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5-HT$_6$ Receptors in the Lateral Habenula: A Potential Regulator of Anxiety in Parkinsonian Rats

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Abstract: *Objectives*: Anxiety represents one of the most frequently observed non-motor manifestations in patients diagnosed with Parkinson's disease (PD), yet its neurobiological mechanisms remain largely unclear. The lateral habenular nucleus (LHb), an essential part of the limbic-monoaminergic system, plays a vital role in emotional regulation and houses serotonin 5-HT$_6$ receptors, which are considered promising candidates for anxiolytic therapies. This research aimed to clarify the role of LHb 5-HT6 receptors in modulating anxiety-like behaviors within Parkinsonian contexts. *Methods:* To model PD, rats underwent unilateral 6-hydroxydopamine (6-OHDA) lesions targeting the medial forebrain bundle (MFB), while control animals received sham operations. Anxiety-related responses were examined utilizing the open field test (OFT) and elevated plus maze (EPM). Pharmacological modulation of LHb 5-HT$_6$ receptors was achieved via microinjection of either the agonist WAY208466 or the antagonist SB258585. To account for potential locomotor confounds, spontaneous locomotor activity was measured. *Results:* Animals subjected to MFB lesions exhibited pronounced anxiety-related behaviors. This was evidenced by a reduction in center zone occupancy in the OFT, along with fewer entries into and less time spent within the open arms of the EPM. In the sham-operated rats, administering WAY208466 into the LHb induced anxiety-like behaviors, whereas SB258585 exhibited anxiolytic effects. Interestingly, lesioned rats responded to WAY208466 with anxiolytic effects, while SB258585 elicited anxiety-like behaviors. Notably, both compounds showed efficacy at lower doses among the lesioned rats compared to the sham controls. These behavioral changes occurred without notable alterations in locomotor activity. *Conclusion:* This study demonstrates that 5-HT$_6$ receptors in the LHb exert bidirectional modulatory effects on anxiety-like behavior. In the PD model, the pharmacological actions of 5-HT$_6$ receptor agents diverged from those observed in intact animals, suggesting that PD pathology may alter LHb 5-HT$_6$ receptor function or sensitivity. These findings indicate that LHb 5-HT$_6$ receptors may represent a promising therapeutic target for managing anxiety symptoms in PD.

Keywords: Parkinson's Disease; Anxiety; 5-HT$_6$; Lateral Habenula; 6-Hydroxydopamine

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1. Introduction

The habenula, situated within the epithalamus, is anatomically divided into the medial (MHb) and lateral (LHb) nuclei. Acting as a functional bridge between the basal ganglia and the limbic system, it plays a pivotal role in modulating midbrain monoaminergic systems [1]. Among these two subdivisions, the LHb is particularly notable for its involvement in affective regulation. The LHb exerts regulatory effects on serotonergic neurons in the dorsal and median raphe, dopaminergic neurons within the ventral tegmental area and substantia nigra pars compacta, and noradrenergic neurons located in the locus coeruleus via its descending projections [2]. Owing to its widespread connectivity with these neuromodulatory centers, the LHb has emerged as a central neural hub implicated in the manifestation of anxiety-like behaviors in rodent models [3].

The 5-HT_6 receptor, first identified in 1993 through cloning from rat striatal mRNA, was subsequently recognized as a distinct subtype within the serotonin receptor family. The receptor is widely distributed in the central nervous system, exhibiting especially high expression in key emotional processing regions [4]. Experimental studies have shown that both activation and blockade of the 5-HT_6 receptor can significantly alleviate anxiety behaviors in animal models [5]. In clinical settings, traditional anxiolytic agents such as loxapine exhibit strong binding affinity for this receptor, underscoring its promise as a pharmacological target in the treatment of anxiety disorders [6].

Parkinson's disease (PD) is characterized by progressive degeneration of the nigrostriatal dopaminergic system, notably involving the selective loss of dopaminergic neurons within the substantia nigra pars compacta (SNc), which gives rise to core motor manifestations such as bradykinesia, resting tremor, and muscle rigidity. In addition to motor dysfunction, accumulating evidence underscores the early emergence of non-motor symptoms such as anxiety, depression, and cognitive decline, which are commonly observed during the initial stages of Parkinson's disease. Among these, anxiety is particularly persistent, often co-occurring with depressive symptoms, and has been shown to substantially impair both quality of life and long-term prognosis in PD patients [7].

