterns of cell signalling and response [13,14,27] (Box 2).

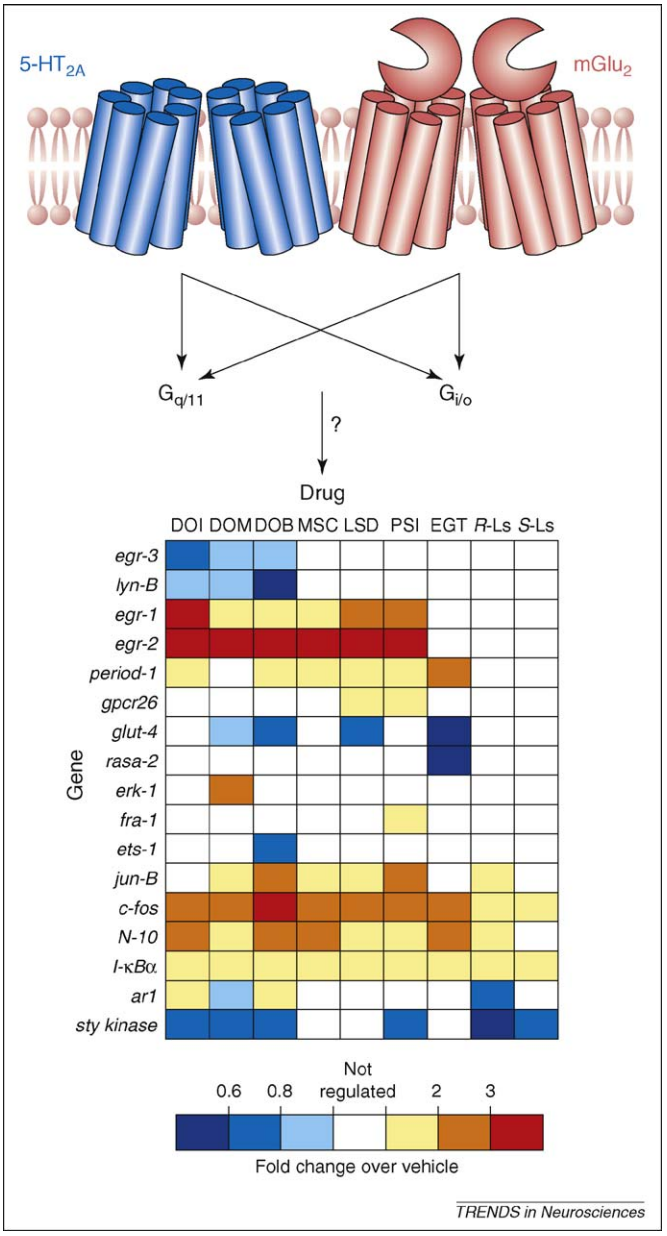

Figure 1. Transcriptome fingerprint (TFP) induced by hallucinogenic and non-hallucinogenic 5-HT$_{2A}$ receptor agonists in the mouse cortex. Gene reporter constructs are extensively used to monitor GPCR activation in tissue culture systems [75]. TFP represents a high-throughput systems-pharmacology-based approach to measure the complex signalling effects of neuroactive chemicals in the mouse brain. The head-twitch response is a mouse behaviour that is induced by 5-HT$_{2A}$ receptor hallucinogenic agonists such as DOI, DOM, DOB, mescaline (MSC), LSD and psilocin (PSI) and not induced by closely related 5-HT$_{2A}$ receptor non-hallucinogenic agonists such as ergotamine (EGT), *R*-lisuride (*R*-Ls) and *S*-lisuride (*S*-Ls) [14,29]. The TFP approach provides an efficient and unbiased search for commonalities among the patterns of response of the psychoactive chemicals in comparison with reference compounds of known properties. As can be seen in the TFP heatmap, there are common cortex signalling responses elicited by all the 5-HT$_{2A}$ receptor agonists and specific responses just elicited by the six hallucinogenic drugs assayed. The common response seems to be due to $G_{q/11}$ protein activation and the hallucinogen-specific response to $G_{i/o}$ protein activation. Further investigation is needed to understand the role of the 5-HT$_{2A}$–mGlu$_2$ receptor complex in the TFP pattern induced by hallucinogenic and non-hallucinogenic 5-HT$_{2A}$ receptor ligands in the mouse brain cortex, in addition to the heterotrimeric G proteins and signalling pathways responsible for psychosis-like states. The question mark indicates that the precise pathways leading from activation of the G proteins to the characteristic gene expression fingerprints in cortical neurons are not known.

