

Review

μ -Conotoxins Modulating Sodium Currents in Pain Perception and Transmission: A Therapeutic Potential

Elisabetta Tosti ¹, Raffaele Boni ² and Alessandra Gallo ^{1,*} 

¹ Department of Biology and Evolution of Marine Organisms, Stazione Zoologica Anton Dohrn, Villa Comunale, 80121 Naples, Italy; elisabetta.tosti@szn.it

² Department of Sciences, University of Basilicata, 75100 Potenza, Italy; raffaele.boni@unibas.it

* Correspondence: alessandra.gallo@szn.it; Tel.: +39-081-583-3233

Received: 28 July 2017; Accepted: 20 September 2017; Published: 22 September 2017

Abstract: The *Conus* genus includes around 500 species of marine mollusks with a peculiar production of venomous peptides known as conotoxins (CTX). Each species is able to produce up to 200 different biological active peptides. Common structure of CTX is the low number of amino acids stabilized by disulfide bridges and post-translational modifications that give rise to different isoforms. μ and μ O-CTX are two isoforms that specifically target voltage-gated sodium channels. These, by inducing the entrance of sodium ions in the cell, modulate the neuronal excitability by depolarizing plasma membrane and propagating the action potential. Hyperexcitability and mutations of sodium channels are responsible for perception and transmission of inflammatory and neuropathic pain states. In this review, we describe the current knowledge of μ -CTX interacting with the different sodium channels subtypes, the mechanism of action and their potential therapeutic use as analgesic compounds in the clinical management of pain conditions.

Keywords: conotoxin; μ -conotoxin; ion current; sodium channel; pain transmission

1. Introduction

Cone snails are carnivorous and venomous molluscs belonging to the *Conus* genus (Figure S1) living mainly in the tropical marine areas. About 700 species of Cone snails express hundreds of peptide toxins collectively known as conotoxins (CTX) aimed to self-defense, competition and predation of other marine species by means of sting-structures that were reported to be fatal for human since from 300 years ago. CTX, however, do not exert only venomous activity but have a lot of pharmacological properties with specific bioactivity in the treatment of neurological disorders and the associated pain perception [1–3].

The presence of disulfide bonds is the essential characteristic for biological function of CTX that allow to divide CTX into two main categories, the disulfide-rich peptides and no-disulfide-rich ones; the first is mainly composed of a maximum of 30 amino acids and the second contains up to 80 amino acids. CTX are categorized into structural families based on the pattern of cysteine residues in terms of both number and position. Furthermore, differently from other peptides that may be subjected to poor absorption, proteolysis and biological half-lives, the presence of disulfide bonds confers to CTX a sort of stability based on the cross-linking between the cysteine side chains [4–6]. A further striking feature of CTX is the presence of a variety of posttranslational modifications which are, however, still to fully elucidate. CTX are used to act in a synergistic way to ensure that the venom exerts the most effective activity against the predated animals. The assemblage of CTX acting contemporarily has been named toxin cabal. Literature reports that different cabals co-exist, exerting different activities, including the modulation of different types of ion currents.

Different distribution of ions across the plasma membrane gives rise to a trans-membrane potential known as resting potential (RP), which is negative in almost all cells studied. Ion currents are due to