Earlier research has demonstrated that nigrostriatal pathway degeneration in Parkinson's disease (PD) impairs serotonergic signaling, resulting in modified expression and functionality of various 5-HT receptor subtypes, disrupted neurotransmitter balance, and progressive loss of serotonergic neurons [8]. In our earlier research, we demonstrated that 5-HT1B receptors within the LHb contribute to the regulation of anxiety-like behaviors in PD rat models, suggesting a potential role for different 5-HT receptor subtypes in mediating anxiety symptoms associated with PD [9]. However, the specific contribution of LHb 5-HT_6 receptors to anxiety modulation in PD models remains unexplored.

This study aims to investigate the underlying mechanisms by: (1) A PD model was induced through unilateral 6-hydroxydopamine (6-OHDA) lesions of the medial forebrain bundle, after which anxiety-like behaviors were assessed using the open field test and elevated plus maze; (2) the behavioral impact of intra-LHb administration of a 5-HT_6 receptor agonist or antagonist was subsequently examined.

2. Materials and methods

2.1. Experimental animals

Male Sprague-Dawley rats, weighing 270 to 310 grams, were sourced from Xi'an Jiaotong University. They were housed under standardized conditions, including a controlled temperature of 21 ± 2 °C, a 12-hour light/dark cycle, and free access to food and water. All experimental protocols complied with institutional animal welfare

regulations, ensuring efforts to minimize animal numbers and reduce discomfort.

2.2. Experimental design

Animals were randomly allocated to either a sham-operated control group or a group receiving lesions of the MFB. Animals underwent assessments four weeks following intracerebral injection of 6-OHDA or vehicle solution (saline supplemented with ascorbic acid). They were subjected to behavioral assessments, histological evaluation, and immunohistochemical analysis. The overall experimental design is outlined in **Figure 1** to maintain data reliability and avoid crossover effects; each animal participated in only one experimental condition. Stereotaxic implantation of guide cannulas was then performed, after which behavioral paradigms were systematically conducted.

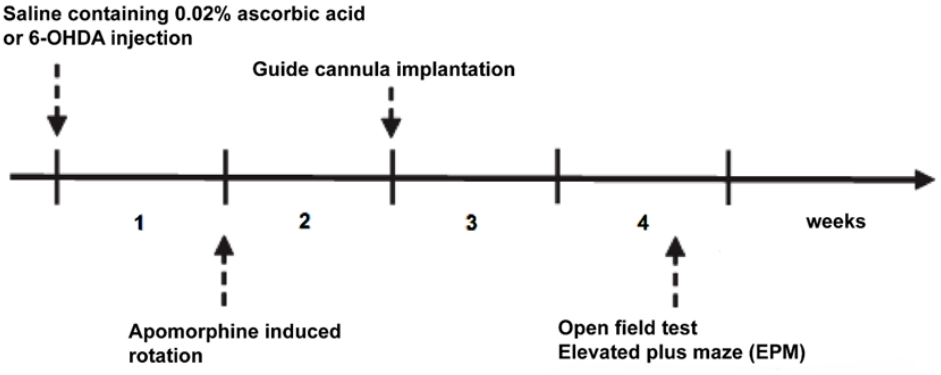

Figure 1. The experimental protocol commenced with 6-OHDA injection, followed by assessment of rotational behavior induced by apomorphine.

2.3. Establishment and verification of the PD model

A unilateral PD model was established via stereotaxic injection of 6-OHDA into the right MFB. To prevent postoperative infection, rats received intraperitoneal penicillin (80,000 U per animal) once daily for two days preceding surgery. Anesthesia was induced via intraperitoneal injection of chloral hydrate (400 mg/kg), and animals were secured in a stereotaxic apparatus with the bregma and lambda positioned on the same horizontal plane. To protect noradrenergic neurons, desipramine (25 mg/kg, i.p.) was administered 30 minutes prior to the lesioning procedure.

