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# An Experimental Study of the Effects of *Mesobuthus eupeus* Scorpion Venom on Plasma Concentrations of Metabolic Hormones and Glucose in Rats

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## Abstract

**BACKGROUND:** *Mesobuthus eupeus* is an indigenous scorpion species in Southwest Iran which is responsible for the majority of scorpion sting cases in Khuzestan province.

**OBJECTIVES:** The effects of *M. eupeus* venom were investigated on the chief metabolic hormones in rats.

**METHODS:** A total of 45 Albino male rats were divided into 3 equal groups: group 1 (control): 0.5 ml normal saline was administered intraperitoneally (IP); group 2 and 3: *M. eupeus* venom was administered with a dose of 1 and 2 mg/kg IP, respectively. Sampling was performed at 8, 24, and 48 hours after venom/saline injection.

**RESULTS:** The levels of thyroxine (T4) and triiodothyronine (T3) were significantly lower in both venom receiving groups (groups 2 and 3) than in the control group, dose-dependently, at all sampling times. There was a significant decrease in insulin level in both intoxicated groups compared to the control group at all sampling times. Glucagon, cortisol and subsequently glucose concentrations were significantly increased in both groups receiving the venom (groups 2 and 3) compared to the control group at 8 and 24 hours following envenomation.

**CONCLUSIONS:** The findings of this study indicate that *M. eupeus* venom can suppress the secretion of essential metabolic hormones including T3, T4, and insulin and stimulate the release of glucagon, and cortisol, leading to hyperglycemia.

**KEYWORDS:** cortisol, endocrine system, insulin, *Mesobuthus eupeus*, scorpion

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## Introduction

Scorpion sting is one of the major health challenges for humans and animals, especially in tropical and developing countries. More than 1,500 scorpion species have been identified worldwide (Lourenço, 2014; Lucas and Meier, 2017) and about 32 species were found in Iran, 12 of which have been detected in Khuzestan (Jalali and Rahim 2014; Rahimi et al., 2015).

The Buthidae are the largest family of scorpions and are found all over the world especially in tropical and semi-tropical regions, particularly the Middle East and Central Asia (Lourenço, 2014; Lucas and Meier, 2017). *Mesobuthus eupeus* is the most abundant species in Iran which is found in Khuzestan province and is responsible for 21.7% of cases of scorpion sting in Khuzestan (Rahimi et al., 2015; Dehghani et al., 2017).

The venom of scorpions, especially the Buthidae family, consists of a variety of toxins and active biological compounds (Khoobdel et al., 2013; Erdeş et al., 2014; Laraba-Djebari et al., 2015) which can affect various tissues (Murthy and Zare, 2001; Murthy and Zare, 2002; Razi Jalali et al., 2015). Scorpion envenomation can lead to the failure of many organs and major metabolic and endocrine disorders through the release of large amounts of catecholamines, and vascular disorders (Petricevich, 2010). In some studies, scorpion stings were found to be associated with alterations in insulin, glucagon, and glucocorticoid secretion level, and in blood glucose levels (Murthy, 2000). However, there are few studies about the effect of scorpion venom on thyroid secretion (Murthy and Zare, 1998).

To the best of the authors' knowledge, there has been no documented data on the effects of *M. eupeus* venom on the endocrine system, including thyroid, endocrine pancreas and adrenal secretions. Since it is a native Iranian species, research into various aspects of the pathogenesis of its venom are important to improve diagnostic and therapeutic methods. Therefore, the present study was designed to investigate the effects of Mesobutupus eupeus envenomation on plasma thyroid hormones (T3 and T4), insulin, glucagon, cortisol, and glucose levels in rats.

## Materials and Methods

### Scorpion venom

The venom of *M. eupeus* scorpion venom used in this study was provided by Razi Vaccine and Serum Research Institute, Ahvaz which was prepared by electric shock and kept in lyophilized form. The concentration of crude venom protein was 815 mg/gvenom. Solutions of 0.05% and 0.1% of venom were prepared in 0.9% sodium chloride solution in suitable volumes proportional to the number of rats in each envenomated group, as described below.

### Laboratory animals

A total of 45 Albino male rats (Wistar strain) weighing 250–300 g aged 4 to 6 months were housed in groups of six, in plastic cages, in an air-conditioned room maintained at a temperature of 24 ± 2 °C and a relative humidity of 55 ±5%, with a 12-h light/12-h dark illumination cycle. They were fed a commercial laboratory pellet diet and tap water ad libitum. All procedures were done in accordance with ethical guidelines for care and use of laboratory animals, discarding of dead animals and protection of the researcher against animal bites and were approved by the Experimental Animals Committee of Shahid Chamran University of Ahvaz, Iran.

