We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Cardiovascular Pathophysiology Produced by Natural Toxins and Their Possible Therapeutic Implications

Robert Frangež, Marjana Grandič and Milka Vrecl
*University of Ljubljana, Veterinary Faculty,
Slovenia*

1. Introduction

Venoms are complex concentrates of biologically highly active molecules known as toxins, and they exist mainly as peptides and proteins. Several natural toxins are produced by plants, bacteria, phytoplanktonic dinoflagellates, sea anemones, insects, fungi and animals. In nature, toxins have two main functions: to capture their preferred prey (e.g. spiders, snakes, scorpions, etc.) or to serve as defence (e.g. bee sting, frog poison, etc.). Toxins produced by micro-organisms are important virulence factors. On the other hand they are also tools to combat diseases. Some of them are used in low quantities as drugs, to prepare vaccines and as important tools in biomedical research. Toxins affecting heart physiology are very effective in the sense of defence and especially in capturing prey. They can disturb electrical (producing arrhythmias) and mechanical activity of the heart affecting pumping or leading even to cardiac arrest. The aim of this chapter is to describe most of the toxins affecting heart function, their targets in the heart tissue, mode of action and the most important clinical effects of envenomation.

2. Main molecular targets of the toxins in the heart

2.1 Sodium channels

Voltage-gated sodium channels are an essential part of excitable membranes and enable fast depolarisation, which is responsible for action potential (AP) generation in cardiomyocytes and in the some parts of the conduction system of the heart. Their density is very low in some parts of the heart's conductive system, e.g. sinoatrial node and atrioventricular node cells, and the highest in Purkinje cells and cardiomyocytes (Fozzard, 1996). Hence, they are targeted by several neurotoxins from plants and animals that use these molecules for defence and protection.

2.2 Calcium channels

Different types of Ca^{2+} -permeable channels have been described in the plasma membrane of heart cells: the L- and T-type channels, both voltage activated, and a background channel (for a review see Carmeliet et al., 1999). Inward current through L-type high voltage-gated

calcium channels is responsible for prolonged AP in cardiac muscle cells and cardiac muscle contraction. L-type voltage-gated Ca^{2+} -channels are especially target for some bacterial (saxitoxin) and animal toxins (atrotxin, maitotoxin, ω -conotoxin, crotoxin).

2.3 Potassium channels

The role of potassium channels is to repolarize the membrane during the AP or to maintain hyperpolarizing potential. They are involved in the regulation of duration of the AP. Therefore, changes in the function of potassium channels may cause life-threatening arrhythmias (Carmeliet et al., 1999). Important potassium channels that can be the target of natural toxins are calcium-activated potassium channels (charybdotoxin, iberiotoxin, apamin) and voltage-gated potassium channels (some dendrotoxins).

3. Biologically active molecules from different sources

3.1 Biologically active molecules from plants

3.1.1 Aconitine

Aconitines are a group of very poisonous alkaloids derived from various aconite species. They are neurotoxins that open TTX-sensitive Na^+ channels in the heart and other tissues (Wang & Wang, 2003). Some of them can bind to the high affinity receptor site 2 of sodium channels ($K_i \sim 1.2 \mu\text{M}$) and some of them to a low affinity binding site ($K_i \sim 11.5 \mu\text{M}$). The compounds of the high affinity group, which increases synaptosomal sodium and calcium activity ($\text{EC}_{50} 3 \mu\text{M}$), are the most toxic and provoke tachyarrhythmia. Binding of aconitine to the site II of voltage-dependent Na^+ channels prolongs the open state responsible for Na^+ influx leading to the permanent depolarization. Now it is commonly accepted that aconitine produces arrhythmias by prolonging opening or delaying the inactivation of voltage-dependent Na^+ channels. Low affinity alkaloids from aconitum species are less-toxic, reduce intracellular calcium activity and induce bradycardia (Friesse et al., 1997).

3.1.2 Grayanotoxins

At least four grayanotoxins (GTXs) have been isolated from the leaves of *Rhododendron decorum* (Ericaceae). These toxins are responsible for so called "mad honey" intoxication. Early in the 1980s it was published that GTXs produce cardiac tachyarrhythmias. The pathophysiological mechanism, underlying tachyarrhythmia, is the triggered activity in the form of oscillatory afterpotentials, as it was shown in feline cardiac Purkinje fibres (Brown et al., 1981). After intoxication, GTXs can produce bradyarrhythmias in man and livestock (Koca & Koca, 2007). It was shown that GTXs-induced cardiac toxicity in rats is a consequence of increased sodium channel permeability and activated vagus nerve (Onat et al., 1991). Intoxication is associated with the fatal bradyarrhythmias that include second degree atrio-ventricular block and circulatory collapse (Okuyan et al., 2010).

3.1.3 Veratridine

Veratrum species plants contain more than 200 different alkaloids, which are the principal toxins. The opening of voltage-gated sodium channels is probably one of the most relevant pathophysiological mechanisms of its toxicity. Veratridine injected intravenously in rats

induced the Bezold-Jarisch-like effect (transient hypotension) accompanied by bradycardia (Chianca et al., 1985). It is well known that persistent sodium current, which can be enhanced during heart ischemia, is one of the major contributors to ischemic arrhythmias. Prolonged cardiac AP, which can also be induced by veratridine, favours the occurrence of early afterdepolarizations that is one of the pathophysiological mechanisms of tachyarrhythmias. Increased Na⁺ uptake activates the Na⁺/Ca²⁺ exchanger that leads to cardiomyocytes' Ca²⁺ overload. The latter can trigger the late depolarization after-potentials (DAPs), which is another pathophysiological mechanism underlying arrhythmias. If the amplitude of the DAPs reaches the threshold potential, a new AP is triggered. Such large, late DAPs often occur in the case of oscillations of the cytosolic Ca²⁺ concentration (Pignier et al., 2010).

Name	Source (produced by)	Chemical structure	Target	Mode of action	Effects	Acute LD ₅₀ in mice	Reference
Cardiotoxic toxins from plants							
Aconitine	Plants from genus <i>Aconitum</i>	Alkaloid	Voltage- gated Na ⁺ channels	Depolariza- tion, AP duration increase	Arrhy- thmias	0.1 mg/kg	Gutser, 1998
Grayanoto- xins (GTX)	Species from genus <i>Rhododendron</i>	Polyhydro- xylated cyclic diterpene	Increase Na ⁺ channel permeability and activate vagus nerve	Alteration of excitability	Fatal cardiac bradyar- rhythmias	1.28 mg/kg <i>i.p.</i>	Brown et al., 1981; Okuyan et al., 2010 ; Scott et al., 1971
Veratridine	Plants in the family <i>Liliaceae</i>	Steroid- derived alkaloid	Binding to the activated Na ⁺ ion channels	Depolariza- tion, AP duration increase	Arrhy- thmias	1.35 mg/kg <i>i.p.</i>	Chianca et al., 1985; Pignier et al., 2010; Swiss & Bauer, 1951

Table 1. Natural cardiotoxic toxins from plants: source, structure, receptors, mode of action, effects on heart and toxicity.

