Preclinical models of antipsychotic drug action

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Abstract

One of the main obstacles faced by translational neuroscience is the development of animal models of psychiatric disorders. Behavioural pharmacology studies indicate that psychedelic drugs, such as lysergic acid diethylamide (LSD) and dissociative drugs, such as phencyclidine (PCP), induce in healthy human volunteers psychotic and cognitive symptoms that resemble some of those observed in schizophrenia patients. Serotonin 5-HT2A and metabotropic glutamate 2 receptors have been involved in the mechanism of action of psychedelic and dissociative drugs. Here we review recent advances using LSD-like and PCP-like drugs in rodent models that implicate these receptors in the neurobiology of schizophrenia and its treatment.

Received 4 March 2013; Reviewed 3 April 2013; Revised 26 April 2013; Accepted 30 April 2013; First published online 10 June 2013

Key words: Antipsychotic drugs, epigenetics, lysergic acid diethylamide, metabotropic glutamate 2 receptor, mouse models, phencyclidine, schizophrenia, serotonin 5-HT2A receptor.

Introduction

Schizophrenia is a chronic mental disorder that afflicts nearly 1% of the population worldwide (Sawa and Snyder, 2002; Freedman, 2003; Tamminga and Holcomb, 2005; Lewis and Gonzalez-Burgos, 2006; Ross et al., 2006; van Os and Kapur, 2009; Abbott, 2010; Dobbs, 2010). The first symptoms of schizophrenia generally occur in late adolescence or early adulthood and continue into adult life. These include positive symptoms, such as hallucinations and delusions, and negative symptoms such as alogia (poverty of speech), avolition (lack of motivation) and anhedonia (lack of pleasure). Cognitive deficits, including altered working memory and disordered thought, are present in the majority of schizophrenia patients and are responsible for a significant portion of impairments and disabilities associated with schizophrenic disorders (Green, 1996; Barch and Ceaser, 2012; Minzenberg and Carter, 2012; Curley et al., 2013). It has also been shown that suicide is one of the principal causes of death in schizophrenia patients, with a 50% lifetime risk for suicide attempts in patients with schizophrenia as compared with approximately 5% in the general population (Meltzer et al., 2003a; Hawton et al., 2005; Pompili et al., 2007; Saha et al., 2007).

It is well established that genetics plays a significant role in schizophrenia and schizophrenia spectrum disorders (International Schizophrenia Consortium, 2008; Stefansson et al., 2008, 2009; Walsh et al., 2008; Purcell et al., 2009; Vacic et al., 2011). However, the study of family members supports the conclusion that genetic factors are not sufficient to cause schizophrenia (Tsuang et al., 2001). As discussed earlier, the lifetime prevalence of schizophrenia in the general population is about 1%. This risk of developing schizophrenia increases with the degree of genetic relatedness to the patient. As an example, third-degree relatives (e.g. first cousins) share about 12.5% of their genes and show a risk of about 2%. Second-degree relatives (e.g. half-siblings) share approximately 25% of the genes and show a risk of 6%; whereas first-degree relatives (e.g. siblings and dizygotic twins) share approximately 50% of the genes and show a risk of about 9%. Monozygotic twins, whose DNA sequences are almost 100% identical, have a concordance for schizophrenia of nearly 50% (McGuffin et al., 1994; Cardno and Gottesman, 2000; Gottesman and Erlenmeyer-Kimling, 2001). Such results support the conclusion that genetics plays a significant role in the aetiology of schizophrenia. At the same time, they also favour a
significant contribution of environmental factors in the development of this complex disease (Lewis and Levitt, 2002; Bale et al., 2010). Epidemiological studies have demonstrated that maternal adverse life-events during pregnancy such as famine, war and death of a relative, increase the risk of schizophrenia in the new-borns (Bradley and Dinan, 2010; Markham and Koenig, 2011). It has also been shown that maternal infection during pregnancy raises the risk for schizophrenia (Yolken and Torrey, 2008; Brown and Derkits, 2010; Patterson, 2011). Of particular interest and one of the focuses of this review is the generation of animal models that may help understand the molecular mechanisms through which maternal/foetal gene×environment interactions contribute to the onset of schizophrenia and other psychiatric disorders later in life.

