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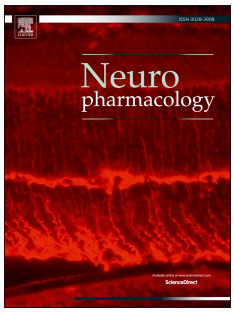

Animal toxins for channelopathy treatment

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Animal Toxins for Channelopathy Treatment

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Ion channels are transmembrane proteins that allow passive flow of ions inside and/or outside of cells or cell organelles. Except mutations lead to nonfunctional protein production or abolished receptor entrance on the membrane surface an altered channel may have two principal conditions that can be corrected. The channel may conduct fewer ions through (loss-of-function mutations) or too many ions (gain-of-function mutations) compared to a normal channel. Toxins from animal venoms are specialised molecules that are generally oriented toward interactions with ion channels. This is a result of long coevolution between predators and their prey. On the molecular level, toxins activate or inhibit ion channels, so they are ideal molecules for restoring conductance in mutated channels. Another aspect of this long coevolution is that a broad variety of toxins have been fine tuned to recognize the channels of different species, keeping many amino acids substitution among sequences. Many peptide ligands with high selectivity to specific receptor subtypes have been isolated from animal venoms, some of which are absolutely non-toxic to humans and mammalians. It is expected that molecules that are selective to each known receptor can be found in animal venoms, but the pool of toxins currently does not override all receptors described as being involved in channelopathies. Modern investigating methods have enhanced the search process for selective ligands. One prominent method is a site-directed mutagenesis of existing toxins to change the selectivity or/and affinity to the selected receptor, which has shown positive results.

Highlights:

- It will be possible to find ligands to any ionotropic receptor in virtue of diverse activity of animals' toxins.
- The main part of animal toxins inhibits ion channels and can be effective in the case of gain-of-function mutations.
- High-affinity toxins leading to complete or prolonged channel blockage/activation have poor prospects.
- Peptide pharmacological properties can be optimized by single mutations to increase their affinity /specificity to the receptor.

Keywords:
Channelopathy, animal venom, peptide toxin, disease, ligand-receptor interaction, drug seeds.

Abbreviations:

ASIC, acid-sensing ion channel; ATP, adenosine triphosphate; BK channel, big potassium channel; CFA, Freund's complete adjuvant; CFTR, cystic fibrosis transmembrane conductance regulator; ClC, chloride channel; CNS, central nervous system; CRISP, cysteine-rich secretory protein; DEG/ENaC, degenerin/epithelial sodium channel; DkTx, double knot toxin; DRG, dorsal root ganglion; GABA, γ-aminobutyric acid; HERG, human *Ether-à-go-go*-related gene; ICK, inhibitor cystine knot; Kir, inwardly rectifying potassium channel; MMP-2, matrix