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Enzymes and toxins in scorpions of Buthidae family Insulin-Glucose Administration reverses metabolic, cardiovascular, ECG Changes and pulmonary oedema in scorpion envenoming syndrome

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Abstract

Death due to scorpion stings is a common event in many countries. Scorpion envenoming syndrome consists of the clinical presentation of pain at the site of sting, nausea, vomiting, sialorrhea, profuse sweating, abdominal pain, tremors, arrhythmias, hypertension, agitation, hyperglycemia, restlessness, prostration, priapism, pulmonary oedema, many other manifestations and may concern the CNS, the autonomous system, the respiratory tract, the pancreas, the cardiovascular system. Scorpion venom consists of a mixture of many pharmacologically active enzymes like phospholipase, hyaluronidase, proteinase, peptidase, urease, gelatinolytic and thrombin-like activities. Scorpion venoms contain free amino acids, histamine, serotonin, tryptamine, glycosaminoglycans, chondroitin sulphate and hyaluronic acid. It has neuropeptides, which target ion channels. Tityustoxin, noxiustoxin, Charybdotoxin, "Pulmonary oedema producing toxin" are observed in many of the scorpion venoms. In spite of zoological differences among dangerous scorpion species having many enzymes and toxins with differences in their chemical structure, symptomatology and clinical signs following Buthidae scorpion stings is quite similar. Scorpion envenoming syndrome results in an autonomic storm, massive release of catecholamines, increased levels of angiotensin II, glucagon, Cortisol, suppressed insulin levels/ hyperinsulinemia, glycogenolysis – hyperglycemia and increased free fatty acid levels (FFA). FFA increase the oxygen consumption, aggravate the ischemic injury to myocardium predisposing to arrhythmias, increase the susceptibility of the ventricles to the disorganized electrical behavior, and produce acute myocarditis, cardiac sarcolemmal defects, Disseminated Intravascular Coagulation (DIC) and many other abnormalities. Under these altered hormonal and metabolic conditions, scorpion envenoming syndrome cause Multi-System-Organ-Failure (MSOF) and death. Thus, scorpion envenoming is a syndrome of fuel – energy deficits and an inability to use the existing metabolic substrates by vital organs causing MSOF and death. Insulin administration reversed the metabolic, ECG and cardiovascular changes and pulmonary oedema in the scorpion sting victims. Insulin has a primary metabolic role in preventing, counter-acting and reversing all the deleterious effects of FFA by inhibiting the catecholamine induced lipolysis, increase intra-cellular K^+, facilitating glucose transport to the myocardium and glucose metabolism through different pathways. Continuous infusion of regular crystalline insulin should be given at the rate of 0.3 U/g glucose and glucose at the rate of 0.1 g/kg body weight/hour, for 48 - 72 hours, with supplementation of potassium as needed and maintenance of fluid, electrolytes and acid-base balance. Administration of insulin-glucose infusion to scorpion sting victims appears to be the physiological basis for the control of the metabolic response when that has become a determinant to survival.

Key words: Buthidae family, scorpion venom, enzymes, toxins, acute myocarditis, autonomic storm

Introduction

Death due to scorpion envenoming syndrome is a common event in various parts of the world. About 800 species of scorpions (Phylum Arthropoda, class Arachnida, order Scorpiones) are known. They are sub-divided into two groups: Buthoids and Chactoids. All the scorpions hazardous to humans belong to Buthidae (Buthoid) family. Scorpion envenomation is a major concern only in less developed countries. Envenomations are common in Mexico, Algeria, Tunisia, Saudi Arabia, Brazil, China, India, Iraq, Iran, Middle East, Central Africa and South Africa. Scorpion venom toxicity has been attributed to the pharmacological properties of toxic polypeptides active in mammals [1-10, 11-20, 21-30, 31-40, 41-53, 59, 60, 66, 68, 72, 75-77].

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Highly toxic venomous scorpions of the world belong to Buthidae family

The highly toxic venomous scorpions of the world belong to *Androctonus, Buthus, Centruroides, Leiurus Quinquestriatus,* and *Tityus* genera come under *Buthidae* family. Riyadh harbors the killer scorpions that belong to *Androctonus crassicauda, Apistobuthus pterygocercus, Buthacus yotvatensis nigroaculeatus, Buthacus leptochelys, Compsobuthus arabicus, Leiurus quinquestriatus and Orthochirus innesi. Buthotus jayokari, Buthotus eupeus, Buthotus schach, Campobuthus matthiesseni, Campobuthus regulosus, Kraepelinia kalpator, Liobuthus kesslerie, Buthotus saulcyi, Hemiscorpius lepturus, Mesobuthus eupeus, Odontobuthus doriae, Odontobuthus odonturus, Olivierus caucasicus, Othochirus scrobiculosus, Razianus zarudnyi, Sassanidotus zarudinyl, Simonoida farzanpayi and Scorpio maurus* are few species of scorpions under Buthidae family in Iran [93].

India harbors the following species of poisonous, killer scorpions that belong to the *Buthidae* family [93]. These killer deadly poisonous scorpions are distributed throughout the length and breadth of India. *Androctonus finitimus* (Pocock), *Baloorthochirus becvari* Kovarik, *Buthacus agarwali* Zambre & Lourenco, *Buthoscorpio politus* (Pocock,) *Buthoscorpio rayalensis, Buthoscorpio sarasinorum* (Karsch), *Charmus brignolii* Lourenco, *Charmus indicus* Hirst, *Charmus sinhagadensis* Tikader and Bastawade, *Compsobuthus* Vachon *andresi* Lourenco, *Compsobuthus* Vachon *atrostriatus* (Pocock), *Compsobuthus* Vachon *rugosulus* (Pocock), *Hemibuthus crassimanus* (Pocock), *Hottentotta jabalpurensis* Kovarik, *Hottentotta pachyurus* (Pocock), *Hottentotta penjabensis* Kovarik, *Hottentotta rugiscutis* (Pocock), *Hottentotta stockwelli* Kovarik, *Hottentotta tamulus* (Fabricius), *Himalayotityobuthus alejandrae* Lourenco, *Himalayotityobuthus martensi* Lourenco, *Isometrus acanthurus* Pocock, *Isometrus assamensis* Oates, *Isometrus brachycentrus* Pocock, *Isometrus corbeti* Tikader and Bastawade, *Isometrus isadensis* Tikader and Bastawade, *Isometrus khammamensis* Kovarik, *Isometrus maculates*, *Isometrus problematicus* Kovarik, *Isometrus rigidulus* Pocock, *Isometrus thurstoni* Pocock,. *Isometrus vittatus* Pocock, *Lychas aareyensis* Mirza & Sanap, *Lychas albimanus* Henderson, *Lychas biharensis* Tikader & Bastawade, *Lychas gravelyi* Henderson, *Lychas hendersoni* (Pocock), *Lychas hillyardi* Kovarik, *Lychas kamshetensis* Tikader & Bastawade, *Lychas kharpadi* Bastawade, *Lychas laevifrons* Pocock, *Lychas mucronatus* Fabricius, *Lychas nigristernis* (Pocock), *Lychas rackae* Kovarik, *Lychas rugosus* (Pocock), *Lychas scaber* (Pocock), *Lychas tricarinatus* (Simon), *Odontobuthus odonturus* (Pocock), *Orthochirus bastawadei* Zambre, *Orthochirus bicolor* (Pocock), *Orthochirus flavescens* (Pocock), *Orthochirus fuscipes* (Pocock), *Orthochirus krishnai* Tikader & Bastawade, 1 *Orthochirus pallidus* (Pocock), *Thaicharmus lowei* Kovarik, Soleglad & Fet, *Vachonus rajasthanicus* Tikader & Bastawade.

