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Nephrotoxic effects of Cnidaria toxins

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ABSTRACT

There are many species of animals in the marine environment which are potentially dangerous to humans. Cnidarians that are responsible for burns are mainly found in tropical waters, but there are several species with cosmopolitan distribution. In some cases, contact with toxins from Cnidarians can cause symptoms of acute kidney damage. Because of an enormous diversity of the toxins produced by individual species of cnidaria, the mechanisms of renal damage are different in different cases. Currently, there is only one antitoxin available to treat burns by Cnidarians, this antitoxin can neutralize the toxin produced by Chironex fleckeri. However, recent studies on animal models give hope for the introduction of a universal biological agent that would be capable of inhibiting the activity of toxins produced by a variety of Cnidaria species.

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Keywords: Cnidaria, box jellyfish, acute kidney injury, treatment

INTRODUCTION

A direct contact with the venom of marine animals poses a considerable health risk to individuals who spend time in marine waters (e.g. while swimming or scuba diving). Cnidaria represent a marine species which is particularly dangerous to humans. Cnidarians are classified into five main groups: (1) sessile Anthozoa (e.g. sea anemones, corals, sea pens), (2) swimming Scyphozoa (jellyfish), (3) Cubozoa (box jellies, e.g. *Chironex fleckeri*), (4) swimming or sessile Hydrozoa (giant colonial Portuguese man-o'-war) and (5) Staurozoa (benthic, stalked jellyfishes) [1]. Cnidarians have two different body forms, the polyp and the medusa. Each year, an estimated 150 million people worldwide suffer burns from jellyfish alone [2]. Cnidarians have specialized cell structures (called cnidocytes), which are mainly found on the tentacles and around the mouth of both jellyfish and polyps. Cnidarians are classified into two groups: those with a cnidocyte, which is a sensory bud (called nematocyst) and those without a cnidocyte (called sporocyst) [3]. The nematocyst consists of a capsule that contains a spirally coiled hollow thread. The thread is usually armed with barbs or hooks and filled with toxins. When activated, the thread is ejected from the capsule at high speed [4]. As a result of stimulation of the cnidocyte, venom is released into the victim [5]. The composition of the venom varies depending on the species and consists of a mixture of proteins, polypeptides, and other molecules, including low molecular weight biogenic amines (e.g. serotonin, histamine, bunodosine, caissarone), neurotoxins, and larger molecules such as enzymes (phospholipases and metalloproteinases). Another feature which

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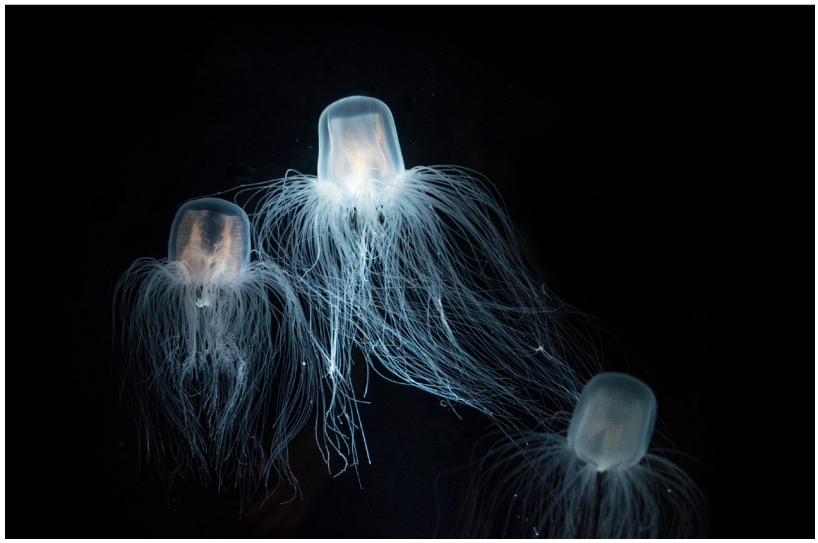

Figure 1. *Chironex fleckeri*

is characteristic for cnidarians is their ability to produce pore-forming toxins (PFTs) [6]. Particular attention should be paid to phospholipase A_2, which is often found in cnidarian toxins. It catalyzes the hydrolysis reaction of glycerophospholipids, releasing fatty acids, among many other compounds. With phospholipase A_2 participation, metabolites of arachidonic acid are formed and then further metabolized. Prostaglandin biosynthesis may contribute to the increase in the concentration of reactive oxygen species. Its activation is the beginning of a chain of events leading to cell damage [7]. Cnidaria produce toxins to kill and then digest their prey, but also to deter predators, and maintain their territory (intra-species spatial competition) [4].

