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Cardiovascular Pathophysiology Produced by Natural Toxins and Their Possible Therapeutic Implications

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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 (Friese 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	Depolarization, AP duration increase	Arrhythmias	0.1 mg/kg	Gutser, 1998
Grayanotoxins (GTX)	Species from genus <i>Rhododendron</i>	Polyhydroxylated cyclic diterpene	Increase Na ⁺ channel permeability and activate vagus nerve	Alteration of excitability	Fatal cardiac bradyarrhythmias	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	Depolarization, AP duration increase	Arrhythmias	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	Reference
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 sulphhydryl- 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	Arrhythmias, 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>)	Heterocyclic 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 Ciguatera

Ciguatera caused by fish poisoning is a foodborne disease caused by eating certain fishes whose meat is contaminated with ciguaterins produced by dinoflagellates such as *Gambierdiscus toxicus*. These toxins include ciguaterin (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	Depolarization, 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 compounds	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	Depolarization, 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 megarhyncha</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	Sinuauricular 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; crotapotin basic phospholipase 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.

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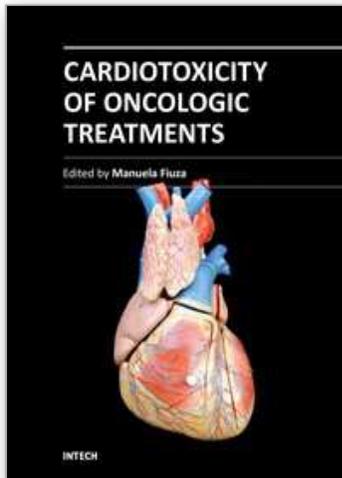
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The possibility of getting a cardiovascular disease or cancer increases with advancing age. At the same time, relevant improvements in cancer therapy have resulted in the improvement of quality of life and the increasement of the survival rate of such 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.

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