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Original Scientific Article

EVALUATION OF THE THERAPEUTIC EFFECTS OF SERRATIOPEPTIDASE IN CHICKS

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ABSTRACT

Serratiopeptidase is a zinc-containing metalloprotease primarily obtained from *Serratia marcescens* isolated from the silkworm guts. This study aimed to assess the antinociceptive, anti-inflammatory, and antipyretic effects of serratiopeptidase in hen chicks. It included 104 hen chicks weighing 70-90 g. The antinociception efficacy was assessed by electrical-stimulation and hot-water test. Anti-inflammatory efficacy was assessed by formalin test. Assessment of therapeutic and antipyretic efficacy was determined by Baker's yeast-induced pyrexia test. In the electrical-stimulation test, 20 and 40 mg/kg of serratiopeptidase induced an antinociceptive effect in 15% and 18%, respectively. In the hot-water test, this effect was observed in 31 and 82%, respectively. In the first phase of the formalin test, an antinociceptive effect was observed for both doses, whereas in the second stage, an anti-inflammatory effect was observed in 56% and 62%, respectively. Serratiopeptidase produced a novel antipyretic effect for both doses on the Baker's-yeast test, pre- and post-injection of the yeast. It was concluded that serratiopeptidase had good activity against pain and acute inflammation, and for the first time, it was demonstrated that serratiopeptidase ameliorated and prevented hyperthermia.

Key words: serratiopeptidase, protective, fever, chicks, analgesic

INTRODUCTION

For the past three centuries, chickens (*Gallus gallus domesticus*) and chicks have been popular animal models in numerous fields of research (1). They have been widely used in studies involving toxicology, analgesia, anesthesia, anti-anxiety effects, etc. (2, 3, 4). Hence, they were used as a model for the current study.

Enzyme-based treatments are efficient due to their selectivity (5, 6). Enzymes are proteins with catalytic abilities and numerous physiological functions used in modern healthcare (7). In the 1950s, researchers in America discovered that parenteral administration of trypsin might counteract inflammation produced by arthritis, bowel inflammation, and lung infections, as well as healing of post-surgical, traumatic, and sports wounds (8). European and Japanese scientists tested numerous enzymes for possible anti-inflammatory action in the 80s and early 90s, and their findings revealed that serratiopeptidase is the most dynamic enzyme in lowering inflammation reactions (9). Serrapeptase, or serratiopeptidase, is an enzyme isolated from the Enterobacterium *Serratia* E15, which is present in silkworms. Serratiopeptidase is commonly used in surgical operations, orthopedics, dentistry, and gynecology because of its antiedematous, analgesic, and anti-inflammatory properties (5). The exact molecular mechanism of serratiopeptidase as an anti-inflammatory drug remains unclear. On the other hand, serratiopeptidase has been shown to directly influence immune cell mobility. At the site of inflammation, the enzyme governs the recruitment of putative motility modifiers (PMMs) and other cells (10). It has been demonstrated that the gastrointestinal system absorbs serratiopeptidase. Although the absorption from the intestine is not well understood, clathrin-mediated endocytosis may be involved. After being taken orally, it enters the systemic circulation and travels through all tissues without changing. Peak concentrations are reached in an hour within the inflamed tissues (11). In contrast

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to conventional anti-inflammatory medications (NSAIDs), serratiopeptidase does not attach to lipoxygenase (LOX) and prevents the production of LOX-catalyzed specialized pro-resolving mediators (SPM) (12). The enzyme may play a role in restoring tissue homeostasis owing to its distinct mechanism and wide substrate affinity. It is a serine protease with high proteolytic activity that may aid wound cleansing and healing (13) by preventing the release of bradykinin from inflamed tissues, thus reducing pain. It aids blood clot removal and prevents atherosclerosis by dissolving fibrin and dead tissue. It improves microcirculation and reduces edema by hydrolysis of bradykinin, histamine, and serotonin (14). Its effects and mechanisms are the same with numerous analgesic and antipyretic drugs. The current study hypothesized that serratiopeptidase may exhibit antipyretic effects along with its known analgesic and anti-inflammatory effects. The study aimed to assess the analgesic, anti-inflammatory, and antipyretic effects of serratiopeptidase in chicks.

MATERIAL AND METHODS

Animals

One-day-old hen chicks were placed in specialized cages for chick breeding and were kept under standard food, water, and environmental conditions in animal houses until the age of 7 days. The experimental procedures were conducted from this age on.

