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ARTICLE

SPECIAL SECTION
Preclinical Models of Schizophrenia

Serotonergic hallucinogens as translational models relevant to schizophrenia

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Abstract

One of the oldest models of schizophrenia is based on the effects of serotonergic hallucinogens such as mescaline, psilocybin, and (+)-lysergic acid diethylamide (LSD), which act through the serotonin 5-HT_{2A} receptor. These compounds produce a 'model psychosis' in normal individuals that resembles at least some of the positive symptoms of schizophrenia. Based on these similarities, and because evidence has emerged that the serotonergic system plays a role in the pathogenesis of schizophrenia in some patients, animal models relevant to schizophrenia have been developed based on hallucinogen effects. Here we review the behavioural effects of hallucinogens in four of those models, the receptor and neurochemical mechanisms for the effects and their translational relevance. Despite the difficulty of modelling hallucinogen effects in nonverbal species, animal models of schizophrenia based on hallucinogens have yielded important insights into the linkage between 5-HT and schizophrenia and have helped to identify receptor targets and interactions that could be exploited in the development of new therapeutic agents.

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Introduction

Substantial evidence indicates that the serotonergic system is involved in the pathophysiology of schizophrenia, but determining the exact role that serotonin (5-HT) plays in the disorder has proven elusive. One of the oldest models of schizophrenia is based on the observation that serotonergic hallucinogens can provoke a 'model psychosis' in normal humans (Geyer and Vollenweider, 2008). The German psychiatrist Kurt Beringer was the first to comment on the similarities between the effects of mescaline and the symptoms of schizophrenia (Beringer, 1923, 1927). Although it was unknown at the time, it is now recognized that mescaline, (+)-lysergic acid diethylamide (LSD) (Fig. 1), and other serotonergic hallucinogens exert their characteristic effects by activating the 5-HT_{2A} receptor (reviewed by: Halberstadt and Geyer, 2011; Nichols, 2004). Soon after the discovery of LSD by Albert Hofmann (Stoll and Hofmann, 1943), it was administered to volunteers by the psychiatrist Walter Stoll. Stoll confirmed that LSD produced mescaline-like effects, but was much more potent, and found that the effects of LSD resemble the symptoms of schizophrenia (Stoll, 1947). Likewise, as had been proposed several decades earlier with mescaline (Knauer and Maloney, 1913), Stoll recommended that psychiatrists self-experiment with LSD in order to gain insight into the mental states and experiences of their patients.

Many other groups subsequently characterized the effects of LSD, mescaline and psilocybin, and concluded that these hallucinogens produced mental states resembling the earliest phases of schizophrenia (Bowers and Freedman, 1966; Keeler, 1965; Osmond and Smythies, 1952; Rinkel et al., 1952, 1955). Other clinicians, however, noted that differences exist between the effects of hallucinogens and the symptoms of schizophrenia, leading them to question the validity of the model psychosis (Mayer-Gross, 1951). One of the most prominent critics was Hollister, who argued that auditory but not visual hallucinations are most prominent in schizophrenia, whereas the opposite is true of hallucinogens (Hollister, 1962). Nevertheless, there are often visual disturbances during the acute phase of schizophrenia, including hallucinations and synaesthesias (McCabe et al., 1972; Freedman and Chapman, 1973). A second criticism made by Hollister is that hallucinogens rarely produce social and emotional withdrawal, but these symptoms are

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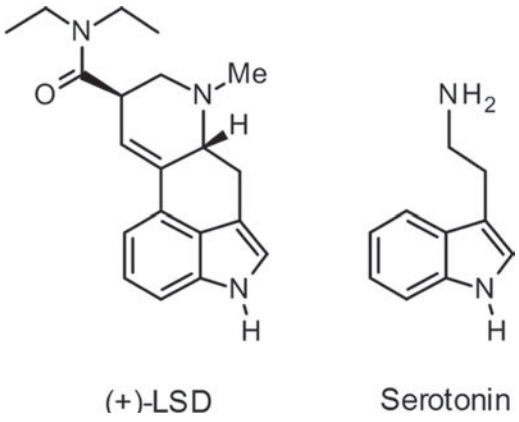

Fig. 1. Chemical structures of (+)-lysergic acid diethylamide (LSD, left panel) and serotonin (right panel).

often found in schizophrenia patients. Subsequent investigations have shown that hallucinogens sometimes produce withdrawal and catatonia-like states, especially when administered at higher doses (Gouzoulis-Mayfrank et al., 1998a).

