Research Paper

The Effects of Sodium Hydrosulfide on Motor Learning in a Rat Model of Parkinson’s Disease

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**ABSTRACT**

**Background:** Hydrogen Sulfide (H2S), a novel endogenous gasotransmitter, plays an important role in neuromodulation and memory performance and also protects neurons against neurotoxin-induced neurodegeneration.

**Objective:** This study aimed to investigate the potential neuroprotective effects of Sodium Hydrosulfide (NaHS), on motor learning in a unilateral 6-Hydroxydopamine (6-OHDA) rat model of Parkinson’s Disease.

**Method:** Male Wistar rats were subjected to unilateral injection of 6-OHDA (15 μg) into the Medial Forebrain Bundle (MFB) and then treated with NaHS for 25 days. Animals were divided into control, sham, sham plus NaHS, Parkinson (6-OHDA), Parkinson plus vehicle (saline), and Parkinson plus NaHS (2.8 and 5.6 mg/kg, IP) groups, (N=8). One-way ANOVA followed by turkey’s test was applied for statistical analyses of the data.

**Finding:** The riding time in fixed and accelerating speed rotarod were significantly decreased in Parkinson rats (6-OHDA group) compared to controls in all training days (P<0.001). Treatment with NaHS (2.8 and 5.6 mg/kg/d) reversed these decreases in a dose-dependent manner, so no significant differences were found in these parameters between the control and Parkinson plus NaHS groups during the accelerating speed rotarod test.

**Conclusion:** In the Parkinson rats, NaHS administration enhanced and improved the endurance time in the rotarod test. These results demonstrate that NaHS treatment enhances rat motor balance and coordination and suggest treatment with NaHS attenuates motor impairments in the Parkinson rats.

**Keywords:** Hydrogen Sulfide, 6-Hydroxydopamine, Rotarod test, Medial Forebrain Bundle (MFB), Parkinson’s Disease

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**Extended Abstract**

1. **Introduction**

Parkinson Disease (PD) is a progressive neurodegenerative disorder characterized by a progressive loss of Substantia Nigra pars compacta (SNc) dopaminergic neurons, which leads to motor symptoms of bradykinesia, rigidity, resting tremor, and postural imbalance [1]. PD is a neurodegenerative condition in which dementia may be observed even in the early stage of the disease together with mild motor disabilities that follows midbrain dopaminergic neuron loss [2].

The prevalence of cognitive dysfunction is high with reports indicating that this non-motor symptom negatively affects the quality of life of about 60% of patients with PD and cause morbidity and mortality in 36% of patients...
at the early onset of the disease [3]. Therefore, the patients suffering from PD, appear to be particularly susceptible to develop cognitive impairments 4-6 times more than what happens with normal aging [4].

Both structural and functional changes of the hippocampus which are involved in cognitive processes such as learning and memory have been observed in PD patients [5, 6]. Several studies have also shown that the reduction of hippocampal volume was accompanied by cognitive deficits in PD patients [7]. Numerous studies have suggested that neuroinflammation and oxidative stress play major roles in the pathogenesis of nigral dopaminergic cell death in PD [8].

6-Hydroxydopamine (6-OHDA) was the first dopaminergic neurotoxin used experimentally to induce PD [9]. The neuronal damage induced by 6-OHDA is mainly due to the great oxidative stress caused by the toxin. For this reason, unilateral injection of 6-OHDA is a good model for studying oxidative stress in the pathogenesis of PD. To date, three main gasotransmitters have been identified: Nitric Oxide (NO), Carbon monoxide (CO), and Hydrogen Sulphide (H$_2$S). It has been discovered that H$_2$S plays multiple functional roles in the body from cardiovascular tone regulation to neuromodulation.

In recent years, it has been demonstrated that H$_2$S as a cytoprotectant, significantly improves spatial learning and memory impairment induced by Aβ and exerts anti-inflammatory, anti-apoptotic, and antioxidant effects [10]. However, the possible role of H$_2$S as an anti-oxidant agent in cognitive dysfunction in a rat model of PD has not yet been fully elucidated. Therefore, the present study was designed to investigate the protective effects of H$_2$S against 6-OHDA-induced motor learning impairment in a unilateral 6-OHDA rat model of PD.

2. Methods and Materials

Animals were first anesthetised with Intraperitoneal (IP) injection of ketamine (100 mg/kg) and xylazine (10 mg/kg) and were then placed in a stereotactic apparatus. Burr holes were drilled in the right side of the skull and 4 μg of 6-OHDA mixed in 2 μL of 0.2% ascorbic acid with 0.9% normal saline was injected into the ascending mesostriatal pathway using stereotactic positioning (4.4 mm posterior to the bregma, 1.2 mm lateral to the midline, and 7.8 mm below the dura) near the MFB at a rate of 0.2 μL.

Administration of normal saline vehicle with the same volume was performed as sham surgery. Then the animals were divided into seven groups; including control, sham, sham plus NaHS (5.6 mg/kg), Parkinson (6-OHDA), Parkinson plus vehicle (saline), and Parkinson plus NaHS (2.8 and 5.6 mg/kg). Animals in the sham plus NaHS and 6-OHDA plus NaHS groups received daily intraperitoneal administration of NaHS (Sigma-USA) post-operation for 25 days. NaHS was dissolved in distilled water. Behavioral tests were performed 24 h after the last injection. Motor coordination was assessed using an automated rotating rod [11, 12]. One-way ANOVA was applied for statistical analyses of the data. The level of significance was less than 0.05.

