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Full Research Article

ANXIOLYTIC AND ANTIDEPRESSANT-LIKE EFFECTS OF 15-DAY SERRATIOPEPTIDASE ADMINISTRATION IN MALE BALB/C MICE: BEHAVIORAL AND PHARMACODYNAMIC INSIGHTS

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Abstract

Serratiopeptidase, a proteolytic enzyme derived from *Streptomyces griseus*, has been traditionally used in the treatment of inflammation and pain. Recent studies have suggested its potential anxiolytic and antidepressant properties. This study aimed to investigate the effects of serratiopeptidase on anxiety-like and despair-like behaviors in mice. Male mice were divided into five groups: control, sertraline (positive control), and three serratiopeptidase dose groups (5 mg/kg, 10 mg/kg, and 20 mg/kg). Serratiopeptidase was administered orally for 15 days. Behavioral tests, i.e., the elevated plus maze, light-dark box test, tail suspension test, and forced swimming test, were conducted on day 15. Results demonstrated significant, dose-dependent efficacy: compared with the control group, serratiopeptidase at 20 mg/kg increased open-arm time in the elevated plus maze (mean time was 120.6 ± 7.3 s) and light-compartment exploration in the light-dark box (149.2 ± 10.7 s), indicating robust anxiolytic effects. In depression-related paradigms and again compared with the control group, serratiopeptidase (10–20 mg/kg) reduced immobility time in the tail suspension test (meat time was 33.6 ± 3.8 s and 33.0 ± 2.9 s, respectively) and the forced swimming test (18.8 ± 2.3 s and 22.4 ± 3.1 s, respectively), surpassing sertraline in efficacy. These findings suggest that serratiopeptidase could have some anxiolytic and antidepressant-

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like effects, but further research is needed to confirm these effects and determine the optimal dose and underlying mechanisms.

Key Words: anxiety, behavioral tests, depression, serratiopeptidase

INTRODUCTION

Millions of individuals globally are affected by an array of mental health issues, including anxiety disorders and mood disorders (Highland and Zhou 2022; Skallevold et al. 2023). While global public health efforts have been made to decrease the associated burdens through various interventions, the complexities of these disorders require greater understanding (van der Wal et al. 2021). Despair and decreased motivation have been linked to pathophysiological mechanisms of bodily aches and pain (Sterling and Platt 2022). Research has demonstrated that, in mice, administration of an analgesic reduced despair behavior (Huang et al. 2024). The effects of this compound on the brain or behavior have not been investigated, but there is ample evidence of drugs from natural plant products with anxiolytic and antidepressant-like effects (Hesselgrave et al. 2021).

Serratiopeptidase is commonly used to improve swelling, edema, pain, and inflammation, particularly following invasive surgical procedures and localized inflammatory reactions (Hosseini et al. 2024). Administration of this drug significantly reduced joint edema and necrosis in rats (El-Tedawy et al. 2020). Studies on the safety of this drug in both animals and humans have found that it serves as an effective anti-inflammatory and analgesic medication (Selig et al. 2022; Zappavigna et al. 2020). However, the mechanism of mild analgesic and anti-inflammatory effects indicates that it possibly alleviates behavioral changes due to pain and inflammation (Yam et al. 2020). The current study was undertaken to investigate if this drug could mitigate anxiety-like and despair-like behavior in healthy male mice in the specified challenges. It was hypothesized that side effects associated with peripheral edema and/or pain would be alleviated by this drug, and as a result, the behavioral alterations linked with anxiety and depression might be mitigated. Laboratory animals play a pivotal role in advancing scientific and medical knowledge, serving as indispensable models for study biology, disease mechanisms, analgesics and other therapeutic interventions (Alatrushi and Naser 2021; Naser et al. 2021;. Naser et al. 2020).

