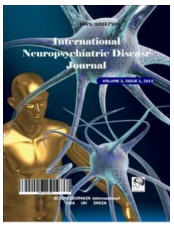

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Atypical Antipsychotic Prevents and Reverses Negative Symptoms in Models of Schizophrenia

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Introduction: Negative symptoms associated with cognitive impairment as a core symptom of schizophrenia with significant poor quality of life and remain an unmet clinical need. Administration of N-methyl-D-aspartate (NMDA) receptor antagonists in rodents has been proposed as an animal model of negative symptoms in this disorder. Evidence from both animal models and human studies implicates a dysfunction of NMDA receptor function may attribute to pathophysiology of schizophrenia.
Objectives: This study was undertaken to investigate the ability of sub-chronic co-administration of clozapine and haloperidol to both prevent and attenuate the social deficits induced by the NMDA receptor antagonist, phencyclidine (PCP) in the social interaction tasks.
Methods: In the first test, female Sprague-Dawley rats were treated with saline, clozapine 5.0 mg/kg or haloperidol 0.05 mg/kg, 30 min later followed by either saline or PCP 2.0 mg/kg twice daily for 7 days, followed by 7 days drug free before tested in social interaction tasks. For the second test, female Sprague-Dawley rats received either vehicle or PCP 2.0 mg/kg for 7 days followed by 7 days drug free. Then rats received clozapine 5.0 mg/kg, haloperidol 0.05 mg/kg or vehicle twice daily for 7 days and were tested 120 min following the last dose of antipsychotic in social interaction tasks.
Results: PCP treatment produced a significantly reduced social behaviours and that effect significantly prevented and improved by clozapine, but not haloperidol.

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Conclusions: These results suggest that antagonism of the consequences of reduced NMDA receptor function could contribute to the superior efficacy of atypical antipsychotic agents in improving negative symptoms in schizophrenia. These negative symptoms impairment likely reflect clinically relevant and can be used to evaluate the antipsychotic potential of new compounds on cognitive symptoms of schizophrenia.

Keywords: PCP; negative symptoms; schizophrenia; NMDA receptors; rats.

1. INTRODUCTION

The psychopathology mechanisms underlying social withdrawal symptoms of schizophrenia associated with and cognitive dysfunction, are not clear. Recent studies suggest an implicate of the hypofunction of the N-methyl-D-aspartate (NMDA) in the pathophysiology of schizophrenia, reduced activation of the NMDA receptor subtype may play a major role in negative symptoms and cognitive dysfunction associated with schizophrenia [1-3]. Negative symptoms and cognitive dysfunction are considered the most significant factor contributing to cause of chronic disability in schizophrenia [1,4,3,5,6] and specifically suggests treatment-resistant disease [7,8]. Thus, there is a need to understand the pathophysiology of negative and translate this knowledge into new therapies. We used pharmacological and behavioural experiments to investigate the role of the NMDA receptor dysfunction in social withdrawal induced by sub-chronic phencyclidine (PCP) administration. Drugs with N-methyl-D-aspartate receptor (NMDAR) antagonist properties, such as phencyclidine (PCP) in rodents has been widely used to model mimic the symptoms of schizophrenia in healthy human subjects [1,4, 3]. Previous studies showed that systemic administration of atypical but not classical antipsychotics attenuated the cognitive deficit social withdrawal produced by subchronic PCP treatment [9,3,10]. There are number of important issues that arise from inspection of the work reviewed above although the evidence seems almost overwhelming in favour of the use of NMDA antagonists to mimic some aspects of negative symptoms in rodents along with associated neuropathological changes. Atypical antipsychotic drugs (APDs) have been found, in some [11,5] but not all [7] studies, to have modest advantages over typical APDs, such as haloperidol, to improve overall behavioural function. This highlights the need for continued efforts to develop superior therapeutic agents with better efficacy to improve negative symptoms associated with schizophrenia. A mechanism, which could clarify in part, the symptomatology and natural course of schizophrenia, was proposed, based on NMDA receptor hypofunction by Olney and Farber [12]. It suggested a dysfunction of the NMDA receptor, which could be reproduced by blocking NMDA receptors pharmacologically with PCP. Since clozapine, but not haloperidol, improves an established and enduring deficit induced by sub-chronic PCP in the other behavioural test, a comparison of their effects will assist our understanding of the mechanism by which PCP induces social behaviour. Specifically, we aimed to determine whether chronic daily injections of clozapine or haloperidol could affect the ability of the potent and selective NMDA antagonist, PCP, to produce social behaviour. It has been proposed that blocking NMDA receptors with PCP also induces excessive release of glutamate [13-15] leading to neurotoxicity in the rat cortex [16,12]. In addition, it has been suggested that sub-chronic PCP treatment can be used to produce behaviour deficits in the rat which may mimic certain aspects of negative symptoms of schizophrenia [17,18,10]. Moreover, several hypotheses have been put forward to explain the mechanisms of negative symptom-like behavioural changes induced by PCP. One of the more widely accepted propositions is that of a disturbance in dopamine- and serotonin-mediated neurotransmission [19,11]. The main evidence for this theory is derived from the efficacy of 5-HT2A-D2 antagonists such as clozapine to improve negative symptoms. Therefore, clozapine and haloperidol were given simultaneously with sub-chronic PCP in an attempt to reduce the NMDA antagonist effects and alleviate the social withdrawal. Furthermore, the aim of this study was to compare the ability of sub-chronic clozapine and haloperidol to both prevent and attenuate the social behaviour deficits induced by PCP in in animal models of schizophrenia. Such work could provide important new information, to support previous behavioural studies and further strengthen the validity of PCP as a useful pharmacological tool to model some of the symptoms of schizophrenia.

