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# Chronic Administration of Haloperidol and Working Memory: Roles of Caudate Putamen Dopamine Receptors

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**Abstract**

**Haloperidol (HAL) is a prototype of the typical antipsychotics with a high affinity for $D_2$ receptors. It is effective in reducing psychotic symptoms, but has poor effects on the negative and cognitive symptoms in schizophrenia patients. In animal studies, our research group has showed that mice given HAL for 6 weeks presented spatial working memory deficit concurrent with the upregulation of $D_1$ and $D_2$ receptors in the caudate putamen. These results are in line with the clinical observation that $D_2$ receptor availability in the striatum was related to the performance of human subjects in tests of working memory. Taken together, results from animal and human studies with HAL suggest that the blockade of striatal $D_1$ and $D_2$ receptors may contribute to this drug-induced working memory deficits. Moreover, the up-regulation of striatal $D_1$ and $D_2$ receptors by HAL may contribute to the antipsychotic-induced supersensitivity to DA thus have clinical implications for the augmented behavioral effects of DA stimulation on the one hand and the diminished anti-dopaminergic effects of antipsychotics on the other.**

**Keywords**: Caudate putamen, Dopamine, Receptors, Haloperidol, Working memory, Schizophrenia.

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## Introduction

Schizophrenia is one of the most severe psychiatric disorders, affecting about 1% of the population [1]. Patients with schizophrenia may experience a wide range of symptoms that have been classified into positive symptoms (hallucinations, delusions, disordered thingking, and paranoia), negative symptoms (social withdrawal and lack of emotion and motivation), and cognitive impairment that adversely affects executive function, attention, memory, and general intellectual functioning [2-4].

Although the etiology and pathophysiology of schizophrenia largely remain elusive, a number of hypotheses have been proposed. Of them, the dopamine (DA) hypothesis posits that hyperactivity of the DA system is responsible for the psychotic symptoms [5]. This hypothesis was mainly based on the fact that all currently available anti-psychotics target on $D_2$ receptors thus exert their therapeutic effects for schizophrenia patients [6]. In addition, amphetamine and cocaine can induce psychosis, and these drugs release or inhibit the reuptake of DA, respectively [7,8]. Moreover, evidence from positron-emission tomography (PET) studies has suggested that hyperactivity of dopaminergic transmission is present in schizophrenics [9].

Psychotic symptoms respond well to the first-generation or typical antipsychotics, but the negative symptoms and cognitive deficits associated with schizophrenia are not improved by these drugs [10,11]. Pertinent to this inefficiency, a recent study found that negative symptoms were associated with cognitive flexibility, planning, visual learning and working memory performance in schizophrenia [12]. These results are consistent with the vast literature highlighting small-to-moderate associations between negative symptoms and all of the core cognitive domains impaired in schizophrenia, namely attention, reasoning and problem solving, speed of processing, verbal/visual memory and working memory [13]. Taken together, previous studies with schizophrenia patients imply that the blockade of D2 receptors in the brain by typical antipsychotics is unable to improve or may exacerbate negative symptoms and cognitive deficits in schizophrenia. In support of this view, low $D_2$ receptor availability, as estimated by antipsychotics plasma levels, was associated with impairments on vigilance and reasoning [14]. Similarly, in clinically stable patients with schizophrenia, aged 50 years or older, those with low $D_2$ receptor availability had impaired attention compared with those with high availability [15]. Moreover, chronic treatment with haloperidol (HAL) was shown to induce working memory deficits in healthy volunteers [16].

Consistent with clinical observations, rats given HAL for

90 days displayed learning performance deficits [17]; and rats administered HAL for 28 days showed impaired short-term recognition memory [18]. Similarly, the author reported that mice given HAL for 6 weeks presented spatial working memory deficit, and this deficit was dose- and time-dependent [19,20]. Moreover, the chronic HAL-induced spatial memory deficits were accompanied with the upregulation of $D_1$ and $D_2$ receptors in the caudate putamen of C57BL/6 mouse [20]. Here the author focused on the association of HAL-induced working memory deficit in mice and changes in caudate putamen DA receptors by presenting the main findings of the previous studies and discussed relevant work by the other investigators.

