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Conopeptides in Addiction Disorders Treatment

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Abstract: *Marine cone snails produce venoms (Conotoxins: CT) that have attracted interest as leads in drug design. CT are small peptides containing one or more disulfide bonds. α-CT specifically target different isoforms of nicotinic acetylcholine receptors (nAChR). In view of the important role of nAChR in normal and disease physiology such as addiction disorders, specific targeting of the relevant nAChR subtypes is an attractive pharmaceutical strategy. In this review the potential of α-CT against addiction disorders will be referred and discussed.*

Keywords: *addictive disorders, alpha-conotoxin, drug development, mechanism of action, nicotinic receptor.*

1. INTRODUCTION

Bacteria, plants, and animals use toxins as component(s) of defensive and/or offensive strategies. Marine cone snails are active predatory invertebrates (phylum *Mollusca*, class *Gastropoda, genus Conus*) living in warm seas oceans, and tidal waters, under rocks in coral reefs, or in mangroves, often buried under sand with siphon protruding out. Cone use conotoxins (CT) to immobilize and capture prey or competitor (snails, worms, fishes). CT are delivered into the preys soft tissue *via* different routes (subcutaneous, intramuscular, intravenous)[1]. The discovery of toxin mRNA in *Conus victoriae* embryos suggest other functions of CT at least during embryonic development [2]. CT are expressed and secreted in discrete regions of the long convoluted venom duct of cone by the apical secretory cells that are specialized in expression, processing, and secretion of a small set of CT [3].

1.1. Conotoxins

Advanced high-throughput sequencing technologies generated a huge amount of data that requires special and dedicated tools to analyze and classify CT sequences. *ConoSorter* is an algorithm utilized in classifying CT into superfamilies and classes according to their protein sequences or RNA sequencing data in a hierarchical stepwise process. ConoSorter classified correctly all sequences previously annotated, identified 158 novel CT precursor transcripts, 106 of which were confirmed by protein mass spectrometry, and identified 13 novel gene superfamilies of CT [4]. The high conserved signal sequence in the precursor of each gene defines the superfamily that are classified on the basis of the evolutionary relationships among CT [5]. Currently, 26 superfamilies have been defined, and new ones are commonly being discovered [1]. CT, each of one is specific for a different target [5], are divided into: α-CT that target nicotinic acetylcholine receptors (nAChR), δ-CT that target voltage-dependent sodium channels (VDSC), κ-CT that target potassium channels, λ-CT characterized by a unique disulfide pattern (C1-C4, C2-C3) that target voltage-and-calcium-gated potassium channels, μ-CT that target VDSC in muscles, and ω-CN that target N-type voltage-dependent calcium channels (VDCC). A synthetic version of ω-CT MVIIA (Ziconotide, PRIALT®) is prescribed as an analgesic drug *via* intrathecal infusion. ω-CT MVIIA is 100 to 1000 more potent than morphine as analgesic [1]. Although CT are generally small peptides, from 6 to 50 amino acids, rich in disulfide bond, they show the proteins structural elements such as α-helices, β-turns, β-sheets and disulfide bonds. According to their secondary and tertiary structure CT show specific pharmacological mode of action, potency and selectivity [1].

This review is centered on α-CT targeting nAChR and on their potential therapeutic use in addiction-disorders. The affinity of α-CT to nAChR is on the order of 10^{-9} to 10^{-8} M, thus α-CT are potent and selective antagonists of nAChR able to discriminate between several different subtypes of nAChR

and represent valuable probes for understanding the specific role of nAChR different subtypes [6]. RgIA, Vc1.1 (as ACV1), and PeIA, as well as the new class of CT named αB-conotoxin VxXXIVA, isolated by *Conus Vexillum,* are the only α-CT that target α9 and α10 nAChR [1].

1.1.1. Alpha-Conotoxins [α(ALPHA)-CT]

Posttranslational processes, subsequent to the translation in large precursor proteins, generate mature active α-CT. α-CT consist of small peptides long 11-19 amino acids [1]. α-CT are classified as a result of their cysteine (C) pattern "CC-C-C" and characterized accordingly with disulfide connectivity "C1-C3" and "C2-C4" and amidated C terminus (NH2-: amide group addition at the end of the polypeptide chain) [1]. The C-C connectivity further divides the α-CT into five subfamilies: α3/5, α4/3, α4/4, α4/6 and α4/7 [1]. All known *Conus* produce at least one α-CT targeting specific nAChR [1].