2. MATERIALS AND METHODS

2.1 Social Interaction

The study design was adapted from that described by Sams-Dodd [18], Lee et al. [20] and Snigdha and Neill [10]. Behaviours are represented as three separate measures in this study.

2.2 Subjects and Housing Conditions

160Female Sprague-Dawley weighing 240 ± 15 g were used as subjects. Rats were housed in groups of 5 (cages measured 38 cm × 59 cm × 24 cm) and kept under standard laboratory conditions on a 12 h light: dark cycle, lights on at 07:00 h. Temperature and humidity conditions were 21±2℃ and 40–50%, respectively. All testing was carried out in the light phase. Food and water were available. All experiments were approved by Animal Experimentation and Ethics Committee of University College Cork.

2.3 Apparatus and Objects

The social behaviour test was performed in an open-field comprising a square box made of opaque Plexiglas (52 cm × 52 cm × 31 cm) placed 27 cm above the floor on a moveable trolley. The floor of the box was white with black gridlines forming nine identical squares. All other walls were black. A video camera connected to a video recorder and monitor was positioned above the box. The object(s) used for the test consisted of a heavy structure made of wood or metal that could not be displaced by the animals. This was done with a view to ascertain that any deficits in interactive behaviour such as sniffing and climbing over and under observed in this study were relevant and specific to the social context since object interaction represents interaction with an inanimate object. Care was taken to ensure that these objects did not have natural significance for the rats.

2.4 Testing

The rats were habituated to the test environment and arena prior to the test day. Habituation consisted of placing all rats from one cage together in the empty test arena for 1 h, on the day before the test day (day 1). On the test day pairs of rats, unfamiliar to each other, receiving either the same treatment (vehicle and vehicle; n = 10 pairs per group) or different treatments (vehicle and PCP; n = 10 pairs per group or vehicle and PCP + Drug treatment; n = 10 pairs per group) were placed in the test arena together for 10 min as described below. An inanimate object can was placed in the centre of the arena for all trials to measure any differences in interaction of the test animal with an unfamiliar animal as opposed to an unfamiliar object, as described by Snigdha and Neill [10]. After each 10-min trial, the object and arena were cleaned with 10% alcohol in an attempt to remove traces of any olfactory cues. All testing was carried out under standard room illumination levels (70 cd/m2).

2.5 Data Collection

Behaviour in both trials was recorded on video for subsequent blind scoring. A behavioural scoring software program (Hindsight, Scientific Programming Services) was used to score the following five parameters:

Following: rat moves after the conspecific around the arena.

Investigative sniffing behaviour: sniffing the conspecific's snout or parts of the body.

Avoiding: actively turning away or freezing when approached by the conspecific animal.

Previous studies revealed that there were no instances of threatening behaviour or biting (termed aggression) in weight matched unfamiliar animals placed in the arena; aggression was hence excluded from the set of behavioural criteria used here.