Enzymes in the scorpion venom

Scorpion venom consists of a mixture of many pharmacologically active proteins. Some proteins are enzymes and others are non-enzymatic in nature. Enzymes are known to have Gelatinolytic activities, Thrombin-like activities, Phospholipase, Hyaluronidase, Proteinase, Peptidase, and Urease activities. Scorpion venoms beside proteins contain non-protein substances like free amino acids, Histamine, Serotonin, Tryptamine, glycosaminoglycans, chondroitin sulphate, hyaluronic acid, and free hexosamines [9, 18].

Mesobuthus tamulus Concanesis, Pocock venom contained numerous biologically active components. It contains four Histamine releasing factors, three neurotoxins and one protease inhibitor [1]. The venom (*Buthus tamulus*) is a complex water soluble substances containing muco-polysacharides, small amounts of Hyaluronidase and Phospholipase, low molecular weight molecules such as Serotonin, Histamine, Protease inhibitors, Histamine releasers and neurotoxins. The neurotoxins have been purified, characterized, and sequenced. These toxins are basic polypeptides with low molecular weight, constituting a single polypeptide reticulated by four disulfide bridges. Scorpion neurotoxins influence mainly excitable membranes releasing neurotransmitters from neurons, ganglia, and nerve endings [3, 8-19, 22, 23, 35, 36].

Enzymes like Phospholipase A_2, Acetylcholine-esterase, Hyaluronidase, Phosphomonoestearase, 5-nucleotidase, Gelatinase are reported in various scorpion venoms. Phospholipase A_2 is present in the venom of *Heterometrus scaber*. Hyaluronidase is present in the venom of *Scorpio maurus palmatus* [20]. Acetylcholinesterase, Alkaline Phosphatase, acid-Phosphatase, inorganic Phosphatase, Adenosine triphosphatase, Phospholipase A_2, Ribonuclease, Deoxyribonuclease, and Hyaluronidase are the enzymes

reported from *Mesobuthus tamulus Concanesis, Pocock* [9]. Presence of many lipid classes like neutral lipids, free fatty acids, phospholipids, glycerides, sterol and steroleasters and Phospholipase A_2, were reported from scorpion *Heterometrus fulvipes* [36]. Histamine, 5-Hydroxytryptamine, Serotonin and Tryptamine are reported in the venoms of *Palamneus gravimanus*, *Leiurus quinquestriatus*, and *Heterometrus scaber* [20].

Existence of hemolytic activity

Marked hemolytic activity is present in the venom of *Heterometrus scaber*, *Scorpio maurus*. Hemolytic action appeared only in the presence of exogenic or endogenic lecithin for the venom *Scorpio maurus*, *Heterometrus scaber*. The crude venom of *S. maurus palmatus* was able to hemolyze washed human erythrocytes. The hemolytic action of this venom may resemble that of snake venoms in the presence of two hemolytic factors, one with a Phospholipase A-like activity and the other with a direct lytic activity [3]. Phospholipase A-like activity is found in the venom of *H. scaber*. The enzyme make-up of the strongly hemolytic venom from H. scaber consists of Phospholipase A-like activity, Acid phosphatase, Ribonuclease, 5'-nucleotidase, Hyaluronidase, and Acetylcholiesterase. *Vejovis spinigerus* and *Hadrusrus arizonensis* venoms contain Acetylcholinesterase activity [3]. *Heterometrus (Palamnaeeus) gravimanus* venom contains proteases, and 5'-nucleotidase. A hyaluronidase activity which plays the role of a spreading factor is observed in the venom of *Scorpio maurus palmatus* [3].

Systemic Inflammatory Response Syndrome related to the release of cytokines following severe envenomation

Scorpion venom contains muco-polysacharides, Hyaluronidase, Phospholipase, serotonin, histamine, and neurotoxins. Neurotoxins are the most important components of the poisonous killer scorpion venom. These low-molecular weight polypeptides cause severe adrenergic and cholinergic activities and affect sodium, potassium, and chloride channels of various cells. The victims may exhibit signs and symptoms involving the CNS, stimulation of autonomic nervous system, respiratory failure, heart failure and death [94]. Sofer et al first reported the involvement of the inflammatory systems following severe scorpion envenomation [40]. These authors documented the elevation of IL-6 in the serum of 8 out of 10 children stung by *L.quinquestriatus* and *B. judaicus*. The activation and release of cytokines may play an important role in the pathophysiology of scorpion envenoming syndrome and may be responsible for some systemic inflammatory manifestations and organ failure. Thus, pro-inflammatory cytokines may play an important role in the pathophysiology of non-cardiogenic pulmonary edema and Adult Respiratory Distress Syndrome (ARDS). Increased circulating levels of IL-1, IL-6 in scorpion sting patients were reported. Injection of *T. serrulatus* crude venom induced a significant increase in lung vascular permeability due to the release of prostaglandin E_2, thromboxene A_2, and a marked leukocyte infiltration of the lung [94].

Biogenic amines

The pain provoked by a scorpion sting has been attributed to the Serotonin, first identified, in the venom of the Buthid *Leiurus quinquestriatus*. 5-Hydroxytryptamine (5HT) has been found in some other species. *V. spinigerus* and *Heterometrus scaber* venoms contain 5-Hydroxytryptamine (5HT), 5-Hydroxytryptophan, Tryptophan and Tryptamine. *Heterometrus gravimanus* venom contains histamine [3, 19, 22].

Scorpion Toxins

Mesobuthus tamulus Concanesis, Pocock venom contains a potent cardiopulmonary toxin, which could account for the manifestation of pulmonary oedema seen after the scorpion envenomation. By Sephadox gel filtration and cat-ion exchange chromatography, a high molecular weight toxin (T3) exhibiting the toxicity on cardio pulmonary parameters was isolated from *Mesobuthus tamulus Concanesis, Pocock* venom and was named as "Pulmonary oedema producing toxin". Another lethal fraction was also isolated (T2), which is a low molecular weight toxin and exhibited neurotoxicity [10, 11, 15, 16, 35].