MFB was targeted using stereotaxic coordinates of AP –4.4 mm, ML 1.2 mm, and DV 7.8 mm, according to the Paxinos and Watson rat brain atlas [10]. Following craniotomy and removal of the dura mater, 6-hydroxydopamine (12 μg in 4 μl) was injected into the designated site. To minimize backflow, the injection needle was maintained in position for 5–10 minutes before withdrawal and subsequent wound closure. Sham-operated animals received an equal volume of vehicle solution (0.02% ascorbic acid in saline) using the same surgical protocol. On postoperative day 7, apomorphine (0.05 mg/kg, s.c.) was administered to assess lesion efficacy. Rats displaying over 20 contralateral rotations within a 5-minute period were considered successfully lesioned, with all experimental subjects exceeding 35 rotations.

2.4. Stereotaxic guide cannula implantation

Two weeks following the 6-OHDA lesion, rats underwent stereotaxic implantation of a guide cannula directed at the right LHb. To prevent infection, intraperitoneal penicillin was administered one day before the procedure.

Anesthesia induction, head stabilization, and surgical site preparation were performed following the same protocol as previously described. The LHb was targeted using the following coordinates derived from the Paxinos and Watson atlas: AP –3.7 mm, ML 0.7 mm, and DV 4.5 mm [10]. After drilling the cranial surface and removing the dura, four anchoring screws were affixed to the skull. A metallic guide cannula was inserted 1 mm above the LHb target site and secured with dental acrylic. A protective stylet was inserted to maintain patency of the cannula, and animals were given a recovery period of seven days before proceeding with subsequent experiments.

2.5. Protocol for drug administration

Microinjections were administered into the LHb via the implanted guide cannula at a volume of 0.5 μl, delivered 10 minutes before the onset of behavioral testing. The experimental agents included physiological saline, the 5-HT_6 receptor agonist WAY208466, and the antagonist SB258585. To minimize procedural stress, animals were acclimated to the injection protocol over three consecutive days prior to testing, during which the stylet was removed, disinfected, and reinserted at consistent daily intervals.

During microinjection, the stylet was carefully removed and a 1 μl Hamilton syringe was used to deliver the solution over a period of 60 seconds. To ensure adequate diffusion, The injector remained in position for an extra 60 seconds prior to the stylet being reinserted. Each animal received two sequential microinjections with a 5-minute interval between administrations. The treatment groups were as follows: (1) Saline / Saline; (2) Saline / WAY208466 at doses of 1.5, 3, or 6 μg; (3) Saline / SB258585 at doses of 1, 2, or 4 μg; and (4) SB258585 (4 μg) followed by WAY208466 (6 μg).

2.6. Behavioral assessments

The open field test (OFT) and elevated plus maze (EPM) were used to evaluate the effects of MFB lesioning and pharmacological manipulation of 5-HT_6 receptors in LHb on motor performance and behaviors indicative of anxiety.

(1) OFT: Each rat was positioned in the center of a square open-field apparatus and permitted to freely explore for a duration of five minutes. Locomotor activity was quantified by counting horizontal crossings, while vertical activity was assessed via the number of rearings. The percentage of time spent in the central area served as a measure of anxiety-related behavior, with lower percentages indicating elevated anxiety levels [11].

(2) EPM: Animals were positioned on the maze's central platform, and their activity was monitored for five minutes. The frequency of entries and duration spent in both open and closed arms were quantified. Anxiety levels were inferred from the percentage of open arm entries and time, with reduced values reflecting increased anxiety [12].

Behavioral testing commenced 10 minutes following intra-LHb drug administration. The experimental group assignments (n = 8 per group) were consistent with those detailed in Section 2.5.

2.7. Data processing and statistical analysis

Statistical analyses were conducted using SigmaStat software. Results are presented as mean ± standard error of the mean (SEM), with significance defined at $P < 0.05$. Comparisons between two groups employed unpaired Student's t-tests, while multiple group comparisons utilized one-way ANOVA followed by Dunnett's post hoc test against the sham group.

