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EFFECTS OF *Androctonus crassicauda* (OLIVIER, 1807) (SCORPIONES: BUTHIDAE) VENOM ON RAT METABOLISM

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ABSTRACT: Scorpions are venomous arthropods of the Arachnida class and are considered relatives of spiders, ticks and mites. There is not any study about the biochemical effects of *Androctonus crassicauda* (Olivier, 1807) venom. Therefore, in the present study, we aimed at evaluating the toxicity of the venom from *A. crassicauda*, which is responsible for a number of deaths of infants, children and adults in tropical and subtropical countries. For this purpose, rats (n=35) were divided into seven groups of five animals each; venom solutions (250µg/kg) were subcutaneously injected into rats; blood samples were taken from each animal at various times; and serum biochemical parameters were measured (levels of total proteins, total bilirubin, albumin, globulin, urea, creatinine, uric acid, glucose, cholesterol, triglycerides, sodium, chlorine, potassium and calcium, and the activity of the enzymes alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, lactate dehydrogenase). Serum levels of glucose, cholesterol, aspartate aminotransferase, alanine aminotransferase and uric acid increased in envenomed animals, compared to controls. There was a statistically positive correlation between Na^+ and Cl^- ions.

KEY WORDS: scorpions, *Androctonus crassicauda*, venom, rats, biochemical parameters.

CONFLICTS OF INTEREST: There is no conflict.

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INTRODUCTION

Scorpion envenomation remains a real health problem in tropical and subtropical regions of the world (23, 38, 44). The venoms of scorpions are dangerous to humans, especially those of species belonging to the genera *Buthus*, *Parabuthus*, *Mesobuthus*, *Tityus*, *Leiurus*, *Androctonus*, and *Centruroides* of the *Buthidae* family (5, 7, 8, 14, 19).

Androctonus crassicauda is one of the venomous species in the Middle East and North Africa (19, 24, 46). It is also found in a wide area including Turkey (Southeastern Anatolia), Azerbaijan, Armenia, Iran, Iraq, Syria, Jordan, Israel, Egypt (Sinai Peninsula), Saudi Arabia, and Yemen (9, 32-34, 45, 46). The venom of *A. crassicauda* is a potent autonomic stimulator (12, 13, 46). Severity of symptoms depends on the size of the victim, the season, and the time elapsed between sting and hospitalization (32, 35, 46). Vomiting, profuse sweating, pain at the sting site, local urticaria, and cool extremities are early signs of autonomic stimulation due to scorpion sting (13, 38, 46). Fatality after scorpion envenomation may be the result of cardiovascular failure complicated by pulmonary edema as well as by respiratory arrest (2, 19, 42, 43).

There is no study on the biochemical effects of *A. crassicauda* venom, which is responsible for a number of deaths of infants and children in countries of the North Africa and the Middle East (19, 43). Thus, here we report the effects of *A. crassicauda* venom on rat serum biochemical parameters measured over a period of time after venom injection.

MATERIALS AND METHODS

Animals

Scorpions: The scorpions were originally collected at Sanliurfa Province in the southeast region of Turkey. They were kept in large plastic boxes under room temperature of 22±2^{o}C, at 60±10% humidity, in the laboratory, were fed with crickets or cockroaches and received water daily.

Experimental animals: Wistar albino rats (160±10g) were used for the lethality assay. Throughout the experiment, they were kept in the experiment room under room temperature of 22±2^{o}C, at 60±10% humidity. The animals were divided into seven groups of five rats each.

Venom

Venom was obtained from living, mature *A. crassicauda* scorpions by electrical stimulation of the telson, as described by Ozkan and Filazi (34). Venom was dissolved in physiological saline solution (200µg/ml).

Lethality Assay

The minimal lethal doses (MLD) of *A. crassicauda* venom were determined by subcutaneous (sc) injections into rats according to the scorpion antivenom production protocol used by Refik Saydam Hygiene Center (RSHC), Ankara, Turkey. The venom dose was determined according to the MLD in rats as 50µg/rat. Venom solutions were subcutaneously injected into each rat at a dose of 250µg/kg.

Experimental Protocol

The venom solutions (250µg/kg dose) were subcutaneously injected into each rat of the test groups. Control group (G0) was treated with 200µl physiological saline solution subcutaneously.

