ANIMAL TOXINS : STRUCTURAL ECONOMY BUT FUNCTIONAL PRODIGALITY

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Animal venoms are complex mixtures of proteins among which some are potent toxins. The toxins are capable of a wide diversity of biological effects on the neuromuscular junction, autonomic ganglia, central nervous system, heart and plasmatic coagulation system. At these sites, they often block critical receptors, ligand gated ion channels or enzymes, sometimes by competing with an endogeneous molecule. A multiplicity of functionally different toxins has been identified and new toxins are currently discovered every year.

What is the structural basis for the functional variability of animal toxins ?

Animal toxins are often small in size with their polypeptide chain comprising less than 120 amino acid residues and several disulphides bridges. Strikingly, the same overall structural architecture is used to exert several different functions. For example, most snake toxins belong to one of three different strutural classes. These are (i) toxins having a "three finger-shaped structure", a group which includes curaremimetic toxins, fasciculins, muscarinic toxins, neuronal toxins, synergistic-type toxins, toxins that block tachykinin receptors, cardio(cyto)toxins and presumably calciceptine, a calcium channel blocker; (ii) toxins folded like phospholipases-A_2 and (iii) toxins folded like trypsin inhibitor. A similar situation is encountered with scorpion toxins. Thus, irrespective of size and function, these toxins share the same 3-D motif which includes a small triple strand of antiparallel ß-sheet linked to a short helix by disulphide bonds. Clearly, analogous structures of an animal toxin can support a variety of biological functions. On the other hand, the same target can be aimed at by toxins having different structures. For example, α-conotoxin GI, a small peptide of 13 amino acid residues produced by a marine snail, competes with a snake curaremimetic toxin, a protein of 60-74 residues, for binding to the nicotinic acetylcholine receptor. These molecules have different architectures but nevertheless, they respectively possess areas that are spatially organized in a similar manner, enabling them to exert comparable functions. Structures of animal toxins are therefore characterized by a remarkable functional adaptability.

Do structurally related toxins have topographically similar functional sites ?

To answer this question, we studied curaremimetic toxins and cytotoxins from cobra venoms which, despite their functional differences, share highly similar architectures. Their polypeptide chain is folded into three adjacent loops (I, II and III) that are rich in ß-sheet and protrude from a little core containing four invariant disulphides. We identifed the two "toxic" sites using a set of genetic and/or chemical mutants of either toxins. Data showed that the "curaremimetic site" is essentially located on loops II and III whereas the "cytotoxic site" is mostly located on loop I and perhaps, at the base of loop II. The two sites are clearly topographically distinct. Therefore, no structurally specific area seems to be responsible for the functional diversity of snake toxins, in contrast to other proteins like, for example, immunoglobulins.

In conclusion, architectures of animal toxins are attractive proteic templates for the design of pharmacological functions.

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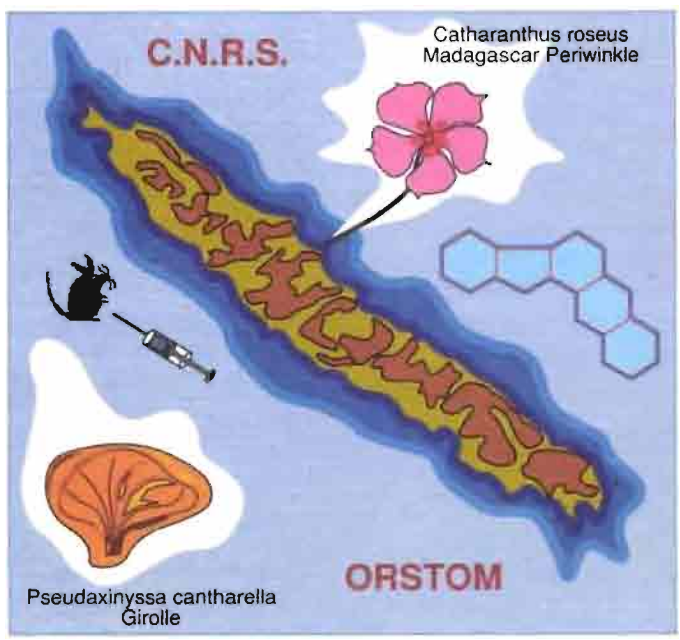

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