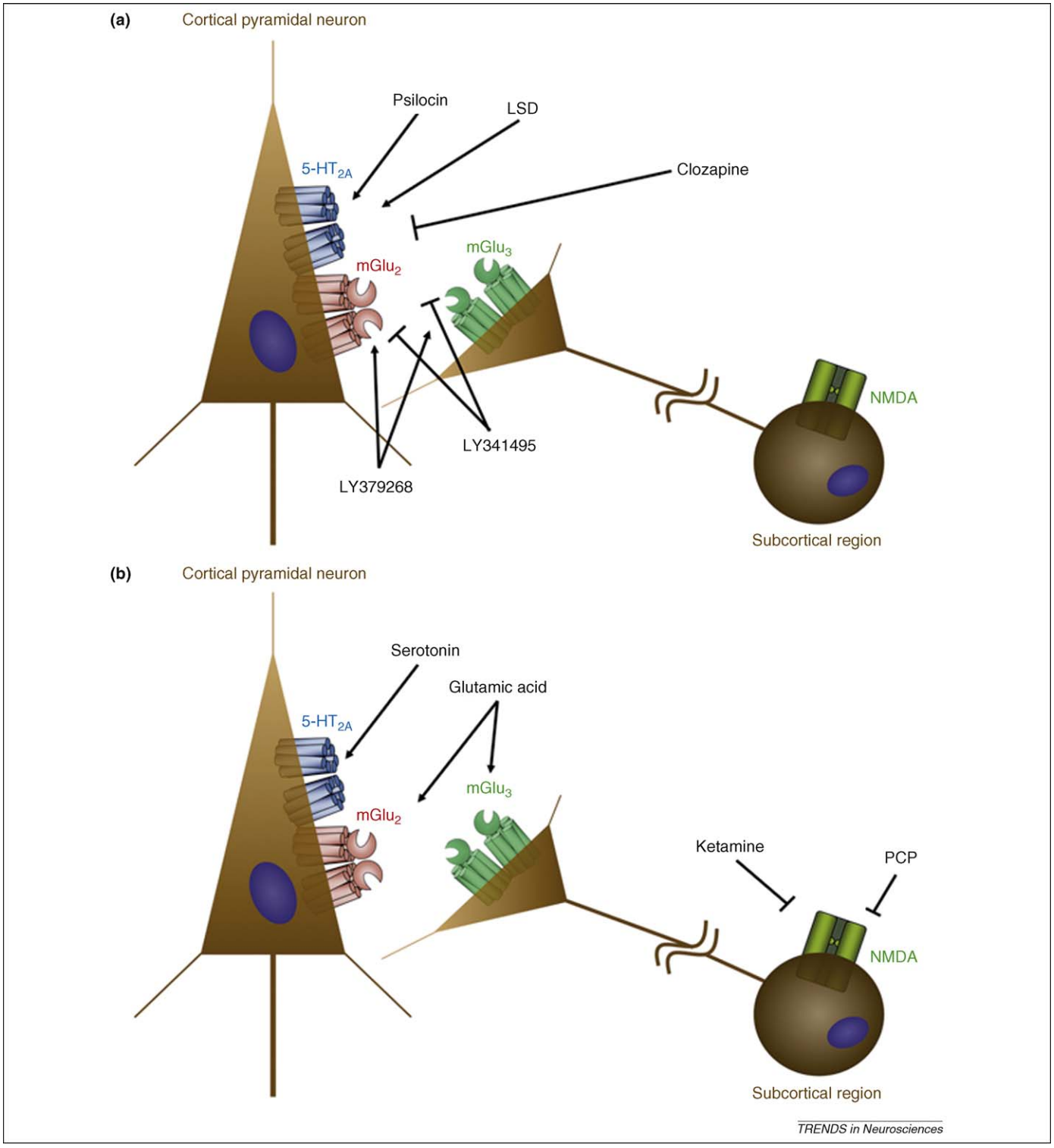

Figure 2. Neuronal circuits implicated in the responses induced by psychoactive chemicals and antipsychotic drugs. Results in tissue culture and murine models suggest that the 5-HT_{2A}–$mGlu_2$ receptor complex expressed by cortical pyramidal neurons represents the target of both psychoactive 5-HT_{2A} receptor agonists and $mGlu_2$ receptor antagonists, in addition to antipsychotic 5-HT_{2A} receptor antagonists and $mGlu_2$ receptor agonists **(a)**. The serotonin and glutamate release induced in the cortex by PCP-like psychoactive drugs targeting subcortical NMDA receptors might affect the signalling properties of the cortical 5-HT_{2A}–$mGlu_2$ receptor complex **(b)**. Concurrently, these results indicate that both LSD-like and PCP-like psychoactive drugs dysregulate the signalling properties of cortical pyramidal neurons and affect cognition and perception processes in the brain cortex. See Box 1 for chemical names.