3. Results

3.1. Effects of MFB lesioning and Intra-LHb 5-HT6 receptor modulation on spontaneous locomotor activity

Open field test results demonstrated that rats receiving lesions of the MFB exhibited a marked reduction in both grid crossings and rearing events compared to sham-operated animals ($P < 0.001$, unpaired Student's t-test), reflecting significant impairment in spontaneous locomotor activity (**Figure 2A** and **Figure 2B**). Microinjection into the LHb of saline, WAY208466, SB258585, or their combination had no significant effect on either horizontal or vertical locomotor indices in both sham and lesioned groups (**Figure 2C**). These results indicate that pharmacological modulation of 5-HT_6 receptors within the LHb does not influence basal motor function. Intra-LHb microinjections of WAY208466, SB258585, or their combination had no significant impact on locomotor performance in either group relative to saline. $P < 0.001$ vs. sham-operated group (unpaired Student's t-test). Data are expressed as mean ± SEM; n = 8 per group.

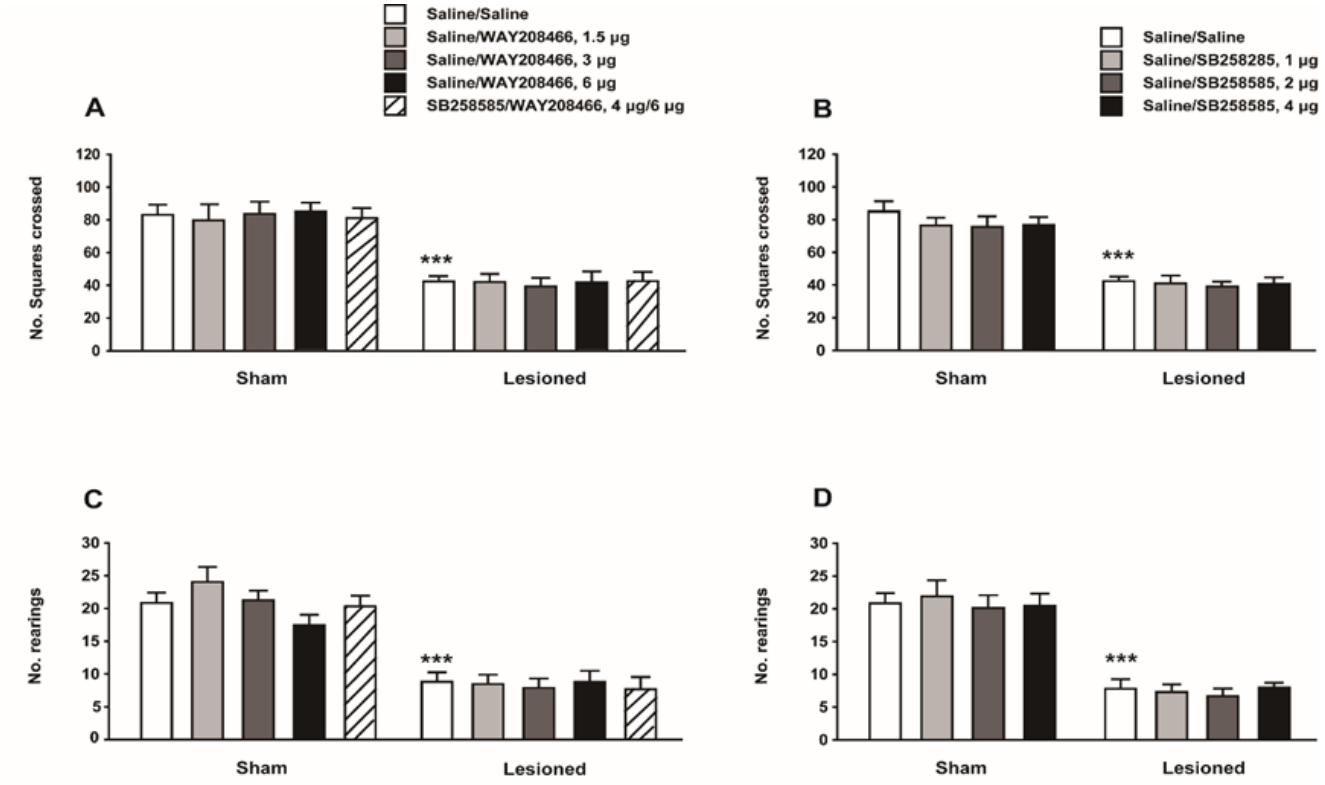

Figure 2. Effects of MFB induced by 6-OHDA and intra-LHb administration of the 5-HT_6 receptor agonist WAY208466 or antagonist SB258585 on locomotor performance in the OFT. MFB-lesioned rats exhibited a significant reduction in both horizontal (A, B: number of grid crossings) and vertical (C, D: rearing frequency) activity compared to sham-operated controls.