Blood samples were collected at the 1^{st} (G1), 2^{nd} (G2), 4^{th} (G4), 8^{th} (G8), 12^{th} (G12) and 24^{th} (G24) hours after venom injection. Animals were monitored for 24h. Under ether anesthesia, each animal had blood samples (2–4ml) collected by cardiac puncture, placed in plain centrifuge tubes and allowed to clot at room temperature (23±1ºC) for 1h; then, serum was collected by centrifugation. All serum samples were stored at 4ºC until used. Serum total proteins, total bilirubin, albumin, globulin, urea, creatinine, uric acid, glucose, cholesterol, triglycerides, sodium, chlorine, potassium and calcium, and the serum activity of enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and lactate dehydrogenase (LDH) were determined by using a Biochemical Analyzer (BiocodeHycel – Lisa 500 Plus).

Statistical Analysis

Data are presented as standard error (S.E.) of the means and were statistically analyzed using SPSS Software. Differences between moments were analyzed by Kruskal-Wallis Test and parameters of each test group were compared with control group by Mann-Whitney Test. Results were considered significant when *p* value was lower than 0.05.

RESULTS

The obtained MLD was 50µg/rat. We show the various blood parameters from seven rat groups in Tables 1 to 5.

The MLD of scorpion crude venom led to an increase in serum total protein levels at the 1st, 2nd and 4th hours after injection, followed by a decrease at the 12th and 24th hours, when compared with those of the control group. Serum albumin levels increased at all moments, but it was significant (p<0.05) only at the 8th and 24th hours compared with those of control rats. Serum globulin levels significantly reduced at the 12th and 24th hours in envenomed rats. There were also statistically significant albumin levels in G8 and G24, and total protein levels in all groups (Table 1).

All groups showed an increase in total bilirubin and direct bilirubin levels together with a reduction in serum urea levels at the 1st, 2nd, 4th and 24th hours, compared with untreated rats. Statistically significant changes in serum urea levels were found at G2 (decrease) and G12 (increase). Uric acid levels increased at the 1st, 2nd, 4th, 8th and 24th hours in envenomed rats, but a statically significant difference was only observed in G1, G4, and G8. Creatinine levels decreased at the 1st and 12th hours but increased in G2, G4, and G8 (Table 2).

Serum glucose levels increased at the 1st, 4th, 12th and 24th hours, compared with those of controls. However, the venom effects on serum cholesterol levels led to an increase at the 1st, 2nd, 4th and 24th hours and a reduction at the 8th and 12th hours, when compared with those of control rats. Serum cholesterol changes were statistically significant in all groups. Serum triglyceride levels significantly increased at the 1st hour in envenomed rats (Table 3).

Serum enzyme activities were variable after envenomation of rats. The activities of ALT, AST and ALP increased in envenomed rats. LDH activity was slightly lower than in controls (Table 4).

A statistically negative correlation between Na^+ and K^+ ions were observed after the administration of *A. crassicauda* venom to rats. Also, a statistically positive correlation between Na^+ and Cl^- ions were observed. Nevertheless, except for G1, all groups showed slightly increased potassium levels after venom administration, when compared with control group (Table 5).

Table 1. Effects of a single sc injection of *Androctonus crassicauda* venom on the levels of serum total proteins (g/dl), albumin (g/dl) and globulin (g/dl) in rats at the 1st (G1), 2nd (G2), 4th (G4), 8th (G8), 12th (G12), and 24th (G24) hours after venom injection. Results are presented as the mean±S.E. (n=5).

MEASURED BIOCHEMICAL PARAMETERS			
Group (h)	**Total Proteins**	**Albumin**	**Globulin**
G0	7.10±0.25*****	3.20±0.08	3.92±0.22
G1	7.57±0.26*****	3.47±0.10	3.80±0.16
G2	7.45±0.15*****	3.52±0.14	3.95±0.08
G4	7.35±0.16*****	3.47±0.06	3.85±0.12
G8	7.26±0.20*****	4.34±0.83*	3.84±0.19
G12	6.84±0.11*****	3.38±0.02	3.44±0.16
G24	6.62±0.04*****	5.98±1.79*	3.37±0.07

*: $p<0.05$, compared with control rats (G0)

Table 2. Effects of a single sc injection of *Androctonus crassicauda* venom on the levels of serum total bilirubin (mg/dl), direct bilirubin (mg/dl), urea (mg/dl), creatinine (mg/dl) and uric acid (mg/dl) in rats at the 1st (G1), 2nd (G2), 4th (G4), 8th (G8), 12th (G12), and 24th (G24) hours after venom injection. Results are presented as the mean±S.E. (n=5).

