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Olanzapine Ameliorated Cognition Deficit in a Schizophrenia Mouse Model.

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ABSTRACT

Background: Cognitive impairment is a core feature of schizophrenia that greatly impacts functioning. Typical antipsychotics do not improve cognition, but some evidence suggests certain atypical antipsychotics like olanzapine may benefit aspects of cognition at optimal doses. This study investigated the dose-dependent cognitive effects of the atypical antipsychotic olanzapine in a mouse model of schizophrenia. Methods: Mice were housed socially or in isolation from weaning to induce schizophrenia-related deficits. Isolated adult mice were treated chronically with olanzapine at doses of 0, 0.5, 1.3, or 5 mg/kg (n=10/group) for 4 weeks. Locomotor activity, recognition memory (novel object recognition test), and working memory (T-maze alternation) were assessed. Results: Isolation increased locomotor activity and impaired recognition and working memory versus social controls. Olanzapine doses of 0.5 and 1.3 mg/kg partially attenuated hyper locomotion. Low doses also improved recognition memory and T-maze performance, suggesting cognitive enhancement. However, the highest 5 mg/kg dose decreased locomotion and recognition memory, indicating potential sedative effects at excessive doses. Conclusions: This study provides preclinical evidence that olanzapine at appropriate low to moderate doses can reverse cognitive deficits in animal models relevant to schizophrenia. However, higher doses may cause sedation and cognitive impairment. Careful optimization of olanzapine dosing may be crucial for mitigating symptoms while improving cognition in schizophrenia.

Introduction

Schizophrenia is a chronic, severe, and debilitating psychiatric disorder characterized by a diverse range of genetic and neurobiological factors that affect the early development of the brain. Schizophrenia manifests in three key aspects: Firstly, there are motivational disturbances, which encompass negative symptoms and involve disruptions in normal emotions and behaviours, poverty of speech, and difficulties in planning and sustaining activities. Secondly, there are psychotic symptoms, known as positive symptoms, which include hallucinations, delusions, and disorganization. Lastly, cognitive dysfunction, which includes difficulties with concentration, impaired executive functioning, and challenges in working memory [12]. Schizophrenia impacts around 0.5% of the global adult population, with onset typically occurring in late adolescence or early adulthood [3]. Even though the exact cause of schizophrenia is unknown, research suggests that a combination of genetic, early environmental (such as complications during birth), and societal (like poverty) variables may play a role [4].

Currently, there is no known cure for schizophrenia, and treatment guidelines recommend a comprehensive approach that combines pharmacological agents and psychological interventions[5]. Two main classes of antipsychotics are commonly employed: typical antipsychotics such as haloperidol and chlorpromazine, and atypical antipsychotic agents such as risperidone, olanzapine, quetiapine, and aripiprazole[6].

Despite pharmacological treatments, factors including poor adherence, cognitive deficits, residual symptoms, and side effects pose challenges to schizophrenia treatment goals [7]. Therefore, The study of cognitive impairments in schizophrenia has gained significant attention due to their strong predictive value for functional outcomes compared to other symptoms[1].

Olanzapine, a thienobenzodiazepine derivative, is classified as an 'atypical' antipsychotic due to its receptor binding profile. It exhibits affinity at various receptor types, including D1-D5 dopamine receptors, serotonergic receptors ($5HT_2$, $5HT_3$, $5HT_6$), muscarinic receptors (subtypes 1-5), adrenergic receptors (alpha 1-2), and histaminergic receptors (H_1) [8].

Several clinical studies have suggested that atypical antipsychotic medications, such as clozapine, risperidone, quetiapine, and olanzapine have a positive impact on cognitive function in individuals diagnosed with schizophrenia. The effect sizes observed in these studies range from small to moderate [91011]. In comparison to typical antipsychotic that have been reported to relatively improve cognitive function [12]. Nevertheless, certain studies have showed inconclusive findings regarding the impact of typical and atypical antipsychotic drugs on cognition. This has led to suggestions that atypical agents may not possess any substantial effects on cognitive function[1314]. As research findings indicate that cognitive impairment, rather than positive symptoms, serves as a more reliable predictor of promising outcomes in social and occupational functioning for individuals with schizophrenia. This suggests that even if psychotic symptoms are effectively controlled in individuals with schizophrenia, the lack of cognitive improvement during treatment with conventional antipsychotic medications could potentially result in unfavourable functional outcomes[15]. In the current study, the effect of chronic administration of different doses of olanzapine on locomotor activity, recognition memory and spatial working memory was investigated using socially isolated mice as an animal model for schizophrenia.

