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Histamine Potentiates Cyclosomatostatin-Induced Catalepsy in Old Rats

Ilya D. Ionov [1,*]; Zoya A. Turgeneva [2]

[1]Centre on Theoretical Problems in Physical and Chemical Pharmacology, Russian Academy of Sciences, Moscow, Russia
[2]Research Group, Timpharm Ltd, Moscow, Russia

*Corresponding author: Ilya D. Ionov, Centre on Theoretical Problems in Physical and Chemical Pharmacology, Russian Academy of Sciences, P. O. Box: 117513, Moscow, Russia. Tel: +7-9160734902; Fax: +7-4954383883, E-mail: newrology@yandex.ru

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Background: The decreased level of somatostatin and increased level of histamine are detected in the Parkinsonian brain. In old Wistar rats, the brain somatostatin deficiency can initiate catalepsy that suggests the pathogenic significance of this abnormality in Parkinson's disease (PD). The ability of histamine to affect the somatostatin deficiency action is not studied.
Objectives: The current study aimed to examine if histamine alters the cataleptogenic activity of the brain somatostatin deficiency in Wistar rats.
Materials and Methods: The animals used in the study were 100 - 110 and 736 - 767 days old. Catalepsy was evaluated by the bar test. The inhibition of the brain somatostatin activity was simulated by I.C.V. administration of cyclosomatostatin (cycloSOM), a somatostatin receptor antagonist.
Results: CycloSOM (0.2, 1.0, and 5.0 μg) and histamine (1.0 and 10.0 μg) alone were ineffective in both young and old animals. In combination, however, cycloSOM and histamine initiated cataleptic response in old rats. Effect of the combination was inhibited by H1 and H2 but not H3 antagonists.
Conclusions: CycloSOM and histamine synergistically exert catalepsy in old rats. In light of these data, the combination of the decreased brain level of somatostatin and increased brain level of histamine may be of pathogenic relevance for extrapyramidal signs in PD.

Keywords: Histamine; Somatostatin; Aging; Catalepsy; Parkinsonian Disorders

1. Background

Bradykinesia and other extrapyramidal signs are the major features of Parkinson's disease (PD). These signs are thought to be linked to an inhibition of the brain dopaminergic system (1, 2). However, the exact mechanism for the extrapyramidal features in PD remains far from fully understood.

In patients with PD, a reduced brain level of somatostatin (SOM) is frequently observed (3-7). In old Wistar rats, an inhibition of brain SOM receptors can produce catalepsy (8), an animal model of parkinsonian bradykinesia and rigidity. In light of these data, it appears that brain SOM deficiency may be of pathogenic relevance in PD.

Another PD-related sign is an increased brain level of histamine (9). This abnormality might influence the effect of SOM deficiency through modulation of SOM receptors. Such a possibility is supported by the observations of Puebla et al. who found an ability of exogenous histamine to decrease the SOM binding to its receptors in neurons (10, 11).

2. Objectives

The current study aimed to examine the influence of histamine on cataleptogenic action of the brain SOM deficiency in rats of different ages.

3. Materials and Methods

3.1. Animals

The research protocol was approved by the local animal care and use committee. The experiments were conducted with male Wistar rats of 100 - 110 and 736 - 767 days old. Since the mean lifespan for these animals was approximately 750 days (12), these animals were considered as young and old.

Rats were housed as described previously (13). Animals were randomly divided into groups of seven animals.

3.2. Drugs

Cyclo (7-aminoheptanoyl-Phe-D-Trp-Lys-Thr [Bzl]) (cyclosomatostatin, cycloSOM), histamine dihydrochloride (histamine), (±)-chlorpheniramine maleate (chlorpheniramine), ranitidine hydrochloride (ranitidine), thioperamide maleate (thioperamide), (±)-ketamine hydrochloride (ketamine), and xylazine hydrochloride (xylazine) were obtained from Sigma-Aldrich (St. Louis, MO, USA). Gentamicin sulfate (Krka, Slovenia) and Polysporin triple antibiotic ointment (Pfizer Canada, Markham, Ontario,

Canada) were used as well. The drugs were dissolved in sterile artificial corticospinal fluid (14). The drug solutions were prepared just before administration. CycloSOM at the doses of 0.2, 1.0, 5.0, and 10.0 μg and histamine at the doses of 1.0 and 10.0 μg were administered intracerebroventricularly (i.c.v.). The doses were selected according to the previous studies (8, 13).

