RESEARCH ARTICLE

THE EFFECTS OF ORAL SERRATIOPEPTIDASE ADMINISTRATION ON MOTOR ACTIVITY, EXPLORATORY BEHAVIOR, AND SEIZURE SUSCEPTIBILITY IN MICE

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ABSTRACT

This study investigated the effects of orally administered serratiopeptidase on motor activity, coordination, exploratory behavior and seizure susceptibility in mice. Male Swiss albino mice (n=8 per group) at doses of 5, 10, and 20 mg/kg via oral gavage for a period of 15 days. A control group received an equivalent volume of distilled water. Motor activity was assessed using the open field test, with horizontal activity (number of squares crossed) and vertical activity (number of rearing) recorded. Motor coordination and exploratory behavior were evaluated using negative geotaxis and a head-pocking test. Then, mice were intraperitoneally administered with 200mg/kg of pilocarpine. The onset of convulsion, number of convulsions and survival rate were assessed. Diazepam (1mg/kg) served as positive control. Serratiopeptidase significantly increased both horizontal and vertical activity in the open field test and improved exploratory behavior, particularly at the 20 mg/kg dose. Motor coordination improvements were also observed, though with a biphasic dose-response pattern. Notably, serratiopeptidase significantly delayed the onset of seizures, reduced seizure frequency, and improved survival rates - effects that were comparable to diazepam at the 10 and 20 mg/kg doses. These findings suggest that oral administration of serratiopeptidase may positively modulate motor function in mice, furthermore, serratiopeptidase possesses anticonvulsant properties and may be a potential therapeutic agent for seizure disorder. Further investigation is warranted to elucidate the exact mechanism of action and to explore the translational relevance of these findings.

Keywords: Convulsion, open field test, mice, pilocarpine, serratiopeptidase

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INTRODUCTION

Seizures result from abnormal or excessive neuronal discharges and are a hallmark of epilepsy, the most common neurological disorder globally (Abed, 2023; Chauhan et al., 2022; Pedley, 2020). Serious medical emergencies can result from certain seizure types, leading to status epilepticus and the possibility of brain injury or death (Ascoli et al., 2021). However, the physical resiliency in the body enabled by neural plasticity can also facilitate quick recovery with support, such as anti-seizure medication and/or hospital management. There are many different theories about the potential causes of seizures (Alavi et al., 2024).

Approximately two to eight percent of the American population will experience at least one seizure event in their lifetime (Bensken et al., 2021). The main therapeutic strategy for the management of seizures is the use of antiepileptic drugs (AEDs), which are effective in most types of idiopathic and symptomatic epilepsy. In general, treatment is much more complex for the so-called difficult-to-control forms as compared to non-chronic focal forms (Ghosh et al., 2021). The enzyme is also known as Serratia E15, S-E15, Serratia Peptidase, and Serrapeptase. Its name is systematically named "Peptidase S3" and the Enzyme Commission number (EC number) is 3.4.24 (Calogero et al., 2017). However, commercially available products are usually called "Serrapeptase." Serrapeptidase was discovered in the intestinal microflora of silkworms and was isolated and identified in the 1960s (Ahmed et al., 2023). In the 1960s, there were reports of tissue-dissolving action in the case of inflammation and other injuries in the silkworms (Ahmed et al., 2023).

Pilocarpine is an agonist on muscarinic receptor, it's tertiary amine and can cross blood brain barrier and produce central nervous impacts, it's widely used in preclinical studies to induce seizure in animals models (Duffy, 2014; Yang et al., 2022). Temporal lobe epilepsy models, especially those induced by pilocarpine, replicate many clinical and neuropathological features of human epilepsy (Henkel et al., 2021). Serratiopeptidase is a proteolytic enzyme produced by the Gram-positive bacterium Serratia sp. E-15 through expressing the gene encoding Serratiopeptidase (Curia et al., 2008; Kumar et al., 2023; Lévesque et al., 2021; Narayanan, 2025). To our knowledge, this is among the few studies exploring the potential anticonvulsant properties of serratiopeptidase, a proteolytic enzyme, in a pilocarpine-induced seizure model. Given the role of inflammation and oxidative stress in seizure pathophysiology, we hypothesized that serratiopeptidase could attenuate seizure severity and improve behavior in a rodent model. The present study aimed to assess its effects on motor activity, coordination, and seizure susceptibility in pilocarpine-induced seizures. We hypothesize that repeated oral administration of serratiopeptidase would improve motor activity and reduce seizure severity in a pilocarpine-induced mouse model through anti-inflammatory and neuromodulatory mechanisms. Additionally, we have specified that the primary outcomes are seizure onset, seizure frequency, and survival, and the secondary outcomes are motor activity, coordination, and exploratory behavior.