Ethical approval

Hen chicks were handled under the ethical standards for laboratory animals. Ethical approval was obtained under No. UM.VET.2022.055 from 1/10/2022 from the Medical and Veterinary Research Ethics Committee at the College of Veterinary Medicine at the University of Mosul.

Materials

Serratiopeptidase (somazin-Bio) was obtained from Bioactive T Pharma, United Kingdom. The serratiopeptidase was dissolved in distilled water. Baker's yeast (SAF-INSTANT®) was utilized to produce fever at 135 mg/kg dose and was dissolved in 5 ml of sterile distilled water. Paracetamol was used as an IV solution in 1 g/100 ml dose obtained from Walter Ritter GmbH/Germany. A digital caliper was used to measure the volume of paw edema. A digital thermometer was used to measure the cloacal temperature which reflects the core body temperature. An electro-stimulator device (Harvard Apparatus, USA) was used to conduct the electric-stimulation test.

Evaluation of the analgesic effect of serratiopeptidase by electrical-stimulation test

Eighteen Hen chicks were divided into the following groups: Control - distilled water 5 ml/kg, orally; Serratiopeptidase 20 mg/kg, orally; and Serratiopeptidase 40 mg/kg, orally. Electrical stimulation for pain threshold was measured using a method originally described by Paul-Murphy et al. 1999 (15) with an electrical stimulator. The procedure involves attaching electrodes under the wing region, directly on the skin moistened with normal saline to increase electrical conductivity. The voltage was increased until the chick exhibited wing flapping or calling. Hen chicks were assessed individually an hour after the drug administration. The percentage of analgesic activity was calculated with the following equation:

$$Analgesic\ activity\ \% = \frac{\text{Mean of control group} - \text{Mean of treated group}}{\text{Mean of control group}} \times 100$$

Evaluation of the analgesic effect of serratiopeptidase by hot-water test

Eighteen hen chicks were divided into the following groups: Control - distilled water 5 ml/kg, orally; Serratiopeptidase 20 mg/kg, orally; and Serratiopeptidase 40 mg/kg, orally. The source of pain in this test was heat stimulation. A water bath with a built-in thermostat set at 55-56 °C was used. The bird was lifted by its left foot, whereas the right was submerged in the hot water until the tarsal joint level. A stopwatch was used to record the time of foot withdrawal. If the chick failed to react within 20 s, its' right foot was removed from the hot water and was submerged in water at room temperature for 15 s to be checked for possible heat-induced burns (16). All groups of chicks were evaluated separately one hour after the drug administration.

Evaluation of the anti-inflammatory and analgesic effects of serratiopeptidase by formalin test

Twenty-four hen chicks were divided into the following groups: Control - distilled water 5 ml/kg orally; Standard - meloxicam 5 mg/kg, intraperitoneally; Serratiopeptidase 20 mg/kg, orally; and Serratiopeptidase 40 mg/kg, orally. After one hour of drug administration, the chicks were injected with 0.05 ml of 0.1% formalin in the left foot plantar region to induce acute pain and inflammatory response. Within 3 min of formalin administration, the positive pain response was acknowledged if there was foot raise. The level of inflammation was assessed by foot volume measurement (mm) before and one hour after formalin administration (17, 18, 19, 20). Anti-inflammatory effects were assessed as follows (percentage):

$$Anti-inflammatory\ efficacy\% = \frac{\text{Alteration in foot volume for the control G} - Alteration\ in\ foot\ volume\ for\ the\ serra\ G}{\text{Alteration in foot volume for the control G}} \times 100$$

Evaluation of the therapeutic effect of serratiopeptidase as an antipyretic against Baker's yeast-induced fever in chicks

A thermistor probe was introduced approximately 2 cm into the cloacal opening. The basal cloacal temperatures were documented using a digital thermometer (CE 0434, Taiwan). The chicks were intraperitoneally injected with Baker's yeast (135 mg/kg). The cloacal temperature of each chick was recorded again 4 h after yeast administration (21).