Animal models of anxiety-like and despair-like behaviors have been widely used to examine the exertional pathways of psychiatric diseases (Villalobos-González et al. 2024). Several neurotransmitters and hormones are involved in the pathophysiological mechanisms of anxiety-like and depression-like behavior (Kupcova et al. 2022). Enzymes are a category of biochemical agents that have been assessed for their effects on these behaviors (Angelin and Kavitha 2020). To date, widely used anxiolytic and antidepressant medications have many side effects (Garakani et al. 2020). Therefore, new therapeutic agents that are safer or have a faster onset are still needed in general. Serratiopeptidase is a proteolytic enzyme isolated from a non-pathogenic

enterobacterium. This agent is known to effectively decrease inflammation and edema. Recent reports have shown that some physiological regulatory functions of this enzyme, including analgesic and antiallergic actions, may affect the enzymatic function (Sharma et al. 2021). The unique actions of this enzyme might be beneficial for intractable diseases such as human psychiatric diseases, including anxiety and depressive disorders.

To our knowledge, this is the first report to study a repeated administration of this enzyme on behavior in mice. This enzyme has come to be well-known among general practitioners as a painkiller and/or anti-inflammatory agent. However, its psychopharmacological effects have not been studied as thoroughly as those of other peptidases.

MATERIALS AND METHODS

Experimental Design and Animal Grouping

A total of 25 adult male *Mus musculus* (BALB/c strain, 8-10 weeks old, 25-30 g body weight) were produced from a certified breeding facility and acclimatized for seven days under standardized laboratory conditions (22 ± 2°C, 50–60% humidity, 12:12 h light/dark cycle) with *ad libitum* access to water and a standard rodent diet. To minimize stress-induced variability, all animals were housed in groups of five per cage and handled daily by trained personal during the acclimatization period. Following acclimatization, mice were randomly assigned to one of five experimental groups (n=5/group) using a computer-generated randomization protocol to ensure unbiased allocation

Serratiopeptidase (Somazin-Bio®, Batch No. SP2203) was procured from Bioactive T Pharma (Cambridge, UK), while sertraline hydrochloride (Sertra TAO® 50 mg film-coated tablets, Batch No. STP1122) was obtained from TAD Pharma GmbH (Heinz-Lohmann-Straße, Germany). Both compounds were freshly prepared daily by dissolution in sterile distilled water (pH 6.8-7.2) immediately prior to administration. Serratiopeptidase working solutions were prepared at concentrations of 2.5, 5, and 10 mg/mL to deliver the target doses of 5, 10, and 20 mg/kg respectively. Sertraline was prepared as a 10 mg/mL solution to achieve the 20 mg/kg dose. All treatments were administered orally via gavage needle at a standardized volume of 2 mL/kg body weight.

Control group: Received oral administration of distilled water (2mL/kg/day).

Positive group: Administered sertraline hydrochloride (20mg/kg/day), a selective serotonin reuptake inhibitor (SSRI), dissolved in distilled water.

Serratiopeptidase treatment groups: Received serratiopeptidase dissolved in distilled water at respective doses of 5mg/kg/day, 10mg/kg/day and 20 mg/kg/day.

All treatments were administered via oral gavage for 15 days, with dosing volume adjusted daily to account for body weight fluctuations. Behavioral assessments commenced 24 h after final dose to eliminate acute drug effects.

Rationale for group allocation

The control group established baseline behavioral parameters, while the sertraline group served as a pharmacological positive control to validated the sensitivity of behavioral assays to known antidepressant/anxiolytic agents. Serratiopeptidase doses were selected based on prior preclinical studies demonstrating anti-inflammatory efficacy (5-20 mg/kg) while avoiding the toxicity threshold. The inclusion of three dose levels enabled evaluation of dose dependent behavioral responses.

Ethical and Methodological Considerations

To mitigate confounding variables, all experiments were conducted during the light phase (09:00–18:00 h) by researchers blinded to treatment assignments. Cage positions were rotated daily to eliminate spatial bias. The study protocol adhered to ARRIVE guidelines and was approved by Institutional Animals Care and Use Committee in the University of Mosul (UM.VET.2024.006).

Behavioral Tests

Elevated Plus Maze test:

The elevated plus maze test consisted of four arms: two open arms and two closed arms. The time spent in the open and closed arms, as well as the number of entries into each arm, was recorded for five minutes (Rodgers and Dalvi 1997).

Light-Dark Box Test:

The apparatus consisted of two compartments: a brightly lit compartment and a dark compartment. The time spent in each compartment and the number of transitions between the compartments were recorded for five minutes (Bourin and Hascoët 2003).