Since *N*-Methyl-D-aspartate (NMDA) antagonists such as phencyclidine (PCP) and ketamine mimic most aspects of schizophrenia (Halberstadt, 1995; Javitt and Zukin, 1991; Javitt, 2007), it has been proposed that these dissociative anaesthetics may be more appropriate models of schizophrenia. Nevertheless, it has been argued that NMDA antagonists and serotonergic hallucinogens may model different subtypes of schizophrenia, with NMDA antagonists producing effects most similar to the disorganized or undifferentiated subtype of schizophrenia, and hallucinogens modelling the paranoid subtype (Abi-Saab et al., 1998). In order to directly compare these two models, Gouzoulis-Mayfrank conducted a double-blind cross-over study with *S*-ketamine and the hallucinogen *N,N*-dimethyltryptamine (DMT) in normal volunteers (Gouzoulis-Mayfrank et al., 2005). This comparison showed that the effects of DMT primarily resembled the positive symptoms of schizophrenia, whereas *S*-ketamine produced effects that more closely resembled the negative symptoms of schizophrenia (Gouzoulis-Mayfrank et al., 2005), indicating that these drugs model different aspects of schizophrenia. Gouzoulis-Mayfrank et al. (1998a) have also used the Altered States of Consciousness (APZ) rating scale to assess whether psychotic patients experience psychedelic experiences similar to those induced by hallucinogens. The APZ was developed by Dittrich to assess altered states of consciousness independent of their etiology (Dittrich, 1998), and is sensitive to the subjective effects of serotonergic hallucinogens, including psilocybin, mescaline and DMT (Gouzoulis-Mayfrank et al., 1999, 2005; Grob et al., 2011; Hermle et al., 1992; Vollenweider et al., 1997). Patients with acute schizophrenia, schizophreniform disorder or schizoaffective disorder had significantly higher APZ scores than normal controls. Additionally, APZ scores were found to be significantly correlated with scores on the Brief Psychiatric Rating Scale, which measures psychotic symptoms. These findings demonstrate that psychotic patients experience hallucinogen-like alterations of perception and consciousness.

Although the use of hallucinogens as a model of psychosis was somewhat controversial during the 1950s, there was much less controversy regarding the possibility that 5-HT itself plays a role in the illness. Serotonin was first isolated from serum in 1948 by Rapport (Rapport et al., 1948), and the next year it was identified as 5-hydroxytryptamine (Rapport, 1949). The similarity of the chemical structures of 5-HT and LSD (Fig. 1), the fact that 5-HT is present in the brains of dogs, rabbits and rats (Twarog and Page, 1953), and the finding that LSD blocked the contractile effect of LSD on smooth muscle (Gaddum, 1953), led Woolley and Shaw (1954) to propose that 5-HT plays a role in mental processing and possibly in the pathogenesis of schizophrenia (Woolley and Shaw, 1954). The link between 5-HT and schizophrenia was supported by the subsequent discovery that reserpine, an indole alkaloid isolated from *Rauwolfia serpentina* that has antipsychotic properties (Braun, 1960; Gore et al., 1957), causes massive depletion of 5-HT (Pletcher et al., 1955). One of the strongest arguments for the involvement of 5-HT in schizophrenia was the discovery of atypical antipsychotics such as clozapine, risperidone and olanzapine, which act in part by blocking 5-HT_{2A} receptors with some selectivity over the dopamine (DA) D_2 receptor (Meltzer et al., 1989; Meltzer, 1991, 1999; Seeman, 2002). Atypical antipsychotics are associated with a lower risk of extrapyramidal side-effects compared with typical antipsychotics, which may be attributable at least partially to 5-HT_{2A} antagonism (Abi-Dargham and Krystal, 2000; Meltzer, 1999; Roth and Meltzer, 2000). Animal studies have indicated that selective 5-HT_{2A} antagonists have antipsychotic-like effects (Geyer et al., 2001; Varty et al., 1999). A subsequent clinical trial confirmed that the selective 5-HT_{2A} antagonist M100,907 (volinanserin, formerly MDL 100,907) was more effective than placebo at treating schizophrenia, but did not show significantly greater efficacy than the typical antipsychotic haloperidol in neuroleptic-responsive patients (de Paulis, 2001). Development of the 5-$HT_{2A/2C}$ antagonist eplivanserin (SR-46349) as a

treatment for schizophrenia was also discontinued after it was found to be less effective than haloperidol in neuroleptic-responsive patients (Meltzer et al., 2004). Although the antipsychotic efficacy of 5-HT_{2A} antagonist monotherapy is apparently rather modest, it is possible that certain subpopulations of psychotic patients may respond more favourably. For example, 5-HT_{2A} receptors may play a specific role in psychosis associated with Parkinson's disease (Ballanger et al., 2010; Huot et al., 2010; Mcfarland et al., 2011), and the 5-HT_{2A} inverse agonist pimavanserin (ACP-103) reduces delusions and hallucinations in Parkinsonian patients (Meltzer et al., 2010).

Because of the apparent similarities between the effects of hallucinogens and some of the symptoms of schizophrenia, several animal models relevant to schizophrenia have been developed based on hallucinogen effects (Geyer and Moghaddam, 2002; Geyer and Vollenweider, 2008; Halberstadt and Geyer, 2013b). These models have facilitated investigation of the role that 5-HT plays in schizophrenia, helped to characterize important interactions between 5-HT and other transmitter systems, and identified novel pharmacotherapeutics that act through receptors for 5-HT and other transmitters. Here, we review four of the animal behavioural models.