Chicks that did not show a minimum increase of 0.5 °C after 4 hours of yeast injection, were excluded. Hen chicks (n=24) were divided into the following groups: Control - distilled water 5 ml/kg, orally; Standard - Paracetamol 250 mg/kg, intraperitoneally; Serratiopeptidase 20 mg/kg, orally; and Serratiopeptidase 40 mg/kg, orally. After the treatment, the cloacal temperature of each chick was verified by placing a digital thermometer in the cloacal opening and was measured for 4 hours in 1-hour intervals. The cloacal temperature percentage reduction was computed by comparing the total temperature drop to an average level of 100%.

Evaluation of the protective effect of serratiopeptidase as antipyretic against baker yeast-induced fever in chicks

Twenty-four chicks were allocated to four groups as follows: Control - distilled water 5 ml/kg, orally; Standard - paracetamol 250 mg/kg, intraperitoneally; Serratiopeptidase 20 mg/kg, orally; and Serratiopeptidase 40 mg/kg, orally. The chicks were then intraperitoneally injected with Baker's yeast in a dose of 135 mg/kg. The cloacal temperature of each chick was recorded 4 h after yeast administration.

Statistical analysis

The data were statistically analyzed using SPSS version 16.0, and the results are reported as mean ± standard error (mean ± SE). To determine whether there was a significant difference between the groups, one-way and two-way analyses of variance (ANOVA) were employed, followed by Duncan's multiple comparisons within probability level ($p<0.05$).

RESULTS

In the electrical-stimulation test, serratiopeptidase 20 and 40 mg/kg groups showed significant analgesic activity ($p<0.05$) compared to the control group with analgesic efficacies of 15 and 28%, respectively (Table 1).

In the thermal stimulation test, serratiopeptidase 20 and 40 mg/kg groups showed significant analgesic activity ($p<0.05$) compared to the control group with analgesic efficacies of 31 and 84 %, respectively (Table 2).

In the formalin test, serratiopeptidase 20 and 40 mg/kg groups had significantly longer foot reaction

Table 1. Evaluation of the analgesic effect of serratiopeptidase by electrical stimulation test

Treatments	Voltage pain threshold	Percentage of analgesic efficacy (%)
Control group	7.88 ± 0.20^{a}	_
Serratiopeptidase 20 mg/kg	9.10 ± 0.28^{b}	15
Serratiopeptidase 40 mg/kg	10.10 ± 0.21^{b}	28

The data reveal a mean ± SEM of six chicks per group.
Data in each column followed by different superscript small letters are significantly different at $p\leq0.05$

Table 2. Evaluation of the analgesic effect of serratiopeptidase by hot water test

Treatments	Time required to lift foot (sec.)	Percentage of analgesic efficacy (%)
Control group	2.26 ± 0.33^{a}	_
Serratiopeptidase 20 mg/kg	2.96 ± 0.15^{b}	31
Serratiopeptidase 40 mg/kg	4.16 ± 0.14^{bc}	84

The data reveal a mean ± SEM of six chicks per group.
Data in each column followed by different superscript small letters are significantly different at $p\leq 0.05$

Table 3. The anti-inflammatory and analgesic effects of serratiopeptidase in the formalin test

Treatments	Time required to elevate left foot (sec)	Recurrence of elevate foot lifting (No.)	Excess in foot volume (mm)	Anti-inflammatory efficacy (%)
Control group	1.0±0.0[a]	42.8±9.9[a]	0.92±0.17[a]	-
Meloxicam 5 mg/kg	2.1±0.2[b]	24.5±2.3[b]	0.40±0.20[b]	56
Serratiopeptidase 20 mg/kg	3.0±0.6[b]	20.8±5.6[b]	0.30±0.19[b]	67
Serratiopeptidase 40 mg/kg	3.5±0.4[b]	20.2±3.2[b]	0.35±0.17[b]	62

The data reveal a mean ± SEM of six chicks per group.
Data in each column followed by different superscript small letters are significantly different at p≤0.05

Table 4. The effect of serratiopeptidase on the fever induced by baker's yeast

Treatments	BBT Temperature	Temperature After 4 hours	Body temperature			
			1h	2h	3h	4h
Control group	40.1±0.08[Aa]	40.95±0.09[Ba]	41.60±0.09[Ba]	41.80±0.03[Ba]	41.60±0.09[Ba]	41.80±0.03[Ba]
Paracetamol 250 mg/kg	40.2±0.08[Aa]	40.90±0.07[Ba]	40.60±0.07[Ba]	40.40±0.08[Bb]	40.60±0.07[Bb]	40.30±0.08[Bb]
Serratiopeptidase 20 mg/kg	40.2±0.12[Aa]	40.92±0.05[Ba]	40.90±0.05[Bb]	40.90±0.08[Bb]	40.80±0.05[Bb]	40.60±0.06[BCb]
Serratiopeptidase 40 mg/kg	40.2±0.10[Aa]	40.93±0.11[Ba]	40.93±0.09[Bb]	40. 93±0.12[Bb]	40.60±0.09[Bb]	40.40±0.09[BCb]

