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Effects of Oxytocin on Parkinson's like symptoms Induced by Haloperidol in Mice

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ABSTRACT

Antipsychotic drugs are mainly used for treatment of psychosis; they are more prone to produce extrapyramidal symptoms due to their higher affinity to dopamine (D2) receptor, and they act as antagonists. Haloperidol as a high-affinity dopamine antagonist predisposed toward a higher risk of extrapyramidal side effects. These adverse neurologic responses include catalepsy, ptosis, akinesia and tremor. Oxytocin is a peptide hormone of the posterior pituitary gland; several studies had suggested that oxytocin has broader effects on the central nervous system. Oxytocin regulates social behaviors, pain perception, anti-inflammatory responses, stress reduction and blood pressure modulation. It acts as a hormone in the peripheral circulation and a neurotransmitter in the central nervous system. Recent research suggests that oxytocin may alter the progression of neurodegenerative diseases due to its anti-inflammatory and antioxidant properties. Oxytocin may provide neuroprotection as a potential therapy for neurodegenerative diseases. Therefore, this work aimed to find out the effects of oxytocin on Parkinson's like symptoms induced by haloperidol in mice. Mice were divided into six groups (n=6 each). Group 1, the control group received 1% Tween 80 solution; group 2 treated with haloperidol at a dose of 2 mg/kg; group 3 received oxytocin at dose of 1iu/kg; group 4 received oxytocin at dose of 10 iu/kg; group 5 received combination of oxytocin (1 iu/kg) and haloperidol (2 mg/kg) and group 6 received combination of oxytocin (10 iu/kg) and haloperidol (2 mg/kg). Intraperitoneal sub-acute administration was applied in three doses on 24, 5 hrs. and 1 hr. before scoring. Parameters scored were catalepsy, ptosis, tremor, akinesia and righting reflex. Oxytocin at a dose of 10 iu/kg antagonized ptosis, akinesia and catalepsy induced by haloperidol; while loss of righting reflex and tremor were not observed.

Keywords- *Parkinson's disease, Haloperidol, Oxytocin, Mice.*

INTRODUCTION

Oxytocin is a peptide hormone of the posterior pituitary gland. It is synthesized in cell bodies of magnocellular neurons located in paraventricular nuclei and supraoptic nuclei of the hypothalamus.[1] Oxytocin is primarily associated with delivery and lactation.[2] However, several studies suggested that oxytocin has broader effects on the central nervous system.[3] It has been shown that oxytocin regulates social behaviors, pain perception, anti-inflammatory responses, stress reduction and blood pressure modulation.[3] Oxytocin is produced by different peripheral tissues such as placenta, ovary, testis, pancreas, adipose tissue, kidney, heart and blood vessels.[4] This peripherally acting oxytocin has its receptor in these tissues.[5] It acts as a hormone in the peripheral circulation and as a neurotransmitter in the central nervous system.[6]

Antipsychotic drugs are mainly used for the treatment of psychosis.[7] Antipsychotics are more prone to produce extrapyramidal symptoms due to their higher affinity to dopamine (D2) receptor, they act as antagonists.[8] Haloperidol is a butyrophenone characterized as a high-affinity dopamine antagonist predisposed toward a higher risk of extrapyramidal side effects.[9] These adverse neurologic responses include catalepsy, ptosis, akinesia and tremor.[7]

Recent research suggests that oxytocin may alter the progression of neurodegenerative diseases due to its anti-inflammatory and antioxidant properties.[4] This ability to provide neuroprotection makes oxytocin a focus of interest as a potential therapy for neurodegenerative diseases.[10] Therefore, this work was aimed to find out the effects of oxytocin on Parkinson's like symptoms.

MATERIALS AND METHODS

Animals: Male Albino mice, weighing 19-33 g, procured from the Animal House, Department of Pharmacology and Clinical Pharmacy, University of Tripoli, Libya. Animals were selected and divided randomly and were provided with a standard pellet diet and water throughout the experiment period. All animal cages were kept well-ventilated and 12h time-regulated light-dark cycle place. The room temperature was adjusted to 22-25°C. Animal care and use were in strict compliance with the standard guidelines. Ethical approval for the experimental methodology was obtained from the Research Ethics Committee for Animal Use, Faculty of Pharmacy, University of Tripoli according to the International Ethical Guidelines for the Use of Animals in Research.

Drugs and chemicals: The following drugs were used: Oxytocin (Rotexmedica-Trittau, Germany) and Haloperidol (Janssen, Belgium).

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Mice were divided into six groups (n=6 each). Mice in group 1, control group, received 1% Tween 80 solution,[11] group 2 treated with haloperidol at a dose of 2 mg/kg,[12] group 3 received oxytocin at a dose of 1iu/kg, group 4 received oxytocin at a dose of 10 iu/kg,[13] group 5 received combination of oxytocin (1 iu/kg) and haloperidol (2 mg/kg) and group 6 received combination of oxytocin (10 iu/kg) and haloperidol (2 mg/kg). All the treatments were injected by intraperitoneal route of administration. Sub-acute administration was applied in three doses on 24, 5 hrs. and 1 hr. before scoring. Parameters scored were catalepsy, ptosis, tremor, akinesia, rigidity and righting reflex.[12]

Statistical analysis

Descriptive statistics was applied to the collected data. K-S statistical goodness of fit test was applied to determine if the experimental data were parametric or nonparametric. The results are expressed as mean ± SEM. Comparison between groups was done using analysis of variance (ANOVA) followed by LSD-*post hoc* test if the experimental data in groups were parametric. Mann-Whitney U test was used if the data in groups were non-parametric. The significance was considered when $P \leq 0.05$.