Materials and methods

Subjects: Post-weaning social isolation (PWSI) model was adopted as it induces symptoms akin to those observed in psychotic disorders. This model is known to result in cognitive impairment and various schizophrenia-related deficits, including anxiety disorders, apathy, social withdrawal, and aggressive behaviour etc[16].

Fifty male mice at weaning age were divided into 2 rearing groups: isolated-reared and socially reared group. 40 mice in the isolation-reared group were housed individually, while mice in the socially reared group were housed in groups of 2-3 mice. All mice were maintained on a 12:12 h dark–light cycle under controlled temperature and humidity. Animals were housed with ad libitum access to food and wa-

ter throughout the experiment. All mice remained in these housing conditions for 8 weeks prior to testing in adulthood. The socially isolated mice were divided equally into 4 groups. Olanzapine was a generous gift from pioneer company were dissolved in hydroxypropyl cyclodextrin 10% solution(vehicle). Mice were injected intraperitoneally (vehicle, 0.5 mg/kg, 1.3 mg/kg, 5 mg/kg) twice daily for one month (the mice weight was 30-40g) at adulthood. The doses of the drugs used in this study were chosen based on previous behavioural and neurochemical research indicating the doses likely to produce the desired pharmacological effects [17-19]. After a month of treatment, the cognitive performances of the mice were assessed in an open field using a locomotor activity test, Novel object recognition test, and T-maze test.

All procedures involving animals and their care were conducted in accordance with the standard ethics of University of Mosul.

Locomotor activity: Locomotion was evaluated using four black opaque Plexiglas chambers measuring 50×50×50 cm each, for a duration of 30 minutes. An Anymaze video tracking system (Stoelting, Wood Dale, IL) was employed for data collection. The mice were placed gently in the centre of the testing chamber individually, under dim red lighting in a quite environment. To ensure cleanliness, the chambers were cleaned with an acetic acid solution between each test. The distance travelled (in meters) was recorded as the dependent variable using the Anymaze system. The test commenced 20 minutes after the administration of the treatments.

Novel object recognition test (NORT): The NORT is a behavioural test used to evaluate the rodents' capacity to identify and differentiate a novel object within their environment i.e. memory and learning. The test is specifically designed to assess a mouse's capability to recognize and differentiate new or novel objects. It capitalizes on the inherent inclination of mice to explore and engage with new stimuli within their environment [21]. The NORT involves several stages described by Janczura et al [22]. During the initial stage, the mouse is introduced into an empty arena and given 10 minutes to freely explore its surroundings. This serves as a habituation phase to familiarize the mouse with the testing arena environment. In the subsequent stage, two identical objects made of plastic building toys are placed in the arena, and the mouse is allowed to interact and explore them for a designated period of time. After 24 hours, one of the objects is replaced with a novel object that shares the same texture and material as the familiar object but differs in shape and colour. The mouse is then returned to the arena. The mouse should spend more time investigating the novel object if its recognition memory is still intact. The amount of time the mouse spends investigating the novel object compared to the familiar object is recorded and analysed as a measure of the recognition memory index. This index was determined by dividing the time spent exploring the novel object by the time spent exploring the familiar object. The higher index corresponded to better memory retention.

Recognition memory index= (Time spent exploring novel object/ Time spent exploring familiar object)

T-maze test: The T-maze test is a spatial working memory task used to assess the ability of mice to navigate and find a reward in a specific goal arm based on their previous trial, thereby measuring their spatial memory formation [23]. A T-maze was constructed using black plexiglass, with a length of 30 cm for both the start and goal arms, a width of 10 cm, and a height of 20 cm. The T-maze included three removable guillotine doors. One door was positioned 15 cm from the start of the start compartment, while the other two doors were located at the beginning of each arm (Figure 1).

