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Review Article

PHARMACEUTICAL PROPERTIES OF VENOM TOXINS AND THEIR POTENTIAL IN DRUG DISCOVERY

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ABSTRACT

Traditional pipelines feeding drugs coming to the market are declining. This is one of the reasons why nowadays the previously abandoned natural extract drug discovery programs are slowly coming back. In this scenario, small molecular metabolites from plants and single cell marine or soil organisms are gaining interest in pharmaceutical research again. Animal venoms are another source for finding new biopharmaceutical lead molecules and research interest in discovering bioactive molecules from venoms is rising. Venoms comprise often highly selective and potent bioactive peptides and small proteins for receptors and enzymes that are valid drug targets. This work discusses drug discovery research on bioactive compounds in venoms and gives older and more recent examples of bioactive compounds found in venoms from different animals. Common pharmaceutical targets that different classes of venom toxins interact with and information on developmental stages of several medicinal venom peptides are also discussed.

Key words: venom, toxin, drug discovery, peptide, pharmaceutical activity

INTRODUCTION

Bioactive peptides are widespread in prokaryotic and eukaryotic organisms. In particular, animal venoms have been the origin of several peptide based drugs (Koh and Kini, 2012). Venom drug discovery programs have delivered drugs such as Captopril, Prialt, Integrilin and Byetta, and many candidates are now progressing in clinical trials. Furthermore, peptides derived from venoms are valid pharmacological tools to study diseases (McCleary and Kini, 2013). For example, a study on the snake toxin α-bungarotoxin led to the isolation of the nicotinic acetylcholine receptor (nAChR) and a new understanding of the disease myasthenia gravis (Kini and Doley, 2010). Captopril is an inhibitor of the angiotensin converting enzyme (ACE), used to treat high blood pressure (Laing and Moura-da-Silva, 2005), which is based on compounds discovered in the venom of the Brazilian snake *Bothrops jararaca*. Other venom-derived bioactives include the highly potent analgesic hannalgesin (Pu *et al.,* 1995) from the venom of the King cobra, and the antithrombotic drug Aggrastat from the venom of the saw-scaled viper. Venoms also contain potent antimicrobial peptides and there has been an increasing stream of publications and patent applications relating to antimicrobial compounds from venoms. Examples are the peptide vgf-1 from venom of the Chinese cobra *Naja atra*, which is active against multidrug resistant *Mycobacterium tuberculosis* (Xie *et al.,* 2003), and the peptide microporin from the venom of the scorpion *Isometrus maculates* that is highly effective against multiple antibiotic resistant bacteria (Zhao *et al.,* 2009). Other examples include opistoporins from scorpion venom (Moerman *et al.,* 2002), the cupiennins, anoplin, parabutoporin (Remijsen *et al.,* 2010), vejovine, hadririne, pandinin and so on. The number and diversity of bioactive peptides in venoms, and the many thousands of animal species that produce them (including various species of snake, scorpion, spider, bee, wasp and cone snail) means that venoms constitute huge libraries of potentially new drugs and useful research tools.

VENOM TOXINS AND THEIR PHARMACEUTICAL POTENTIAL

Venomous animals use venoms, which are complex mixtures consisting for the major part of peptides and enzymes, for prey acquisition, digestion and/or defense against a

predator. From a historical point of view, venoms from snakes for example have been used for arthritis and gastrointestinal problems as well as conditions such as pain and rheumatism to polio. Other examples comprise venoms from spiders for treatment of for example asthma and cancer. Besides snakes, many other organisms produce various forms of toxins for defensive and/or offensive situations. These organisms include jellyfish, scorpions, centipedes, anemones, and some venomous fish species (Lewis and Garcia, 2003). These venom cocktails provide a rich source of bioactive peptides with many diverse potential therapeutic effects. From these, chemotherapeutic, anticoagulant, antidiabetic, thrombolytic, immunosuppressive, anticancer, antihypertensive, antibacterial, antiarrhythmic, and analgesic compounds can be named (Lewis and Garcia, 2003; Xu *et al.,* 2006; Khunsap *et al.,* 2011; Koh and Kini, 2012). A review from 2014 thoroughly discusses toxins from venoms in drug discovery and development pipelines (Harvey, 2014).

