TÜBİTAK

ORIGINAL ARTICLE

Turk J Med Sci
2007; 37 (6): 333-338
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E-mail: medsci@tubitak.gov.tr

Effect of Different Drugs Influencing Monoamine Neurotransmission on Haloperidol-Induced Catalepsy in Mice

Omar Mohamed ABDEL-SALAM
Ayman R. BAIUOMY

Department of Pharmacology,
National Research Centre,
Cairo - EGYPT

Aim: Catalepsy occurs following high dopamine D2 receptor blockade by the typical antipsychotic drug haloperidol. The present study investigated the effect of different drugs affecting monoamine neurotransmission in this animal model of Parkinson's disease in mice.

Materials and Methods: Drugs were intraperitoneally administered with haloperidol 30 min prior to testing. Catalepsy was measured using the bar test.

Results: Catalepsy duration was reduced by the non-selective noradrenaline and serotonin reuptake inhibitors imipramine and amitriptyline (21.1% and 22.3% reduction by 20 mg/kg imipramine and amitriptyline, respectively). Catalepsy duration was increased by the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, fluvoxamine, and citalopram and by the serotonin receptor antagonist and reuptake inhibitor nefazodone (maximal increases of 112.4%, 38.5%, 30.8% and 112.4%, respectively). In contrast, the duration of catalepsy was decreased by the serotonin and dopamine reuptake inhibitor sertraline (56.8%, 52.6%, 35.7%); by sibutramine, a serotonin, dopamine and noradrenaline reuptake inhibitor (56.8%, 52.6%, 35.7%); and by Hypericum perforatum (31.9%, 33.2%, 39.6%) at 5, 10, 20 mg/kg, respectively.

Conclusions: Taken together, data in the present study suggest that drugs which have been reported to increase brain extracellular dopamine levels are likely to benefit motor symptoms in patients with Parkinson's disease.

Key Words: Catalepsy, haloperidol, antidepressants, mice

Monoamin İletimini Etkileyen Farklı İlaçların Ratlarda Haloperidol ile Uyarılmış Katalepsi Üzerine Etkisi

Amaç: Tipik bir antipsikotik olan haloperidol dopamine D2 reseptörlerini bloke ederek katelepsi oluşturur. Farelerde Parkinson hastalığı oluşturulan bu modelde farklı ilaçların monoaminin sinir iletimi üzerine olan etkisi araştırıldı.

Yöntem ve Gereç: Haloperidolle birlikte ilçalar testten 30 dk once intraperitoneal olarak verildi. Katalepsi bar testi kullanılarak ölçüldü.

Bulgular: Katalepsi süresi selektif olmayan noradrenalin ve serotonin reuptake inhibitörleri imipramin ve amitriptilin verilmesi ile azaltıldı. (20mg/kg imipramin ve amitriptilin verilmesi ile sırasıyla %21.1 ve %22.3). Seçici olarak serotonin reuptake inhibisyonu yapan fluoksetine, fluvoksamine, citalopram ve serotonin reseptör antagonisti ve reuptake inhibitörü olan nefazodone ise katalepsi süresini uzattı. (maksimum artışlar %112.4, %38.5, %30.8 ve %112.4). Karşıt olarak katalepsi süresi dopamine ve serotonin reuptake inhibitörü setraline tarafından azaltıldı (%56.8, %52.6, %35.7). Benzer eşekilde serotonin, dopamine ve noradrenalin reuptake inhibitörü olan sibutramin (%76.8, %82.2 and %89.1) ve Hypericum perforatum da katalepsi süresini azalttı (%31.9, %33.2, %39.6).

Sonuç: Bütün veriler göz önüne alındığında beyinde ekstrasellüler dopamin düzeylerini artıran ilaçların Parkinson hastalığında motor semptomların düzeltilmesinde yararlı olacağı kanaatine varıldı.

Anahtar Sözcükler: Katalepsi, haloperidol, antidepresanlar, fare

Received: June 12, 2007
Accepted: November 15, 2007

Correspondence
Omar M. ABDEL-SALAM
Department of Pharmacology,
National Research Centre,
Dokki, Cairo - EGYPT

omasalam@hotmail.com

Introduction

Parkinson's disease is a progressive neurodegenerative disorder, the principal pathological characteristic of which is the loss of dopaminergic neurons of the substantia nigra pars compacta. Patients with Parkinson' disease suffer from motor behavioral impairment in the form of muscular rigidity and bradykinesia in addition to a resting tremor (1). Studies have indicated that depression is a common and potentially debilitating aspect of Parkinson's disease, affecting 40-50% of patients (2,3). Depression in Parkinson's disease might be associated with a specific loss of dopamine and noradrenaline innervation in the limbic system (4). Depression associated with Parkinson's disease is likely to contribute to the development of cognitive disorders and is associated with a significantly increased risk of developing dementia (5,6). Thus, antidepressant drugs are likely to be included in the list of drugs prescribed for patients with Parkinson's disease. For many years, the tricyclic antidepressants (TCAs) and the monoamine oxidase inhibitors (MAOIs) have dominated the pharmacological treatment of depressive disorders. Selective serotonin reuptake inhibitors (SSRIs) have comparable efficacy to the TCAs and a better tolerability profile in patients with depression; they are rapidly being considered as first-line therapy for patients with depressive disorders including that occurring in Parkinson's disease patients (7,8).

