Behavioural Brain Research 224 (2011) 135–139

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Antipsychotic drugs reverse MK-801-induced cognitive and social interaction deficits in zebrafish (*Danio rerio*)

Kelly Juliana Seibt[a,c], Angelo Luis Piato[a,d], Renata da Luz Oliveira[a,c], Katiucia Marques Capiotti[a,c], Monica Ryff Vianna[b,c], Carla Denise Bonan[a,c,*]

[a] *Laboratório de Neuroquímica e Psicofarmacologia, Departamento de Biologia Celular e Molecular, Programa de Pós-Graduação em Biologia Celular e Molecular. Faculdade de Biociências, Pontifícia Universidade Católica do Rio Grande do Sul, Avenida Ipiranga, 6681, 90619-900, Porto Alegre, RS, Brazil*

[b] *Laboratório e Biologia e Desenvolvimento do Sistema Nervoso, Faculdade de Biociências, Pontifícia Universidade Católica do Rio Grande do Sul, Avenida Ipiranga 6681, 90619-900, PortoAlegre, RS, Brazil*

[c] *Instituto Nacional de Ciência e Tecnologia Translacional em Medicina (INCT-TM), 90035-003, Porto Alegre, RS, Brazil*

[d] *Programa de Pós-Graduação em Medicina e Ciências da Saúde, Pontifícia Universidade Católica do Rio Grande do Sul, Avenida Ipiranga, 6690, 90610-000, Porto Alegre, RS, Brazil*

ARTICLE INFO

Article history:
Received 15 March 2011
Received in revised form 26 May 2011
Accepted 30 May 2011

Keywords:
MK-801
Antipsychotic
Memory
Zebrafish
Schizophrenia

ABSTRACT

Schizophrenia is a severe mental illness characterized by positive and negative symptoms and cognitive deficits. Reduction of glutamatergic neurotransmission by NMDA receptor antagonists mimics symptoms of schizophrenia. Modeling social interaction and cognitive impairment in animals can be of great benefit in the effort to develop novel treatments for negative and cognitive symptoms of schizophrenia. Studies have demonstrated that these behavioral changes are, in some cases, sensitive to remediation by antipsychotic drugs. The zebrafish has been proposed as a candidate to study the *in vivo* effects of several drugs and to discover new pharmacological targets. In the current study we investigated the ability of antipsychotic drugs to reverse schizophrenia-like symptoms produced by the NMDA receptor antagonist MK-801. Results showed that MK-801 (5 μM) given pre-training hindered memory formation while both atypical antipsychotics sulpiride (250 μM) and olanzapine (50 μM) improved MK-801-induced amnesia. The same change was observed in the social interaction task, where atypical antipsychotics reversed the MK-801-induced social interaction deficit whereas the typical antipsychotic haloperidol (9 μM) was ineffective to reverse those behavioral deficits. Therefore, MK-801-treated zebrafish showed some behavioral features observed in schizophrenia, such as cognitive and social interaction deficits, which were reverted by current available atypical drugs.

1. Introduction

Schizophrenia is a devastating psychiatric disorder characterized by positive and negative symptoms and cognitive deficits [55]. Positive symptoms refer to newly acquired behaviors, including delusions, hallucinations, and thought disorders whereas the negative symptoms refer to impairments or losses in normal behavior and include deficits in social interaction, emotional expression, and motivation. Cognitive deficits usually manifest as impaired attention/information processing, problem-solving, processing speed, verbal and visual learning, memory, and working memory [51,54].

Alterations in several neurotransmitter systems and neuroanatomical characteristics have been reported in schizophrenic patients [65]. Different theories have attempted to clarify the aetiology of schizophrenia but the exact causes of this complex and multifactorial mental disorder remain unknown. This lack of information might be attributed in part to the difficulties in modeling the disorder. One of the best characterized animal models of schizophrenia is based on NMDA hypofunction [22]. This model is based on observations that NMDA antagonists, such as phencyclidine and MK-801, can mimic the complexity of positive, negative, and cognitive symptoms of the disease [46,60].

MK-801 is a non-competitive antagonist of NMDA subtype of glutamate receptors and acts by means of open-channel blockade [61]. When given to animals, NMDA antagonists cause changes that resemble some features of schizophrenia, including hyperlocomotion, stereotypical behavior, memory impairment [6,9,35,49], and social withdrawal [16,57]. These behavioral changes are, in some cases, blocked by antipsychotic drugs [8,58].

Antipsychotic drugs are widely used for the treatment of psychotic symptoms in patients with several brain disorders, including schizophrenia. Typical (first-generation) antipsychotics alleviate psychotic symptoms, but lead to severe motor side effects due to

* Corresponding author at: Laboratório de Neuroquímica e Psicofarmacologia, Departamento de Biologia Celular e Molecular, Faculdade de Biociências, Pontifícia Universidade Católica do Rio Grande do Sul. Avenida Ipiranga, 6681, 90619-900 Porto Alegre, RS, Brazil. Tel.: +55 51 3353 4158; fax: +55 51 3320 3568.
E-mail address: cbonan@pucrs.br (C.D. Bonan).