### *Chronic administration of haloperidol impaired working memory in mouse*

In an animal study [19] by the auhtor's team, C57BL/6 mice were given HAL (1 mg/kg/day, i.p.), clozapine (CLZ, 10 mg/kg/day, i.p.), or quetiapine (QUE, 10 mg/kg/day, i.p.) for 42 days, during which period mice were subjected to prepulse inhibition (PPI) test on day 14, Y-maze test on days 21 and 42, and social interaction test on day 28. Some of mice were decapitated on days 14 and 21, and the prefrontal cortex (PFC) was dissected out of the brain and processed for HPLC (High Performance Liquid Chromatography) to measure DA and NE (norepinephrine) levels in PFC. The data set in the original experiments were analyzed by two-way analysis of variance followed by Tukey's multiple comparisons. When a p-value was less than 0.05, the difference/effect was considered significant.

HAL is a prototype of the typical antipsychotics, while CLZ and QUE are atypical ones. As reviewed above, HAL is effective in reducing psychotic symptoms, but has poor effects on the negative and cognitive symptoms in schizophrenia patients [21]. CLZ and QUE are effective in improving negative symptoms and cognitive deficits [22-24]. HAL has a high affinity for $D_2$ receptors [25] whereas CLZ and QUE are broad-acting agents, which not only exhibit affinity for a variety of DA receptors, but also for other metabotropic receptors, e.g. those for serotonin (5-$HT_2$A and 5-$HT_1$), NE, acetylcholine and histamine [26-28].

PPI refers to the inhibition of a startle reflex produced by preceding the startling stimulus or pulse with a weak prepulse stimulus. This test provides an operational measure of sensory gating of subjects [29]. The Y-maze is a simple two-trial recognition test to measure exploratory behavior and spatial working memory in rodents. The exploratory behavior is an important component of learning as it allows a subject to acquire the information that may be crucial for its survival [30]. When placed in a T-, Y-, or radial-maze, a mouse or rat displays a strong propensity to alternate arm choices on successive trials. This exploration of novel environmental stimuli is thought to be dependent on the integrity of limbic and non-limbic pathways, including the basal forebrain, the hippocampus, the thalamus, PFC, and the dorsal striatum [31]. In a previous study [32] amphetamine reduced alternation dose-dependently and HAL pretreatment inhibited this effect, suggesting that this paradigm is useful for studying spatial working memory in animal models of schizophrenia. Social interaction test has been used to measure animals' social behaviors and social interaction deficit is believed to be the animal correlate of social withdrawal in humans, a key component of the negative symptoms of patients with schizophrenia [33,34].

In this study, mice given HAL showed different performances in the above behavioral tests than those given CLZ or QUE. Specifically, HAL, but not CLZ and QUE, induced a PPI deficit in C57BL/6 mice; administration of HAL for 42 days, but not 21 days, impaired spatial working memory deficit in mice, and this deficit was independent of the drug-induced decrease in exploratory behavior; HAL, but not CLZ and QUE, decreased the social interactions between mice. All the three drugs showed no effect on DA and NE levels in PFC.

### *Chronic haloperidol-induced spatial memory deficit was accompanied with upregulation of $D_1$ and $D_2$ receptors in the caudate putamen of mouse*

The main goal of another study was to examine effects of chronic HAL treatment on expression levels of $D_1$ and $D_2$ receptors in PFC, hippocampus, and caudate putamen and to associate them with the HAL-induced spatial memory deficits in mouse. It is known that the former two brain regions play critical roles in working memory and neural cells in them express both $D_1$ and $D_2$ receptors [35-37]. For this purpose, three experiments were performed. In the first one, 30 adult male mice were given vehicle (saline, 10 ml/kg, i.p.), HAL 1 mg/kg/day, or HAL 2 mg/kg/day for three weeks. Two days after the last injection, mice were subjected to Y-maze test. In the second experiment, mice received the same injections for six weeks. At the end of this experiment Y-maze test was performed. Mice in the third experiment received the same HAL treatments as those in the second one. They were subjected to Morris water maze test 4 days after the last injection. The Morris water maze test is one of the methods most often used for the evaluation of spatial learning and memory of rodents [38]. Data were analyzed by one or two-way ANOVA where it was appropriate, followed by Tukey's multiple comparisons. The significant level was set at $p<0.05$.

Some of the main findings of this study include: HAL treatment impaired spontaneous alternation of mice in dose- and time-dependent manner (Figure 1A & C); in the mean while, HAL decreased the number of arm entries of mice [Figure 1B & D]. HAL treatment for 6 weeks impaired the acquisition process of mice in Morris water maze test (Figure 2A). In the probe test, HAL 2 mg/kg/day for 6 weeks, but not HAL 1 mg/kg/day for 6 weeks, significantly increased the latency for mice to find the platform in Morris water maze (Figure 2B); the same treatment also led mice to spend less time in the target quadrant (Figure 2C), but had no significant effect on the number of crossing platform area (Figure 2D).

