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Continuous SGB Inhibits Occurrence and Maintenance of Mechanical Hyperalgesia via Reducing Inflammatory Cytokines in Striatum and PAG of PD Nociception Rat Models

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ABSTRACT

AIM: To investigate the effect of stellate ganglion block (SGB) on nociception in Parkinson's disease (PD) rat models, and to clarify the associated mechanism.

MATERIAL and METHODS: To generate PD nociception rat model 6-hydroxydopamine (6-OHDA) injection method was used. Paw withdrawal threshold (PWT) and paw retraction latency (PWL) was used to reflect mechanical stimulation and thermal stimulation, respectively, at pre-modeling and 1, 2, 3, 4 weeks post modeling. The preventive and therapeutic effects of SGB treatment on nociception were observed in Naive, Vehicle, and 6-OHDA group (model). Levels of IL-1β, IL-6, and TNF-α in striatum and periaqueductal gray (PAG) were detected with ELISA.

RESULTS: 6-OHDA injection induced obvious reduction of bilateral PWT from 2 to 4 weeks post modeling, suggesting that PD nociception rat model was successfully established. Continuous SGB prevention inhibited mechanical hyperalgesia at 2, 3 and 4 weeks post modeling, and significantly reversed mechanical hyperalgesia at 3 and 4 weeks post modeling, compared with those of Saline group ($p<0.05$). These results suggest that continuous SGB could effectively prevent and alleviate pain of PD rats. SGB treatment remarkably suppressed levels of inflammatory factors (IL-1 β, IL-6, and TNF-α) in striatum and PAG of PD rats compared with those of rats in Vehicle group ($p<0.05$).

CONCLUSION: Continuous SGB effectively inhibited and reversed mechanical hyperalgesia of PD nociception rats through inhibiting inflammatory response in striatum and PAG.

KEYWORDS: Parkinson's disease, Stellate ganglion block, Pain, Mechanical hyperalgesia, Inflammatory factors, Rats

INTRODUCTION

Parkinson's disease (PD) is a common degenerative disease in central nervous system (CNS) (10,28). Due to the loss of dopaminergic neurons in substantia nigra pars compacta (NSpc) project in striatum, body gradually loses its ability to control autonomous movement. Therefore, PD patients are mainly characterized by bradykinesia, resting tremor, stiffness, and postural instability (23). In addition to the above typical motor dysfunctions, other non-motor symptoms including depression, autonomic nervous disorder, sleep disorders and pain, also seriously affect the prognosis

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of PD patients (33). Epidemiological investigations (3,27) showed that 65%-85% of PD patients experienced various types of acute or chronic pain, therefore, the life quality of PD patients has decreased significantly, bringing a huge burden to family and society. However, little is known about the pathogenesis of chronic pain in PD patients till now. Presently, even no analgesic regimen has been proven to demonstrate satisfactory therapeutic effect on PD patients (16,18). A few previous studies (16,17,21) have shown that deep brain stimulation (DBS) may provide some analgesic effect in the early stage of PD. However, the operation is complex, invasive, expensive, and with some side-effects, all of which seriously limit its clinical applications. Therefore, it is urgent and critical to find a new and effective method to prevent and treat PD patients with chronic pain.

In different pathologic stages of PD, different molecules involve in and cause chronic pain, leading to the difficulty to cure. In recent years, it has been reported that neuroinflammation may be the key mechanism of PD (13). High expression of inflammatory factors in periaqueductal gray (PAG) is directly or indirectly related to occurrence of pain in PD (34), suggesting that anti-inflammatory treatment may improve symptoms of chronic pain in PD patients. Stellate ganglion block (SGB) is a common method of sympathetic nerve regulation in clinic. SGB plays a therapeutic and protective role in a variety of central nervous system (CNS) diseases by regulating inflammatory response, oxidative stress, and immune endocrine function (19,24,25). However, up to now, there is no relevant research focusing on effect of SGB on PD chronic pain.

In this study, the experimental PD rat model was established to observe nociception behavior. At the same time, the preventive and therapeutic effects of SGB on pain of PD chronic pain rat model were evaluated, and the associated potential molecular mechanism was explored. Therefore, this study aimed to investigate effect of SGB on nociception in PD rat models and clarify the associated mechanism. This study is expected to provide new strategies and ideas for preventing and treating chronic pain in PD patients.