0166-4328/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbr.2011.05.034

the blockade of dopamine D_2 receptors [38]. Over the past decade, atypical (second-generation) antipsychotics have been increasingly used in the treatment of schizophrenia in preference to 'conventional' typical drugs [15]. Atypical antipsychotics, although less potent in blocking central D_2 receptors, have affinity for a wide range of other receptors including dopaminergic D_1 and D_4, serotonergic 5-HT_{2A} and 5-HT_6, adrenergic α_1, histaminergic H_1, and muscarinergic M_1 [37].

The teleost *Danio rerio*, popularly known as zebrafish, have many inherent advantages as a model organism, such as low cost, easy handling and maintenance as compared to other vertebrate models and 70–80% genetic homology to humans [7,19,30]. Therefore, zebrafish may be an ideal vertebrate model system for numerous human diseases, where genetic and biological mechanisms of the diseases may be studied [18,23,34]. Zebrafish embryos are permeable to drugs and can easily be manipulated using well-established genetic and molecular approaches [39]. Transparency of zebrafish embryos and early larvae allows direct visualization of tissue morphogenesis as it occurs in a live organism [7]. In addition, zebrafish behavior can be easily observed and quantified in a controlled environment [45]. Behavior-based chemical screens in zebrafish may improve our understanding of neurobiology and drug action and accelerate the pace of psychiatric drug discovery [41,56].

It is well known that systemic administration of the non-competitive NMDA receptor antagonist MK-801 causes an increase in rodent locomotion [14], and this effect was fully replicated in a previous study from our laboratory using the zebrafish as animal model [58]. The present study was designed to determine if MK-801 also causes memory and social interaction impairments in zebrafish. Since various antipsychotics have been reported to modulate MK-801-induced changes, we also examined the ability of typical and atypical antipsychotics to reverse the deleterious effects of MK-801. Therefore, our work evaluated the potential of zebrafish as a reliable animal model to study NMDA antagonist-induced cognitive deficits and negative symptoms and a possible new approach for drug screening.

2. Material and methods

2.1. Animals and maintenance

Adult male zebrafish (<8 months old) were obtained from a local commercial supplier (Redfish, RS, Brazil). All fish were kept in 50 l housing tanks with AquaSafe® (Tetra) conditioned water continuously aerated (7.20 mgO_2/l) at 25 ± 2 °C, under a 14–10 h light/dark photoperiod in at a density of up to five animals per liter. Animals were acclimated for at least 2 weeks before the experiments and were fed three times a day with commercial flake food (TetraMin Tropical Flake®). Groups consisted of 11–12 animals and different animals were used for each experiment. All protocols were approved by the Institutional Animal Care Committee (09/00135, CEUA–PUCRS) and followed Brazilian legislation, the guidelines of the Brazilian Collegium of Animal Experimentation (COBEA), and the Canadian Council for Animal Care (CCAC) Guide on the care and use of fish in research, teaching, and testing.

2.2. Chemicals

Haloperidol, sulpiride, olanzapine, MK-801 hydrogen maleate and dimethylsulfoxide (DMSO) were used. The antypsychotics used were from clinical grade/suppliers, while MK-801 and DMSO were purchased from Sigma–Aldrich (St. Louis, USA). Tank water was used as the vehicle for haloperidol and olanzapine and tank water with 5% DMSO was used as the vehicle to sulpiride.

2.3. Pharmacological treatment

Immediately before the behavioral tests, fish were treated either individually (for inhibitory avoidance protocol) or in groups of five (for social interaction protocol) in 500-ml beakers for 30 min, which are divided in two consecutive 15 min-periods, as follows: (a) In the first 15 min-exposure period, animals were exposed to tank water (CTRL) or 5 μM MK-801. (b) In the second 15 min-exposure, animals were treated with tank water or with one of the antipsychotic drugs (9 μM haloperidol, 50 μM olanzapine or 250 μM sulpiride). Therefore, the following experimental treatments were tested: (i) CTRL plus CTRL, (ii) CTRL plus HAL, (iii) CTRL plus OLA, (iv) CTRL plus SUL, (v) MK-801 plus CTRL, (vi) MK-801 plus HAL, (vii) MK-801 plus OLA (viii) MK-801 plus SUL. An additional control group receiving 5% DMSO was simultaneously tested in both inhibitory avoidance and social interaction tests, showing identical responses to those of the water-treated control group (data not shown).