Scorpion venom - neuropeptides

Scorpion venom is composed primarily of neuropeptides, which target ion channels. Since the movement of sodium ions (Na^+), Potassium ions (K^+), chloride ions (Cl^-) and Calcium ions (Ca^{2+}) in and out of the cells through ion channels is absolutely essential in neural and muscular function, these channels act as primary targets for the offending scorpion venom [14].

Neurotoxins

Neurotoxins present in the scorpion venom affect the gating mechanisms of excitable membrane. Long toxins (60-70 amino acids) interfere with sodium channels, causing cell destruction by the influx of Na^+ and Ca^{2+} ions into the cell. Short toxins (31 -37 amino acids) modify the potassium channel's function and may specially block Ca^{2+} activated L^+ channels. These effects on vascular endothelial cells may exert different reactions on different organs [3, 12, 14, 19-23].

Natriuretic peptide

Scorpion envenomation is considered public health problem in North African countries. The North African scorpion toxin from *Androctonus australis garzonii* increases the atrial natriuretic peptide (ANP) in rat through stimulation of sympathetic cardiac nerves and sodium channels activation [4, 20].

Ion channels

Sodium channels are responsible for the depolarization phase of the action potential and they are found in axons [3, 19-22, 39, 40]. Potassium channels are found in un-myelinated axons and in nerve terminals but to a lesser extent in nodes of Ranvier of mammalian motor axons. These channels contribute to the repolarization of the membrane after an action potential and contribute to the repolarization of the excitability of neurons. Calcium channels are important in nerve terminals, where they play a vital role in the release of neuro-transmitters. Calcium and K^+ channels exist in several different subtypes, which differ in physiological and pharmacological properties [3, 19-22, 39, 40].

Tityustoxin acts by activating the sodium channels

Experimental studies have established that *"Tityustoxin"*, a highly purified fraction of the venom of *T. serrulatus*, acts by activating the sodium channels, causing persistent membrane depolarization in the excitable cells of the organism. This leads to a massive release of neurotransmitters by the Sympathetic and Para-sympathetic nerve endings and also by the adrenal medulla, which in turn causes most of the signs and symptoms in human envenoming [3, 19, 20, 22, 39, 40].

Na^+ channel blocking peptides

Sodium channels are the most common target for scorpion neuro-peptides, and these neuro-toxins are organized into three groups 20]. The yellow scorpion, *Leiurus quinquestriatus* is common in the Middle East and is considered the most toxic scorpion species. The alpha toxins are commonly found in the "old world" scorpion species (*Androctonus australis* Hector, *Leiurus quinquestriatus*, *Buthus tamulus* and *Buthus epeus*), and function by preventing the closure of the voltage gated sodium channels in excitable cells. This results in prolongation of the action potential as well as in repetitive firing [3, 20, 21, 23, 26, 28, 39, 40].

The beta toxins are commonly found in the "New World" scorpion species (*Centruroides suffuses suffuses, Centruroides sculpturaus* and *Tityus serrulatus*) and act on activation process of sodium channel, and provokes spontaneous and repetitive firing of the membrane [3, 19, 20, 21, 22, 23, 26, 28, 39, 40]. Toxin y, found in the Brazilian scorpion *Tityus serrulatus*, accomplishes both tasks, as it blocks the opening and closing of sodium channels [20].

Posani *et al*, working with Mexican scorpions reported the action of the venom from the genus *Centruroides* on peripheral nervous system and muscle preparations. A drastic decrease on the ionic permeability properties of Na and K channels of the node of Ranvier, caused by application of scorpion venoms was observed by many investigators. Na – channel blocking peptides, major components of scorpion venoms, are assumed to be the principal cause of human envenomation due to stings by these arachnids [22].

K^+ channel blocking peptides

K^+ channel blocking toxins belong to a low molecular weight peptide family, with exquisite properties towards K^+ channels, opening the possibility to dissect the intricate molecular mechanisms of action of one of the most diverse receptors present in excitable membranes - the *K^+ channels* [22]. Sodium channel specific toxins are voltage gated. But potassium channel toxins have both voltage-gated and ligand-gated toxins. Potassium channel toxins have two sub-units. Alpha sub-unit is responsible for ion conduction across the membrane. Beta sub-unit is responsible for modulating the properties of the channel [21]. Toxins affecting neuronal K^+ channels have attracted considerable interest. They include *noxiustoxin* from the Mexican scorpion *Naxius Centruroides* and *charybdotoxin* from the old World scorpion *Leiurus quinquestriatus*. These

toxins are highly potent blockers of K^+ currents in neurons, but they differ in selectivity for subtypes of K^+ channels [19]. Potassium channels are found in nearly every excitable tissue, and play important roles in neurotransmitter release. Potassium channel specific toxins are thought to completely block potassium channels.

NTX – like peptides

Using monoclonal antibodies, two new *NTX – like peptides* were purified from the venom of the scorpion *Centruroides limpidus*. *Noxiustoxin* (NTX) was the first peptide purified, sequenced and shown to affect the voltage – dependent K^+ channel of axons [17-22].

Low molecular weight peptides specific for K^+ channels of various excitable tissues

Charybdotoxin (Chtx), a basic polypeptide from the Asian scorpion *Leiurus quinquestriatus*, originally described as a blocker of the *Ca – dependent K channel*, *Leiurotoxin* (LeTx), a low conductance, *apamin-sensitive K^+ channel blocker* from the same venom and *Iberotoxin* (IbTx) , *a high conductance Ca activated K channel* from the venom of the scorpion *Buthus tamulus.* These are examples of low molecular weight peptides specific for K^+ channels of various excitable tissues [17-22].

Serrulatoxins

From the venom of the Brazilian scorpion *Tityus serrulatus* three new low molecular mass peptides (*Serrulatoxins*) were isolated and shown to affect the *Ca dependent K channels of skeletal muscle*.

Sodium channel Toxins

Scorpion venoms contain protein toxins that prolong the opening of Na^+ channels by slowing the inactivation process (the so called alpha scorpion toxins) and cause Na^+ channels to open at membrane potentials at which they would normally be closed (the beta scorpion toxins) [19].

Excitability of neurons - repetitive action potentials

The toxins that affect the activation or inactivation of Na^+ channels can cause an increase in the excitability of neurons, leading to repetitive action potentials. This can lead to an increase in transmitter release. The toxins can produce a sustained depolarization of nerve membranes and nerve terminals.