The idea that there is a hallucinogen-specific signalling caused by psychedelics acting at the 5-HT_{2A} receptor dovetails with the observation that some antipsychotics were discovered by their capacity to block the effects of LSD [28]. Furthermore, the level of expression of 5-HT_{2A} receptors has been reported to be upregulated in postmortem human brain cortex of young untreated schizophrenic subjects when assayed by radioligand-binding approaches [29] (Box 3). These findings indicate that altered 5-HT_{2A} receptor signalling might be involved in some of the psychotic symptoms in patients with schizophrenia. However, some chemicals that are high-affinity 5-HT_{2A} receptor

Box 2. Agonist trafficking of receptor signalling

The most accepted pharmacological model to study agonist–receptor interactions and functional responses is the ternary complex model [76]. This model postulates that the GPCR is in equilibrium between two conformational states: inactive (R) and active (R*). Antagonists present the same affinity for both R and R*, and agonists present a higher affinity for R*, stabilizing the structural conformation and displacing the equilibrium to the active state. *In silico* pharmacological approaches generated the hypothesis that GPCRs are in equilibrium between multiple active and inactive conformational states – a concept termed 'agonist trafficking of receptor signalling' [27]. In this model, different agonists preferentially stabilize different active conformational states, which, in turn, preferentially interact with different G-protein subtypes. Thus, this model provides a mechanism whereby different agonists acting at the same receptor can induce different cellular signalling responses. The agonist trafficking of a receptor signalling model has been demonstrated *in vitro* for several GPCR subtypes [27,77]. Hallucinogenic and non-hallucinogenic 5-HT_{2A} receptor agonists represent an attractive experimental system to investigate agonist trafficking because of their similarities in chemical structures, pharmacological profiles and signalling responses induced in tissue cultures but divergence in the behavioural responses elicited. Recent studies indicate that the mechanism of action of hallucinogenic drugs is based on agonist trafficking and propose, based on results in tissue cultures and murine models, that LSD-like hallucinogens and lisuride-like non-hallucinogens stabilize distinct active 5-HT_{2A} receptor conformations, modulating different patterns of signalling responses responsible for their unique behavioural effects [13,69].

Box 3. Level of expression of the 5-HT_{2A} receptor in the schizophrenia brain

Neurobiological and clinical findings suggest that the 5-HT_{2A} receptor is involved in some of the symptoms of schizophrenia patients. Thus, activation of 5-HT_{2A} receptors by LSD-like drugs induces schizophrenia-like psychosis in humans [19], the cortical 5-HT_{2A} receptor is necessary for the cellular and behavioural effects induced by LSD-like drugs [13], atypical antipsychotics all exhibit a high-affinity blocking 5-HT_{2A} receptors [1] and the function of the $mGlu_2$ receptor inhibiting the responses induced by the 5-HT_{2A} receptor might represent the signalling mechanism by which LY404039 caused its antipsychotic effects in clinical trials [8,29]. Based on these findings, it could be expected that the level of expression of 5-HT_{2A} receptors might be higher in the postmortem human brain cortex of schizophrenic subjects. The onset of schizophrenia is in adolescence or young adulthood, and there is an association between fewer positive symptoms and increased age among schizophrenic patients, which correlates with the lower level of expression of 5-HT_{2A} receptor in older subjects [29]. In concordance with the hypothesis described above, the level of expression of 5-HT_{2A} receptor determined by [^{3}H]ketanserin-binding saturation curves in membrane preparations was significantly higher in the postmortem human brain of young, untreated schizophrenic subjects compared with individually matched control subjects [29]. It is important to note that 11 out of 13 schizophrenia cases included in this study committed suicide [29], and, therefore, further investigation is required because suicidal behaviour might affect the level of expression of 5-HT_{2A} receptor [78,79]. Several publications have reported either unaffected or lower densities of 5-HT_{2A} receptor in the schizophrenia brain [80–84]. It has been demonstrated that demographic variables intrinsic to the postmortem human brain studies affect the biochemical parameters in brain tissue samples [29,85]. Therefore, the higher level of expression of the 5-HT_{2A} receptor in the schizophrenia brain would be unlikely to be observed in samples from heterogeneous groups including treated patients [80–82] or in studies including older patients [81,84]. A recent PET study using the 5-HT_{2A} receptor antagonist [^{18}F]altaserin in a group of first-episode antipsychotic-naïve schizophrenic patients and matched controls reported significantly increased 5-HT_{2A} receptor binding in the caudate nucleus and no differences in 5-HT_{2A} receptor binding in cortical regions [86]. However, even though 5-HT_{2A} receptor binding values did not reach the statistical significance in the cortex, [^{18}F]altaserin binding was higher in 12 out of the 13 tested cortical regions [86]. Although further investigation is required, radioligand-binding assays and PET results indicate a higher density of 5-HT_{2A} receptor in young untreated schizophrenic subjects, which correlates with the blockage of the 5-HT_{2A} receptor by atypical antipsychotics and its activation by psychotomimetics.