3.2. Effects of MFB lesioning and modulation of 5-HT6 receptors in LHb on anxiety-related behaviors

In the open field test, rats with MFB lesions exhibited a significant reduction in time spent within the central zone relative to sham-operated group ($P < 0.001$, unpaired Student's t-test; **Figure 3A**), indicating pronounced anxiety-like behavior resulting from dopaminergic pathway disruption. In sham-operated animals, microinjection

of WAY208466 into the LHb at doses of 1.5, 3, and 6 μg produced a dose-dependent decline in central zone occupancy ($P < 0.01$, one-way ANOVA; **Figure 3B**), with the 6 μg group showing a significant reduction relative to saline controls ($P < 0.01$, Dunnett's test), suggesting an anxiogenic effect. Conversely, LHb infusion of the 5-HT_6 receptor antagonist SB258585 (1, 2, and 4 μg) significantly increased the duration spent in the central zone ($P < 0.01$; **Figure 3C**), with the 4 μg dose reaching statistical significance, indicative of an anxiolytic action.

In the MFB-lesioned cohort, administration of WAY208466 at 3 and 6 μg resulted in a significant increase in the duration spent in the center of the arena (3 μg: $P < 0.05$; 6 μg: $P < 0.01$; **Figure 3B**), indicating an anxiolytic effect in dopamine-depleted states. In contrast, SB258585 (4 μg) significantly decreased central zone occupancy in lesioned animals ($P < 0.01$; **Figure 3C**), indicating a reversal of its behavioral effect observed in intact animals. Importantly, in both sham and lesioned rats, Prior administration of SB258585 completely abolished the behavioral effects of WAY208466 (**Figure 3B**), confirming that the observed changes were specifically mediated through 5-HT_6 receptor signaling pathways.

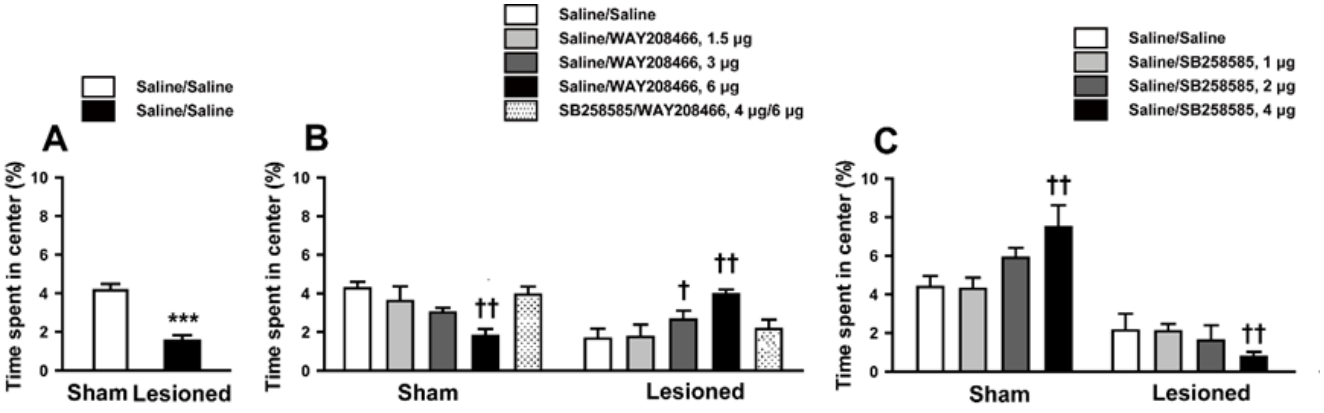

Figure 3. Effects of MFB induced by 6-OHDA and intra-LHb administration of the 5-HT_6 receptor agonist WAY208466 or antagonist SB258585 on anxiety-related behavior in OFT.