MATERIAL and METHODS

Animals

The male Sprague Dawley (SD) rats, weighting 180-220 g, were purchased from the Animal Experimental Center of Fujian Medical University. Rats were fed with well ventilated at 22-25 °C, with condition of 50%-60% humidity, circadian rhythm of 12 h/12 h, and freely accessed to food and water. All experiments were carried out in the morning (8:00-12:00).

This study has been approved by the Ethical Committee of 900 Hospital of the Joint Logistics Support Force (Fuzhou General Hospital of Fujian Medical University) (Approval No. 2019-0061), Fuzhou, China. Animal experiments were conducted in accordance with the National Institutes of Health (NIH) guidance of care and use of laboratory animals and guidelines of International Association for Study of Pain (35).

Establishment of PD Nociception Rat Model

Induction of PD nociception rat model was carried out using 6-hydroxydopamine (6-OHDA)-injection method as described by former studies (9,29), with a few modifications. Briefly, post sevoflurane inhalation anesthesia, rats were fixed to the brain stereotaxic frame, and the head was sterilized with a longitudinal incision (1 cm). According to the rat brain atlas (2) and coordinates reported by Andrzejewski et al. (31), two different injection points were selected in the left striatum. The first point was listed as follows: antero-posterior, bregma of -4.4, lateral of 1.5 mm right of midline, ventral dura of -7.9 mm, and incisor bar of -3.5 mm. Another point was listed as the follows: antero-posterior, bregma of -2.2 mm, lateral of 1.5 mm right of midline, ventral dura of -7.8 mm, and incisor bar of -3.5 mm. The skull of the corresponding point was carefully drilled with a skull drill. The above two target points were injected slowly with 6-OHDA using a 5 μl micro-injector with rate of 1 μl/min. 6-OHDA (Sigma-Aldrich, St. Louis, Missouri, USA) was dissolved in 0.1% ascorbic acid saline, and 3 μg/μl 6-OHDA was injected at each point (6-OHDA group, n=8 per group). After injection, the needle should be kept for 10 min to avoid liquid reflux. The normal rats were not treated with any reagents (assigned as Naive group, n=8 per group), while the control group (assigned as Vehicle group, n=8 per group) was injected with equal volume drug solvent at points as 6-OHDA group. After the operation, the skins were sutured, and the incisions were disinfected. When all experiments were completed, rats were euthanized using pentobarbital (Sigma-Aldrich; Merck KGaA) at a dosage of 150 mg/kg.

Stellate Ganglion Block (SGB) Experiment

SGB induction was conducted as the previous studies described (29,32), with some modifications. In brief, post the sevoflurane inhalation anesthesia, rats were placed in prone position, and the cartilaginous process of the 7th cervical spine was palpated with the posterior approach. A 1 ml syringe needle was inserted forward along the left sagittal position of the 7th cervical spine. When the needle tip lost contact with the vertebral body, the needle tip retreated slightly by about 0.5 mm, no blood, and cerebrospinal fluid were withdrawn, a total of 0.2 ml 0.25% ropivacaine was injected. When SGB rats appeared typical Horner's syndromes post the anesthesia, such as blepharoptosis on block side, narrow eye fission, and pupil narrowing, the stellate ganglion was blocked. To observe effect of SGB on pain of PD rats, rats were divided into SGB prevention group (n=8 per group) and SGB treatment group (n=8 per group). Rats in SGB prevention group were administrated with SGB before onset of hyperalgesia. The SGB was given from the first day to seventh day after PD modeling, blocking once a day for 7 successive days. However, Saline prevention group was injected with the same amount of saline. Rats in SGB treatment group were treated with SGB after emergence of hyperalgesia, from the 2nd week to the 3rd week after PD modeling, blocking once a day for 7 successive days. While Saline treatment group was injected with the same amount of saline. All above SGB and saline treatments were conducted from 9:00 am to 11:00 am every day.

Behavior Measurements

All rats were housed in groups of 4 per single cage and behavioral measurements were started one week post the operation. The paw withdrawal threshold (PWT) and paw withdrawal latency (PWL) were carried out.

The mechanical thresholds were measured using von-Frey triggered PWT as described by the previous studies (1,6), with a few modifications. Briefly, PWT of bilateral hind paws was measured one day before PD modeling and 1, 2, 3 and 4 weeks after PD modeling. Rats were trained to minimize stress before baseline data were collected. During the measurement, rats were placed in an independent test chamber for 30 min, and then the plantar skin of rats was vertically stimulated from the bottom to top with von-Frey fibers (RWD Life Sci. Co. Ltd., Shenzhen, China) of different scales for 3-5 s. The reactions, such as raising, shrinking or licking paws, were regarded as the positive reactions. Each scale was repeatedly stimulated 10 times, and the minimum scale value of 50% positive reaction was recorded as PWT of the foot.

