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Original Article

Synergy of Somatostatin – substance P Receptors Antagonists in the Initiation of Catalepsy in Rats

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Abstract

The parkinsonian brain undergoes a decrease in levels of somatostatin (SST) and substance P (SP). According to previous studies, brain SST deficit in rats simulated by i.c.v. injections of SST receptor antagonist, cyclosomatostatin (cSST), increases the speed of catalepsy development. Nevertheless, it is not clear how the SP, a natural ligand of neurokinin-1 (NK1) receptors, contributes to the growth of catalepsy.

The present study aimed to find out whether simultaneous blockade of central somatostatin and NK1 receptors can lead to catalepsy, a model for parkinsonian bradykinesia and rigidity. The experiments were conducted on Wistar rats. The blockade of somatostatin and NK1 receptors was simulated by intracerebroventricular injections of cSST and substance L-733,060, respectively. Bar test was used to evaluate the catalepsy. No catalepsy was induced by cSST at 1.0 µg and L-733,060 at 10.0 ng injected separately. Nevertheless, co-administration of these agents led to a clear cataleptic response. Cataleptogenic action of the combination was reversed by SP. These results show that cSST and L-733,060 can synergistically induce catalepsy in the rat. According to these findings, Parkinson's disease-associated brain deficit in SST and SP could be relevant for pathogenesis of extrapyramidal dysfunctions. Considering the aforementioned findings, the processes mediated by central SST and NK1 receptors could be possible therapeutic targets for parkinsonism.

Keywords: Catalepsy, Parkinsonian disorders, Somatostatin, Substance P

Background

Bradykinesia and other extrapyramidal disorders are the symptoms of Parkinson's disease (PD) [1], Alzheimer's disease [2], dementia with Lewy bodies [3], psychosis [4], and some other neuropsychiatric disorders. It is assumed that these symptoms are caused by the inhibition of dopaminergic processes in brain regions, such as substantia nigra pars compacta and dorsal striatum [1, 5]. Nevertheless, the details of the mechanism for the dysfunctions of the extrapyramidal system are still unknown [1].

According to previous research, the brain level of somatostatin (SST) and expression of SST mRNA undergo a decrease in patients with PD [6]. These abnormalities may be relevant to the growth of extrapyramidal signs as the substantia nigra contains SST receptors [7] and may be dysregulated by somatostatinergic hypoactivation. The possible effects of this hypoactivation on the development of extrapyramidal disorders are supported by previous research on rats [8] in which intracerebral injections of an SST receptor antagonist, cyclosomatostatin (cSST) [9], promoted the development of catalepsy, a behavior resembling extrapyramidal dysfunction in humans. In these experiments, cSST contributed to catalepsy in middle-aged Wistar rats more effectively, compared to that in young ones.

Another PD-associated brain abnormality is a decreased levels of substance P (SP) in CSF and in tissues of different brain areas, in particular, the substantia nigra [10]; also, a reduction in the binding activity of SP receptors in brain tissues was seen [11].

The significance of the reduced brain SP-ergic activity for the development of parkinsonism is unclear. Currently, there is only sparse and conflicting evidence for participation of SP in extrapyramidal regulation. In rats, exogenous SP was observed to inhibit reserpine- and haloperidol-induced rigidity and tremor [12, 13]; this suggests the ability of SP-mediated processes to hinder the development of experimental extrapyramidal disorders.

Objectives

However, Anderson and co-workers have described

an inhibition of raclopride-induced catalepsy by an antagonist of SP receptors, CP-99,994 [14].
No data are available on whether the simultaneous inhibition of brain somatostatinergic and SP-ergic processes influences extrapyramidal regulation. To address this issue, this study investigated the cataleptogenic activity of cSST combined with L-733,060; the latter is known to block NK1 receptors - the predominant target for SP [15, 16].

Materials and Methods

Animals

The experiments were conducted on male Wistar rats of 530–570 days of age (National Laboratory Animal Resource Centre, Pushchino, Russia). Given that the mean lifespan of male Wistar rats constitutes about 800 days [17], the animals used here can be considered middle-aged. The rats were kept two per cage in a well-aired room at 22 °C and a 12-hour light/dark cycle (lights on at 07:00 a.m.) Standard laboratory rat chow and tap water were provided for the animals *ad libitum*.
All the rats were obtained from the same population and then randomly divided into groups (n = 10). These animals were housed in identical polycarbonate cages (23 x 15 x 8 in.) for two weeks prior to the experiments.
All procedures followed the European Communities Council Directive (2010/63/EU) and were approved by the local Ethics Committee for the Use and Care of Laboratory Animals.