A direct contact with Cnidaria species normally manifests as a localized skin lesion at the site of envenomation. However, in some cases, contact with the most toxic representatives of Cnidaria species may even lead to death [8–11]. In recent years, there have been numerous reports of acute kidney injury (AKI) resulting from Cnidaria envenomation. The possibility of isolating individual toxins and conducting experimental studies on animal models has allowed researchers to determine the mechanism of Cnidaria-related AKI. The aim of this study was to present the most dangerous Cnidarian species with a nephrotoxic potential, as well as to indicate new directions of research in the area of modern treatment methods for Cnidaria envenomation.

CNIDARIANS DANGEROUS TO HUMANS

Of all the Cnidaria species, free-floating jellyfish cause most stings in humans. In contrast, injuries caused by anemones are relatively rare, as most of them are attached to the seabed and usually do not move on their own [12]. There are three classes of Cnidarians which are particularly dangerous to humans, it is therefore very important to identify the species responsible for the burn and envenomation [3]. For example, box Jellyfish (class Cubozoa), which includes the Australian *Chironex fleckeri* (Fig. 1) is considered extremely dangerous.

The Australian *Chironex fleckeri* inhabits the tropical waters of northern Australia and the Indo-Pacific region. The species is especially abundant in the summer [13]. Their tentacles contain millions of nematocysts supplied with a deadly venom [14]. The venom is rich in phospholipase A_2 (PLA_2), CfTx-1, CfTx-2, Cftx-A, Cftx-B. PLA_2 causes cytolytic and hemolytic effects, while CfTx-1 and Cftx-2 have cardiotoxic, cytotoxic, and dermonecrotic effects. Cftx-A and Cftx-B have hemolytic properties [15]. Studies on animal models suggest that *C. fleckeri* toxins have a direct negative effect on heart muscle cells and vascular endothelium [10, 11]. The burn initially causes tingling, paresthesia, burning, itching, and throbbing pain [16]. The skin is reddened, and blisters may occur at the site of the burn. Within 1–2 weeks of exposure the initial lesions can progress into necrosis. The envenomation by *Chironex fleckeri* can also be associated with systemic symptoms such as fever, vomiting, respiratory failure, and kidney failure. Death from poisoning can occur within 2–10 minutes as a result of cardiac arrest and drowning [17]. More than 70 deaths have been documented from *Chironex fleckeri* burns; most of them sustained by children [18].

The Irukandji Jellyfish (*Carukia barnesi*) (Fig. 2) of the Cubozoa class, similarly to *Chironex fleckeri*, is seasonally found in the waters north-east of Australia (from November to May). The venom of *C. barnesi* contains, among

Figure 2. *Carukia barnesi*

others, PLA_2 which has cytolytic and hemolytic properties and CbTX-I and CbTX-II proteins with a neurotoxic potential [19]. A burn can cause a 'catecholamine storm' known as the Irukandji Syndrome [20]. *C. barnesi* is a very small medusa, which allows it to enter even those areas which are protected by special nets. Systemic symptoms usually occur with a delay of 20–40 minutes [21]. It is believed that this is related to the fact that because of the small size of the toxin particles (50–100 kDa), the toxin is distributed through the body via the lymphatic vessels [21]. Mild erythema may occur at the site of contact. Axial symptoms of the Irukandji Syndrome include truncal pain, particularly lower back pain, limb pain, severe tachycardia, and eventually cardiac failure [22]. Acute kidney damage occurs as a result of vasospasm, high blood pressure, and a decrease in blood flow.

Portuguese man-o´-war (*Physalia physalis*) (Fig. 3) belongs to the class Hydrozoa; it is in fact a colony of polyps, which is characterized by the presence of a floating sac (pneumatophore). It is present in the waters surrounding Australia, New Zealand, Indonesia, Florida, Chile, Brazil, Venezuela, and in the Atlantic [23]. *P. physalis* produces physaliatoxin, a glycoprotein with a mass of 240 kDa, which has a cytotoxic as well as hemolytic potential [24]. Moreover, the venom contains PLA_2, a collagenase with cytotoxic and hemolytic properties, as well as an elastase, which is toxic to muscle cells and also exhibits a hemolytic potential. In addition, the toxin produced by *Physalia physalis* was found to contain: PpV19.3 (neurotoxic, cardiotoxic properties), PpV9.4 (hemolytic properties), P1, P3 (neurotoxic properties), DNase (cytolytic properties) [1, 25]. The burns can cause local erythema, blisters, skin necrosis, intense pain, and a burning sensation. In severe cases, systemic symptoms such as vomiting, nausea, hypotension, seizures, cardiac arrhythmias, respiratory failure, and sometimes death may occur [26]. Kidney damage occurs mainly as a result of hemolysis [27].