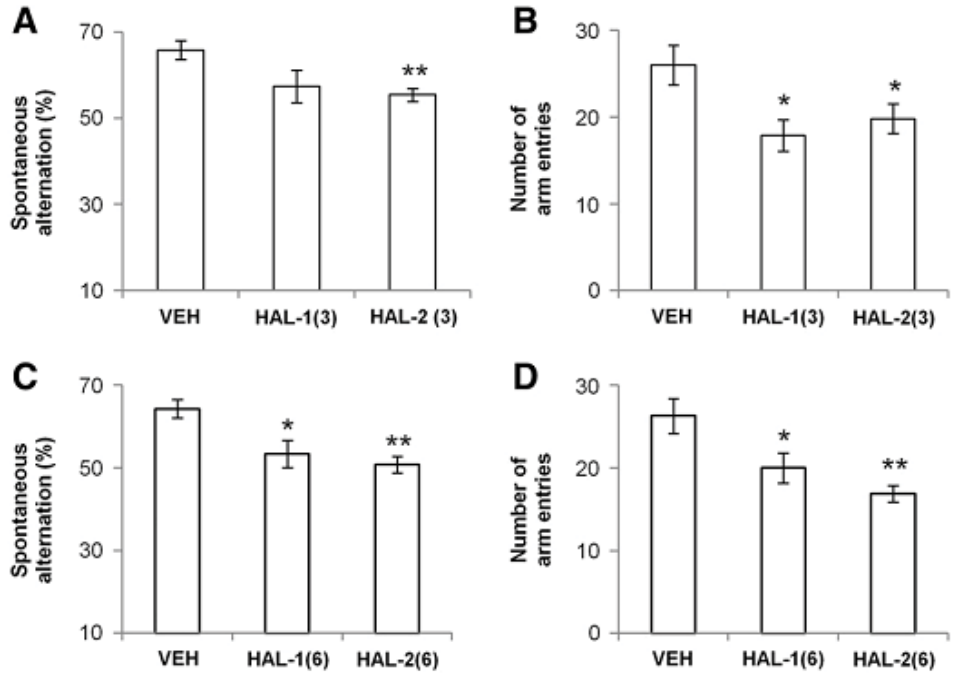


***Figure 1.*** *HAL decreased spontaneous alternation of mice in Y-maze. Mice received daily injection of saline (vehicle) or HAL (1.0 or 2.0 mg/kg/day) for 3 or 6 weeks. Two days after the last injection, they subjected to Y-maze test. (A) and (B) show data from experiment 1; (C) and (D) show data from experiment 2. Data were expressed as means ± SEM (n=10/group). *p<0.05, **p<0.01, compared to VEH groups.*

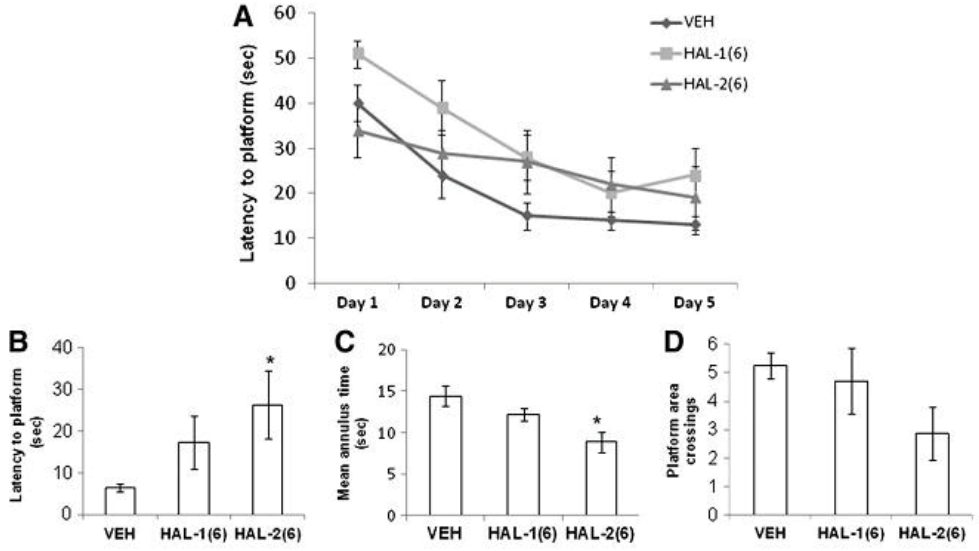


***Figure 2:*** *HAL treatment for 6 weeks impaired the performance of mice in Morris water maze. Mice received daily injection of saline or HAL (1.0 or 2.0 mg/kg/day) for 6weeks. Four days after the last injection, they subjected to Morris water maze test. (A) shows the effects of HAL treatments on the acquisition process of mice in training period. (B), (C), and (D) show the results from the probe test. Data were expressed as means ± SEM (n=10/group). *p<0.05, compared to VEH group.*

All four HAL treatments increased levels of $D_1$ and $D_2$ receptors in caudate putamen of mice (Figure 3).