This can block action potential conduction in axons, and cause an uncontrolled release of transmitter from nerve endings [19]. *Tityus zulianus* (Venezuelan scorpion) has beta toxin that works on skeletal muscle sodium channels. The venom of *Leiurus quinquestriatus*, like many other scorpion venoms, affects the myocardial cells directly as well as by neurotransmitter release [17-22, 39, 40].

Scorpion venom activates beta adrenoceptors and opening of "L-type" of Ca channels

Sofer and his colleagues demonstrated the effect of *Leiurus quinquestriatus Hebreus* venom on calcium uptake in cultured cardiac cells and concluded that the venom exerts its effects through activation of beta adrenoceptors which causes the opening of "L-type" of Ca channels [39, 40].

Toxins inhibit Ca^{2+} release from sarcoplasmic reticulum

Two toxins from the venom of scorpion *Pandinus imperato*r inhibited Ca^{2+} release from sarcoplasmic reticulum of both skeletal and cardiac muscle, by binding to ryanodine receptors [39, 40].

Toxin stimulate Ca^{2+} release

Toxin purified from the venom of *Buthotus hottento*ta stimulated the release of Ca^{2+} release from sarcoplasmic reticulum [5, 39, 40].

Highly toxic venomous scorpions of the world belong to Buthidae family

The largest family of poisonous scorpions is the Buthidae with the most highly toxic species of venomous scorpions of the world belong to *Androctonus, Buthus, Centruroides, Leiurus Quinquestriatus,* and *Tityus* genera [6, 39].

The clinical presentation of scorpion sting victims throughout the world, is similar

In spite of zoological differences among dangerous species (different kinds of poisons, and toxins which differ in chemical structure) symptomatology in humans following sting is quite similar and may concern the CNS, the autonomous system, the respiratory tract, the pancreas and the cardiovascular system. The effect of

the venom also depends upon the age of the offender (scorpion), the season and the size (body weight), age and sex of the victim [6, 39].

`The clinical presentation of pain at the site of sting, nausea / vomiting, sialorrhea, lacrimation, *profuse sweating,* abdominal pain, *tachydispnoea,* precordial pain, *arrhythmias,* hypertension, *agitation,* tremors, hyperglycemia, restlessness, prostration, tachypnea, pulmonary oedema and many manifestations in scorpion sting victims (*Mesobuthus tamulus concanesis, Pocock)* from India or clinical data of scorpion sting patients with severe scorpion envenoming caused by *Tityus serrulatus* from Brazil or Israel, Jerusalem, Tunisia, many more countries in Africa, Middle East, Saudi Arabia, Iran, Iraq, Pakistan, India, China, Nepal, Bangladesh, Srilanka, and elsewhere, more or less, is similar [1-23, 25, 27-33, 51, 53, 62, 63, 67, 75, 78-81].

What is the cause of death in scorpion envenoming syndrome?

Scorpion envenoming syndrome results in a severe autonomic storm *with a* massive release of *epinephrine, norepinephrine,* increased levels of angiotensin II [28], counter-regulatory hormones – glucagon [26], glucocorticoids [26], thyroid hormones [84] and *changes in insulin secretions* suppression of insulin secretion during "ebb" phase, and hyper insulin secretion during "flow" phase, hyperglycemia and increased circulating free fatty acid levels [25- 27, 30, 32-34, 41, 59, 60, 72, 79-84] (Fig. 1).

Sudden increase in Free Fatty Acids is toxic

Free fatty acids increase the oxygen consumption, aggravate the ischemic injury to myocardium predisposing to arrhythmias, heart failure, increase the susceptibility of the ventricles to the disorganized electrical behavior, inhibit cardiac sarcolemmal and erythrocyte Na^+ - K^+ ATPase activity, increase the tendency to intravascular thrombus - Disseminated Intravascular Coagulation (DIC) and many other abnormalities. These hormonal and metabolic changes could be responsible for the pathogenesis of a variety of clinical manifestations in scorpion envenoming syndrome [25- 27, 30, 32-34, 41, 59, 60, 72, 79-84].

Severe scorpion envenoming is a syndrome of fuel-energy deficits & Result in Multi-System-Organ-Failure (MSOF)

Under these conditions, scorpion envenoming syndrome with acute myocarditis, myocardial damage, disseminated intravascular coagulation (DIC), cardiovascular disturbances, peripheral circulatory failure, cardiac pulmonary oedema, Adult Respiratory Distress Syndrome (ARDS), and many other clinical manifestations may cause Multi-System-Organ-Failure (MSOF) and death. Under these altered conditions in the hormonal milieu due to autonomic storm and massive release of catecholamines, scorpion envenoming essentially results in a syndrome of fuel – energy deficits and an inability to use the existing metabolic substrates by vital organs causing MSOF and death [41] (Fig. 1).

Renin -angiotensin system

Increased sympathetic activity causes elevated Renin release by direct stimulation of juxtaglomerular cells. A subsequent increase in angiotensin II secretion enhances the ongoing sympathetic nerve output by a direct action on the brainstem and by a blunting of Baroreceptor mechanisms. Thus, the Renin-angiotensin system is an important facilitator of ongoing Sympathoadrenal traffic [85]. Hyperglycemia was found after envenoming. This could be due to a massive release of catecholamines, increased glucagon, Cortisol and changes in insulin secretion. Severe scorpion envenoming causes an increase in the circulating levels of blood sugar, insulin, glucagon, and Cortisol. Subcutaneous (s.c.) injection or i.v. injection of scorpion venom (*Mesobuthus tamulus Concanesis, Pocock*) in the dogs caused hypo-insulin secretion 30 min after venom injection, and elevated insulin levels 60 min after venom injection. Insulin and blood glucose were higher after 60 and 120 min of venom injection [5-8, 19, 24-34, 41, 52, 72, 79-84].

Leiurus quinquestriatus scorpion venom in the rat pancreatic islets inhibited insulin secretion and stimulation of glucagon secretion. Nor-epinephrine released from the adrenergic nerve terminals of the pancreas may be a more effective stimulus to glucagon secretion than nor-epinephrine reaching the pancreas through the general circulation [59, 60]. Glucocorticoids could also be released following stress or injury. The Sympatho-adrenal axis primarily serves to maintain the pressure necessary for organ perfusion. Thus, during the "ebb phase", the insulin levels are reduced and with the onset of hyper-metabolism, characteristic of the "flow phase", the hormonal environment is changed and the insulin levels are increased [69].

Hormonal actions are synergistic

The simultaneous elaboration of the counter-regulatory hormones is partly responsible for the pathogenesis of a variety of clinical and biochemical manifestations following scorpion envenoming. This could be the reason for glycogenolysis in the atria, ventricles, and liver; and skeletal muscles; hyperglycemia; lipolysis and elevated free fatty acid levels, increased protein breakdown products under the catabolic influence of the counter-regulatory hormones, and a simultaneous suppressed insulin secretion or insulin resistance [26, 27, 30, 32, 34, 41, 50, 79-84, 86, 87, 88] (Fig. 1).