MFB-lesioned rats showed a significant reduction in the percentage of time spent in the central zone (A) compared to sham-operated controls. In sham animals, intra-LHb injection of WAY208466 decreased center time, whereas SB258585 increased it relative to saline. Conversely, in lesioned rats, WAY208466 led to an increase (B), while SB258585 caused a reduction (C) in central zone occupancy. Statistical comparisons were conducted using unpaired Student's t-tests (**$P < 0.001$ vs. sham-operated group), and one-way ANOVA followed by Dunnett's post hoc test within each group (†$P < 0.05$, ††$P < 0.01$ vs. intra-LHb saline). Data are expressed as mean ± SEM; n = 8 per group.

In EPM test, rats subjected to MFB lesions exhibited a significant reduction in both the percentage of time spent in open arms (**Figure 4A**) and the frequency of open arm entries (**Figure 4D**) compared to sham-operated controls ($P < 0.001$ and $P < 0.01$, respectively; unpaired Student's t-test), indicating the development of anxiety-like behaviors following dopaminergic disruption. In the sham group, intra-LHb administration of WAY208466 (1.5, 3, and 6 μg) resulted in a dose-dependent decline in both open arm time (**Figure 4B**) and entry frequency (**Figure 4E**), with the 6 μg dose producing a statistically significant anxiogenic effect ($P < 0.01$). Conversely, SB258585, a 5-HT_6 receptor antagonist, administered at doses of 1, 2, and 4 μg significantly increased both open arm exploration metrics (**Figure 4C** and **Figure 4F**). Notable anxiolytic effects were observed in the 2 μg ($P < 0.01$) and 4 μg ($P < 0.001$) treatment groups. In animals with MFB lesions, WAY208466 at 3 and 6 μg significantly

enhanced both open arm occupancy and entry percentages. Statistically significant increases were observed in open arm time at 3 μg ($P < 0.05$) and 6 μg ($P < 0.001$), and in entries at both doses ($P < 0.01$; **Figure 4B** and **Figure 4E**), suggesting an anxiolytic profile under dopaminergic-deficient conditions. In contrast, SB258585 (4 μg) markedly reduced open arm exploration in lesioned rats (**Figure 4C** and **Figure 4F**), with significant reductions observed in both time and entries ($P < 0.01$), indicating a reversal of its anxiolytic effect in the PD-like state. Pre-treatment with SB258585 completely abolished the behavioral effects of WAY208466 in both sham-operated and lesioned animals (**Figure 4B** and **Figure 4E**), confirming that these behavioral alterations were specifically mediated through 5-HT_6 receptor-dependent mechanisms.