3.2 Cardiotoxic toxins derived from mushrooms

3.2.1 Ostreolysin

Ostreolysin (Oly) is an acidic, 15 kDa protein isolated from the edible oyster mushroom (*Pleurotus ostreatus*) (Berne et al., 2002). It is a toxic, pore-forming cytolysin (Sepčić et al., 2003). When administered intravenously (i.v.), Oly causes electrocardiographic, arterial blood pressure and respiratory changes. Oly produces changes such as transient increase of arterial blood pressure followed by a progressive fall to mid-circulatory pressure accompanied by bradycardia, myocardial ischaemia and ventricular extrasystoles. Oly also induces lysis of rat erythrocytes in vitro and in vivo, resulting in hyperkalemia. Although direct action of the protein on the cardiomyocytes or heart circulation cannot be excluded (Oly is pore-forming toxin), the hyperkalemia resulting from the haemolytic activity seems

to play an important role in its cardiotoxicity (Žužek et al., 2006). Additionally, an important mechanism of the cardiotoxic effect may also be its concentration-dependent contractile effect on elastic blood vessels, such as aorta (Rebolj et al., 2009) and coronary vessels (Juntos et al., 2009).

Name	Source (produced by)	Chemical structure	Target	Mode of action	Effects	Acute LD ₅₀ in mice	Refer- ence
Cardiotoxic toxins derived from mushrooms							
Ostreolysin	Oyster mushroom (<i>Pleurotus ostreatus</i>)	Pore- forming protein	Cell membranes	Pore formation	Bradycardia; myocardial ischaemia; ventricular extrasystoles, hyperkalemia	1.17 mg/kg	Žužek et al., 2006

Table 2. Natural cardiotoxic toxins from mushrooms: source, structure, receptors, mode of action, effects on heart and toxicity.

3.3 Biologically active molecules produced by micro-organisms

3.3.1 Bacterial toxins

3.3.1.1 *Vibrio parahemolyticus* haemolysin (toxin)

Vibrio parahemolyticus toxin is lethal for rats when injected *i.v.* in a dose of 5 µg/kg or higher. It decreases intra-atrial and ventricular conductivity, and produces atrioventricular block. Before cardiac arrest occurs, ventricular flutter develops. The toxin is also toxic for cardiomyocytes in culture. Similar to the heart, the beating rhythm of cardiomyocytes exposed to the toxin increases and then abruptly stops (Honda et al., 1976).

3.3.1.2 Streptolysin O

Streptolysin O is a pore-forming toxin released in the extracellular medium by the majority of group A and some of group C and G *Streptococci*. It belongs to the sulphydryl- or thiol-activated toxins. It is a protein with a molecular weight of about 67 kDa. Streptolysin O is capable of forming cation permeable pores in cholesterol-rich membranes. Administered *i.v.* in high doses it produces sudden cardiac arrest, probably due to a non-specific binding to the lipid bilayers of cardiac cells (for a review see Harvey, 1990).

3.3.1.3 Saxitoxin

Saxitoxin (STX) is produced by certain marine species of dinoflagellates (*Alexandrium sp.*, *Gymnodinium sp.*) and cyanobacteria species (*Anabaena sp.*, some *Aphanizomenon spp.*, *Cylindrospermopsis sp.*). STX, usually administered through shellfish ingestion, is responsible for the human illness known as paralytic shellfish poisoning (PSP). STX acts primarily as a sodium channel blocker; it binds to the binding site 1 (Mebs & Hucho, 1990). Additionally it was found that STX also inhibits L-type Ca²⁺ currents in adult mouse ventricular myocytes (Su et al., 2003).

3.3.1.4 Tetrodotoxin

Tetrodotoxin (TTX) is a toxin of microbial origin. A number of marine bacteria probably produce TTX, especially members of the genus *Vibrio* (most common species is *Vibrio alginolyticus*). The link between this species and production of TTX in animals has not been definitely confirmed as it is not clear whether the source of TTX in animals is the above-mentioned bacteria. TTX has been isolated from many animal species (pufferfish, toads of the genus *Atelopus*, octopuses of the genus *Hapalochlaena*, etc. (Mebs & Hucho, 1990). It was shown that both high and low affinity receptors (sodium channels) for TTX exist on the rat cardiomyocytes. Only a low affinity binding site is functional on the cardiac cells, which has dissociation constant for TTX about three orders of magnitude higher compared to the reported dissociation constant for TTX receptors in muscle and nerve. The concentration needed to block cardiac sodium channels is very high (Renaud et al., 1983). The myocytes in the heart express fast voltage-gated sodium channel and therefore the generation of AP and

Name	Source (produced by)	Chemical structure	Target	Mode of action	Effects	Acute LD ₅₀ in mice	Reference
Microbial toxins							
Bacterial toxins							
Hemolysin TDH, TRH	<i>Vibrio parahaemolyticus</i>	Protein	Heart	Alteration in conductance of the conductive system	Arrhy- thmias, cardiac arrest	Between 2.5 and 5 µg/kg in rats	Honda et al., 1976
Streptolysin O	<i>Streptococci</i> group A, C and G	Protein	Nonspecific binding (membranes rich on cholesterol)	Pore formation	Bradycardia, atrio- ventricular conduction block	8 µg/kg <i>i.v.</i>	Gill, 1982; Harvey, 1990
Tetrodotoxin (TTX)	Bacteria: <i>Pseudoalteromonas tetraodonis</i> , certain species of <i>Pseudomonas</i> and <i>Vibrio</i>	heterocyclic, organic, water- soluble non- protein molecule	Voltage dependent Na ⁺ channels	Shorten the AP duration and decrease the initial depolarizing phase of the AP	Cardiac arrest	10.7 µg/kg <i>i.p.</i> ; 12.5 µg/kg <i>s.c.</i> ; 532 µg/kg <i>i.g.</i>	Mebs & Hucho, 1990; Xu et al., 2003
Saxitoxin	Marine dinoflagellates (<i>Alexandrium sp.</i> , <i>Gymnodinium sp.</i>) and cyanobacteria (<i>Anabaena sp.</i> , some <i>Aphanizomenon spp.</i> , <i>Cylindrospermopsis sp.</i>)	Heterocy- clic guanidine	Voltage- gated Na ⁺ channels- block L-type Ca ²⁺ channels- partial block	Shorten the AP duration and decrease the initial depolarizing phase of the AP	Prolongation of P-Q interval, first degree of atrio- ventricular block, ventricular fibrillation	3 – 10 µg/kg <i>i.p.</i>	Anderson, 2000; Su et al., 2003

Table 3. Natural cardiotoxic toxins from microbes: source, structure, receptors, mode of action, effects on heart and toxicity; *i.g.*- intra-gastric administration

electrical activity is blocked leading to blockade of myocardium excitability and cardiac arrest, although sodium channels are usually not affected in case of intoxication.