**Experimental design**

Animals were randomly divided into 3 equal groups and were treated as follows:

Group 1: (control group) 0.5 ml normal saline intraperitoneally (IP).

Group 2: *M. eupeus* venom at a dose of 1 mg/kg body weight IP (0.5 ml of 0.05% solution for each rat).

Group 3: *M. eupeus* venom at a dose of 2 mg/kg body weight IP (0.5 ml of 0.1% solution for each rat).

The doses of venom were selected based on previous studies by authors (Razi Jalali et al., 2015; 2016).

**Blood collection**

Sampling was performed at 8, 24, and 48 h after venom/saline injection; five rats from each group were sampled each time. Blood samples were collected with heparin via cardiac puncture following anesthesia with chloroform (Merck, Germany). After centrifugation the plasma was separated and stored at -20 ºC for subsequent measurements.

**Plasma biochemical analysis**

The plasma levels of T4 and T3 were measured using ELISA kits (Sigma-Aldrich). Cortisol, insulin and glucagon were also assessed by ELISA (Monobind, Germany) according to the manufacturer's instructions. The amount of glucose was measured using colorimetric kits (Pars Azmun, Iran) via biochemical autoanalyzer (Biotecnica, Bt-1500, Italy).

**Statistical analysis**

Analysis of variance and Tukey post-hoc tests were employed to compare the data between groups using SPSS software version 16 (SPSS Inc., Chicago, Illinois, USA). All values were expressed as mean ± standard error, and $p < 0.05$ was considered as statistically significant.

## Results

**Clinical signs**

The envenomated rats showed behavioral changes from aggression to depression. In addition, hemorrhage and hyperemia in the eyes and mucosal membranes were recorded in both intoxicated groups.

**T3 measurement**

The results of T3 evaluation showed that the levels of this hormone were significantly lower in group 2 than in the control group and in group 3 compared to the rest of the groups, at all sampling times ($p < 0.05$) (Table 1). In addition, in group 3, the amount of

**Table 1.** Plasma triiodothyronine (T3) and thyroxine (T4) concentration as mean ± SE in different groups and sampling times.

| Group | T3 (µg/dl) | | | T4 (µg/dl) | | |
|---|---|---|---|---|---|---|
| | h 8 | h 24 | h 48 | h 8 | h 24 | h 48 |
| Group 1 (control) | 0.08 ± 2.48 *A | 0.11 ± 2.35 A | 0.09 ± 2.32 A | 1.33 ± 23.33 *A | 1.31 ± 24.75 A | 1.93 ± 24.25 A |
| Group 2 (venom 1 mg/kg) | 0.05 ± 1.34 B | 0.05 ± 1.46 B | 0.09 ± 1.91 B | 1.53 ± 18.20 B | 1.28 ± 21.40 B | 1.39 ± 22.80 A |
| Group 3 (venom 2 mg/kg) | 0.04 ± 0.97 **Ca | 0.13 ± 1.05 Cb | 0.12 ± 1.98 Bc | 1.48 ± 17.02 B | 1.35 ± 20.20 B | 1.69 ± 22.40 A |

* Different uppercase letters in each column represent significant difference between groups.

** Different lowercase letters in each row represent significant difference between sampling times.

**Table 1.** Plasma triiodothyronine (T3) and thyroxine (T4) concentration as mean ± SE in different groups and sampling times.

| Group | Insulin (µIU/dl) | | | Glucagon (ng/ml) | | |
|---|---|---|---|---|---|---|
| | 8 h | 24 h | 48 h | 8 h | 24 h | 48 h |
| Group 1 (control) | 12.70 ± 0.92 A* | 12.13 ± 1.81 A | 11.40 ± 1.92 A | 123.67 ± 2.60 A* | 122.25 ± 2.27 A | 121.50 ± 1.19 A |
| Group 2 (venom 1 mg/kg) | 8.40 ± 1.08 B | 9.36 ± 1.29 B | 10.60 ± 1.20 B | 149.20 ± 2.70 Ba** | 154.40 ± 0.67 Bb | 139.80 ± 1.70 Ac |
| Group 3 (venom 2 mg/kg) | 8.13 ± 0.74 B | 7.06 ± 1.29 B | 8.84 ± 1.11 B | 156.50 ± 2.46 Ca | 168.80 ± 1.02 Cb | 136.00 ± 1.81 Ac |

* Different uppercase letters in each column represent significant difference between groups.
** Different lowercase letters in each row represent significant difference between sampling times.