Prior to the test, either vehicle or olanzapine (at doses of 0.5, 1, 3, and 5 mg/kg, administered intraperitoneally) was injected 20 minutes beforehand. The mouse was then returned to its home cage until it was transferred to the testing room. Upon placement in the start compartment for 5 seconds, the door was opened, and the latency for the mouse to visit the forced arm (while the other arm remained closed) and return to the start arm was recorded as the forced trial.

Immediately following the forced trial, the test trial began, allowing the mouse to freely visit either arm. Once the mouse entered one arm, the opposite arm was closed. When the mouse returned to the start

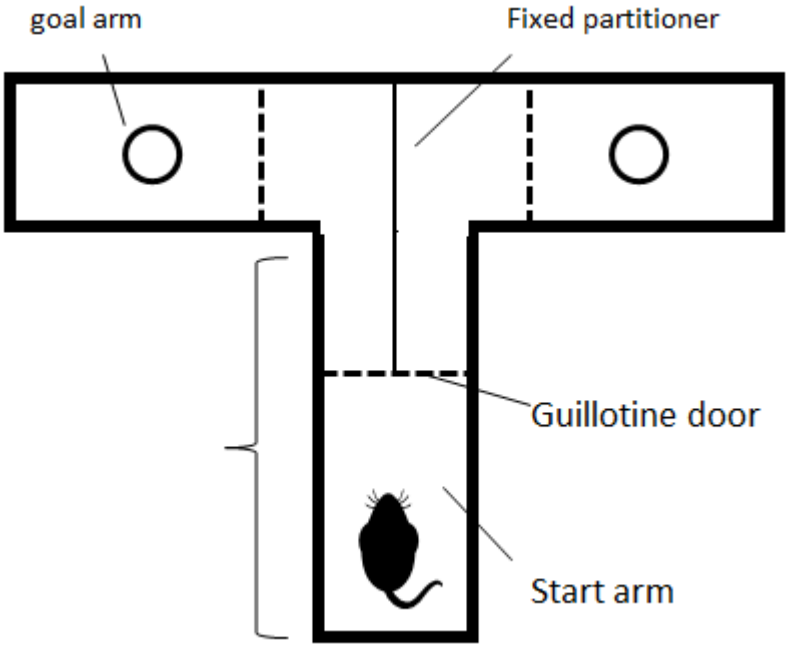

Figure 1. *T-maze apparatus used for alteration test.*

arm, both doors were opened again for the next trial. This process continued for 15 minutes, with a video camera positioned above the T-maze to record the mouse's behaviour.

After each mouse, the maze was cleaned using a 10% diluted bleach spray and dried. The percentage of spontaneous alternation was calculated by dividing the number of visits to alternating arms (visits to arms different from the previously visited one) by the total number of arm visits, multiplied by 100. The percentage of forced arm preference was determined by dividing the number of visits to the forced arm by the total number of arm visits, multiplied by 100.

Data analysis: The data were expressed as mean ± standard error of mean (SEM). For data analysis, a one-way ANOVA was performed in this study. GraphPad Prism 8.4.2 software was utilized to analyse the locomotor, NORT, and T-maze data. Post hoc analysis was conducted using Dunnett's multiple comparisons test. A significance level of $p < 0.05$ was considered as a significant difference. The effects of chronic olanzapine treatment on locomotor activity, recognition memory, and spatial working memory in socially isolated mice are summarized in Table 1.