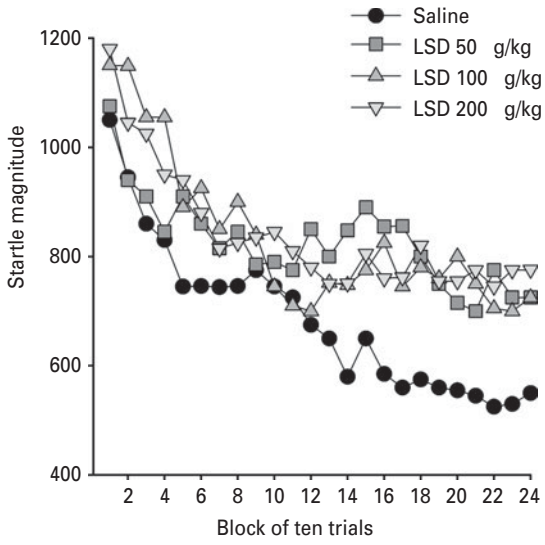

Fig. 2. The effects of LSD on the startle response in rats are shown for 24 blocks of 10 trials each. Each point represents the mean startle amplitude. Male Sprague-Dawley rats (200–250 g) were treated (1 ml/kg i.p.) with vehicle (isotonic saline) or LSD tartrate. After 10 min the animals were placed in a stabilimeter chamber for a 5 min acclimation period, and then exposed to 240 air-puff stimuli (20 ms, 50 psi) with a 15 s inter-trial interval. This study was originally reported in: Geyer and Braff, 1987.

Startle habituation

The startle response is a transient motor response exhibited by humans and other animal species in response to loud acoustic stimuli (acoustic startle) or unexpected tactile stimuli (tactile startle). Repeated exposure to a startling stimulus often leads to a marked response decrement, a process known as habituation (Davis and Heninger, 1972; Groves and Thompson, 1970; Rankin et al., 2009; Szabo and Kolta, 1967). Schizophrenia patients often display an impaired ability to filter out extraneous or irrelevant stimuli, potentially contributing to the distractibility, sensory flooding, and cognitive fragmentation found in many of these patients (McGhie and Chapman, 1961). There is extensive evidence that patients with schizophrenia display startle reflex habituation deficits that may contribute to the sensory overload. Comparison of the eyeblink component of the acoustic startle reflex in schizophrenia and control subjects revealed that startle habituation is significantly impaired in schizophrenia patients (Geyer and Braff, 1982). Subsequent studies confirmed that habituation of the startle response evoked by acoustic stimuli or electrocutaneous stimulation is deficient in schizophrenia patients relative to normal controls (Bolino et al., 1992, 1994; Ludewig et al., 2003; Meincke et al., 2004; Parwani et al., 2000; Taiminen et al., 2000).

Because habituation is a cross-species phenomenon that can be assessed in humans and in laboratory animals using similar procedures, startle habituation in animals has been used to model the information processing deficits that occur in schizophrenia. Tactile and acoustic startle response magnitudes in rats are increased by a variety of serotonergic hallucinogens, including members of the indoleamine (LSD, DMT and psilocin) and phenylalkylamine (mescaline, 2,5-dimethoxy-4-methylamphetamine (DOM), and 2,5-dimethoxy-4-ethylamphetamine (DOET)) chemical classes (Davis and Sheard, 1974; Geyer et al., 1978). Importantly, acute administration of LSD to rats reduced habituation of tactile startle provoked by air-puffs (Fig. 2) (Geyer et al., 1978; Geyer and Braff, 1987), an effect that is lost when LSD is administered chronically (Braff and Geyer, 1980). Mescaline also attenuates habituation of acoustic startle in rats (Davis, 1987), and this effect is blocked by the 5-$HT_{2A/2C}$ antagonists ritanserin, ketanserin, LY 53857 and cinanserin. Psilocybin, however, did not have significant effects on startle reactivity or habituation when tested in human subjects (Gouzoulis-Mayfrank et al., 1998c; Quednow et al., 2012; Vollenweider et al., 2007).

Prepulse inhibition

The presentation of a weak prestimulus at a brief interval (30–500 ms) prior to a startle-inducing stimulus will attenuate the resulting startle response. This phenomenon, known as prepulse inhibition (PPI), has been used as an operational measure of sensorimotor gating, and may reflect mechanisms that exist to regulate sensory input by filtering out extraneous or distracting stimuli (Swerdlow and Geyer, 1998). PPI is a cross-species phenomenon that is extremely robust, unlearned and ubiquitous (Geyer et al., 2001; Swerdlow et al., 2001). Consistent with the view that schizophrenia is a gating or filtering disorder (Carlsson, 1995), PPI has been found to be deficient in schizophrenia patients (Bolino et al., 1994; Braff et al., 1978; Braff and Geyer, 1990; Ludewig et al., 2003; Parwani et al., 2000; Quednow et al., 2006).

Animals treated with hallucinogens show reductions in PPI, indicating that hallucinogens reduce the gating or filtering of sensory stimuli. LSD, 2,5-dimethoxy-4-iodoamphetamine (DOI), 2,5-dimethoxy-4-bromoamphetamine (DOB), and mescaline disrupt PPI in rats (Halberstadt and Geyer, 2010; Johansson et al., 1995; Ouagazzal et al., 2001; Pálenícek et al., 2008; Rigdon and Weatherspoon, 1992; Sipes and Geyer, 1994; Varty and Higgins, 1995;). The selective 5-HT_{2A} antagonists M100,907 and MDL 11,939 block the effects of DOI and LSD on PPI (Halberstadt and Geyer, 2010; Ouagazzal et al., 2001; Padich et al., 1996; Sipes and Geyer, 1995), whereas 5-HT_{1A} or 5-HT_{2C} antagonists are ineffective at preventing their effects. The reduction of PPI induced by DOI is also blocked by the atypical antipsychotics aripiprazole, risperidone and clozapine, but not by the D_2 antagonist haloperidol or the $D_{2/3}$ antagonist raclopride (Kohnomi et al., 2008; Varty and Higgins, 1995). The hallucinogen 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT) also disrupts PPI in rats, but this effect is dependent on 5-HT_{1A} receptor activation, since it is prevented by the selective 5-HT_{1A} antagonist WAY-100635 and not by M100,907 (Krebs-Thomson et al., 2006). The involvement of 5-HT_{1A} receptors in mediating the effects of 5-MeO-DMT on PPI is consistent with numerous findings that the behavioural effects of 5-MeO-DMT are primarily attributable to 5-HT_{1A} activation (Halberstadt et al., 2011; van den Buuse et al., 2011; Winter et al., 2000).