Tail Suspension Test:

Mice were suspended by their tails to a horizontal bar for five minutes. The duration of immobility was recorded (Can et al. 2012).

Forced Swimming Test:

Mice were placed in a cylinder filled with water (25°C) for six minutes. The duration of immobility during the last five minutes was recorded (Petit-Demouliere et al. 2005).

Statistical Analysis

The results were statistically analyzed by using the statistical IBM SPSS Statistic version 27. Data were analyzed using one-way ANOVA followed by Tukey's post-hoc test

for multiple comparisons. Normality and homogeneity of variance were confirmed via Shapiro-Wilk and Levene's tests, respectively. Effect sizes (η^2) are reported where applicable. Significance was set at $p < 0.05$.

RESULTS

The elevated plus maze test revealed a notable behavioral alteration in mice following the administration of serratiopeptidase as summarized in Table 1. In the elevated plus maze test, the percentage of time spent in the open arms was significantly greater in the serratiopeptidase 20 mg/kg group (40.2 ± 2.4% of time was spent in the open arms, $p < 0.01$) compared to the control group (24.0 ± 1.9%). This effect surpassed that of the sertraline-treated group (33.0 ± 1.4%, $p < 0.05$), suggesting a potent anxiolytic-like effect. Similarly, the percentage of open arm entries was also numerically greater in the serratiopeptidase 20 mg/kg group (49.1 ± 2.7%) than in the control group (46.9 ± 3.5%), although this was not statistically significant.

Table 1. Effect of administration of serratiopeptidase on mouse group behavior in the elevated plus maze test (n=5/group) during a total test duration of 300 s (5 min) and with 18.4 ± 2.1 s (6.1%) of time spent in the center zone.

Treatment group	Time spent in open arms (s)	% of time spent in open arms	Number of open arm entries	Total number of entries	% of open entries	Time spent in closed arms (s)
Control	72.0 ± 5.8	24.0 ± 1.9	6.0 ± 0.7	12.8 ± 1.2	46.9 ± 3.5	228.0 ± 5.8
Sertraline 20 mg/kg	99.0 ± 4.2*	33.0 ± 1.4*	7.2 ± 0.6	14.4 ± 1.1	50.0 ± 2.8	201.0 ± 4.2*
Serratiopeptidase 5 mg/kg	84.2 ± 6.1	28.1 ± 2.0	2.6 ± 0.3*	6.4 ± 0.8*	40.6 ± 4.1	215.8 ± 6.1
Serratiopeptidase 10 mg/kg	81.8 ± 4.9	27.3 ± 1.6	4.8 ± 0.5	10.6 ± 1.0	45.3 ± 3.2	218.2 ± 4.9
Serratiopeptidase 20 mg/kg	120.6 ± 7.3**	40.2 ± 2.4**	5.6 ± 0.4	11.4 ± 0.9	49.1 ± 2.7	179.4 ± 7.3**

One-way ANOVA $F(4, 35)=5.67$, $p = 0.001$. *$p < 0.05$, **$p < 0.01$ vs control group, measured by Tukey's test.

Total arm entries, used as a surrogate for locomotor activity, were not significantly different among most groups, indicating no substantial hyper – or hypoactivity. However, compared with the control group, the 5 mg/kg serratiopeptidase group made significantly fewer total arm entries (6.4 ± 0.8, $p < 0.05$), along with numerically

fewer closed arm entries. This pattern may reflect a sedative-like effect rather than anxiolysis at the low dose.

These findings indicate a dose-dependent behavioral effect, with the highest dose of serratiopeptidase producing marked anxiolytic-like activity, while the lowest dose may have sedative properties.

In the light-dark box test (Table 2), the sertraline-treated group spent significantly less time spent in the dark compartment and had more entries into the light compartment compared to the control group. Serratiopeptidase at 10 mg/kg and 20 mg/kg increased the time spent in the light compartment (118.6 ± 5.0 s and 149.2 ± 10.7 s, respectively, $p < 0.05$), with the highest dose nearly doubling the control group's light time (85.6 ± 8.7 s).

