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REVIEW

Leading compounds for the validation of animal models of psychopathology

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Abstract Modelling of complex psychiatric disorders, e.g., depression and schizophrenia, in animals is a major challenge, since they are characterized by certain disturbances in functions that are absolutely unique to humans. Furthermore, we still have not identified the genetic and neurobiological mechanisms, nor do we know precisely the circuits in the brain that function abnormally in mood and psychotic disorders. Consequently, the pharmacological treatments used are mostly variations on a theme that was started more than 50 years ago. Thus, progress in novel drug development with improved therapeutic efficacy would benefit greatly from improved animal models. Here, we review the available animal models of depression and schizophrenia and focus on the way that they respond to various types of potential candidate molecules, such as novel antidepressant or antipsychotic drugs, as an index of predictive validity. We conclude that the generation of convincing and useful animal models of mental illnesses could be a bridge to success in drug discovery.

Keywords Depression · Schizophrenia · Animal models · Antipsychotics · Antidepressants

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Introduction

Animal models in neuroscientific research are of irreplaceable value. They are important tools for the assessment of pathological mechanisms, for the testing of hypotheses that cannot be addressed in clinical studies and for the development of novel pharmacological treatment (Nestler et al. 2002). Psychiatric disorders such as depression and schizophrenia (SCZ) are difficult to replicate in a laboratory animal. At the same time, no animal model is able to fully mimic any mental illness, as these are characterized by specific disturbances in functions that are absolutely unique to humans, such as markedly diminished interest, thought disorders and hallucinations (American Psychiatric Association 2000). However, a general approach is to reproduce particular symptoms of psychiatric diseases (i.e., attention/cognitive deficits) in laboratory animals or to develop models (i.e., the forced swim test) to identify novel compounds as potential treatments (Cryan et al. 2002; Meyer et al. 2009). Ideally, an animal model should reflect the human psychiatric disease in terms of face validity (i.e., reproduce the symptoms of the human mental disease), construct validity (i.e., replicate the neurobiological abnormalities) and predictive validity (i.e., response to the pharmacological treatment in a way that predicts the effects of that treatment in humans). Nevertheless, none of the available animal models are able to mimic all the aspects of neuropsychiatric disorders, in terms of neurobiological mechanisms and disease symptoms and most likely never will. Therefore, the lack of knowledge regarding the mechanisms that underlie diseases such as depression and SCZ, their comorbidity and symptomatic overlap between them (i.e., patients with psychotic depression) is associated with the partial efficacy of the present pharmacological armoury. This raises the central question to be addressed in this review: are current animal models reliable tools with a predictive validity for the development of novel therapeutic compounds?

Table 1 Behavioural effects of clinically prescribed antidepressants in validated animal models of depression (*SSRI* selective serotonin reuptake inhibitor, *SNRI* serotonin and noradreniline reuptake inhibitors)

Rodent model of depression	Behavioural antidepressant-like response	Drug treatment
Olfactory bulbectomy	↓ Hyperactivity in the open field test (after chronic drug administration)	Tianeptine, sertraline (Kelly and Leonard 1994), desipramine (Kelly and Leonard 1996), amitryptiline (Stockert et al. 1988), imipramine (Roche et al. 2008), citalopram (Hasegawa et al. 2005; Nguyen et al. 2009), fluvoxamine (Saitoh et al. 2007), fluoxetine (Freitas et al. 2013; Machado et al. 2012; Roche et al. 2007), buspirone (Sato et al. 2010), agomelatine (Norman et al. 2012), tiagabine (Pistovcakova et al. 2008)
Learned helplessness	↓ Number of failures to escape shock	Imipramine (Besson et al. 1999; Demontis et al. 1993; Gambarana et al. 1995; Geoffroy et al. 1991; Ishida et al. 2005; Iwamoto et al. 2005; Iwata et al. 2006; Joca et al. 2003; Martin and Puech 1991; Martin et al. 1987; Meloni et al. 1993; Takamori et al. 2001), desipramine (Beck and Fibiger 1995; Besson et al. 1999; Centeno and Volosin 1997; Duman et al. 2007; Joca et al. 2006; Martin et al. 1987; Rojas-Corrales et al. 2004; Rusakov and Valdman 1983), chlorimipramine (Rusakov and Valdman 1983), clomipramine (Martin and Puech 1991; Martin et al. 1987; Millan et al. 2001), amitriptyline (Besson et al. 1999; Caldarone et al. 2003; Rusakov and Valdman 1983), trazodone (Rusakov and Valdman 1983), tranylcypromine, mianserine (Takamori et al. 2001), venlafaxine (Millan et al. 2001; Rojas-Corrales et al. 2004), fluvoxamine (Iwamoto et al. 2005; Martin and Puech 1991; Rojas-Corrales et al. 2004; Takamori et al. 2001), mirtazapine (Slattery et al. 2005), fluoxetine (Iwamoto et al. 2005; Marco and Laviola 2012; Marcussen et al. 2008; Page and Abercrombie 1997; Reines et al. 2008; Shumake et al. 2010; Zazpe et al. 2007), paroxetine (Zazpe et al. 2007), sertraline (Duman et al. 2007), St. John's wort extract (Chatterjee et al. 1998), buspirone (Lucki 1991; Martin and Puech 1991); citalopram (Martin and Puech 1991; Millan et al. 2001), escitalopram (Reed et al. 2008), zimelidine (Dabrowska et al. 2008; Joca et al. 2006), lamotrigine (Consoni et al. 2006), agomelatine (Bertaina-Anglade et al. 2006; Dagyte et al. 2011; Popoli 2009; Tardito et al. 2010)
Forced swim test	↓ Time of immobility (↑ swimming or climbing activities) (after acute drug administration)	Amitryptiline (Caldarone et al. 2003), tianeptine (Della et al. 2012; Kelly and Leonard 1994; Solich et al. 2008), imipramine (Bourin et al. 2004; Della et al. 2012; Kulkarni and Dhir 2007; Paulke et al. 2008; Schulte-Herbrueggen et al. 2012; Zanelati et al. 2010), desipramine (Robles-Molina et al. 2012; Simpson and Kelly 2012; Will et al. 2003), venlafaxine (Kulkarni and Dhir 2007), sertraline (Kelly and Leonard 1994; Leggio et al. 2008; Rogoz and Skuza 2006), paroxetine (Akagawa et al. 1999; Leggio et al. 2008), reboxetine (Cryan et al. 2005b; Wong et al. 2000), phenelzine (Bourin et al. 2002; Will et al. 2003), tranylcypromine, agomelatine (Bourin et al. 2002, 2004), fluoxetine (Bourin et al. 2004; Cryan et al. 2005b; Kulkarni and Dhir 2007; Reed et al. 2008; Rogoz and Skuza 2006), paroxetine (Karanges et al. 2011), moclobemide (Cryan et al. 2005b), pramipexol (Rogoz and Skuza 2006; Schulte-Herbrueggen et al. 2012), mirtazapine (Muguruza et al. 2013), St. John's wort extract (Paulke et al. 2008), citalopram (Leggio et al. 2008; Nguyen et al. 2009; Tamburella et al. 2009, 2013), escitalopram (Nguyen et al. 2013; Reed et al. 2008), clomipramine (Consoli et al. 2005, 2007; Leggio et al. 2008; Micale et al. 2006, 2008a, 2008b; Tamburella et al. 2009, 2010, 2013)
	False positive results	Amphetamines (Cryan et al. 2002), caffeine (Slattery and Cryan 2012)
Tail suspension test	↓ Time of immobility (after acute drug administration)	Mianserine, nomifensine, viloxazine (Steru et al. 1985), amitryptiline (Caldarone et al. 2003; Steru et al. 1985), desimipramine (Berrocoso et al. 2013; O'Leary et al. 2007; Steru et al. 1985), imipramine (Berrocoso et al. 2013; Kulkarni and Dhir 2007; Liu and Gershenfeld 2001), reboxetine (O'Leary