Hyperinsulinemia - insulin resistance

Hyperinsulinemia observed in our studies could be equated with insulin resistance. Insulin resistance could be caused by a change in the receptor membrane, a change in hormone-receptor binding characteristics, or a change in the post receptor events [70].

Mechanisms of production of Hyperglycemia

Epinephrine elevates blood glucose and lactate concentration by a series of enzyme activities. In addition, insulin secretion is predominantly inhibited via alpha receptors [26, 27, 30, 32, 34, 41, 50, 79-88]. Epinephrine also can cause glycogenolysis in muscle (35) thus providing substrate in the form of lactate for hepatic gluconeogenesis [3, 4, 96]. In addition to circulating catecholamines, Nor-epinephrine released from nerve endings in the liver might influence glucose production. The liver is richly innervated by Sympathetic and Para – sympathetic nerves; Stimulation of Sympathetic system can lead to increased glucose production, an effect mediated mostly through activation of alpha adrenergic receptors [5-8, 26, 27, 30, 32, 34, 41, 50, 62, 79-88] (Fig. 1).

Role of Glucagon

Glucagon acts mostly on the liver and adipose tissue where it antagonizes the action of insulin. Glucagon raises blood glucose concentration by enhancing the breakdown of liver glycogen to glucose (glycogenolysis) and by promoting gluconeogenesis from lactate, pyruvate, glycerol and amino acids [59, 60, 85].

Role of catecholamines

Catecholamines (Adrenaline and Nor-adrenaline) act similarly (like glucagon) to enhance glycogenolysis but on molar basis, Adrenaline and Nor-adrenaline, are weaker than glucagon; however, Nor-adrenaline released locally at sympathetic nerve terminals might have powerful effects. Catecholamines (Adrenaline and Nor-adrenaline) antagonize insulin; promote glycogenolysis, and leads to hyperglycemia. Catecholamines promote glycogenolysis, in muscle and enhance lactate formation. Adrenaline enhances gluconeogenesis from lactate. Adrenalin inhibits glucose-induced secretion of insulin from the beta cells of islets in endocrine pancreas. Sudden stoppage of insulin secretion leads rapidly to hyperglycemia [59, 60, 85].

Reduction in glycogen content

Epinephrine stimulates inhibition of insulin secretion which in turn stimulates glycogenolysis in the muscle, thus providing a substrate in the form of lactate for hepatic gluconeogenesis [85]. This might explain the reduction in glycogen content of atria, ventricle, and liver and skeletal muscle in rabbits after venom injection and hyperglycemia in the dogs 30 min after venom injection [1, 37, 38, 46, 47, 50, 51, 62, 64, 88].

Small increases in the plasma epinephrine level during insulin deficiency can significantly worsen the resulting hyperglycemia. This occurs as a result of what is probably an additive effect on hepatic glucose production, without any additional change in glucose clearance. The small increase in epinephrine significantly increases the importance of gluconeogenesis, as the period of insulin deficiency becomes prolonged [26, 27, 30, 32, 34, 41, 50, 62, 64, 71, 73, 79-88].

Glucose toxicity

In virtually all tissues except the brain, glucose, at a fixed insulin concentration, promotes its own utilization in a concentration-dependent manner. The superiority of insulin in stimulating glucose oxidation seems to be explained by its anti-lipolytic effect. Even a small increment in serum insulin concentration promptly suppresses lipolysis, and consequently, the use of FFA for energy production, which in turn, enhances glucose oxidation. In contrast, glucose per se is unable to

suppress lipolysis in man. Glucose per se (i.e. hyperglycemia) is a cellular toxin. Hyperglycemia may cause a generalized desensitization of all cells in the body through the down-regulation of the glucose receptors in the glucose transport system [89].

Defect in insulin action - impairment in insulin secretion

In muscles and adipocytes, this would be reflected by a defect in insulin action, whereas at the level of beta cells of the islets of Langerhans, this would be manifested by impairment in insulin secretion.

Haemodynamic abnormalities in short-term insulin deficiency result in magnified lipolysis and beta oxidation of FFA

Hepatic overproduction and peripheral underutilization of ketone bodies

In diabetic keto-acidosis, the simultaneous relative insulin deficiency and excessive secretion of counter-regulatory hormones lead to magnified lipolysis and beta oxidation of FFA with a parallel hepatic overproduction and peripheral underutilization of ketone bodies. The clinical characteristics of patients are drowsiness and over-breathing. In addition, signs of circulatory collapse, such as tachycardia, weak pulse, and low blood pressure are normally present. Similar clinical manifestations are usually observed in scorpion sting victims [4-8, 42, 72, 86, 87].

Insulin levels in scorpion envenoming

Insulin levels, as measured by radioimmunoassay, were significantly suppressed or elevated after venom injection [19, 35-37, 45-48, 50, 52, 55, 57, 118].

Catabolic state with low Insulin / glucagon (I/G) ratio

The insulin/glucagon ratio (I/G ratio) may be more important than the levels of individual hormones. A high I/G ratio produces an anabolic state with more nutrient incorporation into peripheral tissues. When I/G ratio are low, a catabolic state is produced in which nutrients are mobilized. Scorpion envenoming causes a low I/G ratio [37, 39, 119].

"Hyperinsulinemia"

Hyperinsulinemia is said to exist when plasma insulin levels are inappropriate for the blood glucose estimated simultaneously. When insulin levels are elevated with a normal glucose level, "true hyperinsulinemia" is the most appropriate term, while high insulin levels with elevated blood glucose levels may be referred to as "insulin resistance". Elevated insulin levels were observed 30 min following venom injection [36, 37, 39, 50, 51, 55, 56, 57]. We have observed hyperglycemia along with suppressed/ reduced insulin secretion (hypo-insulin secretion) and hyperglycemia along with hyper-insulnemia in all our experimental animals [36, 37, 39, 50, 51, 55- 57]. This was confirmed by Deshpande and his co-workers in their experimental animals [68].

Hyperglycemia and hyper – insulinemia - insulin resistance

Hyperglycemia and hyper-insulinemia - insulin resistance is observed in all our experimental animals [37, 39, 46, 47, 50] and in the studies reported by Prem Kumar Choudhary [118]. Thus, development of insulin resistance is a possibility in scorpion envenoming syndrome.