Lisuride is an LSD congener that acts as a 5-HT_{2A} agonist but does not have hallucinogenic effects in humans. González-Maeso et al. (2007) have proposed that lisuride does not act as a hallucinogen because of agonist-directed trafficking of 5-HT_{2A} responses; i.e. certain 5-HT_{2A} agonists are hallucinogenic because they activate specific signaling pathways that are not recruited by lisuride. Interestingly, although both LSD and lisuride disrupt PPI in rats, they do so by different receptor mechanisms; the PPI disruption induced by lisuride was not blocked by MDL 11,939 or the selective 5-HT_{1A} antagonist WAY-100635, but was prevented by pretreatment with the selective DA $D_{2/3}$ receptor antagonist raclopride (Fig. 3; Halberstadt and Geyer, 2010).

Studies in humans have demonstrated that hallucinogens can alter PPI, although the effect is highly dependent on the specific testing parameters used. One study with psilocybin found that the hallucinogen increased PPI when a 100 ms interstimulus interval (ISI) was used (Gouzoulis-Mayfrank et al., 1998b). Another study confirmed that psilocybin increased PPI at long ISIs (120–2000 ms), but also found that psilocybin reduced PPI when shorter ISIs of 30 ms were used (Vollenweider et al., 2007). Importantly, the ability of psilocybin to reduce PPI at a 30 ms ISI is completely blocked by ketanserin (Quednow et al., 2012), confirming the involvement of 5-$HT_{2A/2C}$ receptors in mediating this effect. Given the similarity of hallucinogen effects on PPI in humans and rats, hallucinogen effects on PPI have been used as a model of the positive symptoms of schizophrenia. Importantly, it was recently reported that specific 5-HT_{2A} polymorphisms modulate PPI levels in normal volunteers and in patients with schizophrenia (Quednow et al., 2008, 2009). These findings raise the possibility that changes in 5-HT_{2A} signaling could contribute to the PPI disruption observed in schizophrenia.

Head twitch response

Hallucinogens induce stereotypical motor responses in many mammalian species, including ear scratching (mice), limb flicks (cats) or head bobs (rabbits). In rats and mice, administration of a variety of hallucinogens produces a paroxysmal rotational head movement known as the head twitch response (HTR) (Bedard and Pycock, 1977; Canal and Morgan, 2012; Corne and Pickering, 1967; Halberstadt and Geyer, 2013a; Yamamoto and Ueki, 1975). Although the HTR is typically assessed by direct observation, and hence experiments can be time-consuming, it was recently reported that a head-mounted magnet and a magnetometer coil can be used to detect the behaviour with extremely high sensitivity and specificity (Halberstadt and Geyer, 2013a). The hallucinogen-induced HTR is blocked by selective 5-HT_{2A} antagonists (Fox et al., 2010; Schreiber et al., 1995) and is absent

