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Original Article

Induction of Catalepsy in Rats by NK1 Receptor Antagonist and Early-life Maternal Separation Synergistically: The Involvement of CRF1 Receptors

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Abstract
A lower level of brain substance P (SP) is detected in Parkinson's disease, and it appears that central SP-ergic deficiency takes place in Parkinsonian patients. The pathogenic relevance of this abnormality is unknown. Another understudied area is the impact of early-life adversities on Parkinsonism. Here, we hypothesized that i) simulation of central SP hypoactivity by intracerebral injections of NK1 receptor (NK1-R) antagonist can initiate catalepsy, a model of Parkinsonian bradykinesia and rigidity, ii) early-life maternal separation (MS) can affect the SP-dependent catalepsy; and iii) the above catalepsy can be mediated by corticotropin-releasing factor type 1 receptor (CRF1-R). The study was performed on Wistar rats. MS of pups was carried out at postnatal days 2-14 for 3 h per day. In adulthood (16-17 weeks of age), 192 male rats with MS history (weight 280-310 g) were examined behaviorally, and catalepsy was assessed by a bar test. In catalepsy assessment, NK1-R antagonist L-733,060 was administered intracerebroventricularly at the doses of 0.1, 1.0, and 10.0 ng. The experiments in undisturbed animals demonstrated that the drug at 10.0 ng produces clear catalepsy, while the dose of 1.0 ng was ineffective. MS per se failed to exert catalepsy; nonetheless, in MS-exposed rats, L-733,060 at 1.0 ng induced a strong cataleptic response. Therefore, MS and NK1-R antagonists supra-additively initiated the development of catalepsy. This catalepsy was significantly reversed by CRF1-R antagonist NBI 35 965. Our findings illustrated, for the first time, that the blockade of central NK1–R can induce catalepsy. This cataleptic response is synergistically potentiated by MS and is mediated by CRF1-R. These data suggest that the combination of central NK1-R hypoactivity and neonatal stress causes extrapyramidal signs. The central processes mediated by NK1-R and CRF1-R might be potential therapeutic targets for Parkinsonism.

Keywords: Catalepsy, CRF1 receptors, Maternal separation, NK1 receptors, Substance P

Background

Bradykinesia and other extrapyramidal dysfunctions are the symptoms of Parkinson's disease (PD), Alzheimer's disease, schizophrenia, and some other disorders. These signs are thought to be linked to the inhibition of dopaminergic processes in the substantia nigra pars compacta and dorsal striatum [1, 2]. The exact mechanism of extrapyramidal features remains far from fully understood. In the PD brain, lower concentrations of substance P (SP) and a decrease in the binding activity of SP receptors were found [3,4]. The influence of the brain SP-ergic deficiency on the extrapyramidal system is unclear.

Up to now, the role of SP in extrapyramidal disorders has been examined only in a few studies conducted on rats. SP reportedly alleviates catalepsy, rigidity, and tremor induced by neurotoxin MPTP or reserpine [5]. Jolicoeur et al. [6] revealed that SP significantly reduces the haloperidol-induced rigidity but does not affect haloperidol-induced catalepsy. These findings suggest the ability of SP-mediated processes to inhibit the development of extrapyramidal symptoms. Nonetheless, Anderson et al. [7] described the inhibition of raclopride-induced catalepsy by an

antagonist of SP receptors, CP-99994.

Another factor affecting the extrapyramidal motor system may be early-life stress. Clinical data suggests that adversities during early life increase the risk of neuropsychiatric disorders associated with abnormal dopaminergic transmission [8]. Studies on rats have demonstrated that early-life stress can markedly affect the dopaminergic system in the substantia nigra and striatum. In these studies, rat pups were periodically separated from their mothers. This procedure, maternal separation (MS), is used extensively as a model of early-life stress (e.g., [9-12]). In the substantia nigra of the MS-exposed rat pups, a decrease was observed in the number of cells expressing tyrosine hydroxylase, a key enzyme in the synthesis of dopamine [12]. Moreover, MS exerted a loss of dopamine [12] and dopamine transporter [13] in the striatum. Meanwhile, the data on the impact of MS on the extrapyramidal system are scarce and contradictory. The only study in this area [14] has indicated that MS in rats decreases haloperidol-induced catalepsy but does not influence morphine-induced one.