The composition of venom varies across species. Venomous animals that immobilize or kill prey by venom injection followed by venom mediated digestion, contain neurotoxins and/or highly active digestive enzymes. The toxins in snake venoms among others are toxins that target neurotransmitters and ion channels, and toxins targeting the muscular, cardiovascular and immune system (Koh *et al.,* 2006). Bees, wasps and ants use their venom for defense when they are threatened, inducing inflammatory, immunological, pain inducing, headache, and/or swelling as responses after injection. (King and Spangfort, 2000). Besides venoms, some organisms (mostly parasites) try to avoid attention of their host and as such use their venom (more often called saliva) to locally prevent immune responses, and use local anesthetics to prevent getting their presence noticed. Additionally, anticoagulants are injected to prevent coagulation of host blood (Motoyashiki *et al.,* 2003). A comprehensive review from 2014 on toxins, and their analogs, derived from venoms in drug discovery is thoroughly described by Harvey (Harvey, 2014). Many toxin derived compounds in the have entered clinical trials (King, 2011). But the same as in traditional small molecule drug development, also many of them fail reaching the market with as main causes lack of efficacy, toxicity effects, or economic reasons.

Snake venoms are continuously being explored for new peptides and proteins with medicinal properties for a wide range of syndromes and diseases (Pu *et al.*, 1995; King, 2011; Diochot *et al.,* 2012; Earl *et al.,* 2012; Koh and Kini, 2012; Vink *et al.,* 2012). One source of venom toxins relevant to both medicine and as pharmacological tools are cone snail venoms (Lewis and Garcia, 2003; Twede *et al.,* 2009, Essack *et al.,* 2012; Vetter and Lewis, 2012). The biggest success was the market approval of Prialt (Ziconotide) for treatment of patients with severe chronical pain. Ziconotide is a peptide drug initially discovered in Conus magus which actions by blocking the spinal cord resided N-type calcium ion channel Cav2.2 (Pope and Deer, 2013). Other conopeptides have been discovered that target sodium ion channels and several receptors (Vetter and Lewis, 2012). When focusing on pharmacological tools, a-bungarotoxins and conotoxins are important compounds in studying subtype selectivity between nicotinic acetylcholine receptors, by selectively blocking them (Lewis *et al.,* 2012). The pharmacological sites of five of the voltage-gated sodium channels for example were defined by venom toxins (Klint *et al.,* 2012). Sea anemones are other marine species with venom toxins that have potential medicinal properties. For example the synthetic peptide derived from the sea anemone Stichodactyla helianthus. This peptides blocks the potassium ion channel Kv1.3 very selectively and as such has potential medicinal effects in autoimmune diseases and/or MS (Beeton *et al.,* 2011; Chi *et al.,* 2012).

Saliva from parasitic species is per definition not a real venom, but it is a biological matrix with high potential for finding novel bioactive compounds for drug discovery pipelines. In saliva from parasites, compounds with anti-coagulation properties are found which for example aids in treatment of cardiovascular diseases (Stibraniova *et al.,* 2013). Arthropods have anti-coagulating (such as anti-platelet proteins), anti-inflammatory, and vasodilating proteins in their saliva. This allows them to feed from the host for longer periods of time without getting noticed by the host, and