3.3.2 Algal toxins affecting heart physiology

Algae are ubiquitous micro-organisms in aqueous environments. Some of them will periodically form harmful “blooms.” *Karenia brevis* is a dinoflagellate that can form harmful blooms known as “Florida red tides”. Blooms are associated with the production of a group of powerful neurotoxins known as brevetoxins.

3.3.2.1 Brevetoxins

Brevetoxin (PbTx) is produced by marine dinoflagellates. It is polyether neurotoxin that targets the voltage-gated sodium channels present in all excitable membranes including heart tissues. Brevetoxins open voltage-gated sodium ion channels in cell membranes and cause uncontrolled sodium influx into the cell leading to the depolarization (Purkerson et al., 1999). Humans can be exposed to PbTx by ingesting brevetoxin-contaminated shellfish or through other environmental exposures. Its affinity for the rat heart tissue is much lower in contrast to the heart tissue of marine animals, but comparable with the skeletal muscle and brain (Dechraoui et al., 2006). At least 10 different brevetoxins have been isolated from seawater blooms and *K. brevis* cultures. PbTx in a dose higher than 25 µg/kg produces heart block, ventricular extrasystoles and idioventricular rhythms in conscious rats. It was concluded that brevetoxin causes changes in the cardiac conduction system and multiple changes in the function of the nervous system (Templeton et al., 1989). Systemic accumulation of the toxin in artificially respiration cats injected with PbTx leads to cardiovascular collapse and death (Borison et al., 1985).

3.3.2.2 Yessotoxins

Yessotoxins (YTXs) are polycyclic ether compounds produced by phytoplanktonic dinoflagellates (algal toxins). They can accumulate in shellfish which are a source of human intoxication through contaminated seafood ingestion. YTX, homoyessotoxin and 45-hydroxy-homoyessotoxin are lethal when administered intraperitoneally (*i.p.*) to mice. Although the mechanisms of the cardiotoxicity of YTX and homoyessotoxins are not well understood, some data from *in vitro* experiments, such as changes of intracellular calcium and cyclic AMP concentrations, alteration of cytoskeletal and adhesion molecules, caspases activation and opening of the permeability transition pore of mitochondria, support their cardiotoxic action (Dominguez et al., 2010; for a review see Tubaro et al., 2010). They induce microscopically visible ultrastructural changes in heart tissue after intraperitoneal and oral exposure. Noticeable intracytoplasmic oedema of cardiac muscle cells was observed within three hours after the *i.p.* administration of YTX at a dose of 300 µg/kg or higher (Terao et al., 1990). In mice YTX produces swelling of cardiomyocytes and separation of organelles in the area near capillaries after oral (10 mg/kg) and *i.p.* (1 mg/kg) toxin administration (Aune et al., 2002).

3.3.2.3 Ciguatoxin

Ciguatera caused by fish poisoning is a foodborne disease caused by eating certain fishes whose meat is contaminated with ciguatoxins produced by dinoflagellates such as *Gambierdiscus toxicus*. These toxins include ciguatoxin (CTX), maitotoxin, scaritoxin and

palytoxin. Ciguatera fish poisoning is primarily endemic in tropical regions of the world. On neuroblastoma cells, CTX induces a membrane depolarization which is due to an action that increases Na⁺ permeability and is prevented by voltage-gated sodium channel blocker TTX (Bidard et al., 1984). Intravenous injections of ciguatoxin evoke dose-dependent effects: bradycardia and atrioventricular conduction block at low doses, ventricular tachycardia at sublethal doses, and heart failure at high doses (up to 160 µg/kg) (Legrand et al., 1982). The Caribbean ciguatoxin (C-CTX-1) stimulates the release of *acetylcholin* (ACh) and produces muscarinic effect on frog atrial fibres (Sauviat, 1999; Sauviat et al., 2002).

Name	Source (produced by)	Chemical structure	Target	Mode of action	Effects	Acute LD ₅₀ in mice	Reference
Algal toxins							
Brevetoxin	Dinoflagellate <i>Karenia brevis</i>	Cyclic polyether	Voltage- gated Na ⁺ channels	Depolari- zation, AP duration increase	Heart block, ventricular extrasystoles and idioventricular rhythms	250 µg/kg <i>i.p.</i>	Purkerson et al., 1999; Templeton et al., 1989; Selwood et al., 2008
Yes- sotoxins	Algae	Polycyclic ether compo- unds	Voltage gated Ca ²⁺ channels	Reduction of the firing and biting frequency of rat cardiac cells	Changes of intracellular Ca ²⁺ and cyclic AMP concentrations, alteration of cytoskeletal and adhesion molecules, caspases activation and opening of the permeability transition pore of mitochondria	444-512 µg/kg <i>i.p.</i>	Tubaro et al., 2003; Dell'Ovo et al., 2008
Ciguatoxin	Dinoflagellate <i>Gambierdiscus toxicus</i>	Polyether toxins	Voltage- gated Na ⁺ channels	Depolari- zation, AP duration increase, arrhythmias	Biphasic inotropic and chronotropic excitatory, and inhibitory effects	0.3 – 10 µg/kg <i>i.p.</i>	Dechraoui et al., 1999
Maitotoxin	Dinoflagellate <i>Gambierdiscus toxicus</i>	N/A	Ca ²⁺ channels	Agonist	AP amplitude increase	0.17 mg/kg <i>i.p.</i>	Igarashi et al., 1999; Mebs & Hucho, 1990

Table 4. Natural cardiotoxic toxins from algae: source, structure, receptors, mode of action, effects on heart and toxicity. (N/A - not applicable).

3.3.2.4 Maitotoxin

Maitotoxin (MTX) plays an important role in the syndrome named ciguatera poisoning. The toxin is derived from *Gambierdiscus toxicus*, a marine dinoflagellate species (for a review see

Mebs & Hucho, 1990). MTX causes dose-dependent effects on the heart. It has positive inotropic effects on heart preparations and causes irreversible contracture of isolated rat cardiomyocytes that can be prevented by specific voltage-dependent Ca^{2+} channel blocker verapamil (Kobayashi et al., 1986). MTX increases dose-dependent increase in Ca^{2+} activity in freshly dispersed cardiomyocytes. This effect of MTX may be inhibited by reducing Ca^{2+} concentration in the culture medium or by the calcium-channel blocker verapamil. Therefore, it has been concluded that MTX specifically activates voltage-dependent Ca^{2+} channels. This influx of Ca^{2+} into the cells is considered an important mechanism for cardiotoxicity of the MTX (Santostasi et al., 1990).

4. Biologically active molecules from animals affecting heart physiology

Animal venoms are usually a complex mixture of polypeptides, enzymes and molecules which can cause cell injury. Polypeptides exert their effect through action on ion channels and in a cell's plasma membrane. Enzymes can cause membrane lysis, pore formation, etc.

4.1 Palytoxin

Palytoxin (PTX) was first toxin isolated from the soft coral *Palythoa toxica*. PTX is one of the most powerful marine biotoxins of a high molecular weight (~ 3.3 kDa). It is the most potent non-proteinic and non-peptidic toxic substance known, with a lethal dose LD_{50} of 0.15 $\mu\text{g}/\text{kg}$ in mice by the *i.v.* route (Moore & Scheuer, 1971).