The thermal hyperalgesia was measured using the heat radiation triggered PWL as described by a former study (14), with some modifications. In short, PWT of bilateral hind paws was measured at 1 day before PD modeling and 1, 2, 3 and 4 weeks after PD modeling. Rats were placed in an independent test chamber for 30 min to eliminate the tension. PWL was detected when rats' hind paws were closed to the glass plate quietly. The rat's plantar skin was irradiated by radiation heat stimulator (RWD Life Sci. Co. Ltd., Shenzhen, China). It was regarded as a positive reaction when the foot was raised, retracted or licked quickly, and the stimulator was turned off immediately. The time from the beginning of irradiation to the closing of stimulator was defined as PWL value. Three plantar tests were conducted on each side with an interval of 10 min. The average PWL values of three times was recorded as the final PWL value. A cutoff time of 30 s was assigned as a limitation to avoid tissues or skins damage. If the rats irradiated for more than 30 s did not show positive reaction, the PWL was recorded for 30 s.

Enzyme Linked Immunosorbent Assay (ELISA)

ELISA analyses for detecting IL-1β, IL-6, and TNF-α in tissues were conducted post behavior measurements. Briefly, rats were anesthetized by intraperitoneally injecting with pentobarbital at a dosage of 50 mg/kg prior to cervical dislocation (rats were euthanized) and brain tissue was quickly removed and placed in a pre-cooled PBS solution. The striatum and dorsolateral area of PAG were dissected and separated under a microscope. Position of the striatum and dorsolateral area of PAG was verified according to the Paxinos Atlas (22). Here, due to the lesion was unilateral, both ipsi and contra-side of PAG tissues were pooled and used. Tissue homogenates were prepared by adding RIPA lyzing liquid containing protease inhibitor to both striatum and PAG tissues. Then, homogenates were centrifuged at 10000 r/min and 4 °C for 10 min, and the supernatants were taken and stored in refrigerator at -80 °C for following experiments. Finally, levels of IL-1β, IL-6, and TNF-α in both striatum and PAG tissues were detected using ELISA with the commercial kits, as instructed by manufacturers (Shanghai Westang Biotech. Co. Ltd., Shanghai, China).

Statistical Analyses

Data were defined as mean±standard deviation (mean±SD) and analyzed using Graphpad Prism 5.0 Statistical Software (GraphPad Prism Software Inc., San Diego, CA, USA). Behavioral measuring data were analyzed using two-way ANOVA, and Bonferroni test was used for comparison between two groups. ELISA data were analyzed using one-way ANOVA, and Tukey test was used for comparison between groups. P value less than 0.05 was defined as statistically significant.

RESULTS

6-OHDA Induced Mechanical Hyperalgesia of PD Rats

According to PWT findings, 6-OHDA-inudced PD rats demonstrated obvious mechanical hyperalgesia in both left foot (Figure 1A, $p<0.05$) and right foot (Figure 1A, $p<0.05$), compared with those in operation control group (Vehicle group). At the second week after 6-OHDA injection, PWT of the bilateral hind paws was significantly decreased compared with that of basal threshold (left foot decreased by 66.6% (Figure 1A), right foot decreased by 61.7% (Figure 1B)), and remained unchanged at least until 4 weeks after 6-OHDA injection (with significant difference from 2 weeks to 4 weeks post 6-OHDA injection, all $p<0.05$). These results suggest that 6-OHDA injection induced nociception in PD rats, as a stable model (Figure 1A, B).

6-OHDA-Injected PD Rats Demonstrated Non Thermal Hyperalgesia

As PWL result indicated, compared with operation control group (Vehicle group), PWL of PD rats demonstrated no significantly changes for both left foot (Figure 2A, $p>0.05$) and right foot (Figure 2A, $p>0.05$), from 2 weeks to 4 weeks post 6-OHDA injection. Therefore, we held the view that 6-OHDA-induced PD rats did not demonstrate thermal hyperalgesia from 2 weeks to 4 weeks post 6-OHDA injection (Figure 2A, B).