Table 1 (continued)

Rodent model of depression		Behavioural antidepressant-like response	Drug treatment
			et al. 2007; Wong et al. 2000), tianeptine (Berrocoso et al. 2013), fluoxetine (Berrocoso et al. 2013; Kulkarni and Dhir 2007; Muguruza et al. 2013; O'Leary et al. 2007), mirtazapine (Muguruza et al. 2013), venlafaxine, duloxetine (Berrocoso et al. 2013; Kulkarni and Dhir 2007), citalopram (Berrocoso et al. 2013)
Chronic mild stress		↑ Responsiveness to rewards (after chronic drug administration)	Fluoxetine (Jindal et al. 2013; Muscat et al. 1992; Mutlu et al. 2012), maprotiline (Muscat et al. 1992), minaserin (Cheeta et al. 1994), imipramine (Marston et al. 2011; Norman et al. 2012; Papp et al. 1996; Przegalinski et al. 1995), buspirone (Papp et al. 1996; Przegalinski et al. 1995), ipsapirone (Przegalinski et al. 1995), agomelatine (Bourin et al. 2004; Dagyte et al. 2011), risperidon (Marston et al. 2011), citalopram (Herrera-Perez et al. 2010; Przegalinski et al. 1995), escitalopram (Christensen et al. 2012), tianeptine (Mutlu et al. 2012)
Social stress—repeated defeat	Resident-intruder	↓ Agressivity, ↑ flight	Acute: SSRIs, SNRIs, tricyclics (Mitchell and Neumaier 2005)
		↑ Aggressivity	Chronic: SSRIs, SNRIs, tricyclics (Mitchell and Neumaier 2005)
		↑ Ambulation in open field test	Fluoxetine, reboxetine (Rygula et al. 2006, 2008)
	Group-housed vs. singly-housed aggressive partner	↑ Ambulation in open field test	Chronic: citalopram, valproate, felbamate (Pistovcakova et al. 2005; Sulcova 1999)

Status of current animal models of depression and their pharmacological validation

Unfortunately, an animal model that perfectly includes the aetiology, pathophysiology and symptoms of depression while allowing an evaluation of the responses to treatments remains difficult to envisage. Although the generation of genetically modified mice could result in animal models mimicking genetic, biochemical or behavioural characteristics of human depression, we have to keep in mind the role of major confounding factors such as background strain, neurodevelopment or interactions between genetic and environmental factors during the interpretation of any findings (Urani et al. 2005). However, various models, each with specific limitations, are able to reproduce most of the aetiological factors and symptoms of the disease or possess a satisfactory predictive value for identifying new compounds. On this basis, we review the validation of rodent models of depression, such as bilateral olfactory bulbectomy (OBX), learned helplessness, the forced swim test (FST) or the tail suspension test (TST) and the chronic mild stress (CMS) or chronic social stress paradigm, according to the effects of pharmacological interventions that have successfully achieved antidepressive-like activities in animals and treatment efficacy in depressive patients.

Olfactory bulbectomy

OBX results in behavioural (i.e., hyperactive response in the open field paradigm) and neurochemical (i.e., changes in the endocrine, immune and neurotransmitter systems) alterations in rats (Cairncross et al. 1975; Jesberger and Richardson 1985; Kelly et al. 1997) and mice (Hellweg et al. 2007; Zanelati et al. 2010; Zueger et al. 2005); the alterations resemble some of those seen in depressed patients and are reversed by chronic treatment with clinically approved or potential antidepressants (Tables 1 and 2). Since the olfactory system in rodents is part of the limbic region in which the amygdala and hippocampus contribute to emotional behaviour, OBX affects the cortical-hippocampal-amygdala circuit, which also seems to be dysfunctional in depressed patients (Song and Leonard 2005). Interestingly, a dysregulation of the functionality of the central reward pathway in bulbectomized rats has also been reported, suggesting that it may have an impact on the development of depression/addiction comorbidity. Thus, OBX could be a useful animal model of these dual diagnosis disorders (Kucerova et al. 2012).