Results

Effect of olanzapine on Locomotor activity: A one-way ANOVA was conducted to examine the effect of rearing condition (socially reared or isolation reared) and olanzapine dose (0, 0.5, 1.3, or 5 mg/kg) on locomotor activity in mice

Figure 2. There was a significant main effect of rearing condition and olanzapine dose on locomotor activity, $F(4, 45) = 61.57$, $p < 0.001$. Post-hoc tests using socially reared mice treated with vehicle as the control group revealed that socially isolated mice treated with vehicle exhibited significantly higher locomotor activity compared to the control group ($p < 0.05$). No significant differences in locomotor activity were found between socially reared controls and socially isolated mice treated with 0.5 or 1.3 mg/kg olanzapine. Nonetheless, socially isolated mice treated with 5 mg/kg olanzapine showed significantly decreased locomo-

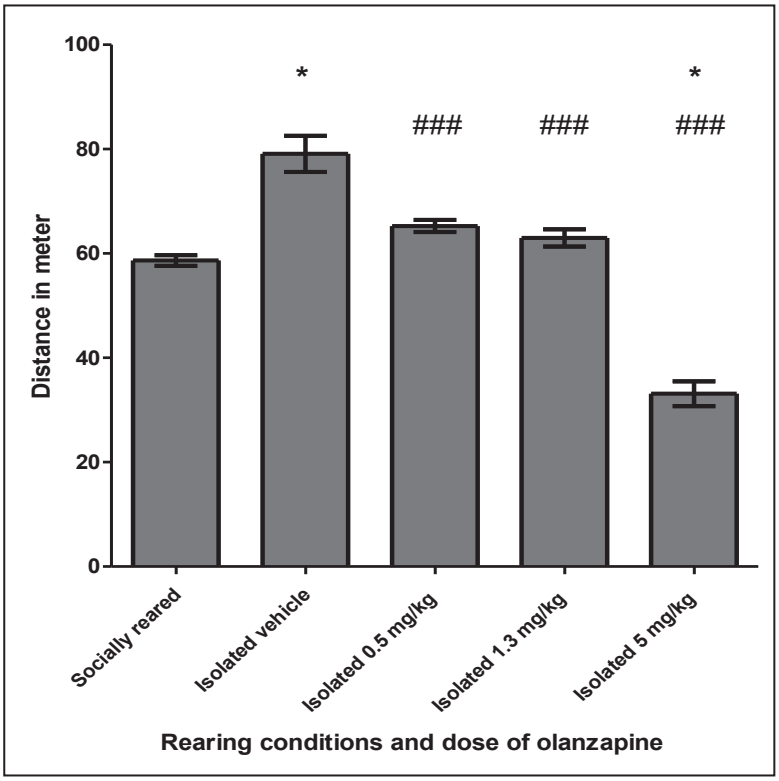

Figure 2. *Effect of olanzapine on locomotor activity. Olanzapine (0.5, 1.3and 5mg/kg) were injected twice a day for 30 days. Data are expressed as mean± SEM. (n=10/group). *p<0.05 vs. socially reared mice, ### p<0.0001 vs. socially isolated mice treated with vehicle.*

tor activity compared to socially reared controls ($p < 0.05$). Additional post-hoc analyses were conducted to specifically examine the effect of olanzapine on socially isolated mice, using the socially isolated mice treated with vehicle as the control group. These tests revealed that olanzapine doses of 0.5, 1.3, and 5 mg/kg all significantly decreased locomotor activity in socially isolated mice compared to vehicle-treated socially isolated controls ($p < 0.0001$). These results suggest that social isolation increase locomotor activity in mice, and low doses of olanzapine were relatively able to normalize this activity, while a higher dose of 5 mg/kg olanzapine results in sedative effects.

Effect of olanzapine on visual memory in NOR test: Data analysis of the recognition index among socially reared and reared in isolation mice exposed to various doses of olanzapine (Figure 3), using one way ANOVA test showed a significant difference in recognition index ($F(4, 45) = 5.921$; $P<0.01$). Post hoc analysis showed that socially isolated mice received either vehicle or 5 mg/kg of olanzapine significantly reduce the recognition index when compared with socially housed mice ($P< 0.01$, and $P< 0.01$ respectively). Further analysis conducted to examine the effect of olanzapine on socially isolated mice using group treated with vehicle as a control group. These tests showed that 0.5 mg/kg of olanzapine significantly improved the recognition index ($P<0.01$). while higher doses of 1.3 and 5 mg/kg did not have a significant effect on recognition index.