antagonists, such as M100907, show limited antipsychotic efficacy in schizophrenia clinical trials [30]. Similar results have also been reported with the selective 5-HT_{2A} receptor antagonist eplivanserin [19]. All atypical antipsychotics, such as olanzapine, clozapine and quetiapine, have in common a high affinity for the 5-HT_{2A} receptor and a modest affinity for the dopamine D_2 receptor [6]. The pharmacology of antipsychotic drugs is further complicated by their binding to many other G-protein-coupled receptor (GPCR) subtypes [31]. Recent studies indicating functional interactions between serotonin and glutamate might help to clarify the mechanisms of antipsychotic drugs and provide new strategies to develop anti-schizophrenia drugs.

Serotonin and glutamate functional interactions

The function of the neurotransmitter serotonin in brain has been strongly associated with specific physiological responses, ranging from modulation of neuronal activity and transmitter release to behavioural changes [23]. Glutamate serves as the principal neurotransmitter of the pyramidal cells, which are the sources of efferent and interconnecting pathways of the cerebral cortex and limbic systems (brain regions implicated in the pathophysiology of schizophrenia). Recently, functional and behavioural interactions between 5-HT_{2A}, NMDA and metabotropic glutamate subtypes 2 and 3 ($mGlu_{2/3}$) receptors have been identified, which might help to unravel the molecular basis of cognitive dysfunction in schizophrenia.

Crosstalk between 5-HT_{2A} and $mGlu_{2/3}$ receptors

The detection of functional interactions between 5-HT_{2A} and $mGlu_{2/3}$ receptors in the rat prefrontal cortex by electrophysiological approaches [32] led to the demonstration of myriad cellular [29,33–35], electrophysiological [21,25,32,36] and behavioural [29,33,37–41] crosstalk between these two receptor subtypes.

One hypothesis to explain how $mGlu_{2/3}$ receptor activation abolishes the responses induced by LSD-like drugs is that the activation of the presynaptic $mGlu_{2/3}$ receptor inhibits glutamate release from cortical terminals induced by activity at 5-HT_{2A} receptors, which are expressed by neurons whose cell bodies are located in thalamic nuclei [21–23,42,43]. However, although 5-HT_{2A} receptors are located both postsynaptically and presynaptically on thalamocortical neurons, the largest concentration of 5-HT_{2A} receptors in the cortex are expressed by intrinsic pyramidal neurons [44,45]. $mGlu_2$-receptor-like immunoreactivity in the cortex is located not only presynaptically but also postsynaptically, whereas $mGlu_3$-receptor-like immunoreactivity distribution is mainly presynaptic [46–48]. The neuroanatomical distribution of 5-HT_{2A}, $mGlu_2$ and $mGlu_3$ receptors raised the possibility of a

direct interaction between postsynaptic cortical 5-HT_{2A} and $mGlu_2$ receptors, which are both highly expressed by pyramidal neurons.

Recent studies have demonstrated that some GPCR form dimers or, potentially, higher-order oligomers [49,50]. The concept of GPCRs as functional dimers and/or oligomers is now well established [51]. The formation of GPCR heterodimers and/or heterocomplexes can affect the ligand-binding properties and the functional responses of the individual receptor components [52]. 5-HT_{2A} and $mGlu_2$ receptors form a functional receptor heterocomplex in the mouse and human brain [29]. Experiments indicate that the heterotrimeric G proteins and signalling pathways specifically activated by LSD-like 5-HT_{2A} receptor agonists in cortical pyramidal neurons require the 5-HT_{2A}–$mGlu_2$ receptor complex, and activation of the $mGlu_2$ receptor inhibits these hallucinogen-specific neuronal signalling pathways. Interestingly, in postmortem human brains of untreated schizophrenia subjects, the level of expression of the 5-HT_{2A} receptor was significantly higher and the level of expression of the $mGlu_2$ receptor was significantly lower when compared with matched control subjects [29] (Box 3). The dysregulation of the components of the 5-HT_{2A}–$mGlu_2$ receptor complex might predispose to psychosis in schizophrenic patients.