Drugs and doses

cSST, SP acetate salt hydrate, ketamine, flunixin meglumine, xylazine, and bacitracin were obtained from Millipore Sigma (St. Louis, MO, USA). Moreover, substance L-733,060) (Tocris Bioscience, Bristol, UK), gentamicin (Krka, Slovenia), and Polysporin Triple antibiotic ointment (Johnson & Johnson Inc.) were employed in this study.
cSST (0.2, 1.0, and 8.0 μg), L-733,060 (0.1, 1.0 and 10.0 ng), SP (0.5 ng) were injected intracerebroventricularly (i.c.v.). cSST and L-733,060 were dissolved in artificial CSF (aCSF; 140 mM NaCl, 3.0 mM KCl, 1.25 mM $CaCl_2$, 1.0 mM $MgCl_2$, 1.2 mM Na_2HPO_4, 0.3 mM NaH_2PO_4, 3.0 mM glucose, 0.2% BSA, 0.03% bacitracin, distilled sterile apyrogenic water; pH 7.2). SP was initially dissolved in a small amount of water and diluted to the desired concentration with aCSF [18]. The solutions used for i.c.v. administration were of pH 7.2.
It should be mentioned that all doses represent the free-base equivalent, and all agents were injected 3-5 min after total dissolution. For co-administration, the solutions of the drugs were mixed. The selection of the doses was based on the findings of prior research [19-21].
The intracerebroventricular injections were made between 8:30 a.m. and 9:30 a.m.

Intracerebral injections

Implantation of guide cannula. The implantation of the stainless steel 26-gauge guide cannula (Plastics One Inc., Roanoke, VA, USA) was carried out as detailed elsewhere [20]. Briefly, prior to the surgery, the rat was injected with gentamicin sulfate (5 mg/kg intramuscular injection). It was anesthetized (ketamine and xylazine, 80 and 8 mg/kg, respectively; i.p.) and kept in a Kopf stereotaxic apparatus (David Kopf Instruments, Tujunga, CA, USA). The cannula was inserted into the left lateral ventricle based on the following stereotaxic coordinates: AP = − 0.8 mm from bregma; ML = 1.6 mm, DV = 3.6 mm from dura [22]. Afterwards, it was secured with screws and cranioplastic cement (Dentsply International, York, PA, USA). The cannula was filled with sterile aCSF; leakage of fluid from the cannula during insertion was a sign of proper cannula placement. Moreover, the position of the cannula was verified histologically. After placement, the guide cannula was sealed with a sterile dummy cannula (obturator, Plastics One Inc., Roanoke, VA, USA).
After the cannula implantation, the rats recovered for 10 days while they were placed in separate cages.

Microinjection procedure

The intracerebral injections were carried out as described previously [20] via a stainless steel 33-gauge injection cannula (Plastics One Inc., Roanoke, VA, USA). The tested solution was injected into the brain at a constant rate of 5 μL/min for 1 min using a Hamilton microsyringe (10 μL; Reno, NV, USA) and an infusion pump (Fisher Scientific; Pittsburg, PA, USA). After completion of the injection, the needle was held in place for 30 s before withdrawal to avoid injection fluid backflow through the cannula and was then replaced by an obturator.

Catalepsy assessment

Catalepsy in rats is a failure to correct an externally forced uncommon posture [23]. The quantitative evaluation of this temporal immobility was performed using the bar test [24, 25]. Briefly, the procedure was carried out in a cleaned box identical to rat's home cage. The animal was put with its forelimbs on the horizontal cylindrical wooden bar (9.0 cm above the surface with a diameter of 1.5 cm). Forepaws of the rat grasped the bar while its hind paws were on the table surface in a resting position. The seconds were measured until the rat

put both paws on the table surface, moved its head in an exploratory manner, or started to climb on the bar. In the present study, this duration is called immobility time/catalepsy duration. For the purposes of the test, the rat was put on the bar three times consecutively and the mean duration of three periods of motionlessness was considered the result of the test. The researcher who measured the durations was unaware of the experimental history of each animal. The durations were measured at 60, 120, 180, and 240 min after the tested solutions were administered. It should be mentioned that the animals were kept in their home cages between the tests. Tactile stimulation of the animals (handling) was reduced to a minimum of 18 h prior to the beginning of the test. All equipment was cleaned with 25% ethanol and dried with paper towels between all the trials.