2. nACHR AS THERAPEUTIC TARGET

nAChR belong to the (super)family of Cys (C)-loop ligand-gated cationic channels. nAChR are functional transmembrane pentamer structures, resembling a rosette, in which each of one structure (subunit α or β, or also γ and δ in muscle nAChR) is arranged symmetrically around a central pore: the ionic channel [7]. Each subunit is approximately long 600 amino acids and consists of four separate transmembrane segments (TM1-TM4) characterized by a large N- and a small C-termini. The second hydrophobic transmembrane segment (TM2) of each subunit forms the wall of the ionic channel, a cylinder of ~8 nm in diameter and ~16 nm in length. The opening of the channel allows ions, present on each side of the plasma membrane, to flow though this dual gradient. The flow of charged ions results in the production of an electrical current that, altering the distribution of charge, changes the voltage across the membrane (depolarization). Membrane depolarization activates the VDCC, thereby increasing the cytoplasmic Ca^{2+} levels. In turn Ca^{2+} from intracellular calcium stores is released [7]. The agonists and competitive antagonists bind at "binding site", named "*orthosteric*", located in the extracellular domain of the α(2-10) subunits at the interface of two adjacent subunits (α and β subunits for heteromeric receptors). Some ligands may bind to distinct "*allosteric*" binding sites. According to the model postulated by Monod-Wyman-Changeux (MWC) nAChR are allosteric receptors that may exist in different conformational states including resting, open-channel or desensitized refractory state [8]. The endogenous neurotransmitter acetylcholine (ACh) or choline or the exogenous high affinity ligand nicotine induce the opening of the channel. Indeed, the name nAChR comes from the observation that nicotine mimics the action of ACh in opening the channel. Various subunits combinations may be formed by the several sub-types creating homomeric [i.e. $(\alpha7)_5$ or $(\alpha9)_5$] or heteromeric structures that are characterized by different stoichiometry [i.e. $(\alpha4)_2(\beta2)_3$ or $(\alpha4)_3(\beta2)_2$ or $(\alpha4)_2(\beta2)(\alpha5)_2$ or $(\alpha6)_2(\beta2)_3$, $(\alpha6)_2(\beta2)_2(\beta3)$, $(\alpha6)(\alpha4)_2(\beta2)_2$, or $(\alpha6)_2(\alpha4)_2(\beta2)(\beta3)$] [7]. α7 subunits may co-assemble with other subunits forming heteromeric receptors [7]. The α7β2 combination is detectable in the basal forebrain neurons and in the hippocampal interneurons. The different stoichiometry determines different properties of nAChR such as: agonist affinity (i.e.agonists, competitive antagonists or allosteric effectors), potency, conductance-rapidity, ions uptake, activation/desensitization-kinetics. When α5 subunit is incorporated in α3-containing nAChR the Ca^{2+} permeability increases significantly [7]. α7-nAChR displays the highest permeability (P) P_{Ca2+}/P_{Na+} ratio (= 90-97) counterbalanced by an extreme fast desensitization. These properties support the important role of α7-nAChR in modulating neurotransmitter release, gene expression, neuroprotection and/or neurotoxicity [7]. ACh may elicit stable nAChR activation after binding of two binding sites in heteromeric receptors, or three binding sites at non-consecutive subunit interfaces in homomeric receptors. Homomeric receptors can bind up to five molecules of agonist [7]. The β subunits also mostly contribute to the physiological and pharmacological properties (desensitization, inward rectification, and functional rundown) of the receptor. ACh, in the case of α7 nAChR, triggers a rapid activation and in turn an almost complete desensitization. On the contrary, allosteric agonists activate α7-nAChR more slowly causing low levels of apparent desensitization [7].

