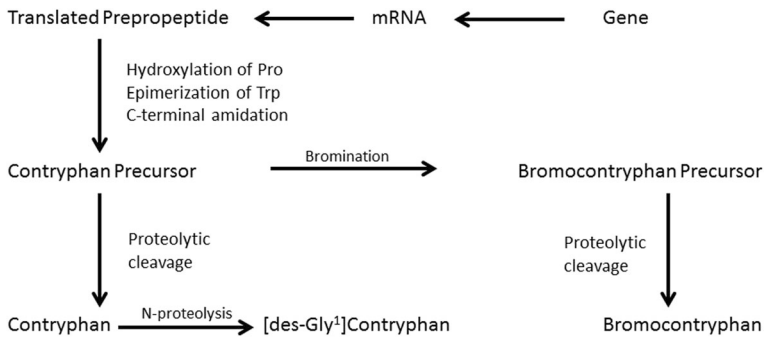

Fig. 1 Pathway of contryphan formation. It is presumed that bromination precedes the final proteolytic cleavage. The presence of two non-brominated forms, contryphan and [des-Gly^{1}]contryphan, in native venom may be due to incomplete post-translational processing with the [des-Gly^{1}]analog arising from a non-physiological post-mortem proteolysis. Reprinted with permission from Jimenez et al. [21]. Copyright by the American Chemical Society (1997)

potassium channels are the real targets of contryphan-Vn. Also, binding experiments carried out on membrane preparations of transformed HEK 293 cells overexpressing human VGPC, $K_V1.1$ and $K_V1.2$ did not evidence a competition of contryphan-Vn for the BgK (sea anemone neurotoxin) binding site [24].

Glacontryphan-M is a contryphan purified from *Conus marmoreus* venom that contains Gla (γ-carboxyglutamic acid) residues [22]. These Gla residues hold a malonate-like side chain which can chelate divalent metal ions. As such, the binding of calcium ions to glacontryphan-M induces perturbations of the N-terminal residues Gla^{2}, Ser^{3}and Gla^{4}, and the Cys^{11}-Cys^{5}-Pro^{6} region of the intercysteine loop, resulting in an increased exposure and slight reorientation of the stacked aromatic rings of His^{8} and *D*-Trp^{7} relative to the positioning of Trp^{10}.

Biological role in the venom

The biological activity of contryphans is that of causing a "stiff-tail" syndrome in mice when injected intracranially or triggering body tremor and mucous secretion when injected intramuscularly into fish [22]. At higher doses, contryphan-R induces more generalized excitatory effects in mice such as barrel rolling and seizures [20]. The first identification of a functional target for a contryphan was for contryphan-Vn from *Conus ventricosus*, which affects both voltage-gated and Ca^{2+}-dependent potassium channels [22]. Later, glacontryphan-M was identified as a calcium-dependent antagonist of L-type voltage-gated Ca^{2+} channels (VGCC) expressed in mouse pancreatic β-cells.

The structural investigation of glacontryphan-M suggests that the function of Gla in VGCC blockage by glacontryphan-M is one of the following [22]:

1. To modify the structure of glacontryphan-M so that functional determinants interact with the channel.
2. To enable glacontryphan-M to bind to the membrane surface. The Gla residues facilitate the interaction with specific calcium channel sites via bridging of calcium and membrane components.

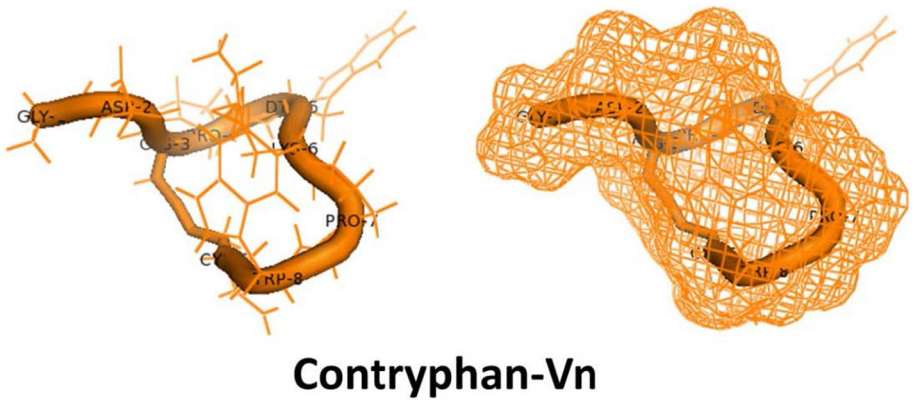

Fig. 2 Three-dimensional representation of contryphan-Vn indicating amino acids and disulfide bond (*left*) and mesh structure (*right*). Figures were created with Pymol [82] (PDB 1N3V)