Activation of $mGlu_{2/3}$ receptors reduces behavioural stereotypy, hyperlocomotion and working memory deficits produced by NMDA antagonists [7,53]. Recent clinical trials with the $mGlu_{2/3}$ receptor agonist LY404039 have reported significant improvements in both positive and negative symptoms of schizophrenia [8]. The specific function of $mGlu_2$ and $mGlu_3$ receptors as potential antipsychotic targets has remained obscure owing to the absence of selective $mGlu_2$ and/or $mGlu_3$ receptor ligands. Recent experiments with $mGlu_2$ and $mGlu_3$ receptor knockout mice indicate that the $mGlu_2$ but not the $mGlu_3$ receptor mediates the actions of the glutamate agonists LY314582, LY379268 and LY404039 in mouse models of psychosis with PCP and amphetamine [54–56]. One way to reconcile the mechanisms of action of LSD-like drugs and the atypical and glutamate classes of antipsychotics is to hypothesize that hallucinogens, atypical antipsychotics and metabotropic glutamate agonist antipsychotics all act at the same 5-HT_{2A}–$mGlu_2$ receptor complex. In this formulation, the molecular target of both atypical antipsychotics and LSD-like drugs is the 5-HT_{2A} receptor moiety and that of the new glutamate antipsychotics [8] is the $mGlu_2$ receptor moiety. Additional work will be required to test this hypothesis and to investigate the contribution of the $mGlu_3$ receptor expressed on presynaptic terminals projecting to the cortex to the efficacy of glutamate antipsychotic drugs (Figure 2a).

Functional interactions between 5-HT_{2A} and NMDA receptors

The brain regions responsible for the effects of PCP-like drugs have been the focus of intense research in the last few years. In rodents, NMDA antagonists induce behavioural responses that include increased activity, head weaving, deficits in paired pulse inhibition and social interactions, in addition to cognitive deficits, in particular disruption in sensory motor gating (a phenomenon found consistently among schizophrenia cohorts). Systemic administration of PCP-like drugs evokes marked hyperlocomotion and stereotyped behaviours [57,58] in addition to a marked increase in the spontaneous discharge rate of the majority of medial prefrontal cortical neurons [59]. The extracellular concentrations of serotonin and glutamate in cortical regions are increased by systemic administration of PCP-like drugs [58,60,61]. On the contrary, intra-cortical administration of PCP-like drugs does not induce firing activity [62] nor serotonin and glutamate release in cortical neurons [58]. Collectively, these results indicate that the behavioural abnormalities elicited by acute PCP-like drugs are induced through excitatory inputs into brain cortical neurons from subcortical regions (Figure 2b).

It has been recently reported that the head-twitch behavioural response (rapid lateral movements of the head similar to the pinna reflex) is reliably elicited by a variety of psychedelics (e.g. DOI, DOM, DOB, mescaline, LSD and psilocin) and is absent in 5-HT_{2A} receptor knockout mice (Figure 1). Furthermore non-hallucinogenic 5-HT_{2A} receptor agonists, such as *R*-lisuride, *S*-lisuride and ergotamine, do not induce this behavioural response [13,14]. Thus, head-twitch seems to serve as a mouse bioassay that is able to predict the hallucinogenic-specific signalling and effects of 5-HT_{2A} receptor agonists in humans. Interestingly, PCP-like drugs also induce head-twitch and head-weaving responses (slow, side to side or lateral head movement) in rodents [63] and NMDA receptor antagonists enhance the 5-HT_{2A}-receptor-mediated head-twitch response in mice [64]. In animal models, clozapine, ritanserin, amesergide and ketanserin block PCP-dependent locomotion [65,66] and head-twitch responses [63], which indicates a potential role of circuits working through the 5-HT_{2A} receptor in mediating the behavioural responses induced by NMDA antagonism. Similar results were reported with the selective 5-HT_{2A} receptor antagonist M100907 [67]. Atypical antipsychotics reverse the cellular responses produced by PCP-like drugs in cortical pyramidal neurons [65,68] and block the serotonin and glutamate release in the prefrontal cortex [58]. Importantly, local administration of clozapine in the prefrontal cortex paralleled the effects of intraperitoneal administration on the PCP response [58], which reinforces the potential role of cortical 5-HT_{2A} receptor circuits in the mechanism of action of both PCP-like and LSD-like drugs (Figures 2a,b). In the same context, recent findings have demonstrated that the serotonin precursor L-5-hydroxytryptophan (5-HTP) [69] induces a head-twitch response in mouse via 5-HT_{2A} receptors, indicating that serotonin could have hallucinogenic activity *in vivo*. $mGlu_2$ receptor activation abolishes the hallucinogen-specific signalling activated by LSD at the 5-HT_{2A}–$mGlu_2$ receptor complex [29]. Microdialysis experiments in the cortex have demonstrated that extracellular glutamate increases more slowly than extracellular serotonin after intraperitoneal administration of PCP-like drugs [57,58]. These observations support the speculation that serotonin and glutamate acting through the 5-HT_{2A}–$mGlu_2$ receptor complex might each be responsible for different LSD-like and PCP-like symptoms of schizophrenia.