Since MS is a stress-like event, the involvement of the corticotropin-releasing factor (CRF) system in the regulation of MS effect can be suggested. This system has been found to play a major role in endocrine, autonomic, and behavioral responses to stress. CRF-sensitive receptors (CRF-R) of two types are currently known; CRF_1-R is believed to be the main CRF receptor in the brain, and the expression of CRF_2-R is limited [15]. An increase in the density of brain CRF_1-R was detected in rats with MS history [16]. Given this, we hypothesized that i) simulation of central SP hypoactivity by intracerebral injections of SP receptor antagonist can initiate catalepsy, a model of Parkinsonian bradykinesia and rigidity, ii) early-life maternal separation (MS) can influence the SP-dependent catalepsy, and iii) intrabrain injections of CRF_1-R antagonist can modulate the MS effect.

Objectives

The goal of the presented investigation was to evaluate the role of central NK1 receptor hypoactivity and early-life stress in initiation of catalepsy in Wistar rats.

Materials and Methods

In the present experiments, the simulation of central SP-ergic deficiency was performed by intracerebroventricular (ICV) injection of L-733,060, which is known to block NK1 receptors (NK1-R)-the predominant target for SP [3]. The involvement of the CRF system in the observed effects was evaluated by using the CRF_1-R antagonist, NBI 35965 [17].

Animals and maternal separation

All procedures were performed in accordance with the European Communities Council Directive 2010/63/EU. The experimental protocol received authorization from the Ethics Committee for the Use and Care of Laboratory Animals of the Centre on Theoretical Problems in Physical and Chemical Pharmacology (# A36/06092022/4). In the present experiments, virgin female Wistar rats from our animal colony ("Timpharm" Animal Farm, Moscow region, Russia), weighing 230-240 g on arrival, were used. The rats were kept under standard laboratory conditions (change of bedding once a week, 12:12 h light/dark cycle, lights on at 7 a.m., room temperature 22°C, relative humidity 55±5%) with access to standard rat chow and water ad libitum. After seven days of habituation, females were mated with sexually experienced male Wistar rats in standard laboratory cages (60 cm × 40 cm × 20 cm) for 10 days; each female rat was mated with one male rat. From potential pregnancy day 18 onwards, pregnant females were single-housed for undisturbed delivery in standard plastic laboratory cages (47 x 31 x 20 cm). On the day of delivery, litters were reduced to eight pups.

MS was performed as detailed elsewhere [18,19]. In brief, pups and their mothers were housed in plastic cages (47 x 31 x 20 cm); the separation was carried out once daily between postnatal day (PND) 2 and 14 from 10:00 a.m.-10:20 a.m. The pups were removed from the home cage and placed for 180 min in a novel cage with fresh bedding; the cage was placed in a dark incubator at 32°C-34°C (PND 2-7) and 28°C-30 °C (PND 8-14). During separation, the same cages were used every day, and none of the cages were cleaned during the procedure. The animals in the control group were left entirely undisturbed. On day 22, all the pups were weaned.

The pups were group-housed with same-sex siblings (three per group) in plastic cages (60 x 38 x 26 cm). The animals were maintained in colony rooms under standard laboratory conditions and had *ad libitum* access to standard laboratory rat chow and tap water. At 16-17 weeks of age, male animals with MS history (weight 280-310 g) were randomly assigned to 16 groups of 12.

Drugs and doses

L-733,060 hydrochloride (L-733,060) and NBI 35965 hydrochloride (NBI 35965) were obtained from Tocris Bioscience (Bristol, UK). Ketamine, xylazine, flunixin meglumine, bacitracin (Millipore Sigma, St. Louis, MO, USA), gentamicin (Krka, Slovenia), and Neosporin ointment (Johnson & Johnson Inc.) were used as well. L-733,060 and

NBI 35965 were injected as solutions in artificial CSF (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). The solutions of these drugs had a pH of 7.2. The doses of 0.1, 1.0, and 10.0 ng for L-733,060 and 7.5 ng and 75.0 ng for NBI 35965 were used. All doses were calculated as the free bases; the drugs were infused for 3-5 min after completely dissolving in the artificial CSF. For co-administration, the solutions of the drugs were mixed. The doses were chosen based on previous studies [20,21]. Animals received intracerebroventricular infusions between 08:30 a.m. and 09:00 a.m.