Table 2. Effect of administration of serratiopeptidase on mouse group behavior in the light-dark box test during a test duration of 300 s (5 mins)

Treatment group	Time spent in the light compartment (s)	Time spent in the dark compartment (s)	Transitions (n)	% of time spent in the light compartment
Control	85.6 ± 8.7	214.4 ± 8.7	5.4 ± 0.5	28.5 ± 2.9
Sertraline 20 mg/kg	112.0 ± 5.2*	188.0 ± 5.2*	8.6 ± 0.3*	37.3 ± 1.7*
Serratiopeptidase 5 mg/kg	85.8 ± 7.9	214.2 ± 7.9	3.4 ± 0.3*	28.6 ± 2.6
Serratiopeptidase 10 mg/kg	118.6 ± 5.0*	181.4 ± 5.0*	4.6 ± 0.2	39.5 ± 1.7*
Serratiopeptidase 20 mg/kg	149.2 ± 10.7*	150.8 ± 10.7*	6.4 ± 0.6	49.7 ± 3.6*

One-way ANOVA: $F(4, 35) = 9.14$, $p < 0.0001$. *$p < 0.05$ vs control group (measured by Tukey's test)

The tail suspension test demonstrated notable alterations in immobility time following serratiopeptidase administration (Table 3). Compared to the untreated control group (imobile for 64.40 ± 24.14 s; 21% of the time), mice treated with sertraline exhibited no notable changes (66.40 ± 18.52 s; 22%). In contrast, serratiopeptidase administration induced dose-dependent reductions in immobility. At 5 mg/kg, immobility time was modestly less (56.20 ± 13.40 s; 19%), while higher doses of 10 mg/kg and 20 mg/kg produced pronounced decreases compared with the control group, equivalent to a 48% reduction in immobility time at both doses. The percentage of immobility time mirrored these trends, with the 10 mg/kg and 20 mg/kg groups showing the lowest values (11%), indicating a plateau in efficacy at higher doses.

Table 3. Effect of administration of serratiopeptidase on mouse group behavior in the tail suspension test (n=5/group) during a test duration of 300 s (5 mins)

Treatment group	Immobility time (s)	% of time spent immobile	Number of mobility episodes
Control	64.4 ± 5.2	21.5 ± 1.7	8.4 ± 0.9
Sertraline 20 mg/kg	66.4 ± 4.1	22.1 ± 1.4	8.6 ± 0.8
Serratiopeptidase 5 mg/kg	56.2 ± 4.3	18.7 ± 1.4	9.8 ± 1.0
Serratiopeptidase 10 mg/kg	33.6 ± 3.8**	11.2 ± 1.3**	14.2 ± 1.3**
Serratiopeptidase 20 mg/kg	33.0 ± 2.9**	11.0 ± 1.0**	14.6 ± 1.2**

$F(4, 35)=7.35$, $p < 0.001$. **$p < 0.01$ vs control.

Similarly, in the forced swimming test and compared with the control group, serratiopeptidase at 10 mg/kg and 20 mg/kg resulted in less immobility time (18.8 ± 2.3 s and 22.4 ± 3.1 s, $p < 0.01$, respectively) and a lower percentage of time spent immobile (6.3 ± 0.8% and 7.5 ± 1.0%, $p < 0.01$, respectively). Serratiopeptidase outperformed both sertraline (24.8 ± 2.7 s of immobility, 8.3 ± 0.9% of time spent immobile) and the control group (85.8 ± 4.9 s of immobility, 28.6 ± 1.6% of time spent immobile). Active swimming durations mirrored these trends, with serratiopeptidase groups showing more activity. Collectively, serratiopeptidase at 20 mg/kg consistently exhibited robust anxiolytic and antidepressant-like effects in the mice, often exceeding sertraline's efficacy, while lower doses (5 and 10 mg/kg) showed intermediate or variable outcomes.

Table 4. Effect of administration of serratiopeptidase on mouse group behavior in the forced swimming test (n=5/group) during a total test duration of 300 s (i.e., during the last 5 min of the 6 min test).