The antipsychotic drugs currently available for clinical use are able to ameliorate some of the symptoms in schizophrenia patients, rather than to reverse the underlying alterations responsible for the disease. Because of this, schizophrenia is still defined as an incurable psychiatric disorder and its treatment typically continues for life. It is reasonable to suspect that schizophrenia, as currently defined, represents a unique human disorder and, consequently, modelling its phenotypic expression in rodent models remains controversial (Arguello and Gogos, 2006; Powell and Miyakawa, 2006; Powell and Geyer, 2007; Geyer, 2008; Pratt et al., 2008; Kellendonk et al., 2009; O'Tuathaigh et al., 2009; Nestler and Hyman, 2010; van den Buuse, 2010; Fernando and Robbins, 2011; Geyer et al., 2012). The neurodevelopmental stages, as well as the anatomical location and neuronal circuits involved in processes of cognition and perception, differ between humans and rodents, which also raises concerns with respect to the translation of preclinical findings into clinical use. Consequently, one of the limitations in molecular psychiatry in general and in schizophrenia research in particular, is the development of rodent models that may help identify new targets for antipsychotic drug development. In this review, we summarize recent advances in our understanding, based on rodent models of psychedelic or dissociative drug exposure, of not only the complex mechanisms associated with antipsychotic drug action, but also the origins of schizophrenia itself.

Pharmacological models of psychosis and antipsychotic drug action

Glutamatergic dissociative drugs such as phencyclidine (PCP), ketamine and dizolcipine (MK801), behave as non-competitive N-methyl-D-aspartate receptor antagonists (Morris et al., 2005; Kristiansen et al., 2007). In an innovative study, Krystal et al. (1994) demonstrated that administration of sub-anaesthetic doses of ketamine into healthy volunteers induces negative symptoms and alterations in working memory and cognition that resemble those observed in schizophrenia patients. A single administration of ketamine does not recreate positive symptoms such as hallucinations, although paranoia and thought disorder are induced (Krystal et al., 1994). Follow-up studies testing the effects of dissociative drugs in healthy volunteers further validated these findings, suggesting alterations in time and sensory perception, thought, speech, mood and affect that resemble some of the psychotic states, negative symptoms and cognitive deficits associated with schizophrenia (Vollenweider et al., 1997a, b, 2000; Adler et al., 1999; Newcomer et al., 1999; Umbricht et al., 2000, 2002; Cho et al., 2005; Krystal et al., 2005; Schmidt et al., 2012, 2013; Driesen et al., 2013). This is supported by the effects of chronic abuse of PCP, which commonly lead to a misdiagnosis of schizophrenia (Rainey and Crowder, 1975; Allen and Young, 1978; Pearson, 1981; Cosgrove and Newell, 1991), whereas PCP administration to schizophrenia patients who are not receiving antipsychotic treatment aggravates positive symptoms (Lahti et al., 2001). Together, these findings point toward a potential dysregulation in glutamatergic synaptic transmission as potentially involved in negative and cognitive symptoms of schizophrenia, as well as in positive symptoms, and support the use of PCP-like dissociative drugs in animals as a preclinical model of psychosis-like behaviour.