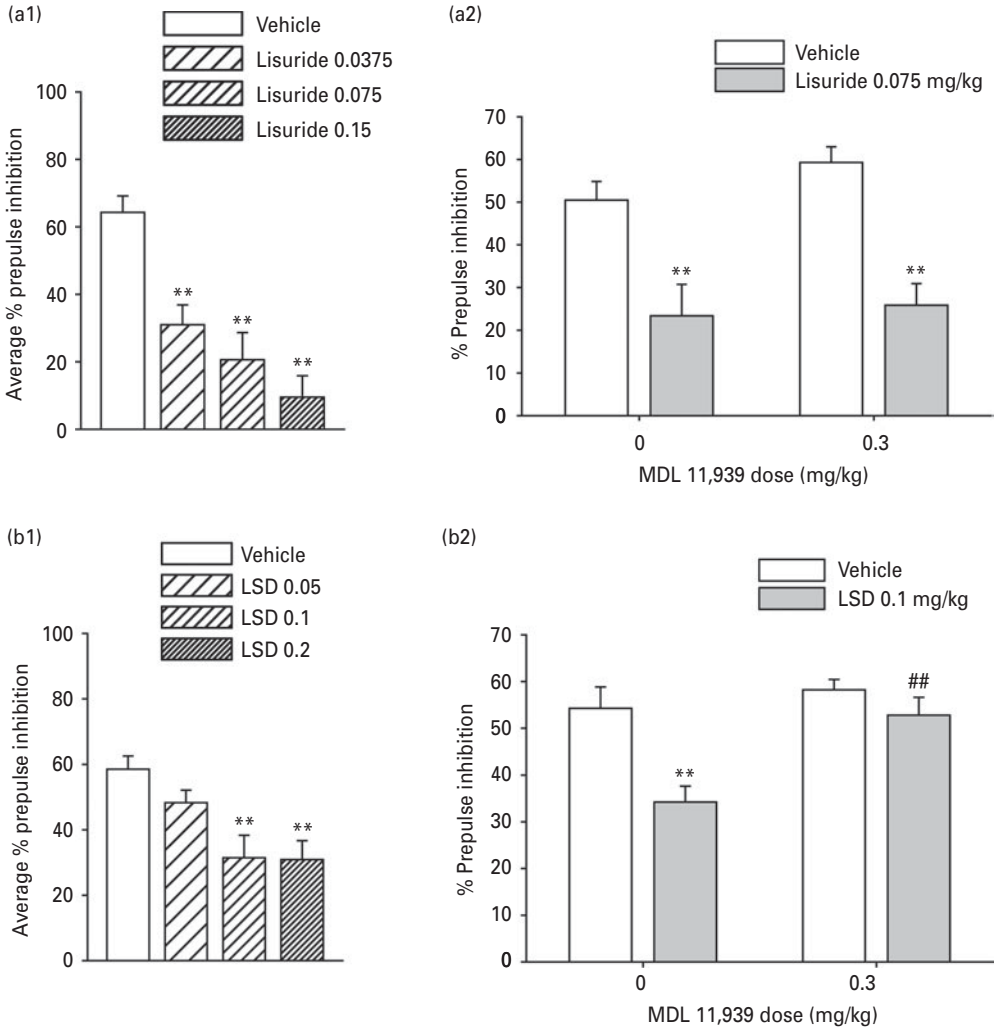

Fig. 3. Effects of lisuride (a) and LSD (b) on prepulse inhibition in rats. (a1) Effect of lisuride (0.0375, 0.075 and 0.15 mg/kg, s.c.) on average prepulse inhibition. (a2) Effects of the selective 5-HT_{2A} antagonist MDL 11,939 on the disruption of PPI induced by lisuride. (b1) Effect of LSD (0.05, 0.1 and 0.2 mg/kg, s.c.) on average prepulse inhibition. (b2) Effects of the selective 5-HT_{2A} antagonist MDL 11,939 on the disruption of PPI induced by LSD. Values represent mean±S.E.M. for each group. Drug doses are mg/kg. *$p<0.05$, **$p<0.01$, significantly different from vehicle control; $^{\#\#}p<0.01$, significantly different from LSD-treated animals. Male Sprague–Dawley rats (250–275 g) were placed in a stabilimeter chamber 30 min after treatment with MDL 11,939, 10 min after treatment with lisuride hydrogen maleate, or 5 min after treatment with LSD tartrate. After a 5 min acclimation period to 65 dB broadband background noise,%prepulse inhibition was assessed using a combination of startle trials (a 40 ms 120 dB pulse of broadband white noise) and prepulse trials (a 20 ms acoustic prepulse at either 68, 71 or 77 dB, an 80 ms delay, and then a 40 ms 120 dB startle pulse) presented in a pseudo-randomized order. Data from Halberstadt and Geyer, 2010.

in 5-HT_{2A} knockout mice (González-Maeso et al., 2007; Halberstadt et al., 2011; Keiser et al., 2009), suggesting that this behaviour is a consequence of 5-HT_{2A} activation. 5-HT_{2A} receptors in the prefrontal cortex (PFC) may be responsible for mediating the HTR induced by hallucinogens, as evidenced by the fact that infusion of DOI directly into this region induces the behaviour in rats (Willins and Meltzer, 1997), and loss of the HTR in 5-HT_{2A} knockout mice can be rescued by selective restoration of the receptor in cortical regions (González-Maeso et al., 2007). In recent years, the HTR has been widely adopted as a rodent behavioural proxy for hallucinogen effects in humans. In fact, there is evidence that the HTR is one of the few behaviours that can reliably distinguish hallucinogenic and non-hallucinogenic 5-HT_{2A}

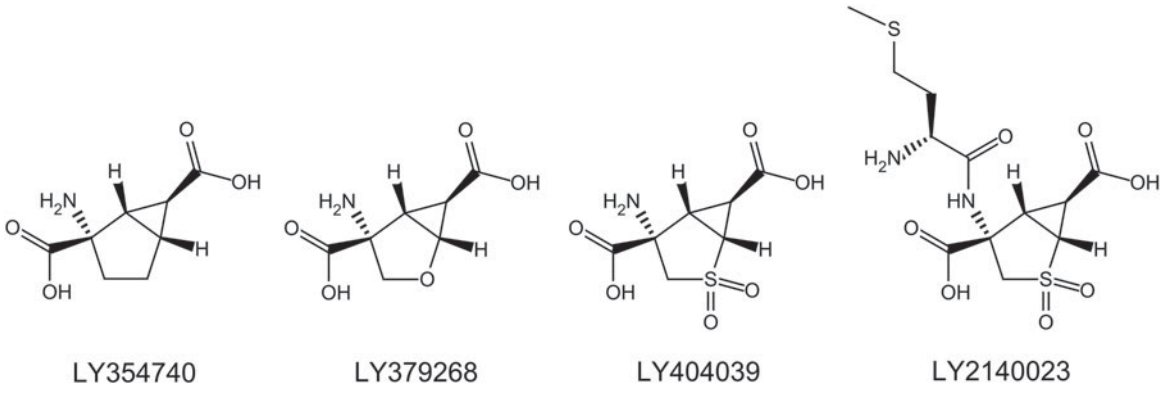

Fig. 4. Chemical structures of orthosteric $mGlu_{2/3}$ receptor agonists.

agonists (González-Maeso et al., 2007). Nevertheless, there is little evidence to support using the HTR as an animal model of hallucinations or of mental states that are directly relevant to schizophrenia. For example, many non-hallucinogenic compounds that increase 5-HT release and indirectly activate the 5-HT_{2A} receptor, including d-fenfluramine (Darmani, 1997) and even some benzodiazepines (Tadano et al., 2001), can induce the HTR. Furthermore, although many antipsychotics can block the hallucinogen-induced HTR due to their 5-HT_{2A} antagonist activity, selective 5-HT_{2A} antagonists such as M100,907 have only limited efficacy as antipsychotics when administered to schizophrenia patients.