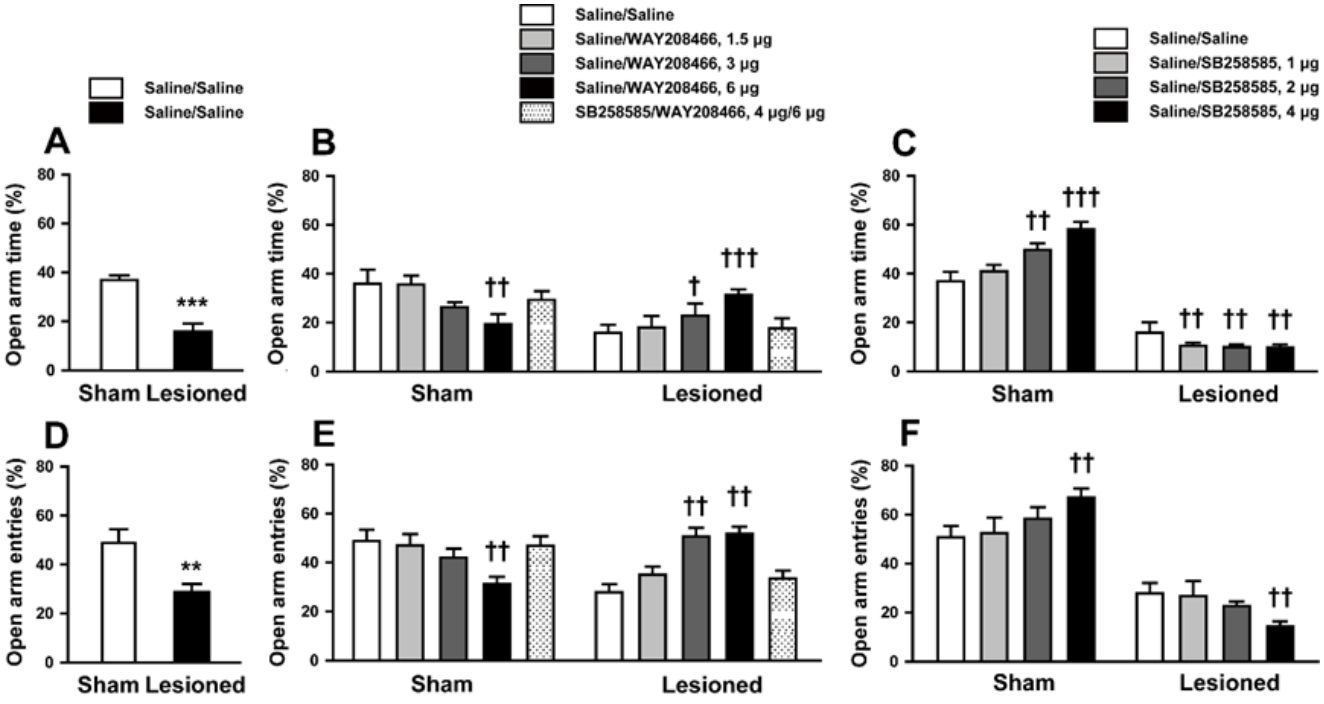

Figure 4. Effects of MFB induced by 6-OHDA and intra-LHb administration of the 5-HT_6 receptor agonist WAY208466 or antagonist SB258585 on anxiety-related behavior in the EPM.

Rats with MFB lesions exhibited a significant reduction in both the percentage of time spent in open arms and the number of open arm entries compared to sham-operated controls. In the sham group, intra-LHb injection of WAY208466 reduced both behavioral indices, whereas SB258585 produced an increase relative to saline. In contrast, among lesioned animals, WAY208466 enhanced open arm time (B) and entries (E), while SB258585 reduced these measures (C, F). Statistical significance was denoted by $^{**}P < 0.01$ and $^{***}P < 0.001$ when compared with sham-operated groups using unpaired Student's t-tests, and by $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.01$, $^{\dagger\dagger\dagger}P < 0.001$ relative to intra-LHb saline within the same group as determined by one-way ANOVA followed by Dunnett's post hoc test. Values are expressed as mean ± SEM; with n = 8 per group.

4. Discussion

The findings indicate that unilateral 6-OHDA-induced lesions of the MFB led to marked anxiety-like behavior in rats. In sham-operated animals, intra-LHb delivery of agonist WAY208466 triggered anxiogenic responses,

whereas the antagonist SB258585 produced anxiolytic effects. Interestingly, these effects were reversed in MFB-lesioned animals: WAY208466 reduced anxiety-like behaviors, while SB258585 increased them. Notably, both compounds were effective at lower doses in lesioned rats compared to their sham counterparts.

The open field test (OFT), a well-established paradigm for assessing locomotor and emotional behavior in rodents, revealed that MFB lesions significantly decreased both horizontal crossings and rearing frequency, reflecting impaired motor function resulting from nigrostriatal dopaminergic degeneration—findings that align with previous literature [13, 14]. Importantly, neither WAY208466 nor SB258585 altered baseline locomotor parameters in either experimental group, thereby excluding the possibility that changes in anxiety-related outcomes were confounded by drug-induced motor effects. Although various neurotransmitter systems are implicated in the regulation of anxiety-like behavior, potential interference from auxiliary pharmacological agents was also considered [15]. Chloral hydrate and desipramine have been reported to transiently modulate serotonergic activity [16]. However, since behavioral testing was performed 1–3 weeks after their administration, any lingering pharmacodynamic effects are presumed minimal.

Anxiety is widely recognized as a prevalent non-motor symptom in PD, the extent to which animal models reliably display anxiety-like behaviors remains a topic of ongoing debate [17]. Variability in findings across studies may be attributed to factors such as differences in lesion location, severity, unilateral versus bilateral manipulation, and the timing of behavioral assessments. In this study, rats subjected to MFB lesions showed a marked reduction in the duration spent within the central zone during OFT, as well as reduced open arm activity in the EPM—both indicative of heightened anxiety-like behavior. These results align with prior studies that validate this model's ability to replicate emotional disturbances associated with PD [18].

The LHb has emerged as a critical node in the neural circuitry underlying anxiety regulation [19]. Among the serotonin receptor subtypes, the 5-HT_6 receptor is highly expressed in LHb and has emerged as a potential target for therapies aimed at modulating anxiety-related behaviors [20]. However, the behavioral effects of 5-HT_6 receptor ligands remain inconsistent across studies. Some investigations report that agonists such as WAY208466 produce anxiolytic outcomes, potentially via enhancement of GABAergic transmission or suppression of glutamatergic activity, while others suggest that antagonists like SB258585 exert anxiolytic effects through mechanisms beyond serotonergic signaling, including modulation of GABAergic or cholinergic pathways [21, 22]. These discrepancies imply that 5-HT_6 receptor-mediated regulation of anxiety may engage multiple and context-dependent neurotransmitter systems.

For the current study, intra-LHb administration of WAY208466 in sham-operated rats induced anxiogenic behavior, whereas SB258585 produced an anxiolytic response—findings partially consistent with prior reports [23]. Interestingly, this pharmacological profile was reversed in MFB-lesioned animals, with WAY208466 exhibiting anxiolytic effects and SB258585 promoting anxiety-like behaviors. Microdialysis data have shown that WAY208466 reduces extracellular levels of monoamines, including dopamine (DA), serotonin (5-HT), and norepinephrine (NA), in regions such as the prefrontal cortex, striatum, and amygdala [24]. Given the established role of monoamine depletion in anxiety pathophysiology, the anxiogenic effect observed in sham rats may be attributed to reduced monoaminergic signaling within limbic structures [25]. Conversely, the anxiolytic action of SB258585 may reflect its capacity to enhance GABAergic tone, mimic benzodiazepine-like effects, or promote acetylcholine release [26].

This study provides the first evidence that under Parkinsonian conditions, microinjection of WAY208466 into the LHb elicits pronounced anxiolytic effects, while the antagonist SB258585 exacerbates anxiety-like

behaviors—opposite to their effects observed in neurologically intact animals. These findings suggest that the functional role or pharmacological sensitivity of 5-HT_6 receptors within the LHb is altered in the context of PD. The reduced effective doses required in MFB-lesioned rats relative to sham-operated controls further support the notion of receptor upregulation or enhanced sensitivity following dopaminergic denervation. This interpretation is consistent with prior reports of increased glutamatergic activity in the LHb of PD models [27]. Given the frequent co-manifestation of anxiety and depression in PD and their common dependence on monoaminergic signaling, the observed shift in 5-HT_6 receptor pharmacodynamics may reflect broader neurochemical adaptations [28]. Our previous research has also demonstrated that 5-HT_6 receptor modulation influences depressive-like behaviors in the dorsal hippocampus of PD rats, likely through dopaminergic and noradrenergic mechanisms [29].

5. Conclusion

The results suggest that unilateral MFB lesions in Parkinsonian models may lead to enhanced expression or functional sensitivity of 5-HT_6 receptors within the LHb. This receptor-level adaptation likely increases neuronal responsiveness to both agonists and antagonists, thereby modifying LHb output to downstream limbic and monoaminergic circuits. Such alterations may underlie the observed behavioral shifts and provide novel mechanistic insights into the pathophysiology of anxiety in PD, highlighting the 5-HT_6 receptor as a potential target for therapeutic intervention in dopamine-depleted states.

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Disclosure statement

The authors declare no conflict of interest.

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