The maintenance of a balanced cholinergic homeostasis is crucial for the function of the central and peripheral nervous system, the neuromuscular junction and the non neuronal epithelial cells. A "*malfunctioning*" of nAChR due to mutations, impaired expression levels, or interactions with "non-canonical" effectors (i.e. β-amyloid) are eventually associated with diseases such as *myasthenia*

gravis, epilepsy, schizophrenia, Alzheimer's diseases, nicotine addiction and cancer [9]. The casual role of nAChR genes mutations and Mendelian disorders are recently highlights [10]. Variant (single nucleotide polymorphisms: SNPs) affecting nAChR genes are involved in nicotine- or alcohol-addiction, lung cancer, COPD, dementia and schizophrenia [11-13]. α4, α6, α7 sub-types are specifically involved in addiction-disorders, thus it is important to have tools to discriminate between them. The expression of α4β2 is largely up-regulated by nicotine whereas α6β2 are down-regulated [12, 14].

2.1. α-Conotoxins in Clinical Development

α-CT are, not only valuable pharmacological tools to dissect the specific role of nAChR subtypes, but potential drug candidates. Currently, only three α-CT, namely: AuIB, PeIA and Vc1.1, are under clinical exploitation for chronic pain treatment [1, 15], their mechanisms of action has been reviewed recently [15]. The potential of α-CT to be leads for the next generation of drugs is great and currently there are some promising pre-clinical results.

3. ADDICTION DISORDERS

The new fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [16] combines substance-abuse and substance-dependence within "*addictions and related disorders*" and adds "*craving or a strong desire or urge to use a substance*" to the previous *criteria*. DSM-5 considers tobacco use disorder, as other substance use disorders, while the previous DSM-4 did not have a category for tobacco abuse. Nicotine is the major addictive drug present on tobacco. According to an extremely simplified description nicotine, acting principally on α4β2, α6 and α7 placed on dopaminergic, glutaminergic and GABAergic neurons in the ventral tegmental area (VTA) of the midbrain, initiates neuroadaptive changes at both cellular and circuit levels. Nicotine influences the release of extracellular dopamine (DA) in the nucleus accumbens (NA). This process may be the key pathway accountable for nicotine reward and reinforcement. After activation, nAChR following long lasting presence of nicotine, become desensitized. When the brain nicotine levels decline, and in turn the levels of DA, withdrawal symptoms, including craving, appear while, in the meantime, nAChR recover and may be reactivated by a new dose of nicotine [17-18]. A description of addiction is beyond the objective of this review, for our purposes is important to know that different subtypes of nAChR play different role and that may be a potential target to counteract addiction. DA neurons express heteromeric nAChR containing the α4, α5, α6, β2 and β3 subunits in various combinations with the predominant subtypes being α4β2α5, α4α6β2β3 and homomeric α7 [17-18]. GWAS studies identified SNPs in the gene cluster CHRNA5-CHRNA3-CHRNB4 or CHRNA6-CHRNB3 as associated with nicotine- or alcohol-dependence [11]. rs16969968 SNP encodes the Asp398Asn (D398N) polymorphism in the exon 5 of CHRNA5 resulting in an aspartic acid (G allele) change to asparagine (A allele). rs16969968 is in perfect linkage disequilibrium with rs1051730 (CHRNA3) thus interchangeable. rs1051730 influences the level of response to alcohol intake [11]. nAChR containing α5 are located in the medial habenulo-interpeduncular nucleus (mHb-IPN) and in rodents are related with the control of nicotine self-administration, when α5 nAChR is not functioning the signaling diminishes and determines more nicotine consumption [19].

Since α-CT inhibit nAChR subtypes with high selectivity and potency, they are valuable tools not only for exploring nAChR function but in the case of addiction to specifically target specific subtypes. Currently, α-CT are under exploitation at pre-clinical levels as reported in Table 1 [20-31].

Table1. *α-CT sequence, nAChR subtype selectivity, IC_{50} values and activity in addiction-disorders.*

Conotoxin	Source	nAChR*	Activity	Ref
ArIB: **Modified toxin V11L,V16D:** 20 amino acid sequence: DECCSNPACRLNNPHDCRRR	*C. arenatus*	α7 IC_{50} = 1.09 nM	NA shell and anterior cingulate *cortex* infusion in adult male Long-Evans rats determines a significant increase in active lever pressing, breakpoints, and nicotine intake	20-21
AuIB:** 15 amino acid sequence: GCCSYPPCFATNPDC. The globular (native) isomer shows the disulfide connectivity C2-C8 and C3-C15 and the ribbon isomer C2-C15 and C3-C8	*C. aulicus*	α3β4 IC_{50} = 0.75 μM	25 pM infusion into either the interpeduncular nucleus or medial habenula decreases morphine self-administration in naïve female Long-Evans derived rats	22-23