Questions, however, have arisen considering the safety of SSRIs in Parkinson's disease. In reports of adverse reactions in patients given fluoxetine, there were notifications of extrapyramidal events that may be caused by the drug (9), and among patients with Parkinson's disease treated with SSRIs, there were cases of worsening parkinsonism (10). The addition of sertraline (11,12) or citalopram (13) to the antiparkinsonian drug regimen has also been associated with treatment-emergent extrapyramidal syndrome side effects. The risk estimate of SSRIs causing extrapyramidal symptoms appeared to be higher in patients concurrently using antipsychotic medication (14). In addition, the start of SSRI therapy in levodopa users was followed by a faster increase in antiparkinsonian drug treatment (15). Alterations in serotonergic neurotransmission have been suggested to be involved in the modulation of the basal ganglia and in the pathophysiology of human involuntary movement disorders. There is also an evidence to suggest abnormalities of 5-hydroxytryptamine (HT)2C transmission in the basal ganglia of patients with Parkinson's disease (16).

The aim of this study was to examine drugs influencing monoamine mechanisms, especially those used in the treatment of depressive disorders, in an animal model of Parkinson's disease caused by injection of haloperidol in mice. Compounds studied included the conventional TCAs, imipramine and amitriptyline; the SSRIs fluoxetine, fluvoxamine and sertraline; the serotonin receptor antagonist and reuptake inhibitor nefazodone; and *Hypericum perforatum* (St. John's wort) extract, which acts to inhibit the re-uptake of several neurotransmitters, including serotonin, norepinephrine, dopamine, gamma-aminobutyric acid and L-glutamate (17-19). In addition, the effect of sibutramine, a drug used in obesity that weakly inhibits norepinephrine and 5-HT reuptake (20), was examined.

Catalepsy, a behavioral immobility associated with varying degrees of enhanced muscular rigidity, serves as an experimental animal model of parkinsonism (21). Typical antipsychotics, such as haloperidol, produce extrapyramidal side effects, including a parkinsonian-like syndrome which is attributed to blockade of D2 in the striatum (22). Catalepsy induced by haloperidol represents a useful model of Parkinson's disease and has been used for detecting antipsychotic drugs with extrapyramidal side effect liability (23,24) and for evaluating the utility of antidepressant drugs for the treatment of depression associated with Parkinson's disease (25,26).

Materials and Methods

Male Swiss albino mice (22-25 g) were used. Mice were housed under standardized conditions with free access to food and water. Catalepsy, defined as a reduced ability to initiate movement and a failure to correct posture, was measured by means of the bar test. To test for catalepsy, mice were positioned so that their hindquarters were on the bench and their forelimbs rested on a 1 cm diameter horizontal bar, 4 cm above the bench. The length of time the mice maintained this position was recorded by stopwatch to a maximum of 180 s. This procedure was conducted 30 min after drug administration. Haloperidol was administered via intraperitoneal (i.p.) route at the dose of 2 mg/kg. The tested drug was administered intraperitoneally together with haloperidol. Mice were judged to be cataleptic if they maintained this position for 30 s or more.

Drugs

Haloperidol (Kahira Pharm and Chem. IND, Cairo, ARE), fluoxetine hydrochloride (Amoun Pharmaceuticals, Cairo, ARE), imipramine hydrochloride, (Novartis Pharmam Cairo, ARE), amitriptyline hydrochloride (Kahira Pharm and Chem. IND, Cairo, ARE), nefazodone hydrochloride (Bristol Myers Squibb, Cairo, ARE), sertraline hydrochloride (Pfizer, Cairo, ARE), citalopram hydrobromide (Lundbeck, Denmark), fluvoxamine maleate (Solvay Pharmaceuticals, Holland), sibutramine hydrochloride (EVA Pharma, Cairo, ARE), and St. John's wort (*Hypericum perforatum*) extract (Safamood, ATOS Pharma, Cairo, ARE) were used. The doses of drugs employed in the study were based upon the human dose after conversion to that of rat (27).