Genetics

The etiology of schizophrenia is multifactoral, with evidence for both genetic and environmental factors [70–72]. Research on understanding the genetics of the disease is progressing rapidly. The stage is now set to begin to think about how the complex gene–environment interactions that cause the disease lead to the disruptions in brain neurochemistry and function.

The heritability of schizophrenia is estimated at 73–90%. Because genetic causes of schizophrenia are under strong negative reproductive selection, the predisposing genetic lesions are postulated to be rare and heterogeneous. Potentially pathogenic mutations have been identified in the genes for DISC1, PDE4B and NPAS3. Recent genome-wide studies of copy-number variation have confirmed the earlier reported schizophrenia association of a deletion of the 22q11.2 region also implicated in velo-cardio-facial syndrome and DiGeorge syndrome. The association of schizophrenia with two other large deletions in the 1q21.1 and 15q13.3 loci and with several microdeletions have also been identified [3,4,73]. Increased risk of schizophrenia due to gene–environment interactions (the genetic predisposition to an environmental insult) and epistasis (dependence of phenotype on the interactions among two or more genes) are both consistent with the current epidemiological and genetic studies. Contributing environmental and epidemiological factors that have been implicated in increasing the risk of schizophrenia include foetal hypoxia and folate deficiency, cannabis use, urban birth or upbringing and migration. The first empirical test of gene–environment interaction in families having at least one proband diagnosed with a schizophrenia spectrum disorder was recently reported [74]. The authors studied the interaction between severe obstetrical complications and polymorphisms for schizophrenia candidate genes. Among the 13 candidate genes studied, the genes encoding AKT1, BDNF, GRM3 and DTNBP all showed a significant interaction with birth complications in the probands [74]. The multifactoral genetics and gene–environment pathoetiology of schizophrenia is well established. Little is known about how gene–environment effects affect brain development and lead to alterations in brain neurochemistry and the symptoms of schizophrenia. The investigation of the molecular and structural basis of neuronal signalling with the use of psychotomimetic drugs might open new avenues for the generation of mutant mouse models of psychosis and help in understanding the neurobiological alterations responsible for schizophrenia.

Concluding remarks

The serotonin hypothesis of schizophrenia has been of considerable value in leading to the development of most of the atypical antipsychotic medications. One feature that was used to screen for many of the atypical antipsychotic drugs, such as ritanserin, was its ability to block the LSD activity at 5-HT_{2A} receptors [28]. Thus, understanding the mechanism of hallucinogens continues to have the potential to provide important clues about the basis for psychosis in this disease. Furthermore, psychedelics have a rich and subtle pharmacology in which closely related 5-HT_{2A} receptor agonists vary dramatically in their capacity to cause LSD-like neuropsychological effects. This provides an excellent experimental system in which the signalling and circuit mechanisms underlying psychedelics has been mapped using systems pharmacology and mouse genetic models [13,29]. The results obtained with the investigation of the mechanism of action of LSD-like and PCP-like drugs provide approaches for the rational design of new types of antipsychotic drugs and points towards a unification of the serotonin and glutamate hypotheses of schizophrenia. The challenge remains to relate the dopamine hypothesis of schizophrenia to this emerging serotonin-glutamate hypothesis. The remarkable concordance of research on psychedelics and antipsychotics indicates that the study of the mechanisms of psychotomimetic drugs of abuse will continue to facilitate the development of better therapies for schizophrenia.

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