Insulin resistant state

The relationship between insulin resistance, plasma insulin level, and glucose intolerance is mediated to a significant degree by changes in ambient plasma FFA concentration. Plasma FFA levels can be suppressed by relatively small increments in insulin concentration. Consequently, an elevation of circulating FFA concentration can be prevented if large amounts of insulin are secreted. If hyperinsulinemia can not be maintained, plasma FFA concentration will not be suppressed normally, and the increase in plasma FFA concentration will result in increased hepatic glucose production. Short-term hyperglycemia can induce insulin resistance [89].

Causes of insulin resistance

In any insulin-resistant state, the cause of insulin resistance can be due to an abnormal beta cell secretory product, circulating insulin antagonists, or target tissue

defect in insulin action. Insulin resistance could be caused by a change in the receptor number, hormone-receptor binding characteristics, or post-receptor events. Insulin receptors are probably down-regulated by high concentrations of agonist hormone/s [59, 60, 65, 70, 89]. Insulin resistance as a result of pre-receptor abnormalities involves metabolic (elevated counter-regulatory hormonal and non-hormonal) factors. Circulating insulin antagonists as a cause of insulin resistance have been clearly demonstrated in a variety of clinical syndromes. Excess endogenous or exogenous glucocorticoids are often associated with carbohydrate intolerance. Availability of substrates and plasma levels of glucagon, glucocorticoids stimulate hepatic glucose production through increased activity of hepatic gluconeogenic enzymes [59, 60, 65, 70, 89].

Post-receptor resistance can be caused by other hormones [37]. Hormonal antagonists consist of all counter-regulatory hormones, such as growth hormone, Cortisol, glucagon, and epinephrine. Increases in circulating levels of glucagon, Cortisol and catecholamines have been demonstrated in scorpion envenoming [37, 39]. In addition, a rise in corticosteroids decreases peripheral glucose utilization by diminishing the activity of glucose transporters and inhibiting insulin-mediated translocation of these facilitative transporters. Additionally, glucocorticoids affect insulin receptor affinity and number, decreasing insulin binding to its receptor. States of Catecholaminergic hyperactivity antagonize insulin effects through several mechanisms. Catecholamines stimulate hepatic glucose production by direct stimulation of glycogenolysis and gluconeogenesis and indirectly by increasing glucagon secretion. Additionally, catecholamines decrease peripheral glucose disposal both *in vitro* and *in vivo* Catecholaminergic hyperactivity [90].

The accelerated receptor degradation has been found to be responsible for a decreased number of receptors. The effect of acidic pH to accelerate insulin dissociation from the receptor is markedly reduced, leading to an inhibition of receptor recycling and acceleration of receptor degradation [90]. An increase in pH (acidosis) has been demonstrated in the experimental scorpion envenoming [47, 50]. Tissue insensitivity to insulin is an important pathogenic disturbance that contributes to glucose intolerance [62, 90].

Severe scorpion envenoming syndrome is thus a syndrome of fuel-energy deficits and an inability of the vital organs to utilize the existing metabolic substrates. This ultimately may result in Multi-System-Organ-Failure (MSOF) and death. These changes are bought about by a massive release of catecholamines, Angiotensin II, glucagon, Glucagon, Glucocorticoids, and either insulin deficiency, suppressed insulin secretion, or insulin resistance.

Scorpion envenoming causes sudden increase in Free Fatty Acids

Massive release of catecholamines, release of Angiotensin II, increased glucagon, increased Cortisol and/ or hypo-insulin secretion or insulin resistance thus produced can cause hyperglycemia and activate the hormone sensitive lipase, promote free fatty acid mobilization and produce a sudden increase in free fatty acid levels after venom injection [41, 42, 26, 27, 28, 31, 32, 35, 59, 60] We have demonstrated release of Angiotensin II, increased glucagon, increased Cortisol and/ or hypo-insulin secretion, hyperglycemia and a sudden increase in free fatty acid levels after venom injection (Fig. 1).

Significance of sudden increase in serum Free Fatty Acids

The catecholamines make available for active tissues more oxidizable substrates and at the same time depress the oxidation of glucose. There may be an excess of free fatty acids in the ischemic myocardium especially at the time when sudden death from arrhythmias are known to be common [59-62] .The excess of un-oxidizable free fatty acids could be toxic.

Physiological Basis of the increased FFA levels in scorpion envenoming

Glucagon is a powerful lipolytic agent, releases FFA and glycerol in to circulation [26, 27, 59, 60, 61, 62]. Adrenalin and noradrenalin activate specific *lipase* in adipose tissue and muscle which breaks down triglycerides to FFA and glycerol. This lipolysis might be mediated by cyclic AMP. This action is antagonized by insulin (Fig. 1).

The catecholamines make available for active tissue more oxidizable structures, such as FFA, glycerol, and ketone bodies, and at the same time depress the oxidation of glucose. The lipolytic action of adrenaline is

brief and the action of noradrenalin is prolonged. The catecholamines promote lipolysis in adipose tissue and proteolysis in muscle [26, 27, 59, 60, 61, 62].

SCORPION (Buthidae family) VENOM
Enzymes, Toxins-Neuropeptides, Pulmonary edema producing toxins
Scorpion envenoming syndrome
↓
Autonomic storm
↓
Massive release of Catecholamines
Angiotensin II
Hypertension, Hypotension
Hemoconcentration, Leucocytosis
↓
Increased levels of
Glucagon, Cortisol, Thyroid (T3, T4) Hormones
↓
Suppressed Insulin Secretion
Hyperglycemia, Sudden increase in Free Fatty Acid Levels
↓
Cardiac sarcolemmal defects
Acute Myocarditis
Arrhythmias, Conduction defects, Ischemia & infarction like patterns
Inhibition of Cardiac Sarcolemmal Na+-K+ ATPase Activity
Inhibition of Erythrocyte Na+-K+ ATPase Activity
Increased osmotic fragility of RBC, Haemolysis, Hyperkalemia
Cardiogenic & Non-cardiac pulmonary edema
ARDS, Disseminated Intravascular Coagulation, Hypocalcemia
Lactic acidosis, Ketacidosis
Death
Insulin Administration
Reversal of cardiovascular, metabolic& ECG changes
Reversal of Pulmonary Oedema

Fig-1 Mechanism of death in scorpion envenoming syndrome and its reversal by administration of insulin

Effect of increased Free Fatty Acids on the Heart

The use of increased amounts of Free Fatty Acids results in increased oxygen consumption. This could aggravate the ischemic injury to myocardium, predisposing to arrhythmias and heart failure. The elevated free fatty acids also increase the susceptibility of the ventricles to the disorganized electrical behavior and produce ectopic beats in the vulnerable period of cardiac cycle [61].