Catalepsy was defined as a significant ($p < 0.05$) increase in the immobility time in comparison with the vehicle-treated group.

Outline of experiments

Four separate tests were performed, and dose-response relationship for the effects of cSST and L-733,060 was studied in the first two tests. The *subthreshold* dose of cSST and the highest ineffective dose of L-733,060 were determined; these doses were used in further research. The third experiment was conducted to evaluate the cataleptogenic effect of the cSST+L-733,060 combination. In the final test, the ability of the combination to produce a cataleptic response in the presence of NK1 receptor agonist, SP, was examined.

Statistical analysis

The Shapiro-Wilk *W* test was employed to evaluate the normality of data distribution. Furthermore, the homogeneity of variances was analyzed using Levene's test. Based on the results, the assumptions of normality and homogeneity of variances were confirmed. Analysis of immobility durations was performed by a repeated-measures ANOVA (independent factors: treatments and time) in SPSS software (version 22). Between-group pairwise comparisons were made using two-sided *t*-test with Bonferroni corrections.

It should be mentioned that a P value of less than 0.05 was considered statistically significant. No outliers were removed from the data sets. Data were presented as mean ± SD.

Results

Cataleptogenic action of cSST

cSST on its own strongly influenced the immobility time; the repeated-measures ANOVA has shown effects of treatment ($F_{[3,28]} = 25.285$, $p = 0.000$), time ($F_{[3,84]} = 5.312$, $p = 0.002$), and time x treatment interaction ($F_{[9,84]} = 3.513$, $p = 0.001$). Between-group pairwise comparisons revealed that cSST at 8.0 μg significantly increased the variable of interest compared to vehicle and to cSST at 0.2 μg and 1,0 μg ($p < 0.001$ for all time points in all three comparisons) (Figure.1).

In all further experiments, cSST was used in the dose of 1,0 μg.

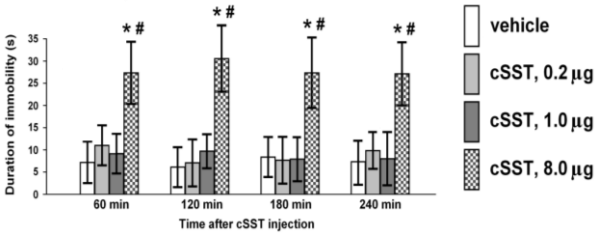

Figure 1. Cataleptogenic action of cSST. Data are presented as mean ± SD; n = 8.
* significant difference from the vehicle-treated group, $p < 0.001$,
# significant difference from the groups treated with cSST at 0.2 and 1,0 μg, $p < 0.001$

Cataleptogenic action of L-733,060

The NK1 receptor antagonist at the tested doses of 0.1, 1.0, and 10.0 ng did not influence the immobility time ($F_{[3,28]} = 0.328$, $p = 0.805$). In addition, no effect of time was observed ($F_{[3,84]} = 2.624$, $p = 0.056$). Nevertheless, time x treatment interaction took place ($F_{[9,84]} = 2.188$, $p = 0.031$) (Figure 2).

Cataleptogenic action of cSST combined with L-733,060

cSST at 1,0 μg was used in combination with L-733,060 at 10.0, 1.0, or 0.1 ng. The repeated-measures ANOVA indicated that the duration of immobility significantly depends on cSST, L-733,060, and time ($F[1,56] = 25,448$, $p = 0.000$; $F[3,56] = 15.158$, $p = 0.000$; and $F[3,168] = 20.959$, $p = 0.000$; respectively). Also, a significant interaction between cSST and L-733,060 took place ($F[3,56] = 11.158$, $p = 0.000$).