without blood clotting occurring around the area of feeding (which allows detachment from the host after feeding). These compounds possess very interesting properties from a biopharmaceutical point of view. An added advantage of lead compounds developed from salivary proteins is that they are often anti-immunogenic and antigenic. This reduces probability of immunogenic side effects (Schwalie and Schultz, 2009, Stibraniova, Lahova *et al.,* 2013). Other effects known to be exerted by compounds in saliva from certain ticks and mosquitos are vasodilation, migration of leukocytes, platelet aggregation, coagulation (Mizurini *et al.,* 2013), angiogenesis, and complement activation. One specific class of salivary proteins are the evasins from tick saliva, and aegyptin from moquito saliva (Calvo *et al.,* 2007; Deruaz *et al.,* 2008; Deruaz *et al.,* 2013; Mizurini *et al.,* 2013). Evasins are chemokine-binding proteins. Evasin-1 binds to CCL3, CCL4 and CCL14, evasin-3 binds to CXCL8 and CXCL1, and evasin-4 binds to CCL5 and CCL11 (Deruaz *et al.,* 2008), while other proteins have also been found with chemokine modulating activity (Hajnicka *et al.,* 2001). Examples of potential medical uses involving evasins are evasin-1 for treatment of idiopathic pulmonary fibrosis (Russo *et al.,* 2011) and evasin-4 for treatment of post-infarction myocardial survival (Braunersreuther, Montecucco *et al.,* 2013). Aegyptin, found in saliva from a mosquito, is a collagen binding protein that inhibits the aggregation and adhesion of platelets (Calvo *et al.,* 2007, Mizurini *et al.,* 2013).

PHARMACEUTICAL TARGETS OF VENOM TOXINS

Antiplatelet agents

Targets of anti-platelet compounds in some venoms include thrombin, ADP receptors, integrins and metalloproteinases. Disintegrins from several snake venoms function as agonist (thereby preventing the binding of fibrinogen) (Bledzka *et al.,* 2013). Integrin $\alpha_2\beta_1$ for example is responsible for platelet adhesion and agonistic lectin-like proteins have been found in venoms from snakes (Arlinghaus and Eble, 2012). Some three-finger toxins have anti-platelet activity (Chanda *et al.,* 2013), while venom derived metalloproteinases disrupt platelet adhesion and aggregation (Santos-Martinez *et al.,* 2008).

Pro- and anti-coagulant agents

Many snake venoms have thrombin like enzymes which show similarity to thrombin, an important enzyme in the coagulation cascade (Valeriano-Zapana *et al.,* 2012), while prothrombin activators are also found in snake venoms with comparable functions as Factor X (Tans and Rosing, 2001; Joseph and Kini, 2004, Segers *et al.,* 2006). Thrombin inhibitors and activators have also been identified in snake venoms, and these inhibitors can act as potential anti-coagulation agents (Matsui *et al.,* 2000). After the bleeding of a wound stops the clot must dissolve again, which is facilitated by fibrinolysis for which the serine proteinase plasmin is responsible. In this process, fibrin is converted into soluble products. Dissolving clots has potential therapeutic applications and as such fibrin(ogen)olytic enzymes (e.g. serine proteinases and metalloproteinases) from snake venoms are interesting to study from a pharmaceutical point of view (Lu *et al.,* 2005). For hypertension, the angiotensin converting enzyme (ACE) is a major target (treatment of hypertension and heart failure), and is of interest in cardiovascular diseases and diabetic nephropathy (Kearney *et al.,* 2005). Next to many ACE inhibiting compounds identified in plants (Somanadhan *et al.,* 1999), venoms comprise another source of candidate peptides with ACE inhibiting potential. Captopril in this regard is the best known example of an ACE inhibiting drug derived from snake venom. Many proteins found in tick and mosquito saliva targeting coagulation, such as thrombin and factor Xa inhibitors (Lai *et al.,* 2004), and platelet aggregation inhibitors (Sun *et al.,* 2006), are interesting study for their potential as anti-coagulation agents. Yet other targets of tick salivary proteins are T-cells, B-cells, dendritic cells and complement factors C3 and C5 in a immunosuppressive manner (Hajnicka *et al.,* 2011; Wikel 2013).