Intracerebral injections

The injections were performed using stainless steel 26-gauge guide cannulae and 33-gauge injection cannulae (Plastics One Inc., Roanoke, VA, USA).

Lateral ventricle cannulation

The procedure was performed as detailed elsewhere [22] using a Kopf stereotaxic apparatus (David Kopf Instruments, Tujunga, CA, USA). Briefly, the rats received an intraperitoneal injection of ketamine and xylazine at 80 and 8 mg/kg, respectively. A guide cannula was stereotaxically inserted into the right lateral ventricle according to the following coordinates from the rat brain atlas [23]: AP = -0.8 mm from bregma; ML=1.6 mm, DV=3.6 mm from the dura. The correct location of the cannula was confirmed by autopsy. After the operation, the guide cannula was sealed with a sterile dummy cannula (obturator, Plastics One Inc., Roanoke, VA, USA). The incision area was treated topically with Neosporin, and the animal was given an injection of flunixin meglumine at 2.5 mg/kg intramuscularly. The cannulated rats recovered for 10 days in individual cages with *ad libitum* access to food and water.

Microinjection procedure

The ICV infusion was conducted according to the previously described method [22]. An injection cannula was attached to 10 µL Hamilton microsyringe (Reno, NV, USA). The tested solution was injected at a constant rate of 2.5 µL/min for 2 min, and the rate was controlled by an infusion pump. When the injection was complete, the cannula remained in place for 30 sec to prevent fluid backflow.

Catalepsy assessment

Catalepsy in rats is a failure to correct an externally imposed unusual posture [24]. The quantitative evaluation of this temporal immobility was performed using a bar test [25, 26]. In a nutshell, the procedure was carried out in a cleaned box identical to the home cage of rats. The animal was placed with its forelimbs on the horizontal cylindrical wooden bar (9.0 cm above the surface, diameter of 1.5 cm). The forepaws of the rat grasped the bar while its hindpaws rested on the table surface. An amount of time (in seconds) until the animal broke the initial posture was measured; this time is herein termed as immobility time/duration of catalepsy. To complete one test, the animal was placed on the bar consecutively three times, and the mean of these three periods of motionlessness was accepted as the outcome of this test. The time measurements were performed by an experimenter unaware of each animal's experimental history. The tests were carried out 60, 120, 180, and 240 min after the ICV administration of the tested solutions, with the animals being kept in their home cages between tests. All equipment was cleaned with 25% ethanol and dried with paper towels between all the trials. Catalepsy was defined as a significantly ($P<0.05$) increased immobility in comparison with the control vehicle-treated group.

Selection of results for statistical analysis

All 192 animals were cannulated and tested for catalepsy. Thereafter, their brains were histologically examined; in each experimental group, the first eight animals with proper cannula placements were included in the data analyses. The data from other animals were discarded.

Outline of experiments

Three separate experiments were performed. In the first experiment, the dose-response relationship for the effect of L-733,060 was studied using undisturbed animals. The highest ineffective dose of L-733,060 was determined; this dose was used in further studies. The next experiment aimed to evaluate the cataleptogenic effect of L-733,060 in animals exposed to MS. The effect of the CRF_1-R antagonist, NBI 35965, on catalepsy induced by the combination of L-733,060 and MS was evaluated in the third experiment.

Statistical analysis

The normality of the data distribution and homogeneity of variances were assessed using the Shapiro-Wilk test and Levene's test, respectively. The assumptions of normality and homogeneity of variances were accepted. The data were analyzed in SPSS software (version 22) using ANOVA with repeated measures (independent factors: treatments and time) followed by pairwise multiple

comparisons with Bonferroni corrections. A p-value less than 0.05 was considered statistically significant. Data are expressed as mean±SD.

Results

Cataleptogenic action of l-733,060

In the first part of the study, we evaluated the cataleptogenic activity of L-733,060 in animals that were not disturbed in the early postnatal period. The NK1-R antagonist strongly affected the duration of immobility. ANOVA with repeated measures demonstrated the effects of treatment ($F_{[3,28]}$ = 6.748; P=0.001). L-733,060 at the dose of 10.0 ng significantly increased the variable of interest (significant difference between the L-733,060 and vehicle groups; P<0.005 for all time points). The doses of 0.1 and 1.0 ng were without effect (P>0.156 and 0.059 for all time points, respectively) (Figure 1).
L-733,060 at 1.0 ng was used in all further experiments.