High levels of free fatty acids produce inhibition of Na^{+} - K^{+} *ATPase* activity [74] and produce cardiac sarcolemmal defects. Alterations in cardiac sarcolemmal Na^{+} - K^{+} *ATPase*, Mg^{++} *ATPase* and Ca^{2+} *ATPase* activities indicate cardiac sarcolemmal defects [34]. The increased Free Fatty Acids, by altering the functions of platelets, may increase the tendency to intravascular thrombus and result in disseminated intravascular coagulation [76]. Scorpion stings can be accompanied by enzymatic and electrocardiographic evidence of myocardial damage. Examination of myocardial ultra structure following scorpion sting reveals various types of cellular damage. Echocardiographic and radionuclide studies in human victims have shown depressed L.V. systolic function in patients tested within a few hours of scorpion sting [2-8, 39, 40, 61, 62, 64, 65, 67].

O_2 demand/ supply ratio - ischemia

Myocardial ischemia immediately following administration of scorpion venom is related to increased myocardial oxygen consumption associated with catecholamine release coupled with a decrease in oxygen supply due to transient reduction of coronary blood flow [2-8, 39, 40, 61, 62, 64, 65, 67].

Metabolism of normal myocardium and role of insulin

Under normal conditions, the myocardium derives its energy from the aerobic metabolism of substrates extracted from the plasma. The most important fuels are Free Fatty Acids (FFA), glucose, triglycerides, amino acids, Pyruvate and lactate. At rest, the myocardial extraction of many of these substrates is generally related to their arterial concentrations, but the relative uptake of each compound may be modified by hormones and utilization of other substrates. Thus, glucose transport into the myocardial cell depends on insulin, and increases of plasma insulin concentration enhance the extraction of glucose by the heart [2-8, 25 - 28, 30, 31, 32, 34, 39, 40, 61, 62, 64, 65, 67, 79-84].

On the other hand, myocardial glucose utilization is negatively correlated with plasma FFA levels, which means that high plasma FFA concentrations inhibit glucose uptake by the heart. In the human heart, a 10% increase of plasma FFA decreases the myocardial extraction of glucose by 17%, while a 10% increase of

plasma insulin enhances glucose utilization by an average of 24%. We have consistently demonstrated a sudden increase in FFA levels (200 to 300%) in the experimental scorpion envenoming [25, 26, 27, 28, 30, 31, 32, 34, 41, 79-84].

Myocardial vulnerability

While myocardial vulnerability may finally be determined by critical extra and intra cellular gradients in the availability of Ca^{2+}, Mg^{++} and K^{+} , the intracellular concentrations of these ions, are in turn, dependent on factors which influence their transference across the cell and mitochondrial membranes. A decreased availability of Ca^{2+} can interfere with Actin-Myosin coupling so that contractility is impaired. An excess of K^{+} could alter the action potential so that self perpetuating re-entry currents are established [61-65]. We have demonstrated hyperkalemia [91]. Low concentrations of myocardial Mg^{++} are associated with arrhythmias and sudden death. We have demonstrated alterations in cardiac sarcolemmal Mg dependent *Na^{+} - K^{+} ATPase* and *Mg^{++} ATPase* activities [24].

Accumulation of excess intra cellular FFA: Detergent effect on cell membranes

Accumulation of excess intra cellular FFA could have a detergent effect on cell membranes [31]. This accumulation could result from decreased oxidation in the myocardium and catecholamine-induced hydrolysis of stored triglycerides in addition to increased uptake resulting from higher concentrations in arterial blood. Elevated concentrations of plasma FFA have been associated with an increased prevalence of serious ventricular arrhythmias and death in man and in dogs. High plasma FFA levels with increased ST elevation in the ECG and plasma CK enzyme levels were reported [2-8, 26, 27, 30, 32, 33, 34, 79-84, 91].

Excess un-oxidized FFA - toxic to the myocardium

Excess un-oxidized FFA probably becomes toxic to the myocardium only when there is acute ischemia. The biochemical consequences which result from the intra cellular accumulation of excess un-oxidized FFA for Ca^{2+} will occur simultaneously with protein binding, possibly making less ionic calcium available for passage into the sarcotubular reticulum. This might interfere with tropomyosin-troponin activation of Actin-Myosin coupling [61-65]. Magnesium – fatty acid complexes could result and any intra cellular depletion of Mg^{++} would be exaggerated. This might lead to uncoupling of oxidative phosphorylation, possibly by interfering with a Magnesium-dependent ATPase system (Mg^{++} ATPase). Cardiac sarcolemmal Na^{+} - K^{+} ATPase is also a Magnesium-dependent ATPase system [34, 61-65].

Fatty acids may be transported intra-cellularly in the un-esterfied form and have specific affinities for certain subcellular structures. Esterification of certain phospholipids of the mitochondrial and cell membranes may be altered when there is excess un-oxidized FFA. Different cell membranes have lipoprotein layers with variable permeability for ions, and this could also be changed if the intra cellular accumulation of FFA were to have a detergent action leading to cat-ion loss. Excess un-oxidized fatty acids or metabolites could alter the stabilization of lysosomal membranes and mitochondrial integrity, and together they can have a synergistic effect [34, 41, 61-65, 74]. Elevated FFA levels with incidence of different types of arrhythmias, conduction defects, ischemia, and infarction – like patterns in ECG have been shown in our experimental animals with scorpion envenoming [24 -34, 41, 79-84, 91] and in scorpion sting victims [2, 4-8, 39, 40]. Increased FFA oxidation can inhibit glycogen synthatase activity directly by causing a dissociation of its sub-units.

FFA stimulates gluconeogenesis

An elevated rate of FFA oxidation also has important effects on the hepatic glucose metabolism. *In vitro* studies have demonstrated that FFA stimulates gluconeogenesis [61-65, 74]. The following sequence might explain the relationship between plasma FFA concentrations, lipid oxidation, and glucose metabolism at the level of the liver:

1. Increased plasma FFA, by mass action, enhance their cellular uptake, which leads to an increase in lipid oxidation that provides the stimulus for activation of the key enzymes involved in the regulation of gluconeogenesis;

2. At the same time, the augmented rate of lipid oxidation provides a continued source of energy (ATP) and substrate to drive gluconeogenesis;

3) In addition, the uptake of circulating gluconeogenic precursors by the liver is elevated. The inhibitory influence of insulin on gluconeogenesis is much more resistant than its restraining action on glycogenolysis.

In addition to respiratory acidosis, metabolic acidosis could also be the basis of acidosis resulting in cardiovascular deficiency and death in envenoming [30]. Both experimental dogs and pigs due to scorpion envenoming developed a marked metabolic acidosis. This phenomenon is also a common feature of envenomed human victims that may be present with no apparent organ failure. This finding strongly suggests a decrease in peripheral organ oxygen utilization relative to demand [2, 4-8, 39, 40].