Histamine H1, H2, and H3 receptor antagonists (chlorpheniramine, ranitidine, and thioperamide, respectively) were used to determine the type of receptors involved in the histamine effect. The antagonists were used I.C.V. at equimolar doses. These drugs were injected simultaneously with histamine. The choice of 8 μg chlorpheniramine dose, was based on the results of a previous study (15). Ranitidine and thioperamide were administered at the doses of 7 μg and 8 μg, respectively.

3.3. Surgery

The surgical operations were done under aseptic conditions. Additionally, before surgery each rat was injected gentamicin sulfate, 5 mg/kg intramuscularly. The animal was anaesthetized with intraperitoneal administration of ketamine and xylazine (80 and 8 mg/kg, respectively) and placed in a Kopf stereotaxic apparatus (David Kopf Instruments, Tujunga, CA, USA). For i.c.v. administration, a 26-gauge stainless steel guide cannula (Plastics One Inc., Roanoke, Va, USA) was stereotaxically implanted into the third ventricle using the following coordinates from bregma: AP = 0.2 mm; V = 9.0 mm; L = 0 mm (16). The guide cannula was secured with screws and cranioplastic cement (Dentsply International, York, PA, USA). Leakage of the cerebrospinal fluid from the cannula during its implantation was used as the criterion for proper actions (17). Additionally, the location of the cannula track was verified during sectioning. The animals showing cannula misplacement were excluded from the study.

After placement, the guide cannula was sealed with a sterile dummy cannula (obturator, Plastics One Inc., Roanoke, VA, USA). The incision area was treated topically with Polysporin triple antibiotic ointment. The animals were allowed to recover for 10 days during which they were caged individually.

3.4. Intrabrain Injection Procedure

On the experiment day, the obturator was removed and a tested solution (a total volume of 5 μL) was injected using a handheld microsyringe and 33-gauge stainless steel internal cannula (Plastics One Inc. Roanoke, VA, USA).

3.5. Induction and Evaluation of Catalepsy

Catalepsy, a prolonged maintenance of an externally imposed abnormal posture, was assessed by means of the bar test (18, 19). The rat was gently placed with its forepaws on a wooden horizontal bar (1.5 cm in diameter × 25 cm long) positioned 7.5 cm above a wooden platform. The duration of catalepsy was measured as the time (s) the animal maintained an imposed posture. These test procedures were performed at 60, 120, 180 and 240 minutes after I.C.V. administration of the drug (s).

3.6. Statistical Analysis

Data are expressed as mean ± standard error of mean. Kolmogorov-Smirnov one-sample test was used to assess the normality of the data distribution. Since the normality assumptions could not be accepted, comparisons were made with a two-way repeated-measure ANOVA on ranks followed by a non-parametric Tukey's test. Differences with a P value of less than 0.05 were considered statistically significant.

4. Results

In young rats, cycloSOM the doses of 0.2 - 10.0 μg failed to produce catalepsy (no significant difference was observed between drug- and vehicle-treated groups, $P > 0.05$, n = 7, data not shown). In contrast, in the old rats cycloSOM at the dose of 10.0 μg initiated a marked cataleptic response ($P < 0.05$; n = 7), whereas smaller doses (0.2, 1.0, and 5.0 μg) were ineffective (no significant difference was observed between drug- and vehicle-treated groups, $P > 0.05$, n = 7) (Table 1). Histamine, at the doses of 1.0 and 10.0 μg, failed to induce catalepsy both in young and old rats ($P > 0.05$, n = 7; data not shown).

Table 1. Cataleptic Response to Cyclosomatostatin in Old Rats [a,b]

Age Group and Drug, μg	The Duration of Catalepsy, s			
	60 min	120 min	180 min	240 min
Old rats				
Vehicle	10.1 ± 1.3 [c]	9.7 ± 1.1 [c]	9.6 ± 1.3 [c]	9.7 ± 1.4 [c]
CycloSOM				
0.2	9.7 ± 1.3 [c]	9.1 ± 1.2 [c]	9.2 ± 1.2 [c]	9.4 ± 1.3 [c]
1.0	11.0 ± 1.5 [c]	10.7 ± 1.4 [c]	10.3 ± 1.4 [c]	9.7 ± 1.4 [c]
5.0	14.1 ± 1.9 [c]	13.6 ± 1.8 [c]	12.8 ± 1.7 [c]	11.7 ± 1.9 [c]
10.0	17.3 ± 2.3 [d]	15.8 ± 2.2 [d]	15.0 ± 2.1 [d]	15.4 ± 2.1 [d]

[a] Measurements are expressed as Mean ± SEM (n = 7).
[b] The groups were compared at the same time points.
[c] Means followed by the same letter were not significantly different, $P > 0.05$.
[d] $P < 0.05$, significant difference from the vehicle-treated group.