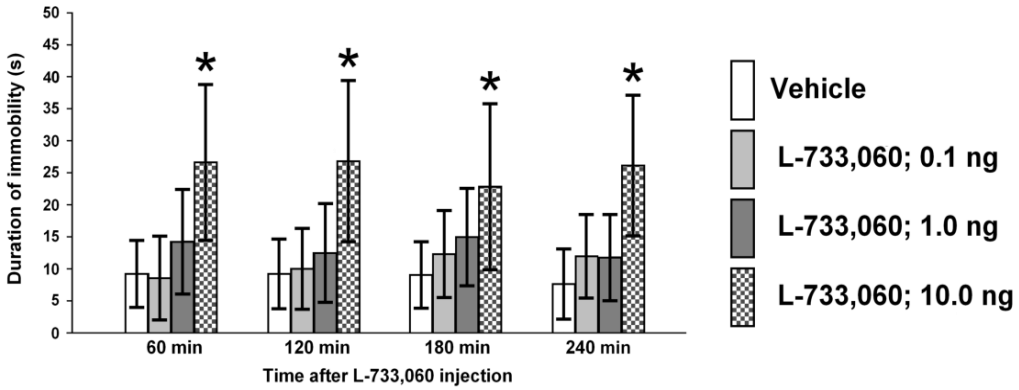

Figure 1. Study of dose-response relationships for cataleptogenic activity of NK1-R antagonist L-733,060 in undisturbed animals. The drug at 10.0 ng induces catalepsy; the dose of 1.0 ng is subthreshold.
Data are presented as mean±SD (n=8).
*P<0.005, the difference from the vehicle group at the same time point

Cataleptogenic activity of the MS + l-733,060 combination

MS per se did not influence the immobility time ($F_{[1,28]}$=1.612; P=0.07), and there was no difference between the MS-exposed and undisturbed animals (P>0.095 for all time points). In a similar vein, L-733,060 (1.0 ng) per se did not affect the duration of immobility in undisturbed animals (**$F_{[1,28]}$** =1.548; P=0.16), and there was no significant difference between the drug and vehicle groups (P> 0.136 for all time points). Nonetheless, L-733,060 significantly increased the immobility time in the MS-exposed rats (**$F_{[1,28]}$** = 5.966; P=0.021). In these animals, the duration of immobility was significantly longer than that in the vehicle-treated undisturbed rats (P< 0.006 for all time points) (Figure 2).

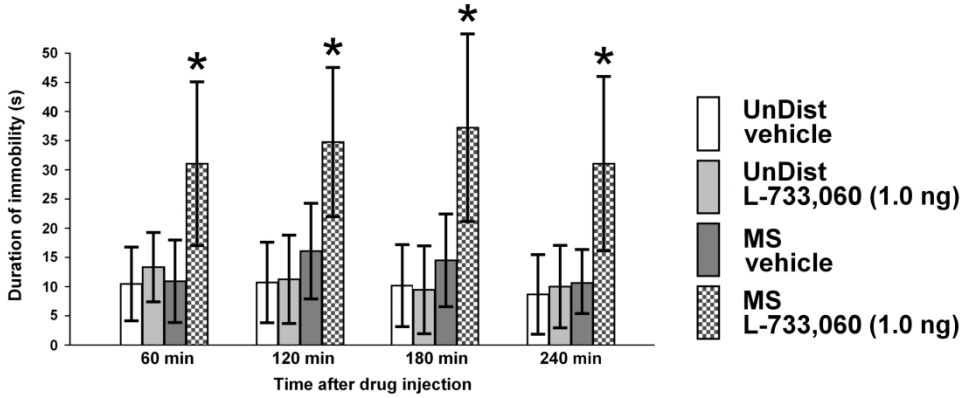

Figure 2. Influence of maternal separation (MS) on L-733,060-induced catalepsy. MS and NK1-R antagonist (1.0 ng) individually are ineffective; however, their combination induces a significant cataleptic response.
UnDist – undisturbed animals.
Data are presented as mean±SD (n=8).
*P<0.006, difference from the UnDist+vehicle group at the same time point