There is, however, substantial evidence that the HTR has utility as a behavioural tool to study the neural basis for hallucinogen effects, which may have direct relevance to understanding the positive symptoms of schizophrenia. For example, the HTR induced by DOI in rats and mice is suppressed by the selective metabotropic glutamate $(mGlu)_{2/3}$ receptor agonists LY354740 and LY379268 (Fig. 4) and enhanced by the-selective $mGlu_{2/3}$ antagonist LY341495 (Gewirtz and Marek, 2000; Klodzinska et al., 2002). Likewise, the $mGlu_2$ positive allosteric modulator (PAM) biphenyl-indanone A inhibits the HTR induced by (–)-DOB (Benneyworth et al., 2007). Chronic treatment with the $mGlu_{2/3}$ antagonist LY341495 has been shown to down-regulate cortical 5-HT_{2A} sites and attenuate the HTR induced by LSD in mice (Moreno et al., 2013). Deletion of the $mGlu_2$ gene in mice has been shown to produce a reduction of the HTR to LSD and DOI and a profound loss of high-affinity 5-HT_{2A} binding sites in frontal cortex (Moreno et al., 2011a). Indeed, there is extensive electrophysiological, neurochemical and behavioural evidence that $mGlu_{2/3}$ receptors regulate the response to 5-HT_{2A} activation (Benneyworth et al., 2007; Gewirtz et al., 2002; Klodzinska et al., 2002; Marek et al., 2000; Molinaro et al., 2009; Winter et al., 2004; Wischhof et al., 2011; Wischhof and Koch, 2012). These findings are significant because there is some evidence that $mGlu_{2/3}$ agonists may possess antipsychotic efficacy. Although pomaglumetad methionil (LY2140023; Fig. 4), a methionine amide prodrug for the selective orthosteric mGlu2/3 agonist LY404039, reduced schizophrenia symptoms in an initial phase II trial (Patil et al., 2007), follow-up studies were either inconclusive (Kinon et al., 2011) or failed to show evidence for efficacy (Lilly, 2012). Although Lilly has discontinued further clinical trials, it appears that the clinical response to pomaglumetad methionil may depend on the presence of specific single nucleotide polymorphisms (SNPs) in the 5-HT_{2A} receptor (Liu et al., 2012). Importantly, according to a recent press release, a phase II trial conducted by Janssen Pharmaceuticals demonstrated that the selective $mGlu_2$ PAM ADX71149 (Fig. 5) has efficacy in medicated schizophrenia patients with residual negative symptoms (Addex, 2012), although peer-reviewed data have yet to appear in the literature. One potential explanation

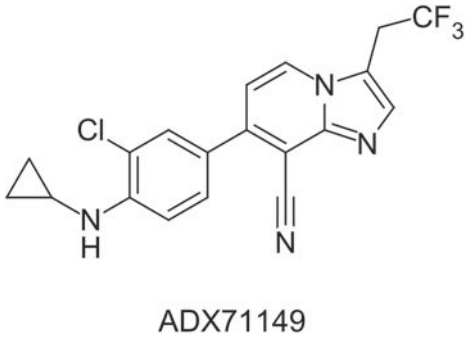

Fig. 5. Chemical structure of the selective $mGlu_2$ receptor positive allosteric modulator ADX71149.

for the interactions between $mGlu_2$ and 5-HT_{2A} is that these receptors may be co-localized in cortical neurons, where they can form functional complexes (Gonzalez-Maeso et al., 2008; Moreno et al., 2012). There is evidence that the behavioural effects of some antipsychotic drugs in mice may be directly mediated by these $mGlu_2$/5-HT_{2A} complexes (Fribourg et al., 2011). The receptor heterodimers may play a specific role in mediating the HTR because the loss of the behavioural response in $mGlu_2$ knockout mice can be rescued by viral-mediated over-expression of $mGlu_2$ in frontal cortex, whereas expression of a mutated form of $mGlu_2$ that is incapable of forming complexes with 5-HT_{2A} did not rescue the behaviour (Moreno et al., 2012). Nonetheless, it is possible that functional or circuit interactions may actually be involved in mediating the interactions between 5-HT_{2A} and $mGlu_2$ receptors, and further work is required to conclusively demonstrate that $mGlu_2$ and 5-HT_{2A} heterodimers are responsible for mediating the crosstalk between these systems (Delille et al., 2012, 2013).