Table 2. Cataleptic Response to Cyclosomatostatin and Histamine in Rats [a,b]

Age Groups and Drugs, μg	The Duration of Catalepsy, s			
	60 min	120 min	180 min	240 min
Young rats				
Vehicle	9.1±1.2 [c]	8.9 ± 1.2 [c]	8.4 ± 1.1 [c]	8.3 ± 1.1 [c]
CycloSOM, 1.0	9.9 ± 1.3 [c]	9.5 ± 1.3 [c]	9.3 ± 1.2 [c]	9.1 ± 1.2 [c]
CycloSOM, 5.0	10.2 ± 1.3 [c]	10.0 ± 1.4 [c]	9.8 ± 1.3 [c]	8.9 ± 1.2 [c]
CycloSOM, 1.0 + histamine, 1.0	10.4±1.4 [c]	9.9±1.4 [c]	10.1±1.3 [c]	9.8±1.3 [c]
CycloSOM, 5.0 + histamine, 1.0	10.8 ± 1.4 [c]	10.5 ± 1.4 [c]	10.7 ± 1.4 [c]	9.9 ± 1.3 [c]
CycloSOM, 1.0 + histamine, 10.0	10.6 ± 1.5 [c]	10.4 ± 1.4 [c]	9.9 ± 1.3 [c]	10.4 ± 1.4 [c]
CycloSOM, 5.0 + histamine, 10.0	11.1 ± 1.5 [c]	10.7 ± 1.4 [c]	10.9 ± 1.5 [c]	10.6 ± 1.4 [c]
Old rats				
Vehicle	10.0 ± 1.3 [c]	9.8 ± 1.1 [c]	9.5 ± 1.3	9.8 ± 1.4 [c]
CycloSOM, 1.0	10.8 ± 1.5 [c]	10.5 ± 1.4 [c]	10.1 ± 1.3 [c]	9.9 ± 1.3 [c]
CycloSOM, 5.0	13.2 ± 1.8 [c]	12.9 ± 1.7 [c]	12.6 ± 1.7 [c]	11.5 ± 1.5 [c]
CycloSOM, 1.0 + histamine, 1.0	13.4 ± 1.8 [c]	12.9 ± 1.7 [c]	13.2 ± 1.8 [c]	13.0 ± 1.7 [c]
CycloSOM, 5.0 + histamine, 1.0	14.3 ± 1.9 [c]	14.1 ± 1.9 [c]	13.6 ± 1.8 [c]	13.8 ± 1.8 [c]
CycloSOM, 1.0 + histamine, 10.0	16.8 ± 2.2 [d]	17.3 ± 2.3 [d]	16.3 ± 2.2 [d]	15.6 ± 2.1 [d]
CycloSOM, 5.0 + histamine, 10.0	25.8 ± 3.4 [d,e]	26.9 ± 3.6 [e,f]	24.6 ± 3.4 [d,e]	23.7 ± 3.2 [e,f]

[a] Measurements are expressed as Mean ± SEM (n = 7).
[b] The groups were compared at the same time points.
[c] Means followed by the same letter are not significantly different, P > 0.05.
[d] P < 0.05, significant difference in the group that received the same dose of cycloSOM without histamine.
[e] P < 0.05, significant difference in the group that received cycloSOM (1.0 μg) and histamine (10.0 μg).
[f] P < 0.01, significant difference in the group that received the same dose of cycloSOM without histamine.

Table 3. Effects of Histamine Antagonists on Catalepsy in Old Rats [a,b]