MEASURED BIOCHEMICAL PARAMETERS					
Group (h)	**Total Bilirubin**	**Direct Bilirubin**	**Urea**	**Creatinine**	**Uric Acid**
G0	0.12±0.02	0.08±0.01	49.00±3.84	0.59±0.02	1.04±0.05
G1	0.42±0.31	0.34±0.24	38.75±3.61	0.55±0.00*****	2.15±0.38*****
G2	0.60±0.07	0.39±0.04	31.50±2.53*****	0.62±0.06*	1.90±0.41
G4	0.45±0.18	0.30±0.11	47.50±4.92	0.65±0.06*****	1.92±0.33*
G8	0.29±0.06	0.14±0.03	51.00±3.49	0.60±0.03	1.66±0.20*
G12	0.68±0.24	0.36±0.13	64.00±1.81*****	0.51±0.02	0.80±0.10
G24	0.26±0.05	0.13±0.02	42.50±3.77	0.59±0.02	1.30±0.14

*: $p<0.05$, compared with control rats (G0).

Table 3. Effects of a single sc injection of *Androctonus crassicauda* venom on the levels of serum total glucose (mg/dl), cholesterol (mg/dl) and triglycerides (mg/dl) in rats at the 1st (G1), 2nd (G2), 4th (G4), 8th (G8), 12th (G12), and 24th (G24) hours after venom injection. Results are presented as the mean±S.E. (n=5).

MEASURED BIOCHEMICAL PARAMETERS			
Group (h)	**Glucose**	**Cholesterol**	**Triglycerides**
G0	150.00±8.03	44.00±4.43*****	99.00±10.95
G1	176.50±14.90	49.75±2.80*****	154.50±41.84
G2	148.50±10.34	50.00±3.16*****	89.00±7.04
G4	186.00±15.87	56.00±2.34*****	93.50±23.51
G8	133.00±15.96	33.20±2.97*****	81.60±12.99
G12	159.80±4.22	35.20±2.90*****	85.80±8.14
G24	181.50±12.21	46.00±2.48*****	93.25±17.23

*: $p<0.05$, compared with control rats (G0).

Table 4. Effects of a single sc injection of *Androctonus crassicauda* venom on the levels of serum alanine aminotransferase (ALT; U/l), aspartate aminotransferase (AST; U/l), alkaline phosphatase (ALP; U/l), gamma-glutamyl transferase (GGT; U/l), and lactate dehydrogenase (LDH; U/l) in rats at the 1st (G1), 2nd (G2), 4th (G4), 8th (G8), 12th (G12), and 24th (G24) hours after venom injection. Results are presented as the mean±S.E. (n=5).

MEASURED BIOCHEMICAL PARAMETERS					
Group (h)	**ALT**	**AST**	**ALP**	**GGT**	**LDH**
G0	32.60±1.88	152.20±15.40	248.60±26.82	4.60±0.40	3.92±0.22
G1	58.00±12.62*****	164.25±50.51	334.50±16.44	2.75±2.95	4.12±0.16
G2	102.00±30.16*****	310.75±79.96	339.50±41.14	4.75±4.50	3.95±0.08
G4	62.50±9.12*****	224.50±69.83	368.00±46.67	4.50±1.32	3.85±0.12
G8	54.20±11.84*****	296.40±49.95	234.40±74.15	4.00±0.00	3.84±0.19
G12	58.80±9.11*****	233.80±35.29	409.80±60.12	4.00±0.02	3.44±0.16
G24	76.00±33.75*****	259.00±44.20	299.75±45.12	3.75±0.62	3.37±0.07

*: $p<0.05$, compared with control rats (G0).

Table 5. Effects of a single sc injection of *Androctonus crassicauda* venom on the levels of serum sodium (Na^+; mmol/l), potassium (K^+; mmol/l), chlorine (Cl^-; mmol/l), and calcium (Ca^{2+}; mg/dl) ions in rats at the 1st (G1), 2nd (G2), 4th (G4), 8th (G8), 12th (G12), and 24th (G24) hours after venom injection. Results are presented as the mean±S.E. (n=5).