Continuous SGB Prevention Inhibited Mechanical Hyperalgesia in PD Rats

PWT in left foot of PD rats in SGB group was significantly increased at 2, 3 and 4 weeks, compared with that in Saline group (Figure 3A, $p<0.05$), increasing by 75.5%, 74.7% and 89.0%, respectively. At the same time, PWT in the right foot of PD rats in SGB prevention group was significantly increased at 2, 3 and 4 weeks, compared with that in Saline group (Figure 3B, $p<0.05$), increased by 88.0%, 78.2% and 67.4%, respectively. These results suggest that the preventive stimulation of continuous SGB could significantly inhibit occurrence of bilateral mechanical hyperalgesia in PD rats.

Continuous SGB Treatment Reversed Mechanical Hyperalgesia in PD Rats

For the left foot of PD rats, PWT in SGB treatment group was

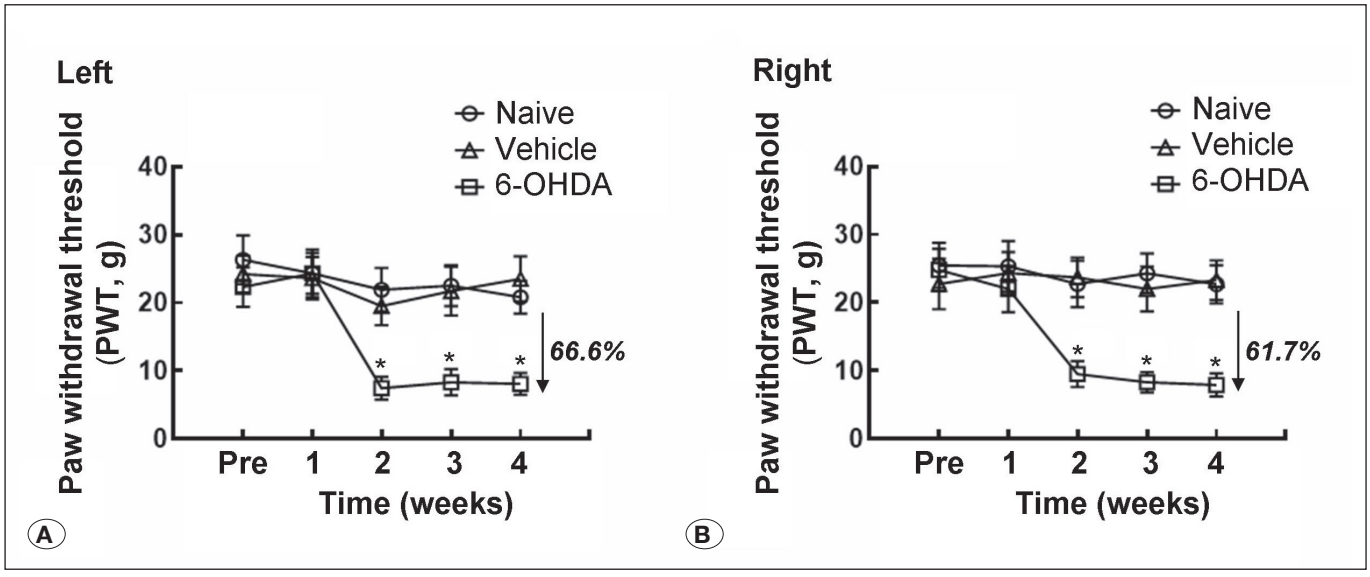

Figure 1: Mechanical thresholds measurement was determined by PWT in PD rats before modeling and 1-4 weeks post modeling (n=8 per group). **A)** Left hindpaw PWT. **B)** Right hindpaw PWT. *p<0.05 vs. vehicle group.