Serotonin (5-HT), and in particular the 5-HT2A receptor, has received much attention with regard to schizophrenia and psychosis (Geyer and Vollenweider, 2008; Aghajanian, 2009; Gonzalez-Maeso and Sealfon, 2009b; Geyer et al., 2012). The hallucinogenic properties of the semi-synthetic compound d-lysergic acid diethylamide (LSD) were discovered serendipitously by Albert Hofmann in 1943 (Hofmann, 1959). The 5-HT hypothesis about the mechanism of action of LSD was proposed based on the structural similarities between 5-HT and hallucinogenic drugs such as LSD and psilocin, and the identification of 5-HT as a neurotransmitter (Dahlstrom and Fuxe, 1964). Later in the 1980s, Richard Glennon, Milt Titeler and their collaborators showed a highly significant correlation between the affinities of 22 hallucinogenic compounds for 5-HT2 binding sites and their hallucinogenic potency in humans (Glenon et al., 1984). This milestone work also demonstrated a significant correlation
between the 5-HT2 binding affinities of these agents and drug discrimination ED50 values in rats (Glennon et al., 1984). Further work in healthy volunteers showed that the psychoactive effects of psychedelic drugs such as LSD, mescaline, psilocybin, and N,N-dimethyltryptamine drugs share several features with schizophrenia, including: perceptual disturbances; sensory processing; cognition; changes in brain metabolism; self-representation (Young, 1974; Hermle et al., 1992; Vollenweider et al., 1998; Gouzoulis-Mayfrank et al., 2005; Quednow et al., 2011; Carhart-Harris et al., 2012). Indeed, LSD effects were one of the earliest models of schizophrenia (Keeler, 1965) and are currently believed to model in normal subjects positive symptoms (e.g. hallucinations and delusions) comparable to those seen in drug-naive first-episode schizophrenia patients (Geyer and Vollenweider, 2008; Gonzalez-Maes and Sealfon, 2009b; Geyer et al., 2012) through a mechanism that involves activation of the 5-HT2A receptor in cortical glutamatergic neurons (Beique et al., 2007; Gonzalez-Maes et al., 2007; Celada et al., 2008). It has also been suggested that relatives of schizophrenic patients are more susceptible to the psychotic responses induced by LSD (Anastasopoulos and Photiades, 1962). Although LSD-like drugs as a model of psychosis have limitations (Hays and Tilley, 1973), these findings suggest that a better understanding of their molecular mechanism of action may provide additional insights into the brain processes underlying non-drug-induced psychoses.

Given that schizophrenia is exclusively human, the generation of animal models remains controversial. However, based on their effects in healthy volunteers, psychedelic and dissociative drugs have been considered effective as a tool to model distinct aspects of schizophrenia in rodents and consequently disruption of their behavioural effects has been used as a model that predicts antipsychotic responses in terms of positive, negative or cognitive deficits, depending on the behavioural paradigm used, as well as on whether PCP-like or LSD-like drugs are employed to model psychosis. Some of these behavioural models include those following.

**Modulation of locomotor activity**

In rodents, PCP-like drugs induce hyperlocomotor activity and modulation of this behavioural effect has been repeatedly used as a model of antipsychotic action. It has been suggested that the 5-HT2A receptor is at least in part involved in the effects of atypical (e.g. clozapine, risperidone and olanzapine), but not typical (e.g. haloperidol and chlorpromazine), antipsychotics on the hyperlocomotor response induced by dissociative drugs (Gleason and Shannon, 1997; Bradford et al., 2010; Fribourg et al., 2011; Yadav et al., 2011b). The authors demonstrated that the locomotor response induced by PCP-like drugs in mice was reduced by haloperidol only at doses at which it also reduces the locomotor response in the absence of PCP-like drugs. In contrast, the atypical antipsychotics clozapine and olanzapine reduced the locomotor activity induced by PCP-like drugs at doses that were significantly lower than those that alone affect exploratory behaviour. Atypical antipsychotics all have in common a high affinity for the 5-HT2A receptor and a much lower affinity for the dopamine D2 receptor (Miyamoto et al., 2005; Lieberman et al., 2008). Typical antipsychotics, on the contrary, have an antagonistic effect at the dopamine D2 receptor that has been involved in their mechanism of action (Carlsson et al., 2001; Meltzer et al., 2003b). Importantly, it has been demonstrated that selective 5-HT2A receptor antagonists such as volinanserin (M100907) reduce the locomotor hyperactivity induced by PCP-like drugs in rats and that these doses by themselves do not affect exploratory behaviour (Maurel-Remy et al., 1995). Similar data were obtained in mice (Carlsson, 1995). The role of 5-HT2A receptors in the effects of clozapine on the locomotor response induced by PCP-like drugs has been recently supported by the use of 5-HT2A knockout mice (Fribourg et al., 2011). Although the pre-synaptic component of the serotonergic system plays an important role in the antipsychotic-like properties of clozapine (Yadav et al., 2011a), these results with knockout mice suggest that the 5-HT2A receptor is at least involved in the therapeutic-like effects of atypical antipsychotics, using hyperlocomotor activity induced by PCP-like drugs as a rodent model of psychosis. Recent findings also point toward a role of 5-HT2A receptors expressed in cortical glutamatergic neurons in the effects of high doses of clozapine, but not haloperidol or risperidone, on locomotor suppression (McOmish et al., 2012; Williams et al., 2012).