The data reveal a mean ± SEM of six chicks per group.
Data in each column followed by different superscript small letters are significantly different at p≤0.05
Data in each row followed by different superscript capital letters are significantly different at, p≤0.05

Table 5. The effect of serratiopeptidase on the fever induced by baker's yeast

Treatments	Percentage of reduction (%)			
	1h	2h	3h	4h
Control group	-	-	-	-
Paracetamol 250 mg/kg	43	71	28	14
Serratiopeptidase 20 mg/kg	3	3	16	44
Serratiopeptidase 40 mg/kg	0	0	45	72

%Inhibition = $\frac{B - Cn}{B - A} \times 100$
A: refers to normal body temperature.
B: refers to temperature after fever initiation.
Cn: refers to temperature beyond 60, 120, 180, 360 min

time compared to the control group and had significantly lower occurrences of foot repetitive raising compared to the control group (Table 3). The anti-inflammatory effectiveness for both groups was 67% and 62%, respectively.

The Baker's yeast-induced fever test was observed with a gradual increase of cloacal temperature, peaking at about 4 hours. Serratiopeptidase (20 and 40 mg/kg) groups significantly reduced pyrexia after 4 hours with a maximum inhibition of 72% in the 40 mg/kg group (Table 4). The antipyretic effect of paracetamol 250 mg/kg at 4 hours had considerably reduced the cloacal temperature. Paracetamol 250 mg/kg reduced fever by 71% at 2 hours. Serratiopeptidase 20 mg/kg had antipyretic effects in 3%, 3%, 16%, and 44% at 1, 2, 3, and 4 h, respectively. Serratiopeptidase 40 mg/kg produced an antipyretic effect in 0%, 0%, 45, and 72%, respectively (Table 5).

Serratiopeptidase (20 and 40 mg/kg) significantly prevented the body temperature increase of the chicks injected with the baker yeast solution after one, two, three, and four hours of administration compared to the control. Serratiopeptidase had a similar effect to that of paracetamol (Table 6).

Table 6. The protective effect of serratiopeptidase on the fever induced by baker's yeast

Treatments	Time in hours				
	0	1	2	3	4
Control group	40.25±0.08^{Aa}	40.11±0.10^{Ba}	40.50±0.12^{Ba}	40.65±0.11^{Ba}	40.90±0.10^{Ba}
Paracetamol 250 mg/kg	40.20±0.10^{Aa}	40.30±0.11^{Ab}	40.32±0.08^{Ab}	40.20±0.11^{Ab}	40.22±0.11^{Ab}
Serratiopeptidase 20 mg/kg	40.20±0.17^{Aa}	40.22±0.12^{Ab}	40.28±0.12^{Ab}	40.25±0.12^{Ab}	40.23±0.12^{Ab}
Serratiopeptidase 40 mg/kg	40.22±0.07^{Aa}	40.23±0.11^{Ab}	40.20±0.10^{Ab}	40.22±0.12^{Ab}	40.20±0.09^{Ab}

The data reveal a mean ± SEM of six chicks per group.
Data in each column followed by different superscript small letters are significantly different at $p \leq 0.05$
Data in each row followed by different superscript capital letters are significantly different at, $p \leq 0.05$

DISCUSSION

Acute and chronic inflammatory illnesses are among the world's most serious health concerns. While various drugs are known to treat inflammatory conditions, long-term treatment frequently results in stomach ulcers, bone marrow suppression, and retention of water and electrolytes (22). For this reason, researchers in the field of pharmacology have worked to develop and manufacture anti-inflammatory drugs with fewer side effects. Serratiopeptidase is a natural feed additive (phytobiotic) that could have this effect (23). Our study assessed the antinociceptive, anti-inflammatory, and antipyretic effects of serratiopeptidase in hen chicks. Serratiopeptidase in oral doses of 20 and 40 mg/kg produced a significant increase in pain threshold in chicks that underwent electrical-stimulation test and hot water test. These findings of the current study are in agreement with previous studies on mice (24, 25) and rats (26).

