3. To ensure a localized enrichment of calcium ions at the channel opening which facilitates a change in the structure of the channel. This allows glacontryphan-M to bind to an antagonist-binding site with higher affinity.

Other contryphans targeting Ca^{2+} channels are Lo959 an Am975 (Table 2), identified in the venom glands of *Conus loroisii* and *Conus amadis*, respectively. Both Lo959 and Am975, which differ only in one posttranslational modified residue, target high voltage-activated Ca^{2+} channels. Intriguingly, while Lo959 increases the Ca^{2+} current, Am975 causes inhibition of VGCC [25].

ConoCAPs

General features of conoCAPs

ConoCAPs or cardioactive peptides from cone snails are described by Möller et al. [26]. The conoCAPs (a, b, c, Table 3) reported in this work have up to 78 % of sequence homology with crustacean cardioactive peptides (CCAP, amino acid sequence PFCNAFTGC*). The discovery of conoCAPs in cone snail venom emphasizes the significance of their gene plasticity to have mutations as an adaptive evolution in terms of structure, cellular site of expression, and physiological function.

Contrary to CCAP, conoCAP-a decreases heart rate (HR) and blood pressure in rats. These effects are in accordance with the reduced systolic calcium amplitude and contraction recorded in single ventricular myocytes from rat hearts. Moreover, analogs of conoCAP-a were used to determine structure-function relationships. The reduction in HR was lost when the Cys residues were substituted by Ala or when they were S-methylated. On the other hand, less significant changes were observed when intracystine amino acids were replaced by Ala [26].

Pharmacological properties of conoCAPs

When conoCAP-a was applied on rat cardiac myocytes, the amplitude of systolic $[Ca^{2+}]_i$ and contractile activity gradually decreased. Therefore, it was expected that conoCAP-a would affect L-type Ca^{2+} channel (LTCC) current since systolic Ca^{2+} transient in cardiac muscle is triggered by Ca^{2+} entry via these channels. However, voltage-clamp experiments measuring LTCC showed that conoCAP-a had no effect on LTCC current, ruling out LTCC as a target of the peptide. Likewise, conoCAP-a did not affect other cell membrane channels and membrane receptors involved in the cardiovascular physiology. Further studies are needed to indicate the specific target of conoCAP-a.

Table 3 Characteristics of conoCAPs. Their amino acid sequences, respective species and references are indicated

Peptide	Amino acid sequence	Species	Target	Source
ConoCAP-a	PFCNSFGCYN[a]	*C. villepinii*	?	[26]
ConoCAP-b	VFCNGFTGCG[a]	*C. villepinii*	?	[26]
ConoCAP-c	LFCNGYGGCRG[a]	*C. villepinii*	?	[26]

[a]C-terminal amidation

ConoGAYs

General features of conoGAYs

ConoGAYs are a new class of disulfide-poor conotoxins with one disulfide bond, recently found in the venom gland of *Conus australis*. The name conoGAY originates from the first three amino acids of the peptide AusB (Table 4). Contrary to most disulfide-poor conotoxins, no post-translational modifications were observed in AusB. The authors investigated the effect of conoGAY-AusB on a large panel of ion channels. As such, the peptide was electrophysiologically screened against a panel of Na_Vs, K_Vs and nAChRs as expressed heterologously in *Xenopus laevis* oocytes. In addition, a broad screening was performed against a collection of microorganisms (29 gram-negative bacteria, ten gram-positive bacteria and two yeast strains) [84]. Unfortunately, the real target of this peptide remains to be revealed.

Conantokins

General features of conantokins

Conantokins are a class of conopeptides (17–27 amino acids) without cysteine residues that selectively influence NMDA (N-methyl-D-aspartate) receptors (Table 5) [4, 27]. Conantokin-G (Con-G) from *Conus geographus* was introduced in 1984 as "the sleeper peptide", because it induces a sleep-like state in mice when injected intracerebrally [28]. Similarly, conantokin-T from *Conus tulipa*, discovered by Haack et al. [29], induces sleep-like symptoms in young mice (10–13 days old); however, these manifestations are of smaller duration than those produced by Con-G. On account of these sleep-like symptoms, the conopeptides were named after the Philippino word for sleepy, antokin, resulting in "conantokin" [30]. Curiously, in mice older than three weeks, the same peptides induce hyperactive behavior which is more dramatic for Con-T than for Con-G [29, 31]. Later it was shown that both Con-G and Con-T interact with NMDA receptors in an antagonistic way [30, 32], produced by a competitive antagonism at the glutamate binding site of the NMDA receptor [27].

Conantokins show a disproportionately large number of acid labile post-translational γ-carboxyglutamic acid (Gla) residues. These Gla residues play a critical role in the chelation of divalent cations, which causes a stabilization of the α-helical secondary structure of the conantokins [27]. As such, conantokin-G requires the presence of divalent cations to form a stable α-helix, while conantokin-T adopts a stable structure, both in the