4.2 Iberiotoxin

Iberiotoxin (IbTX) is derived from the venom of Eastern Indian red scorpion *Buthus tamulus*. IbTX selectively inhibits current through the calcium-activated potassium channels. IbTX in a 2 μM concentration increased the stimulation-induced ACh release (Kawada et al., 2010). It was reported that some patients who had been stung by a scorpion had signs such as hypertension and supraventricular tachycardia (Bawaskar & Bawaskar, 1992), to which may contribute also IbTX.

4.3 Batrachotoxins

Batrachotoxins (BTXs) are neurotoxic steroidal alkaloids first isolated from a Colombian poison-dart frog. BTXs are lipid-soluble toxins that bind with a high affinity to the type 2 receptor site of voltage-gated sodium channels in nerve and muscle membranes, keeping them in an open state (Albuquerque et al., 1971; Huang et al., 1984). This results in cell depolarization since BTXs inhibit inactivation of sodium channels. BTXs seem to play the most important role in cardiotoxicity. The cardiotoxic effects of BTXs accompanied by arrhythmia and cardiac arrest are connected to the activation of voltage-gated sodium channels in cardiac cells (Mebs & Hucho, 1990). It can evoke premature heart beat and fatal ventricular fibrillation associated with the haemodynamic arrest (Albuquerque et al., 1971).

4.4 Atrotoxin

Atrotoxin (ATX) is isolated from a venomous rattlesnake species *Crotalus atrox* found in the United States and Mexico. ATX binds reversibly to the voltage-gated calcium channels,

leading to the increase of voltage-dependent calcium currents in single, dispersed guinea pig ventricular cells. ATX acts as a specific Ca^{2+} channel agonist (Hamilton et al., 1985).

4.5 Equinatoxins

Equinatoxins are pore-forming proteins isolated from the sea anemone *Actinia equine*. First evidence that equinatoxins are cardiotoxic was provided by Sket et al. (1974) by administration of tentacle extract of sea anemone *i.v.* into rats. Later, the isolation of three cardiotoxic proteins named Equinatoxin I, II and III with median lethal doses of 23, 35 and 83 $\mu\text{g}/\text{kg}$ in mice, respectively (Macek & Lebez, 1988), was reported. EqT II is a pore forming toxin that through *de novo* formed pores evokes significant increase of intracellular Ca^{2+} activity, which cannot be blocked by conventional sodium and calcium channel blockers and probably plays an important role in direct (cytotoxic) or indirect cardiotoxicity through coronary vessel contraction and drop of the coronary perfusion rate (Frangež et al., 2000; Frangež et al., 2008; Zorec et al., 1990). All three equinatoxins are highly haemolytic and can cause a dose-dependent increase in potassium activity in blood plasma, leading to arrhythmias and cardiac arrest. Administered *i.v.* they produce dose-dependent disturbances in electrical activity of the heart accompanied by blood pressure changes. Additional information about direct dose-dependent cardiotoxic effects of EQT IIs were provided from the experiments on Langendorff's heart preparations. It causes a concentration-dependent drop of the perfusion rate, decreases left ventricular pressure and produces arrhythmias followed by cardiac arrest (Bunc et al., 1999).

4.6 Cardiotoxic-cytotoxic protein from cobra *Naja kaouthia*

A cytolytic protein was isolated from the Indian monocellate cobra (*Naja kaouthia*) venom. Intraperitoneal median lethal dose was estimated to be 2.5 mg/kg in Balb/C in male mice. *In vitro* the toxin produces auricular blockade as shown on isolated guinea pig auricle (Debnath et al., 2010).

4.7 Taicatoxin

Taicatoxin (TCX) is a snake toxin derived from the Australian taipan snake *Oxyuranus scutellatus scutellatus*. TCX reversibly and specifically blocks voltage-dependent L-type calcium channels in nanomolar concentrations (Brown et al., 1987). TCX decreases the plateau of AP in cardiomyocytes leading to a decrease in contractility. TCX has a negative chronotropic effect and evokes arrhythmias (Fantini et al., 1996). Electrocardiographic abnormalities were described in patients envenomed with a number of different species including *Oxyuranus spp.* Electrocardiographic changes include septal T wave inversion and bradycardia, and atrioventricular block. One of possible mechanisms which might be responsible for such clinical signs is a calcium channel blockade on cardiomyocytes (Lalloo et al., 1997).

4.8 Conotoxins

Conotoxins are peptides derived from the marine snail *Conus geographus* and consist of 10 to 30 amino acid residues. Many of these peptides modulate the activity of different ion

channels. ω -conotoxin inhibits N-type voltage-dependent Ca^{2+} channels. It decreases the magnitude of cardiac AP and possesses a negative inotropic effect (Nielsen, 2000).

4.9 Crotoxin

Crotoxin (CTX) is derived from the venom of the South American rattlesnake, *Crotalus durissus terrificus*. *In vitro*, CTX decreases contractile force, increases the P-R interval and displaces the S-T segment. Arrhythmias are uncommon. The reduction of the contractile force and the increase in creatine kinase (CK) activity are ascribed to the release of free fatty acids and lysophospholipids, and to a cellular lesion (Santos et al., 1990; Zhang et al., 2010).

4.10 Sarafotoxin and bibrotoxin

Sarafotoxins (SRTs) and bibrotoxins are a group of extremely poisonous cardiotoxic snake venom peptides that show a striking structural similarity to endothelins (Becker et al., 1993; Kloog et al., 1988). SRTs are highly lethal peptides: in mice, the LD_{50} is 15 $\mu\text{g}/\text{kg}$ body weight equalling the LD_{50} for endothelin (Bdolah et al., 1989), which is quite surprising for a peptide naturally occurring in the plasma of healthy humans. Sarafotoxin S6C, the most acidic endothelin-like peptide, shows reduced vasoconstrictive potency and is a highly selective natural ET_B R agonist (over 100 000 times higher affinity for the ET_B R vs. the ET_A R; [Williams et al., 1991]).

4.11 Anti-arrhythmic toxin from tarantula *Grammostola spatulata*

Gs-Mtx-4 is an amphipathic peptide toxin derived from the venom of the tarantula spider (*Grammostola spatulata*) with a molecular weight of 4 kDa (Hodgson & Isbister, 2009). It is the only toxin known that specifically affects cationic stretch activated ion channels and is therefore able to inhibit atrial fibrillation (Bowman et al., 2007).