MATERIAL AND METHODS

Animals

Male Swiss albino mice aged 6-8 weeks at the start of the experiment were used. Mice were housed in standard laboratory conditions. Mice were housed in groups of 4-5 per cage to standard rodent chow and water *ad libitum*. Randomization was performed using computer-generated sequences, and all behavioral assessments and seizure observations were conducted by blinded experimenters.

Ethical Consideration

The study adhered to the ARRIVE 2.0 guidelines and was approved by the Institutional Animal Care and Use Committee (UM.VET.2024.006) by the University of Mosul/College of Veterinary Medicine.

Drugs and Treatments

Serratiopeptidase was dissolved in distilled water

to prepare the required concentrations (5,10 and 20 mg/kg). Pilocarpine hydrochloride (eye drop 2%) was diluted with distilled water to prepare the required concentration (200 mg/kg) for intraperitoneal injection. Diazepam was diluted in sterile saline and administered i.p at a dose of 1 mg/kg. Doses were selected based on prior studies reporting anti-inflammatory and behavioral effects of serratiopeptidase in rodents (Ahmed et al., 2013; Naser, 2024).

Control Groups

Vehicle Control: Mice received an equivalent volume of distilled water (the vehicle for serratiopeptidase) via oral gavage.

Positive Control: Mice received diazepam (1mg/kg, i.p.).

Experimental Design

Mice were randomly divided into five groups (n=8 per group):

Vehicle Control (distilled water, oral gavage).

Serratiopeptidase 5 mg/kg (oral gavage).

Serratiopeptidase 10 mg/kg (oral gavage).

Serratiopeptidase 20 mg/kg (oral gavage).

Positive Control (Diazepam 1mg/kg, i.p.)

Behavioral Assessments

Serratiopeptidase and vehicle were administered daily for 15 days. On the Day 16 the mice in all groups except positive control underwent for behavioral assessments.

1. Open Field Test (for Motor Activity): The open field apparatus consisted of square arena (40x40x30cm) with the floor divided into 225 equal squares. Mice were placed individually in the center of the open field and allowed for a defined period (5minutes) (Sturman et al., 2018). The following parameters were recorded:

Horizontal activity: Number of squares crossed with all four paws.

Vertical activity: Number of rearing (standing on hind limbs).

2. Negative Geotaxis Test: This test was performed to assess coordination and balance. Each mouse was placed head-downwards on a 45° inclined plane. The time taken for the mouse to turn itself 180° (so that its head was pointing upwards) was recorded in seconds. A maximum cutoff time (not specified) was likely used (Motz and Alberts, 2005).

3. Head-Poking Test: This test was used to evaluate exploratory behavior. This apparatus likely consisted of circular arena diameter of 30cm and contained 8 holes (2 cm diameter each). Each mouse was placed in the arena, and the number of times the mouse poked its head into the holes was recorded over a 5-minute period (Al-Shalchi and Mohammad, 2024; Soni and Parle, 2017).

Seizure Assessment

On Day 17, all groups except the positive control were administered pilocarpine (200 mg/kg, i.p.) to induce seizures. The positive control group received diazepam 30 minutes before pilocarpine administered. Following pilocarpine administration, mice were continuously observed for 1 hour for seizure activity (Bröer and Löscher, 2015).

The following parameters were recorded:

Latency to the first convulsion (onset of convulsion): Time elapsed from pilocarpine injection to the first observed seizure.

Numbers of convulsions: The total number of seizures observed during the observation period.

Survival rate: The number of mice surviving the observation period.

Statistical Analysis Data are expressed as mean± standard error of the mean (SEM). Statistical analysis was performed using on-way analysis of variance (ANOVA) followed by appropriate *post hoc* tests for multiple comparisons. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Open Field Test

Horizontal activity (Locomotion): The control group exhibited a baseline horizontal activity of 76.75±7.74 squares crossed. The 5mg/kg serratiopeptidase group showed a moderate increase in horizontal activity (91.25±8.22 squares crossed) compared to the control group. The 10mg/kg serratiopeptidase group displayed a slight decrease in horizontal activity (83.25± 8.52 squares crossed) compared to the 5mg/kg group, but still higher than the control group. The 20 mg/kg serratiopeptidase group demonstrated the highest horizontal activity (96.13±6.65 squares crossed).