T3 significantly increased over time, so that the highest hormone level was at 48 h post injection ($p < 0.05$).

**T4 measurement**

Based on the results of T4 measurement (Table 1), the hormone levels decreased in both envenomated groups (groups 2 and 3) in comparison with the control group, so that the difference was significant at 8 and 24 h ($p < 0.05$). However, with the passage of time at 48 h after venom injection, this decrease was moderated and there was no significant difference between groups at any of the sampling times.

**Insulin measurement**

Based on the results (Table 2), there was a significant decrease in insulin level in the intoxicated groups (groups 2 and 3) compared to the control group at all sampling times ($p<0.05$).

**Glucagon measurement**

The administration of venom significantly increased glucagon level in group 2 compared to the control group and in group 3 compared to the previous two groups at 8 and 24 h post injection ($p < 0.05$) (Table 2). Additionally, in both intoxicated groups, the maximum amount of hormone was observed at 24 h post injection ($p < 0.05$).

**Cortisol measurement**

A significant increase in cortisol concentration was noted in both groups receiving the venom (groups 2 and 3) compared to the control group at 8 and 24 h following envenomation ($p<0.05$) (Table 3). However, in both mentioned groups, the level of cortisol decreased significantly at 48 h in comparison to the previous sampling times ($p < 0.05$).

**Glucose measurement**

Glucose levels in both venom injected groups (groups 2 and 3) were significantly increased compared to the control group at all sampling times ($p < 0.05$) (Table 3). However, there was no significant difference between two envenomed groups in terms of glucose levels.

## Discussion

In the present study, injection of *M. eupeus* venom resulted in a significant reduction in the thyroid hormones (T3 and T4). The highest decrease was observed in the third group (high dose venom) at 8 h after injection, considering the half-life of T3 which is only 1 day while the half-life of T4 is 5-7 days. These changes might be attributable to an autonomic storm through the release of catecholamines and angiotensin II following

**Table 1.** Plasma triiodothyronine (T3) and thyroxine (T4) concentration as mean ± SE in different groups and sampling times.

| Group | Cortisol (µg/dl) | | | Glucose (mg/dl) | | |
|---|---|---|---|---|---|---|
| | 8 h | 24 h | 48 h | 8 h | 24 h | 48 h |
| Group 1 (control) | 2.36 ± 0.11 A* | 3.11 ± 0.39 A | 2.41 ± 0.55 A | 86.67 ± 6.61 A* | 84.25 ± 4.20 A | 87.50 ± 5.52 A |
| Group 2 (venom 1 mg/kg) | 9.34 ± 1.17 Ba** | 8.74 ± 0.75 Ba | 4.20 ± 0.27 Ab | 129.00 ± 4.78 B | 138.60 ± 3.45 B | 126.40 ± 4.41 B |
| Group 3 (venom 2 mg/kg) | 9.82 ± 1.29 Ba | 8.63 ± 0.75 Ba | 3.92 ± 0.26 Ab | 138.00 ± 3.08 B | 145.60 ± 6.08 B | 134.40 ± 3.70 B |

* Different uppercase letters in each column represent significant difference between groups.

** Different lowercase letters in each row represent significant difference between sampling times.

envenomation, which led to a decrease in insulin secretion and subsequent reduction of T3 and T4 concentration in the blood. These findings are consistent with other previous studies in this regard. In a study performed by Murthy and Zare (1998) a significant decrease in T4 and T3 levels was observed following the injection of Mesobuthus tamulus venom in dogs. They also obtained similar results regarding T3 concentration in rabbits. In addition, while anti-venom administration resulted in an increase in serum T3 level in dogs, it could not prevent venom induced hormonal changes in rabbits. However, the intracerebroventricular injection of Kaliotoxin (KTX) fraction of Androctonus australis venom, in another study, resulted in the stimulation of neuro-endocrine response with significant rise in serum T3, T4, and TSH levels at 24 h post-injection in rats which was associated with inflammatory cell infiltration and imbalanced redox status in both hypothalamus and thyroid tissue (Ladjel-Mendil et al., 2016). This diversity in the results might be due to the difference in the type of studied scorpion species and venom as well as the route of venom administration.