5. Natural toxins as drugs

Some of the natural toxins acting on the cardiovascular system are very potent and highly specific for some receptors in cardiac and neuronal tissue. They can block, activate and even modulate the ion channels activity in excitable membranes. Although they are very stable molecules and possess high receptors specificity, they are seldom used as therapeutic drugs. Information about their three dimensional structure and data from structure-function studies of protein toxins may provide useful information for synthesis of smaller analogues with lower toxicity. Few natural toxins have potential in clinical use for treatment of cardiovascular dysfunction. Some of them have a positive inotropic effect, i.e. grayanotoxin, veratridine (Brill & Wasserstrom, 1986; Tirapelli et al., 2008). Due to their high toxicity, none of the described natural cardiotoxic substances are used as therapeutic drugs for treating cardiovascular diseases. Recently, sarafotoxins have been utilized to develop new, low molecular weight substances with metalloproteinase inhibitory activity. The modified molecule of the sarafotoxin 6b is used as a starting point, which has retained metalloproteinase inhibitory activity and removed vasoconstrictor activity. From this, the peptide (STX-S4-CT) was developed, which will hopefully provide a foundation for further development of improved candidate molecules (Hodgson & Isbister, 2009). Some promising

Name	Source (produced by)	Chemical structure	Target	Mode of action	Effects	Acute LD ₅₀ in mice	Source
Animal toxins							
Palytoxin	Soft coral: <i>Palythoa toxica</i>	Aliphatics carbon chain containing a series of heterocyclic rings	Na ⁺ /K ⁺ - ATPase; Hemolysin	Voltage- dependent K ⁺ channels	Haemolysis, arrhythmias	0.15 µg/kg	Sosa et al., 2009
Equinatoxin I, II, II	Sea anemone: <i>Actinia equina</i>	Proteins	Haemolysin	New cation non-selective pore formation	Dose-dependent arrhythmias, cardiac arrest, haemolysis	25,30 and 83 µg/kg <i>i.v.</i>	Maček & Lebez, 1988; Sket et al., 1974
Batrachotoxins (BTX)	Some frogs species (poison-dart frog), melyrid beetles and birds (<i>Ifrita kowaldi</i> , <i>Colluricincla megarrhyncha</i>)	Steroidal alkaloids	Na ⁺ channels	Depolarize, lengthen the AP	Arrhythmias, extrasystoles, ventricular fibrillation	2 µg/kg <i>s.c.</i>	Albuquerque et al., 1971; Mebs & Hucho, 1990
Atrotoxin	Snake: <i>Crotalus atrox</i>	N/ A	Ca ²⁺ channels	Agonist, AP amplitude increase	Arrhythmias	89.4 – 137 µg <i>i.v.</i>	Hamilton et al., 1985; Barros et al., 1998
Cardiotoxic- cytotoxic protein (MW 6.76 kDa)	Indian monocellate cobra (<i>Naja kaouthia</i>)	Protein	Heart	Sinuaauricular blockade	Arrhythmias	2.5 mg/kg <i>i.p.</i>	Debnath et al., 2010
Taicatoxin (TCX)	Australian taipan snake <i>Oxyuranus scutellatus</i>	N/ A	Ca ²⁺ channels	Antagonist	Bradycardia, atrioventricular block	N/ A	Brown et al., 1987; Lalloo et al., 1997
Omega- conotoxin	Cone snail from genus <i>Conus</i>	Peptide	N-type voltage- dependent Ca ²⁺ channels	Antagonist	Decreases the magnitude of AP plateau, negative inotropic effects	N/ A	Nielsen, 2000
Crotoxin (CTX)	South American rattlesnake (<i>Crotalus durissus terrificus</i>)	Protein; crotaopotin basic phospolipase A ₂	L-type Ca ²⁺ channels	Agonist	Elongation of AP duration, an increase of its amplitude	55.5 – 70.5 µg/kg <i>i.p.</i>	Rangel-Santos et al., 2004
Sarafotoxin (SRTs) and bibrotoxin	Snake: <i>Atractaspis engaddensis</i>	Peptide	Endothelin receptors	Agonist	Arrhythmias	15 µg/kg	Bdolah et al., 1989
GsMtx-4	Spider – tarantula: <i>Grammostola spatulata</i>	Peptide	Stretch activated ion channels (SACs)	Antagonist	Inhibits atrial fibrillation	N/ A	Bowman et al., 2007

Table 5. Natural cardiotoxic toxins from animals: source, structure, receptors, mode of action, effects on heart and toxicity. (N/ A - not applicable).

results in the treatment of cardiovascular disorders were also obtained with GsMtx-4 toxin isolated from tarantula *Grammostola spatulata* venom. This toxin is able to inhibit the stretch activated ion channels (SACs) and consequently inhibits atrial fibrillation. Due to its described properties, it can be used as a framework for developing a new class of anti-arrhythmic drugs, which would be directed against pathophysiologic mechanisms of atrial fibrillation, instead of just dealing with the symptoms as with many current therapies (Hodgson & Isbister, 2009).

6. Conclusion

Severe acute toxic insult caused by natural toxins can cause functional changes in heart tissue physiology or even cardiac cell death. Most of the natural toxins derived from plants, bacteria, phytoplanktonic dinoflagellates, fungi and animals target ionic channels in excitable membranes of cardiac cells or cardiac cell membranes itself, produce alteration in AP (e.g. depolarization, repolarization, alterations in its duration) or significant changes in intracellular ion activity. These changes may lead to reversible or even irreversible life threatening cardiac arrhythmias and eventually heart failure.

7. References

- Albuquerque EX., Daly JW. & Witkop B. Batrachotoxin: chemistry and pharmacology. *Science*, Vol. 172, No. 987, (Jun 1971), pp. 995-1002, 0036-8075
- Anderson D. (August 2010). The harmful algae page. Available from <http://www.redtide.whoi.edu/hab/>
- Aune T., Sørby R., Yasumoto T., Ramstad H. & Landsverk T. Comparison of oral and intraperitoneal toxicity of yessotoxin towards mice. *Toxicon*, Vol. 40, No. 1, (Jan 2002), pp. 77-82, 0041-0101
- Barros SF., Friedlanskaia I., Petricevich VL. & Kipnis TL. Local inflammation, lethality and cytokine release in mice injected with *Bothrops atrox* venom. *Mediators of inflammation*, Vol. 7, No. 5, (Sep 1998), pp. 339-346, 0962-9351
- Bawaskar HS. & Bawaskar PH. Management of the cardiovascular manifestations of poisoning by the Indian red scorpion (*Mesobuthus tamulus*). *British Heart Journal*, Vol. 68, No. 5, (Nov 1992), pp. 478-480, 0007-0769
- Bdolah A., Wollberg Z., Ambar I., Kloog Y., Sokolovsky M. & Kochva E. Disturbances in the cardiovascular system caused by endothelin and sarafotoxin. *Biochemical pharmacology*. Vol. 38, No. 19, (Oct 1989), pp. 3145-3146, 0006-2952
- Becker A., Dowdle EB., Hechler U., Kauser K., Donner P. & Schleuning WD. Bibrotoxin, a novel member of the endothelin/sarafotoxin peptide family, from the venom of the burrowing asp *Atractaspis bibroni*. *FEBS Letters*, Vol. 315, No. 1, (Jan 1993), pp. 100-103, 0014-5793
- Berne S., Krizaj I., Pohleven F., Turk T., Macek P. & Sepčić K. Pleurotus and Agrocybe hemolysins, new proteins hypothetically involved in fungal fruiting. *Biochimica et Biophysica Acta*, Vol. 1570, No. 3, (Apr 2002), pp. 153-159, 0304-4165
- Bidard JN., Vijverberg HP., Frelin C., Chungue E., Legrand AM., Bagnis R. & Lazdunski M. Ciguatoxin is a novel type of Na⁺ channel toxin. *Journal of Biological Chemistry*, Vol. 259, No. 13, (Jul 1984), pp. 8353-8357, 1083-351X
- Borison HL., McCarthy LE. & Ellis S. Neurological analysis of respiratory, cardiovascular and neuromuscular effects of brevetoxin in cats. *Toxicon*, Vol. 23, No. 3, (1985), pp. 517-524, 0041-0101