Vertical activity (Exploration/ Rearing): The 5mg/kg serratiopeptidase group exhibited a moderate increase in vertical activity (20.75±2.50 rearing) compared to the control. Both the 10 mg/kg (22.38±4.56 rearing) serratiopeptidase groups displayed further increases in vertical activity.

Negative Geotaxis Test

The results of the 15-day oral administration of serratiopeptidase on motor coordination and exploratory behavior in mice are summarized in Table 2. In the Negative Geotaxis test, control mice demonstrated a mean latency of 8.00 ± 4.27 seconds. Treatment with serratiopeptidase at 5 mg/kg and 10 mg/kg resulted in slight, non-significant increases in latency to 10.40 ± 2.61 and 11.60 ± 6.60 seconds, respectively, suggesting a mild delay in motor response. However, at the highest dose of 20 mg/kg, the latency was markedly reduced to 4.80 ± 1.20 seconds, indicating an apparent improvement in motor coordination compared to the control, although this difference was not statistically significant.

Head Poking Test

In the Head Poking test, which reflects exploratory behavior and general activity, the control group showed 10.20 ± 2.71 pokes in 3 minutes. Serratiopeptidase treatment at increasing doses induced a dose-dependent rise in head poking behavior: 11.40 ± 2.63 (5 mg/kg), 13.40 ± 1.40 (10 mg/kg), and significantly up to 17.40 ± 2.10 pokes at 20 mg/kg ($p \leq 0.05$). This statistically significant increase at the highest dose indicates a stimulatory effect of serratiopeptidase on exploratory activity, which may reflect enhanced cognitive engagement or reduced anxiety-like behavior in mice.

Pilocarpine- induced Seizure Model

Negative control Mice in this group experienced rapid onset of convulsion (8 minutes), a high number of seizures (10.3), and a survival rate of 6/8 (75%). This reveals the baseline effect of pilocarpine.

Positive control (Diazepam) this group significantly delayed the onset of convulsions (32.75 minutes) and reduced the number of seizures (5.8). All mice in this group survived (8/8, 100%), revealing the effectiveness of diazepam as an anticonvulsant.

Serratiopeptidase

5 mg: delayed the onset of convulsion (14.5 minutes) and reduced the number of seizures (4.5) compared to the negative control. However, the survival rate was lower (4/8, 5%).

10 mg and 20 mg; Both doses significantly delayed the onset of convulsion (24.5 and 24.25 minutes, respectively) and reduced the number of seizures (3.5 in both cases). The survival rate in both groups was 8/8 (100%), comparable to the positive control.

Table 1 The influence of oral serratiopeptidase (15 day of administration) on motor activity and exploratory behavior in mice

Parameters / Groups	Horizontal Activity (Squares Crossed)	Vertical Activity (Rearings)
Control Group	76.75 ±7.74	16.00 ±2.67
Serratiopeptidase (5mg/kg)	91.25 ±8.22	20.75 ± 2.50
Serratiopeptidase (10mg/kg)	83.25 ±8.52	22.38 ± 4.56
Serratiopeptidase (20mg/kg)	96.13 ±6.65	24.25 ±1.68

10 mg and 20 mg: Both doses significantly delayed the onset of convulsions (24.5 and 24.25 minutes, respectively) and reduced the number of seizures (3.5 in both cases). The survival rate in both groups was 8/8 (100%), comparable to the positive control.

The data are mean ± SE of 8 mice/group.

Table 2 The effect of 15-day oral administration of serratiopeptidase on negative geotaxis test and gead poking test

Parameters / Groups	Negative Geotaxis\60 sec	Head Poking \3 min
Control	8.00 ± 4.27	10.20± 2.71
Serratiopeptidase (5 mg/kg)	10.40 ± 2.61	11.40 ± 2.63
Serratiopeptidase (10 mg/kg)	11.60 ± 6.60	13.40± 1.40
Serratiopeptidase (20 mg/kg)	4.80 ± 1.20	17.40± 2.10*

The data are mean ± SE of 8 mice/group
* Significantly different from the data of control group at ($p \leq 0.05$).

Table 3 The effect of serratiopeptidase (15 day of administration) on the convulsion induced by pilocarpine 200 mg/kg

	Onset of Convulsion (minute)	Number of Convulsions	Survival Percentage
Negative Control (Distilled Water)	8.00±2.0	10.3±2.1	6/8
Positive Control (Diazepam 1mg/kg IP)	32.75±3.2*	5.8±1.2*	8/8
Serratiopeptidase (5 mg)	14.50±2.7*A	4.5±0.6*	4/8
Serratiopeptidase (10 mg)	24.50±2.4 *AB	3.5±0.4*	8/8
Serratiopeptidase (20 mg)	24.25±0.5*A B	3.5±0.3*	8/8

The data are mean ± SE of 8 mice/group.

* Significantly different from the data of control group at ($p \leq 0.05$).
A Significantly different from the data of positive control at ($p \leq 0.05$).
B Significantly different from the data of group of 5 mg at ($p \leq 0.05$).

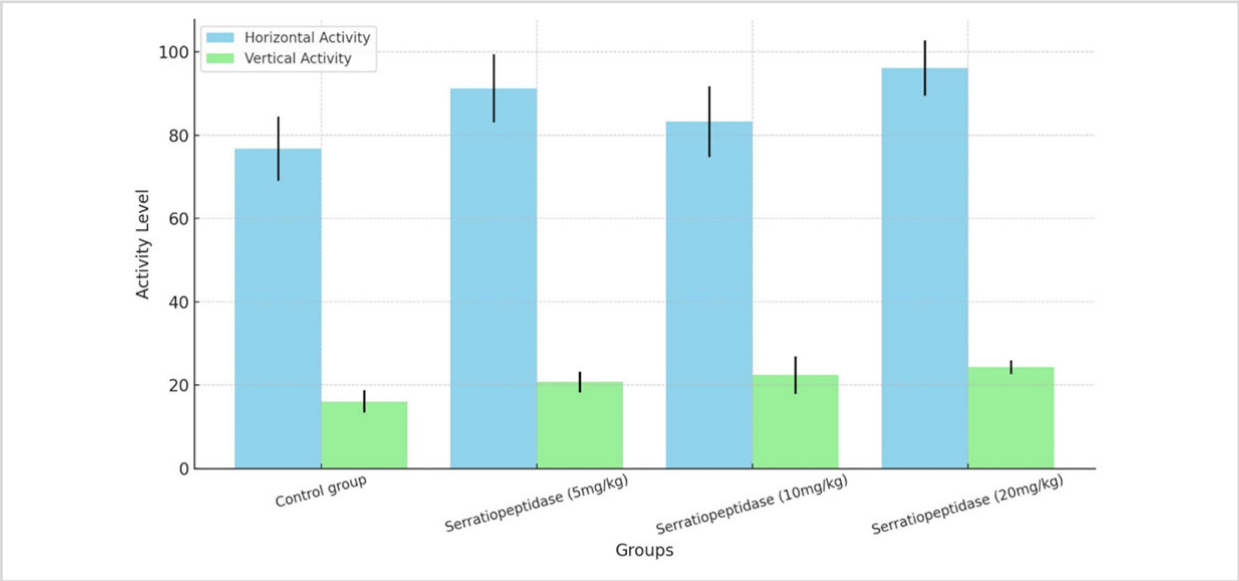

Figure 1 Effect of serratiopeptidase on motor activity in mice

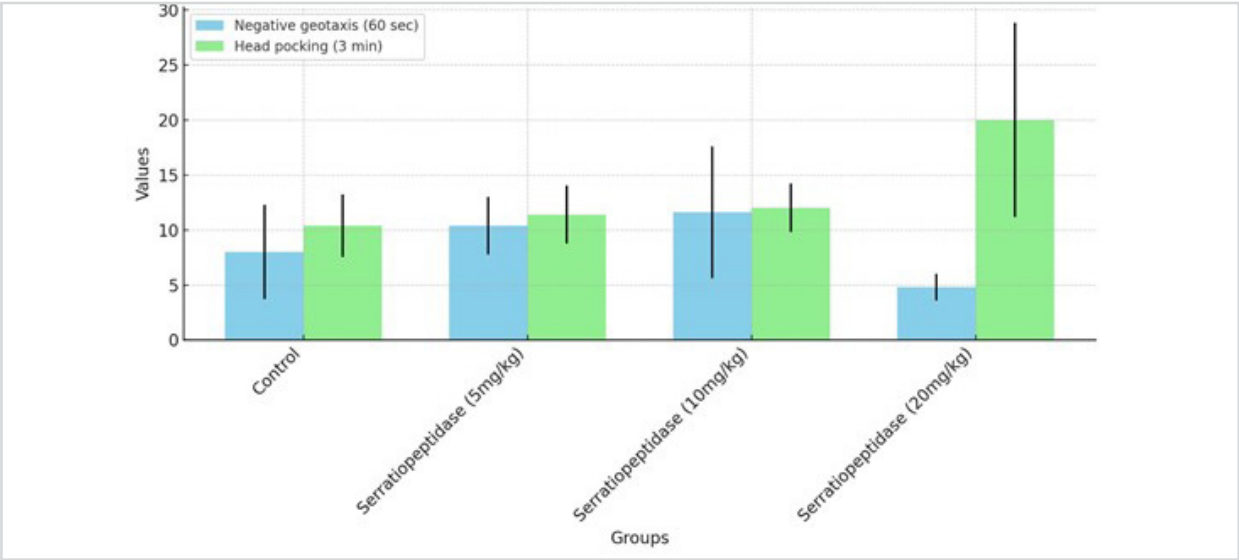

Figure 2 Effect of serratiopeptidase on negative geotaxis and head poking tests

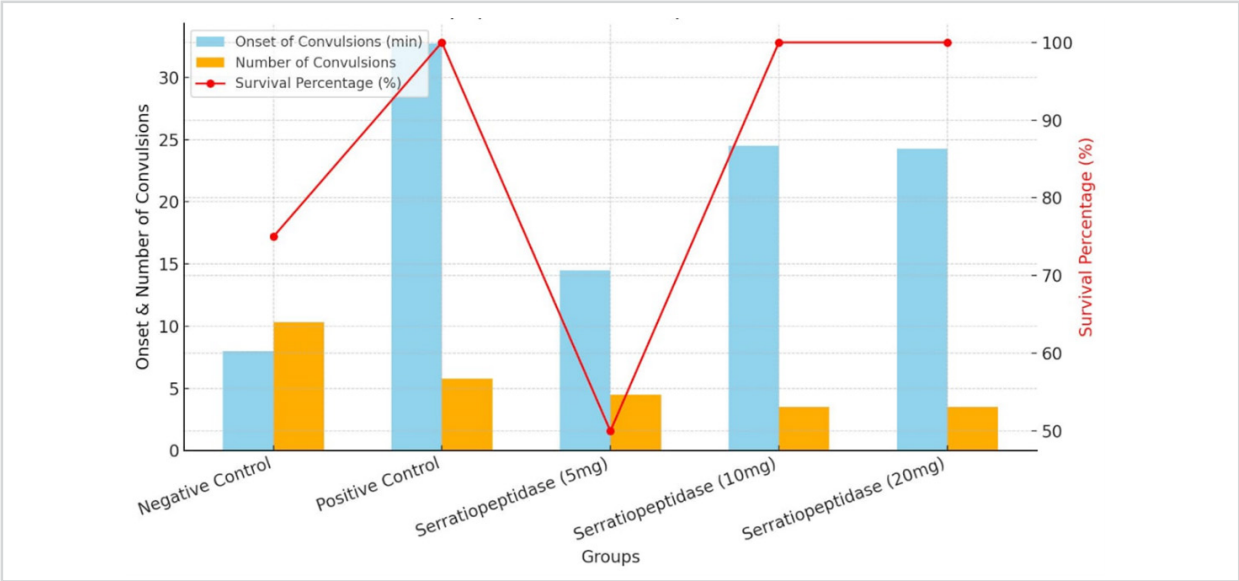

Figure 3 Effect of serratiopeptidase on pilocarpine-induced convulsions

DISCUSSION AND CONCLUSION

This study investigated the impacts of repeatedly orally administered serratiopeptidase on motor activity, exploration behavior and its possible anticonvulsant efficacy in a pilocarpine-induced seizures model in mice. The findings provide evidence that serratiopeptidase can modulate motor function, exploration and exert protective effects against pilocarpine-induced seizures.

Effect on motor activity: The results revealed a significant increase in both horizontal and vertical motor activity in mice treated with serratiopeptidase compared to the control group. Several potential mechanisms could underlie these observed effects. Serratiopeptidase is known for its anti-inflammatory properties (Nair, 2022). It is possible that subtle, subclinical inflammation could be affecting motor function and exploratory drive (Cordone, 2024; Jia, 2022), and the anti-inflammatory effect of serratiopeptidase could be mitigating this. Alternatively, serratiopeptidase may influence neurotransmitter system involved in motor control and behavior, such as dopaminergic or serotonergic systems (Ahmed et al., 2013; Naser, 2024). Many studies demonstrated serratiopeptidase having an inhibitory effect on brain cholinesterase, which is responsible for degradation of excitatory neurotransmitter acetylcholine (Jadhav et al., 2020; Naser and Albadrany, 2024). Future studies exploring these mechanisms are necessary to fully elucidate the underlying processes.

The results of Negative Geotaxis and Head Poking test present a complex picture of serratiopeptidase's effects on motor coordination and exploratory behavior. The Negative Geotaxis effect test results suggest a biphasic dose response. While the lower doses (5 mg and 10 mg) seemed to impair motor coordination (though not statistically significant), the highest dose (20 mg) appeared to improve it. This non-linear dose response warrants further investigation to understand the underlying mechanism. At the lower doses of 5 mg and 10 mg, the slight increase in time suggests a possible negative effect on motor coordination or muscle strength at these doses. This could be to various reasons such as mild muscle relaxation; serratiopeptidase has some anti-inflammatory effects, which might lead to mild muscle relaxation at doses, slightly hindering the mice's ability to quickly turn over (Malanga

and Wolff, 2008; Malm and Borisch, 2015). Another reason, interference with nerve signaling; it's possible that doses subtly interfere with nerve impulses involved in motor control. High dose of 20mg effect, the significant decrease in time, is intriguing. It suggests a potential improvement in motor function. This could be due to:enhancement of muscle strength or coordination or stimulatory effect on the nervous system (Sheffler and Chae, 2007). The head poking reveals a different pattern. The highest dose of serratiopeptidase lead to a significant increase in head pokes, suggesting increase exploratory and/or potentially anxiety-related behavior. This finding raises concerns about potential behavioral side effects of higher doses of serratiopeptidase. High dose of 20 mg's effect of the substantial increase to 17.4 poks is particularly noteworthy, which may be due to exacerbations of underlying neurological processes. If these mice have an underlying predisposition to repetitive movements (which is common in some mouse strains) (Barr and Barbe, 2002; Moy et al., 2008), the serratiopeptidase might be exacerbating those tendencies. Other interpretation relatesto inducing or unmasking repetitive behavior; it's possible that the high dose directly induces these repetitive movements, or unmasks them by affecting certain brain circuits (Rossini and Pauri, 2000; Shadmehr, 2017).

Several factors could contribute to those observed effects. The anti-inflammatory properties of serratiopeptidase is one of them: The varying effects at different doses could be related to the modulation of inflammatory pathways at different concentrations. Furthermore, it's possible that serratiopeptidase interacts with the neurotransmitter system like dopamine, serotonin, or acetylcholine. Different doses could differentially affect these systems. Although the behavioral data at 20 mg/kg suggest functional enhancement, the exaggerated head-poking behavior raises concerns regarding potential neurotoxicity. High doses of proteolytic enzymes may exert off-target effects, such as degradation of extracellular matrix proteins or interference with synaptic structure and function (Rudmann, 2013). Furthermore, overactivation of microglia or astrocytes in response to enzymatic stress could paradoxically induce neuroinflammation, disrupting neural circuitry and promoting abnormal behavior (Barr and Barbe, 2002; Moy et al., 2008).

The study also revealed that serratiopeptidase possessed significant anticonvulsant activity in the pilocarpine-induced seizure model. Pretreatment with serratiopeptidase resulted in a significant delay in the onset of convulsions and a reduction in the number of seizures compared with negative control group. Notably, the 10 and 20 mg/kg doses of serratiopeptidase exhibited comparable efficacy to diazepam, a commonly used benzodiazepine anticonvulsant, in reducing seizure severity and improving survival rates. These findings suggest that serratiopeptidase may offer a therapeutic benefit in the management of seizure. The potential mechanism underlying these anticonvulsant impacts may include modulation of neurotransmitter systems (Sills & Rogawski, 2020). Pilocarpine induces seizure by activating cholinergic muscarinic receptors, and serratiopeptidase may interfere with this process by modulating cholinergic neurotransmission, or by affecting other neurotransmitter systems involved in seizure generation and propagation, such as GABAergic or glutamatergic systems (Akyuz et al., 2021). Neuroinflammation and oxidative stress play a crucial role in the pathophysiology of seizures (Parsons et al., 2022). Serratiopeptidase's known anti-inflammatory and antioxidant properties could contribute to its anticonvulsant effects by mitigating these pathological processes. Concerning the blood- brain barrier modulation, some studies suggest that serratiopeptidase may enhance drug delivery across the blood-brain barrier (Tiwari, 2017). This potentially facilitates the access to endogenous anticonvulsant substances or improves the clearance of pro-convulsant substances from the brain.

This study has several limitations, including the use of only male mice, which necessitates further research in humans for broader applicability, as well as the lack of formal seizure-scoring and pharmacokinetic data. Additionally, the precise

mechanism by which serratiopeptidase influences motor activity, coordination, exploratory behavior, and seizures, remains unclear. Future studies should address these gaps by incorporating sham groups, biochemical analyses, and mechanistic investigations.

In conclusion, this study provides evidence that orally administered serratiopeptidase can modulate motor function. Also, serratiopeptidase has dose-dependent effects on motor coordination and exploratory behavior in mice. While the highest tested dose of 20mg appeared to improve motor coordination, it also significantly increased exploratory/repetitive behavior. These findings highlighted the need for careful dose selection and further investigation into the mechanism of action and potential behavioral side effects of serratiopeptidase. Finally, serratiopeptidase exerts anticonvulsant activity in a pilocarpine-induced seizure model in mice. These findings suggest that serratiopeptidase may have a potential for management of seizure disorders.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CONTRIBUTIONS

Authors: YMAh and ASN contributed equally in all aspects.

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EFEKTI ORALNE APLIKACIJE SERATIOPEPTIDAZE NA MOTORNU AKTIVNOST, EKSPLORATIVNO PONAŠANJE I SKLONOST KONVULZIJAMA KOD MIŠEVA

SAŽETAK

U ovom istraživanju ispitivani su efekti oralno aplicirane seratiopeptidaze na motornu aktivnost, koordinaciju, eksplorativno ponašanje i sklonost konvulzijama kod miševa. Mužjacima švicarskih albino miševa (n=8 po grupi) su oralnom sondom aplicirane doze od 5, 10 i 20 mg/kg u trajanju od 15 dana. Kontrolnoj grupi je apliciran isti volumen destilirane vode. Motorna aktivnost je procijenjena testom otvorenog polja, pri čemu su zabilježene horizontalna (broj pređenih kvadratića) i vertikalna (broj podizanja) aktivnost. Motorna koordinacija i eksplorativno ponašanje su procijenjeni korištenjem negativne geotaksije i testom guranja glave. Potom je miševima aplicirano 200 mg/kg pilokarpina. Zabilježeni su početak konvulzija, broj konvulzija i stopa preživljenja. Dijazepam (1mg/kg) je služio kao pozitivna kontrola. Seratiopeptidaza je signifikantno povećala horizontalnu i vertikalnu aktivnost na testu otvorenog polja i poboljšala eksplorativno ponašanje, posebno u dozi od 20 mg/kg. Zabilježena su i poboljšanja u motornoj koordinaciji, iako je postojao bifazni odgovor na dozu. Značajno je da je seratiopeptidaza signifikantno odložila početak konvulzija, smanjila njihovu učestalost i poboljšala stope preživljenja - efekti koji su bili komparabilni s dijazepamom u dozama od 10 i 20 mg/kg. Ovakvi rezultati sugeriraju da oralna primjena seratiopeptidaze može pozitivno modulirati motornu funkciju kod miševa, štoviše, seratiopeptidaza posjeduje antikonvulzantna svojstva i može imati ulogu potencijalnog terapijskog agensa za kontrolu konvulzija. Potrebna su daljnja istraživanja kako bi se razjasnio tačan mehanizam djelovanja i istražila translacijska relevantnost ovih nalaza.

Ključne riječi: Konvulzija, miševi, pilokarpin, seratiopeptidaza, test otvorenog polja