LtIA: 15 amino acid sequence: GCCARAACAGIHELC **4**/7 conotoxin which lacks the highly conserved SXP sequence maintaining high potency	*C. litteratus*	α3β2>α6α3β2β3: IC_{50} = 9.79 nM α6α3β2β3: IC_{50} = 84.4 nM α6/α3β4: IC_{50} = 5990 nM α9α10: IC_{50} >10.00 nM α4β2: IC_{50} >10.00 nM	0.6 mg/kg attenuates naloxone-induced increase in jumping in morphine-dependent mice. Lt14a does not modulate ENK or MOR and KOR. Lt14a inhibiting CREB1 gene expression (downstream nAChR pathway) attenuates naloxone-induced morphine withdrawal symptoms	24-25
MII (α-CTxMII): 16 amino acid sequence: GCCSNPVCHLEHSNLC Disulfide bonds: C2-C8 and C3-C16	*C. magus*	α3β2 Increased binding affinity when ACh is bound to the receptor	Inhibits nicotine (10μM)-evoked [^{3}H]DA overflow from superfused rat striatal slices	24-26
MII[E11A]: 16 amino acid sequence: GCCSNPVCHLAHSNLC Synthetic peptide. E11 A	Synthetic peptide	α3β2: IC_{50} = 8.72 nM α6α3β2β3: IC_{50} = 0.16 nM	100 nM pretreatment blocks ethanol-evoked increases in function in DA neurons in the VTA suggesting an important role of α6 activity in this process Abolishes evoked DA release and decreases spontaneous DA release from striatal synaptosome of transgenic mice that express gain-of-function α6β2 nAChR***	27-29
PIA: 18 amino acid sequence: RDPCCSNPVCTVHNPQIC Disulfide bonds: C1-C3 and C2-C4	*C.purpurascens*	α6β2β3 > α3β2 α6α3β2β3: IC_{50} = 0.40 nM α3β2: IC_{50} = 1.7 nM	PIA+MII perfused into the VTA of adult male Sprague Dawley rats inhibits nicotine-elicited DA release in NA and habituated locomotion.	30-31

IC_{50} : half-maximal inhibitory concentrations. Be aware that various biological assays and receptors from different species (including human, rat, mouse and electric torpedo ray) were used to determine the IC_{50}. The given IC_{50} values should only act as rough guide with more detailed information found in the listed references.

*: Most of the α–CT listed have been tested on a wide range of nAChR subtypes, however only the subtypes that show less than 10 μM potency are listed ranked by potency; **:Analgesic properties; ***: These mice are hypersensitive to both nicotine and ACh and show elevated levels of extracellular DA levels in comparison to non-transgenic controls.

AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, ENK: endogenous opioid enkephalin, KOR: κ-opioid receptor, MOR: δ-opioid receptor, Ref.: references

4. CONCLUSION

The chronic diseases, now non-communicable diseases (NCDs), are the consequences of few risk factors including tobacco (including second-hand smoke exposure) and excessive alcohol consumption, thus tobacco and alcohol use continues to be the leading cause of avoidable poor health, disability, and death worldwide related to high health-care costs [32]. Pharmacological approaches against dependence are based on nicotine substitution therapy, Varenicline, a partial agonist of α4β2 and a full agonist of α7, and Bupropion, a DA and norepinephrine (NE) reuptake inhibitor and a non-competitive antagonist to β2 [33-36]. These drugs reduce withdrawal symptoms and craving [33-36]. α-CT have proved to be particularly valuable for "in vitro" and "in vivo" proof-of-concept studies. Different subtypes of nAChR may be identified as drug targets, consequently α-CT may have a huge potential to become leads for the next generation of drugs. Preclinical data support their possible use in addictive disorders. The big challenge is the translation of CT bioactivity into therapeutically relevant molecules since different issues connected with safety, pharmacokinetics and delivery are still not be exploited. A second challenge is the bio-sustainable venom supplies since α-CT chemical synthesis and folding make difficult to produce stable α-CT in large quantities. Ultimately, it shall be to decipher how many of the peptides produce by *Conus* may have clinical utility.

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