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Invited review

Pharmacological screening technologies for venom peptide discovery

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ABSTRACT

Venomous animals occupy one of the most successful evolutionary niches and occur on nearly every continent. They deliver venoms via biting and stinging apparatuses with the aim to rapidly incapacitate prey and deter predators. This has led to the evolution of venom components that act at a number of biological targets – including ion channels, G-protein coupled receptors, transporters and enzymes – with exquisite selectivity and potency, making venom-derived components attractive pharmacological tool compounds and drug leads. In recent years, plate-based pharmacological screening approaches have been introduced to accelerate venom-derived drug discovery. A range of assays are amenable to this purpose, including high-throughput electrophysiology, fluorescence-based functional and binding assays. However, despite these technological advances, the traditional activity-guided fractionation approach is time-consuming and resource-intensive. The combination of screening techniques suitable for miniaturization with sequence-based discovery approaches – supported by advanced proteomics, mass spectrometry, chromatography as well as synthesis and expression techniques – promises to further improve venom peptide discovery.

Here, we discuss practical aspects of establishing a pipeline for venom peptide drug discovery with a particular emphasis on pharmacology and pharmacological screening approaches.

Contents

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1. Introduction

List of abbreviations

AChE	Acetylcholinesterase
AC	Adenylate cyclase
ACE	Angiotensin-converting enzyme
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AlphaScreen	Amplified Luminescence Proximity Homogeneous Assay Screen
ATP	Adenosine triphosphate
cAMP	3',5'-cyclic adenosine monophosphate
Ca_V	Voltage-gated Ca^{2+} channels
CNG	Cyclic nucleotide—gated ion channels
FDA	Food and drug administration
FRET	Fluorescence Resonance Energy Transfer
GPCRs	G protein-coupled receptors
GTP	Guanidine triphosphate
5-HT	5-hydroxytryptamine
IP_3	Inositol trisphosphate
MTs	Muscarinic toxins
NMDA	N-methyl-D-aspartate
TRP	Transient receptor potential channels
Na_v	Voltage-gated Na^+

1.1. History of drug discovery from venoms

Venomous organisms occur on nearly every continent on earth and populate the air (bees, wasp, assassin flies), water (platypus, cone snails, anemone, fish, jellyfish, octopi, platypus, crustaceans) and land (snakes, Gila monsters, centipedes, ants, spiders, caterpillars, scorpions, ticks, shrews, solenodons, slow loris) within various climates. These animals use their venoms to protect themselves from predators and to capture prey (Casewell et al., 2013).

Animal venoms are complex mixtures of bioactive compounds and contain many hundreds if not thousands of individual proteins, peptides and small molecules (Vetter et al., 2011). In light of the vast number of venomous species - each of which produces a unique combination of biomolecules - venoms can be considered a huge natural library of largely unexplored bioactive compounds that likely contains many promising candidates for a broad range of medical applications (Prashanth et al., 2014).

While many thousands of individual venom-derived toxins have been isolated and characterized, the majority of these originate from the venom of spiders, snakes, scorpions and cone snails, reflecting in part the complexity of these venoms as well as the medical importance of envenomation by these animals. In addition, there has been a bias in particular towards highly abundant toxins from animals that produce comparatively large quantities of venom as it can be technically challenging to extract molecules that are found in the venom cocktail at low concentration (Prashanth et al., 2012). However, advancements in bioanalytical technologies, including mass spectrometry, high-performance liquid chromatography and pharmacological screening technologies, are increasingly providing insights into the pharmacological and structural diversity of less abundant venom peptides (Menez, 2002). Also, progress in the areas of genomics, transcriptomics and bioinformatics has led to the rapid expansion of known venom peptides (Prashanth et al., 2012, 2014). Thus, the vast number of venomous animals combined with the compositional complexity of venoms and the presumed selection for biological activity makes venom-based drug discovery an attractive approach. However, while collections of several hundreds of crude venoms are readily available, establishment of venom compound libraries in a practical sense – specifically the systematic collection of purified venom components in sufficient quantities for detailed activity studies – remains largely unrealized to date. While attempts to produce actual venom peptide libraries have been commenced (EU Venomics Project, 2017), the number of readily available individual venom components (currently in the order of tens of thousands of components, eg via http://www.venomtech.co.uk) nowhere near rivals the number of small molecules available to pharmaceutical companies. Nonetheless, venom-based drug discovery approaches at least to a certain extent circumvent the need for synthetic venom peptide libraries as they are not inherently reliant on compound libraries and more often simply involve the molecular identification of bioactive components and the targeted production of a limited number of compounds.

1.2. Success of venom components as pharmaceutical products

Historically, whole animal venoms were used for the medical treatment of a broad range of diseases including asthma, cancer, polio, and multiple sclerosis (King, 2011) owing to their potent effects on mammalian biological systems. However, the systematic investigation of venoms or venom components as leads for therapeutics has only gained significant momentum in the past decades. While there are many examples illustrating the development of therapeutics from venom-derived compounds, one of the best-known success stories is that of captopril. It is the founding member of angiotensin-converting enzyme (ACE) inhibitors which are used for the treatment of hypertension, congestive heart failure, diabetic nephropathy and post-myocardial infarctions (Fox and Serrano, 2007; Harvey, 1992) and have undoubtedly saved countless lives. The peptidic precursor of captopril, termed bradykinin-potentiating peptide, was isolated from the venom of the Brazilian viper *Bothrops jararaca*, and belongs to a family of snake venom

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