Co-administration of cSST with L-733,060 at 10.0 ng at all time points significantly increased the immobility time compared to the injections of vehicle ($p < 0.001$). The combination of cSST with L-733,060 at 1.0 ng and 0.1 ng was ineffective; there was no difference between the duration of Cataleptogenic action of cSST. Data are presented as mean ± SD; n = 8.

* significant difference from the vehicle-treated group, $p < 0.001$,
# significant difference from the groups treated with cSST at 0.2 and 1,0 μg, $p < 0.001$.

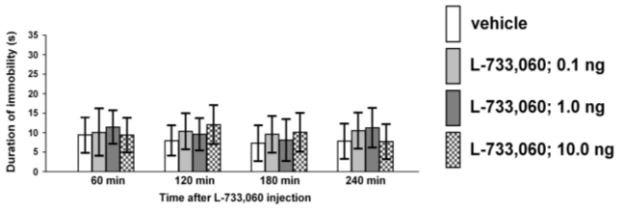

Figure 2. Cataleptogenic activity of L-733,060. Data are presented as mean ± SD; n = 8.

immobility in the combination-treated groups and that in the control vehicle-treated group ($p \geq 0.47$) (Figure 3).

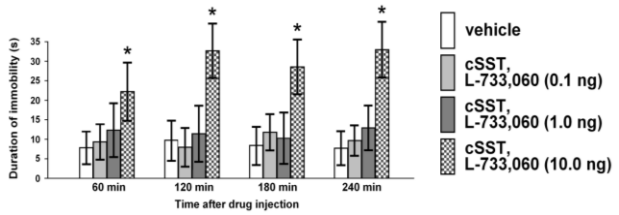

Figure 3. Cataleptogenic activity of the cSST+ L-733,060 combination. Data are presented as mean ± SD; n = 8.
* significant difference from the vehicle-treated group, $p < 0.001$.

Influence of exogenous SP on the effect of cSST+L-733,060 combination

To verify the role of NK1 receptor blockade in the effect of the cSST+L-733,060 combination, the rats received cSST (1.0 μg) in combination with a) 10.0 ng of L-733,060 or b) 10.0 ng of L-733,060 plus 0.5 ng of substance P, a NK1 receptor agonist. One group of animals was treated with SP alone (Figure. 4).

The repeated-measures ANOVA results revealed that the duration of immobility significantly depends on cSST+L-733,060 combination ($F_{[1,28]} = 49.198$, $p = 0.000$), SP ($F_{[1,28]} = 12.637$, $p = 0.001$), and time ($F_{[3,84]} = 7.382$, $p=0.000$); also, a strong interaction between cSST+L-733,060 combination and SP was found ($F_{[1,28]} = 16.901$, $p = 0.000$).

The cSST+L-733,060 combination significantly increased the immobility time compared to the vehicle ($p \leq 0.00002$ for all time points).

The NK1 receptor agonist SP significantly reduced the effect of cSST+L-733,060 combination ($p \leq 0.0006$ for all time points) (Figure 4).

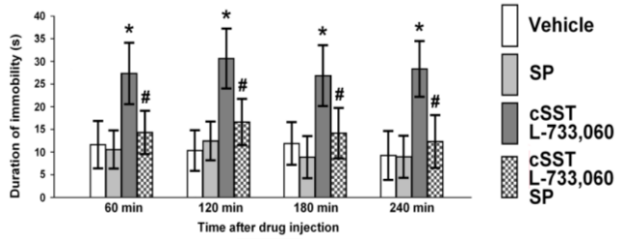

Figure 4. Influence of SP on the cSST+L-733,060 combination effect. Data are presented as mean ± SD; n = 8.
*significant difference from the vehicle-treated group, $p \leq 0.00002$,
significant difference from the cSST+L-733,060 group, $p \leq 0.0006$.

Discussion

Previously, blockade of the brain SST receptors by cSST was found to promote catalepsy in Wistar rats [8]. Here, we examined the combination of cSST with L-733,060, a substance having NK1 receptor-blocking activity. The drugs administered separately, failed to initiate catalepsy, however, their combination resulted in a clear cataleptic response. The activity of the combination was decreased by a NK1 receptor agonist, SP; this suggests that blockade of the NK1 receptors contributes to the effect of the combination.