According to the results of this study, glucagon levels were significantly increased in the venom treated groups at 8 and 24 h after injection in a dose-response manner. However, the levels of this hormone returned to normal in both groups at 48 h after envenomation. This effect is probably mediated through the adrenergic stimulation of endocrine pancreas as well as other tissues. Similar alterations in glucagon secretion were also reported by Johnson and Ensinck (1976) following pancreas perfusion with Leiurus quinquestriatus scorpion toxin in rats. This reduction in glucagon secretion was associated with the stimulation of sympathetic nerve terminals in pancreas tissue and increased norepinephrine release which was successfully prevented in the presence of alpha and beta-adrenergic blocking agents in rat. In addition, subcutaneous administration of Mesobuthus tamulus scorpion venom resulted in an increased blood glucagon in dogs. These hormonal changes seem to result in an imbalance in the carbohydrate metabolism and the inability of vital organs to use metabolic substrates (Murthy and Haghnazari, 1999).

The present study revealed that there was a significant decrease in insulin levels in the envenomated rats compared to the control group, with the highest reduction at 8 and 24 h after venominjection. In other experimen-

tal studies, hypoinsulinemia or insulin resistance was reported following the injection of various scorpion spp. venom. During the study conducted by Murthy and Haghnazari (1999) and Zare et al. (1994), the same alterations in insulin level was recorded following Mesobuthus tamulus venom administration in dogs. Furthermore, Androctonus australis hector scorpion toxin was associated with severe inflammatory response, liver tissue damage and hyperglycemia accompanied by hyperinsulinemia, indicative of insulin resistance in a previous study in rats. It is also possible that the insulin measured after venom injection was not functionally active. Moreover, pretreatment with cytokine antagonists, in the same study, significantly decreased inflammatory biomarkers and plasma glucose levels as well as hepatic tissue damage and metabolic disorders which was suggestive of the crucial role of inflammatory cytokines (IL-6 and TNF-α) in the complications induced by the scorpion venom (Taibi- Djennah and Laraba-Djebari, 2015).

In addition, exogenous insulin administration was demonstrated to reverse hemodynamic, cardiovascular, metabolic, electro-cardiographic (ECG) changes and pulmonary oedema in the experimental animals and in the scorpion sting victims which represents the key role of insulin suppression in the pathogenesis of the toxin and also suggests that the insulin receptor and the signaling pathways are not defective (Murthy, 2013, 2014a; Murthy et al., 1988, 1990, 1991; Yugandhar et al., 1999). It appears that scorpion envenomation, including *M. eupeus*, results in a substantial release of catecholamines and Angiotensin II which can inhibit glucose-induced secretion of insulin from the beta cells of islets in the endocrine pancreas as well as antagonizing the actions of insulin by promoting glycogenolysis which leads to hyperglycemia. The suppression of insulin secretion or insulin resistance along with a rise in catabolic counter-regulatory hormones including glucagon, cortisol and glucose level might be responsible for the pathogenesis of a variety of clinical symptoms. Consequently, *M. eupeus* venom, like many other scorpion species, can induce a syndrome of energy scarcity and inability of vital organs to consume the metabolic substrates causing multi-organ system failure (Murthy, 2014b).

In the current experiment, the injection of scorpion venom in both groups led to a significant increase in cortisol levels. The highest hormone concentration was observed at 8 h after receiving the toxin and decreased over time, so that cortisol changes were not significant within 48 h. Other previous studies have found similar findings. Subcutaneous administration of M. tamulus resulted in an increased blood cortisol in dogs and rabbits (Murthy and Haghnazari, 1999; Zare et al., 1994). Excessive release of catecholamines following scorpion venom intoxication is, once again, likely responsible for increased endogenous glucocorticoids which, in turn, is often associated with carbohydrate intolerance (Murthy, 2014b).

The results of glucose measurements in the present study showed a significant increase in the level of this analyte after injection of *M. eupeus* venom at all sampling times compared to control group. Considering that there was no significant difference between the two groups of venom recipients, it seems that changes in glucose do not correlate with the dose of injected venom. Hyperglycemia has already been observed following injection of various scorpion spp. toxins including *Mesobuthus tumulus* (Mur-

thy and Haghnazari; 1999 Zare et al., 1994), Androctonus australis hector (Taibi-Djennah and Laraba-Djebari, 2015), Tityus serrulatus (Andrade et al., 2004), and Indian black scorpion (More et al., 2004). These effects are most likely due to the increased circulating levels of catabolic counter-regulatory hormones, including glucagon, cortisol and epinephrine, which act synergistically as well as simultaneous suppression in insulin secretion that induce sustained hepatic glucose production and inability of tissues to utilize it.