Drugs and Doses	The Duration of Catalepsy, s			
	60 min	120 min	180 min	240 min
Vehicle	9.9 ± 1.2 [c]	10.3 ± 1.2 [c]	9.8 ± 1.2 [c]	10.0 ± 1.3 [c]
Chlorpheniramine (H1 receptor antagonist, 8.0 μg)	10.2 ± 1.4 [c]	9.8 ± 1.3 [c]	10.0 ± 1.4 [c]	9.4 ± 1.3 [c]
Ranitidine (H2 receptor antagonist, 7 μg)	9.6 ± 1.3 [c]	10.1 ± 1.4 [c]	0.1 ± 1.4 [c]	9.8 ± 1.3 [c]
Thioperamide (H3 receptor antagonist, 8 μg)	9.6 ± 1.3 [c]	10.4 ± 1.4 [c]	9.7 ± 1.3 c	10.2 ± 1.4 [c]
CycloSOM (5.0 μg) + histamine (10.0 μg)	22.7 ± 3.1 [d]	23.8 ± 3.3 [d]	19.4 ± 2.7 [e]	17.2 ± 2.4 [e]
CycloSOM (5.0 μg) + histamine (10.0 μg) +chlorpheniramine(8.0 μg)	12.8 ± 1.7 [c]	13.4 ± 1.9 [c]	12.8 ± 1.7 [c]	12.0 ± 1.8 [c]
CycloSOM (5.0 μg) + histamine (10.0 μg) + ranitidine (7 μg)	11.6 ± 1.6 [c]	11.9 ± 1.6 [c]	12.2 ± 1.6 [c]	11.4 ± 1.5 [c]
CycloSOM (5.0 μg) + histamine (10.0 μg) + thioperamide (8 μg)	19.4 ± 2.6 [e]	18.1 ± 2.5 [e]	17.9 ± 2.4 [e]	17.3 ± 2.3 [e]

[a] Measurements are expressed as mean ± SEM (n = 7).
[b] The groups were compared at the same time points.
[c] Means followed by the same letter are not significantly different, P > 0.05.
[d] P < 0.01, significant difference in the vehicle-treated group.
[e] P < 0.05, significant difference in the vehicle-treated group.

In young animals, co-administration of ineffective doses of cycloSOM (1.0 or 5.0 μg) and histamine (1.0 or 10.0 μg) induced no catalepsy. In old rats, however, the combination of cycloSOM and histamine (10.0 μg) caused catalepsy; the effect was dependent on the cycloSOM dose (cycloSOM at 5.0 μg was significantly more effective than at 1.0 μg, P < 0.05 or 0.01; n = 7, Table 2).

Thus, histamine renders the old animal susceptible to ineffective doses of cycloSOM. This effect appears to be dependent on the dose of histamine, as it was observed at a dose of 10 μg but not at 1 μg (Table 2). The sensitivity to histamine was reduced by chlorpheniramine and ranitidine but not thioperamide (Table 3). In all likelihood, histamine effect is at least partly mediated by histamine H1 and H2 receptor activation.

5. Discussion

In the authors' previous experiments, the brain somatostatin deficiency alone produced catalepsy in old rats. As shown there, cycloSOM initiates cataleptic response at the dose of 10 μg, while smaller doses are inactive (8). Similar results were obtained in the present work, wherein cycloSOM at the doses of 0.2 - 5.0 μg had no effects. Exogenous histamine in the present experiments also had no cataleptogenic effect when taken alone. However, a sub-effective dose of cycloSOM in combination with ineffective dose of histamine produced a marked cataleptic response in the old rats (Table 2). The response was inhibited by specific H1 and H2 receptor antagonists. Thus, histamine through specific H1 and H2 receptors aggravated cataleptogenic action of sub-effective dose of somatosta-

tin receptor blocker. In essence, a synergy between somatostatin deficiency and histamine took place in the initiation of catalepsy.

The mechanism of this synergy was obscure since very few data are available in the literature on somatostatin-histamine interaction in the brain. To the best of the authors knowledge, the only published studies on this point were those of Puebla et al. (1995, 1996) wherein an ability of exogenous histamine to reduce the affinity of somatostatin binding sites within neuronal membranes was found (10, 11). The nature of this effect was unclear.

Anyhow, the present results further support the participation of histamine in PD development. As already noted above, histamine level increased in the brain of the patients with PD. In rats, histamine selectively damages dopaminergic neurons of the substantia nigra (20), i.e., induces the main histopathological feature of PD. A blockade of histamine receptors enhances the antiparkinsonian effects of L-DOPA in primate model of PD (21). In the present experiments, histamine potentiated Parkinsonian-like effects of such a PD-related abnormality as the bran somatostatin deficiency. As it seems, all these findings should be taken into account when considering the mechanisms of PD.

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Authors' Contributions

Ilya D. Ionov: study concept and design, acquisition of data, analysis and interpretation of data, writing of the manuscript, administrative, technical, and material support, and study supervision; Zoya A. Turgeneva: acquisition of data and statistical analysis.

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