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Bioactive toxins from stinging jellyfish

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ABSTRACT

Jellyfish blooms occur throughout the world. Human contact with a jellyfish induces a local reaction of the skin, which can be painful and leave scaring. Systemic symptoms are also observed and contact with some species is lethal. A number of studies have evaluated the *in vitro* biological activity of whole jellyfish venom or of purified fractions. Hemolytic, cytotoxic, neurotoxic or enzymatic activities are commonly observed. Some toxins have been purified and characterized. A family of pore forming toxins specific to Medusozoans has been identified. There remains a need for detailed characterization of jellyfish toxins to fully understand the symptoms observed *in vivo*.

1. Introduction

Cnidarians are found in seas and oceans throughout the world. They are characterized by their specialized cells, the cnidocytes, which are used for prey capture, defense, and locomotion (Anderson and Bouchard, 2009). The phylum is divided into two clades, Anthozoa, which includes sea anemones and corals, and Medusozoa, comprising the classes Staurozoa, Hydrozoa, Schyphozoa, and Cubozoa (Daly et al., 2007). During their lifecycle, most Medosozoans take the form of a free-floating medusa, which is commonly named jellyfish (Tibballs, 2006).

Jellyfish swarms can significantly impact human activities and ecosystems because of their venomous and gelatinous nature (Brotz et al., 2012). They affect tourism, fishing, and aquaculture industries as well as other users that rely on coastal water pumping. Human envenomation by jellyfish induces a large variety of symptoms, ranging from a slight local effect to life-threatening symptoms (Fenner, 1998; Cegolon et al., 2013). Additionally, some people are susceptible to allergic reactions (Tibballs et al., 2011). Jellyfish are relatively common in the Mediterranean area or in Australia (Mariottini and Pane, 2010; Tibballs, 2006). The most dangerous species are found in this last country (Tibballs, 2006). Conversely, blooms of hazardous jellyfish species constitute an emerging risk in other areas, such as the Aquitaine coast of France or in China (Labadie et al., 2012; Kang et al., 2014).

Like all cnidarians, jellyfish produce venom for defense and prey capture, neutralization, and digestion (Mebs, 2002). Cnidarian venom is a mix of toxins with a wide range of biological activities (Šuput, 2009). Neurotoxic, cytolytic, and enzymatic (proteases, phospholipases) toxins have been described in the phylum (Frazão et al., 2012; Mariottini and Pane, 2013). The complex mix of toxic substances is injected into the prey by nematocysts, which are produced by nematocytes, a subtype of cnidocytes. Some toxins have also been found in other types of tissues or cells in cnidarians (Moran et al., 2012; Zhang et al., 2003).

Understanding and treating the symptoms observed after human envenomation relies partly on *in vitro* characterization of the biological activities of those toxins. This review will focus on the toxins or partially purified bioactive fractions that have been isolated from jellyfish venom to date. First, the jellyfish species of interest will be introduced, along with a brief summary of their impact on human health. Then, the general principles for jellyfish toxin purification will be presented, and the toxins and

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in vitro biological activities of jellyfish belonging to the classes Cubozoa, Schyphozoa, and Hydrozoa will be described. Last, the observed biological activities will be summarized. The jellyfish species cited in this paper, and their phylogenic relationship, are given in Fig. 1.

2. Human envenomation

2.1. Class cubozoa

In the order Chirodropida, the Australian box jellyfish *Chironex fleckeri* is known to be the most dangerous jellyfish in the world (Tibballs, 2006). Contact with its tentacle induces a local cutaneous inflammatory reaction which is very painful and can leave permanent scarring (Brinkman and Burnell, 2009). Systemic symptoms can also be observed, including excruciating pain, impaired consciousness, hypertension, hypotension, and cardiac and respiratory failure (Brinkman and Burnell, 2009). Death can occur within minutes after the envenomation, most probably because of cardiac and respiratory effects (Tibballs, 2006).

Other species from the order Chirodropida can induce local pain, cutaneous inflammation, and scarring (Bailey et al., 2005; Brinkman and Burnell, 2009; Cegolon et al., 2013). *Chiropsalmus quadrigatus* and *Chiropsalmus quadrumanus* venoms can be harmful to the cardiovascular and respiratory systems, and can be fatal to humans (Nagai et al., 2002; Cegolon et al., 2013).

In the order Carybdeida, contact with jellyfish from the family Carybdeidae typically induces local cutaneous inflammation and pain (Brinkman and Burnell, 2009; Cegolon et al., 2013; Peca et al., 1997; Nagai et al., 2000a). Contact with other families in this order can induce the Irukandji syndrome (Gershwin et al., 2013; Bentlage et al., 2010). The biology and ecology of jellyfish causing Irukandji was recently reviewed by Gershin and coworkers (Gershwin et al., 2013). A large number of species may cause Irukandji or Irukandji-like symptoms. Most of these species belong to the order *Carybdeida*, the main genera being *Alatina*, *Carukia*, *Malo*, and *Morbakka*. Symptoms similar to Irukandji have also been described after contact with species from other classes of cnidarians (Gershwin et al., 2013; Carrette et al., 2012).

The Irukandji syndrome is described as a set of delayed systemic effects that appears on average 25–40 min after contact with the jellyfish and can last from a few hours to several days (Carrette et al., 2012; Tibballs et al., 2012). It was first described in Australia, but has been reported at latitudes from 53°N to 38°S. The sting is hardly noticed and produces an erythema, which heals without scarring. The systemic symptoms can include vomiting, nausea, intense muscle pain, cramps, lower back pain, headache, sweating, agitation, distress, and hypertension. Severe cases involve cardiac dysfunction (Carrette et al., 2012; Tibballs et al., 2012). Current knowledge links this syndrome to an excess of circulating catecholamines, including adrenaline and noradrenaline (Gershwin et al., 2013).

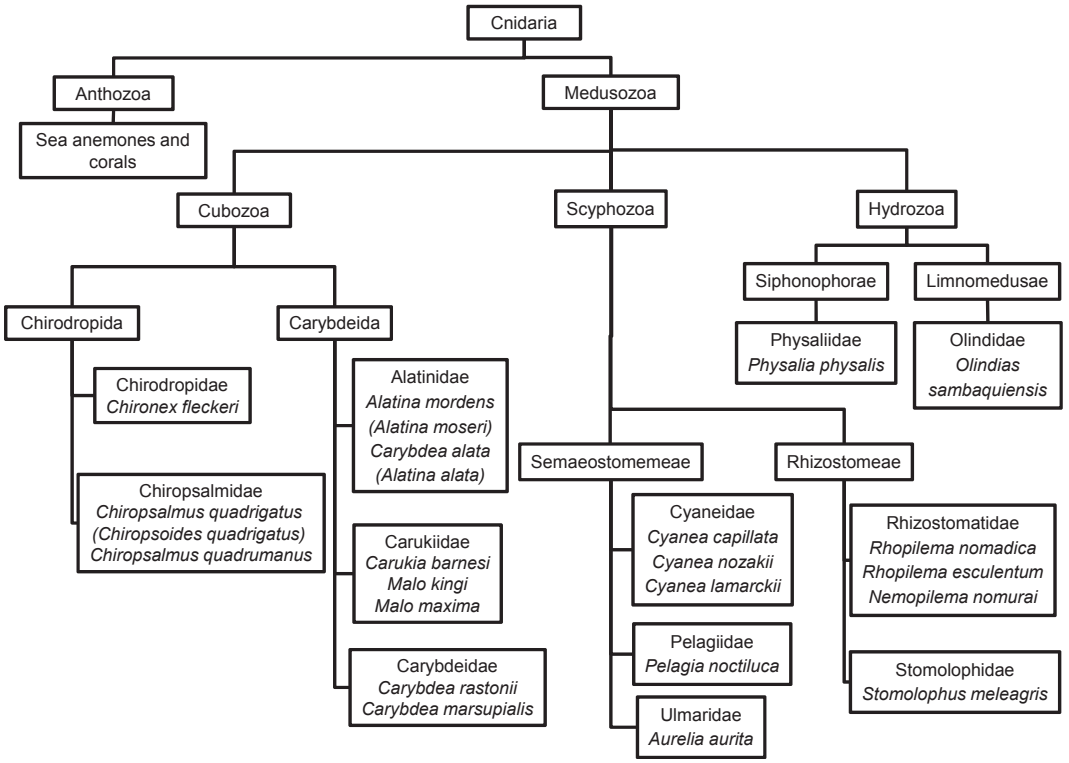

Fig. 1. Summary of the jellyfish species included in this review, classified by phylum, clade, class, order, family, genus. Source: World register of marine species (WoRMS), consulted on July 18, 2014 http://www.marinespecies.org/index.php. Species name are those used in the publication. Names between brackets are the accepted names of the species in the WoRMS.