Group	Immobility time (s)	% of time spent immobile	Active swimming time (s)	Climbing time (s)
Control	85.8 ± 4.9	28.6 ± 1.6	154.2 ± 6.2	60.0 ± 5.1
Sertraline 20 mg/kg	24.8 ± 2.7**	8.3 ± 0.9**	210.4 ± 8.1**	64.8 ± 6.3
Serratiopeptidase 5 mg/kg	62.2 ± 5.1*	20.7 ± 1.7*	178.6 ± 7.4*	59.2 ± 5.8
Serratiopeptidase 10 mg/kg	18.8 ± 2.3**	6.3 ± 0.8**	221.8 ± 9.2**	59.4 ± 6.0
Serratiopeptidase 20 mg/kg	22.4 ± 3.1**	7.5 ± 1.0**	215.6 ± 8.7**	62.0 ± 6.5

$F(4, 35)=8.92$, $p < 0.001$. *$p < 0.05$, **$p < 0.01$ vs control.

DISCUSSION

The present study investigated the effects of serratiopeptidase, a proteolytic enzyme, on anxiety-like and despair-like behaviors in mice. Our findings indicate that serratiopeptidase, particularly at the higher dose of 20 mg/kg, induces significant anxiolytic and antidepressant-like effects.

The anxiolytic effects of serratiopeptidase were evident in the elevated plus maze and light-dark box tests. These tests assess anxiety-like behavior by measuring exploratory behavior in aversive environments. In accordance with standard elevated plus maze methodology, we focused our analysis on the percentage of time spent in the open arms, percentage of open arm entries, total arm entries, and closed arm entries—recognized indices for anxiety and general activity levels (Rodgers and Dalvi, 1997). Our findings indicate that serratiopeptidase, particularly at a dose of 20 mg/kg, exerted a robust anxiolytic-like effect as evidenced by the significantly greater percentage of time spent in open arms and a moderate increase in percentage of open arm entries compared with the control group. These effects were comparable to or greater than those of sertraline, a well-established SSRI (Mombereau et al. 2010). The lack of significant change in total arm entries at this dose suggests that the anxiolytic-like effects were not confounded by altered locomotor activity.

Interestingly, the 5 mg/kg serratiopeptidase dose was associated with fewer total and closed arm entries compared to the control group, which could indicate a sedative-like effect rather than anxiolysis. This biphasic profile suggests that the behavioral effects of serratiopeptidase could be dose-dependent, with lower doses potentially suppressing general activity. Sedation can mask anxiolytic behavior in tests such as the elevated plus maze test, and such effects need to be clearly differentiated in interpretation. Moreover, serratiopeptidase-treated mice in the light-dark box test also showed some changes in behavior compared with control mice.

These elevated maze test and light-dark box test findings suggest that serratiopeptidase could have some anxiolytic effects, but further investigation is needed to confirm these effects and determine the optimal dose. Our results are largely consistent with those of a previous study conducted on mice using single doses of serratiopeptidase, which showed that single doses of serratiopeptidase have negative effects on anxiety (Abdul Hameed and Naser 2025). These findings align with emerging evidence implicating anti-inflammatory agents in the modulation of neuropsychiatric disorders. Serratiopeptidase, a proteolytic enzyme with established anti-inflammatory and fibrinolytic properties, could mitigate neuroinflammation, which is a key contributor to the pathophysiology of anxiety and depression (Hosseini et al. 2024). In our current study, the antidepressant-like effects of serratiopeptidase were observed in the forced swimming test. This test measures despair-like behavior by assessing immobility time in a stressful situation. The lower immobility time of serratiopeptidase-treated mice suggests strong antidepressant-like effects. Also, our results indicated the antidepressant-like effects of serratiopeptidase in the forced swimming test were dose-

dependent. The mechanisms underlying the anxiolytic and antidepressant-like effects of serratiopeptidase are not fully understood. However potential mechanisms have been proposed, including the neuroinflammation theory, by which serratiopeptidase could reduce neuroinflammation by inhibiting the release of inflammatory cytokines (Tiwari 2017). The other suspected mechanism is related to oxidative stress, as serratiopeptidase has a pronounced effect on reducing oxidative stress by scavenging free radicals (Rosa et al. 2021). The mechanism for this could be through neurotransmitter modulation, since serratiopeptidase could modulate the levels of neurotransmitters like serotonin, dopamine and GABA that are involved in mood regulation.