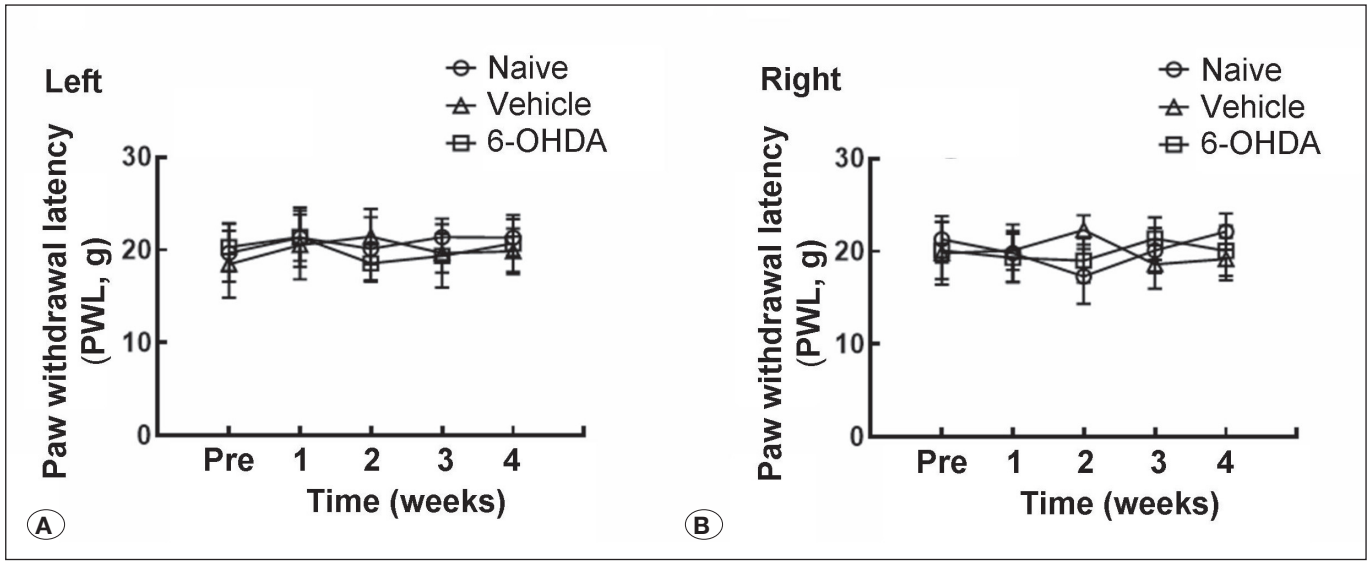

Figure 2: Thermal hyperalgesia measurement was identified by PWL in PD rats before modeling and 1-4 weeks post modeling (n=8 per group). **A)** Left hindpaw PWT. **B)** Right hindpaw PWT. *p<0.05 *vs.* vehicle group.

significantly increased at 3 and 4 weeks, compared with that of Saline group (Figure 4A, p<0.05), increasing by 79.4% and 83.1%, respectively. While, for the right foot of PD rats, PWT in SGB treatment group was remarkably increased at 3 and 4 weeks, compared with that of Saline group (Figure 4B, p<0.05), increasing by 65.3% and 85.9%, respectively. These results indicated that post emergence of mechanical hyperalgesia in PD rats, the bilateral mechanical hyperalgesia of PD rats was significantly reversed when undergoing continuous SGB stimulation.

SGB Treatment Suppressed Inflammation in Striatum of PD Rat Brain

ELISA findings showed that levels of IL-1 β, IL-6, and TNF-α in striatum tissues of PD model rats (6-OHDA group) were significantly increased (Figure 5, p<0.05), compared with levels of those in Vehicle group, with increasing rate of 124.4%, 270.2% and 206.0%, respectively (Table I). However, levels of IL-1β, IL-6 and TNF-α in striatum tissues were significantly decreased by continuous SGB (Figure 5, p<0.05), which were 29.8%, 38.6% and 35.7% lower than those in PD model group, respectively (Table I).