Figure 3. *Physalia physalis*

Figure 4. *Phylodisscus semoni*

Table 1. Toxins, properties, and recommended medical treatments

Cnidaria class	Toxins	Properties	Clinical picture	The main mechanism for kidney damage	Treatment
Chironex fleckeri Cubozoa	Phospholipase A2	Cytolytic hemolytic	Paresthesia, skin necrosis, itching, pain, fever, vomiting, symptoms of respiratory failure, AKI	Hemolysis	4–6% vinegar — 30 s, sea water, bioCSL's box jellyfish antivenom
	CfTx-1	Cardiotoxic, cytotoxic, nephrotoxic			
	CfTx-2	Cardiotoxic, cytotoxic, nephrotoxic			
	CfTx-A	Hemolytic			
	Cftx-B				
Carukia barnesi Cubozoa	Phospholipase A2	Cytolytic hemolytic	Irukandji syndrome delayed onset — 20–40 min, typical symptoms: back pain, limb pain, severe hypertension, sweating, cardiac dysfunction	Prerenal kidney failure due to vasoconstriction, reduced perfusion, cardiac dysfunction	4–6% vinegar — 30 s, analgesics: opioids*, clonidine, magnesium sulphate — to relief pain, RR measurements nitrates**
	CbTx-I	Neurotoxic			
	CbTx-II	Neurotoxic			
Physalia physalis Hydrozoa	Physaliatoxin	Cytotoxic hemolytic		Rhabdomyolysis	Sea water to rinse remaining tentacles, hot water
	Phospholipase A2				
	Elastase	Myotoxic Cytolytic hemolytic			
	PpV19.3	Neurotoxic Cardiotoxic			
	PpV9.4	Hemolytic			
	P1	Neurotoxic			
	P3	Neurotoxic			
	DNase	Cytolytic			
Phyllodiscus semoni Anthozoa	PsTX-T	Nephrotoxic	Jaundice, petechiae or mucosal bleeding, kidney damage	TTP (Thrombotic Thrombocytopenic Purpura)/atypical HUS	

*with the exception of pethidine

**contraindicated with concurrent use of phosphodiesterase inhibitors

The night sea anemone (*Phyllodiscus semoni*) (Fig. 4), which belongs to the Anthozoa class, is particularly toxic to humans. It inhabits waters of the western Pacific, as well as the waters surrounding Indonesia, and southern Japan. The venom causes hemolysis and AKI [28]. It contains the PsTX-T toxin and the PsTX-115 protein, which are both nephrotoxic, as shown on animal models [29]. In addition, proteins with hemolytic potential were isolated from the night sea anemone. They include PsTX-20A, PsTX-60A and PsTX-60B. The membrane-attacking complex and perforin activate the complement and are responsible for the occurrence of hemolytic-uremic syndrome (HUS) [29].

Table 1 lists the toxins produced by individual classes of Cnidaria species, clinical symptoms, and initial medical treatments for envenomation.

NEPHROTOXIC EFFECTS OF CNIDARIA TOXINS

AKI in humans is well documented in cases of contact with jellyfish and sea anemones [30]. According to the Kidney Disease Improving Global Outcomes (KDIGO), AKI is defined by a serum creatinine increase ≥ 0.3 mg/dL (26.5 μmol/L) within 48 hours or an increase ≥ 1.5 times baseline or urine volume < 0.5 mL/kg/h for 6 hours [31]. Production of PFTs, which are responsible for damaging the integrity of cell membranes, is characteristic for Cnidaria envenomation [32]. The consequence of membrane damage is an uncontrollable movement of ions: influx of Na^+, Ca^{2+}, and loss of K^+ ions [28]. The resulting damage is caused by a significant loss of plethora of macromolecules, while the continuous increase in cytosolic Ca^{2+} leads to

Table 2. Laboratory tests essential in AKI diagnosis

Laboratory tests	Interpretation
Low hemoglobin concentration with accompanying thrombocytopenia and schistocytes present in the blood film, high LDH, high potassium concentration	Microangiopathic hemolytic anemia
High creatinine and urea concentration	Acute kidney injury
High CK and myoglobin concentration, high potassium, phosphorus and uric acid concentration, dark urine	Rhabdomyolysis
Low hemoglobin concentration, elevated reticulocyte count, increased total and free bilirubin, increased LDH concentration, decreased haptoglobin concentration	Hemolysis

cell damage. The influx of Ca^{2+} into cells is responsible for several clinical symptoms observed following a contact with the toxin [29]. In turn, PLA_2 can cause acute damage to the renal tubules [33].