The anti-nociceptive effect of serratiopeptidase is mediated by its inhibitory effect on the release of pain-induced autacoids such as bradykinin, histamine, and serotonin (14). The peak analgesic effect of orally administered serratiopeptidase is achieved at one hour. Serratiopeptidase intestinal absorption was evaluated in lymph, plasma, and inflammatory tissue extracts from rats by sandwich enzyme immunoassay (EIA) (27). Serratiopeptidase is absorbed through the gut and delivered directly into the bloodstream after oral intake (27). However, because this enzyme is a peptide, it is prone to enzymatic breakdown in the gastrointestinal system and has minimal membrane permeability because of the hydrophilic properties (28). This can be a limiting factor for its therapeutic use.

Serratiopeptidase was administered to rats in 1 mg/kg and 30 mg/kg oral doses and was measured in the lymph and plasma, respectively. The levels in the lymph and plasma were dose-dependent. The peak plasma concentration was reached 15-30 minutes after administration and was reduced after 6 h (29). In the formalin test, serratiopeptidase demonstrated an analgesic effect in the first phase and an anti-inflammatory effect in the second phase. Mammdoh et al. (25) suggested that skin ointment containing serratiopeptidase demonstrated anti-inflammatory and analgesic effects in a formalin test conducted on a mouse model. A formalin test conducted on albino rats by Jadav et al. (11) reported that a 20 mg/kg serratiopeptidase dose has a higher effect in reducing edema than a 10 mg/kg. Formalin-induced acute inflammation is caused by cell injury that stimulates the generation of chemical mediators such as bradykinin, 5Hydroxytrptamine, prostaglandins, and histamine (30, 31). Serratiopeptidase hydrolyzes bradykinin, histamine, and serotonin which are causing edema (32, 33).

Fever, or pyrexia, is one of the most important clinical sign that can occur as a result of bacterial, viral, or parasitic infection or as a result of tissue damage, graft rejection, and other pathological conditions (34).

Antipyretics are drugs that reduce elevated body temperature. The regulation of body temperature involves a balance between generating and losing body heat. The hypothalamus organizes the set point at which body temperature is preserved (34). This set point is raised in pyrexia, and nonsteroidal anti-inflammatory drugs such as aspirin enhance its return to normal by inhibiting cyclooxygenase production in the CNS, especially prostaglandin E2 (PGE2), also known as endogenous pyrogen (35). Serratiopeptidase has been previously demonstrated to have pain-relieving and anti-inflammatory

effects, being confirmed in the current research. We expected and developed a hypothesis that it may also counteract fever. Actually, our results supported this hypothesis. Serratiopeptidase showed therapeutic and preventive effects against fever induced by yeast solution. This result has been recorded for the first time in a scientific publication. We propose that this antipyretic property is exerted by inhibition of cyclooxygenase responsible for the formation of prostaglandins from arachidonic acid. The prostaglandin E2 affects the hypothalamus by increasing its set point for body temperature. Another proposed mechanism of action for serratiopeptidase is its inhibition of interleukins, especially interleukin-1, which also affects the hypothalamus (24).

Cyclooxygenase 1 is mostly responsible for the decomposition of arachidonic acid and for the synthesis of nearly all pro-inflammatory and inflammatory mediators (24, 36). Serratiopeptidase is known to attract these molecules and thus exert its anti-inflammatory effect (31). These enzymes act at the site of inflammation, modify cell adhesion molecules, and regulate inflammatory cytokines (37, 38). In the absence of serratiopeptidase, the injury site produces prostaglandins which cause nociception and edema. It is important to note that serratiopeptidase exclusively interacts with the cyclooxygenase pathway and does not affect the lipooxygenase pathway (5, 39).

CONCLUSION

Our results demonstrate that serratiopeptidase has analgesic effects for acute mechano-thermal pain, anti-inflammatory effects for acute inflammation, and antipyretic properties in yeast-induced fever in poultry. These effects of serratiopeptidase along with the no known side effects could be utilized in post-surgical treatments.

CONFLICT OF INTEREST

The authors declare that they have no known conflict of interest in the conduction of the current study.

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AUTHORS' CONTRIBUTION

The authors shared the work equally in designing and conducting the experiments, statistical analysis, and writing.

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