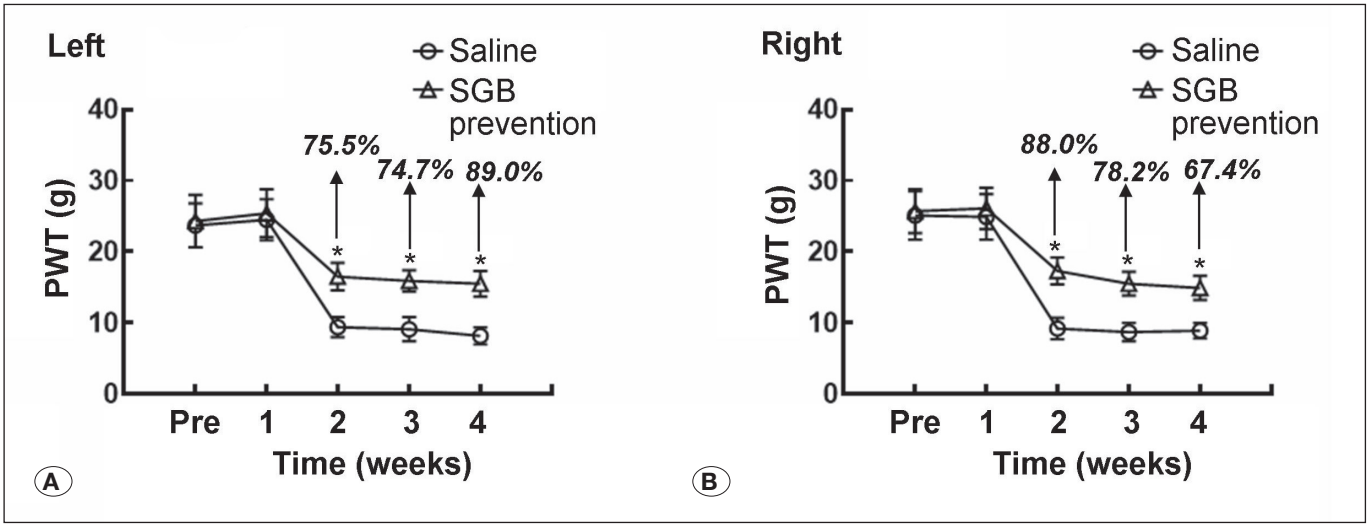

Figure 3: Preventive effects of SGB treatment on development of mechanical hyperalgesia in PD rats before modeling and 1-4 weeks post modeling (n=8 per group). **A)** Left hindpaw. **B)** Right hindpaw. *p<0.05 *vs.* vehicle group.

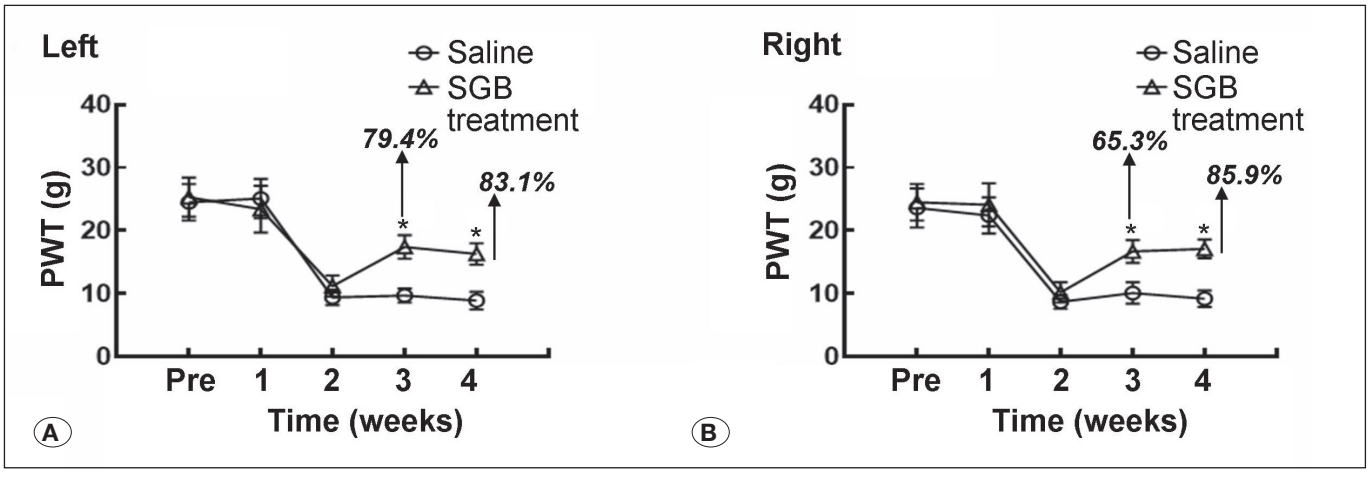

Figure 4: Reversible effects of SGB treatment on maintenance of mechanical hyperalgesia in PD rats before modeling and 1-4 weeks post modeling (n=8 per group). **A)** Left hindpaw. **B)** Right hindpaw. *p<0.05 vs. vehicle group.

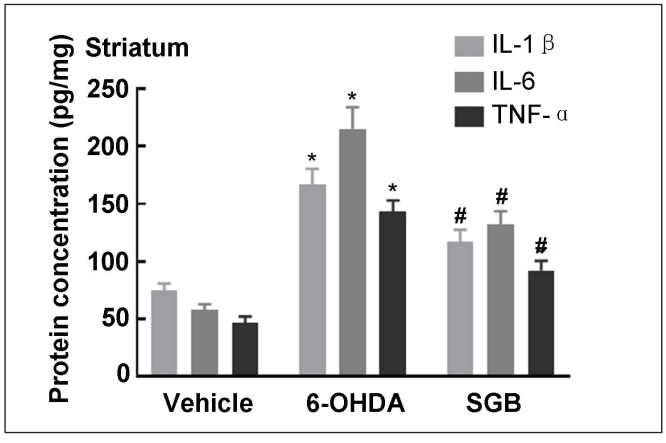

Figure 5: Inhibitive effects of SGB treatment on inflammatory factors, including IL-1β, IL-6 and TNF-α, in striatum tissues of PD rats (n=8 per group). *p<0.05 vs. vehicle group, #p<0.05 vs. 6-OHDA group.