These results suggest that social isolation impairs recognition memory in mice, and this deficit is reversed by a low dose of olanzapine. In contrast, higher doses of olanzapine appear to reduce recognition

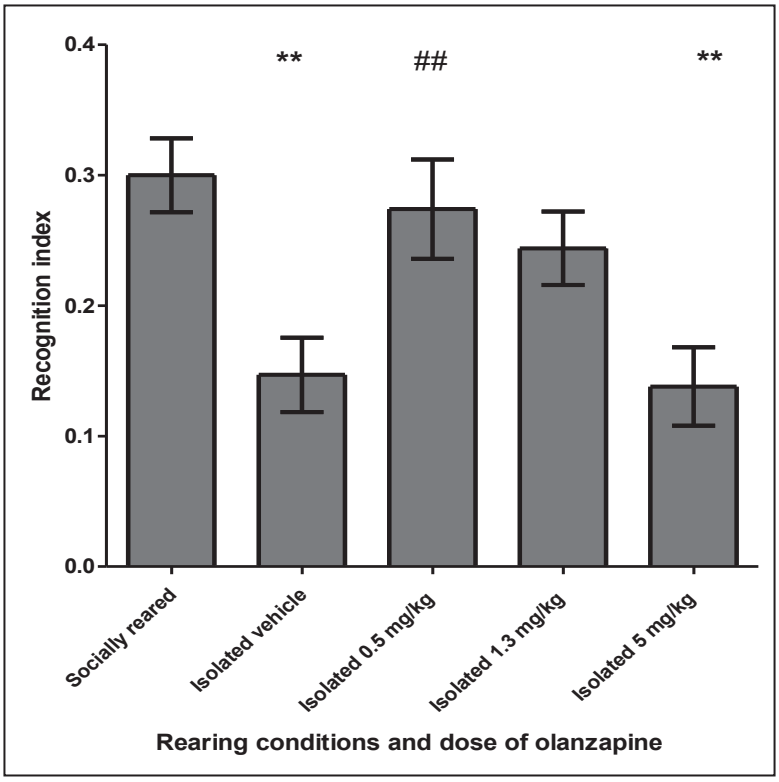

Figure 3. *Effect of olanzapine on recognition index in NOR test. Olanzapine (0.5, 1.3and 5mg/kg) were injected twice a day for 30 days. Data are expressed as mean± SEM. (n=10/group). **p<0.01 vs. socially reared mice, ## p<0.001 vs. socially isolated mice treated with vehicle.*

index in socially isolated mice.

Effect of olanzapine on working memory in T-maze test: A one-way ANOVA was performed to investigate the impact of rearing condition (socially reared or isolation reared) and olanzapine dose (0, 0.5, 1.3, or 5 mg/kg) on the number of T-maze alterations in mice. The results indicated a significant main effect for both rearing condition and olanzapine dose on alterations ($F(4, 45) = 8.654$, $p < .001$). Post-hoc analyses revealed that socially isolated mice exhibited significantly fewer alterations compared to socially reared mice ($p < .001$). Furthermore, among socially isolated mice, those administered with 0.5 mg/kg and 1.3 mg/kg olanzapine showed significantly higher alterations compared to socially isolated mice treated with vehicle ($p < 0.05$ and $p < 0.0001$, respectively). Interestingly, the higher dose of 5 mg/kg olanzapine did lead to a significant increase in alterations compared to the vehicle-treated isolated mice. However, it was observed that the number of alterations started to decrease compared to the 1.3 mg/kg dose, albeit still higher than the alterations observed in vehicle-treated isolated mice. These results indicate that social isolation impairs working memory performance on the T-maze alteration task, and a low dose of olanzapine was able to reverse this deficit. However, higher doses of olanzapine may be less effective at improving alterations than lower doses in isolated mice.