HEMOGLOBINURIA

Intravascular hemolysis results from the breakdown of erythrocytes under the influence of toxins released by Cnidaria with a hemolytic potential. The hemolytic properties of the Cnidaria toxins have been well described for the *Physalia physalis* and box jellyfish species [34]. Clinical symptoms characteristic of hemolysis include sudden yellowing and abnormal paleness of the skin, in addition to general symptoms resulting from anemia such as decreased exercise tolerance, tachycardia, or dyspnea. Laboratory signs of hemolysis are listed in Table 2. Free hemoglobin (Hb) binds with haptoglobin (Hp), and the complex is metabolized in the liver. In the case of Hp saturation, the only way to remove free Hb is filtration in the renal glomeruli. Free Hb has a direct toxic effect on renal tubules as it induces enzymes responsible for oxidative stress [35]. In addition, the forming casts mechanically disrupt the urine flow in renal tubules [36, 37]. The pathophysiology of renal damage in hemoglobinuria is based on three mechanisms: direct damage to tubular epithelial cells, vasoconstriction leading to reduced kidney perfusion, and tubular obstruction by casts. Treatment may be difficult because in the case of cnidarian toxins there is no possibility of causal treatment. Maintaining proper hydration and forcing diuresis is crucial. Isotonic salt is recommended. In some cases, it is necessary to start renal replacement therapy [38].

RHABDOMYOLYSIS

Rhabdomyolysis (RML) is caused by damage to striated muscle cells, which results in a release of large amounts of myoglobin into the peripheral circulation [39]. Cases of RML have been reported following contact with *Physalia physalis* [40]. The classic presentation of this condition includes muscle pain, weakness, dark urine (due to the presence of myoglobin), and markedly elevated serum creatine kinase (CK) levels, exceeding the upper limit five to ten times. Measurement of CK activity is helpful in estimating the risk of kidney damage. Low risk of kidney damage corresponds to a CK value of less than 5,000 U/L. Individuals with CK level between 5,000 and 15,000 U/L are at a high risk of kidney damage. At CK values > 15,000 U/L, there is a high risk of requiring renal replacement therapy [41]. Other laboratory parameters and tests characteristic of RML are listed in Table 2. Similar to hemolysis, the mechanisms leading to AKI include direct damage to tubular epithelial cells, vasoconstriction leading to reduced kidney perfusion, and tubular obstruction by casts. Myoglobin can bind nitric oxide (NO), which leads to its neutralization and eliminates its vasodilatory effect. In turn, vasoconstriction leads to renal hypoperfusion and ischemia [42]. Regardless of the etiology, treatment should be aggressive. Prevention of renal damage in the form of intravenous fluid therapy should be implemented as soon as possible to maintain renal perfusion, minimize ischemic damage, and increase urine production. Dissolution of the heme dye partially removes obstructing intratubular casts and increases urinary excretion of potassium [43]. In addition to an isotonic salt infusion, sodium bicarbonate is used in selected cases in the treatment of rhabdomyolysis when the CK concentration exceeds 5,000 U/l and the blood pH is lower than 7.5 [44].

HEMOLYTIC-UREMIC SYNDROME

Phyllodiscus semoni is a highly toxic sea anemone. Its venom has multiple unfavorable effects, including, hemolysis, renal injuries, or even death. Characteristic symptoms of HUS (hemolytic-uremic syndrome) include jaundice, skin petechiae or bleeding from mucous membranes, and kidney damage. The mechanism of nephrotoxicity has been well documented in studies conducted on animal models. The toxin PsTX-T obtained from *P. semoni* nematocysts has shown nephrotoxic properties in the form of damage to the glomerular endothelium in a similar way to an atypical HUS (aHUS) [45]. The underlying mechanisms of renal injuries in humans are not clearly understood. Data available in the literature regarding treatment is based only on case

reports. Making the correct diagnosis involves performing a detailed differential diagnosis including TTP (thrombocytopenic purpura), typical HUS, and the genetic background responsible for aHUS. Currently, complement inhibitors (anti-C5 antibody, Eculizumab) are used for the treatment of atypical HUS in humans. Based on the results of studies on animal models, anti-complement therapy might be an option to treat HUS caused by sea anemone toxin [29].