Impact of CRF1 receptor blockade on catalepsy induced by l-733,060 and MS

To evaluate the involvement of CRF_1-R-dependent mechanisms in the regulation of L-733,060-induced catalepsy, the maternally separated animals were injected with L-733,060 in combination with CRF_1-R antagonist, NBI 35 965. In the first part of the examination, NBI 35 965 was used at 7.5 ng. In these experiments, L-733,060 produced distinct cataleptic response ($F_{[1,28]}$ = 21.247; P=0.000). The duration of immobility in the L-733,060 group was higher than in the vehicle group (P< 0.007 for all time points). NBI 35 965 per se failed to affect the variable ($F_{[1,28]}$ =0.320; P= 0.576), and the measures in the drug and vehicle groups did not differ (P> 0.117 for all time points. There was no interaction between NBI 35 965 and L-733,060 ($F_{[1,28]}$ =0.599; P=0.445). The variables in the L-733,060 + NBI 35 965 groups did not differ from those in the L-733,060-only group (P> 0.086 for all time points) (Figure 3).

The experiments with NBI 35 965 at 75.0 ng yielded the following results. L-733,060 significantly affected the duration of immobility ($F_{[1,28]}$ =15.047; P=0.001), and the variables in the L-733,060-only and vehicle groups were significantly different (P<0.003). NBI 35 965 was found to significantly affect the variable of interest ($F_{[1,28]}$ =11.423; P=0.002); the drug per se did not affect the time of immobility (there was no difference between the drug-treated and vehicle-treated animals, P>0.174 for all time points). A significant interaction was detected between NBI 35 965 and L-733,060 ($F_{[1,28]}$ =16.108; P= 0.000). Catalepsy induced by L-733,060 was significantly inhibited by NBI 35 965 (P< 0.007 for all time points) (Figure 4). Therefore, the blockade of CRF_1-R inhibited the L-733,060+MS-induced cataleptic response.

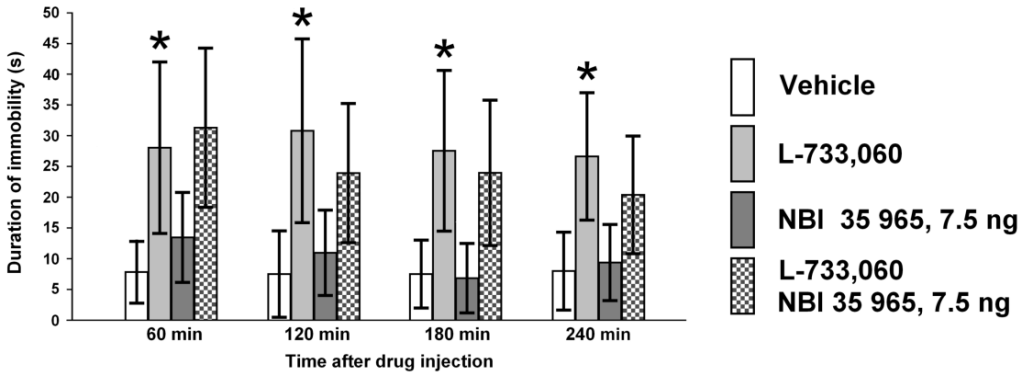

Figure 3. Effect of NBI 35965 at 7.5 ng on catalepsy induced by L-733,060 and MS. CRF_1 receptor antagonist NBI 35965 at the used dose is ineffective. Data are presented as mean±SD (n=8)
*P<0.007, the difference from the vehicle group at the same time point

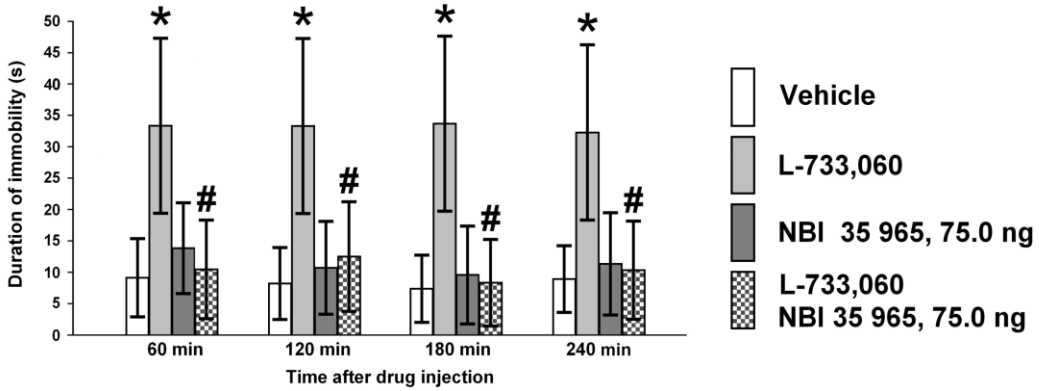

Figure 4. Effect of NBI 35965 at 75.0 ng on catalepsy induced by L-733,060 and MS CRF_1 receptor antagonist NBI 35965 at the used dose significantly inhibits the L-733,060 +MS effect.
Data are presented as mean ± SD; n=8.
***P**<0.003, the difference from the vehicle group at the same time point
#P< 0.007, difference from the L-733,060-only group at the same time point