Lactate and peripheral ischemia

Although measurement of Lactate to Pyruvate ratio would have been necessary to be certain of peripheral ischemia as opposed to increased glucose utilization, the presence of decreased HCO_3 and persistent metabolic acidosis in our envenomed animals [30] strongly suggests that increased lactate was at least in part due to peripheral ischemia [2, 4-8, 39, 40].

Production of ketone bodies in scorpion envenoming could be mediated by suppression of endogenous insulin secretion [30] due to massive release of catecholamines. Tissue anoxia caused by massive release of catecholamines result in lactic acidosis. Our findings of decrease in the arterial Oxygen tension, steep rise in P CO_2, reduction in pH and fall in HCO_3^- in the envenomed animals [30] concur with those reported by Gueron et al [11-18, 105, 106]. We have reported a reduction in FFA levels, disappearance of different arrhythmias, conduction defects, ischemia, and infarction – like ECG patterns with normal sinus rhythm after insulin administration in experimental envenoming [40, 41] and in scorpion sting victims [47, 50].

Insulin counteracts all the deleterious effects of FFA by

a) Inhibiting the catecholamine-induced lipolysis in the adipose tissue, thus reducing the plasma FFA level,

b) Facilitating the glucose transport to the myocardium and glucose metabolism through different pathways; and

c) Increasing the intracellular potassium concentrations

Insulin administration reversed metabolic changes and other abnormalities due to envenoming. Insulin stimulates activation of glycogen synthetase system. This could be the reason for an increase in glycogen content of cardiac, skeletal muscles and liver of the insulin, alpha blocker + sodium bicarbonate treated animals after envenomation. Moreover, glycogen availability may be an important independent determinant of cardiac function. Elevated glycogen in heart partially protects against mechanical deterioration in anoxia [125]. Insulin stimulates glycogen synthesis [4]. Thus insulin counter-acts the effects of catecholamines favoring glucose uptake and inhibition of glucose release from liver. This could be the reason for an increased glycogen content of atria, ventricle, liver and skeletal muscle after insulin administration.

Insulin administration suppresses the release of FFA from adipose tissue and this effect is immediate and even faster than the effect on plasma glucose levels [4, 96]. Insulin stimulates lipogenesis [85]. This could be the reason for the sudden reduction of free fatty acid levels and increased triglyceride levels in the venom poisoned animals after administration of insulin. Moreover, infusion of glucose in these animals along with insulin, will suppress fat mobilization by favoring re-esterification. In our hands, administration of insulin or insulin + alpha blocker (Tolazodine) + Sodium bicarbonate [47] successfully reversed the metabolic as well as ECG changes.

Insulin assists in the recovery of myocardial contractility after ischemic arrest and increases cardiac output. Insulin also assists glucose transport and can accelerate ATP production in ischemic areas. Insulin stimulates cardiac sarcolemmal Na^+ - K^+ ATPase activity, inhibits Ca^{2++} ATPase activity, and stabilizes lysosomal membranes. The Na+ - K+ pump has a key function in the exchange of substances between the cells and its surroundings, in trans-epithelial transport, and in transmission of information. Three isoforms of Na^+ - K^+ ATPase alpha sub-unit have been identified. The functional implications of having three isoforms of the Na^+ - K^+ ATPase enzyme are still unknown. The only observation that points towards a special function is that the affinity of the alpha 2 isoforms for Na^+ from muscles and adipocytes is increased by insulin [92].

The activity of Na^+ - K^+ pump in the intact membrane is determined by a combined effect of the cyto-plasmic and extra cellular Na^+ to K^+ concentration ratios and other factors. Insulin, epinephrine, and nor-epinephrine have a stimulating effect on the pump. The alterations in the cardiac sarcolemmal and red blood cell Na^+ - K^+ ATPase activities and reduction in insulin secretion are shown in scorpion envenoming.

We concur with Gueron et al that the management of human severe scorpion envenomation should be directed toward neutralizing the over stimulated autonomic nervous system [84-90]. All patients with systemic manifestations, such as severe hypertension, Hypovolemia, pulmonary oedema or patients in shock should be admitted to a critical care unit under close electrocardiographic, and haemodynamic monitoring. These facilities are not available in many of the developing countries where scorpion envenoming is a rural emergency. We feel that the administration of insulin-glucose infusion is directed toward neutralizing the over stimulated autonomic nervous system. The administration of insulin-glucose infusion will also regulate severe hypertension, Hypovolemia, pulmonary oedema or patients in shock.

Summary of cardiovascular, hormonal & metabolic changes

The initial transient hypertension followed by hypotension, cardiovascular manifestations, metabolic disturbances, electrocardiographic changes, and adult respiratory distress syndrome and many other clinical manifestations produced by scorpion venom toxicity could be due to

1. Action of catecholamines causing increased myocardial oxygen consumption due to positive and chronotropic effects, coronary vasoconstriction, peripheral vasoconstriction and increased after load, Lipolysis resulting in increased FFA;

2. Action of angiotensin II resulting in coronary and peripheral vasoconstriction, potentiation of catecholamine mediated effects,

3. Insulin deficiency

4. Increased FFA resulting increased myocardial oxygen consumption; and

5. Arrhythmogenic effect of catecholamines, angiotensin II and free fatty acids.

Insulin administration resulted in glycogenesis, lipogenesis, stopped arrhythmias and reversed the ECG changes to sinus rhythm.

Administration of insulin

Administration of insulin under these circumstances should counter-act the metabolic effects of catecholamines, stimulate lipogenesis, glycogenesis, reverse the metabolic and electrocardiographic changes in acute myocarditis induced by Indian red scorpion (Buthus tamulus) venom in the experimental dogs. The dose of insulin is 0.3 Units of regular insulin per gram of glucose, and glucose 0.1 g Kg^1 per hour. Blood glucose, serum electrolytes, electrocardiogram, and arterial blood gases should be investigated on admission. In addition to regular clinical observations, estimations of blood glucose should be carried out two hourly and of serum electrolytes 12- hourly. Glucose levels should be maintained between 130 and 180 mg dl^1 of blood.

Insulin administration produced a reduction in FFA, an increase in triglyceride levels and increased tissue glycogen content in cardiac and skeletal muscle and that of liver. The increase in arterial blood pressure “hypertension” came back to normal pressure after insulin administration in the experimental animals and scorpion sting victims. The fall in arterial blood pressure “hypotension” came back to normal pressure after insulin administration in the experimental animals and scorpion sting victims.

Conclusion

It is concluded that the venom from the scorpions of Family Buthidae produce autonomic storm, massive release of epinephrine, nor-epinephrine (catecholamines), an elevation in angiotensin levels, an increase in counter-regulatory hormones and suppressed insulin secretion or insulin resistance, cause metabolic and cardio-respiratory changes . The metabolic, cardio-respiratory changes and electrocardiographic changes are reversed by administration of insulin.

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