- Bowman CL., Gottlieb PA., Suchyna TM., Murphy YK. & Sachs F. Mechanosensitive ion channels and the peptide inhibitor GsMTx-4: history, properties, mechanisms and pharmacology. *Toxicon*, Vol. 49, No. 2, (Feb 2007), pp. 249-270, 0041-0101
- Brill DM. & Wasserstrom JA. Intracellular sodium and the positive inotropic effect of veratridine and cardiac glycoside in sheep Purkinje fibers. *Circulation Research*, Vol. 58, No. 1, (Jan 1986), pp. 109-119, 1524-4571
- Brown BS., Akera T. & Brody TM. Mechanism of grayanotoxin III-induced afterpotentials in feline cardiac Purkinje fibers. *European Journal of Pharmacology*, Vol. 75, No. 4, (Nov 1981), pp. 271-281, 0014-2999
- Brown AM., Yatani A., Lacerda AE., Gurrola GB. & Possani LD. Neurotoxins that act selectively on voltage-dependent cardiac calcium channels. *Circulation Research*, Vol. 61, No. 4, (Oct 1987), pp. 16-19, 0009-7330
- Bunc M., Drevenšek G., Budihna M. & Šuput D. Effects of equinatoxin II from *Actinia equina* (L.) on isolated rat heart: the role of direct cardiotoxic effects in equinatoxin II lethality. *Toxicon*, Vol. 37, No. 1, (Jan 1999), pp. 109-123, 0041-0101
- Carmeliet E. Cardiac ionic currents and acute ischemia: from channels to arrhythmias. *Physiological reviews*, Vol. 79, No. 3, (Jul 1999), pp. 917-1017, 0031-9333
- Chianca Júnior DA., Cunha-Melo JR. & Freire-Maia L. The Bezold-Jarisch-like effect induced by veratridine and its potentiation by scorpion toxin in the rat. *Brazilian Journal of Medical and Biological Research*, Vol. 18, No. 2, (1985), pp. 237-248, 0100-879X
- Debnath A., Saha A., Gomes A., Biswas S., Chakrabarti P., Giri B., Biswas AK., Gupta SD. & Gomes A. A lethal cardiotoxic-cytotoxic protein from the Indian monocellate cobra (*Naja kaouthia*) venom. *Toxicon*, Vol. 56, No. 4, (Sep 2010), pp. 569-579, 0041-0101
- Dechraoui MY., Naar J., Pauillac S. & Legrand AM. Ciguatoxins and brevetoxins, neurotoxic polyether compounds active on sodium channels. *Toxicon*, Vol. 37, No. 1, (Jan 1999), pp. 125-143, 0041-0101
- Dechraoui MY., Wacksman JJ. & Ramsdell JS. Species selective resistance of cardiac muscle voltage-gated sodium channels: characterization of brevetoxin and ciguatoxin binding sites in rats and fish. *Toxicon*, Vol. 48, No. 6, (Nov 2006), pp. 702-712, 0041-0101
- Dell'Ovo V., Bandi E., Coslovich T., Florio C., Sciancalepore M., Decorti G., Sosa S., Lorenzon P., Yasumoto T. & Tubaro A. In vitro effects of yessotoxin on a primary culture of rat cardiomyocytes. *Toxicological sciences*, Vol. 106, No. 2, (Dec 2008), pp. 392-399, 1096-6080
- Dominguez HJ., Paz B., Daranas AH., Norte M., Franco JM. & Fernández JJ. Dinoflagellate polyether within the yessotoxin, pectenotoxin and okadaic acid toxin groups: characterization, analysis and human health implications. *Toxicon*, Vol. 56, No. 2, (Aug 2010), pp. 191-217, 0041-0101
- Fantini E., Athias P., Tirosh R. & Pinson A. Effect of TaiCatoxin (TCX) on the electrophysiological, mechanical and biochemical characteristics of spontaneously beating ventricular cardiomyocytes. *Molecular and Cellular Biochemistry*, Vol. 160, No. 161, (Jul-Aug 1996), pp. 61-66, 1573-4919
- Fozzard HA. & Hanck DA. Structure and function of voltage-dependent sodium channels: comparison of brain II and cardiac isoforms. *Physiological Reviews*, Vol. 76, No. 3, (Jul 1996), pp. 887-926, 0031-9333
- Frangež R., Meunier F., Molgo J. & Šuput D. Equinatoxin II increases intracellular Ca^{2+} in NG 108-15 cells. *Pflügers archive: European Journal of Physiology*, Vol. 439, Suppl. 3, (2000), pp. R100-1, 0031-6768
- Frangež R., Šuput D. & Molgó J. Effects of equinatoxin II on isolated guinea pig taenia caeci muscle contractility and intracellular Ca^{2+} . *Toxicon*, Vol. 51, No. 8, (Jun 2008), pp. 1416-1423, 0041-0101