TREATMENT

Therapeutic problems we are dealing with are primarily related to the lack of guidelines based on EBM (Evidence-Based Medicine). The meta-analysis conducted by McGee on the recent treatments of jellyfish burns, revealed no study that would bring breakthrough results [46]. There are many reasons behind the difficulties in providing appropriate treatment. In some cases, it is difficult to determine the species of the animal and thus the type of toxin that had caused the envenomation. One solution that allows an experienced diagnostician to recognize a jellyfish species involves applying an adhesive tape to the area of the skin where fragments of previously neutralized jellyfish fragments remain [47]. The second problem is the lack of possibility of using specific antitoxin in first aid conditions. The effectiveness of the currently available antitoxin for *C. fleckeri* is still a subject of debate. A rapid penetration of toxins into the capillaries immediately triggers a quick onset of symptoms of severe poisoning and delayed administration of antitoxin means that it may be ineffective [48, 49]. Indications for administration of the antitoxin include cardiac arrest, heart failure, acute respiratory failure, and pain that does not subside after analgesics [50]. For travelers arriving at places where burns are common, the choice of external agents may be problematic. Vinegar applied to the burn site does not neutralize the toxin that has already been released, it only leads to limiting a further release of toxin, and it also has no analgesic properties. It should be remembered that in some cases, the use of vinegar may promote further release of the toxin, as in the case of *Physalia physalis* and other jellyfish occurring outside of the tropical waters [51]. Ice packs, warm water, and topical anesthesia can be used in pain relief only after the procedure of neutralizing nematocysts is completed [52]. The diagnosis of a generalized reaction to the toxin is tantamount to an urgent need to transport such a person to the hospital. The possibility of AKI should be considered already at this stage of the procedure. Monitoring vital parameters such as heart rate and blood pressure is essential. The purpose of performing an ECG is to detect rhythm and conduction disorders early. Laboratory tests should include not only creatinine concentration measurement, but also parameters such as: CK, LDH, ALT activity measurement, general urinalysis, haptoglobin concentration, which may be helpful in early differentiation of the mechanism of kidney damage. To sum up, first aid after a contact with cnidarian toxins will depend on the geographical region where the event occurred. If these were tropical waters of Australia or the Indo-Pacific, the first choice would be vinegar at a concentration of 3–6% [53]. In the case of other waters, it is recommended to use hot water. Alcohol, fresh water, or any other substances should not be directly applied to damaged skin at any instance, as this may cause a release of toxins from the intact nematocysts [51].

The venom of cnidarians is a mixture of active substances, the effects of which cannot always be predicted. Therefore, the knowledge of pathological mechanisms developing in humans as a result of burns is still insufficient. The toxin can directly damage cells, but also generate inflammation and form complexes with other proteins. New directions of research include the development of specific inhibitors of toxic venom components. One of the most common proteins among animal toxins is PLA_2. PLA_2 is present in the composition of toxins not only of cnidarians, but also of other animals, such as snakes. It catalyzes the hydrolysis reaction of glycerophospholipids, releasing fatty acids. With PLA_2's participation, metabolites of arachidonic acid are formed and then further metabolized. The biosynthesis of prostaglandins can contribute to an increase in the concentration of reactive oxygen species. Its activation is the beginning of a chain of events leading to cell damage [7]. PLA_2 inhibition may be a fundamental action preventing the escalation of damage caused directly and through interactions with other proteins, which lead to coagulopathy. Currently, a PLA_2 inhibitor, varespladib (LY315920), is in the research phase [7]. Studies on animal models have shown the inhibitor's effectiveness in blocking PLA_2, as well as its nephroprotective effect (in ameliorating hemolysis, rhabdomyolysis and renal function) [54].

CONCLUSIONS

Prevention is the best method of action in the event of contact with Cnidaria. Providing appropriate care to an injured person can be complicated, especially if a burn takes place away from the shore. People who are planning to go diving or surfing in waters inhabited by Cnidaria species, should familiarize themselves with local announcements and recommendations concerning the prevention and treatment of burns by cnidarian species. The best preventive methods include keeping up to date with announcements and wearing protective clothing (a wetsuit). It is possible to apply external preparations and solutions to the injured skin, although the effectiveness of such treatment has not been established in studies. Also, it needs to be kept in mind that even dead marine fauna is potentially dangerous to

humans, because it still contains toxic substances which can cause envenomation.

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