Supplementary Materials

Table 1. Conotoxin superfamily classification and families involved.

Gene Superfamily Name	Families Involved or Target Defined
A	α-conotoxins, ι-conotoxins, κ-conotoxins, ϱ-conotoxins
B	NMDA receptors
B2	Undefined
B3	α-conotoxins
C	α-conotoxins, neurotensin receptors
D	α-conotoxins
E	Undefined
F	Undefined
G	Undefined
H	Undefined
H2	Undefined
I1	ι-conotoxins
I2	κ-conotoxins
I3	Undefined
I4	Undefined
J	α-conotoxins, κ-conotoxins
J2	Undefined
K	Undefined
L	α-conotoxins
M	α-conotoxins, ι-conotoxins, κ-conotoxins, μ-conotoxins
M2	Undefined

Table 1. Conotoxin superfamily classification and families involved, continued.

Gene Superfamily Name	Families Involved
N	Undefined
N2	Undefined
O1	γ-conotoxins, δ-conotoxins, κ-conotoxins, μ-conotoxins, ω-conotoxins
O2	γ-conotoxins
O3	Undefined
O4	Undefined
P	Undefined
Q	Undefined
R	Undefined
S	α-conotoxins, σ-conotoxins
T	μ-conotoxins, τ-conotoxins, χ-conotoxins
U	Undefined
V	Undefined
W	Undefined
Y	Undefined
Ikot-Ikot	AMPA receptors
conoCAP	Undefined
Conopressin	Vasopressin/Oxytocin receptors
Conkunitzin	κ-conotoxins
Conodipine	Like PLA_2

Taken and modified from Robinson & Norton, 2014 [21]; Himaya & Lewis, 2018 [29]. AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, NMDA: N-methyl-D-aspartate receptor, PLA_2: phospholipase-A_2 activity, Undefined: Putative conotoxins without family or unidentified function.

Table 2. Conotoxin Cys framework category and families involved.

Framework	Cys Pattern	# Cys	Family
I	CC-C-C	4	α-, ϱ-, χ-conotoxin
II	CCC-C-C-C	6	α-conotoxin
III	CC-C-C-CC	6	α-, κ-, ι-, μ-conotoxin
IV	CC-C-C-C-C	6	α-, κ-, μ-conotoxin
V	CC-CC	4	ε-, μ-conotoxin
VI/VII	C-C-CC-C-C	6	κ-, μ-, γ-, ω-conotoxin
VIII	C-C-C-C-C-C-C-C-C-C	10	α-, σ-conotoxin
IX	C-C-C-C-C-C	6	Undefined
X	CC-C.[PO]C	4	χ-conotoxin
XI	C-C-CC-CC-C-C	8	κ-, ι-conotoxin
XII	C-C-C-C-CCC-C	8	κ-, δ-conotoxin
XIII	C-C-C-CC-CC-C	8	Undefined
XIV	C-C-C-C	4	α-, κ-conotoxin
XV	C-C-CC-C-CC-C	8	γ-conotoxin
XVI	C-C-CC	4	Undefined
XVII	C-C-CC-CCC-C	8	Undefined
XVIII	C-C-CC-CC	6	Undefined
XIX	C-C-C-CCCC-C-C-C	10	Undefined
XX	C-CC-C-CC-C-C-C-C	10	α-conotoxin
XXI	CC-C-C-CCC-C-C-C	10	Undefined
XXII	C-C-C-C-C-CC-C	8	Undefined
XXIII	C-C-C-CC-C	6	Undefined
XXIV	C-CC-C	4	Undefined

XXV	C-C-C-C-CC	6	Undefined
XXVI	C-C-C-C-CCCC	8	Undefined

Taken and modified from Akondi *et al.,* 2014[18].

Table 3. Generic classification and basic structure features from conotoxins.

S-family	Family	Structure Involved			Target	Mode of Action
		Cys Framework	Cys Connectivity	Electrostatic Surface		
A	α,	I, II, IV, XIV	(C_1-C_3, C_2-C_4 for I and XIV)	TS	nAChRs	Inhibitors
	ι,	III	-	UN	VGSCs	Modulators
	κ,	IV	-	Patch	VGKCs	Blockers
	ρ	I	(C_1-C_3, C_2-C_4)	-	GPCRs	Inhibitors
B3	α	XXIV	-	TS	nAChRs	Inhibitors
C	α	-	(C_1-C_2)	TS	nAChRs	Inhibitors
D	α	XX	-	TS	nAChRs	Inhibitors
I1	ι	XI	(C_1-C_4, C_2-C_6, C_3-C_7, C_5-C_8)	UN	VGSCs	Modulators
I2	κ	XI	-	Patch	VGKCs	Blockers
J	α,	XIV	(C_1-C_3, C_2-C_4)	TS	nAChRs	Inhibitors
	κ	XIV		Patch		
L	α	XIV	(C_1-C_3, C_2-C_4)	TS	nAChRs	Inhibitors
M	α,	III	(C_1-C_4, C_2-C_5, C_3-C_6)	TS	nAChRs	Inhibitors
	ι,	III	(C_1-C_5, C_2-C_4, C_3-C_6)	UN	VGSCs	Modulators
	κ,	III	(C_1-C_4, C_2-C_5, C_3-C_6)	Patch	VGKCs	Blockers
	μ	III, IV	(C_1-C_4, C_2-C_5, C_3-C_6)	Patch	VGSCs	Blockers