Discussion

It is well-established that most patients with schizophrenia have major cognitive problems affecting attention, working memory, executive abilities, ver-

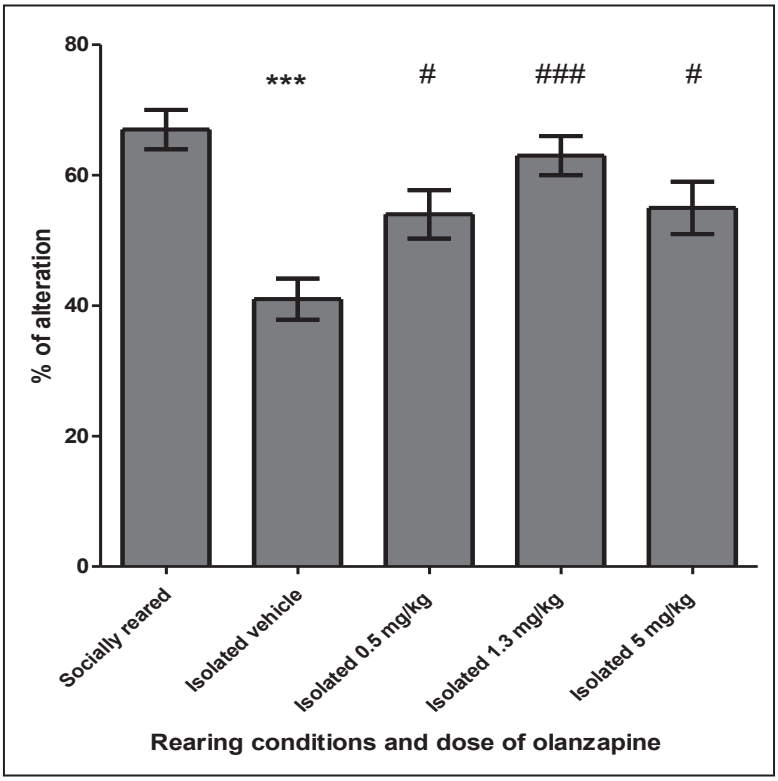

Figure 4. *Effect of olanzapine on % of alteration in T-maze test. Olanzapine (0.5, 1.3and 5mg/kg) were injected twice a day for 30 days. Data are expressed as mean± SEM. (n=10/group). ***p<0.0001 vs. socially reared mice, # p<0.05 vs. socially isolated mice treated with vehicle, ### p<0.0001 vs. socially isolated mice treated with vehicle.*

bal learning and memory[24]. These cognitive impairments are seen as a primary and central deficit in schizophrenia that greatly impacts patients' ability to function properly in daily life and society [25]. Although, typical antipsychotic can effectively decrease positive symptoms, they demonstrate minimal benefits on cognitive deficits in schizophrenia. However, some atypical antipsychotics have exhibited potential for improving cognitive dysfunction in schizophrenia patients[11]. One such medication is olanzapine; therefore, the present study examined the effects of the atypical antipsychotic olanzapine on locomotor activity, visual memory, and spatial working memory in mice reared under social or isolated conditions. Olanzapine was found to have some beneficial effects on cognitive deficits induced by social isolation stress at specific doses. These results align with previous research indicating that low doses of antipsychotics can potentially reverse some of these deficits.

Specifically, this study found that social isolation significantly increased baseline locomotor activity in mice compared to socially housed controls. This hyperlocomotion align with other studies [2627]. The administration of olanzapine at 0.5 and 1.3 mg/kg to socially isolated mice, decrease the locomotor activity by 17 % and 20 % respectively, when compared with group the control group (isolated mice injected with saline). While a higher dose of olanzapine of 5 mg/kg significantly decreased locomotor activity in comparison with the control group. The results indi-

Table 1 Effects of chronic olanzapine treatment on locomotor activity, recognition memory, and spatial working memory in socially isolated mice.

Treatment Group	Locomotor Activity	Novel Object Recognition Test	T-maze Alternation Task
Socially reared	58.65 ± 1.07	0.30 ± 0.03	67.00 ± 3.00
Isolated + saline	79.09 ± 3.69	0.15 ± 0.03	41.00 ± 3.14
Isolated + 0.5 mg/kg olanzapine	65.26 ± 1.20	0.27 ± 0.04	54.00 ± 3.71
Isolated + 1.3 mg/kg olanzapine	63.00 ± 1.72	0.24 ± 0.03	63.00 ± 3.00
Isolated + 5 mg/kg olanzapine	33.12 ± 2.48	0.14 ± 0.03	55.00 ± 4.01