2.6 Drug Treatment and Preparation

In the first test (Prevention), following the habituation period, female Sprague-Dawley rats were treated with saline, clozapine 5.0 mg/kg or haloperidol 0.05 mg/kg, 30 min later followed by either saline or PCP 2.0 mg/kg twice daily for seven days, followed by seven days drug free before tested in social interaction task. For the second test(Reversal), female Sprague-Dawley rats received either vehicle or PCP 2.0 mg/kg for seven days followed by seven days drug free. Then rats received clozapine 5.0 mg/kg, haloperidol 0.05 mg/kg or vehicle twice daily for seven days and were tested 120 min following the last dose of antipsychotic in social task. The PCP dosing regimen was based on previous study [21,22]. This dose of clozapine has been shown to reverse a acute and sub-chronic [21-

24], PCP-induced cognitive deficit. An identical dose of haloperidol improved an acute d-amphetamine-, but not PCP-induced cognitive deficit acute in the rats [25]. Following drug treatment, the animals were given a one-week drug free period prior to social interaction task. This was based on a previous study [23,24], which suggested that at least a 1-week period of withdrawal was necessary to avoid behaviour being influenced by any residual drug effects. Drug doses were calculated as the base equivalent weight. PCP HCL was dissolved in 0.9% saline; clozapine was dissolved in a minimum volume of acetic acid, made up to volume with 0.9% saline and pH adjusted to 6 with 0.1 M NaOH. Haloperidol was prepared in saline.

2.7 Statistical Analysis

All data are expressed as mean ± S.E.M. (n = 10 pairs per group). Social Interaction: Data were analysed by a factorial one-way ANOVA. This detected the effect of drug treatment on each behaviour set observed during the test. Further analysis by a post hoc unpaired t-test was carried out, where appropriate, to compare individual group means. Attentional Set-Shifting Test: Trials to criterion, errors to criterion, and correct and incorrect response times were recorded for every rat at each stage. A paired Student's t-test was carried out to compare difficulty between phases within the same treatment group and compare between treatment groups within the same phase.

3. RESULTS

Experiment 1: The influence of 7 days co-administration of clozapine and haloperidol with PCP (Prevention). As can be seen from Figs. 1-3, co-administration of clozapine but not haloperidol completely prevented the disruptive effect of PCP on social behaviours. Detailed analysis using unpaired t-tests showed that co-administration of clozapine significantly prevented the PCP-induced reduction in the normal explorative sniffing and following behaviours ($p < 0.001$) which was significantly reduced in PCP-treated animals ($p < 0.001$), Figs. 1-2. A significant effect was also observed on avoiding behaviours with the clozapine treated animals spending significantly less time avoiding the conspecific compared to the PCP group ($p < 0.001$). In contrast, co-administration of haloperidol had no significant effect to prevent any social behaviour deficits induced by PCP).

Experiment 2: The influence of 7 days administration of clozapine and haloperidol on sub-chronic PCP-induced Cognitive Deficit (Reversal). Detailed analysis using unpaired t-tests showed that sub-chronic treatment with clozapine restored the normal explorative sniffing and following behaviours ($p < 0.001$) which was significantly reduced in PCP-treated animals ($p < 0.001$). A significant effect was also observed on avoiding behaviours with the clozapine treated animals spending significantly less time avoiding the conspecific compared to the PCP group ($p < 0.001$), whereas the D2 receptor antagonist haloperidol treatment with failed to restore any social behaviour deficits induced by PCP.

4. DISCUSSION

This study confirms that sub-chronic PCP treatment produces robust social behaviour deficits in female rats. The main findings of this study the social behaviours reduction induced by PCP were prevented by pre-treatment with clozapine, but not haloperidol. This is the first demonstration of the preventive effect of an atypical APD clozapine on subchronic PCP-induced disruption in social behaviours in rats. We also found that the effect of clozapine improved the social behaviours deficits induced by PCP in social behaviours tasks. It has been suggested that sub-chronic PCP treatment can be used to produce behaviour deficits in the rat which may mimic certain aspects of negative symptoms of schizophrenia [17,26] and [10]. Moreover, several hypotheses have been put forward to explain the mechanisms of negative symptom-like behavioural changes induced by PCP. One of the more widely accepted propositions is that of a disturbance in dopamine- and serotonin-mediated neurotransmission [9,19]. The main evidence for this theory is derived from the efficacy of 5-HT2A-D2 antagonists such as risperidone and clozapine to improve negative symptoms. However recently, some data contradicting this hypothesis has been emerging [7,10]. Furthermore, some recent data also throw light on the more active role of 5-HT1A receptor activation in modulating glutamatergic dysfunction observed in schizophrenia and in animal models of the disease. Glutamate release is decreased by 5-HT1A activation [27]. and evidence of a 5-HT1A/glutamatergic interaction has also been described at the neuroendocrine level [28]. The mechanism(s) underlying the consequence of the NMDA hypofunction state in humans, several lines of evidence suggest that a large number of