SGB Treatment Attenuated Inflammation in PAG of PD Rat Brain

Levels of IL-1 β, IL-6 and TNF-α in PAG tissues of PD model rats were significantly higher compared to those of Vehicle group (Figure 6, p<0.05), increasing by 177.8%, 183.6% and 171.6%, respectively (Table II). However, continuous SGB could also effectively attenuate levels of IL-1 β, IL-6 and TNF-α in PAG tissues compared to those of 6-OHDA group (Figure 6, p<0.05), with inhibition rates of 42.9%, 40.9% and 46.4%, respectively (Table II). These results suggest that continuous SGB could effectively alleviate inflammatory response in PAG of PD rats.

DISCUSSION

In this study, we investigated effects of SGB on nociception of PD model rats, and discussed the associated mechanism. We discovered that there was no obvious thermal hyperalgesia in

Table I: Increasing Rates of Inflammatory Factors of 6-OHDA vs. Vehicle Group and Decreasing Rates of Inflammatory Factors of SGB vs. 6-OHDA Group, in Striatum Tissues of PD Rats

Groups	IL-1β	IL-6	TNF-α
Vehicle	100%	100%	100%
6-OHDA	100%+124.4%*	100%+270.2%*	100%+206.0%*
SGB	124.4%-29.8%#	270.2%-38.6%#	206.0%-35.7%#

**p<0.05: 6-OHDA vs. Vehicle group; #p<0.05 vs. SGB vs. 6-OHDA group. The values of Vehicle group were assigned as the baselines (100%).*

Table II: The Changing Rates of Inflammatory Factors Among Vehicle, 6-OHDA and SGB Group in PAG Tissues of PD Rats

Groups	IL-1β	IL-6	TNF-α
Vehicle	100%	100%	100%
6-OHDA	100%+177.8%*	100%+183.6%*	100%+171.6%*
SGB	177.8%-42.9%#	183.6%-40.9%#	171.6%-46.4%#

**p<0.05: 6-OHDA vs. Vehicle group; #p<0.05 vs. SGB vs. 6-OHDA group. The values of Vehicle group were assigned as the baselines (100%).*

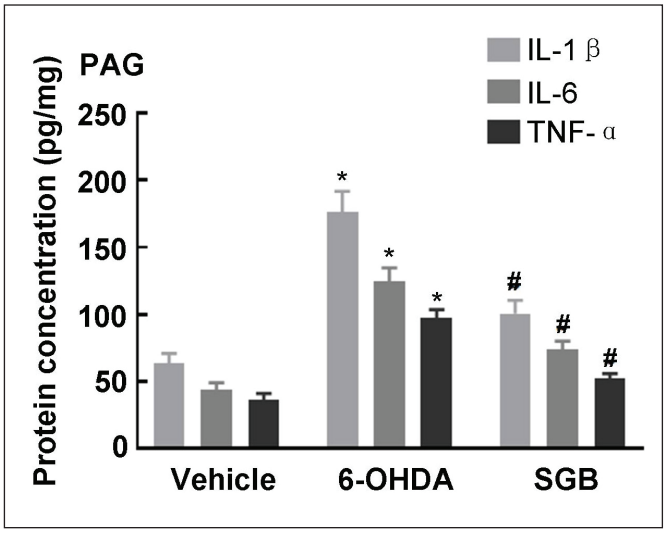

Figure 6: Reductive effects of SGB treatment on inflammatory factors, including IL-1β, IL-6 and TNF-α, in PAG tissues of PD rats (n=8 per group). *p<0.05 vs. vehicle group, #p<0.05 vs. 6-OHDA group.

the classical PD model rats induced by intrastriatal injection of 6-OHDA within 4 weeks after operation. However, the bilateral mechanical hyperalgesia began to appear in PD rats at the second week post the operation, and lasted at least until the fourth week. All findings indicated that the experimental PD nociception rat model was successfully established. Continuous SGB for 7 days could significantly inhibit occurrence of the bilateral mechanical hyperalgesia in PD rats. While after occurrence of hyperalgesia, continuous SGB could significantly reverse its maintenance, proving that SGB can effectively prevent and treat nociception in PD rats. 6-OHDA injected into striatum tissues of PD rats induced obvious inflammatory reaction in striatum and PAG, which demonstrates that expression of pro-inflammatory cytokines, including IL-1β, IL-6 and TNF-α, was significantly increased. However, continuous SGB could significantly reduce levels of pro-inflammatory cytokines in striatum and PAG, and alleviate inflammatory response. In summary, these findings suggest that SGB can inhibit occurrence and maintenance of PD chronic pain through reducing inflammatory response in striatum and PAG of PD rats.