Discussion

As evidenced by the results of this study, a blockade of brain SP-sensitive receptors with NK1-R antagonist L-733,060 can initiate catalepsy-a rat model of parkinsonian bradykinesia and rigidity. Another new finding of the present study is the dependence of L-733,060-induced catalepsy on adversity in the early postnatal period. L-733,060 at a dose ineffective in the undisturbed rats produced a clear cataleptic response in the MS-exposed animals. In these experiments, MS alone was without effect. Therefore, the NK1-R antagonist and MS appear to interact supra-additively to initiate catalepsy. This synergistic effect was counteracted by NBI 35965; apparently, it is mediated by central CRF_1-R.

The cataleptogenic activity of NK1-R antagonist at a relatively high dose (10.0 ng) may be underlined by an inhibitory action on central dopaminergic processes. In previous studies, it has been demonstrated that SP stimulates dopamine release from rat striatal slices *in vitro* [27, 28] and rat and cat striatum *in vivo* [29-31]. Given this, an inhibition of brain SP-ergic processes through a blockade of SP receptors may lead to an inhibition of dopaminergic neurotransmission. Central dopaminergic deficiency is believed to be pathogenically important in catalepsy [32, 33]. Taking this into account, the observed cataleptogenic action of the NK1-R antagonist does not seem surprising.

The mechanism behind the L-733,060 – MS synergy is not yet clear. We have noted above that MS is thought to be a stress-like state [9-12]. Stress possibly dysregulates the extrapyramidal system. Indeed, epidemiological studies have pointed to the detrimental effects of stress on the development of Parkinsonism [34, 35]. In experiments on rats, stressful procedures (e.g., tail pinch and floor cooling) increased the sensitivity of the animals to the cataleptogenic action of morphine [36], and in mice, chronic restraint stress per se can produce a cataleptic state [37]. Sinani et al. [38] reported that MS leads to a marked decrease in the binding activity of dopamine D2 receptors in the dorsal striatum– an area intimately involved in Parkinsonism. MS in our experiments may aggravate the development of L-733,060-induced catalepsy by further inhibiting central dopaminergic activity.

At the same time, the mechanism of the synergy between L-733,060 and MS may also be mediated by endocrine consequences of MS. As previously reported, MS of rat pups results in a later increase in plasma corticosterone levels [39-41]. Corticosterone is known to pass from blood into the brain [42]; therefore, MS can be thought to increase central corticosterone levels in adulthood. This glucocorticoid reportedly can decrease SP concentrations in brain tissue [43]. In general, these data suggest that in our experiments, MS per se may inhibit the brain SP-ergic processes, thereby enhancing catalepsy initiated by NK1-R antagonist, L-733,060.

Conclusions

The findings of this study, for the first time, revealed that the inhibition of central NK1-R can initiate the development of catalepsy; this cataleptic response is potentiated by neonatal maternal separation. These data suggest that the combination of central NK1-R hypoactivity and neonatal stress causes extrapyramidal signs. It appears that the central processes mediated by NK1-R and CRF1-R might be potential therapeutic targets for parkinsonism.

Compliance with ethical guidelines

All ethical principles were considered in the present study.

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Authors' contributions

IDI proposed conception and design of the study, directed the project, participated in the data interpretation, wrote the draft of manuscript, prepared the figures;
MDK, MOL, NYaM, and LIM discussed the conception and design of the study, performed the research, participated in the data interpretation, discussed the draft of manuscript; PNK discussed the conception and design of the study, participated in experimental work, performed the statistical analysis of the data, participated in the data interpretation, discussed the draft of manuscript.
All authors read and approved the text of the article and agreed to be accountable for all aspects of the work.

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Conflicts of Interest

The authors declare no conflict of interest.

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