Antibacterials, antifungals and antivirals

Certain wasps procreate by injecting their offspring into parasitized species and to prevent infection, defensin-like antimicrobial

peptides are present in the venom of these wasps (Ye *et al.,* 2010). Other antibacterial peptides found in venoms comprise the peptides pilosulin 3 and 4 found in a jumper ant (Inagaki *et al.,* 2004), although these peptides also possess allergenic properties. Venom and/or saliva from many honeybees have antifungal activity. Also, the larvae of some bees have antibacterial and antifungal secretions to protect their bee hives (Ergin *et al.,* 2006). Melittin for example, a protein found in honeybee venom, has antiviral properties against different viruses such as HIV-1 and the herpes simplex virus (Wachinger *et al.,* 1998). As this compound is also hemolytic and an allergen, the interest in its medicinal properties are limited, but it does stay a valid starting point for development of more suitable derivatives.

Anticancer agents

Bee venom has several desirable pharmacological effects such as anti-inflammatory, antimutagenic, radioprotective, and anticancer effects. For the reported anticancer effects, induction of apoptosis and necrosis, and growth inhibition can be named (Jang *et al*., 2003; Hu, Chen *et al.* 2006; Han *et al.;* 2007). The venom derived phospholipase A2 crotoxin interacts with the epidermal growth factor receptor and showed activity in a phase I clinical trial, next to showing activity in several cell lines. Apamin, which is yet another bee venom toxin, can activate p53 in certain tumors which can lead to a reduction in tumor growth (Orsolic, 2012). Integrins are suggested as drug targets for cancer cell adhesion, migration and angiogenesis inhibition. In the example of contortrostatin, a disintegrin from snake venom, it proved effective in inhibiting tumor growth, angiogenesis and metastasis in ovarian and breast cancer. Additionally, other disintegrins targeting integrin $\alpha_1\beta_1$ have demonstrated reduction of angiogenesis and metastasis (Koh and Kini, 2012).

Ion channel targets

Major targets of venom toxins are ion channels, which are also important pharmaceutical targets for among others neurodegenerative and pain related diseases. Animal toxins targeting ion channels are mainly short to medium sized peptides found in a large variety of species. Venom toxins are known to very specifically and often very potently (in different modes; e.g. agonistic or antagonistic manner) target different ion channels such as voltage-gated potassium, sodium, and calcium channels, and also ligand-gated nicotinic acetylcholine receptors (Dutertre and Lewis, 2010). In venom cocktails they mainly act as neurotoxins, but individually many are highly selective and potent and as such are considered as biopharmaceutical candidates and/or pharmacological tools (Joseph and Kini, 2004; Barber *et al.,* 2013; Brady *et al.,* 2013, Min *et al.,* 2013; Kularatne and Senanayake, 2014; Tsetlin, 2015). The neurotoxin alpha-cobratoxin for example might be interesting in relation to multiple sclerosis (Reid, 2007). Another example, Prialt, was developed from a conotoxin and is a potent drug against severe chronical pain.

CONCLUSION

Venoms are a promising source for finding novel bioactives targeting several enzymes and receptors involved in disease. Drug discovery approaches focussing on venom derived bioactives demand a different workflow than traditional small molecule drug discovery and development pipelines. Venom derived biopharmaceutical lead compounds are discovered and developed in a way that combines both traditional small molecular drug discovery, biopharmaceutical research, and traditional natural extract drug discovery programs (i.e. from plants). For venoms, the discovery and identification aspect is in part similar to traditional natural extract drug discovery programs. With venom derived drug discovery, however, straightforward medicinal peptide synthetic approaches can be used to optimize leads pharmacologically and toxicologically, which is often more complicated in case of small molecules identified from plant extracts. Furthermore, bioactive peptides and proteins can be over-expressed and produced in large fermentors that are also applied standard biopharmaceutical development processes. In case of venom peptides, genetic modification allows structural modification of the peptides for pharmacological optimization purposes. By rationally modifying amino acids of these

bioactive peptides, their pharmacological properties can be altered and optimized. Venom based drug discovery processes and academic research is not mainstream yet, but it is expected that it will slowly gain more interest and volume considering the many different highly potent and selective compounds that are yet to be discovered from venoms. As this field of research is strongly technology driven, advancements in analytics, biotechnology, biology, biochemistry, and peptide synthesis all are expected to contribute to better and more efficient drug discovery from the exiting natural recourses that venoms are.

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