Although a large number of experimental animal models of PD, such as 6-OHDA-induced PD model, have been reported, there are also some disputes about location of mechanical hyperalgesia (left foot or right foot or bilateral) (7,8,11,30). Therefore, to avoid the above disputes of 6-OHDA injection molding, this study referred to the modeling method as described by Domenici et al. (9) and adopted method of 2-point injection of 6-OHDA into the left striatum. We found that from the second week after injection of striatum, PWT was decreased significantly on both sides of rats, and remained unchanged at least until the fourth week after modeling. These findings are consistent with a previous study (4) reporting that mechanical hyperalgesia of PD rats was bilateral (4). In addition, our study did not find the thermal hyperalgesia sign in PD rat model, which is different from the previously published studies (4,5). A previous study (5) reported that PWL was shortened in rats at the 4th week after operation, which may be due to fact that 6-OHDA was injected into the bilateral striatum at the same time. In our study, only 6-OHDA was injected into the left striatum. The differences of the above results further indicated that there may be different mechanisms for occurrence of mechanical and thermal hyperalgesia in PD. Additionally, all current basic researches on PD pain, including this study, only detected the stimulation induced pain in animals. However, this study paid less attention to the spontaneous nociception, which can simulate the clinical pain and needs to be further investigated in future.

In this study, we systematically evaluated effect of continuous SGB on nociception in PD rats for the first time. Our study confirmed that continuous SGB can not only significantly inhibit mechanical nociception sensitivity in PD rats, but also effectively reverse mechanical nociception sensitivity of PD rats. These results showed that SGB can prevent and treat PD nociception. Some other studies (7,11,20) have shown that SGB plays an analgesic role through reducing inflammatory response in 6-OHDA injection site and PAG. A former study reported that number of neurons with positive c-fos in PAG of PD rats is significantly higher than that of control group (26). Gee et al. also confirmed that PAG mediated down-pain modulating system disorder may be a mechanism of PD nociception (12). A recent study found that levels of inflammatory factors (IL-1 β, IL-6, and TNF-α) in PAG were significantly increased in PD state, and were related to occurrence of PD pain, which are consistent with results of our study (34). A previous study identified that dopamine receptor agonists injecting into striatum tissues could alleviate pain response in rats, suggesting that downregulation of dopamine system function in striatum is directly involved in occurrence of pain (20). Findings of Magnusson and Fisher further supported the behavior of mechanical pain sensitivity in 6-OHDA induced rats to damage dopaminergic neurons in striatum (20). In fact, more and more researches have confirmed that loss of dopaminergic neurons in PD brain is related to excessive inflammatory response. Inhibition of inflammatory response could effectively play a neuroprotective role and reduce apoptosis of dopaminergic neurons (15). In this study, we found that continuous SGB can reduce high expression of IL-1 β, IL-6 and TNF-α in striatum tissues of PD rats for the first time, suggesting that SGB may inhibit inflammatory response in PD nociception rat model. Therefore, striatum and PAG might be possible targets responsible for inducing the reduced cytokine expression.

Although this study received a few interesting results, there are also some limitations. First, lesion size of rat model and tyrosine hydroxylase (TH) expression have not been validated for identifying model establishment. Second, whether the established PD rat model is unilaterally lesioned with 6-OHDA in the left striatum has not been determined.

CONCLUSION

According to 6-OHDA injection-induced PD model in this study, we found that continuous SGB can effectively inhibit and reverse the mechanical hyperalgesia of PD rats through inhibiting inflammatory response in striatum and PAG for the first time. The findings of this study would provide a reliable, stable and effective experimental animal model for the basic research of PD pain, and provide a simple and effective treatment strategy for the clinical prevention and treatment of PD pain.

AUTHORSHIP CONTRIBUTION

Study conception and design: GL
Data collection: ML, WH, YS, YZ
Analysis and interpretation of results: ML, WH
Draft manuscript preparation: ML, WH
Critical revision of the article: ML, GL
Other (study supervision, fundings, materials, etc...): ML, WH, GL
All authors (ML, WH, YS, YZ, GL) reviewed the results and approved the final version of the manuscript.

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