Although there is substantial evidence that some forms of schizophrenia have genetic etiologies, environmental events, especially during pregnancy, also play a role. Two rodent models – maternal variable stress and prenatal immune challenge – have been developed to study whether adverse prenatal events can produce schizophrenia-like effects. Interestingly, it was recently shown that the HTR is altered in both models. Maternal variable stress and prenatal immune activation with polyinosinic:polycytidylic acid significantly increased the HTR evoked by DOI in adult mice, and reduced the antipsychotic-like behavioural effects of the $mGlu_{2/3}$ agonist LY379268 (Holloway et al., 2013; Moreno et al., 2011b). These behavioural alterations were accompanied by up-regulation of the 5-HT_{2A} receptor and down-regulation of the $mGlu_2$ receptor (Moreno et al., 2011b). A similar pattern of changes in 5-HT_{2A} and $mGlu_2$ binding and mRNA expression has been found in the prefrontal cortex of unmedicated schizophrenia patients *post-mortem* (Gonzalez-Maeso et al., 2008; Muguruza et al., 2012). Gonzalez-Maeso and colleagues have also reported that crosstalk between $mGlu_2$ and 5-HT_{2A} receptors is altered in schizophrenia patients (Moreno et al., 2012). Taken together, these findings indicate that alterations of 5-HT_{2A} receptor signaling may contribute to the pathophysiology of schizophrenia. However, the finding that the 5-HT_{2A} receptor is upregulated in schizophrenia needs to be replicated because numerous *post-mortem* studies have found either no change or *reductions* of 5-HT_{2A} binding site densities and mRNA expression in the cortex of schizophrenia patients (reviewed by Quednow et al., 2010). Likewise, other groups have reported that cortical $mGlu_2$-like immunoreactivity and mRNA expression levels are not downregulated in schizophrenia subjects *post-mortem* (Crook et al., 2002; Ghose et al., 2008, 2009; Gupta et al., 2005). Although many of the earlier studies were confounded by antipsychotic treatment, which could potentially reduce 5-HT_{2A} expression, PET studies with [^{18}F]altanserin, [^{18}F]septoperone, or [^{11}C]*N*-methylspiperone in antipsychotic-naive subjects found either no change (Erritzoe et al., 2008; Lewis et al., 1999; Okubo et al., 2000; Trichard et al., 1998) or reductions (Ngan et al., 2000; Rasmussen et al., 2010) of radiotracer binding to cortical 5-HT_{2A} receptors.

Interval timing

The perception of time is essential for survival and is required for the precise organization of sequences of activity as well as the anticipation of behavioural outcomes and future events. Time perception occurs over multiple timescales, ranging from milliseconds to days (Buhusi and Meck, 2005), and encompasses a diverse variety of functions such as sensory and motor timing and circadian activity. Interval timing falls within this larger framework of temporal processing and refers to the discrimination of durations, typically in the seconds to minutes range. Deficits of timing have been reported in patients with a variety of neuropsychiatric disorders. Given the crucial importance of temporal processing to the regulation of behaviour and interaction with the world, timing impairment would have significant consequences for these patient populations.

It has been proposed that impaired temporal processing is a core deficit of schizophrenia (Bonnot et al., 2011; Caroll et al., 2008; Ward et al., 2012). Schizophrenia patients consistently overestimate and under-produce temporal durations in behavioural studies (Caroll et al., 2009a, b; Densen, 1977; Rammsayer, 1990; Tysk, 1983; Wahl and Sieg, 1980; Waters and Jablensky, 2009), and interval timing is less accurate and more variable in schizophrenia patients than in normal controls (Caroll et al., 2008, 2009a, b; Davalos et al., 2003, 2011; Lee et al., 2009; Tysk, 1984). The fact that the timing deficits occur over multiple time scales (<100 ms to several minutes) and have been demonstrated using tasks with varying degrees of difficulty indicates that the timing impairment is not a consequence of more generalized mnemonic or attentional deficits (Caroll et al., 2009a, b; Davalos et al., 2011). Furthermore, timing

impairments occur independently of working memory deficits (Elvevåg et al., 2003). There is also evidence that schizophrenia patients show less activation of brain regions thought to be involved in timing when performing an auditory time estimation task (Davalos et al., 2011; Volz et al., 2001). Finally, schizophrenia patients exhibit impaired processing of the temporal relationship between sensory stimuli (Braus, 2002; Schmidt et al., 2011; Tenckhoff et al., 2002; Todd, 2006) and impaired ability to predict when events will occur (Turgeon et al., 2012). Together, these findings demonstrate that there is a fundamental deficit of timing and temporal perception in schizophrenia.

There are several potential functional consequences of impaired temporal perception in schizophrenia. Timing deficits could impair perceptual and cognitive processing and alter the temporal coordination of behaviour, contributing to the behavioural disorganization, contextually inappropriate behaviour, and planning deficits observed in schizophrenia. Additionally, accurate temporal perception is required to infer causality (e.g. Maeda et al., 2012) and the sensory consequences of actions (Waters and Jablensky, 2009). Disturbed interval timing could potentially alter the perceived sequence of mental thoughts and sensory events, resulting in erroneous causal attributions (Haggard et al., 2003; Waters and Jablensky, 2009) and delusional thinking. Laboratory studies have shown that even minor changes in inter-sensory temporal relationships can produce perceived violations of temporal contiguity in normal subjects (Cunningham et al., 2001), and it is possible that changes in timing in schizophrenia patients could potentially give rise to feelings that thoughts or actions are being controlled by outside forces.