RESULTS

Effect of oxytocin on catalepsy induced by haloperidol

The results showed that mice injected with haloperidol (2 mg/kg) exhibited extrapyramidal side effects such as akinesia, ptosis, rigidity and catalepsy. Mice injected with haloperidol at a dose of 2 mg/kg showed an increase in catalepsy compared to control group at $P = 0.000$.

Mice received combined treatment of oxytocin (1 iu/kg) and haloperidol showed an increase in catalepsy; also, mice that received the combined therapy of oxytocin (10 iu/kg) and haloperidol exhibited catalepsy, both compared to control group at $P = 0.000$ and $P = 0.000$ respectively.

Mice received combined treatment of oxytocin (1 iu/kg) and haloperidol (2 mg/kg) showed a significant increase in catalepsy compared to oxytocin treated group at a dose of 1 iu/kg ($P = 0.000$); the combined treatment produced a decrease in catalepsy compared to mice treated with 2 mg/kg haloperidol alone ($P = 0.000$). Mice injected by combined therapy of oxytocin (10 iu/kg) and haloperidol (2 mg/kg) showed an increase in catalepsy compared to oxytocin at a dose of 10 iu/kg treated mice ($P = 0.000$); in the same time the combined treatment produced a decrease in catalepsy compared to mice treated with 2 mg/kg haloperidol alone ($P = 0.000$) (Table 1).

Table 1: Effect of oxytocin on catalepsy induced by haloperidol

Catalepsy (30 seconds)						
Treatments (n=6)	Control (1% Tween 80)	Haloperidol (2mg/kg)	Oxytocin (1iu/kg)	Oxytocin (10 iu/kg)	Oxytocin (1iu/kg) +haloperidol (2mg/kg)	Oxytocin (10iu/kg) +haloperidol (2mg/kg)
Mean ± SEM	0.0 ± 0.00	**30.0 ± 0.00** *****	0.0 ± 0.00	0.0 ± 0.00	9.6 ± 1.74 ***, #, ¥**	11.1 ± 1.04 ***, #, £**

***,** Significantly different compared to control group at $P \leq 0.05$; #, significantly different compared to haloperidol at $P \leq 0.05$; ¥, significantly different compared to oxytocin 1 iu/kg #, significantly different compared to haloperidol at $P \leq 0.05$; **£**, significantly different compared to oxytocin 10 iu/kg.

Effect of oxytocin on akinesia induced by haloperidol

In the present study, mice injected with haloperidol (2 mg/kg) showed a decrease in number of steps moved compared to control group at $P = 0.000$. Mice injected with oxytocin at a dose of 1 iu/kg or 10 iu/kg, each alone, did not show change in number of steps moved at $P = 0.088$ and $P = 0.118$, respectively.

Mice treated with combined treatment of oxytocin (1 iu/kg) and haloperidol (2 mg/kg) showed a decrease in number of steps moved compared with control group at $P = 0.000$. While administration of oxytocin (1 iu/kg) and haloperidol (2 mg/kg), together, produced an increase in number of steps moved compared to haloperidol-treated group ($P = 0.000$).

Mice received combined treatment of oxytocin (10 iu/kg) and haloperidol (2 mg/kg) showed a decrease in number of steps moved compared with control group at $P = 0.000$, also compared to oxytocin at a dose of 10 iu/kg treated mice ($P = 0.000$). At the same time, mice received combined treatment showed an increase in number of steps moved compared with haloperidol-treated group ($P = 0.010$) (Table 2).

Effect of oxytocin on ptosis induced by haloperidol

Mice injected with haloperidol (2 mg/kg) showed an increase in eyelids droop compared to control group at $P = 0.000$. Mice received oxytocin (1 iu/kg) or (10 iu/kg) each alone did not show change in their eyelid condition compared to control group ($P = 1.000$ and 1.000, respectively).

Table 2: Effect of oxytocin on akinesia induced by haloperidol

Number of steps moved (30 seconds)						
Treatments (n=6)	Control (1% Tween 80)	Haloperidol (2 mg/kg)	Oxytocin (1iu/kg)	Oxytocin (10 iu/kg)	Oxytocin (1iu/kg) +haloperidol (2 mg/kg)	Oxytocin (10 iu/kg) + haloperidol (2 mg/kg)
Mean ± SEM	56.1 ± 0.83	12.6 ± 1.22 *	52.3 ± 1.05	52.6 ±1.52	32.1 ± 2.53 *, #, ¥	36.3 ± 1.72 *, #, £

*, Significantly different compared to control group at $P \leq 0.05$; #, significantly different compared to haloperidol at $P \leq 0.05$; ¥, significantly different compared to oxytocin 1 iu/kg; #, significantly different compared to haloperidol at $p \leq 0.05$; **£**, significantly different compared to oxytocin 10 iu/kg.