The psychedelic 5-HT2A/2C receptor agonist 2,5-dimethoxy-4-iodoamphetamine (DOI) has been shown to affect locomotor activity in mice (Gonzalez-Maes et al., 2007; Halberstadt et al., 2009, 2013) and rats (Krebs-Thomson et al., 1998; Van Oekelen et al., 2003; Marona-Lewicka et al., 2005). Low doses of DOI significantly increase locomotor activity, an effect that is absent in 5-HT2A knockout mice (Halberstadt et al., 2009). However, locomotor activity and exploratory behaviour is reduced in mice injected with higher doses of DOI, an effect that remains unaffected in
5-HT$_{2A}$ knockout mice and is reversed by the selective 5-HT$_{2C}$ receptor antagonist SER-082 (Halberstadt et al., 2009). These results suggest that both 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors are involved in the inverted U-shaped dose–response effect of DOI on the locomotor response in mice. A more detailed characterization of the effects of phenylalkylamine psychedelics, including low doses of DOI, mescaline, 2,5-dimethoxy-4-ethylamphetamine, 2,5-dimethoxy-4-propylamphetamine, 2,4,5-trimethoxyamphetamine and 4-bromo-3,6-dimethoxybenzocyclobuten-1-ylmethylamine (TCB-2), shows increased locomotor activity in wild-type mice, an effect that is blocked by M100907 and abolished in 5-HT$_{2A}$ knockout mice (Halberstadt et al., 2013). Interestingly, the effect on locomotor hyperactivity induced by phenylalkylamine psychedelics is not induced by the non-psychedelic phenylalkylamine 2,5-dimethoxy-4-tert-butylamphetamine (DOTB; Halberstadt et al., 2013). These findings suggest that activation of the 5-HT$_{2A}$ receptor by psychedelics, but not by non-psychedelics, increases locomotor activity in mice, which may serve as a model of hallucinogenic potential in humans. Using pharmacological tools in rats, it has been shown that the effects of the phenylalkylamine DOI on exploratory behaviour are reversed by the 5-HT$_{2A}$ receptor antagonist M100907, whereas those of the ergoline LSD are not (Krebs-Thomson et al., 1998). Together, these findings in mice and rats support the link between activation of the 5-HT$_{2A}$ receptor and the unique behavioural effects of phenylalkylamine psychedelics. However, further work is needed to define the pharmacological and molecular mechanisms, such as activation of dopamine D$_2$ receptors (Marona-Lewicka et al., 2005) underlying the differential effects of phenylalkylamine and ergoline psychedelics on locomotor activity and other rodent behaviours.

**Head-twitch behaviour**

Head-twitch behavioural response in rodents is a rapid lateral movement of the head similar to the pinna reflex (Canal and Morgan, 2012). It has been shown to be induced by a variety of psychedelic 5-HT$_{2A}$ receptor agonists such as DOI, 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane, 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane (DOB), mescaline, LSD, TCB-2 and psilocin (Gonzalez-Maeso et al., 2003, 2007; Benneyworth et al., 2008; Canal et al., 2010; Fox et al., 2010; Halberstadt and Geyer, 2013) and reversed by 5-HT$_{2A}$ receptor antagonists (Fantegrossi et al., 2005; Benneyworth et al., 2008; Fribourg et al., 2011). This behaviour is different as compared to head-weaving (slow, side-to-side lateral head movements induced by dissociative drugs; Kozenkov and Gonzalez-Maeso, 2012) and wet-dog shake behaviour (repetitive shaking of the body commonly observed in rodents during morphine withdrawal; Martin et al., 1963). Importantly, the head-twitch behaviour induced by psychedelic drugs is absent in 5-HT$_{2A}$ knockout mice (Gonzalez-Maeso et al., 2003) and rescued in mice that express 5-HT$_{2A}$ receptors only in cortical glutamatergic neurons (Gonzalez-Maeso et al., 2007). Direct injection of psychedelic drugs into medial prefrontal cortex provides additional evidence that head-twitch behaviour is mediated through cortical 5-HT$_{2A}$ receptors (Willins and Meltzer, 1997; see also Gresch et al., 2002 for data suggesting a role of cortical 5-HT$_{2A}$ receptors in the discriminative stimulus properties of LSD).