Statistics

All results are expressed as mean ± SE. Multiple group comparisons were performed by one-way analysis of variance followed by Duncan multiple range test. $P < 0.05$ was considered statistically significant.

Results

Results are presented in Table 1. Haloperidol administered i.p. at the dose of 2 mg/kg produced a significant cataleptic response. The duration of haloperidol-induced catalepsy was significantly reduced, by 13.4% and 21.1%, by 10 and 20 mg/kg imipramine, respectively. Amitriptyline at 20 mg/kg significantly reduced catalepsy, by 22.3%. Sertraline (5, 10, 20 mg/kg) markedly decreased catalepsy by 56.8%, 52.6% and 35.7%, respectively. The effect of haloperidol was significantly and potently inhibited by sibutramine (76.8%, 82.2% and 89.1%, at 5, 10, 20 mg/kg, respectively). The duration of catalepsy was also decreased dose-dependently by *Hypericum perforatum* (31.9%, 33.2% and 39.6%, at 5, 10 and 20 mg/kg, respectively). In contrast, the SSRIs fluoxetine, fluvoxamine and citalopram increased haloperidol-induced catalepsy. The effect of haloperidol was significantly increased by 18% and 112.4% after fluoxetine 10 and 20 mg/kg, by 22% and 38.5% after fluvoxamine 10 and 20 mg/kg, and by 21% and 30.8% after citalopram 10 and 20 mg/kg, respectively. Catalepsy was also significantly increased by all doses of nefazodone (61.6%, 84.1% and 112.4% increase by 5, 10 and 20 mg/kg, respectively).

Table 1. Effect of different drugs acting on monoamine transmission on the duration of haloperidol-induced catalepsy in mice.

Treatment	Duration of catalepsy (sec)	% inhibition (vs control value)
Saline	63.6 ± 3.5	
Imipramine		
5 mg/kg	67.2 ± 2.6	
10 mg/kg	55.1 ± 2.7	-13.4%
20 mg/kg	50.2 ± 3.6*	-21.1%
Saline	65.8 ± 3.1	
Amitrpitiline		
5 mg/kg	68.6 ± 3.5	
10 mg/kg	59.1 ± 3.6	-10.2%
20 mg/kg	51.4 ± 4.3*	-22.3%
Saline Sertraline	79.8 ± 8.7	
5 mg/kg	34.5 ± 5.7*	-56.8%
10 mg/kg	37.8 ± 5.4*	-52.6%
20 mg/kg	51.3 ± 5.1*	-35.7%
Saline 77.1 ± 6.7		
Sibutramine		
5 mg/kg	17.9 ± 1.6*	-76.8%
10 mg/kg	13.7 ± 1.2*	-82.2%
20 mg/kg	8.4 ± 0.7*	-89.1%
Saline	79.7 ± 5.6	
Hypericum perforatum		
5 mg/kg	54.3 ± 5.6*	-31.9%
10 mg/kg	53.2 ± 5.3*	-33.2%
20 mg/kg	48.1 ± 2.1*	-39.6%
Saline	53.2 ± 5.8	
Fluoxetine		
5 mg/kg	43.6 ± 5.4	
10 mg/kg	62.8 ± 6.8	+18.0%
20 mg/kg	113.0 ± 10.8*	+112.4%
Saline	96.4 ± 6.1	
Fluvoxamine		
5 mg/kg	78.6 ± 8.0	
10 mg/kg	117.6 ± 6.2*	+22.0%
20 mg/kg	133.5 ± 7.8*	+38.5%
Saline	73.3 ± 6.2	
Citalopram		
5 mg/kg	83.6 ± 6.2	+14.1%
10 mg/kg	88.6 ± 5.6	+21.0%
20 mg/kg	95.9 ± 7.8*	+38.8%
Saline	73.3 ± 5.1	
Nefazodone		
5 mg/kg	118.5 ± 12.5*	+61.6%
10 mg/kg	135.0 ± 11.4*	+84.1%
20 mg/kg	155.7 ± 9.9*	+112.4%

Catalepsy was induced by intraperitoneal administration of haloperidol at the dose of 2 mg/kg. Tested drug was administered intraperitoneally together with haloperidol. Catalepsy was measured by means of the bar test 30-min after drug administration. $P<0.05$ compared to saline-treated control group (one-way ANOVA and Duncan multiple range test).

Discussion

The present study investigated the effect of a number of drugs influencing monoamine neurotransmission on catalepsy induced in mice by haloperidol. Findings in the present study indicated that the duration of catalepsy was decreased by the tertiary amine tricyclics, imipramine and amitriptyline, which is in accordance with other earlier studies (25,28). These agents, which served as the cornerstone of antidepressant therapy for almost 30 years, are non-selective noradrenaline and to much less extent serotonin reuptake inhibitors. In contrast to other antidepressant drugs such as the SSRIs, the tertiary amine tricyclics possess anticholinergic and antihistaminic properties, which are likely to be of relevance to the effects of these agents on catalepsy.