## Discussion

A number of animal studies reported working memory deficits related chronic or sub-chronic (3-4 weeks) administration of antipsychotics. In monkeys, chronic blockade of $D_2$ receptors by HAL (0.07-0.20 mg/kg/day, twice daily for 1-4 months) produced severe impairments in working memory [39]. In rats, both HAL (1.5 mg/kg/day, i.p. for 28 days) and CLZ impaired short-term recognition memory [18]. In another study, HAL impaired most non-mnemonic parameters and tended to have a detrimental effect on choice accuracy in the delayed non-matching-to-position task [40]. In the first study presented here, administration of HAL for 42 days, but not 21 days, impaired spatial working memory indicated by spontaneous alternation decrease in mice, and this deficit was independent of the drug-induced decrease in exploratory behavior [19]. This result is in accordance with previous animal studies showing that rats given HAL for 90 days displayed learning performance deficits [17] and that rats administered HAL for 28 days showed impaired short-

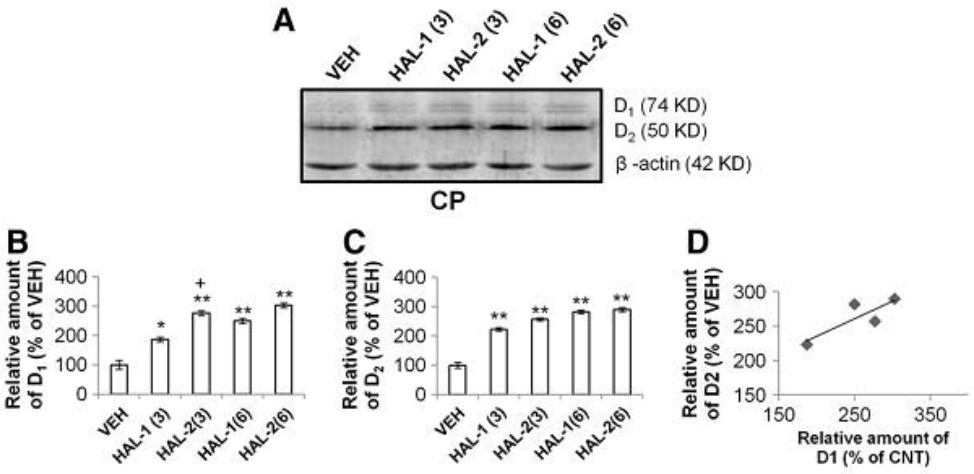


***Figure 3:*** *HAL treatment up-regulated the levels of $D_1$ and $D_2$ receptors in the caudate putamen. (A) is a typical Western-blot image showing the immunoreactive bands of $D_1$ and $D_2$ receptors of caudate putamen samples. (B) and (C) show the relative levels of $D_1$ and $D_2$ receptors in HAL-treated mice, respectively, after having been normalized using the VEH group as the comparator. (D) shows a positive correlation between the up-regulated $D_1$ and $D_2$ receptors in caudate putamen of HAL-treated mice. Data wer eexpressed as means ± SEM (n=5/group). *p<0.05, **p<0.01, compared to VEH group; +p<0.05, compared to HAL-1(3)*

term recognition memory [18]. Similar to HAL, raclopride (another $D_2$ antagonist) was shown to reduce spatial working memory accuracy in rhesus monkeys [41]. These animal studies mimicked clinical observations that chronic treatment with HAL induces working memory deficits in humans [15,16,42-44].

Recent studies have emphasized the importance of DA projections from caudate putamen to the PFC for working memory function, although this system has rarely been studied in humans. In a recent human study, PET data revealed that caudate DA function was correlated with working memory capacity. In addition, delay-related FMRI (functional magnetic resonance imaging) activation in a left inferior prefrontal region was related to both caudate DA and task accuracy [45]. These data suggest that caudate DA function plays a unique role in mediating working memory capacity and load-dependent PFC activation. In line with this suggestion, individuals with higher $D_2$ receptor measures in the right caudate performed less accurately on the spatial working memory task, exhibiting a higher number of errors within each search sequence [46].