MEASURED BIOCHEMICAL PARAMETERS				
Group (h)	**Na^+**	**K^+**	**Cl^-**	**Ca^{2+}**
G0	142.60±0.67	4.52±0.05	106.40±1.16	10.34±0.08
G1	137.75±0.62*****	4.40±0.24	98.00±1.08*****	10.25±0.21
G2	136.25±1.31*****	4.58±0.10	99.00±1.47*****	10.35±0.11
G4	136.25±1.03*****	4.78±0.16	99.75±1.31*****	10.15±0.17
G8	137.60±1.03*****	4.60±0.26	100.40±1.02*****	10.20±0.20
G12	136.80±1.28*****	4.80±0.13	100.60±1.40*****	10.86±0.15
G24	139.00±0.00*	4.60±0.00	102.50±0.28*	10.42±0.19

*: $p<0.05$, compared with control rats (G0).

DISCUSSION

More than 1,500 species of scorpions have been described in the world. Hazardous scorpions all belong to the Buthidae family (33, 46, 48). Scorpion venoms are composed of different concentrations of neurotoxins, cardiotoxins, nephrotoxins, phosphodiesterases, hyaluronidases, glycosaminoglycans, histamines, serotonins, tryptophans, and cytokine releasers (11, 25). The lethal fraction of venom from different species of scorpions has similar effects on the autonomic nervous system (6). The symptoms caused by scorpion stings in animal models are similar to those observed in humans (36). Numerous studies have emphasized that adrenergic signs occur with a low venom dose, while cholinergic signs occur with high venom concentrations (18, 38). The various clinical presentations range from local to serious autonomic and central nervous system symptoms, with death due to multisystem organ failure, especially cardiac and respiratory failure (1, 19, 38, 39, 42, 43). In animal models, elimination of toxins is carried out mainly by the kidneys (40). Following venom injection, the highest toxin concentration has been found in the kidneys, liver, heart and lungs (3, 37). Alves *et al.* (3) stated that scorpion venom caused a great increase in renal edema, which is related to the decreased glomerular

filtration rate and urinary flow. Also, acute renal failure has been reported to occur after scorpion stings (25, 37, 39, 41).

The present findings (hyponatremia, hypochloremia and relative hyperkalemia) corroborate the results of previous studies (2, 15, 17, 25, 29, 40). The levels of uric acid and urea (G12) also increased in animals envenomed with *A. crassicauda* venom.

A direct effect of scorpion venom on myocardium has been shown in several studies (4, 6, 21, 40). Some researchers have reported that ALT and AST activities in the serum change during scorpion envenomation (22, 26, 31, 37, 49). Similarly, ALT and AST activities were observed following *A. crassicauda* venom injection. The enzyme AST is found in the liver and heart at high concentrations; therefore, the increase in its levels is attributed to myocardial infarction and hepatic failure (2, 4, 11, 31, 37, 49). On the other hand, ALT is a liver-specific enzyme. Therefore, the increase in AST and ALT levels may be due to a direct effect of the venom on the liver and heart.

Many studies have emphasized that blood glucose levels increase after envenomation resulting in hyperglycemia in animal models (10, 16, 22, 27-31, 49) and patients (2, 11, 12, 47). In the present study, hyperglycemia was seen after *A. crassicauda* venom administration. Several studies have reported that this might be due to a massive release of catecholamines, increased glucagon and cortisol levels, changes in thyroid hormone levels, and changes in insulin secretion (20, 27-30). According to the obtained results, it can be concluded that *A. crassicauda* venom has neurotoxic effects, which enhance the release of catecholamines with consequent stimulation of autonomic nervous system.

In summary, this analysis showed that rats experimentally envenomed with *A. crassicauda* venom showed acute renal failure, liver dysfunction, and cell destruction. The venom could also be the cause of cardiac problems. *Androctonus crassicauda* venom showed its toxicity by altering the electrolytes balance, especially sodium and chlorine ion levels in the serum.

Every patient stung by a scorpion in the southeast region of Turkey must be accepted as an emergency case and hospitalized by medical professionals. These patients should be subjected to: (a) electrolyte evaluation; (b) glucose level measurement to evaluate hyperglycemia; (c) liver enzymes measurement to evaluate liver dysfunction and cell destruction; (d) monitoring in terms of cardiac and pulmonary failure; and (e) urinalysis to help evaluate renal failure.

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