Fluoxetine, the prototype of SSRIs and one of the most commonly used drugs as first-line therapy in pharmacotherapy of depression (29), increased catalepsy caused by haloperidol in the present study. Other investigators have reported a decrease in haloperidol catalepsy in mice by fluoxetine, the effect being more evident with 5 mg/kg than with the higher dose of 25 mg/kg (26). In the present study, however, the administration of 5 mg/kg fluoxetine failed to affect catalepsy, while higher doses of 10 or 20 mg/kg clearly increased catalepsy duration. This discrepancy in results could be due to the timing of administration of fluoxetine in relation to haloperidol. In rats, fluoxetine displayed differential effects on dopamine neurons in the ventral tegmental area (VTA) compared with substantia nigra pars compacta (SNC). Single i.p. injection of 2.5 mg/kg fluoxetine increased the number of spontaneously active dopamine neurons in SNC and VTA. In contrast, a single injection of 5 mg/kg fluoxetine increased the number of spontaneously active dopamine neurons in VTA (30).

Catalepsy duration was increased by the serotonin receptor antagonist and reuptake inhibitor nefazodone in accordance with the findings of Benazzi (31). The SSRIs fluvoxamine and citalopram also enhanced the haloperidol-induced catalepsy in the present study. In this context, worsening of Parkinson's disease in man by citalopram was reported (13). In rats, endogenous 5-HT acting on 5-HT2C receptors tonically inhibits basal dopamine release in the prefrontal cortex, while stimulation of 5-HT2C receptors with an exogenous agonist preferentially inhibits stimulated release (32). Enhanced serotonergic neurotransmission thus acts to inhibit dopamine release. Furthermore, haloperidol administration in rats leads to an adaptive increase in 5-HT2C signaling, which may contribute to abnormal motor function associated with antipsychotic use (33), and blocking 5-HT2C attenuates haloperidol-induced catalepsy (34). SSRIs are thus expected to exert adverse effects on the catalepsy induced by typical antipsychotics, e.g. haloperidol, which was observed in the present study.

Sertraline, another SSRI, on the other hand, inhibited the catalepsy with the maximal effect observed at the minimal dose used (5 mg/kg). With the higher dose of 20 mg/kg, the inhibitory effect of sertraline is reduced. Sertraline appears to be a potent dopamine reuptake inhibitor (35). This might explain the reduction of catalepsy by sertraline observed in the present study. In other studies, a decrease in haloperidol catalepsy in mice was found after the administration of 1 or 5 mg/kg sertraline (26).

Sibutramine is an anti-obesity drug with serotonin, dopamine and noradrenaline reuptake inhibitory properties (36). In the present study, the effect of haloperidol was significantly and potently inhibited by sibutramine. Studies indicated that sibutramine exhibits neurochemical and behavioral dopaminomimetic activity in vivo, which is mediated by dopamine reuptake inhibition. Sibutramine antagonized methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP)-induced dopamine depletion in the mouse brain (37). It was also suggested that the effect of sibutramine on energy expenditure in rats is predominantly due to a dopamine-dependent increase in locomotor activity (38). Sibutramine (5 mg/kg, p.o.) increased extracellular dopamine and 5-HT levels in rat striatum (39).

In the present study, haloperidol-induced catalepsy was also reduced by *Hypericum perforatum* extract. This herbal remedy is widely used in the pharmacotherapy of mild to moderate depression (40). The exact mechanism of action is not yet clear, but an increase in brain levels of serotonin, noradrenaline or dopamine has been observed, suggesting a mechanism similar to that of SSRIs or tricyclic antidepressants. However, hyperforin also inhibits the uptake of gamma-aminobutyric acid (GABA) and L-glutamate (17,18). In addition, authors have suggested that *Hypericum* or its active principle hyperforin may be acting as a reserpine-like drug (19).

In conclusion, the present paper provides evidence for worsening of haloperidol-induced catalepsy by the administration of fluoxetine, fluvoxamine and citalopram. It therefore looks as if enhancing serotonergic neurotransmission would have adverse effect on haloperidol-induced catalepsy. The study indicates an anti-cataleptic effect of imipramine, amitriptyline, sertraline, sibutramine and *Hypericum perforatum*. It is suggested that increasing noradrenergic neurotransmission and/or anti-muscarinic effects account for the catalepsy-reducing effect of imipramine or amitriptyline, whereas dopaminergic-enhancing properties of sertraline, sibutramine and *Hypericum perforatum* contribute at least in part to their catalepsy-inhibitory effects.

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