A long-lasting question in neuropsychopharmacology has been the molecular mechanisms underlying the unique behavioural responses induced by psychedelics as compared with those induced by non-psychedelic 5-HT$_{2A}$ receptor agonists (Nichols, 2004; Gonzalez-Maeso and Sealfon, 2009a). Thus, non-psychedelic 5-HT$_{2A}$ receptor agonists such as lisuride, ergotamine and DOTB, bind with high affinity to and activate the 5-HT$_{2A}$ receptor with similar potencies and efficacies as those observed by psychedelic drugs (Egan et al., 1998; Hoyer et al., 2002). It has been recently shown that only 5-HT$_{2A}$ receptor agonists with psychedelic potential in humans induce a significant head-twitch behaviour in mice and that this behavioural response is not induced by non-psychedelic drugs such as lisuride and ergotamine (Gonzalez-Maeso et al., 2003, 2007). Similar results have recently been reported with the use of a head-mounted magnet and a magnetometer coil (Halberstadt and Geyer, 2013). Together, these findings suggest that head-twitch behaviour may be used as a rodent behavioural model of psychedelic potential in humans.

Modulation of psychedelic-dependent head-twitch behaviour has also been tested as a model of antipsychotic action (see later for discussion).

**Prepulse inhibition of startle**

The development of psychosis is the most striking element of schizophrenia, but deficits in the sensory gating have now been shown as core features of the illness (Barch and Ceaser, 2012; Lewis et al., 2012; Minzenberg and Carter, 2012). Prepulse inhibition (PPI) is a behavioural model that measures sensorimotor gating. In this model, a weak pre-stimulus (auditory or tactile) reduces the startle response to...
a subsequent intense startling stimulus (Geyer and Ellenbroek, 2003). Patients with schizophrenia exhibit deficits in PPI models of the acoustic startle reflex (Ludewig et al., 2003) and impaired PPI response can be used as a measure of alterations in sensorimotor gating in healthy volunteers (Heekeren et al., 2007). PCP-like drugs produce PPI deficits in mice (Dulawa and Geyer, 1996), rats (Mansbach and Geyer, 1991) and non-human primates (Javitt and Lindsley, 2001; Linn and Javitt, 2001). It has also been demonstrated that the psychedelic drugs DOI and LSD disrupt PPI, an effect that is reversed by selective 5-HT2A antagonists such as M100907 (Sipes and Geyer, 1997; Ouagazzal et al., 2001; McFarland et al., 2011). However, compounds that lack psychedelic action (such as lisuride and yohimbine) also disrupt PPI of the acoustic startle in rodent models (Bell et al., 2003; Swerdlow et al., 2003; Powell et al., 2005; Halberstadt and Geyer, 2010). Although this raises concerns about the validity of assessing deficits in PPI as a rodent behaviour model that predicts psychedelic activity, the possibility of cross-species measurements of sensorimotor gating supports the use of PPI of startle in the identification of new antipsychotic medications with special emphasis on attentional deficits present in schizophrenia patients.