3. Results

The overall results showed no statistically significant differences in different parameters between the sham, control, and sham plus NaHS groups. Furthermore, no statistically significant difference was found between the 6-OHDA and 6-OHDA plus vehicle (saline) groups with respect to different parameters. Data are not shown. Therefore, these data are not depicted graphically and the data obtained from the 6-OHDA plus saline (6-OHDA group) and 6-OHDA plus

![Figure 1](image-url). Comparison of latency to fall in control and experimental groups

Effects of NaHS on 6-OHDA-induced impairment in motor learning of the rats in the rotarod test. All values are represented as Mean±SEM. * P<0.05; Relative to the control group.
NaHS (2.8 and 5.6 mg/kg) groups were compared with each other and with the control group.

The riding time in fixed and accelerating speed rotarod significantly decreased in Parkinson rats (6-OHDA group) compared to controls, in all of the training days. Treatment with NaHS (2.8 and 5.6 mg/kg/d) reversed these decreases in a dose-dependent manner, so no significant differences were found between the control and Parkinson plus NaHS groups in these parameters during the fixed and accelerating speed rotarod test (Figure 1).

Our results showed that microinjection of 6-OHDA into the MFB depressed motor performances of animals on the rotarod and remarkably decreased the time that animals balanced steadily on the rotarod, whereas administration of NaHS (2.8 and 5.8 mg/kg) reversed the inhibitory effects of 6-OHDA on rotarod and considerably increased the animals’ endurance time on rotarod. These results demonstrate that NaHS enhances rat motor balance and coordination in a unilateral 6-OHDA rat model of PD.

4. Conclusion

In the Parkinson rat group, NaHS administration enhanced and improved the endurance time in the rotarod test. These results demonstrate that NaHS treatment enhances rat motor balance and coordination and suggest that treatment with NaHS attenuates motor impairments in the Parkinson rat group.

Ethical Considerations

Compliance with ethical guidelines

This research was approved by the Ethics Committee of the Qazvin University of Medical Sciences (code: IR.QUMS.REC.1396.476).

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Authors’ contributions

Conception, design and revising the article critically for important intellectual content: Mohammad Hossein Esmaeili; acquisition, Analysis and interpretation of data: Mohammad Hossein Esmaeili, Esmaeil Abbasi, Neda Farshad; and Drafting the article: Mohammad Hossein Esmaeili, Hashem Haghdost Yazdi.

Conflict of interest

The authors declared no conflict of interest.

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بررسی اثرات هیدروسولفید سدیم بر یادگیری حرکتی در مدل موش صحرایی پارکینسونی

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چکیده

سولفید هیدروژن که نوعی ناقل گازی درون زای جدید است، نقش مهمی در تعدیل عصبی و حافظه دارد و از نورون‌ها در مقابل مواد سمی، مانند کربنات و اکسید، ناحیه حادثه‌برانگیز محافظت می‌کند.

هدف از این مطالعه بررسی اثرات بالقوه محافظت نورونی هیدروسولفید سدیم بر یادگیری حرکتی در مدل موش پارکینسونی یک طرفه هیدروکسی دوپامین است.

روز تحت درمان با 25-هیدروکسی دوپامین به صورت یک طرفه به ناحیه دسته مغز جلویی میانی تزریق شد و موش‌ها 6 روز تحت درمان با جهاد و دارای سالنیت سایه‌گیری می‌شد. حیوانات به گروه‌های کنترل، شم، شم به همراه هیدروسولفید سدیم قرار گرفتند. حیوانات به گروه‌های کنترل و شم به همراه هیدروسولفید سدیم قرار گرفتند. بقیه موش‌ها به همراه هیدروسولفید سدیم قرار گرفتند.

استقامت در موش‌های گروه پارکینسونی در مقایسه با گروه کنترل به طور معنی‌داری در آزمون روتارود با سرعت چرخش ثابت و یافته ها. درمان با هیدروسولفید سدیم این کاهش را به صورت بازی با دنیای و سلولی با تولید کربنات کورنی ممکن کرده‌است. در این ناحیه، پژوهش‌های مختلف دست‌یافته در مورد کاهش سطح کربنات کورنی دانسته است. در این مطالعه، که می‌تواند بهبود و افزایش معنی‌داری استقلال در آزمون روتارود آن را بهبود بخشید.

نتیجه‌گیری

تزریق هیدروسولفید سدیم به موش‌های پارکینسونی، باعث بهبود در استقلال و افزایش معنی‌داری استقلال در آزمون روتارود آن را بهبود بخشید. هیدروسولفید سدیم، برای کاهش تأثیرات پارکینسونی، به طور معنی‌داری استفاده می‌شود.

کلیدواژه‌ها:

سولفید هیدروژن، هیدروکسی دوپامین، آزمون روتارود، دسته مغز جلویی میانی، بیماری پارکینسون