Combined administration of oxytocin (1 iu/kg) and haloperidol (2 mg/kg) did not change eyelid condition compared with haloperidol-treated group alone (P = 0.405); this combination produced an increase in eyelid droop compared to oxytocin (1 iu/kg) treated group alone (P = 0.000).

Mice received combined treatment of oxytocin (10 iu/kg) and haloperidol (2 mg/kg) showed an increase in eyelid droop induced by injection of haloperidol compared with control group at P = 0.035 and with oxytocin (10 iu/kg mg/kg) alone treated mice (P =0.035); while this combined treatment produced a decrease in eyelid compared with mice treated with 2 mg/kg haloperidol alone (P = 0.000) (Table 3).

Effects of oxytocin on tremor and righting reflex induced by haloperidol

Mice received different treatments in this study did not show tremor and loss of righting reflex as control group.

Table 3: Effect of oxytocin on ptosis induced by haloperidol

Eyelids droop over the eye = 4						
Treatments (n=6)	Control (1%Tween80)	Haloperidol (2 mg/kg)	Oxytocin (1iu/kg)	Oxytocin (10 iu/kg)	Oxytocin (1iu/kg) +haloperidol (2 mg/kg)	Oxytocin (10iu/kg) + haloperidol (2 mg/kg)
Mean ± SEM	0.0 ± 0.00	2.3 ± 0.21*	0.0 ± 0.00	0.0 ± 0.00	2.1 ± 0.47*, ¥	0.6 ± 0.42**, #, £**

***,** Significantly different compared control to treated group at $P \leq 0.05$; #, significantly different compared to haloperidol at $P \leq 0.05$. ¥, significantly different compared to oxytocin 1 iu/kg; **£**, significantly different compared to oxytocin 10 iu/kg.

DISCUSSION

In the present study, mice injected with haloperidol exhibited extrapyramidal side effects such as akinesia, ptosis and catalepsy. Oxytocin alone did not produce any effect but it antagonized haloperidol side effects.

Parkinson's disease is a progressive movement disorder of the nervous system; it leads to problems with movement, tremors, stiffness and impaired balance. Advanced Parkinson's disease may have difficulty walking and talking. Substantia nigra is the most brain area affected; in this area, dopamine is released.[14] Parkinson's disease causes motor symptoms including slow movement, tremors, involuntary movement, rigidity, trouble walking and imbalance.[15]

The main pathological feature of Parkinson's disease is cell death of dopamine-releasing neurons within the basal ganglia, mainly pars compacta of substantia nigra and partially striatum; the nigrostriatal pathway of the dopaminergic system plays a central role in motor control.[16]

Brain dopamine is critically involved in movement control, and its deficiency is the primary cause of motor symptoms in Parkinson's disease.[12]

Haloperidol is an antipsychotic; it is a potent blocker of central dopamine receptors and produces rigidity after its administration.[17] Haloperidol blocks postsynaptic dopamine D2 receptors in the mesolimbic system.[18] Haloperidol administration in mice reduces the activity

of mice due to its effect on dopamine receptor and the development of symptoms of Parkinson's disease and motor-function changes.[19]. Therefore, in this study, the Parkinson's model is applied using haloperidol.[12, 19]

Oxytocin has broad peripheral and central effects.[20] It is important in social cognition, functioning and even fear conditioning.[21]

In the present study, the extrapyramidal side effects were significantly antagonized by oxytocin. Haloperidol treatment causes dopaminergic receptor blockade particularly the D2 subtype of dopamine receptors increasing dopamine turnover rate (it refers to the accelerated process of dopamine being produced, released and metabolized in the brain more rapidly than usual).[22] In the brain, dopamine affects movement, emotions and the reward system.[23] Treatment with oxytocin significantly reversed the side effects induced with haloperidol by promoting dopamine release in certain brain regions like the Mes corticolimbic pathway, thereby counteracting these side effects.[24] This effect is due to oxytocin interaction with the dopaminergic system in the Mes corticolimbic pathway, which increases reward and motor activity.[25] Haloperidol is known to induce motor disturbances resembling Parkinsonian symptoms, including catalepsy.[26] In models of Parkinson›s disease, oxytocin protects nigrostriatal dopamine neurons against excitotoxic damage, which is crucial since dopamine depletion is linked to cataleptic behaviors.[27,28] This suggests that an increase in oxytocin levels has been associated with improved dopamine signaling, indicating a protective role against conditions that induce catalepsy.[27] Therefore, oxytocin may counteract the effects of haloperidol-induced extrapyramidal side effects through the increase of dopamine levels in the Mes corticolimbic dopamine system.

CONCLUSION

The present study conclude that mice injected with haloperidol exhibited Parkinson's like symptoms; the extrapyramidal side effects observed were akinesia, ptosis and catalepsy. The combined treatment of oxytocin with haloperidol showed that oxytocin antagonized the haloperidol side effects.

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