In this study, the venom injected rats showed some behavioral changes from aggression to depression. This might be due to the effects of venom on central nervous system. Although this issue is not directly relevant to the present study, there is considerable evidence showing the direct participation of the central nervous system in the envenoming process provoked by scorpions (Sadeghian, 2003; Nencioni et al., 2018) with numerous proposed mechanisms including: alterations in coagulation of blood leading to disseminated intravascular coagulation; high level of catecholamines induced, vasospasm causing hypoperfusion, and ischemia in previously compromised areas of the brain; high blood pressure during autonomic storm resulting in rupture of vessels, causing hemorrhagic stroke; and the presence of myocarditis, thromboembolic phenomenon, or shock leading to cerebral infarction (Sengupta et al., 2009; Thomas et al., 2017).

In addition, hemorrhage and hyperemia in the eyes and mucosal membranes were recorded in both intoxicated groups which might be attributed to a possible coagulopathy following scorpion intoxication (Rahmani and Jalali, 2012; Seyedian et al., 2014). However, in this study, laboratory tests were not carried out to confirm this.

In conclusion, the findings of this study indicate that *M. eupeus* venom can affect the endocrine system by suppressing the secretion of essential metabolic hormones including T3, T4, and insulin and excessive release of glucagon, and cortisol, leading to hyperglycemia and disorders in the overall metabolism of the body. These alterations might be responsible for the pathogenesis of a variety of clinical symptoms following envenomation. However, the identification of other aspects and mechanisms involved in the toxicity of this scorpion species venom requires more research.

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## Conflict of Interest

The authors declare that there is no conflict of interest.

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# مطالعه تجربی اثرات سم عقرب *مزوبوتوس اوپئوس* بر غلظت پلاسمایی هورمون‌های متابولیک و گلوکز در موش صحرایی

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## چکیده

**زمینه مطالعه:** *مزوبوتوس اوپئوس* یک گونه عقرب بومی در جنوب غربی ایران است که مسئول اکثر موارد عقرب گزیدگی در استان خوزستان می‌باشد.

**هدف:** اثر سم عقرب *مزوبوتوس اوپئوس* بر هورمون‌های متابولیک اصلی در موش صحرایی مورد بررسی قرار گرفت.

**روش کار:** ۴۵ سر موش صحرایی نر آلبینو به ۳ گروه مساوی تقسیم شدند: گروه ۱ (کنترل): ۰/۵ میلی‌لیتر نرمال سالین به صورت داخل‌صفاقی دریافت کردند، گروه ۲ و ۳: سم عقرب *مزوبوتوس اوپئوس* به ترتیب با دوز ۱ و ۲ میلی‌گرم به ازای هر کیلوگرم به صورت داخل صفاقی دریافت نمودند. نمونه‌گیری در زمان ۸، ۲۴ و ۴۸ ساعت پس از تزریق سم و یا سالین انجام گرفت.

**نتایج:** مقادیر تیروکسین (T۴) و تری‌یدوتیرونین (T۳) در هر دو گروه دریافت کننده سم (گروه ۲ و ۳) نسبت به گروه کنترل در همه زمان‌ها به صورت وابسته به دوز به طور معنی‌داری پایین‌تر بود. همچنین کاهش معنی‌داری در میزان انسولین در هر دو گروه دریافت کننده سم در مقایسه با گروه کنترل در همه زمان‌ها مشاهده گردید. غلظت گلوکاگن، کورتیزول و گلوکز در هر دو گروه دریافت کننده سم (گروه ۲ و ۳) در مقایسه با گروه کنترل پس از ۸ و ۲۴ ساعت به‌طور معنی‌داری افزایش یافته بود.

**نتیجه گیری نهایی:** یافته‌های این مطالعه نشان داد سم عقرب *مزوبوتوس اوپئوس* قادر به سرکوب ترشح هورمون‌های متابولیک اصلی شامل T۳ و T۴ و انسولین و تحریک ترشح گلوکاگن و کورتیزول می‌باشد که در مجموع منجر به هیپرگلایسمی می‌شوند.

**واژه‌های کلیدی:** *مزوبوتوس اوپئوس*، عقرب، سم، سیستم درون‌ریز، انسولین، گلوکاگن

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