O1	γ,	VI/VII	(C_1-C_4, C_2-C_5, C_3-C_6)	-	NPC	(See Table 1)
	δ,	VI/VII	(C_1-C_4, C_2-C_5, C_3-C_6)	Patch	VGSCs	Modulators
	κ,	VI/VII	(C_1-C_4, C_2-C_5, C_3-C_6)	Patch	VGKCs	Blockers
	μ,	VI/VII	(C_1-C_4, C_2-C_5, C_3-C_6)	Patch	VGSCs	Blockers
	ω	VI/VII	(C_1-C_4, C_2-C_5, C_3-C_6)	Patch	VGCCs	Blockers
O2	γ	VI/VII, XV	-	-	NPC	(See Table 1)
S	α,	VIII	-	TS	nAChRs	Inhibitors
	σ	VIII	-	-	SGICh	(See Table 1)
T	μ,	V	(C_1-C_3, C_2-C_4)	Patch	VGSCs	Blockers
	τ,	V	(C_1-C_3, C_2-C_4)	-	SR	(See Table 1)
	χ	X	(C_1-C_4, C_2-C_3)	-	Noradrenaline transporters	Inhibitors

TS, total surface interaction from toxin is important**. Patch,** interaction surface reduced**. UN,** undefined**.** In some cases, such as α- or μ-conotoxins, the contact surface drives the toxin position in the target.

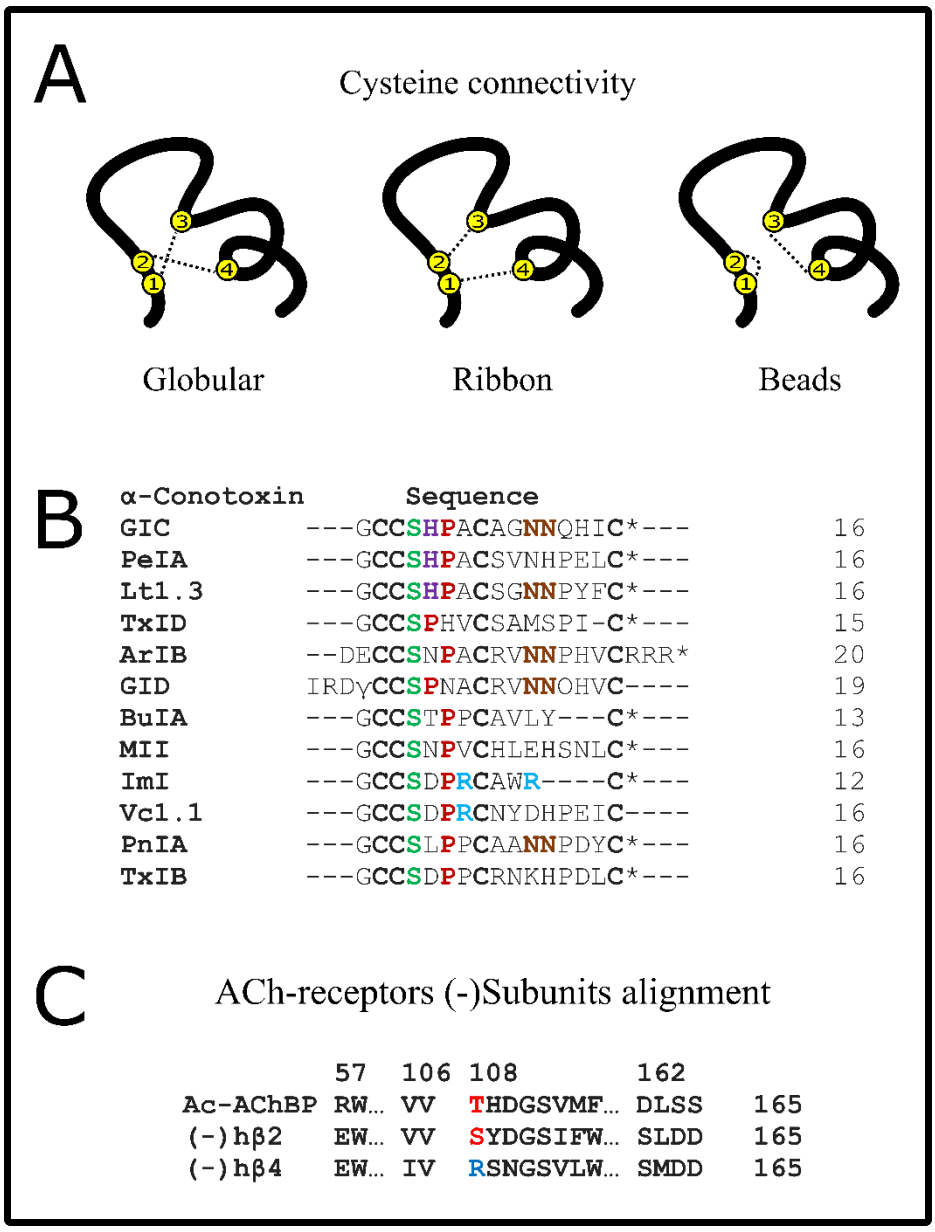

Figure 1. Supplementary figure. **A**, cysteine connectivity adopts different isomers in α-conotoxins. Structures as described by the authors in the text. **B**, some α-conotoxin alignments showing key amino acid residues highlighted. * C-terminal amidated, **O** hydroxyproline and γ gamma carboxylic glutamic acid. **C**, ACh receptors (-)subunits alignment.