There is evidence that the serotonergic system modulates temporal perception and interval timing (Ho et al., 2002; Sysoeva et al., 2010). One line of evidence has emerged from the differential-reinforcement-of-low-rate 72-s (DRL 72-s) paradigm (in which rats must wait 72 s between responses to obtain reinforcement), which is used as a screen for antidepressant drugs. A variety of serotonergic ligands, including M100,907 and the 5-HT releasing drug fenfluramine, alter the performance of rats under the DRL 72-s schedule (Marek et al., 2005; Richards et al., 1993), which may reflect a change in the accuracy of temporal discrimination. Additionally, serotonergic hallucinogens markedly alter the subjective experience of time (Heimann, 1994). Under the influence of mescaline or LSD, human subjects reported that these drugs could speed up or slow down the passage of time, or even produce a feeling of timelessness (Beringer, 1927; DeShon et al., 1952; Hoch et al., 1952; Kenna and Sedman, 1964; Serko, 1913). Boardman and colleagues found that administration of low p.o. doses of LSD to volunteers increased the variability of 1 min duration judgments, but did not consistently produce underestimations or overestimations (Boardman et al., 1957). By contrast, subjects given 1 or 2 μg/kg LSD p.o. reliably underproduced longer durations (15–240 min) (Aronson et al., 1959). More recent studies have shown that psilocybin disrupts interval timing in human volunteers (Wackermann et al., 2008; Wittmann et al., 2007).

Hallucinogens also disrupt interval timing in rodent models. Interval timing is often assessed in rodents using immediate and retrospective timing schedules. An example of an immediate timing schedule is the free-operant psychophysical task, where intermittent reinforcement is provided for responding on two levers, and the animal must respond on lever A during the first half of each trial and on lever B during the second half of the trial (Stubbs, 1980). The discrete-trials task is an example of a retrospective timing schedule; in this task, a lamp is illuminated for a variable duration, and then two levers are presented. Responding on lever A is reinforced if the stimulus duration is shorter than a specific value; responding on lever B is reinforced if the stimulus duration is longer than the value (Body et al., 2002a). For both tasks, timing is measured by T_{50} (the time when %B responding is equal to 50%), a measure of timing accuracy, and by the Weber fraction, a measure of timing precision. Since similar tasks are used to assess interval timing in humans (e.g. Penney et al., 2008; Sysoeva et al., 2010), the results of these timing tasks are directly translatable across species. In rats, DOI alters performance in the free-operant timing task (Body et al., 2003, 2006a, b; Cheung et al., 2007) and the discrete-trials task (Asgari et al., 2006; Hampson et al., 2010). In the discrete-trials task, DOI increases the Weber fraction (indicating increased variability of timing), but does not consistently displace T_{50}. DOI does not alter performance on a similar non-temporal task (light-intensity discrimination), demonstrating that DOI is specifically altering timing and not the mnemonic or attentional processes required to perform the task (Hampson et al., 2010). In the free-operant procedure, DOI reduced T_{50}, suggesting an increase in the speed of the internal clock. The effects of DOI on interval timing are blocked by ketanserin (Asgari et al., 2006; Body et al., 2003) and M100,907 (Asgari et al., 2006; Body et al., 2006a, b). It is not clear why DOI has qualitatively different effects on performance in the

discrete-trials and free-operant procedures, but it is not unusual to find that pharmacological agents do not uniformly alter timing maintained under different reinforcement schedules (Body et al., 2013). Despite these differences, it is clear that DOI alters timing in rats in a 5-HT_{2A} receptor-dependent manner. Fenfluramine also disrupts interval timing in rats, and this effect is blocked by ketanserin (Body et al., 2004), indicating that endogenous 5-HT alters timing by activating 5-$HT_{2A/2C}$ receptors. 5-HT_{2A} receptor polymorphisms are linked to altered timing in humans (Sysoeva et al., 2010), further demonstrating that the 5-HT_{2A} system plays an important role in regulating temporal perception.

Summary and conclusions

Nearly a century has passed since it was first recognized that hallucinogens produce a schizophrenia-like state that can be used to model psychosis. Since that time, there have been substantial advances in neuropharmacology and biological psychiatry, but laboratory models based on the effects of hallucinogenic drugs still play an important role in modern work to characterize the etiology of the illness and identify novel pharmacotherapeutics. Despite the continuing use of hallucinogens as models of psychotic disorders, it could be argued that the most important legacy of the work with hallucinogens during the first half of the twentieth century is the recognition that 5-HT acts as a transmitter substance in the brain and that it might play a role in the group of schizophrenias. Although the degree to which serotonergic alterations contribute to the development and symptoms of schizophrenia remains unclear, it is now known the effects of hallucinogens in humans are mediated primarily by the serotonin 5-HT_{2A} receptor. Importantly, in the four behavioural models discussed above – startle habituation, prepulse inhibition of startle, head twitch response and interval timing – the 5-HT_{2A} receptor has been identified as playing a fundamental role in mediating hallucinogen effects. In addition to the role that the 5-HT_{2A} receptor plays in mediating hallucinogen effects, this receptor is an important target of atypical antipsychotic drugs, and there is at least some evidence that interactions with this site may contribute to their therapeutic profile. Moreover, it is now recognized that interactions between 5-HT_{2A} and mGlu receptors may play a role in the development of schizophrenia and in the putative antipsychotic efficacy of mGlu2/3 agonists. The fact that an animal behavioural model based on hallucinogen effects played a major role in the discovery and characterization of these novel interactions demonstrates the continuing importance of this type of model and indicates that it will likely be even more important in the future.

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