**Behaviour models of metabotropic glutamate 2-dependent antipsychotic action**

All antipsychotic drugs currently used in the clinic are dopaminergic and serotonergic receptor ligands. Relatively recent findings using dissociative (Moghaddam and Adams, 1998) and psychedelic (Gewirtz and Marek, 2000) drugs in preclinical models of antipsychotic responses led to the first clinical studies with the metabotropic glutamate 2 and 3 (mGlu2/3) receptor orthosteric agonist LY404039 (active compound of LY2140023; Patil et al., 2007; orthosteric agonists bind to the same binding site as the endogenous neurotransmitter glutamate). These data suggested that LY2140023 represents a potential new approach to treat schizophrenia. However, in two follow-up studies, Eli Lilly and Company published double-blind phase 2 clinical trials showing that neither LY2140023 nor olanzapine were more efficacious than placebo (Kinon et al., 2011), which are inconclusive findings, and that LY2140023 does not separate from placebo whereas the positive control risperidone was efficacious (Eli Lilly and Company, 2012a). These findings preceded the press release that announced the decision to stop the on-going phase 3 clinical trial of the orthosteric mGlu2/3 agonist for the treatment of schizophrenia (Eli Lilly and Company, 2012b). These discouraging findings contrast recent publications with the allosteric positive modulator of the mGlu2 receptor ADX71149 from Addex Inc. in partnership with Janssen R&D (Addex Therapeutics, 2012). Allosteric positive modulators bind to a site distinct from that of the endogenous neurotransmitter; they do not affect basal receptor activity but potentiate the effect of orthosteric agonists. The clinical data show safety and tolerability and demonstrate an effect in negative symptoms of schizophrenia patients (Addex Therapeutics, 2012). Although promising, more molecular, preclinical and clinical data are needed to validate whether activation of the mGlu2 receptor may serve as a new approach to treat this psychiatric disease.

Another question of interest is the therapeutic-like efficacy of different orthosteric mGlu2/3 agonists and allosteric mGlu2 receptor agonists. Most of the preclinical studies assessing the role of mGlu2 and/or mGlu3 receptors in the antipsychotic-like effects of mGlu2/3 receptor agonists have been conducted with orthosteric mGlu2/3 receptor agonists such as LY379268 and LY354740 (Gewirtz and Marek, 2000; Klodzinska et al., 2002; Linden et al., 2004; Winter et al., 2004; Gonzalez-Maes et al., 2008; Woolley et al., 2008; Uslaner et al., 2009; Horiguchi et al., 2011; Jones et al., 2011; Moreno et al., 2011b). At present, there is only one study describing the antipsychotic-like effects of the orthosteric mGlu2 receptor agonist LY404039 (active compound of its prodrug LY2140023 in clinical trials; Fell et al., 2008). The authors tested the effects of LY404039 on the hyperlocomotor activity induced by PCP and amphetamine in mice. While there are limits to the extrapolation of these findings to humans, only a relatively high dose of LY404039 (10 mg/kg) significantly reduced the PCP-induced locomotor activity in wild-type mice (Fell et al., 2008). This antipsychotic-like effect was absent in mGlu2 knockout, but not in mGlu3 knockout, mice. Similar mGlu2-dependent effects have been reported with the mGlu2/3 receptor agonist LY379268 (Woolley et al., 2008). Thus, the effect of LY379268 on the PCP-induced locomotor activity was observed in wild-type and mGlu3 knockout, but not mGlu2 knockout mice (Woolley et al., 2008). However, and importantly, the antipsychotic-like effect of LY379268 on PCP-induced behaviour was seen at doses below 1 mg/kg (Woolley et al., 2008). Consistent with the hypothesis that mGlu2, and not mGlu3, is necessary for the antipsychotic-like effects of mGlu2/3 agonists, data with the allosteric mGlu2 agonists biphenyl-indanone A (Benneyworth et al., 2007) and LY487379 (Galici et al., 2005) show antipsychotic-like behavioural effects using the
tested (Geyer et al., 2012), which raises concerns about the validity of this therapeutic-like behaviour. Recent findings have shown that a functional crosstalk between mGlu2 and 5-HT2A receptors is necessary for the antipsychotic-like effects of LY379268 (Gonzalez-Maeso et al., 2008; Fribourg et al., 2011; Moreno et al., 2011a, 2012). Thus, it was shown that the antipsychotic-like effect of LY379268 (5 mg/kg) on the hyperlocomotor behaviour induced by the PCP-like drug MK801 was mGlu2-dependent and absent in 5-HT2A knockout mice (Fribourg et al., 2011). The authors also demonstrate that some, but not all, mGlu2 receptor agonists bind mGlu2 receptor in complex with the 5-HT2A receptor and alter the pattern of heterotrimeric G protein coupling in a way that predicts their antipsychotic-like behavioural effects (Fribourg et al., 2011). This represents the first biochemical assay that predicts psychoactive behavioural effects of a variety of serotonergic and glutamatergic compounds (Fribourg et al., 2011). Whether the antipsychotic-like effects of LY404039 and other orthosteric mGlu2/3 and allosteric mGlu2 receptor agonists require expression of the 5-HT2A receptor remains to be investigated. Nevertheless, examples of non-antipsychotic drugs that induce antipsychotic-like behaviour in rodents include methysergide, mianserin and ketanserin (Ninan and Kulkarni, 1998; O'Neill et al., 1998; Fletcher et al., 2011; Fribourg et al., 2011; Yadav et al., 2011b; Mestre et al., 2013).

Behaviour models of chronic antipsychotic treatment

In schizophrenia patients, antipsychotic drugs are administered chronically (weeks to months of continuous treatment; Agid et al., 2003). However, most of the animal behaviour models of antipsychotic action are based on a single administration of the drug to be tested (Geyer et al., 2012), which raises concerns about the validity of this therapeutic-like behaviour. Recent findings have shown that down-regulation of 5-HT2A receptor may be one of the mechanisms underlying the antipsychotic-like effects induced by chronic treatment with antipsychotic drugs (Yadav et al., 2011b). The authors assessed the effects of chronic treatment with antipsychotic drugs (clozapine, olanzapine and haloperidol) and with 5-HT2A receptor antagonists/inverse agonists (ketanserin, M100907, M11939, SR46349B and primavanserin) on 5-HT2A receptor protein level and PCP-induced hyperlocomotor activity (Yadav et al., 2011b). Interestingly, chronic treatment with clozapine and olanzapine, but not haloperidol, induced down-regulation of 5-HT2A receptor protein in mouse frontal cortex and decreased the psychosis-like effects of PCP. These effects were not observed after chronic treatment with M100907, M11939, SR46349B or primavanserin. Chronic treatment with the non-antipsychotic ketanserin down-regulated 5-HT2A receptor protein, whereas PCP induced hyperlocomotion was not affected (Yadav et al., 2011b).

Another approach to determine the therapeutic-like effects of chronic treatment with antipsychotic drugs is based on the use of LSD as a mouse model of psychosis (Gonzalez-Maeso et al., 2008; Kurita et al., 2012; Moreno et al., 2013a, b). Administration of psychedelic 5-HT2A receptor agonists induces expression of the immediate early genes c-fos, egr-1 and egr-2 in mouse somatosensory cortex (Gonzalez-Maeso et al., 2003, 2007; Moreno et al., 2013a, b). The authors found that chronic (21 d), but not sub-chronic (2 d), treatment with clozapine eliminates the induction of c-fos, egr-1 and egr-2 by LSD 1 d after the final injection (Moreno et al., 2013b). The induction of c-fos, egr-1 and egr-2 by LSD was not affected with chronic treatment with haloperidol. These findings correlate with the effect of chronic clozapine, but not chronic haloperidol, on 5-HT2A receptor binding in mouse somatosensory cortex. Thus, chronic, but not sub-chronic, treatment with clozapine down-regulated [3H]ketanserin binding, an effect that was not observed after chronic treatment with haloperidol (Moreno et al., 2013b). These findings suggest that down-regulation of 5-HT2A receptor is one of the mechanisms underlying the therapeutic effects of chronic treatment with antipsychotic drugs. Further work is needed to understand the cellular networks responsible for down-regulation of this receptor with antagonists/inverse agonists such as clozapine and olanzapine, as well as their sedative effects (McOmish et al., 2012; Williams et al., 2012).

Rodent models of maternal adverse life-events during pregnancy

While it is clear that genetics plays an important role in schizophrenia (Stefansson et al., 2008, 2009; Walsh et al., 2008; Purcell et al., 2009; Vacic et al., 2011), the genetic mechanisms of transmission are complex as demonstrated by studies of familial segregations and monozygotic twins. Thus, twin studies have shown that the risk for both identical twins to develop schizophrenia is 30–50% (see earlier). Such results point
toward a significant contribution of environmental factors in the development of this neurodevelopmental disease. Interestingly, epidemiological studies repeatedly suggest that maternal environmental factors during pregnancy, such as pathogen infection (e.g. virus, bacteria and protozoa; Menninger, 1919; Brown et al., 2001, 2004, 2005; Babulas et al., 2006; Sorensen et al., 2009; Yudofsky, 2009) and adverse life-events such as famine (Susser et al., 2008), war (van Os and Selten, 1998; Malaspina et al., 2008) and death or illness in a first-degree relative (Khashan et al., 2008) increase the risk of schizophrenia in the adult offspring. Also shown has been an association between foetal hypoxia or anoxia due to obstetric complications during labour and delivery and schizophrenia (Buka et al., 1993; Hirshfeld-Becker et al., 2004; Mittal et al., 2008; Nicodemus et al., 2008). Interestingly, recent findings demonstrate that mouse models of maternal viral infection and maternal variable stress may serve as preclinical models for future studies to investigate the mechanisms and alterations in gene×environment interactions responsible for schizophrenia symptoms.

Radioligand binding assays in post-mortem human brain samples suggest that 5-HT2A receptor binding is increased and mGlu2/3 binding is decreased in frontal cortex of untreated schizophrenic subjects (Gonzalez-Maeso et al., 2008; Moreno et al., 2012; Muguruza et al., 2012). Similar alterations have been reported in two mouse models of maternal adverse life-events: influenza virus infection (Moreno et al., 2011b); variable and unpredictable stress (Holloway et al., 2013). Thus, adult mice born to influenza virus infected mothers show up-regulation of 5-HT2A receptor and down-regulation of mGlu2/3 receptors (Moreno et al., 2011b). These biochemical changes correlate with behavioural alterations: increased head-twitch behaviour induced by the psychedelic drug DOI; decreased effect of LY379268 on the MK801-dependent locomotor activity (Moreno et al., 2011b). Interestingly, a similar pattern of biochemical and behavioural changes has been shown in adult mice born to stressed mothers during pregnancy (Holloway et al., 2013). It has also been suggested that the existence of epigenetic modifications at the promoter regions of 5-HT2A (Htr2a), mGlu2 (Grm2) and mGlu3 (Grm3) genes correlates with this pattern of expression and their behavioural function (Matrisciano et al., 2012). As reviewed earlier, both maternal infection and maternal severe stress during pregnancy are implicated as having an aetiological role in schizophrenia. Numerous experimental investigations have provided robust evidence that adverse life experiences profoundly modulate immune cell functions (Maes et al., 1998; Steptoe et al., 2001; Vanbesien-Maillot et al., 2007; Garcia-Bueno et al., 2008) and it is thought that activation of the maternal immune system produces cytokines and chemokines that ultimately alter neurogenesis and migration of neurons during brain development, contributing to schizophrenia risk (Nawa and Takei, 2006; Bilbo and Schwarz, 2009; Deverman and Patterson, 2009). Further investigation is necessary to understand the gene×environment interactions as well as the contribution of specific components of the maternal immune system responsible for schizophrenia and other neurodevelopmental disorders in the adult offspring.

Conclusions

In this review, we summarize some of the current knowledge of animal models of psychosis and antipsychotic action. The antipsychotics currently used in clinical practice are designed to treat the symptoms of the disease. As yet, the underlying mechanisms responsible for the onset of psychosis in schizophrenia patients remain largely unknown. About 30% of the patients are considered treatment resistant and will continue to experience schizophrenia symptoms despite the use of antipsychotic drug treatment. Recent preclinical (Kurita et al., 2012) and clinical (Citrome et al., 2004; Meltzer et al., 2011) findings have proposed the use of epigenetic drugs to inhibit histone deacetylation in order to improve the clinical efficacy of the currently available antipsychotic drugs. Although psychedelic and dissociative drugs as a model of schizophrenia have limitations, some of the findings summarized in this review suggest that their use in animal models may serve as a tool to find new antipsychotic drugs for treatment and also prevention of schizophrenia and other psychotic disorders.

Acknowledgements

This study was supported by NIH R01 MH084894, Dainippon Sumitomo Pharma, NARSAD and The Mortimer D. Sackler Foundation (I.G.M.).

Statement of Interest

None.

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