The MK-801 and haloperidol doses were chosen based on previous studies with zebrafish [25,58,63]. The doses of other antipsychotic agents used in this study were chosen based on drug potencies observed in humans [40,47], rats [33,53], and zebrafish [58,59]. Previous studies have shown that haloperidol, sulpiride, and olanzapine *per se* did not induce changes in the locomotion in zebrafish [58].

2.4. Behavioral analysis

2.4.1. Inhibitory avoidance

Long-term memory was evaluated using an inhibitory avoidance (IA) protocol described in detail by Blank et al. [11]. Briefly, a glass tank (18 cm × 9 cm × 7 cm length × height × width) divided in two equally sized compartments, designated here as dark and white, by a sliding guillotine-type partition (9 cm × 7 cm) was used. The tank water level was 3 cm and the partition raised 1 cm above the tank floor to allow zebrafish to swim freely from one side of the tank to the other. Two electrodes extending through the wall height and placed on each end side of the dark walls attached to an 8 V stimulator administered a final 3 ± 0.2 V AC shock when manually activated. On training session, animals were placed in the white side of the tank while the partition between compartments was closed. After 1 min of adaptation with the new environment the partition was raised, allowing fish to cross to the dark side of the tank. When animals entered the dark side with their entire body the sliding partition was closed and a pulsed electric shock administered for 5 s. Fish were then removed from the apparatus and placed in the dedicated temporary tank. Animals were tested 24 h after training. The test session repeated the training protocol except that no shock was administered and animals immediately removed from the dark compartment. The latency to completely enter the dark compartment was measured on both sessions and the test latencies used as an index of retention.

2.4.2. Social interaction

The zebrafish is a schooling fish that may exhibit preference for its conspecifics under certain circumstances. The rationale behind using a group of five fish as subjects is that this social setting biases behavior toward schooling. Fish were placed in groups of five in a small experimental tank (30 cm × 15 cm × 10 cm length × height × width). On one side of the experimental tank an empty fish tank was placed, and on the other side a tank of identical size held 15 zebrafish, hereon designed "stimulus fish". The experimental fish were allowed to acclimate to the experimental tank for a 30 s period, after which their behavior was video recorded. In order to quantify their preference between the "stimulus fish" side of their tank in detriment of the empty tank, the experimental fish tank was divided in two equal sections and the amount of time the five experimental fish spent on the side of the tank closer to the conspecific school was measured using an event recorder program [24].

2.5. Statistical analysis

Results are expressed as mean ± S.E.M. In the social interaction test comparisons between groups were made by two-way ANOVA followed by Tukey's *post hoc* test. Inhibitory avoidance data are expressed as medians ± interquartile ranges and data were analyzed by Kruskal–Wallis non-parametric analysis of variance followed by Mann–Whitney *U*-test (two-tailed) for comparisons among treatment groups. Significance was set at $p < 0.05$. All data were evaluated with SPSS 18.0 for Windows.

3. Results

Fig. 1 shows the effects of haloperidol (HAL), sulpiride (SUL), and olanzapine (OLA) on MK-801-induced amnesia in the inhibitory avoidance task. Significant and consistent differences ($p < 0.05$, Wilcoxon) between training and test sessions were observed in all groups except for MK-801 and MK-801 plus HAL ($p > 0.05$). These results show that only the atypical antipsychotics (sulpiride and olanzapine) were able to reverse the memory impairment induced by MK-801.

Fig. 2 shows the effects of HAL, SUL, and OLA on MK-801-induced social interaction impairment in zebrafish. As expected, MK-801 significantly decreased ($p < 0.001$) the time of social interaction when compared to controls, whereas HAL, SUL, and OLA *per se* were devoid of effects. However, when zebrafish were treated with HAL, SUL, and OLA after MK-801 pre-treatment, a two-way ANOVA revealed a main effect of pre-treatment

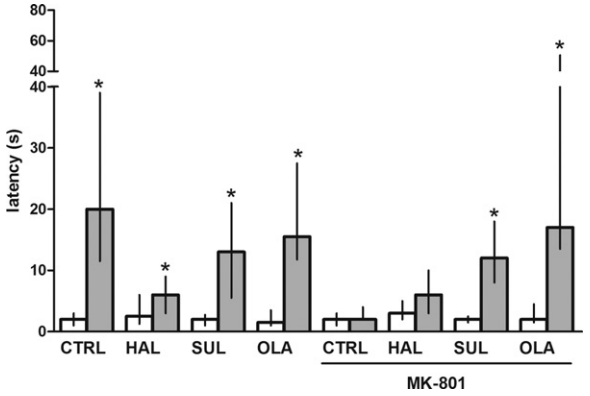

Fig. 1. Effects of haloperidol (HAL), sulpiride (SUL) and olanzapine (OLA) on MK-801-induced amnesia in the inhibitory avoidance task. Significant differences (*$p < 0.05$, Wilcoxon test) between training and test sessions were observed in all groups, except for MK-801 and MK + HAL ($p > 0.05$). Data are expressed as medians ± interquartile ranges and were analyzed by Kruskal–Wallis non-parametric analysis of variance followed by Mann–Whitney *U*-test (two-tailed) for comparisons among treatment groups.

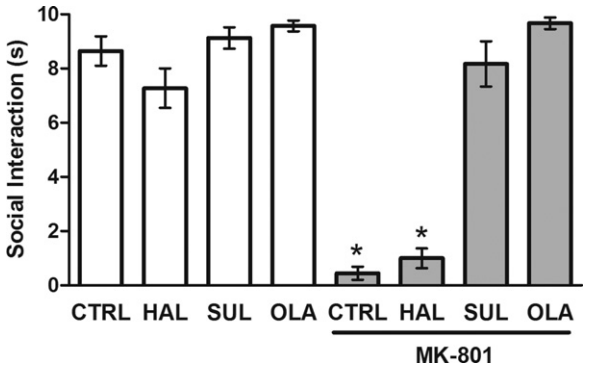

Fig. 2. Effects of haloperidol (HAL), sulpiride (SUL) and olanzapine (OLA) on MK-801-induced social interaction deficits in zebrafish. Data are expressed as mean ± S.E.M. *$p < 0.01$ × control group.

($F_{(1,67)} = 87.4$, $p < 0.001$), treatment ($F_{(3,67)} = 46.2$, $p < 0.001$), and of pre-treatment × treatment interaction ($F_{(3,65)} = 25.6$, $p < 0.001$). *Post hoc* analyses indicated that treatment with SUL and OLA, but not with HAL, reversed the effects of MK-801 in the social interaction test. Therefore, atypical antipsychotic drugs reversed MK-801-induced cognitive and social interaction deficits in zebrafish. No changes in latency for inhibitory avoidance and social interaction were induced by DMSO (data not shown).

4. Discussion

Schizophrenic patients suffer from enduring and persistent symptoms, as well as deficiencies in cognitive abilities and social interaction. Given the negative impact of cognitive and social dysfunction on long-term function and quality of life, the lack of effective treatment is clearly a key unmet clinical need [27]. There is evidence that, at least some of the pathology and symptomatology (particularly cognitive and negative symptoms) of schizophrenia results from a dysfunction of the glutamatergic system, which may be modeled in animals through the use of NMDA receptor antagonists.

There is a growing interest in zebrafish as a model organism in behavioral pharmacology [29,64]. Zebrafish, a vertebrate model organism amenable to high throughput screening, is an attractive system to model and study the mechanisms underlying human diseases. In a previous work [58], our group characterized the behavioral effects of MK-801 and investigated the effect of typical and atypical antipsychotic treatments on locomotor activity as well as on the hyperlocomotion induced by MK-801 in this animal model. In the present study, using social interaction and memory deficits as key schizophrenia-like symptoms, we demonstrated that acute MK-801 treatment induced a deficit in cognition and social interaction in zebrafish, which was completely restored by acute administration of atypical antipsychotics, but not by a typical antipsychotic.

It is currently accepted that the glutamatergic neurotransmitter system plays an important role in the aetiopathogenesis of schizophrenia, as supported by findings on various aspects of neural substrates ranging from molecular interactions to the neuronal networks in the human brain [26,42]. Moreover, administration of non-competitive antagonists of NMDA glutamate receptors (phencyclidine, ketamine, and MK-801) has been reported to induce behavioral abnormalities related to symptoms of schizophrenia, such as impairment of information processing and attention, as well as hyperlocomotion in response to a novel environment, which are all ameliorated by antipsychotic use [4,14,58].

Modeling cognitive impairment in animals can be of great benefit in the effort to develop novel treatments for psychotic, negative, and cognitive symptoms of schizophrenia. Previous studies have shown that acute MK-801 impairs working memory in the delayed alternation task in rodents [9,67] whereas no information is available on the behavioral effects of MK-801 chronic treatment and/or withdrawal. Acute phencyclidine treatment, other NMDA receptor antagonist, impairs performance at rats in the Morris maze, and this effect can be reversed by clozapine and other atypical antipsychotics, but not by haloperidol [17]. In accordance with these studies, we found that acute treatment with MK-801 caused memory impairment in the inhibitory avoidance task, and MK-801-induced cognitive impairment was ameliorated by atypical antipsychotics, such as sulpiride and olanzapine, but not by typical, such as haloperidol.

According to Rung et al. [57], social deficits can be considered a core negative symptom in schizophrenia. Social withdrawal in rats, in response to non-competitive NMDA-receptor antagonists, is an accepted model for negative symptoms of schizophrenia [10,20,57]. Haloperidol, a typical antipsychotic, does not reverse acute NMDA antagonist-induced deficits in social investigation [12], and conflicting data exist for clozapine, which is either inactive [12] or effecting in reversing social investigation deficits [10]. Acute treatment with the atypical drugs ziprasidone and aripiprazole has been reported to reverse subchronic phencyclidine-induced deficits in social investigation, whereas similar treatment with haloperidol or clozapine has no effect [60]. In this study, sulpiride and olanzapine prevented the MK-801-induced social withdrawal in zebrafish whereas haloperidol was ineffective. The fact that social interaction is diminished by NMDA glutamate antagonists in zebrafish and improved by some atypical antipsychotics suggests that NMDA antagonist-reduced social interaction might represent an useful model for evaluating novel antipsychotics in this species.

Neurochemical data suggest that NMDA antagonists increase serotonin release, which in turn activates serotonin 5-HT_{2A} receptors on glutamatergic neurons in the cerebral cortex to release glutamate [2,3]. The increased glutamate release may act on post-synaptic AMPA/kainate receptors causing changes in behavioral responsiveness and inducing the neuropathological changes observed with NMDA antagonist exposure [48,52]. Despite the fact that atypical antipsychotics do not directly target glutamatergic receptors, the ability to modulate the glutamatergic system has been proposed as the basis of olanzapine and sulpiride atypical profile [32,43]. Atypical antipsychotics show marked polypharmacology, with affinities for a wide range of other receptors.

Evins et al. [21] have shown that clozapine, an atypical antipsychotic, alters serum glutamate concentrations [21], facilitates NMDA-mediated neurotransmission [5], and antagonizes NMDA antagonist-mediated behaviors. Thus, this drug may also facilitate NMDAR activity indirectly through inhibition of the glycine transporter, up-regulating glycine binding to its positive modulatory site on the NMDAR [36]. However, it remains unclear whether the increased NMDA receptor binding can be attributed to increased NMDAR expression, an alteration of receptor conformation or affinity for MK-801 [28]. Behaviorally, chronic administration of clozapine restores NMDAR function after phencyclidine treatment [50] and reverses the prepulse inhibition (PPI) deficits induced by ketamine and MK-801 [1,13,44]. Su et al. [62] showed that the atypical antipsychotic risperidone inhibits NMDA antagonist-induced glutamate release in the medial prefrontal cortex by blocking serotonin 5-HT_{2A} receptors on glutamatergic terminals, leading to attenuation of the activity of cortico-subcortical glutamatergic neurons [62]. Therefore, it is possible that atypical drugs such as olanzapine and sulpiride inhibit MK-801-induced social interaction and cognitive impairments through a similar mechanism.

Monoaminergic, cholinergic, GABAergic and peptidergic neurons can be identified early on zebrafish development, developing in similar spatial and temporal patterns than those observed in mammals [31]. Additionally, zebrafish maintains the typical brain structural organization observed in vertebrates, enabling extrapolation of findings from zebrafish to mammals, despite specific embryological aspects and relative position of homologous structures [for a detailed review see Ref. [66]]. The general subdivision of vesicles during brain development and their resulting structures are evolutionary conserved, and zebrafish shows telencephalic regions that are homologous to the hippocampus and amygdala, critical for memory and emotion processing, in addition to multiple diencephalic nuclei, reinforcing zebrafish advantages in screens for drugs with potential neural effects [31,66]. Despite some proteomic and neuroanatomical differences between zebrafish and mammals, the effects of drugs that act on the dopaminergic and serotonergic systems (receptor agonists or antagonists, transporter inhibitors, etc.) on zebrafish behavior are similar to those observed in rodents [19,25,58]. However, there are no studies evaluating affinity, efficacy and transduction mechanisms for duplicated zebrafish receptors in relation to different drugs, such antipsychotics.

The behavioral syndrome produced by NMDA antagonists has been widely used as an animal model to study the mechanism of action of conventional and atypical antipsychotics. Our interest to establish this behavioral syndrome in zebrafish was supported by numerous practical advantages of this species in behavioral experimentation combined to its substantial genetic similarity to mammals. In this work we demonstrated that MK-801-treated zebrafish mimics some behavioral features observed in schizophrenia, such as cognitive and social interaction deficits, which responded positively to available atypical treatments, supporting the use of this animal model for drug screening.

Acknowledgements

This work was supported by DECIT/SCTIEMS through Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS, Proc. 10/0036-5 – PRONEX/Conv. 700545/2008), and by the FINEP research grant "Rede Instituto Brasileiro de Neurociência (IBN-Net)" 01.06.0842-00. K.J.S. was a recipient of a fellowship from Programa PROBOLSAS/PUCRS. R.L.O. was a recipient of a fellowship from CAPES. A.L.P and K.M.C were recipients of CNPq fellowships. M R.V. and C.D.B. were also recipient of Research scholarship from CNPq.

References

[1] Abdul-Monim Z, Reynolds GP, Neill JC. The effect of atypical and classical antipsychotics on sub-chronic PCP-induced cognitive deficits in a reversal-learning paradigm. Behav Brain Res 2006;169:263–73.
[2] Adams BW, Moghadam B. Effect of clozapine, haloperidol, or M100907 on phencyclidine-activated glutamate efflux in the prefrontal cortex. Biol Psychiatry 2001;50:750–7.
[3] Aghajanian GK, Marek GJ. Serotonin, via 5-HT2A receptors, increases EPSCs in layer v pyramidal cells of prefrontal cortex by an asynchronous mode of glutamate release. Brain Res 1999;825:161–71.
[4] Amitai N, Semenova S, Markou A. Cognitive–disruptive effects of the psychotomimetic phencyclidine and attenuation by atypical antipsychotic medications in rats. Psychopharmacology 2007;193:521–37.
[5] Arvanov VL, Liang X, Schwartz J, Grossman S, Wang RY. Clozapine and haloperidol modulate N-methyl-D-aspartate- and non-N-methyl-D-aspartate receptor mediated neurotransmission in rat prefrontal cortical neurons in vitro. J Pharmacol Exp Ther 1997;283:226–34.
[6] Bakshi VP, Geyer MA. Multiple limbic regions mediate the disruption of prepulse inhibition produced in rats by the noncompetitive NMDA antagonist dizocilpine. J Neurosci 1998;18:8394–401.
[7] Barbazuk WB, Korf I, Kadavi C, Heyen J, Tate S, Wun E, et al. The syntenic relationship of the zebrafish and human genomes. Genome Res 2000;10:1351–8.
[8] Bardgett ME. Behavioral models of atypical antipsychotic drug action. In: Csernansky JG, Laurello J, editors. Atypical antipsychotics: from bench to bedside. New York: Marcel Dekker; 2004. p. 61–93.
[9] Bardgett ME, Points M, Ramsey-Faulkner C, Topmiller J, Roflow J, McDaniel T, et al. The effects of clonidine on discrete-trial delayed spatial alternation in two rat models of memory loss. Neuropsychopharmacology 2008;33:1980–91.
[10] Becker A, Grecksch G. Ketamine-induced changes in rat behaviour: a possible animal model of schizophrenia. Test of predictive validity. Prog Neuro-Psychopharmacol Biol Psychiatry 2004;28(8):1267–77.
[11] Blank M, Guerim LD, Cordeiro RF, Vianna MR. A one-trial inhibitory avoidance task to zebrafish: rapid acquisition of an NMDA-dependent long-term memory. Neurobiol Learn Mem 2009;92(4):529–34.
[12] Boulay D, Depoortère R, Louis C, Perrault G, Griebel G, Soubrié P. SSR 181507, a putative atypical antipsychotic with dopamine D2 antagonist and 5-HT1A agonist activities: improvement of social interaction deficits induced by phencyclidine in rats. Neuropharmacology 2004;46(8):1121–9.
[13] Bubenikova V, Votava M, Horacek J, Palenicek T, Dockery C. The effect of zotepine, risperidone, clozapine and olanzapine on MK-801-disrupted sensorimotor gating. Pharmacol Biochem Behav 2005;80:591–6.
[14] Bubenikova-Valesova V, Horacek J, Vrajova M, Höschl C. Models of schizophrenia in humans and animals based on inhibition of NMDA receptors. Neurosci Biobehav Rev 2008;32:1014–23.
[15] Crossley NA, Constante M, McGuire P, Power P. Efficacy of atypical v. typical antipsychotics in the treatment of early psychosis: meta-analysis. Br J Psychiatry 2010;196(6):434–9.
[16] de Moura Linck V, Herrmann AP, Goerck GC, Iwu MM, Okunji CO, Leal MB, et al. The putative antipsychotic alstonine reverses social interaction withdrawal in mice. Prog Neuro-Psychopharmacol Biol Psychiatry 2008;32:1449–52.
[17] Didriksen M, Skarsfeldt T, Arnt J. Reversal of PCP-induced learning and memory deficits in the Morris' water maze by sertindole and other antipsychotics. Psychopharmacology (Berl) 2007;193:225–33.
[18] Dodd A, Curtis PM, Williams LC, Love DA. Zebrafish: bridging the gap between development and disease. Hum Mol Genet 2000;9(16):2443–9.
[19] Egan RJ, Bergner CL, Hart PC, Cachat JM, Canavello PR, Elegante MF, et al. Understanding behavioral and physiological phenotypes of stress and anxiety in zebrafish. Behav Brain Res 2009;205(1):38–44.
[20] Ellenbroek BA, Cools AR. Animal models for the negative symptoms of schizophrenia. Behav Pharmacol 2000;11(3–4):223–33.
[21] Evins AE, Amico ET, Shih V, Goff DC. Clozapine treatment increases serum glutamate and aspartate compared to conventional neuroleptics. J Neural Transm 1997;104:761–6.
[22] Farber NB. The NMDA receptor hypofunction model of psychosis. Ann N Y Acad Sci 2003;1003:119–30.
[23] Gerlai R, Lahav M, Guo S, Rosental A. Drinks like a fish: zebrafish (*Danio rerio*) as a behavior genetic model to study alcohol effects. Pharmacol Biochem Behav 2000;67(4):773–82.
[24] Gerlai R. Zebra fish: an uncharted behavior genetic model. Behav Genet 2003;33(5):461–8.
[25] Giacomini NJ, Rose B, Kobayashi K, Guo S. Antipsychotics produce locomotor impairment in larval zebrafish. Neurotoxicol Teratol 2006;28:245–50.
[26] Goff DC, Coyle JT. The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. Am J Psychiatry 2001;158:1367–77.
[27] Goldberg TE, Gold JM. Neurocognitive deficits in schizophrenia. London, UK: Blackwell; 1995.
[28] Gray L, van den Buuse M, Scarr E, Dean B, Hannan AJ. Clozapine reverses schizophrenia-related behaviours in the metabotropic glutamate receptor 5 knockout mouse: association with N-methyl-D-aspartic acid receptor up-regulation. Int J Neuropsychopharmacol 2009;12(1):45–60.
[29] Grossman L, Stewart A, Gaikwad S, Utterback E, Wu N, Dileo J, et al. Effects of piracetam on behavior and learning in adult zebrafish. Brain Res Bull 2011;85(1–2):58–63.

[30] Guo S. Linking genes to brain, behavior and neurological diseases: what can we learn from zebrafish? Genes Brain Behav 2004;3:63–74.
[31] Guo S. Using zebrafish to assess the impact of drugs on neural development and function. Expert Opin Drug Discov 2009;4(7):715–26.
[32] Heresco-Levy U. Glutamatergic neurotransmission modulation and the mechanisms of antipsychotic atypicality. Prog Neuropsychopharmacol Biol Psychiatry 2003;27:1113–23.
[33] Ichikawa J, Kuroki T, Dai J, Meltzer HY. Effect of antipsychotic drugs on extracellular serotonin levels in rat medial prefrontal cortex and nucleus accumbens. Eur J Pharmacol 1998;351:163–71.
[34] Ivetac I, Becanovic J, Krishnapillai V. Zebrafish: genetic tools and genomics. Asia-Pac J Mol Biol Biotechnol 2000;8:1–11.
[35] Jacobs PS, Taylor BM, Bardgett ME. Maturation of locomotor and Fos responses to NMDA antagonists, PCP and MK-801. Dev Brain Res 2000;122:91–5.
[36] Javitt DC. Glutamate as a therapeutic target in psychiatric disorders. Mol Psychiatry 2004;9:984–97.
[37] Jones DNC, Gartlon JE, Minassian A, Perry W, Geyer M. Developing new drugs for schizophrenia: from animals to the clinic. Animal and translational models for CNS drug discovery. In: McArthur RA, Borsini F, editors. Psychiatric disorders, vol. 1. New York: Elsevier; 2008. p. 199–261.
[38] Kapur S, Zipursky R, Jones C, et al. Relationship between dopamine D2 occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. Am J Psychiatry 2000;157:514–20.
[39] Kari G, Rodeck U, Dicker AP. Zebrafish: an emerging model system for human disease and drug discovery. Clin Pharmacol Ther 2007;82:70–80.
[40] Kiang M, Daskalakis ZJ, Christensen BK, Remington G, Kapur S. Actigraphic measurement of the effects of single-dose haloperidol and olanzapine on spontaneous motor activity in normal subjects. J Psychiatry Neurosci 2003;28:293–9.
[41] Kokel D, Peterson RT. Chemobehavioural phenomics and behaviour-based psychiatric drug discovery in the zebrafish. Brief Funct Genomic Proteomic 2008;7(6):483–90.
[42] Kristiansen LV, Huerta I, Beneyto M, Meador-Woodruff JH. NMDA receptors and schizophrenia. Curr Opin Pharmacol 2007;7:48–55.
[43] Large CH. Do NMDA receptor antagonist models of schizophrenia predict the clinical efficacy of antipsychotic drugs? J Psychopharmacol 2007;21:283–301.
[44] Levin ED, Petro A, Caldwell DP. Nicotine and clozapine actions on pre-pulse inhibition deficits caused by N-methyl-D-aspartate (NMDA) glutamatergic receptor blockade. Prog Neuropsychopharmacol Biol Psychiatry 2005;29(4):581–6.
[45] Levin ED, Bencan Z, Cerutti DT. Anxiolytic effects of nicotine in zebrafish. Physiol Behav 2007;90(1):54–8.
[46] Li JT, Su YA, Guo CM, Feng Y, Yang Y, Huang RH, et al. Persisting cognitive deficits induced by low-dose, subchronic treatment with MK-801 in adolescent rats. Eur J Pharmacol 2011;652(1–3):65–72.
[47] McClelland GR, Cooper SM, Pilgrim AJ. A comparison of the central nervous system effects of haloperidol, chlorpromazine and sulpiride in normal volunteers. Br J Clin Pharmacol 1990;30:795–803.
[48] Moghaddam B, Adams B, Verma A, Daly D. Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathways from NMDA receptor-blocked to dopaminergic and cognitive disruptions associated with the prefrontal cortex. J Neurosci 1997;7:921–7.