Learned helplessness

Learned helplessness might model in animals a human situation of unpredictable and uncontrollable events leading to consequences: "stress-coping depression". Thus, the animal model is considered to provide specificity towards antidepressant pharmacotherapy (Chourbaji et al. 2005; Christensen 1993; Maier 1984; Miller and Seligman 1976; Seligman and Beagley 1975; Sherman et al. 1982; Vollmayr and Henn 2001). Animals exposed to inescapable and unavoidable electric shocks in one situation later fail to escape shock in a

different situation in which escape is possible. A drug is considered to be effective as an antidepressant if the learned helplessness is reduced (the number of failures to escape is decreased). However, we need to assess a depressive-like phenotype in experimental animals and exclude some subjects from the study. In mice, approximately 30 % of individuals reportedly become helpless after shock exposure. However, the remaining animals show helpless behaviour with high escape latency and thus a low number of failures to escape might be attributable to variable pain sensitivity (Chourbaji et al. 2005). Parameters for inescapable shock and the testing of learned helplessness to minimize artifacts have been stated in a study published elsewhere (Chourbaji et al. 2005). Two rat lines have also been established by selective breeding, namely helpless and non-helpless, which differ in neurochemical and behavioural parameters that are known to be related to depression (Henn and Vollmayr 2005).

Forced swim test and tail suspension test

These two tests are widely used paradigms specifically developed to test new antidepressants. In the FST (also known as Porsolt's test; Porsolt et al. 1977), rodents are forced to swim in an inescapable cylinder and will eventually adopt a characteristic immobile posture that is interpreted as a passive stress-coping strategy or depression-like behaviour (behavioural despair). The FST has shown its ability to detect a broad spectrum of substances that are therapeutically effective in human depression, as these drugs shift passive-stress coping towards active coping, which is detected as reduced immobility (Table 1). Furthermore, the quantity of the different movements, such as climbing or swimming behaviour, has a predictive value for differentiating between noradrenergic (NAergic) and serotonergic (5-HTergic) activity (Cryan et al. 2002). However, care must be taken with regard to the strain (variations have been shown between inbred and outbred mice and rats) used for the test because of differential spontaneous locomotor activity possibly reducing the duration of immobility (Crawley et al. 2007; Petit-Demouliere et al. 2005). False positive results can be obtained when testing drugs with psychostimulant activity, e.g., amphetamines, caffeine (Cryan et al. 2002; Slattery and Cryan 2012).

Similar assumptions and interpretations to those for the FS, can be drawn from the TST (Steru et al. 1985). In this test, mice are suspended by their tails for a defined period of time during which their immobility is decreased by several antidepressants. The percentage of animals showing passive behaviour should be counted and then compared with that after vehicle or active drug treatment, as several mouse strains have been shown to be essentially resistant to tail-suspension-induced immobility (Cryan et al. 2005a). The test however is sensitive to acute treatment only and its validity for non-monoamine antidepressants is uncertain (Berrocoso et al. 2013; Cryan et al. 2005b).

Chronic mild stress

Chronic mild stress procedures (food or water deprivation, 45° cage tilt, intermittent illumination, soiled cage, paired housing or low-intensity stroboscopic illumination), applied for a period of several consecutive weeks decrease the responsiveness to rewards (consumption of a 1 % sucrose solution) in rats or mice; this is reversed by chronic administration of antidepressant drugs. This "chronic mild stress model" is considered to represent anhedonia in depression (Papp et al. 1996; Willner 1984, 1997; Willner et al. 1992). In comparison with other animal models of depression, it has been evaluated as a high perspective research approach, despite its procedural complexity and difficult reproducibility (Porsolt 2000). Chronic treatment with clinically used antidepressants normalizes sucrose drinking (Table 1).

Drug-withdrawal-induced anhedonia

A withdrawal from abuse of psychoactive compounds (e.g., cocaine, amphetamines) is known to be associated with states of depression in humans and depressive-like states in animals (Barr and Phillips 1999; Jang et al. 2013; Renoir et al. 2012). The animal model "drug-withdrawal-induced anhedonia" is based on experimental experience with laboratory rodents; upon their withdrawal from long-term treatment with psychostimulatory agents, they show mild food and water avoidance as depressive-like symptoms (anhedonia) in response to rewards in various paradigms, e.g., place preference, i.v. drug self-administration, electric intracranial self-stimulation or sucrose solution preference (Barr and Phillips 1999; Cryan and Mombereau 2004). Rates of reward responding is increased by subsequent treatment with antidepressants, e.g., imipramine and amitriptyline (Kokkinidis et al. 1980).

Chronic social stress

Repeated social stress was suggested as an aethologically relevant animal model of depression in mice (Keeney and Hogg 1999), rats (Rygula et al. 2005) and tree shrews (Fuchs 2005). Any behaviour indicative of social conflict such as threat, attack, fight or escape, avoidance or subordination is called agonistic behaviour and encompasses the actions of both the instigator and the victim (Scott 1966). Compared with control individuals, the animals that are subjected to repeated agonistic encounters exhibit significantly reduced locomotor activity in the open field test, which, in turn is normalized by previously clinically proven or potential antidepressants, e.g., citalopram or valproate and by potential

antidepressants, e.g., felbamate (Pistovcakova et al. 2005; Sulcova and Pistovcakova 2008; Table 1).

Alterations of hypothalamic-pituitary-adrenal functions have been established in states of depression and stress, including social stress conditions, in both humans and animals (Blanchard et al. 2001; Kubera et al. 2011; Mathews et al. 2006; Morris et al. 2012). In rodents, social defeat and subordination are stressful, especially in males (Blanchard et al. 2001; Martinez et al. 1998). Animals that are subjected to repeated agonistic encounters are used for testing potential antidepressant treatment effects (Mitchell 1994, 2005; Sulcova 1999). The same stress procedure results in increased release of corticosterone and dopamine (DA). Felbamate decreases NA concentrations and inhibits the stress-induced rise in corticosterone and DA. Modulation of stress hormone release has been suggested to be induced by the action of felbamate on glutamate neurotransmission and neuroendocrine changes might contribute to behavioural effects of the drug (Pistovcakova et al. 2005). The mood-stabilizing action of felbamate and other anti-epileptic drugs has been proposed by clinicians for further verification (Cavanna et al. 2010).

Current leading compounds for development of new antidepressants

Pharmacological analyses of action of clinically approved antidepressants support the predictive validity of the animal models presented. However, consideration of the behavioural and molecular phenotypes corresponding to the human disorders suggests that these models are also useful for the improvement of our knowledge of the neuronal mechanisms of the disease, the biomarkers of its specific symptoms and the integration of basic and clinical methodologies (translational medicine) for the development of new antidepressants (Borsini 2012; Cryan et al. 2002; Dzirasa and Covington 2012; Kluge et al. 2011; Neumann et al. 2011; Rupniak 2003). Taking into account that the 5-HT hypothesis of depression has not been abandoned (Albert and Benkelfat 2013), the targets of potential relevance as treatments for mood disorders are also those involved in the regulation of several other neuronal systems in the brain, including the opioid system (Pradhan et al. 2011), the cholinergic system (Drevets et al. 2013), the endocannabinoid system (Marco and Laviola 2012; Micale et al. 2013), the neuropeptidergic signalling system (Griebel and Holsboer 2012), the melatoninergic system (Lanfumey et al. 2013) and the glutamatergic system (Connolly and Thase 2012; Hashimoto 2011; Javitt 2012; Machado-Vieira et al. 2012; Mathews et al. 2012; Serafini et al. 2013; Tokita et al. 2012). Thus, attention should be given to compounds influencing these systems, which have been shown to produce antidepressant-like effects in animal models. Currently, the compounds that modulate glutamatergic neurotransmission are reported to hold the greatest promise for the development of new antidepressants (Serafini et al. 2013). Suggested mechanisms are based on the antagonistic influence on ionotropic N-methyl-D-aspartate (NMDA) receptors, the modulation of metabotropic glutamate receptors, especially the negative modulation of mGlu2/3 and mGlu5 receptors (Chaki et al. 2013) and the positive modulation of mGlu2 and mGlu7 receptors (Sanacora et al. 2012). The animal model studies with leading glutamatergic compounds are cited in Table 2.

Status of current animal models of SCZ and their pharmacological validation

SCZ, described by Kraepelin in 1896 as a dementia praecox, is a unique human disorder for which modelling in animals might prove problematic because of the lack of a uniform set of symptoms in patients and indictions of the heterogeneity of the disorder. Thus, a greater understanding of the disorder might arise from modelling specific signs and symptoms, as opposed to the entire syndrome. In line with this strategy, several efforts have been directed at developing animal models that allow the translation of the symptomatology in SCZ and prediction of antipsychotic activity. Although positive symptoms such as hallucinations and delusions cannot be measured in animals, the most reliable behavioural indices of positive symptoms in animal models are hyperlocomotor activity and behavioural stereotypes that mimic the psychomotor agitation and presence of stereotyped behaviour in acutely psychotic patients (Young et al. 2010). The rationale for the use of these indices is based upon the principle that the hyperfunction of the mesolimbic DAergic system, which seems to be involved in the enhanced locomotor activity and stereotyped behaviours, is consistent with the clinical conditions in which enhanced subcortical DAergic activity plays a pivotal role in precipitating positive symptoms (Murray et al. 2008). The loss of selective associative learning in the form of the disruption of latent inhibition, which is also induced by hyperdopaminergic activity at the subcortical level, seems to be another cross-species translational index relevant to positive symptoms of SCZ (Weiner 2003). Indeed, some behavioural aspects of SCZ can be modelled and objectively assessed in rodents. More specifically, anhedonia and social behaviour as hallmarks of negative symptoms in humans can be assessed in rodents, together with prepulse inhibition, which reflects disrupted sensory gating abilities both in schizophrenic patients and in experimental animal models (Young et al. 2010). Finally, the various cognitive aspects affected in the disease, as identified by the NIH Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative (Marder and Fenton 2004), can be

Table 2 Antidepressant-like effects of glutamatergic leading compounds in animal models of depression (*NMDA* N-methyl-D-aspartate, *AMPA* α-amino-3-hydroxy-5-methylisoxazole-2-proprionic acid)

Pharmacological mechanism	Compound: animal models (references)
NMDA receptor antagonist	Ketamine: learned helplessness, tail suspension test (Koike et al. 2011), forced swim test (Engin et al. 2009; Lindholm et al. 2012), chronic mild stress (Garcia et al. 2009)
mGlu2/3 receptor antagonist	MGS0039: tail suspension test (Koike et al. 2011), learned helplessness (Yoshimizu et al. 2006), olfactory bulbectomy (Palucha-Poniewiera et al. 2010), forced swim test (Kawasaki et al. 2011); LY341495: tail suspension test (Chaki et al. 2004; Koike et al. 2013)
mGlu2/3 receptor allosteric negative modulator	RO4491533: tail suspension test (Campo et al. 2011)
mGlu2 receptor allosteric potentiator	THIIC: forced swim test (Fell et al. 2011)
mGlu5 receptor uncompetitive antagonist	MTEP: tail suspension test, forced swim test (Belozertseva et al. 2007; Li et al. 2006)
mGlu5 receptor negative allosteric modulator	GRN-529: tail suspension test, forced swim test (Hughes et al. 2013)
mGlu7 receptor allosteric agonist	AMN082: tail suspension test, forced swim test (Bradley et al. 2012)
NMDA receptor glycine-site partial agonist	GLYX 13: learned helplessness, forced swim test (Ashton and Moore 2011; Burgdorf et al. 2013)
AMPA receptor potentiator	LY 451646: forced swim test (Lindholm et al. 2012)

experimentally addressed in animal models by the use of specific test batteries (Peleg-Raibstein et al. 2012). Among the several approaches used to create experimental animal models of SCZ, which also include the lesion model (Jones et al. 2011) and genetic-based preparations (Inta et al. 2010), we will examine, in the following discussion, (1) pharmacological models and (2) neurodevelopmental models that are the most used in drug discovery studies (Tables 3, 4)

Pharmacological models

Hyperfunction of the DAergic system in the mesolimbic pathway was the original tenet for the occurrence of SCZ; thus, the first animal models were developed on the basis of the pharmacological manipulation of the DAergic system in an attempt to mimic this dysregulation (Carlsson et al. 2001). In rodents, repeated treatment with the DA-releasing agent amphetamine induced a persistent sensitization exaggerating the hyperactivity caused by an acute amphetamine challenge, which was prevented by antipsychotic pre-treatment. This model is supported by the observation that chronic psychostimulant abuse can lead to psychotic episodes, whereas low doses of amphetamine worsen the symptoms (Featherstone et al. 2007). Amphetamine sensitization is also characterized by deficits in prepulse inhibition or latent inhibition and in prefrontal-cortex-dependent cognitive tasks, whereas hippocampal function is unaltered (Peleg-Raibstein et al. 2012; Russig et al. 2002, 2005; Tenn et al. 2005). Furthermore, it is accompanied by neurochemical (i.e., increase in DA, NA and 5-HT efflux in nucleus accumbens, striatum or prefrontal cortex) and structural changes (i.e., reduction of parvalbumin and brain-derived neurotrophic factor expression in the medial prefrontal cortex and hippocampus, respectively) (Doucet et al. 2013; Morshedi and Meredith 2007; Motawaj and Arrang 2011; Salomon et al. 2006). However, it fails to induce any deficits in social activity as an index of negative symptoms and therefore limits the conformity to available human data (Srisurapanont et al. 2003, 2011). Similarly, the preferential DA receptor agonist apomorphine has induced a SCZ-like phenotype in rodents (Peleg-Raibstein et al. 2012). Overall, behavioural changes induced by DA-stimulating drugs have been employed as models of psychosis or cognitive-related abnormalities but they fail to capture cardinal aspects of negative symptoms.

The glutamate hypothesis of SCZ has been developed from the observation that NMDA receptor antagonists induce, in normal humans, a psychosis-like state (plus negative and cognitive symptoms) that closely resembles SCZ, leading to the establishment of glutamatergic models of SCZ (Javitt 2012). In animals, acute phencyclidine (PCP) treatment induces hyperactivity and disruption of prepulse inhibition; this is reversed by atypical but not typical antipsychotics (Mouri et al. 2007). However, both classes of antipsychotic agents are able to counteract the ketamine-induced deficits, suggesting a different involvement of D2 receptors in the PCP or ketamine effects (Neill et al. 2010). Acute PCP treatment affects social activity and sucrose consumption, as indices of negative symptoms and various different cognitive domains (Mouri et al. 2012; Turgeon and Hulick 2007). More conflicting results have been obtained from repeated PCP treatment, which elicits reduced (Snigdha and Neill 2008) or no effects (Sams-Dodd 2004) on social behaviour and an improvement in negative-like symptoms (Brigman et al. 2009). PCP-induced deficits have also been found in various cognitive domains, which are counteracted by atypical antipsychotics (Amitai et al. 2007; Kunitachi et al. 2009). However, in clinical practice, antipsychotics do not

Table 3 Pharmacological models of schizophrenia (*5-HT* serotonin, *AMY* amygdala, *ARI* aripiprazole, *BDNF* brain-derived neurotrophic factor, *BLA* basolateral amygdala, *CB* cerebellum, *CLZ* clozapine, *DA* dopamine, *DRD2* dopamine D2 receptor, *FC* frontal cortex, *GLU* glutamate, *HPC* hippocampus, *HP* haloperidol, *mPFC* medial prefrontal cortex, *ND* not determined, *NE* noradrenalin, *NOR-1* nuclear orphan receptor 1, *PFC* prefrontal cortex, *PPI* prepulse inhibition, *PV* parvalbumin, *OLA* olanzapine, *RIS* risperidone)

Drug	Positive-like symptoms	Negative-like symptoms	Spatial/working memory	Latent inhibition	Prepulse inhibition	Neurochemical changes	Antipsychotic response	References
Dopamine agonists								
Amphetamine	Yes	No	Deficit	Deficit	Deficit	↑ Mesolimbic DA ↑ NE and 5-HT in the PFC ↓ PV in the mPFC ↓ BDNF in the HPC	Deficits reversed by CLZ and HP	Doucet et al. 2013, Featherstone et al. 2007, Morshedi and Meredith 2007, Motawaj and Arrang 2011, Peleg-Raibstein et al. 2012, Russig et al. 2002, 2005, Salomon et al. 2006, Srisurapanont et al. 2003, 2011, Tenn et al. 2005
Apomorphine	Yes	ND	Deficit	Deficit	Deficit	↓ mGluR5 in the PFC	PPI deficit reversed by CLZ	Geyer and Ellenbroek 2003, Gourgiotis et al. 2012, Leng et al. 2003, Melo et al. 2009, Posch et al. 2012, Shao et al. 2010
NMDA receptor antagonists								
Phencyclidine	Yes	Yes	Deficit	Deficit	Deficit	↓ DA and GLU in the PFC ↓ PV in the FC,HPC and CB ↓ CaMKII in the PFC ↓ ERK in the HPC and AMY ↑ 5-HT in the PFC	Deficits reversed by HP, CLZ, ARI, RIS and OLA	Amitai et al. 2007, Bullock et al. 2009, Kunitachi et al. 2009, Li et al. 2011, Mouri et al. 2007, 2012, Noda et al. 2000, Pollard et al. 2012, Turgeon and Hulick 2007
Ketamine	Yes	Yes	Deficit	Deficit	Deficit	↓ PV in the HPC	Deficits reversed by HP, CLZ and RIS	Enomoto and Floresco 2009, Gama et al. 2012, Gao et al. 2009, Maehara et al. 2011, Neill et al. 2010, Pitsikas et al. 2008, Razoux et al. 2007, Rujescu et al. 2006
Dizocilpine (MK-801)	Yes	Yes	Deficit	Deficit	Deficit	↑ GLU and 5-HT in the mPFC ↓ PV in the mPFC, HPC and BLA	Deficits reversed by HP, CLZ, OLA and RIS	Feinstein and Kritzer 2013, Gaisler-Salomon et al. 2008, Gururajan et al. 2012, Lopez-Gil et al. 2007, 2012, Mutlu et al. 2012, Ozdemir et al. 2012, Romon et al. 2011, Uehara et al. 2012, Wiescholleck and Manahan-Vaughan 2013
5-HT agonist								
Lysergic acid diethylamide (LSD)	Yes	Yes	ND	ND	Deficit	↑ DRD2, 5-HT2c and NOR1 in the mPFC	CLZ reversed positive symptoms. HP has no effects on PPI disruption	Marona-Lewicka et al. 2011, Moreno et al. 2011, 2013, Ouagazzal et al. 2001, Palenicek et al. 2010
Muscarinic acetylcholine receptor antagonist								
Scopolamine	Yes	Yes	Yes	Deficit	Deficit	ND	PPI deficit reversed by CLZ and HP	Barak and Weiner 2010, 2011b, Depoortere et al. 2007, Guan et al. 2010, Harada et al. 2012, Johnson et al. 2005, Shannon and Peters 1990, Singer and Yee 2012

Table 4 Neurodevelopmental models of schizophrenia (*5-HT* serotonin, *AMY* amygdala, *CLZ* clozapine, *DA* dopamine, *dHPC* dorsal hippocampus, *GLU* glutamate, *HPC* hippocampus, *HP* haloperidol, *MAM* methylazoxymethanol, *mPFC* medial prefrontal cortex, *NAc* nucleus accumbens, *PFC* prefrontal cortex, *PV* parvalbumin, *OLA* olanzapine, *RIS* risperidone, *SER* sertindole, *vHPC* ventral hippocampus, *VTA* ventral tegmental area)

Experimental method	Positive-like symptoms	Negative-like symptoms	Spatial/working memory	Latent inhibition	Prepulse inhibition	Neurochemical changes	Antipsychotic response	References
Prenatal manipulation								
Prenatal MAM exposure	Yes	Yes	Deficit	Deficit	Deficit	↑ DA activity at the VTA ↓ PV and mGlu5 in the mPFC ↔ Reelin in the HPC	Hyperactivity of DA neurons in the VTA reduced by HP and SER	Gastambide et al. 2012, Lodge et al. 2009, Lodge and Grace 2009, Matricon et al. 2010, Moore et al. 2006, Snyder et al. 2012, Valenti et al. 2011, Zimmerman et al. 2013
Prenatal polyinosinic: polycytidylic acid exposure	Yes	Yes	Deficit	Deficit	Deficit	↓ PV in the HIP ↓ DA in the mPFC and vHPC ↑ 5-HT in the AMY and NAc ↓ Reelin in the dHPC ↑ GAD67 in the vHPC	Deficits are reversed by RIS and CLZ	Bitanihirwe et al. 2010, Cardon et al. 2010, Harvey and Boksa 2012, Meyer et al. 2009, 2010, Piontkewitz et al. 2009, 2011, 2012, Vuillermot et al. 2012, Wolff and Bilkey 2010
Postnatal manipulation								
Postweaning isolation rearing	Yes	Yes	Deficit	Deficit	Deficit	↑ Mesolimbic DA ↑ GAD67 in the AMY ↓ PV and reelin in the vHPC ↓ CB1 and GluR1in the PFC ↑ Plasma tryptophan metabolites	Deficits reversed by HP, OLA, RIS and CLZ	Cassidy et al. 2010, Gilabert-Juan et al. 2012, Harte et al. 2007, Hermes et al. 2011, Marsden et al. 2011, Moller et al. 2011, 2013, Zamberletti et al. 2012a, 2012b
Neonatal ventral hippocampal lesion	Yes	Yes	Deficit	Deficit	Deficit	↑ DA in the PFC ↓ PV in the HPC ↓ GAD67 in the mPFC	Deficits reversed by HP, CLZ and RIS	Bringas et al. 2012, Lee et al. 2012, Macedo et al. 2012, Naert et al. 2013, O'Donnell 2012, Richtand et al. 2006, Swerdlow et al. 2012

improve cognition in patients; thus, further studies are necessary to assess the mechanisms underlying the PCP effect on cognition. Interestingly, the recent use of genetically modified mice has revealed that various components of the glutamatergic systems, such as specific glutamate receptor subtypes or various components of their intracellular transduction mechanism, might be involved in the pathophysiology of SCZ (Inta et al. 2010). Hallucinogens such as lysergic acid diethylamide (LSD) or cholinergic receptor antagonists, e.g., scopolamine, have induced, in humans and animals, psychotic-like effects, thus supporting the 5-HTergic or cholinergic hypothesis of SCZ, respectively. Therefore, the full potential of 5-HT or cholinergic manipulations in preclinical research of SCZ needs to be further validated (Barak 2009; Vollenweider et al. 1998).

Neurodevelopmental models

In the last few decades, human epidemiological data have supported the finding that pre-perinatal environmental factors such as malnutrition, infection and obstetric complications increase the risk of the development of SCZ (Brown et al. 2013). This knowledge has stimulated the development of models based on direct pre-perinatal damage of the central nervous system (CNS); such models replicate several behavioural and neurochemical

changes linked to the disease. In agreement with this approach, rats exposed in utero on gestional day 17 to methylazoxymethanol (MAM), an antimitotic agent that methylates DNA, show behavioural (hyperactivity, cognitive and social deficits or prepulse inhibition disruption) and histopathological (decreased parvalbunin expression, hyperdopaminergia) patterns similar to those observed in SCZ (Lodge et al. 2009; Lodge and Grace 2009). Although the MAM model seems to have face validity for SCZ symptoms and construct validity in terms of the structural and DAergic changes observed, only a few recent studies have been performed to detect the antipsychotic activity of current agents (Belujon et al. 2012; Valenti et al. 2011) or novel compounds (Brown et al. 2013; Gastambide et al. 2012, 2013; Gill et al. 2011) and thus the predictive validity of this model is not extensively established. Similarly, maternal administration of the viral mimetic polyinosinic:polycytidylic acid induces, in the offspring, a spectrum of neurochemical and behavioural SCZ-related changes that were partially reversed by antipsychotics (Bitanihirwe et al. 2010; Ozawa et al. 2006). An alternative approach makes use of environmental manipulations during postnatal brain development and maturation, such as maternal separation, isolation rearing, early handling or brain lesions. These procedures are based on the hypothesis that they can deflect the physiological development, within the CNS, of an aberrant maturation process prone to the emergence of psychotic-like behaviour and of social, cognitive or attention/gating deficits that are sensitive to the existing antipsychotics.

The advantage of neurodevelopmental over pharmacological models of SCZ is the ability to perform behavioural and neurochemical investigations in the absence of confounding drugs and to identify new classes of antipsychotics by the use of agents operating on multiple pharmacological mechanisms.

New potential pharmacological targets in the treatment of SCZ: lessons from animal models

Current pharmacological treatment for SCZ is primarily focused on modulating DA and 5-HT signalling, which is generally effective in treating positive symptoms. However, it is less effective in treating the negative and cognitive symptoms and can induce several side effects, such as the extrapyramidal side effect, weight gain and diabetes mellitus. Furthermore, a significant proportion of patients are refractory to all current treatments; thus, the development of new approaches for treating SCZ is urgently needed (Keefe 2007). At the same time, we are becoming increasingly aware that the pathophysiology underlying SCZ cannot merely be explained by simple changes in monoamine signalling but involves more complex alterations in activity through key brain circuits that are critical for sensory, cognitive and emotional processing (Lisman et al. 2008; Marek et al. 2010). These brain circuits are modulated by DA and 5-HT, by the major excitatory and inhibitory neurotransmitters glutamate and GABA, which are critical for signalling through these circuits and by acetylcholine. Thus, all these factors represent potential targets for pharmacological intervention (Table 5). Based on the hypothesis that impaired NMDA function in important cellular compartments of the limbic forebrains might represent a critical feature underlying the pathophysiology of SCZ, the mGlu2/3 receptor agonists (Cartmell et al. 1999; Fabricius et al. 2011; Hackler et al. 2010; Harich et al. 2007; Hikichi et al. 2013; Johnson et al. 2005, 2011; Moghaddam and Adams 1998; Nakazato et al. 2000; Patil et al. 2007; Profaci et al. 2011; Schlumberger et al. 2009; Takamori et al. 2003), the mGlu2- (Galici et al. 2005; Harich et al. 2007; Nikiforuk et al. 2010) and mGlu5-positive allosteric modulators (PAMs; Clifton et al. 2013; Darrah et al. 2008; Gastambide et al. 2013; Gilmour et al. 2013; Horio et al. 2012; Kinney et al. 2005; Kjaerby et al. 2013; Schlumberger et al. 2009, 2010; Stefani and Moghaddam 2010; Vales et al. 2010) and the mGlu group III orthosteric agonists (Palucha-Poniewiera et al. 2008; Wieronska et al. 2012, 2013) have all shown preclinical efficacy in reversing SCZ-like symptoms in several experimental models. Although the positive results have not been fully confirmed by clinical trials, the mGlu receptor ligands seem to represent the first non-dopamine D2 receptor-based antipsychotics (Hashimoto et al. 2013). To obtain a more efficient NMDA receptor activation through an increased synaptic glycine concentration, selective glycine transporter-1 (GlyT-1) inhibitors have been shown to be effective in specific preclinical models of SCZ (Alberati et al. 2012; Hagiwara et al. 2013; Chen et al. 2010; Karasawa et al. 2008; Nagai et al. 2012; Shimazaki et al. 2010; Yang et al. 2010). Although definitive trials remain ongoing, encouraging results to date have been reported (Javitt 2012). Several lines of evidences suggest that alterations in central muscarinic or nicotinic cholinergic neurotransmission are involved in the pathophysiology of SCZ (Jones et al. 2012). Thus, based on the above premise, the M1/M4 muscarinic acetylcholine receptor (mAChR) agonist xanomeline (Barak and Weiner 2011b; Jones et al. 2005; Thomsen et al. 2010; Woolley et al. 2009), the M1 or M4 PAMs (Brady et al. 2008; Chan et al. 2008; Jones et al. 2005; Thomsen et al. 2010; Vanover et al. 2008) and the α7 nAChr agonist/activators (Barak 2009; Feuerbach et al. 2009; Hauser et al. 2009; Rezvani et al. 2010; Roncarati et al. 2009; Wallace and Porter 2011; Wishka et al. 2006) have been shown to be effective in animal studies. Despite the promising preclinical data, additional studies are needed to develop more selective mAChRs subtype compounds (i.e., molecules without agonistic activity at M2 and M3 mAChRs) to avoid undesirable cholinergic side effects (Langmead et al. 2008). Among the phosphodiesterases (PDEs), which are a class of enzymes within the intracellular

Table 5 Leading compounds in experimental models of schizophrenia (*5-HT* serotonin, *mAChR* muscarinic acetylcholine receptor, *MAM* methylazoxymethanol, *nAChR* nicotinic acetylcholine receptor, *ND* not determined, *NMDA* N-methyl-D-aspartate, *PAMs* positive allosteric modulators, *PDE* phosphodiesterase, *PPI* prepulse inhibition)

Drugs	Animal models	Positive-like symptoms	Negative-like symptoms	Cognitive dysfunctions	Sensorimotor gating deficits in PPI	References
mGlu2/3 agonists						
LY354740, LY404039, LY379268, MGS0008 MGS0028 BINA CBiPES	Amphetamine, NMDA antagonist, Neonatal ventral hippocampal lesion	Improvement	ND	Improvement	Improvement	Cartmell et al. 1999, Fabricius et al. 2011, Hackler et al. 2010, Harich et al. 2007, Hikichi et al. 2013, Johnson et al. 2005, 2011, Moghaddam and Adams 1998, Nakazato et al. 2000, Patil et al. 2007, Profaci et al. 2011, Schlumberger et al. 2009, Takamori et al. 2003
mGlu2 PAM						
LY487379	Amphetamine, NMDA antagonist	Improvement	ND	Improvement	Improvement	Galici et al. 2005, Harich et al. 2007, Nikiforuk et al. 2010
mGlu5 PAM						
CDPPB ADX47273 CPPZ LSN2463359 LSN2814617	Amphetamine, NMDA antagonist, MAM	Improvement	Improvement	Improvement	Improvement	Clifton et al. 2013, Darrah et al. 2008, Gastambide et al. 2012, Horio et al. 2012, Kinney et al. 2005, Kjaerby et al. 2013, Schlumberger et al. 2009, 2010, Stefani and Moghaddam 2010, Vales et al. 2010, Vardigan et al. 2010
mGlu group III orthosteric agonists						
LSP1-2111 ACPT-I	Amphetamine, NMDA antagonist,	Improvement	Improvement	Improvement	ND	Palucha-Poniewiera et al. 2008, Wieronska et al. 2012, 2013
Glycine transporter 1 inhibitors						
RG1678 Sarcosine d-Serine	Amphetamine NMDA antagonist Polyinosinic: polycytidylic acid	Improvement	Improvement	Improvement	Improvement	Alberati et al. 2012, Hagiwara et al. 2013, Chen et al. 2010, Karasawa et al. 2008, Nagai et al. 2012, Shimazaki et al. 2010, Yang et al. 2010
M1/M4 mAChR agonists						
Xanomeline	Amphetamine NMDA antagonist Scopolamine	Improvement	Improvement	Improvement	Improvement	Barak and Weiner 2011a, Thomsen et al. 2010, Woolley et al. 2009
M1/M4 mAChR PAMs						
TBPB LY2033298 BQCA AC-260584 VU0152100	Amphetamine Apomorphine Scopolamine	Improvement	ND	Improvement	Improvement	Bradley et al. 2010, Brady et al. 2008, Chan et al. 2008, Jones et al. 2008, Vanover et al. 2008

Table 5 (continued)

Drugs	Animal models	Positive-like symptoms	Negative-like symptoms	Cognitive dysfunctions	Sensorimotor gating deficits in PPI	References
α7 nAChR agonist/activator						
SSR180711 RG3487 SEN12333 TC-5619 MEM3454 JN403	Amphetamine, apomorphine NMDA antagonist	Improvement	Improvement	Improvement	Improvement	Barak 2009, Feuerbach et al. 2009, Hauser et al. 2009, Rezvani et al. 2010, Roncarati et al. 2009, Wallace and Porter 2011, Wishka et al. 2006
PDE4/PDE10A inhibitors						
Rolipram Papaverine TP-10 MP-10 Vp1-15 THPP-1	Amphetamine NMDA antagonist	Improvement	Improvement	Improvement	Improvement	Davis and Gould 2005, Grauer et al. 2009, Kanes et al. 2007, Schmidt et al. 2008, Siuciak et al. 2008, Smith et al. 2013, Weber et al. 2009
H3 antagonists/inverse agonists						
ABT-239 Pitolisant GSK-189254 GSK207040 Irdabisant A-431404	Amphetamine NMDA antagonist MAM	Improvement	ND	Improvement	Improvement	Brown et al. 2013, Fox et al. 2005, Ligneau et al. 2007, Mahmood et al. 2012, Medhurst et al. 2007, Raddatz et al. 2012, Southam et al. 2009
5-HT_6 agonists/antagonists						
EMD386088 E-6801 PRX-07034 GSK-742457	NMDA antagonist Scopolamine	ND	ND	Improvement	No effect	Burnham et al. 2010, de Bruin et al. 2013, Kendall et al. 2011, Mohler et al. 2012, Nikiforuk et al. 2013

signal transduction cascade associated with brain abnormalities in SCZ, PDE4 and PDE10A seem to be novel therapeutic targets (Andreasen et al. 2011). Interestingly, specific PDE4 or PDE10A inhibitors ameliorate positive symptoms and cognitive/attention deficits (Davis and Gould 2005; Grauer et al. 2009; Kanes et al. 2007; Schmidt et al. 2008; Siuciak et al. 2008; Smith et al. 2013; Weber et al. 2009). Several compounds are currently undergoing clinical testing, mostly in clinical phase I trials in which SCZ is the leading indication (Kehler 2013). Studies on histamine function in the CNS have focused largely on the effects mediated via H3 receptor signalling. Hence, H3 receptors antagonists or inverse agonists have advanced into clinical assessment based on their effectiveness as cognition enhancers in experimental models of human diseases such as attention deficit hyperactivity disorder, SCZ and Alzheimer's disease (Brown et al. 2013; Fox et al. 2005; Ligneau et al. 2007; Mahmood et al. 2012; Medhurst et al. 2007; Raddatz et al. 2012; Southam et al. 2009; Vohora and Bhowmik 2012). In addition, the serotonin 5-HT_6 receptors have been identified as a potential target for the treatment of cognitive deficits in various disorders (Mitchell and Neumaier 2005). The 5-HT_6 receptor is almost exclusively expressed in brain areas associated with learning and memory and a large number of studies have shown that 5-HT_6 antagonists (de Bruin et al. 2013; Mitchell et al. 2006; Mohler et al. 2012) and 5-HT_6 agonists (Burnham et al. 2010; Kendall et al. 2011; Nikiforuk et al. 2013) have beneficial effects in several domains of cognition. Although the explanation for their similar pro-cognitive effect is unavailable, they might act on various neuronal subpopulations (Kendall et al. 2011; Schechter et al. 2008) and trigger diverse signalling pathways (Yun et al. 2007).

Conclusive remarks and future prospectives

In conclusion, the development of reliable and predictive animal models for neuropsychiatric disorders is a major challenge for assuring successful drug development. The field desperately needs better animal models of depression

and SCZ because of the partial efficacy of present pharmacological treatment. Without improved models of human disease, we cannot know whether particular molecular and cellular findings in animals are relevant to the clinical situations. Improved animal models of depression could come from various sources, such as mutant mice exhibiting particular depressive symptoms or human genetic studies identifying the genetic abnormalities that increase an individual's risk. Given the complexity of the neurobiological mechanisms involved in the SCZ, the recreation of the diversity of the disease in a single animal model might not be possible. Thus, the development and use of symptom-focused tests is important, whereby the goal is to replicate specific symptoms such as anhedonia or the seven cognitive domains as identified by the NIH-MATRICS consensus committee, which are impacted in SCZ, rather than the entire syndrome. Therefore, novel potential pharmacological targets (see Tables 2, 5) and positive control compounds will probably be needed for each of these domains. Nevertheless, all the findings reviewed above suggest that the identification of candidate compounds and the validation of efficacious treatments that can be used as positive controls in the development of new preclinical paradigms remain to be of paramount importance.

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