Data shown are means ± standard error of the mean.

cate that low doses of olanzapine at 0.5 and 1.3 mg/kg were able to restore the locomotor activity of socially isolated mice towards the levels exhibited by socially reared control mice, though the hyperactivity was not fully reversed back to normal control levels by the low olanzapine doses. The finding that low doses of olanzapine partially normalized the hyperlocomotion induced by social isolation aligns with previous observations that olanzapine can attenuate heightened locomotor activity in animal models at specific doses. For example, studies have shown olanzapine reverses hyperlocomotion caused by psychotomimetic drugs like amphetamine, PCP and MK-801 in both rats and mice [17, 28, 29].

Olanzapine is thought to exert these effects primarily through dopamine D2 receptor antagonism, blocking the locomotor stimulation from mesolimbic dopamine hyperactivity and D2 receptor binding in striatal region induced by social isolation[30] . D2 receptor antagonism by olanzapine likely reduces the heightened dopaminergic drive from isolation, attenuating behavioural disinhibition and psychomotor activation[31]. Additionally, olanzapine enhances serotonin 5-HT2A neurotransmission via antagonism, which modulates dopamine release and locomotion [32]. This 5-HT2A blockade might also contribute to olanzapine effect on locomotion. Noteworthy, that the olanzapine had potent antagonistic activity at serotonin 5-HT2A receptors, stronger than its affinity for dopamine D2 sites[8]. Furthermore, Olanzapine's actions on muscarinic, adrenergic, and other receptors also influence motor activity[8].

The results also, demonstrated that that a high 5 mg/kg dose of olanzapine significantly decreased locomotor activity compared socially isolated control. This suggests that excessive dopamine D2 receptor blockade may produce sedative and motor suppressing effects at this dosage. Blocking over 80% of D2 receptors can impair motor function and induce sedation[33]. High doses of olanzapine likely cause excessive D2 occupancy. Besides, Olanzapine can cause sedation at high doses through multiple receptor mechanisms including excessive blockade of histamine H1 receptors, anticholinergic effects via muscarinic antagonism, and α1 adrenergic blockade, all of which depress CNS activity[8, 33, 34] this combination of dopamine, histamine, acetylcholine and adrenergic effects that suppress arousal and wakefulness is enhanced at supratherapeutic doses leading to sedation.

Also, the study evaluated the recognition memory in mice treated with different doses of olanzapine by using NOR test. NOR test was developed by Ennaceur and Delacour in 1988 which exhibits high sensitivity in detecting changes in animal behaviour [35]. Memory recognition is a cognitive process that involves the ability to identify previously encountered objects or

stimuli. The NOR test is commonly used to assess this aspect of memory in rodents. The discrimination index, which measures the preference for the novel object, is a key parameter in this test.

The study found that social isolation significantly impairs recognition memory in mice which indicates impaired memory and decreases interest in novel objects which similar to that demonstrated by schizophrenic patients[36].

Low doses of olanzapine at 0.5 and 1.3 mg/kg tended to improve the recognition index in socially isolated mice, indicating some reversal of the isolation-induced memory deficits. This suggests that these lower doses of olanzapine have a beneficial effect on memory recognition in socially isolated animals. The finding aligns with previous observations that olanzapine can ameliorate memory function in socially isolated mice. For example, Mutlu et al., 2011 reported that olanzapine at dose of 0.4 and 0.6 mg/kg reversed MK-801-induced memory impairment in the NOR test [37]. Another study indicated that olanzapine significantly mitigated hyperlocomotion and ameliorated impaired working memory in rats with schizophrenia induced by neonatal ventral hippocampus lesions [38].