these drug-induced effects are dose-dependent manifestations of the same general disinhibition process in which NMDA antagonists abolish GABAergic inhibition, resulting in the simultaneous excessive release of acetylcholine and glutamate [15,29]. Progressive increases in the severity of NMDA receptor hypofunction within the brain produce an increasing range of effects on brain function, which may contribute to psychosis in schizophrenia [15,12].

Clozapine improved the reversal learning deficit induced by PCP, without affecting the similar deficit of the reversal learning task produced by the dopamine releaser amphetamine [14,25] Clozapine has a complex pharmacology that includes indirect interactions with NMDA receptors [20,30], as well as direct interaction with a range of neurotransmitter receptors, including dopamine, serotonin and acetylcholine [31,3,32,33]. However, antagonism of 5-HT2A receptors, which positively regulate glutamate release in the cortex, has also been suggested to be important for antipsychotic efficacy [33-36,27,9,19,11,5]. Thus, the effect of clozapine has been attributed in part to 5-HT2A effects [31,13], because blockade of these receptors

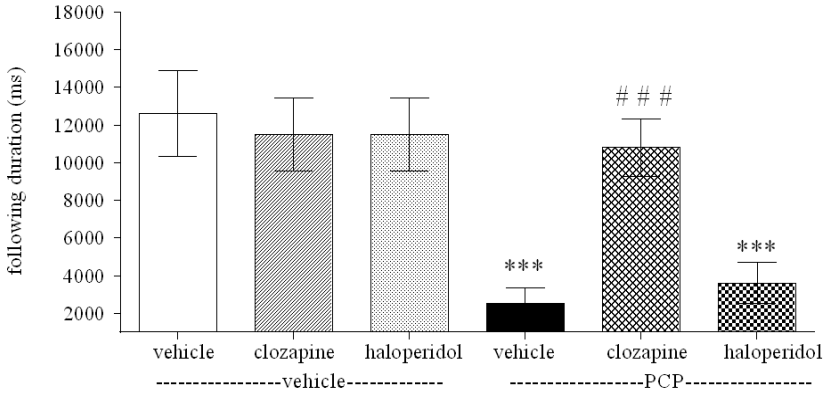

Fig. 1. The influence of sub-chronic co-administration of clozapine (5.0 mg/kg) or haloperidol (0.05 mg/kg) followed by treatment with vehicle or PCP on following duration of the social interaction task

*Data are shown as mean ± s.e.m. duration ms (n=10). Significant reduction in following duration of the social interaction compared with the vehicle group; ***P<0.001. Significant improvement in following duration compared to PCP alone # # # P<0.001, ANOVA followed by LSD t- test*

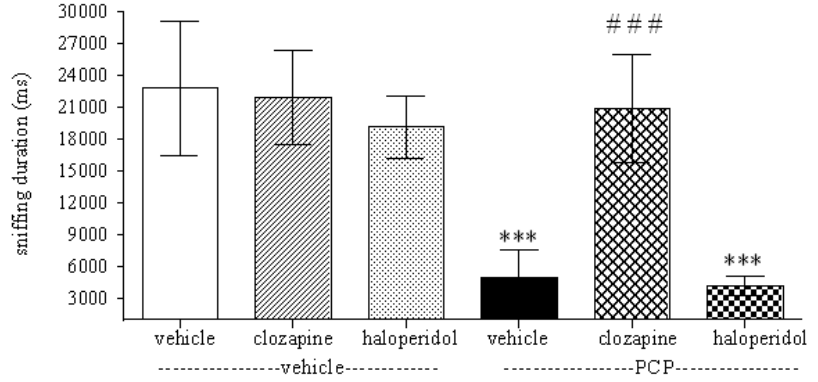

Fig. 2. The influence of sub-chronic co-administration of clozapine (5.0 mg/kg) or haloperidol (0.05 mg/kg) followed by treatment with vehicle or PCP on sniffing duration of the social interaction task

*Data are shown as mean ± s.e.m. duration ms (n=10). Significant reduction in following duration of the social interaction compared with the vehicle group; ***P<0.001. Significant improvement in following duration compared to PCP alone # # # P<0.001, ANOVA followed by LSD t- test*

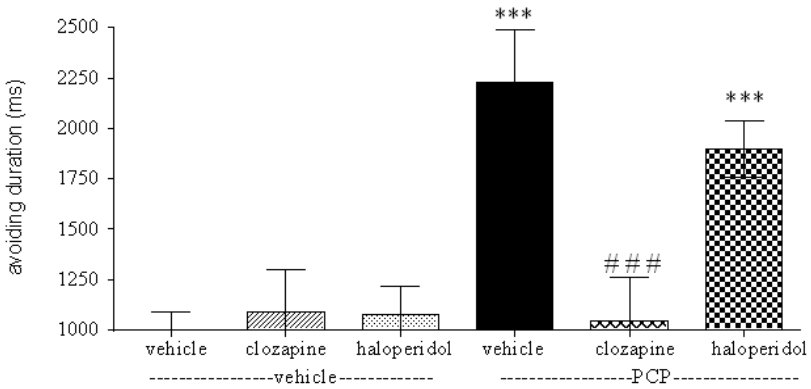

Fig. 3. The influence of sub-chronic co-administration of clozapine (5.0 mg/kg) or haloperidol (0.05 mg/kg) followed by treatment with vehicle or PCP on sniffing duration of the social interaction task

*Data are shown as mean ± s.e.m. duration ms (n=10). on avoiding duration of the social interaction task. Data are shown as mean ± s.e.m. duration ms (n=10). Significant increase in avoiding duration of the social interaction compared with the vehicle group; ***P<0.001. Significant decrease in avoiding duration compared to PCP alone # # # P<0.001, ANOVA followed by LSD t- test*

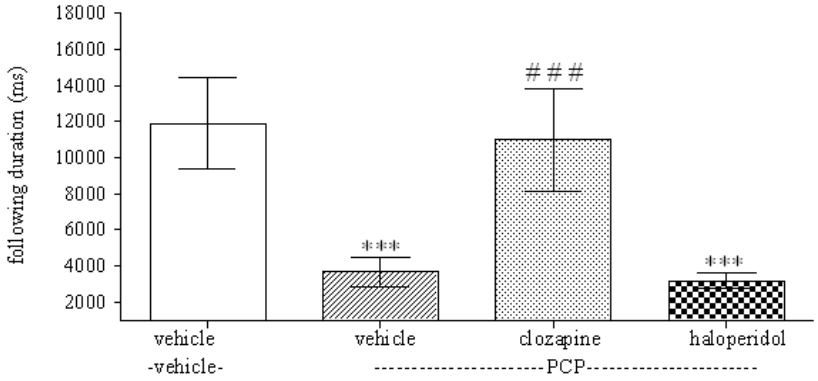

Fig. 4. The effect of sub-chronic administration of clozapine (5 mg/kg) or haloperidol (0.05 mg/kg) on the PCP-induced deficit on following duration of the social interaction task

*Data are shown as mean ± s.e.m. duration ms (n=10). Significant reduction in following duration of the social interaction compared with the vehicle group; ***P<0.001. Significant improvement in following duration compared to PCP alone # # # P<0.001, ANOVA followed by LSD t- test*

might be expected to reduce glutamate release associated with PCP [32]. The idea that PCP induced glutamate activation may be secondary to activation of 5-HT2A receptors is consistent with results of studies suggesting that some of the behavioural and dopaminergic effects of PCP and other NMDA antagonists in the rodent are attenuated by the selective 5-HT2A antagonist, M100907 [35-38]. In addition, prefrontal cortex has also been implicated in playing a role in social interaction in particular is innervated by a prominent dopaminergic projection [34,6,39] and there are several pharmacological interventions which can modulate DA release in the prefrontal cortex. Dopamine D2 and serotonin 5-HT2A receptor antagonism by clozapine, increases the effect of 5-HT1A receptor activation on DA release in the prefrontal cortex [40]. Selective 5-HT1A receptor agonists, increase DA release in the prefrontal cortex. [41], suggesting that 5-HT1A induced DA release in the prefrontal cortex may be the potential basis for mechanism of action of Clozapine. Furthermore, ability o of Clozapine to increase DA release in the prefrontal cortex is blocked by WAY100635, a 5-HT1A receptor antagonist [42]. Together with previous findings regarding the beneficial effects of clozpine but not haloperidol on