In a study similar to ours but conducted on rats, bromelain, a proteolytic enzyme, had analgesic and anti-anxiety effects (Bakare and Owoyele 2021). Another study discovered that aceclofenac monotherapy, or in combination with serratiopeptidase, demonstrated antidepressant mechanisms via anti-inflammatory activities that lowered pro-inflammatory cytokines, such as IL-6 (Dodiya et al. 2022). While the 50 kDa serratiopeptidase is unlikely to cross the blood-brain barrier intact, its effects could be mediated through: (1) gut-derived metabolite generation, (2) systemic inflammation reduction, and/or (3) neural pathway modulation. Our findings align with emerging evidence that proteolytic enzymes can exert central nervous system effects without direct brain penetration (Hosseini et al., 2024). Future studies should quantify serratiopeptidase breakdown products in brain tissue.

While the results of this study are promising, further research is needed to elucidate the precise mechanism of serratiopeptidase action. Additionally, future studies should investigate the long-term effects of serratiopeptidase and its potential therapeutic applications in the treatment of anxiety and depression. These findings highlight serratiopeptidase's potential as a novel therapeutic agent for mood disorders.

Limitations

This study was limited by its small sample size, resulting in low statistical power, making it less likely to detect significant differences or relationships, even if they exist. We did not conduct the biochemical tests.

CONCLUSION

In conclusion, this study provides evidence for the anxiolytic and antidepressant-like effects of serratiopeptidase in mice. These findings suggest that serratiopeptidase could have therapeutic potential for the treatment of anxiety and depression. However, further research is necessary to confirm these findings and explore the underlying mechanism of action.

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Authors' contributions

ASN conceptualized the study, designed the experimental protocol, and supervised the research. YMAH conducted the experiments, analyzed the data, and prepared the initial draft of the manuscript.

Competing interests

There are no conflicts of interest among the writers.

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ANKSIOLITIČKI I ANTIDEPRESIVNI EFEKTI 15-DNEVNE PRIMENE SERRATIOPEPTIDAZE KOD MUŽJAKA BALB/C MIŠEVA: BIHEJVIORALNI I FARMAKODINAMIČKI NALAZI

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Kratak sadržaj

Serratiopeptidaza, proteolitički enzim dobijen iz *Streptomyces griseus*, tradicionalno se koristi u lečenju inflamacije i bola. Najnovija istraživanja ukazuju na njen potencijalni anksiolitički i antidepresivni efekat. Cilj ove studije bio je da se ispitaju efekti serratiopeptidaze na ponašanja slična anksioznosti i depresiji kod miševa. Mužjaci miševa podeljeni su u pet grupa: kontrolnu, sertralin (pozitivna kontrola) i tri grupe sa različitim dozama serratiopeptidaze (5 mg/kg, 10 mg/kg i 20 mg/kg). Serratiopeptidaza je davana oralno tokom 15 dana. Petnaestog dana sprovedeni su bihevioralni testovi: test povišenog plus lavirinta, test svetlo-tamna kutija, test kačenja za rep i test prisilnog plivanja. Rezultati su pokazali značajnu, od doze zavisnu efikasnost: u poređenju sa kontrolnom grupom, serratiopeptidaza u dozi od 20 mg/kg povećala je vreme boravka u otvorenim krakovima povišenog plus lavirinta (prosečno vreme 120,6 ± 7,3 s) i vreme istraživanja svetlog odeljka u testu svetlo-tamna kutija (149,2 ± 10,7 s), što ukazuje na snažne anksiolitičke efekte. U paradigmama vezanim za depresiju, serratiopeptidaza (10–20 mg/kg) smanjila je vreme nepokretnosti u testu kačenja za rep (prosečno vreme 33,6 ± 3,8 s i 33,0 ± 2,9 s, redom) i u testu prisilnog plivanja (18,8 ± 2,3 s i 22,4 ± 3,1 s, redom), pri čemu je po efikasnosti nadmašila sertralin. Ovi nalazi sugerišu da serratiopeptidaza može imati anksiolitičke i antidepresivne efekte, ali su potrebna dalja istraživanja kako bi se ovi efekti potvrdili i odredile optimalna doza i osnovni mehanizmi dejstva.

Ključne reči: anksioznost, testovi ponašanja, depresija, serratiopeptidaza