Thus, the combination of cSST and L-733,060 at individually ineffective doses produced strong catalepsy. In essence, these data suggest some sort of synergy between cSST and L-733,060.

The cataleptogenic activity of the cSST+L-733,060 combination, apparently, is due to a blockade of brain somatostatinergic and SP-ergic receptors. This blockade could produce a reduction of central dopaminergic transmission, an effect that is believed to be pathogenically related to catalepsy [26, 27]. Indeed, exogenous SST increases dopamine release in rat and cat striatum in vivo [28-31] and in rat striatal slices in vitro [31]; apparently, dopaminergic neurons are stimulated by a somatostatinergic mechanism. In light of this, a reduction of brain somatostatinergic activity by cSST may inhibit dopaminergic transmission in the striatum and, as a result, initiate catalepsy. At the same time, SST might impact catalepsy indirectly through cholinergic mechanism. SST was shown to inhibit acetylcholine release from rat striatal tissue [32]; given this, cSST-induced somatostatinergic hypoactivity possibly stimulates striatal cholinergic processes. These processes might enhance catalepsy. Such a view is supported by findings that the development of catalepsy is associated with an increase in striatal acetylcholine; in another experiment with pharmacological inhibition of catalepsy, a positive correlation between a decrease in duration of catalepsy and an accompanying decrease in striatal acetylcholine level was observed [14]. The stimulatory influence of acetylcholine on catalepsy is also supported by the ability of anticholinergics to inhibit haloperidol-induced catalepsy in rats [33].

At the same time, central dopaminergic transmission can be modulated by SP. This agent reportedly stimulates dopamine release from rat and cat nigrostriatal area in vivo [34- 36] and rat striatal tissue in vitro [37, 38]. These data suggest that brain SP stimulates central dopaminergic processes. The ability of exogenous SP to inhibit reserpine- and haloperidol-induced extrapyramidal symptoms [12, 13] supports this view. Discordant

with these findings, however, is that a NK1 antagonist CP-96345 can exert a stimulatory effect on striatal dopamine release; this agent reportedly increases dopamine outflow induced by methamphetamine [39]. This discordance, possibly, could be attributed to some features of the methamphetamine model.

Collectively, the above data suggest that the blockade of brain SST and NK1 receptors by cSST and L-733,060 inhibit brain dopaminergic processes; in this connection, the cataleptogenic activity of the cSST+L-733,060 combination is not unexpected.

Mechanism of the synergy between cSST and L-733,060 is obscure. Of relevance here might be the ability of SP to raise the brain SST level [40] and increase the density of SST receptors in brain tissues [41]; these findings suggest that SP-mediated processes enhance somatostatinergic activity. In light of this, SP receptor antagonist, L-733,060, *per se* may induce somatostatinergic hypoactivity thereby aggravating cSST-induced inhibition of striatal dopaminergic transmission and, as a result, further enhancing catalepsy.

Conclusions

We found here for the first time, that in rats the concurrent inhibition of the brain SST and SP activities synergistically initiates catalepsy In light of this, it seems quite possible that PD-associated brain deficit in somatostatin and substance P is relevant for pathogenesis of extrapyramidal disorders. The presented findings may offer a novel understanding of the mechanism of extrapyramidal regulation. Apparently, further studies of this issue could extend our understanding of cross-talk between the brain somatostatin- and SP-dependent systems and contribute to the establishment of new approaches to treatment of extrapyramidal disorders, including parkinsonism.

Compliance with ethical guidelines

All the studies were performed in accordance with the European Communities Council Directive (2010/63/EU) and approved by the local Ethics Committee for the Use and Care of Laboratory Animals.

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Conflicts of Interest

No conflict of interest was reported.

Authors' contributions

IDI proposed conception and design of the study, directed the project, performed the research, participated in the data interpretation, wrote the draft of manuscript, prepared the figures, corrected the text of the article; MDK, IIP, NPG, and VIT discussed the conception and design of the study, performed the research, participated in the data interpretation, discussed the draft of manuscript and the corrections inserted to the text of the article; SAG participated in experimental work and in the data interpretation, performed the statistical analysis of the data, prepared the figures. All authors read and approved the manuscript and agreed to be accountable for all aspects of the work.

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