However, the highest dose of olanzapine (5 mg/kg) had a different effect. At this dose, olanzapine significantly reduced the recognition index in socially isolated mice when compared to socially reared mice. Olanzapine has several pharmacological properties that may contribute to beneficial effects on cognition. For example, research shows olanzapine potently increases acetylcholine release in the hippocampus as measured by in vivo microdialysis in rats [39]. Additional preclinical studies demonstrate olanzapine treatment elevates extracellular acetylcholine levels in the medial prefrontal cortex of rats [40]). Enhanced cortical and hippocampal acetylcholine signalling mediated by olanzapine may underlie improvements in memory and learning [41,42]. Furthermore, olanzapine leads to a dose-dependent elevation of extracellular dopamine concentrations in the prefrontal cortex of rats [43]. Augmenting prefrontal dopamine availability is thought to enhance working memory and executive function[44].

Lastly, the research revealed that olanzapine effectively mitigated the deficits in working memory. The compromised performance in the T-maze task highlights the presence of impaired working memory, a significant aspect of cognitive dysfunction seen in schizophrenia. The 1.3 mg/kg dose appeared to be the most effective at increasing alterations compared to saline, while the lower dose of 0.5mg/kg and a higher dose of 5 mg/kg doses showed fewer alterations than the 1.3 mg/kg dose. In line with this results, previous study reported that olanzapine at dose 0.5mg/kg exhibited the ability to reverse memory impairments in mice treated with MK-801, while haloperidol did not show the same effect in Morris water maze[45]. Mutlu et al reported improvement in spatial memory in MK-801-induced memory impairment mice after single injection of olanzapine at (0.4, 0.8 and 1.25 mg/kg) doses in radial arm maze test46. Another study stated that olanzapine caused significant improvement in spatial learning, memory and cognitive function in ketamine-induced rat model of schizophrenia[47]. However, some studies showed conflicting results on the effect of olanzapine on memory and cognition. Terry et al suggest that prolonged oral administration of clinically relevant doses of chlorpromazine or olanzapine can lead to impaired performance in tasks assessing spatial learning and working memory in rats [48]. Another study also showed that of the four monkeys given olanzapine, two displayed impaired working memory after being administered the higher dose of 0.1 mg/kg. One of those monkeys, also exhibited significant cognitive deficits compared to the control group even after receiving the lower 0.05 mg/kg dose. Overall, 50% of the monkeys showed detrimental effects on working memory after chronic treatment with olanzapine, with one monkey demonstrating significant impairment at both dosages tested [49]. Recent study showed that rats receiving chronic olanzapine treatment made significantly fewer correct entries on average in the rewarded T-maze alternation test compared to control rats. This finding indicates the olanzapine impaired specific facets of working memory in these rats. In particular, the medication appeared to negatively impact the short-term memory needed to correctly alternate arm choices in seeking food rewards within the T-maze [50].

There are several potential reasons for the inconsistent results between the studies. First, the duration of

olanzapine treatment varied among the studies. Second, findings from healthy animals may not extend to animal with schizophrenia induced by different mechanisms. Lastly, Dosage and inter-species differences could account for the conflicting evidence regarding cognitive impacts.

In conclusion, this study provides evidence that the atypical antipsychotic olanzapine can have dose-dependent effects on reversing cognitive deficits associated with schizophrenia in an animal model of social isolation. Particularly, low to moderate doses of olanzapine were capable of attenuating hyperlocomotor activity to a certain extent while simultaneously enhancing working memory and recognition memory as measured by the new object recognition test and the T-maze alternation test, respectively. The cognitive benefits of lower olanzapine doses are thought to be mediated by enhanced dopamine and acetylcholine neurotransmission in brain regions critical for learning and memory. However, the highest dose of olanzapine impaired locomotion and recognition memory, likely due to excessive dopamine blockade leading to sedation. More research is needed to fully elucidate the complex dose- and time-dependent cognitive. Dosage and treatment regimens should be carefully optimized to achieve symptomatic relief with minimal sedation and maximize cognitive benefit.

Conclusion

Taken as a whole, this study provides further preclinical evidence that olanzapine may have the potential to ameliorate aspects of cognition related to memory and executive function at suitable doses in schizophrenia. Nonetheless, translational studies in patient populations are necessary to further evaluate the actual cognitive impacts of olanzapine treatment. Careful consideration of the risks and benefits will enable ideal use of olanzapine and other antipsychotics for managing both symptoms and cognitive deficits in schizophrenia. □

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