- Friese J., Gleitz J., Gutser UT., Heubach JF., Matthiesen T., Wilffert B. & Selve N. Aconitum sp. alkaloids: the modulation of voltage-dependent Na⁺ channels, toxicity and antinociceptive properties. *European Journal of Pharmacology*, Vol. 337, No. 2-3, (Oct 1997), pp. 165-74, 0014-2999
- Gill DM. Bacterial toxins: a table of lethal amounts. *Microbiological Reviews*, Vol. 46, No. 1, (Mar 1982), pp. 86-94, 0146-0749
- Gutser UT., Friese J., Heubach JF., Matthiesen T., Selve N., Wilffert B. & Gleitz J. Mode of antinociceptive and toxic action of alkaloids of Aconitum spec. *Naunyn-Schmiedeberg's archives of pharmacology*, Vol. 357, No. 1, (Jan 1998), pp. 39-48, 0028-1298
- Hamilton SL., Yatani A., Hawkes MJ., Redding K. & Brown AM. Atrotoxin: a specific agonist for calcium currents in heart. *Science*, Vol. 229, No. 4709, (Jul 1985), pp. 182-184, 0036-8075
- Harvey AL. (1990). Cytolytic toxins. In: *Handbook of Toxinology*, Shier TW and Mebs D, pp. 1-66. Marcel Dekker Inc., New York.
- Hodgson WC. & Isbister GK. The application of toxins and venoms to cardiovascular drug discovery. *Current Opinion in Pharmacology*, Vol. 9, No. 2, (Apr 2009), pp. 173-176, 1471-4973
- Honda T., Goshima K., Takeda Y., Sugino Y. & Miwatani T. Demonstration of the cardiotoxicity of the thermostable direct hemolysin (lethal toxin) produced by *Vibrio parahaemolyticus*. *Infection and Immunity*, Vol. 13, No. 1, (Jan 1976), pp. 163-171, 0019-9567
- Huang LY., Moran N. & Ehrenstein G. Gating kinetics of batrachotoxin-modified sodium channels in neuroblastoma cells determined from single-channel measurements. *Biophysical Journal*, Vol. 45, No. 1, (Jan 1984), pp. 313-322, 0006-3495
- Igarashi T., Aritake S. & Yasumoto T. Mechanisms underlying the hemolytic and ichthyotoxic activities of maitotoxin. *Natural Toxins*, Vol. 7, No. 2, (1999), pp. 71-79, 1056-9014
- Juntes P., Rebolj K., Sepčić K., Macek P., Zuzek MC., Cestnik V. & Frangez R. Ostreolysin induces sustained contraction of porcine coronary arteries and endothelial dysfunction in middle- and large-sized vessels. *Toxicon*, Vol. 54, No. 6, (Nov 2009), pp. 784-792, 0041-0101
- Kawada T., Akiyama T., Shimizu S., Kamiya A., Uemura K., Sata Y., Shirai M. & Sugimachi M. Large conductance Ca²⁺-activated K⁺ channels inhibit vagal acetylcholine release at the rabbit sinoatrial node. *Autonomic Neuroscience: Basic & Clinical*, Vol. 156, No. 1-2, (Aug 2010), pp. 149-151, 1566-0702
- Kloog Y., Ambar I., Sokolovsky M., Kochva E., Wollberg Z. & Bdolah A. Sarafotoxin, a novel vasoconstrictor peptide: phosphoinositide hydrolysis in rat heart and brain. *Science*, Vol. 242, No. 4876, (Oct 1988), pp. 268-270, 0036-8075
- Kobayashi M., Kondo S., Yasumoto T. & Ohizumi Y. Cardiotoxic effects of maitotoxin, a principal toxin of seafood poisoning, on guinea pig and rat cardiac muscle. *The Journal of Pharmacology and Experimental Therapeutics*, Vol. 238, No. 3, (Sep 1986), pp. 1077-1083, 0022-3565
- Koca I. & Koca AF. Poisoning by mad honey: a brief review. *Food and Chemical Toxicology*, Vol. 45, No. 8, (Aug 2007), pp. 1315-1318, 0278-6915
- Lalloo DG., Trevett AJ., Nwokolo N., Laurenson IF., Naraqi S., Kevau I., Kemp MW., James R., Hooper L., David R., Theakston G. & Warrell D. Electrocardiographic abnormalities in patients bitten by taipans (*Oxyuranus scutellatus canni*) and other elapid snakes in Papua New Guinea. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, Vol. 91, No. 1, (Jan-Feb 1997), pp. 53-56, 0035-9203

- Legrand AM., Galonnier M. & Bagnis R. Studies on the mode of action of ciguateric toxins. *Toxicon*, Vol. 20, No.1, (1982), pp. 311-315, 0041-0101
- Macek P. & Lebez D. Isolation and characterization of three lethal and hemolytic toxins from the sea anemone *Actinia equina* L. *Toxicon*. Vol. 26, No. 5, (1988), pp. 441-451, 0041-0101
- Mebs D. & Hucho F. (1990). Toxins acting on ion channels and synapses. : *Handbook of Toxinology*, Shier TW and Mebs D, pp. 493-597. Marcel Dekker Inc., New York.
- Moore RE. & Scheuer PJ. Palytoxin: a new marine toxin from a coelenterate. *Science*, Vol. 172, No. 982, (Apr 1971), pp. 495-498, 0036-8075
- Nielsen KJ., Schroeder T. & Lewis R. Structure-activity relationships of omega-conotoxins at N-type voltage-sensitive calcium channels. *Journal of Molecular Recognition*, Vol. 13, No. 2, (Mar-Apr 2000), pp. 55-70, 0952-3499
- Okuyan E., Usulu A. & Ozan LM. Cardiac effects of "mad honey": a case series. *Clinical Toxicology (Phila)*, Vol. 48, No. 6, (Jul 2010), pp. 528-532, 1556-3650
- Onat F., Yegen BC., Lawrence R., Oktay A. & Oktay S. Site of action of grayanotoxins in mad honey in rats. *Journal of Applied Toxicology*, Vol. 11, No. 3, (Jun 1991), pp. 199-201, 0260-437X
- Pignier C., Rougier JS., Vié B., Culié C., Verscheure Y., Vacher B., Abriel H. & Le Grand B. Selective inhibition of persistent sodium current by F 15845 prevents ischaemia-induced arrhythmias. *British Journal of Pharmacology*, Vol. 161, No. 1, (Sep 2010), pp. 79-91, 0007-1188
- Purkerson SL., Baden DG. & Fieber LA. Brevetoxin modulates neuronal sodium channels in two cell lines derived from rat brain. *Neurotoxicology*, Vol. 20, No. 6, (Dec 1999), pp. 909-920, 0161-813X
- Rangel-Santos A., Dos-Santos EC., Lopes-Ferreira M., Lima C., Cardoso DF. & Mota I. A comparative study of biological activities of crotoxin and CB fraction of venoms from *Crotalus durissus terrificus*, *Crotalus durissus cascavella* and *Crotalus durissus collilineatus*. *Toxicon*, Vol. 43, No. 7, (Jun 2004), pp. 801-810, 0041-0101
- Rebolj K., Batista U., Sepčić K., Cestnik V., Macek P. & Frangež R. Ostreolysin affects rat aorta ring tension and endothelial cell viability in vitro. *Toxicon*, Vol. 49, No. 8, (Jun 2007), pp. 1211-1213, 0041-0101
- Renaud JF., Kazazoglou T., Lombet A., Chicheportiche R., Jaimovich E., Romey G. & Lazdunski M. The Na⁺ channel in mammalian cardiac cells. Two kinds of tetrodotoxin receptors in rat heart membranes. *The Journal of Biological Chemistry*, Vol. 258, No. 14, (Jul 1983), pp. 8799-8805, 0021-9258
- Santos PE., Souza SD., Freire-Maia L. & Almeida AP. Effects of crotoxin on the isolated guinea pig heart. *Toxicon*, Vol. 28, No. 2, (1990), pp. 215-224, 0041-0101
- Santostasi G., Kutty RK., Bartorelli AL., Yasumoto T. & Krishna G. Maitotoxin-induced myocardial cell injury: calcium accumulation followed by ATP depletion precedes cell death. *Toxicology and Applied Pharmacology*, Vol. 102, No. 1, (Jan 1990), pp. 164-173, 0041-008X
- Sauviat MP. Muscarinic modulation of cardiac activity. *Journal de la Société de Biologie*, Vol. 193, No. 6, (1999), pp. 469-480, 1295-0661
- Sauviat MP., Marquais M. & Vernoux JP. Muscarinic effects of the Caribbean ciguatoxin C-CTX-1 on frog atrial heart muscle. *Toxicon*, Vol. 40, No. 8, (Aug 2002), pp. 1155-1163, 0041-0101
- Selwood AL., Ginkel R., Wilkins AL., Munday R., Ramsdell JS., Jensen DJ., Cooney JM. & Miles CO. Semisynthesis of S-desoxybrevetoxin-B2 and brevetoxin-B2, and assessment of their acute toxicities. *Chemical Research in Toxicology*. Vol. 21, No. 4, (Apr 2008), pp. 944-950, 0893-228X