[49] Nilsson M, Waters S, Waters N, Carlsson A, Carlsson ML. A behavioural pattern analysis of hypoglutamatergic mice – effects of four different antipsychotic agents. J Neural Transm 2001;108:1181–96.
[50] Ninan I, Jardemark KE, Wang RY. Olanzapine and clozapine but not haloperidol reverse subchronic phencyclidine-induced functional hyperactivity of N-methyl-D-aspartate receptors in pyramidal cells of the rat medial prefrontal cortex. Neuropharmacology 2003;44:462–72.
[51] Nuechterlein KH, Barch DM, Gold JM, Goldberg TE, Green MF, Heaton RK. Identification of separable cognitive factors in schizophrenia. Schizophr Res 2004;72:29–39.
[52] Olney JW, Newcomer JW, Farber NB. NMDA receptor hypofunction model of schizophrenia. J Psychiat Res 1999;33:523–33.
[53] Parikh V, Terry AV, Khan MM, Mahadik SP. Modulation of nerve growth factor and choline acetyltransferase expression in rat hippocampus after chronic exposure to haloperidol, risperidone, and olanzapine. Influence of long-lasting administration of neuroleptics on cortical NMDA. Psychopharmacology (Berl) 2004;172:365–74.
[54] Pearlson GD. Neurobiology of schizophrenia. Ann Neurol 2000;48:556–66.
[55] Porsolt RD, Moser PC, Castagne V. Behavioral indices in antipsychotic drug discovery. J Pharmacol Exp Ther 2010;333(3):632–8.
[56] Rihel J, Prober DA, Arvanites A, Lam K, Zimmerman S, Jang S, et al. Zebrafish behavioral profiling links drugs to biological targets and rest/wake regulation. Science 2010;327(5963):348–51.
[57] Rung JP, Carlsson A, Ryden MK, Carlsson ML. (+)-MK-801 induced social withdrawal in rats, a model for negative symptoms of schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2005;29:827–32.
[58] Seibt KJ, Oliveira Rda L, Zimmermann FF, Capiotti KM, Bogo MR, Ghisleni G, et al. Antipsychotic drugs prevent the motor hyperactivity induced by psychotomimetic MK-801 in zebrafish (*Danio rerio*). Behav Brain Res 2010;214(2):417–22.
[59] Sison M, Gerlai R. Behavioral performance altering effects of MK-801 in zebrafish (*Danio rerio*). Behav Brain Res 2011;220(2):331–7.
[60] Snighda S, Neill JC. Efficacy of antipsychotics to reverse phencyclidine-induced social interaction deficits in female rats-a preliminary investigation. Behav Brain Res 2008;187:489–94.
[61] Stuchlík A, Petrásek T, Vales K. Effect of alpha(1)-adrenergic antagonist prazosin on behavioral alterations induced by MK-801 in a spatial memory task in Long-Evans rats. Physiol Res 2009;58:733–40.
[62] Su YA, Si TM, Zhou DF, Guo CM, Wang XD, Yang Y, et al. Risperidone attenuates MK-801-induced hyperlocomotion in mice via the blockade of serotonin 5-HT 2A/2C receptors. Eur J Pharmacol 2007;564:123–30.
[63] Swain HA, Sigstad C, Scalzo FM. Effects of dizocilpine (MK-801) on circling behavior, swimming activity, and place preference in zebrafish (*Danio rerio*). Neurotoxicol Teratol 2004;26:725–9.
[64] Tsang M, Zebrafish:. A tool for chemical screens. Birth Defects Res C Embryo Today 2010;90(3):185–92 [Review].
[65] Wong AH, Van Tol HH. Schizophrenia: from phenomenology to neurobiology. Neurosci Biobehav Rev 2003;27:269–306.
[66] Wullimann MF, Mueller T. Teleostean and mammalian forebrains contrasted: evidence from genes to behavior. J Comp Neurol 2004;475:143–62.
[67] Zajaczkowski W, Czyrak A, Wedzony K. A competitive antagonist of NMDA receptors CGP 40116 attenuates experimental symptoms of schizophrenia evoked by MK-801. Pol J Pharmacol 2003;55:703–11.