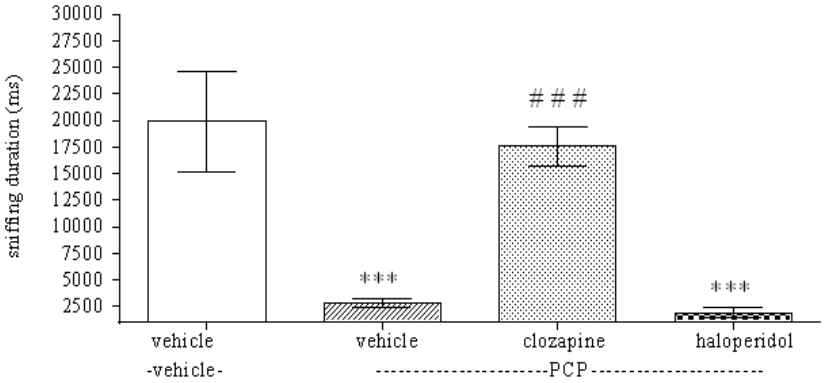

Fig. 5. The effect of sub-chronic administration of clozapine (5 mg/kg) or haloperidol (0.05 mg/kg) on the PCP-induced deficit on sniffing duration of the social interaction task

*Data are shown as mean ± s.e.m. duration ms (n=10). Significant reduction in following duration of the social interaction compared with the vehicle group; ***P<0.001. Significant improvement in following duration compared to PCP alone # # # P<0.001, ANOVA followed by LSD t- test.*

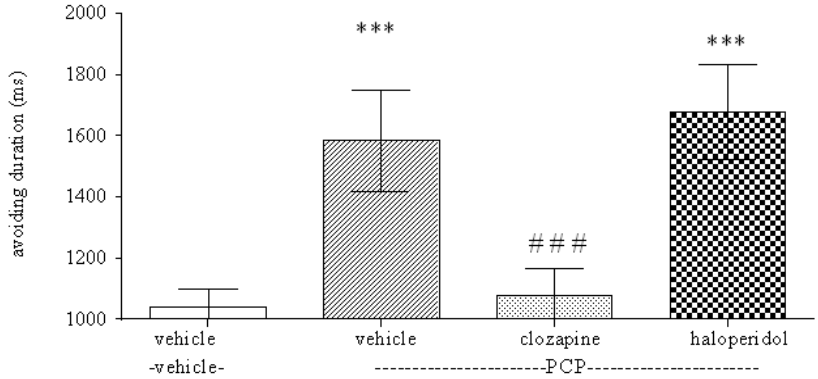

Fig. 6. The effect of sub-chronic administration of clozapine (5 mg/kg) or haloperidol (0.05 mg/kg) on the PCP-induced deficit on sniffing duration of the social interaction task

*Data are shown as mean ± s.e.m. duration ms (n=10). on avoiding duration of the social interaction task. Data are shown as mean ± s.e.m. duration ms (n=10). Significant increase in avoiding duration of the social interaction compared with the vehicle group; ***P<0.001. Significant decrease in avoiding duration compared to PCP alone # # # P<0.001, ANOVA followed by LSD t- test*

PCP-induced social behaviour deficits, these findings support the hypothesis that partial agonism at 5-HT1A receptors has an important role in improving the negative symptom.

5. CONCLUSION

These results suggest that antagonism of the consequences of reduced NMDA receptor function could contribute to the superior efficacy of atypical antipsychotic agents in improving negative symptoms in schizophrenia. These negative symptoms likely reflect clinically relevant and can be potential new targets for the development of new antipsychotics with a broad spectrum in the treatment of negative symptoms in schizophrenia.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the author(s).

COMPETING INTERESTS

Author has declared that no competing interests exist.

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