Pertinent to the above mentioned human studies, animal studies reported an up-regulation of striatal D2-like receptors after sub-chronic and chronic antipsychotic administration [37,47-49]. In rats, chronic HAL treatment resulted in a strong increase in 3H-nemonapride, 3H-spiperone, and 125I-sulpiride binding to striatal areas [50]. Rats treated chronically with HAL showed enhanced striatal $D_2$ binding (average increase of 42%), whereas those treated with CLZ did not [49]. In cats, continuously high (80% for 24 h/day) $D_2$-receptor blockade led to a robust upregulation of striatal $D_2$-receptors that was maximal at 1-week withdrawal and still detectable at 2-week withdrawal. This pattern of $D_2$-receptor blockade also induced behavioral tolerance to the effect of HAL on spontaneous locomotor activity [51].

In the second study presented here, HAL treatment for 3 and 6 weeks increased expression levels of $D_1$ and $D_2$ receptors in caudate putamen of mice, while the treatments caused deficits in working memory, spatial learning and memory. The concurrent existence of increased $D_2$ receptors in caudate putamen and the impaired spatial learning and memory shown in this study suggests that the normal function of $D_2$ receptors in caudate putamen is necessary for mice to perform spatial learning and memory tasks. In support of this suggestion, infusion of the $D_2$ receptor antagonist sulpiride into caudate putamen of rats resulted in less time swimming near the trained platform location in the Morris water maze [52]. Moreover, over-expression of $D_2$ receptors selectively in the striatum of the $D_2$ transgenic mice led to impairment in tasks that require working memory and behavioral flexibility [53]. Together, all these animal studies provided evidence supporting the clinical observation that $D_2$ receptor availability in the striatum was related to the performance of human subjects in tests of episodic memory [54].

The up-regulation of $D_1$ receptor in caudate putamen by HAL may be considered a compensatory effect in response to the occupation of the existing $D_1$ receptors by HAL. In other words, the free $D_1$ receptors available for endogenous DA to act in caudate putamen were relatively insufficient in mice chronically treated with HAL. This insufficiency may be an important contributor to the decreased spontaneous alternation of mice in Y-maze and to impaired spatial learning and memory of these animals in Morris water maze. This explanation is of very help in understanding the previous results of systemic administration (i.m.) of SCH23390, a $D_1$-like antagonist, impaired spatial working memory in rhesus monkeys [41] and of chronic treatment with HAL significantly disrupted learning processes in rats [55]. In these studies, D1 receptors in striatum were certainly the targets of SCH23390 and HAL.

The up-regulation of striatal $D_1$ and $D_2$ receptors by HAL

may contribute to the antipsychotic-induced super sensitivity to DA as the striatum mediates many of the behaviors that are altered in DA supersensitive subjects. This possibility was demonstrated in a study by Samaha, et al. [56]. The authors pretreated rats with either HAL, or the atypical antipsychotic olanzapine, using doses and a mode of administration that are clinically relevant. Under these conditions, only HAL treatment evoked DA super sensitivity, as indicated by sensitization to the behavioral effects of amphetamine following cessation of antipsychotic treatment. Similarly, prior HAL, but not olanzapine, enhanced conditioned reward following an amphetamine challenge, and this was potentially linked to enhanced behavioral sensitivity to amphetamine and amphetamine-induced engagement of the caudate-putamen [57]. As such, it was proposed that antipsychotic-induced DA super sensitivity might contribute to the high rates of drug abuse and addiction in schizophrenia [58]. Moreover, this super sensitivity to DA has been linked to augmented behavioral effects of DA stimulation on the one hand and to diminished anti-dopaminergic effects of antipsychotics on the other [59].

## Conclusion

Chronic administration of HAL impaired spatial learning and memory in mice while it up-regulated expression levels of caudate putamen $D_1$ and $D_2$ receptors in mice. These results provided evidence supporting the clinical observation that $D_2$ receptor availability in the striatum was related to the performance of human subjects in tests of working memory. Taken together, results from animal and human studies with HAL suggest that the blockade of striatal $D_1$ and $D_2$ receptors may contribute to this drug-induced working memory deficits. Moreover, the up-regulation of striatal $D_1$ and $D_2$ receptors by HAL may contribute to the antipsychotic-induced super- sensitivity to DA thus have clinical implications for the augmented behavioral effects of DA stimulation on the one hand and diminished anti-dopaminergic effects of antipsychotics on the other.

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