- Sepčić K., Berne S., Potrich C., Turk T., Maček P. & Menestrina G. Interaction of ostreolysin, a cytolytic protein from the edible mushroom *Pleurotus ostreatus*, with lipid membranes and modulation by lysophospholipids. *European Journal of Biochemistry*, Vol. 270, No. 6, (Mar 2003), pp. 1199-1210, 0014-2956
- Scott PM., Coldwell BB. & Wiberg GS. Grayanotoxins. Occurrence and analysis in honey and a comparison of toxicities in mice. *Food and Cosmetics toxicology*, Vol. 9, No. 2, (Apr 1971), pp. 179-184, 0015-6264
- Sket D., Drašlar K., Ferlan I. & Lebez D. Equinatoxin, a lethal protein from *Actinia equina*. II. Pathophysiological action. *Toxicon*, Vol. 12, No. 1, (Jan 1974), pp. 63-68, 0041-0101
- Sosa S., Del Favero G., De Bortoli M., Vita F., Soranzo MR., Beltramo D., Ardizzone M. & Tubaro A. Palytoxin toxicity after acute oral administration in mice. *Toxicology Letters*, Vol. 191, No. 2-3, (Dec 2009), pp. 253-259, 0378-4274
- Su Z., Sheets M., Ishida H., Li F. & Barry WH. Saxitoxin blocks L-type ICa. *The Journal of Pharmacology and Experimental Therapeutics*, Vol. 308, No. 1, (Jan 2004), pp. 324-329, 0022-3565
- Swiss ED. & Bauer RO. Acute toxicity of veratrum derivatives. *Proceedings of the Society for Experimental Biology and Medicine*. Vol. 76, No. 4, (Apr 1951), pp. 847-849, 0037-9727
- Templeton CB., Poli MA. & LeClaire RD. Cardiorespiratory effects of brevetoxin (PbTx-2) in conscious, tethered rats. *Toxicon*, Vol. 27, No. 9, (1989), pp. 1043-1049, 0041-0101
- Terao K., Ito E., Oarada M., Murata M. & Yasumoto T. Histopathological studies on experimental marine toxin poisoning. The effects in mice of yessotoxin isolated from *Patinopecten yessoensis* and of a desulfated derivative. *Toxicon*, Vol. 28, No. 9, (1990), pp. 1095-1104, 0041-0101
- Tirapelli CR., Ambrosio SR., da Costa FB. & de Oliveira AM. Diterpenes: a therapeutic promise for cardiovascular diseases. *Recent Patents on Cardiovascular Drug Discovery*. Vol. 3, No. 1, (Jan 2008), pp. 1-8, 2212-3962
- Tubaro A., Dell'ovo V., Sosa S. & Florio C. Yessotoxins: a toxicological overview. *Toxicon*, Vol. 56, No. 2, (Aug 2010), pp. 163-172, 0041-0101
- Tubaro A., Sosa S., Carbonatto M., Altinier G., Vita F., Melato M., Satake M. & Yasumoto T. Oral and intraperitoneal acute toxicity studies of yessotoxin and homoyessotoxins in mice. *Toxicon*. Vol. 41, No. 7, (Jun 2003), pp. 783-792, 0041-0101
- Wang SY. & Wang GK. Voltage-gated sodium channels as primary targets of diverse lipid-soluble neurotoxins. *Cellular Signalling*, Vol. 15, No. 2, (Feb 2003), pp. 151-159, 0898-6568
- Williams DL. Jr., Jones KL., Colton CD. & Nutt RF. Identification of high affinity endothelin-1 receptor subtypes in human tissues. *Biochemical and Biophysical Research Communications*, Vol. 180, No. 2, (Oct 1991), pp. 475-480, 0006-291X
- Xu Q., Huang K., Gao L., Zhang H. & Rong K. Toxicity of tetrodotoxin towards mice and rabbits. *Wei sheng yan jiu*, Vol. 32, No. 4, (Jul 2003), pp. 371-374, 1000-8020
- Zhang P., Lader AS., Etcheverry MA. & Cantiello HF. Crotoxin potentiates L-type calcium currents and modulates the action potential of neonatal rat cardiomyocytes. *Toxicon*, Vol. 55, No. 7, (Jun 2010), pp. 1236-1243, 0041-0101
- Zorec R., Tester M., Maček P. & Mason WT. Cytotoxicity of equinatoxin II from the sea anemone *Actinia equina* involves ion channel formation and an increase in intracellular calcium activity. *The Journal of Membrane Biology*, Vol. 118, No. 3, (Dec 1990), pp. 243-249, 0022-2631
- Žužek MC., Maček P., Sepčić K., Cestnik V. & Frangež R. Toxic and lethal effects of ostreolysin, a cytolytic protein from edible oyster mushroom (*Pleurotus ostreatus*), in rodents. *Toxicon*, Vol. 48, No. 3, (Sep 2006), pp. 264-271, 0041-0101

Cardiotoxicity of Oncologic Treatments

Edited by Prof. Manuela Fiuza

ISBN 978-953-51-0273-1

Hard cover, 194 pages

Publisher InTech

Published online 28, March, 2012

Published in print edition March, 2012

The possibility of getting a cardiovascular disease or cancer increases with advancing age. At the same time, relevant improvements in cancer therapy have resulted in the improvement of quality of life and the increasement of the survival rate of such patients. As a result we have larger number of patients that experience the cardiac side effects of chemotherapy. The extent of cardiotoxicity is variable, depending on the type of drug used, combination with other drugs, prior mediastinal radiotherapy and the presence of cardiovascular risk factors or history of heart disease. Early detection of the patients proneness for developing cardiotoxicity is the key issue to decrease morbidity and mortality. It also facilitates more tailored therapeutic interventions. Therefore, the collaboration and interaction of cardiology and oncology may contribute to reducing the cardiovascular adverse effects and improving the results in the treatment of patients with cancer.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Robert Frangež, Marjana Grandič and Milka Vrecl (2012). Cardiovascular Pathophysiology Produced by Natural Toxins and Their Possible Therapeutic Implications, *Cardiotoxicity of Oncologic Treatments*, Prof. Manuela Fiuza (Ed.), ISBN: 978-953-51-0273-1, InTech, Available from:

<http://www.intechopen.com/books/cardiotoxicity-of-oncologic-treatments/cardiovascular-pathophysiology-produced-by-natural-toxins-and-their-possible-therapeutic-implication>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen