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Neurobiology and Therapeutic Applications of Neurotoxins Targeting Transmitter Release

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ABSTRACT

Synaptic transmission is a fundamental neurobiological process enabling exchange of signals between neurons as well as neurons and their non-neuronal effectors. The complex molecular machinery of the synaptic vesicle cycle and transmitter release has emerged and developed in the course of the evolutionary race, to ensure adaptive gain and survival of the fittest. In parallel, a generous arsenal of biomolecules and neuroactive peptides have co-evolved, which selectively target the transmitter release machinery, with the aim of subduing natural rivals or neutralizing prey. With the advance of neuropharmacology and quantitative biology, neurotoxins targeting presynaptic mechanisms have attracted major interest, revealing considerable potential as carriers of molecular cargo and probes for meddling synaptic transmission mechanisms for research and medical benefit. In this review, we investigate and discuss key facets employed by the most prominent bacterial and animal toxins targeting the presynaptic secretory machinery. We explore the cellular basis and molecular grounds for their tremendous potency and selectivity, with effects on a wide range of neural functions. Finally, we consider the emerging preclinical and clinical data advocating the use of active ingredients of neurotoxins for the advancement of molecular medicine and development of restorative therapies.

Keywords

exocytosis; nano-carriers; therapeutic targeting; presynaptic; molecular medicine; drug delivery; tetanus toxin; SNARE proteins

1. INTRODUCTION

The incredible diversity of neuroactive molecules and peptides found in bio-toxins surpasses that of all man-made synthetic formulas. Over millions of years of evolution and selection using unlimited resources, natural processes have introduced and fine-tuned an incredible wealth of biomolecules and peptides, offering a vast source of raw material for drug discovery. Conceived and refined with the ultimate purpose of assault or defence, biological poisons and venoms have acquired unprecedented potency and selectivity for interference with specific functions, to disrupt or derail a wide range of fundamental neurobiological processes. It is hardly surprising, therefore, that throughout human history, bio-toxins have found a wide range of use, from medications against arthritis and gastrointestinal ailments, to highly sophisticated warfare means (Madsen 2001; Escoubas and King 2009; King 2011; Serna et al. 2018). Recent advances in basic and translational research have illuminated an entirely new dimension for the use of toxin ingredients, which allowed the dissection and analysis of essential physiological and neurobiological processes along with the growing recognition of their vast therapeutic potential (Lewis and Garcia 2003; Fabbri et al. 2008; Dolly et al. 2009; Ghazaryan et al. 2015; Ovsepian et al. 2016b).

Despite the exhilarating history and variety of applications in the past, the modern era of venom-based drug discovery commenced with the discovery of an inhibitor of angiotensin converting enzyme (ACE) - Captopril, the blockbuster anti-hypertensive compound found in the venom of the viper *Bothrops jararaca* (Creager and Roddy 1994). Since then, a large-scale hunt for bio-toxin derived peptides has been launched, with numerous ingredients identified, which empower their ample potency, target specificity and high stability, capable of modulating the functions of a wide range of ion channels, receptors and specific sub-cellular processes such as synaptic vesicle trafficking and neurotransmitter release. Given their relatively small size, most toxins can be readily synthetized and modified to accurately fulfil immediate medical needs, thereby offering a virtually unlimited source of biomaterials for developing new classes of bio-therapeutics (Lewis and Garcia 2003; King 2011; Harvey 2014; Utkin 2015). Advances in high-throughput screening with careful structural and functional characterisation of bio-molecules also accelerated toxin and venom-based drug discovery (Robinson et al. 2017; Peigneur and Tytgat 2018). Currently, toxin-derived therapeutics stand alongside numerous approved medications on the market, protected by patents, with their properties increasingly used for the treatment of an extending variety of disorders, including cancer, inflammation, neurological and neurodegenerative disease, cardiovascular ailments and a range of other conditions (Beraud and Chandy 2011; Hmed et al. 2013; Silva et al. 2015). Notwithstanding that

only a fraction of bio-therapeutic candidates has been pharmacologically characterized, there is growing recognition of the ever-widening range of their effects on biological processes and mechanisms.

Toxins that have specific neuronal action have become of major interest, owing to their effects on fundamental processes with the capability for targeting / delivering of bio-cargo and therapeutic vectors to neurons and specific neuronal types (Dolly et al. 1994 ; Dolly 2003; Lalli et al. 2003; Singh 2010; Ovsepian et al. 2016b). The rapidly expanding usage of botulinum toxins (BoNTs) and their chimeras has played a major role in stimulating interest in the medical utility of bio-toxins, signifying yet another remarkable milestone in the history of medicine, and testifying to the fluidity of the borderlines between poison and remedy, as professed by renowned Paracelsus (Paracelsus 1538). Indeed, the ability of BoNTs to subdue hyper-active secretory glands and relax tense muscles as well as facilitate targeted delivery of therapeutic cargo or viral vectors to neurons and nerve terminals have taken centre stage in a range of recent studies of bio-toxins under preclinical settings as well as in extensive clinical applications (Jankovic 2004; O'Leary et al. 2011; Edupuganti et al. 2012; O'Leary et al. 2013; Dolly et al. 2014; Ovsepian et al. 2015). Such developments, without doubt, stimulate interest and in-depth research, discovering an increasing number of molecular targets and potential application areas.

This review aims to present a digest of the most studied neurotoxins targeting transmitter release mechanisms at central and peripheral synapses. Essential facets of presynaptic biology and transmitter release are discussed, with effects of different neurotoxins on various processes critically overviewed from basic and translational neuroscience points of view. Unlike a number of recent specialist reviews (Robinson and Hash 1982; Adams and Berecki 2013; Dolly et al. 2014; Yan and Wang 2015; Ovsepian et al. 2016a; Pirazzini et al. 2017) presenting an in-depth coverage of biology and pharmacology of neurotoxins, this study offers a general perspective on prevailing presynaptic neurotoxins, providing a first-hand reference to specialists interested in the biology of neurotoxins as well as neuroscientists and clinicians with a general interest in their translational therapeutic utility.

2. BOTULINUM TOXINS

Even though the deadly nature of botulism has been recognized over centuries, the mechanistic grounds for the incredible noxiousness of botulinum neurotoxins have emerged only recently (Sobel 2005; 2009; Fleck-Derderian et al. 2017), inferring their unique and highly-efficient features **(FIG.1)**. To date, eight BoNT serotypes (A–G and X) have been identified and characterized, which are produced by gram-positive anaerobic *Clostridium botulinum*, *Clostridium beratii*, and *Clostridium butyricum* as single-chain (SC) proteins (Mr ~150 kDa) (Simpson 2004; Dolly et al. 2014; Zhang et al. 2017). In addition to these archetypal BoNTs of *Clostridia* origin, recently, two botulinum-like neurotoxins of non-*Clostridia* origin have been identified and characterised (Zornetta et al. 2016; Zhang et al. 2017).

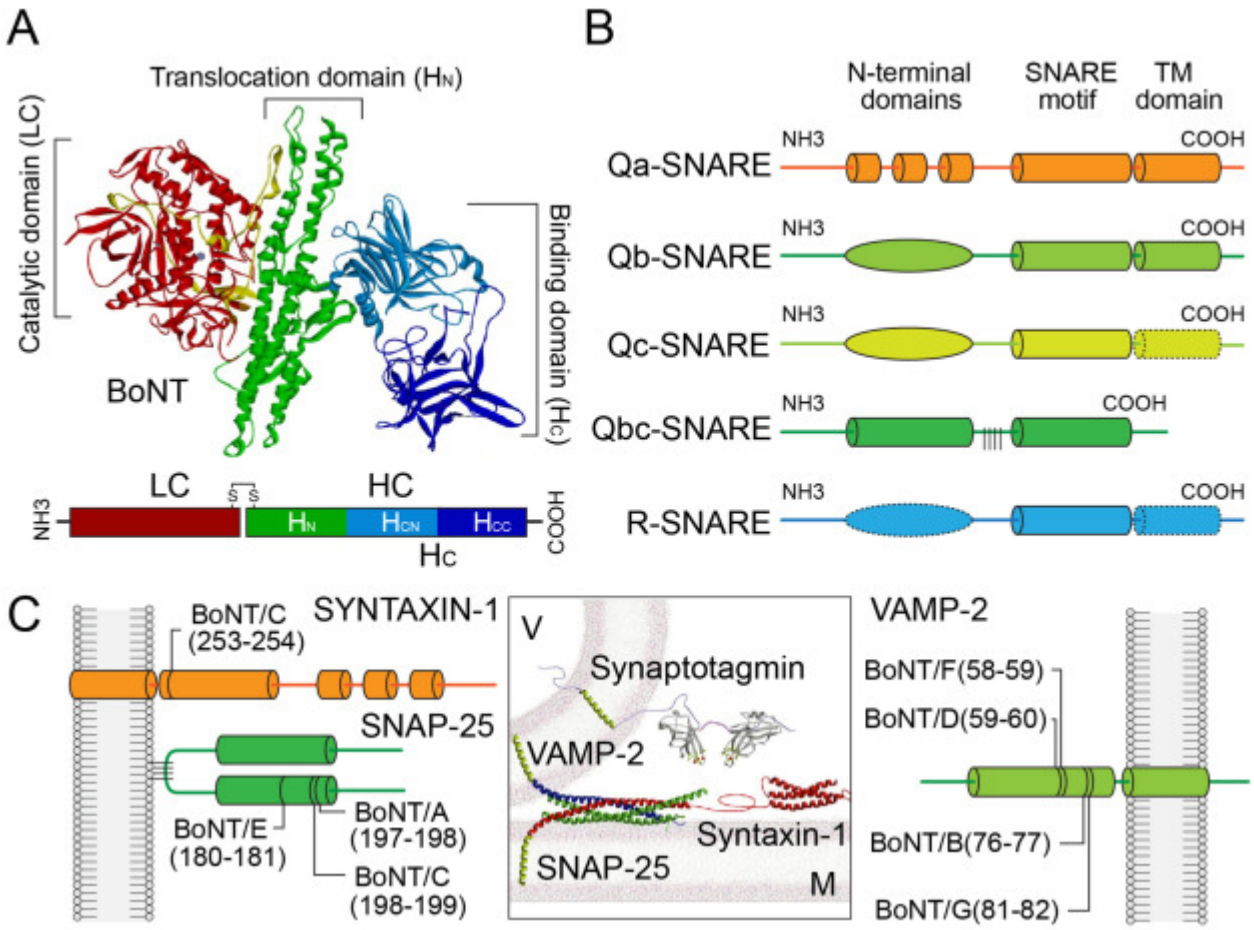

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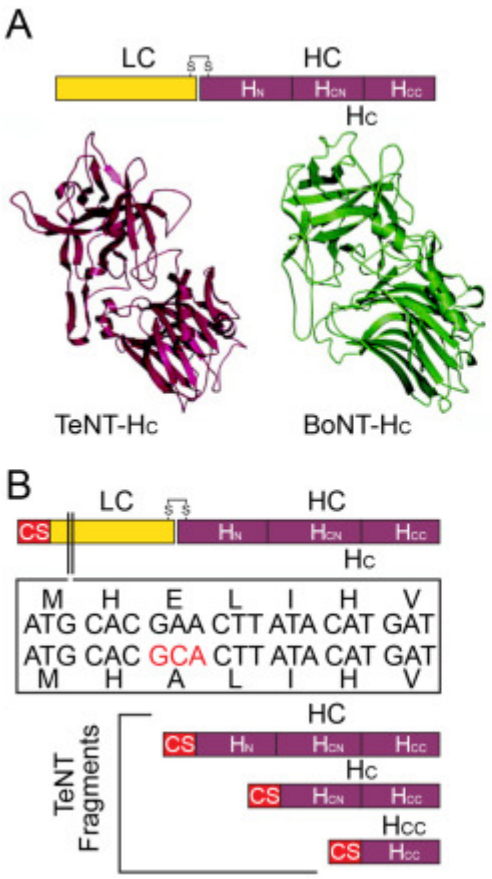
Figure 1. Botulinum neurotoxins and their synaptic targets. (A) Crystal structure of botulinum neurotoxin type A (BoNT/A) (top) with color coded schematic illustration of various domains (bottom). The C-terminal binding domain (H_{CC}) of the heavy chain (HC) adopts a trefoil fold to bind the membrane surface of neurons while the N-terminal jelly-roll motif (H_{CN}) is proposed to interact with the translocation domain (H_N) to facilitate the delivery of the light chain (LC) protease into the neuronal cytoplasm. The translocation domain is represented by a pair of long helices reminiscent of a viral coiled-coil motif and a long loop (or translocation belt) that wraps around and protects the catalytically active site. The LC contains the conserved HExxH motif characteristic of zinc-dependent proteases. Adapted with permission from (Ovsepian et al. 2016b). (B) Principal SNARE proteins and their schematic structures. The C-terminal of SNAREs corresponds to the transmembrane (TM) domain; the central portion contains the SNARE motif enabling assembly into a super-stable complex that drives membrane fusion, while the N-terminal of Qa-SNAREs (syntaxins in neurons) possesses antiparallel three-helical bundles. In Qbc SNAREs (SNAP-23 and SNAP-25 in neurons), duplicated SNARE motifs are connected by a linker that is frequently palmitoylated (vertical lines) and anchors the protein to the neuronal membrane. During vesicular fusion at nerve terminals Qbc SNAREs contribute two α-helices to the four-helical core complex, with the other two provided by Qa (syntaxins) and R SNAREs (VAMPs). Dashed borders highlight domains that are missing in some subfamily members. Modified with permission from (Jahn and Scheller 2006). (C) Neuronal SNAREs (left: Syntaxin-1 and SNAP-25; right: VAMP-2) constituting molecular targets of *Clostridial* neurotoxins, which recognize and cleave these proteins at specific scissile bonds (illustration represents rat SNAREs). For further details of SNARE cleavage in various other species, including humans, the readers are referred to (Humeau et al. 2000). Middle insert:

schematic of the surface plasma membrane (M) and vesicle membranes (V) with SNARE complex assembly shown at their interface. A crystal structure of SNARE core complex with four parallel α-helices associated in the ternary complex is adapted from (Sutton et al. 1998). The C-terminals, which points toward the vesicle and surface membrane are on the left.

Botulinum toxins are relatively large modular bio-molecules, which upon entry into bodily fluids are converted from an inactive single chain into an active di-chain (DC) (known as one of the most poisonous biomaterials) by endogenous proteases. Structurally, BoNTs are very sophisticated and are comprised of a long heavy chain (HC) constituting membrane binding H_C and translocation H_N domains linked to a light chain (LC) protease **(FIG.1A)**. BoNT HC (~100 kDa) is thought to enable neuronal targeting via high-affinity binding to the neuronal membrane at neuromuscular junctions (NMJ) of motor nerve endings, a step followed by H_N-mediated translocation of the LC (~50 kDa) protease into the neuronal cytosol, causing neuro-paralysis (Lacy and Stevens 1997; Lacy et al. 1998; Brunger and Rummel 2009; Montal 2010). The initial interaction of BoNTs with gangliosides and protein-receptors at nerve terminals, known as a binding step, is followed by rapid internalization of the toxin, a process that depends on synaptic activity and recovery of the synaptic vesicle membrane after exocytosis, demonstrated for the first time directly at mammalian motor nerve terminals (Dolly et al. 1984; Black and Dolly 1986; Montecucco 1986; Black and Dolly 1987; Dolly 2003). After the uptake, BoNTs are trafficked inside synaptic vesicles, passing through an acidic phase with conformational changes, which facilitate the translocation of the LC metalloprotease into the neuronal cytosol, where it is exposed to the thioredoxin-thioredoxin reductase system, resulting in reduction of the disulfide bridge followed by Hsp90-mediated refolding (Pirazzini et al. 2014; Pirazzini et al. 2016; Pirazzini et al. 2017; Tehran et al. 2017; Tehran and Pirazzini 2018). The latter step is essential for LC targeting and cleavage of soluble N-ethylmaleimide sensitive factor attachment protein receptor (SNARE) proteins **(FIG.1B, C)**. Because of the central role of SNAREs in synaptic vesicle docking and their Ca^{2+}-dependent fusion with surface membrane and exocytosis, their cleavage by BoNTs leads to blockade of synaptic transmission (Binz et al. 1990; Blasi et al. 1993; Schiavo et al. 1993; Capogna et al. 1996; Foran et al. 1996). Through such a multistep process, the proteases of BoNT/A and /E reach and cleave the SNARE protein SNAP-25, although at different sites (Fig. 1C, 2C). BoNT/B, /D, /F and /X proteases, on the other hand, cut and neutralize another SNARE protein synaptobrevin, which is known also as vesicle associated protein (VAMP I/II), while the type C1 protease cleaves simultaneously two SNAREs, SNAP-25 and syntaxin (**FIG.1C,2C**). Recently, two novel botulinum-like non-*Clostridia* neurotoxin BoNT/Wo and BoNT/En have been discovered, with the former targeting VAMP I/II, while the latter cleaves and inactivates at the same time VAMP I/II and SNAP-25 proteins (Tehran and Pirazzini 2018). In this way, after encountering synaptic terminals and delivering their LCs into the neuronal cytosol, BoNTs arrest neurotransmitter release within hours, with inhibitory effects that can last from several days to many months, until the affected nerve terminal resumes exocytosis (Foran et al. 2003a; Pirazzini et al. 2017).



C

	Neurotoxins	Receptors	Target SNAREs	Scissile bond
C - NTs	BoNT/A	SV2A,B,C	SNAP-25	Q197-198R
	BoNT/B	Syt-I/II	VAMP I/II	Q76-77F
	BoNT/C1	None	SYNTX. 1A SNAP-25	K253-254A R198-199A
	BoNT/D	SV2A,B,C	VAMP I/II	K61-62L K59-60L
	BoNT/E	SV2A,B	SNAP-25	R180-181I
	BoNT/F	SV2A,B,C	VAMP I/II	Q60-61K Q58-59K
	BoNT/G	Syt-I/II	VAMP I/II	A83-84A A81-82A
	TeNT	SV2 Nidogen 1/2	VAMP I/II	Q76-77F
NC - NTs	BoNT/X	TBD	VAMP I/II	R66-67A (II)
	BoNT/Wo	TBD	VAMP II	W98-99W
	BoNT/En	TBD	VAMP I/II SNAP-25	A68-69D K63-64I

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Figure 2. Tetanus toxin, *Clostridial* and non-*Clostridial* neurotoxins, receptors and SNARE cleavage. (A) Schematized illustration of the structure of TeNT (top) and crystal structure of H_C binding domains of BoNT/A and TeNT (bottom). Note remarkable structural similarities of protein architecture. Adapted, with permission from (Turton et al. 2002). Similar to BoNTs, the C-terminal binding domain (Hcc) of TeNT adopts a trefoil fold to bind the membrane surface of neurons, while the N-terminal jelly-roll motif interacts with the translocation domain (HN). The light chain (LC) of TeNT, like BoNT LC contains the conserved HExxH motif characteristic of zinc-dependent proteases. (B) Schematics of TeNT-derived recombinant core streptavidin (CS) fusion proteins: detoxified full-length tetanus toxin (TeTIM) (top) and TeNT binding fragments (TeNT fragments) (bottom) fused with CS made for targeting viral vectors to motor nerve terminals. CS-TeTIM was produced through the fusion of CS and detoxified tetanus toxin (TeNT) (red; E234A point mutation) genes. (C) A summary table of *Clostridial* neurotoxins (the seven serotypes of BoNTs and TeNT) and the recently discovered non-*Clostridial* neurotoxins with their protein receptors, target SNARE proteins and scissile bonds. TBD stands for ‘to be defined’.

To date, the secretion of all transmitter types, from both small and large dense-core vesicles have been shown to be susceptible to the paralytic effects of BoNTs, provided that the BoNT LC can get into the intracellular environment (Ashton and Dolly 1988; McMahon et al. 1992; Ashton and Dolly 2000; Dolly 2003; Ovsepian and Dolly 2011; Sudhof and Rizo 2011). From a basic science viewpoint, the variety of BoNT serotypes that cleave one or more SNAREs at different sites is highly advantageous in dissecting the role of individual SNAREs in driving

exocytosis. The usage of such discriminating probes, hence, can yield major insights into the complicated multistage cellular and molecular processes operating at presynaptic terminals. For instance, BoNT/A-induced inhibition of transmitter release from peripheral and central neurons can be reversed by increasing the intracellular Ca^{2+} concentration, while similar manipulations with intracellular Ca^{2+} failed to counter the paralytic effects induced by other serotypes tested so far (Capogna et al. 1997; Sakaba et al. 2005; Meng et al. 2009). Likewise, the role of different SNAREs in neurotransmitter release at different synapses and neuron types can be dissected using BoNT serotype-specific inhibitors, which showed promise in restoring synapses from paralysis in *ex vivo* and *in vivo* models (Edupuganti et al. 2012; Kiris et al. 2014; Guo et al. 2015). Importantly, these differences not only have fundamental implications for improving the current understanding of molecular mechanisms that control transmitter release, but, also, for the utility of different BoNTs to target specific mechanisms operating at specialized motor nerve endings in neuromuscular junctions, autonomic neurons and synapses, as well as in pain sensing nociceptors (Dolly et al. 2009).

From a translational view point, elucidation of the multistep processes enabling the binding and internalization of BoNTs into synaptic terminals and their action on the secretory machinery provide a framework for deciphering the action mechanisms and key targets for therapeutic interventions. Indeed, BoNTs have been used with astounding success for the treatment of a wide range of neurological conditions related to hyperactivity the periphery, especially effective in various forms of dystonia and other dysfunctions of involuntary motor movement, including spasticity and glandular hypersecretion (Jankovic 2004; Bentivoglio et al. 2009; Elia et al. 2009; Jankovic 2009; Dolly and O'Connell 2012). More recently emerging data suggests also the therapeutic utility of BoNTs for the treatment of chronic pain and neuro-inflammatory responses associated with numerous neurological conditions (Aoki 2003; Qerama et al. 2010; Oh and Chung 2015). In all of these applications, the therapeutic utility of BoNTs relies primarily upon inhibiting excessive release of classical transmitters, neuromodulator peptides and other substances. Importantly, the ameliorative effects come with high specificity and readily reversible changes to neural tissue (de Paiva et al. 1993; de Paiva et al. 1999; Meunier et al. 2002). The exceptional longevity of BoNT/A action, which appears to be due to stability of its protease, is also particularly attractive for developing long-acting therapeutics, while shorter acting BoNT/E and BoNT/D may afford transient effects lasting over several days (Foran et al. 2003b). Thus, in addition to offering a convenient toolkit for advancing fundamental research of synapses and targeting different neuronal types, some BoNTs exhibit promising therapeutic capabilities with potential applications for amelioration of muscle hyperactivity, soothing overactive nociceptors as well as taming overactive secretory glands. In addition to natural BoNTs, the toolkit of neurotoxins has become enriched with newly created recombinant BoNT-derived peptides and bio-pharmaceutics, produced by the fusion of different BoNT domains specifically tailored to meet particular needs, or through other molecular and biochemical modifications. These include generation of mosaic proteins by fusion of various BoNT subunits (Wang et al. 2008; Dolly et al. 2009; Meng et al. 2009), an array of conjugates of light chain and

N-terminus of HC heterodimer (Shone et al. 1985; Chaddock et al. 2000a; Chaddock and Marks 2006) as well as lectin conjugates or other neuron-specific ligands for enhanced targeting and delivery of biomolecules (Chaddock et al. 2000a; Chaddock et al. 2000b; Duggan et al. 2002). Another approach utilized targeted mutations, to generate non-toxigenic mutant strains or detoxified BoNTs with maintained neuronal binding and delivery of therapeutic payload (O'Leary et al. 2011; O'Leary et al. 2013; Ovsepian et al. 2015; Ovsepian et al. 2016b). Proof of concept for these approaches has already been obtained, affording effective targeting of presynaptic functions and modulating SNARE-dependent synaptic secretion machinery in *in vitro* and *in vivo* models (O'Leary et al. 2011; Edupuganti et al. 2012). Earlier attempts have been also made towards the use of the BoNT H_C binding domain for enhanced delivery of bio-therapeutics to neurons and synapses, with however modest outcome (Goodnough et al. 2002; Bade et al. 2004; O'Leary et al. 2011; Edupuganti et al. 2012), prompting interest in the utility of detoxified full-length botulinum toxin protease mutant (BoTIM), which is superior over its binding H_C domain. Recently, dedicated nano-carriers derived from detoxified full-length BoNTs fused with core streptavidin (CS) have been validated in a range of *in vitro* and *in vivo* pre-clinical applications (O'Leary et al. 2011; Edupuganti et al. 2012; Dolly et al. 2014; Ovsepian et al. 2016b). Taken together, the discussed herein preclinical and clinical research of BoNTs and their validation as nano-carriers for improved neuron targeting and drug delivery have spawned new areas of research and avenues for elucidating further their biology and medical utility, with major translational relevance.

TETANUS TOXIN

As is the case with most potent toxins from bacteria, the tetanus toxin (TeNT) is a highly deadly poison (Montecucco and Schiavo 1994; Fishman 2009). It is produced by the anaerobic *Clostridium tetani* germinating in infected wounds. From this location, the toxin is released via autolysis and systemically spreads into the circulation, reaching peripheral autonomic and motor nerve endings in the NMJ, which represent the primary site of entry into neurons (Cook et al. 2001). While the nature of the TeNT receptor complex at the peripheral synapses has remain elusive over many years, recently it was shown that the presence of nidogens (also known as entactins), which are extracellular matrix linker molecules, are critical for the high-affinity binding and internalization of TeNT (Bercsenyi et al. 2014). Like BoNTs, TeNT is produced as a ~150 kDa single-chain protein, that is post-translationally nicked into a di-chain composed of a ~100 kDa heavy chain (HC) and ~50 kDa light chain (LC) protease linked via a disulfide bridge and non-covalent interactions (Craven and Dawson 1973; Rossetto et al. 2001; Fishman 2009). Similar to neuro-paralysis with blockade of synaptic transmission induced by BoNTs, the inhibition of neurotransmitter release caused by TeNT is a complex and multi-step process. Like BoNTs, TeNT shows excellent neuro-selectivity due to specific receptor-mediated binding to nerve terminals, a characteristic largely attributed to the C-terminal domain of the HC **(FIG.2A)**. This initial step is followed by internalization of TeNT into nerve terminals. However, unlike BoNTs exerting toxic effects at first entry sites at the periphery, upon internalization,

TeNT highjacks the fast intra-axonal transport system of neurons to reach the spinal cord and brain stem (Brooks et al. 1957; Schwab and Thoenen 1976; Benecke et al. 1977; Takano et al. 1983; Bomba-Warczak et al. 2016). Therein, TeNT crosses synapses and enters into the presynaptic terminals of inhibitory interneurons where it blocks the release of neurotransmitters (GABA and glycine), causing disinhibition of large motor neurons that leads to spastic paralysis. The latter, if untreated, causes death, due to violent convulsions driven by muscular hypertonus, and breathing failure (Fishman 2009). At central synapses, TeNT exerts potent effects at the presynaptic terminals of interneurons, where H_N enables pH-dependent translocation of an active LC protease into the neuronal cytosol (Schiavo et al. 1991; Schiavo et al. 1992a; Schiavo et al. 1992b; Emsley et al. 2000). Upon release from synaptic vesicles, the active protease of TeNT cleaves VAMP I/II, one of three main neuronal SNARE proteins, disabling the formation of the supra-molecular SNARE complex (contributed by VAMP, syntaxin and SNAP-25), a reaction driving synaptic vesicle exocytosis. Thus, despite shared features with BoNTs, there are fundamental differences between the two, responsible for different paralytic effects.

The unique capability of TeNT to target and enter motor nerve terminals and autonomic nerves at the periphery, and travel from there to the central nervous system via retro-axonal transport has generated considerable interest for translational research and clinical application (Ovsepian et al., 2016). In fact, TeNT is the only known substance that has the potential for selective enhancement of motor functions, capable of overcoming flaccid muscles and muscle weakness caused by brain and spinal cord injuries (Brooks et al. 1957; Sasse et al. 2005; Dillingham 2007). Observation in humans and experimental animals show that TeNT could be beneficial for inducing a state of elevated activity in a target population of motor neurons and muscles even in vaccinated animals and humans (Fishman 2009). This unique and highly advantageous feature of TeNT is currently under close investigation, with positive attempts reported for its use in treatment of several conditions related to acute and chronic muscle weakness (Fezza et al. 2000; Fishman 2009). An illustrative example of such application is TeNT injection into the pharyngeal muscle for suppression of snoring and related with it breathing apnoea, which leads to sleep improvement without adverse effects (Sasse et al. 2005). New TeTx therapies that could prevent and reverse muscle atrophy associated with immobility have also been considered, which would complement current rehabilitation regimes for patients with limb trauma (Matthews et al. 2014).

Another area of TeNT research presenting clinical relevance that has created much interest is its potential as a nano-carrier for neuron targeting and drug / vector delivery to the central nervous system (Toivonen et al. 2010; Ovsepian et al. 2016b). Given the tight protection of the brain and spinal cord by the blood brain barrier (BBB), which prevents over 98% of small and 100% of large molecules from entry into the central nervous system, the enhanced capacity for cargo and vector delivery by TeNT is highly advantageous for the transfer of therapeutic load or genes to central neurons. Since the first report of the cytoplasmic delivery of TeNT LC by

BoNT/A HC in isolated mouse phrenic nerve hemi-diaphragm preparations (Weller et al. 1991), both TeNT and BoNT HC have been utilized to endow neurotropism on different bio-cargo and vectors (Dobrenis et al. 1992; Knight et al. 1999; Bade et al. 2004; Francis et al. 2004; Andreu et al. 2008). Some studies however have found that the neuron targeting and trafficking of TeNT is not replicated faithfully by TeNT HC (Weller et al. 1986; Fishman and Carrigan 1987; 1988; Weller et al. 1991; Fishman 2009). Moreover, in terms of counteracting the paralytic action of TeNT, a full-length but enzymically inactive mutant of TeNT (TeTIM) is >30 fold more effective than H_C (Li et al. 2001), an observation that supports the superiority of TeNT and TeNT toxoid, over its HC in binding to nerve terminals (Weller et al. 1986; Fishman 2009). The efficacy of the HC translocation or HC-tethered payload delivery into the cytoplasm of the target cell is also controversial and requires further research (Francis et al. 2000; Fishman 2009).

Hence, while instructive as model carriers and showing promise in preclinical *in vitro* studies, TeNT C-terminal binding fragments have proven to be generally disappointing as delivery vehicles (Fishman 2009; Ovsepian et al. 2016b). This could be due to the close cooperation between various domains of BoNTs and TeNT for maximal performance, with conclusive data presented recently for better performance of the detoxified full-length TeNT (TeTIM) over its binding fragments in antagonizing the paralytic effects of TeNT (Li et al. 2001; O'Leary et al. 2013; Ovsepian et al. 2015) **(FIG.2B)**. Indeed, BoTIM/B or TeTIM fused with core streptavidin have shown superior targeting and delivery capacities as carriers. These new molecules also have been found to be better vehicles for delivery of fluorescence reporters and viral vectors to the motor nerve terminals and spinal cord neurons *ex vivo* as well as *in vivo* (O'Leary et al. 2011; Edupuganti et al. 2012; Ovsepian et al. 2015; Ovsepian et al. 2016b). In all neuron-binding, internalization and retrograde transport assays, CS-TeTIM out-performed CS fusion proteins of HC or H_C, with CS of CS-TeTIM readily detectable in axon terminals of motor neurons and in spinal cord neurons (O'Leary et al. 2013; Ovsepian et al. 2015; Ovsepian et al. 2016b). These findings agree with data showing that detoxified TeNT is superior to TeNT binding domains at counteracting TeNT-induced cleavage of VAMP I/II in rat cultured neurons (Ovsepian et al. 2015). Results from studies of chimeric BoNTs and TeNT further support the notion of cooperation between different domains, warranting their superior performance and potency (Wang et al. 2008; Wang et al. 2012; Ovsepian et al. 2015; Ovsepian et al. 2016b).

All in all, TeNT emerges to have broadly two major areas for therapeutic application. Firstly, the unique ability for selective enhancement of motor functions makes it capable for overcoming flaccid muscles and muscle weakness caused by brain and spinal cord injuries, as well as for treatment of other conditions related with muscle weakness. Secondly, its excellent capacity to target nerve endings and penetrate from the periphery to central neurons makes is highly valuable as a potential nano-carrier for cargo and therapeutic gene delivery to central neurons. Despite major structural similarities with BoNTs, TeNT display several important differences, that makes this wonder molecule highly interesting in its own right **(FIG.2A, C)**. Careful comparison of multistep reactions involving BoNTs, TeNT and their proteolytic targets is

warranted for further advancement of carriers and bio-therapeutics, with uncompromised performance. While concerns remain over risks related to residual toxicity of TeNT derived carriers, advances in recombinant technologies and selective immune-suppressants inspire optimism in the future medical usage of these wonder molecules. Indeed, meeting many important criteria, TeTIM holds considerable potential for use as a carrier in a variety of neurological and degenerative diseases affecting motor neurons, including ALS and primary lateral sclerosis, various forms of neuromuscular atrophy and palsy, with anticipated benefits.

3. LATROTOXIN

α-Latrotoxin is another potent toxin targeting the molecular machinery of exocytosis, which has a high affinity for receptors that are expressed specifically on neuronal and endocrine cells. α-Latrotoxin is enriched in the venom of the widow spiders of the genus *Latrodectus*, with the most widely known amongst them the black widows, *L. mactans*. In addition to α-latrotoxin, the venom of *Latrodectus* contains a plethora of other peptides displaying a range of activities (Yan and Wang 2015). Most of these peptides target neuromuscular transmission in insects (α- and δ-latroinsectotoxins) or crustacea (α-latrocrustotoxin) (Duan et al. 2006), which constitute the natural prey of the black widow spider. From the rich cocktail of toxins produced by the black widow spider, only α-latrotoxin is specific for vertebrates (Garb and Hayashi 2013). Despite the scaremongering, bites from a black widow spider do not present a major health problem for humans because they rarely cause serious disease (Sudhof 2001; Ryan et al. 2017). Only in the most serious cases do black widow spider bites cause latrodectism, a syndrome consisting of generalized muscle pain, abdominal cramps, profuse sweating, a rise in blood pressure and tachycardia, with death encountered only on very rare occasions (Sudhof 2001; White and Weinstein 2015). The distress caused by α-latrotoxin is thought to be due to dramatically increased release of neurotransmitters, and especially acetylcholine. When injected systemically, the primary target of α-latrotoxin is the neuromuscular junction, where the toxin triggers exocytosis of acetylcholine contained in clear synaptic vesicles (Ceccarelli et al. 1988; Matteoli et al. 1988). Induced by α-latrotoxin, secretion of peptides and catecholamines from sensory neurons and endocrine cells has also been widely documented (Meldolesi et al. 1983; Barnett et al. 1996; De Potter et al. 1997). In fact, α-latrotoxin has been capable of activating massive release of all mediators from all secretory cell types tested so far (Silva et al. 2009a).

Due to potent synaptic effects, α-latrotoxin is a useful molecular probe for studying neurotransmission in mammals and humans. **Fig.3(A-D)** presents an overview of the structure and receptors along with the mechanisms of the effects of α-latrotoxin on synaptic transmission in vertebrates. Similar to other toxins targeting the presynaptic release machinery, the effect of α-latrotoxin on synaptic release is a complex and multi-step process. To induce synaptic activity changes, the toxin should initially bind to specific receptors on synaptic terminals (Sudhof 2001). Analysis of α-latrotoxin effects revealed that it stimulates transmitter release by two distinct mechanisms, both reliant upon toxin binding to three structurally unrelated receptors:

neurexins, latrophilin 1 and receptor-like protein tyrosine phosphatase σ (McMahon et al. 1990; Rosenthal et al. 1990; Ushkaryov et al. 2008) **(FIG.3B, C)**. Neurexins are brain-specific cell adhesion molecules, which bind to α-latrotoxin in a Ca^{2+}-dependent manner. After binding, α-latrotoxin experts its effects via two pathways: (1) Ca^{2+}-dependent, which involves α-latrotoxin insertion into the plasma membrane and pore formation (Orlova et al. 2000) and (2) Ca^{2+} independent action, reliant on receptor-mediated signalling (Davletov et al. 1998; Ashton et al. 2001). In the presence of extracellular Ca^{2+}, thus, α-latrotoxin bound to latrophilin operates as a Ca^{2+} ionophore while in the absence of Ca^{2+}, the effects of α-latrotoxin are due to stimulation of signal transduction and enhancement of synaptic activity by phosphorylation of SNARE proteins such as SNAP-23, syntaxin IV, and VAMP VIII, through protein kinase C (PKC) as well as PKC-independent pathways (Hiramatsu et al. 2010; Yan and Wang 2015). The latter mechanisms rely on latrophilin binding to G proteins, namely Gα/o and Gαq/11 (Rahman et al. 1999; Serova et al. 2008), which leads to activation of phospholipase C (PLC) and efflux of Ca^{2+} from internals stores with elevation of cytoplasmic Ca^{2+}, which subsequently triggers transmitter release **(FIG.3D)**.

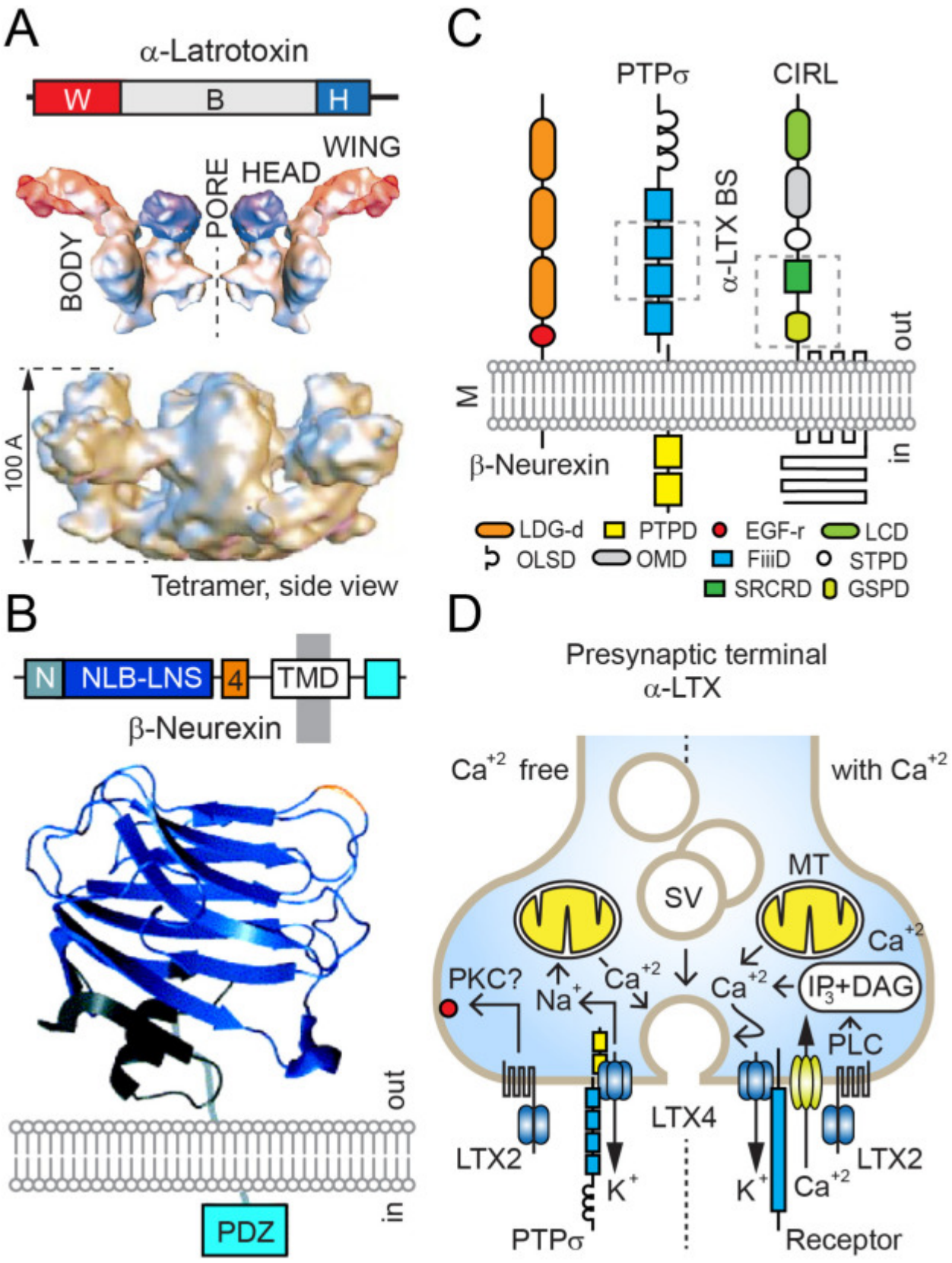

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Figure 3. Schematics of Latrotoxin structure, its receptors and action mechanisms at the presynaptic terminal. (A) Top: schematized α-latrotoxin (LTX) with three structural domains coded in different colors: wing – red (W); body – grey (B) and head– blue (head). The wing domain is the putative receptor-binding domain;

the body makes up the transmembrane domain while the head makes the channel mouth. Middle and bottom panels - a side view of α-LTX dimer with its structural subdomains and tetramer, respectively. Through assembly into tetramers, α-LTX forms an aqueous pore mediating Ca^{2+} influx. Crystal structure panels are adapted with permission from (Orlova et al. 2000). (B) Schematic diagram (top) of the structure of the α-LTX receptor β-Neurexin and with corresponding 3D reconstruction (bottom). β-Neurexins are composed of an extracellular N-terminal sequence (N) that is specific to β-neurexins, a single LNS (laminin, neurexin, sex-hormone binding globulin) domain that is essential for neuroligin binding (NLB) (blue yonder color) followed by Band4.1 actin binding domain (orange color) and a transmembrane domain (TMD) (while color) linked to a cytoplasmic tail that contains a PDZ-interaction site on the C-terminus (light blue color). Note that the putative monomer of β-neurexin-1 contains two seven-stranded β-sheets that form a fold, and splice sites that are localized within loops at the edge of the fold (orange color indicated by arrow), which might act as a protein-interaction surface. *Neuroligins* preferentially *bind to* β-n*eurexins* without an *insert*. It is attached to the surface membrane through TMD and is stabilized by PDZ. Adapted with permission from (Dean and Dresbach 2006). (C) A schematic of the domain structure of all three α-LTX receptors: M – membrane; LDG-d – Laminin A G-domain; EGF-r – EGF repeat; OLSD – O-linked sugar domain; FiiiD – Fibronectin III domain; PTP – Protein tyrosine phosphatase; PTPD – PTP domain; LCD – Lectin domain; OMD – olfactomedin domain; STPD – STP-rich domain; SRCRD – Secretin receptor cys-rich domain; GSPD – GSP domain. Schematics are adapted with modifications from (Krasnoperov et al. 2002). (D) Diverse mechanisms of α-LTX action at the neurosecretory machinery. Right, in the presence of extracellular Ca^{2+} and left in the absence of Ca^{2+}; the pathways shown are briefly described in the text. For more information, the readers are referred to (Ushkaryov et al. 2008). DAG – diacyl-glycerol; LTX2 – α-LTX dimer; LTX4 – α-LTX tetramer; MT – mitochondria; PLC – phospholipase C; IP3 – inositol 3 phosphate. Possible pathways for Ca^{2+}-independent exocytosis include: (1) high-concentration of Na^{+} mimicking Ca^{2+} and the internalized domains of α-LTX interacting with components of the exocytosis machinery and triggering exocytosis.

It must be stressed, that the effects of α-latrotoxin on neurotransmitter release in the absence or presence of Ca^{2+} are fundamentally different and show different kinetic and dynamic characteristics (Tsang et al. 2000; Silva et al. 2009b). In general, most of the toxins effects are induced by elevated Ca^{2+} influx via presynaptic channel-pores (Davletov et al. 1996), requiring the involvement of VAMP I/II and SNAP-25 (Capogna et al. 1996; Davletov et al. 1996; Davletov et al. 1998; Ashton et al. 2001). Through a combination of genetic methods and electrophysiology, it has been shown that α-latrotoxin induced Ca^{2+}-dependent transmitter release recruits VAMP plus SNAP-25 and active zone protein Munc13-1 (Deak et al. 2009). In contrast, Ca^{2+}-independent release uses a non-classical pathway, which does not involve the regulated exocytosis machinery and departs from the canonical action-potential induced secretory pathway (Capogna et al. 1996; Ushkaryov et al. 2008; Deak et al. 2009). The latter ability makes α-latrotoxin uniquely potent and a ubiquitous activator of secretion, capable of depleting even BoNT/A-treated presynaptic terminals as well as stimulating transmission at synapses lacking one or another SNAREs (Deak et al. 2009; Mesngon and McNutt 2011). Of note, at low amounts (pM), the neuro-stimulant effects of α-latrotoxin causes no detectable morphological changes, while at high dose (nM), the massive synaptic activity induced by the

toxin can be followed by morphological changes in nerve terminals and degeneration of nerve terminals (Linial et al. 1995; Yan and Wang 2015).

Because of the potent and multifaceted effects on transmitter release, α-latrotoxin has been used as a probe for studies of fundamental molecular and cellular processes driving and modulating exocytosis (Sudhof 2001; Ushkaryov et al. 2008; Sudhof and Rizo 2011). Even though the effects of this toxin in various systems are well-documented, numerous questions remain concerning the underlying molecular processes. Indeed, after all the years of α-latrotoxin use in research, the understanding of its Ca^{2+}-independent effects remain uncomplete (Silva et al. 2009b). It is expected, therefore, that novel recombinant variants of toxin and more unconventional approaches will have to be employed to address remaining questions. In particular, it is of major interest to work out what is the physiological role of α-latrotoxin receptors and what are the functional consequences of their interactions with endogenous ligands? Likewise, the signalling mechanisms and molecular pathways mediating α-latrotoxin effects are a matter of great interest due to the unique ability of the toxin to facilitate transmitter release at central and peripheral synapses.

The potency and selectivity of targeting synaptic mechanisms endow α-latrotoxin with unique therapeutic potentials, which include countering the paralytic effects of BoNTs or overcoming long-lasting inhibition, neuromuscular paralysis and synaptic weakness (Duregotti et al. 2015). Research in this direction has already shown that both, the severity and duration of paralysis induced by BoNTs could be lessened by α-latrotoxin (Mesngon and McNutt 2011) leading to complete regeneration of the NMJ (Duregotti et al. 2015). In light of the poor efficacy of currently tested BoNT inhibitors, this finding stimulated interest in α-latrotoxin as a potential lead for developing a means to counter synaptic weakness caused by BoNTs (Mesngon and McNutt 2011), independently or in combination with currently available small molecular BoNT inhibitors. It is important to note that both, functional and structural effects of α-latrotoxin at motor nerve terminals are completely reversible, hence, providing a useful model for studying synaptic regeneration after neuromuscular paralysis (Duregotti et al. 2015; Rigoni and Montecucco 2017). Another area of potential interest for α-latrotoxin is its utility for activation of secretion independently from membrane voltage and Ca^{2+} influx. As a potent inducer of Ca^{2+}-independent exocytosis, α-latrotoxin holds promise for ameliorating or correcting dysfunction and disease related to reduced release of ligands and hormones targeting nervous and cardiovascular functions as well as metabolic processes and disease, including type I diabetes (Holz and Habener 1998; Saez et al. 2010). Finally, the structural homology of α-latrotoxin to glucogen-like peptide -1 (GLP1) has been suggested to present opportunities for its use as a regulator of food intake, applicable to the treatment of obesity and diabetes and related chronic metabolic disorders (Lewis and Garcia 2003; Perry and Greig 2003; Gejl et al. 2017).

AGATOXINS

Unlike neurotoxins that directly target the molecular machinery of exocytosis, there are several families of neurotoxins which interfere with transmitter release indirectly. Amongst these, peptides modulating presynaptic ion channels have generated much interest due to their remarkable potency and relevance to drug-development across several fields (Terlau and Olivera 2004; Kaczorowski et al. 2008; Harvey 2014). Toxins targeting Ca^{2+} channels are of special interest due to the central role played by voltage-gated Ca^{2+} currents in triggering transmitter release at central and peripheral synapses. Much effort has been made in investigating the pharmacology of bio-toxins that modify properties of voltage gated Ca^{2+} channels (Ca_V), with agatoxins from the funnel web spider *Agelenopsis aperta* venom holding the centre stage. Currently, three structural subclasses, α-, μ- and ω-agatoxins, are distinguished, which are selective for ligand-gated cation channels, Na_V and Ca_V channels, respectively (Adams 2004; Pringos et al. 2011; Nimmrich and Gross 2012). Over 33 types of α-agatoxins have been identified, which are composed of polyamines attached to the aromatic moiety antagonizing NMDA and AMPA receptors (Parks et al. 1991; Usherwood and Blagbrough 1991; Bixel et al. 2001). These toxins target both the pre- and post-synaptic compartments of the synapse, with their effects documented in insects and mammals (Quistad et al. 1990; Parks et al. 1991). μ-Agatoxins, on the other hand have 6 subtypes, composed of 35-37 amino acid C-terminally amidated peptides constrained by four disulfide-bonds (Skinner et al. 1989). These toxins are specialized for insects, leading to increased voltage-sensitivity of axons and promoting transmitter release with repetitive firing of motor neurons, causing paralysis (Prikhodko et al. 1996). Finally, ω-agatoxins target voltage-gated (post-) and pre-synaptic Ca_V, affording selective probes for analyzing regulated synaptic transmission in the central nervous system and at the periphery **(FIG.4A-C)**.

A

ω-AGATOXINS

Groups	Sub-groups	Target channel
ω-AGA-I	ω-AGA-IA	L-type
	ω-AGA-IB	(?)
ω-AGA-II	ω-AGA-IIA	N-type
ω-AGA-III	ω-AGA-IIIA	L,N,P,Q,R-type
	ω-AGA-IIIB	L,N-type
	ω-AGA-IIIC	L,N-type
ω-AGA-IV	ω-AGA-IVA	P-type
	ω-AGA-IVB	P-type

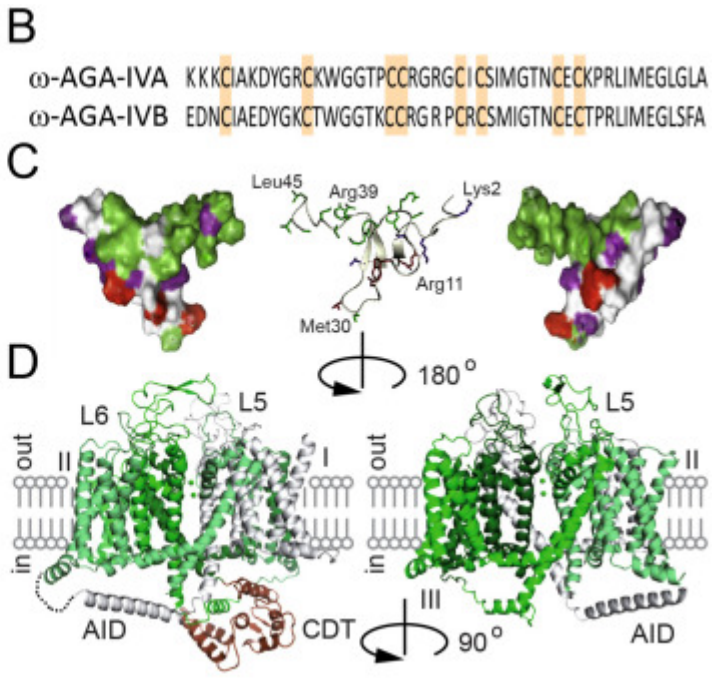

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Figure 4. Ω-Agatoxins and presynaptic voltage-gated Ca^{2+} channels. (A) A summary table listing four groups of ω-agatoxins, with their sub-groups and target Ca^{2+} channel types. (B) Sequence alignment of ω-Aga-IVA and ω-Aga-IVB, which show the most promising characteristics as therapeutic candidates, with conserved cysteine residues highlighted in orange color. Adapted with permission from (Adams 2004). (C) 3D structure of ω-Aga-IVA in micelles (left and right) and the ribbon structure with the lowest-energy (middle). Color coded models for residues with significant chemical shift perturbations (CSPs): red, 0.05 parts per million (ppm) < d < 0.01 ppm, purple, 0.1 ppm < d < 0.4 ppm and green, d > 0.4 ppm. Modified and adapted with permission from (Ryu et al. 2017). (D) The crystal structure of the α-subunit of L-type ($Ca_V1.1$) channel (side view, two perspectives with 90°rotation) embedded in the lipid bilayer of the surface membrane. The tentatively assigned Ca^{2+} ions in the selectivity filter vestibule are presented within the ion channel pore as green spheres. The structure shown here was primarily modelled and refined with a 3.6Å class I electron microscopic map. AID – α1 interaction domain and CTD – C terminal domain, respectively. Modified and adapted with permission from (Wu et al. 2015).

Produced as a single polypeptide chain precursor, ω-agatoxins are post-translationally processed with removal of a hepta-peptide and conversion of L- to D-serine, leading to formation of a mature di-chain. Based on structural differences and selectivity for Ca_V channel subunits, four different groups of ω-agatoxins have been distinguished **(FIG.4A)**, which modify Ca^{2+} currents either via changing channel gating properties or by blockade of the channel pore (Bourinet and Zamponi 2017). Accordingly, type I, II and IV ω-agatoxins are known to block Ca^{2+} currents mediated via L, N and P type voltage-gated Ca^{2+} channels, respectively, while type III ω-agatoxin non-selectively blocks currents mediated by all neuronal high-voltage gated Ca^{2+} channels. Each ω-agatoxin blocks synaptic transmission only partly if applied alone, but they virtually abolish synaptic release if working together in an additive mode (Pringos et al. 2011). Due to drastic and selective action on the neuronal system of insects, some ω-agatoxins have been evaluated as candidate bio-pesticides (Prikhodko et al. 1996; Pringos et al. 2011). ω-Agatoxin groups can be divided onto sub-groups, with ω-agatoxins-IIIA and ω-agatoxins-IVA targeting most potently vertebrate Ca_V channels, while ω-agatoxins-IIIA display selectivity for high-voltage-activated L-, N-, P/Q, and R-type channels (Cohen et al. 1992; Mintz et al. 1992; Yan and Adams 2000). ω-Agatoxin-IVA, on the other hand, is a potent and selective blocker of P-type Ca_V currents, sparing other Ca_V channel subunits (McDonough et al. 2002) **(FIG.4A)**. Even through ω-agatoxin IVA and ω-agatoxin IVB share conserved cysteine residues **(FIG.4B, C)** (Ryu et al 2017), the high-selectivity of ω-agatoxin IVA for Ca^{2+} currents mediated via the P-type channel has made it a valuable tool for pharmacological isolation and analysis of P-type Ca^{2+} currents in a wide range of neuronal preparations (Llinas et al. 1992; Randall and Tsien 1997). Capitalizing on this unique feature of ω-agatoxin IVA and selective enrichment of the P-type channel in specific neuronal compartments of different neuron types as well as brain structures, a range of neurophysiological discoveries on mechanisms of neurotransmitter release and postsynaptic excitability have been made (Llinas et al. 1992; Uchitel et al. 1992; Ovsepian and Friel 2008; Llinas 2014). Unlike most spider toxins-derived Ca^{2+} channel blockers obstructing the ion channel pore, ω-agatoxin IVA appears to block the P-type current

by binding close to the external mouth of the channel linked to gating, shifting the activation voltage of the channel towards more positive potentials and stabilizing it in a closed state (Mintz et al. 1992; McDonough et al. 2002). Interestingly, although ω-agatoxin IVA blocks neurotransmission at neuromuscular junctions of the rat, crab, and crayfish, it has no effect in equivalent synapses of insects (Meir et al. 1999).

While the potency and selectivity of ω-agatoxin IIIA and ω-agatoxin IVA for high-voltage activated Ca^{2+} channels hold major promise for manipulations of neural excitability and synaptic functions in selected groups of neurons, further research is necessary for an all-inclusive understanding of their pharmacological profile and specificity, in order to clearly delineate areas for their therapeutic usage (Saez et al. 2010; Pringos et al. 2011; Inagaki et al. 2014). Research in this direction has been facilitated by recent studies revealing the atomic resolution structure of voltage-gated Ca^{2+} channels, which elucidate fundamental facets of their biology and pharmacology (FIG. 4D). The ubiquitous prevalence and key role of high-voltage gated Ca^{2+} channels in triggering synaptic transmission throughout the central and peripheral nervous system make this family of ion channels especially interesting and medically relevant. Evidence from behavioural and electrophysiological reports showed the remarkable modulation of spinal nociceptive processing by ω-agatoxin IVA sensitive P-type channels (Diaz and Dickenson 1997; Park and Luo 2010), with its intrathecal administration decreasing the late phase of nociceptive behaviour in formalin tests applied to behaving animals (Malmberg and Yaksh 1994). ω-Agatoxin IVA also proved beneficial in preventing the development of secondary hyperalgesia and allodynia after an intradermal injection of capsaicin (Sluka 1997) or progression of inflammation in the knee joint (Sluka 1998) when applied via micro-dialysis, through a fibre implanted in the spinal dorsal horn. This finding suggests the possible use of ω-agatoxin IVA for the alleviation of inflammation-related sensitization of neural circuits. In recordings from spinal cord sensory interneurons, ω-agatoxin IVA reduced discharges of nociceptive neurons in the late phase of the formalin response (Diaz and Dickenson 1997). In the knee joint proprioceptor neurons of the spinal cord, ω-agatoxin IVA also decreased the neuronal response to innocuous and noxious pressure, in carrageenan induced inflammation models (Nebe et al. 1997). The same group subsequently demonstrated that P-type channels may contribute to inflammation-related enhanced excitability of spinal cord neurons, due to excessive release of modulator peptides and transmitters at central primary sensory inputs, with activation of corresponding receptors. Taken together, these findings imply that ω-agatoxin sensitive P/Q-, R- and N-type channels can take part in inflammation related central sensitization, and present a therapeutic candidate for treatment of enhanced nociception and for general anti-nociceptive therapy (Yaksh 2006; Lewis et al. 2012). The medical utility of selective P-type channel blockers has also been discussed in the context of treatment of Ca_V channelopathies. Through attenuation of the hyper-excitability of cortical circuits, ω-agatoxin is expected to ameliorate the fits of episodic ataxia, seizures and migraine headaches. By lowering cortical excitability, the P/Q-type Ca^{2+} channel blockade will attenuate synaptic transmission and can decrease the activity in cortical circuits. Several studies have shown that

a selective P-type channel blockade with ω-agatoxin IVA can prevent cortical spreading depression in migraine models (Kunkler and Kraig 2004; Tottene et al. 2011), an advantageous feature stimulating further research to harvest the beneficial potentials of this neurotoxin family.

Overall, the results of the studies discussed above encourage further research and development of new approaches, to take advantage of selective Ca^{2+} channel blocker agatoxins and their synthetic analogs, with their preclinical application for treatment of a range of conditions, including enhanced nociception and central sensitization, pathological activity of brain circuits and prophylactic treatment of channel hyperactivity. Better understanding of the biology of agatoxins and their effects on ion channels should facilitate clinical translation and the design of new classes of medication for better control of presynaptic Ca^{2+} channel functions.

CONOTOXINS

The remarkable pharmacological diversity of toxins produced by marine cone snails that are endowed with high selectivity and potency has been well recognized and has become of a major interest for therapeutic screening. The group of cone snails (genus *Conus*) is comprised of over 800 predatory species (Tucker and M.J. 2009), with each containing 50-200 distinct biologically-active peptides empowering their highly evolved hunting strategies (Jenkins and Van Houtan 2016). The venom gland of each cone species can secrete large amounts of unique neurotoxic peptides, commonly referred to as conopeptides, with most of them exhibiting a broad range of pharmacological activities. More than 80,000 natural toxins exist in various cone snails around the world, which render them one of the largest libraries of natural candidates for drug development (Livett et al. 2004; Daly and Craik 2009; Vetter and Lewis 2012; Olivera et al. 2015). As it emerges, in the process of venom production, cone snails utilize a strategy equivalent to a ‘peptide combinatorial-library’ system, which facilitates the generation of a wide diversity of novel pharmacologically-active components through a hyper-mutation process (Olivera et al. 1985). The resultant rich collection of conopeptides is highly advantageous for meeting the biological needs of cone snails in a turbulent environment of fast-moving prey, presenting a major survival challenge, which cone snails have overcome by advancing their sophisticated venomous apparatus for the synthesis, storage and delivery of an impressive diversity of toxins (Olivera et al. 2015).

Based on molecular structure and cysteine composition, conopeptides are divided into two main groups: (1) conopeptides that lack or have only one disulfide cross-link and (2) disulfide-rich conopeptides, or active toxic peptides, which represent predominant venom constituents. **FIG. 5(A, B)** presents a summary table of seven super-families of S-S rich conopeptides, with their families and target channels / ligand-gated receptors with schematic representation of their expression sites in a primary sensory neuron. Typical conotoxins are small (12-30 amino acids) and exhibit highly constrained structures stabilized by intramolecular bridges fine-tuned by post-translational modifications **(FIG.5C, D)**. The vast diversity of conotoxins mirrors the

multiplicity of their targets. Although conotoxins are remarkably miscellaneous in terms of their structure and function, in general, they fall into several distinct categories, based on sequence homology, cysteine bond structure, and functions, with most families described as targeting receptors and ion channels associated with the nervous system or muscle activity. Each superfamily has a remarkable structural (distinct cysteine arrangements) and functional diversity, with α-, μ- and ω-conotoxins representing the best characterized families. The presynaptic effects of conotoxins on neurotransmission are largely due to inhibition of voltage-gated Ca^{2+} channels. From 14 ω-conotoxin variants characterized, ω-conotoxin-GVIA from *Conus geographus* and ω-conotoxin MVIIA from *Conus magus* exhibit high affinity and selectivity for blocking N-type Ca^{2+} channels ($Ca_V2.2$), while ω-conotoxins-MVIIC reversibly block P/Q-type ($Ca_V2.1$) channels (Bourinet and Zamponi 2017). Unlike ω-agatoxins utilizing several mechanisms for blockade of the voltage gating of Ca^{2+} channels, all ω-conotoxins prevent Ca^{2+} influx by occluding the pore through tight binding and generally slow dissociation (Mintz et al. 1992; Boland et al. 1994; Ellinor et al. 1994). Similar mechanisms also mediate the α-conotoxin-induced blockade of the nicotinic receptor-channel complex **(FIG.5D)**. The potent and ubiquitous capability of conotoxins as Ca^{2+} channels blockers has been widely considered for basic neuroscience research for the analysis of neuronal voltage-gated Ca^{2+} currents, as well as for therapeutic intervention with neurotransmission machinery. The latter makes conotoxins especially attractive for pharmacological use as a source for new drug discovery (Livett et al. 2004; Twede et al. 2009). The medical use of ω-conotoxins is largely viewed in conjunction with its potent and specific targeting of presynaptic Ca^{2+} currents in both the central and peripheral nervous system. Potential areas of interest include but are not limited to epilepsy, neuromuscular disorders and other neurological diseases associated with dysregulation of synaptic activity. Importantly, ω-conotoxins have displayed a highly beneficial characteristic as blockers of voltage-gated Ca^{2+} channels of nociceptors, showing analgesic effects. In this regard, a synthetic form of ω-conotoxin MVIIA (ziconotide, also known as Prialt) has generated major interest for being the first ω-conotoxin to enter into clinical trials, and was approved by the FDA for the management of chronic pain as well as cancer- or AIDS-related neuropathy (Patel et al. 2017). Isolated from *C. magnus*, ω-conotoxin MVIIA inhibits neurotransmitter release through blockade of N-type Ca^{2+} channels and attenuates nociception in a variety of animal models, including in a persistent pain model (i.e. formalin test), post-operative pain, chronic inflammatory pain and neuropathic pain (Layer and McIntosh 2006; Lee et al. 2010). Remarkably, ω-conotoxin MVIIA is effective in morphine tolerant rats with its prolonged intrathecal infusion not producing drug-resistance (Wang et al. 2000a; Wang et al. 2000b; Layer and McIntosh 2006). Along with preclinical utility in animal models, ω-conotoxin MVIIA has also been used in the clinic. Prior to its approval by the FDA for management of severe pain in patients' refractory to other analgesic treatments, ω-conotoxin MVIIA was administered to 1200 patients in three double-blind, placebo-controlled studies and four open label long-term studies (Webster et al. 2008). In another study, a double-blind, randomized trial in 111 cancer and AIDS patients with treatment refractory chronic pain, intrathecal ω-conotoxin

MVIIA administration produced statistically significant and lasting analgesia. It is worth noting, however, that due to a narrow therapeutic window with inability to cross the blood-brain barrier and considerable side effects, ω-conotoxin MVIIA use is currently limited to intrathecal delivery in patients who have failed to respond to other treatments (Sanford 2013).

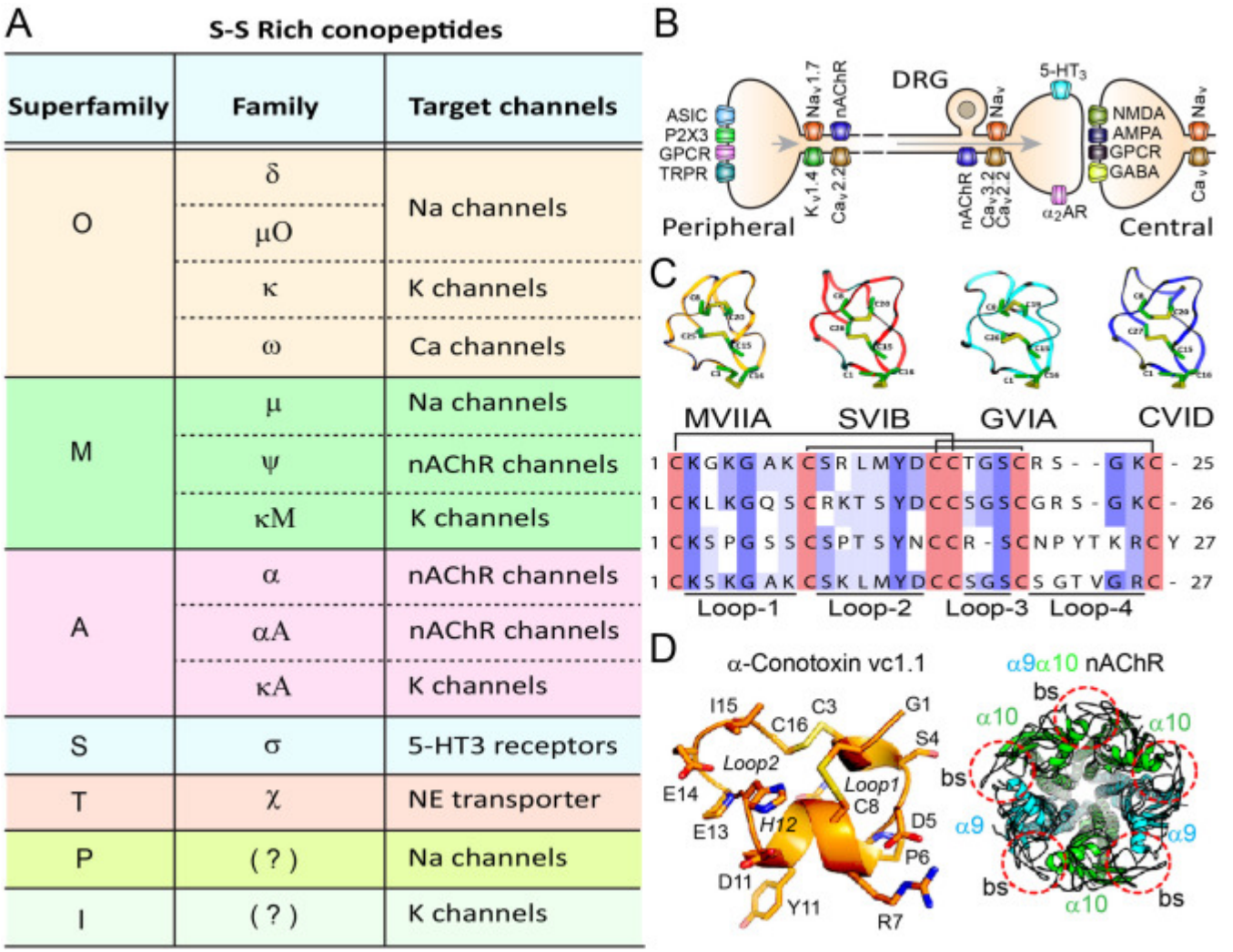

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Figure 5. Pharmacological versatility and molecular targets of conotoxins in central and sensory neurons. (A) A summary table of seven super-families of S-S rich conopeptides, with their families and target channels / ligand-gated receptors in neurons. (B) Schematic diagram of the molecular targets of conotoxins and their location at peripheral nerve endings of primary sensory neurons and central synapses implicated in conotoxin-derived developing anti-nociceptive therapies. ASIC – acid sensitive ion channel; P2X3 – P2X purinoceptor 3; GPCR – G-protein coupled receptor; TRPR – transient receptor potential receptor; nAChR – nicotinic acetylcholine receptor; K_V – voltage-gated potassium channel; Na_V – voltage-gated sodium channel; CaV – voltage-gated calcium channel; 5-HT – serotonin receptor; GABA – gamma amino-butyric acid receptor; AMPA and NMDA – α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and N-methyl-D-aspartate glutamatergic receptors. (C) The backbones of ω-conotoxins are presented as a ribbon diagram (upper). Structural differences between various ω-conotoxins (listed above) with a multiple sequence alignment of four of the most prevalent ω-conotoxins colored by their degree of conservation: from white (not

conserved) to dark blue (highly conserved) (top and bottom, respectively). Structural alignment of the 3D rendered structures of MVIIA, SVIB, GVIA and CVID represent differences in their spatial conformation. Adapted and modified with permission from (Ramirez et al. 2017). (D) The structure of Vc1.1 solved using NMR-derived distance and angle restraints, with the backbone and side chains shown (left). Structure of nAChR (aerial view with toxin) with conotoxin-binding sites corresponding to each subunit marked in red circles. Adapted with permission from (Yu et al. 2013).

At present, conotoxins are closely considered as a combinatorial source for natural Structure Activity Relationship (SAR) candidates for producing small, non-peptide mimetics of conotoxins (Duggan and Tuck 2015). As mentioned, several conotoxins have already passed the primary tests, with the best recognized commercial ω-conotoxin MVIIA approved by the FDA to treat intractable chronic pain in cancer and AIDS patients (Rigo et al. 2013a; Rigo et al. 2013b; Eisapoor et al. 2016). The utility of conotoxins for a wider range of applications has not only demonstrated their potential therapeutic value but has also stimulated more interest from biotech and pharmaceutical companies to support conotoxin research. In addition to ω-conotoxin MVIIA, other conopeptides are currently undergoing rigorous trials, with ω-conotoxin CVID successfully completing phase II trials, albeit with high cytotoxicity. It is important to stress that the clinical studies of ω-conotoxin MVIIA revealed significant side effects such as gait disruptions, dizziness, nystagmus, confusion, somnolence, fever, postural hypotension, urinary retention, nausea and vomiting (Staats et al. 2004). Due to high medical relevance and research progress, increasing numbers of conopeptides are currently under investigation and validation as drug leads. Nevertheless, like other peptide drug candidates, the inability of these peptides to cross the blood-brain barrier remains a major challenge and urges for finding more effective delivery means.

BETA-BUNGAROTOXIN

Since the pioneering research and isolation of crotoxin from the venom of *Crotalus durissus terrificus*, a wide range of snake venom proteins and peptide complexes have been identified and characterized (Slotta and Fraenkel-Conrat 1938). Most of these have proven to be potent neurotoxins of various biochemical identity, including phospholipase A_2 (PLA2) or PLA2-like molecules, metalloproteases, serine proteases, C-type lectin related proteins (CLRPs) and three-finger toxins (3FTxs) with a wide range of biological activities (Kwong et al. 1995; Koh et al. 2006; Doley and Kini 2009). Over the past two decades, the effects of these molecules on different cell types has been investigated and characterized, with their pharmacological effects described at the neuromuscular junction. Among these, bungarotoxins (BuTxs) isolated from the venom of different *Bungarus* species have been most thoroughly investigated, with the venom of *B. multicinctus* (Taiwan banded krait) best characterized **(FIG.6A)**. Based on electrophoretic mobility, the crude venom has been separated into four distinct fractions, three toxic (α, β and γ) and one non-toxic (Kullmann et al. 2009). It has been reported that α-BuTx belongs to 3FTxs and binds to post-synaptic nicotinic receptors at the neuromuscular junction,

while the β- and γ-BuTxs belong to PLA2 and act at presynaptic terminals to reduce acetylcholine release (Halliwell and Dolly 1982b; a; Chang et al. 1999a; Lewis and Garcia 2003; Lewis and Gutmann 2004). The initial studies have been followed by identification of an additional, κ-BuTx, also with a postsynaptic site of action. However, unlike α-BuTx, κ-BuTx shows little effect at the neuromuscular junction but is more specific to nicotinic acetylcholine receptor (nAChR) subunits enriched in postsynaptic compartments of central synapses (Kullmann et al. 2009). Currently, over one hundred different α-BuTxs have been purified and tested as postsynaptic toxins, while β-BuTxs are the most investigated proteases with a presynaptic site of action. Like many peptides isolated from snake venom, after entry into the circulatory system, BuTx targets the peripheral nerves and synapses, causing paralysis of skeletal muscles. The postsynaptic action mechanism of α-BuTx is rather straightforward and results from its competitive binding to postsynaptic nAChRs in skeletal muscles (Changeux 1990; Mulle and Changeux 1990; Chang et al. 1999b; Servent and A. 2001; Fruchart-Gaillard et al. 2006). At a molecular level, α-BuTx binds to the α1 nAChR, a mechanism that qualifies it as a curare-mimetic. In addition to peripheral synapses, α-BuTx is also capable of blocking neuronal cholinergic receptors in the central nervous system, but to a lesser extent.

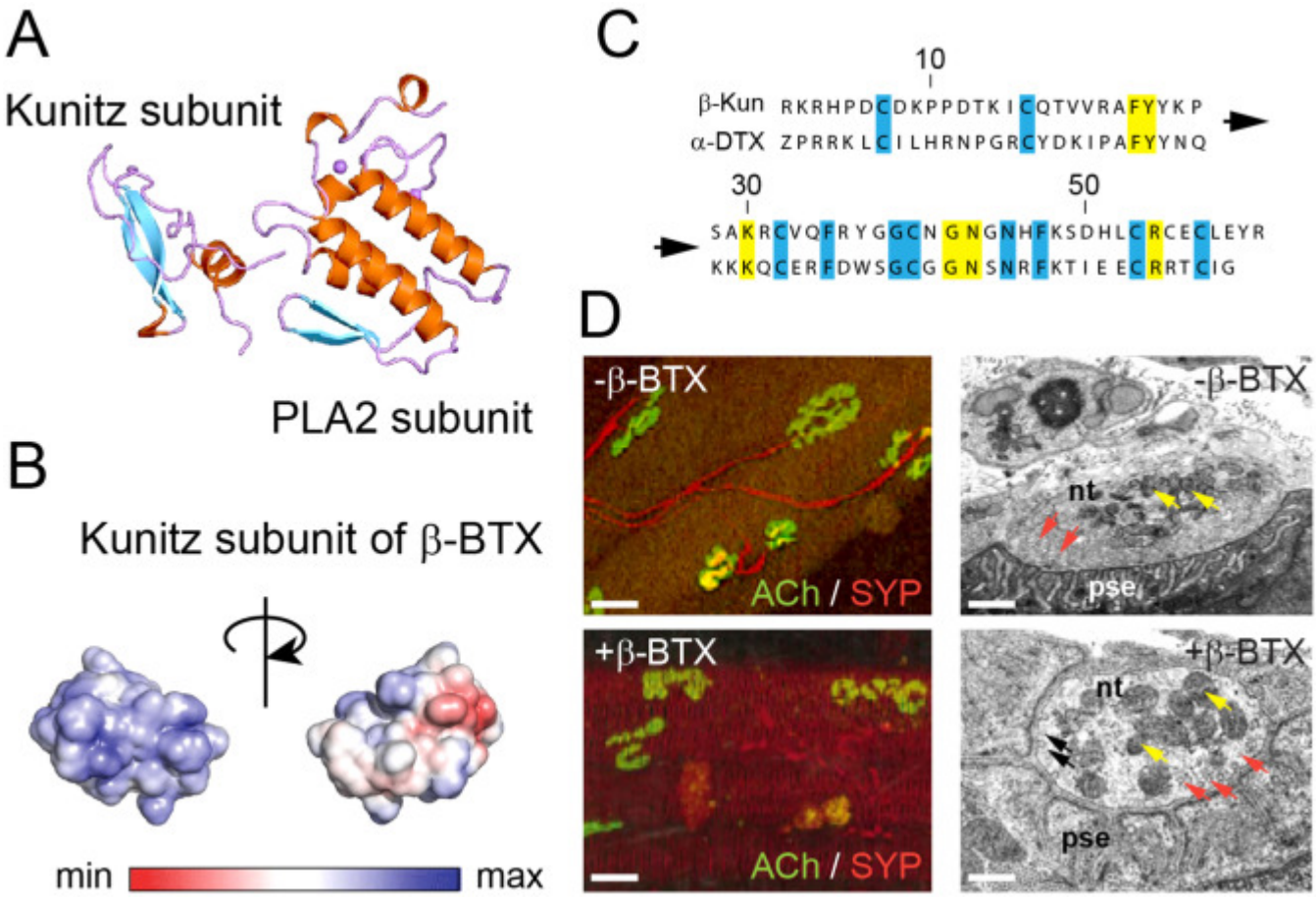

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Figure 6. Structure of β-bungarotoxin (BTX) and its inhibitory effects on presynaptic terminals. (A) 3D structure of β-BTX highlighting the Kunitz subunit implicated in ion channel binding and phospholipases 2

(PLA2) enzymatic subunit responsible for the paralytic effects of the venom on synaptic transmission. (B) Electrostatic potential of the Kunitz subunit of β-BTX B2 chain rendered in 3D on the solvent-accessible surface in PyMOL with surface electrostatic potential representation from two perspectives. Scale bar indicates the electrostatic potential ranging from -5000 to + 5000 kt/e. Negative regions - in red; positive regions - in blue; neutral regions - in gray. Adapted with permission from (Zupunski and Kordis 2016). (C) Sequence alignment of β-Kun and α-DTX with conserved residues highlighted in blue and yellow. (D) Double neurofilament and ACh receptor labeling of the mouse muscle used to study the effects of β-BTX on the innervation of motor units in the skeletal muscles. Control preparation (- β-BTX) reveals a typical pattern of innervations of motor units by nerve endings. A preparation made 6 h after the inoculation with toxin (+β-BTX) reveals the breakdown of the axon with however retained ACh receptors. Electron micrographs showing strong depletion of presynaptic vesicles at the neuromuscular junction by β-BTX, leading to blockade of synaptic transmission: yellow arrows – mitochondria; red arrows – clear synaptic vesicles filled with acetylcholine; black arrows – synaptic vesicle fusion profiles; nt – nerve terminal; pse – post synaptic element. Adapted with permission from (Dixon and Harris 1999).

As already noted, β-BuTx is a potent PLA2 complex with selective presynaptic site of action. Like other PLA2 enzymes, β-BuTx exists as a monomer and tends to interact with other PLA2 (or PLA2-like) molecules to form complexes, either through covalent or non-covalent bonds **(FIG.6A)**. As a relatively large basic protein (p*I*=9.5), with a molecular weight of 21 800 kDa (Kelly and Brown, 1974), β-BuTx is the only known covalent PLA2 (phospholipase A2) complex consisting of two dissimilar polypeptide chains - A and B, which are held together by a single disulfide bond (Kondo et al. 1978a; Kondo et al. 1978b). The A chain is homologous to Group I PLA2 enzymes, while the subunit B chain is structurally homologous to BPTI, the so called Kunitz type of PLA2 serine proteinase inhibitors, showing similarities with dendrotoxins (Kondo et al. 1978b; C. 1997; Doley and Kini 2009) **(FIG.6C)**. A number of isoforms of polypeptide A and B chains have been isolated and characterized, which are produced by the association of three different types of A chains and two different types of B chains. The disruption of acetylcholine release at motor nerve terminals is critical for neurotoxicity and neuro-paralytic effects of β-BuTx, which typically becomes synergized by other active ingredients in the venom. As it is the case with other neurotoxins, synaptic transmission blockade caused by β-BuTx is a multistep process with initial reduction in acetylcholine release followed by transient enhancement and tailed by a profound inhibition, leading to complete neurotransmission block (Sen et al. 1976; Strong et al. 1976; Lewis and Gutmann 2004; Koh et al. 2006; Sun et al. 2010). The molecular processes underlying these stepwise changes remain controversial and involve functional as well as structural changes **(FIG.6D)**. The initial phase in β-BuTx appears to involve modulation of the presynaptic Ca^{2+} and K^{+} currents, due to direct binding of β-BuTx. The interactions of β-BuTx with K^{+} channels are thought to orient the PLA2 phospholipase subunit of the toxin towards the membrane (Nicholls et al. 1985; Tibbs et al. 1989). This step is followed by conformational changes of PLA2, which hydrolyses phospholipids in the external leaflet of the membrane leading to formation of an excess of phospholipids and fatty acids. These intermediates of lipolysis in turn promote exocytosis of synaptic vesicles, leading to

gradual depletion of presynaptic terminals and neurotransmission blockade (Chen and Lee 1970; Cull-Candy et al. 1976; Rigoni et al. 2004; Rigoni et al. 2008). Increase in the cation conductivity of the presynaptic membrane and particularly Ca^{2+}-channels at this stage, transiently facilitates SNARE-mediated transmitter release. Interestingly, β-BuTx also appears to enter into the nerve endings, a process that is very rapid and apparently depends on SNAREs but is not linked with ATP-ase activity (Montecucco and Rossetto 2000).

Interaction of β-BuTx with cytosolic proteins has been demonstrated both *in vitro* and *in vivo*, which may be partly responsible for the specific association of β-BuTx with mitochondria, leading to the opening of mitochondrial pores (Rigoni et al. 2008) and activating the release of alarmins (Zornetta et al. 2012). Amplified phospholipase activity inside neurons is a crucial determinant of β-BuTx intoxication; hence blockade of the uptake of this toxin resultant of targeted phospholipolysis could be a very important stage for preventing impairments of neurotransmission. It has been shown that the phospholipase activity of β-BuTx binding to the specific sites of the mitochondrial membrane is essential in the opening of membranous pores, resulting in ATP deficit and mitochondrial degeneration (Rigoni et al. 2008; Logonder et al. 2009; de Carvalho et al. 2014). In addition to transient facilitation of transmitter release, an increase in intracellular Ca^{2+} concentration upregulates the activity of hydrolases, which cause slow-onset extensive damage and degeneration of nerve terminals **(FIG.6D)**. Overall, inhibition of synaptic transmission by β-BuTx is associated with loss of synaptic vesicles, mitochondrial damage and degeneration of motor nerve terminals, transient upregulation of voltage-gated Na^{+} channels and a reduction in immunoreactivity of SNARE proteins, effects that have been largely attributed to the increased activity of PLA2 at presynaptic terminals (Vulfius et al. 2017). Despite that structural and functional alterations associated with β-BuTx intoxication can be severe, they are generally reversible, and as such can provide a useful experimental model for studying synaptic and nerve regeneration after damage or degeneration (Duregotti et al. 2015; Negro et al., 2017; Rigoni and Montecucco 2017).

Despite the potency and selectivity of β-BuTx in targeting presynaptic functions at neuromuscular junctions, the therapeutic use of this peptide is hampered by toxicity-related degenerative changes of axons and nerve terminals. Nevertheless, the phospholipase activity of PLA2 from the β-BuTx B chain has shown great promise for its potent non-steroid anti-inflammatory effects. Moreover, the PLA2 inhibitor effects with specific affinities for various PLA2 enzymes have been shown to exert potent anti-enzymatic, anti-mycotic, anti-edema-inducing, anti-cytotoxic and anti-bacterial activities (Soares et al. 2003; Koh et al. 2006; Kullmann et al. 2009). In addition to the above-mentioned capabilities with their potential downstream effects on neuronal and synaptic processes, changes in the activity of endogenous PLA2 are thought to be crucial in inflammatory processes related to numerous acute and chronic neurological disorders accompanying neurodegenerative diseases, such as Alzheimer’s and Parkinson’s diseases as well as brain tumours (Ross et al. 1998; Farooqui et al. 1999; Sun et al. 2010). As treatment for these disorders with non-specific inhibitors has

been of limited success, future research is required to better understand the biology of β-BuTx, to harvest its specific pharmacological effects for therapeutic benefit.

DENDROTOXINS

Enriched in the venom of green mamba *Dendroaspis angusticeps*, DTXs have proven to be strong stimulators of both, neuromuscular junctions at the periphery and central synapses, causing hyperexcitability of axons with convulsive symptoms (Harvey 2001). Structurally, dendrotoxins are a family of single-chain homologous polypeptides (Strydom 1973a; Harvey and Karlsson 1982; Parcej and Dolly 1989; Dolly and Parcej 1996) **(FIG.7A, B)**. Biochemical analysis with fractionation studies showed that DTXs represents a collection of small proteins, which are purified and categorized as α-DTX, β-DTX, γ- DTX and δ-DTX (Benishin et al. 1988). In addition to DTXs isolated from *D. angusticeps*, several related peptides have also been found in venoms of the Western green mamba and the Black mamba (toxins I and K) (Strydom 1973b; c; Harvey and Karlsson 1982). Three homologues of DTX were also isolated from the sea anemone *Anemonia sulcata* (Schweitz et al. 1995). Despite close similarity with Kunitz serine protease inhibitors, DTXs are very weak trypsin inhibitors. The high selectivity and binding of DTXs to K^+ channels played a pivotal role in purification and characterization of the pore forming α-subunit of mammalian K^+ channels (Parcej and Dolly 1989; Dolly and Parcej 1996; Dolly and Bagetta 2002). Made of 57-60 amino acid residues cross-linked by three disulfide bridges, DTXs selectively bind α-subunits of several low-voltage activated K_V1 channels, the largest subfamily of K^+ channels. This reaction is driven by electrostatic interactions between the positively charged amino acid residues in the DTX cationic domain and negatively charged residues in the ion pore of the K^+ channel near the extracellular surface, leading to mechanical shielding of the channel pore (Imredy and MacKinnon 2000; Harvey 2001) **(FIG.7C)**. Through such process, DTXs inhibit A-type and slowly-inactivating K^+ currents in a variety of neuronal preparations and in heterologous systems (Tytgat et al. 1995; Gamkrelidze et al. 1998; Ovsepian et al. 2013; Bagchi et al. 2014; Ovsepian et al. 2016a).

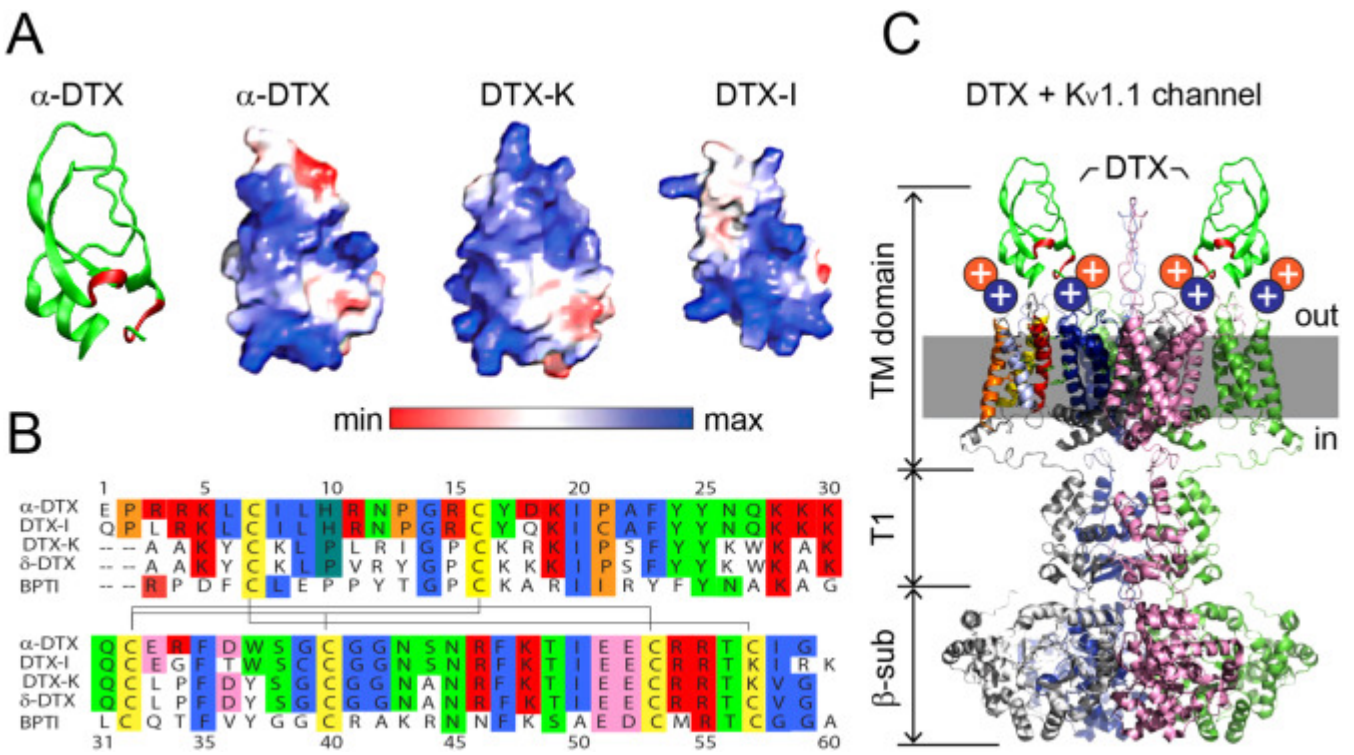

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Figure 7. Dendrotoxins: structure and pharmacological targets at presynaptic terminals. (A) Left: 3D structure of α-DTX; positively charged amino acid residues in the N-terminus and the β-turn region implicated in binding of potassium channels colored in red. Left-middle to right: surface electrostatic potential representation of α-DTX, DTX-K and DTX-I aligned, respectively. Negative regions - in red; positive regions - in blue; neutral regions - in gray. Scale bar indicates electrostatic potential ranging from -5000 to + 5000 kt/e. Adapted with permission from (Garcia-Fernandez et al. 2016). (B) Amino acid sequences of different dendrotoxin variants highlighting structural similarities and extent of evolutionary conservation, which produce comparable molecular architecture and folding conformation. α-DTX and bovine pancreatic trypsin inhibitor (BPTI) also show 35% sequence identity as well as identical disulfide bonds. Despite the structural homology, dendrotoxins do not appear to exhibit any measurable inhibitory protease activity. (C) Crystal structure of $K_V1.1$ α-subunit of potassium channels, with transmembrane (TM) domain, intracellular T1 domain and β-subunit. Note that the pore or K_V channels are formed by tetramerization of four α-subunits with four axilliary β-subunits (colored in green, blue, grey and pink). Positively charges residues of DTX form bonds with negative extracellular residues shielding the pore of the channel and blocking the K^+ efflux. Adapted with permission from (Ovsepian et al., 2016).

Using ^{125}I DTX radiolabelling methods, immunoprecipitation and pharmacology, these toxin peptides were instrumental in defining the distribution of K_V1 channels throughout the nervous system and their biology. It has been demonstrated that K_V1 channels are integral membrane proteins composed of four identical or distinct α-subunits (homo- or hetero-tetramers respectively) that form the ion conductive pore, while associated with them four axillary β-subunits enable their trafficking and stabilization on the surface membrane (Parcej and Dolly

1989; Dolly et al. 1994; Dolly and Parcej 1996) **(FIG.7C)**. Pharmacological analysis and biophysical profiling of cloned DTX-sensitive K^+ channels showed that DTX-K is remarkably active on homo-tetramers of the $K_V1.1$ subunit as compared to any other member of the K_V1 channel family (Robertson et al. 1996; Bagchi et al. 2014). Detailed characterization of the affinity of DTXs for predominant K_V1 subunits showed a $K_V1.1<K_V1.2<K_V1.6$ relation (Dolly et al. 1994; Scott et al. 1994; Wang et al. 1999a; Wang et al. 1999b; Gutman et al. 2005). Of note, all four subunits in the DTX-sensitive K^+ channel can interact simultaneously with the toxin, with however binding of only one toxin molecule sufficient for block the K^+ current. Acting upon channels expressed at presynaptic terminals of motor nerve endings, α-DTXs cause enhancement of acetylcholine release and muscular hyperactivity (Anderson and Harvey 1988; Harvey 2001; 2014). In the Ranvier nodes of frog sciatic nerves, DTX-I prolongs the duration of the action potential by blocking a fraction of the K^+ currents (Weller et al. 1985), with toxin-sensitive K_V1 channel subunits located primarily in the paranodal regions. Due to such a specialized location, the binding of DTX-I to the K^+ channel and its effects on action potentials are significantly enhanced in demyelinated axons of multiple sclerosis mouse models (Bagchi et al. 2014). In sensory neurons, α-DTX produces repetitive action potential firing, which leads to the blockade of rapid-activating and slowly-inactivating K^+ currents (Stansfeld et al. 1987; McAlexander and Undem 2000). In central neurons, α-DTX promotes repetitive action potential firing (Halliwell et al. 1986; Poulter et al. 1989; Ovsepian et al. 2013; Bagchi et al. 2014; Ovsepian et al. 2016a) while DTX-I has been shown to augment long-term potentiation (Kondo et al. 1992). In projection neurons of the deep cerebellar nucleus, α-DTX was shown to dampen depolarizing inputs and attenuate rebound excitation (Ovsepian et al. 2013), while in upstream cerebellar Purkinje cells it enhances inhibitory postsynaptic currents via presynaptic effects (Southan and Robertson 1998a; b). Like at the neuromuscular junction, the enhancing effect of DTX on inhibitory transmission in Purkinje neurons is due to increased quantal content of synaptic release. The same mechanisms but acting at excitatory inputs underlies DTX-induced epileptiform hyperactivity when in high amounts injected into the brain (Velluti et al. 1987; Coleman et al. 1992), capable of causing neuron degeneration, an effect that could be countered by NMDA antagonists (Bagetta et al. 1994).

Along with their utility for research into the fundamental biology of K^+ channels and synaptic transmission mechanisms, DTXs have shown major translational promise. As a neurotoxic compound, DTXs have been instrumental in modelling neuronal degeneration and epileptic seizures, providing a platform for experimental and pre-clinical studies. Through a combination of pharmacological tests and genetic approaches, important mechanistic insights have been gained recently into the role of DTX-sensitive K_V channel subunits in different pathophysiological mechanisms underlying seizure and neuronal death (Robbins and Tempel 2012; Ovsepian et al. 2016a). New avenues for research towards the development and validation of strategies for neuroprotection and stabilizing activity of brain circuits have been recognized and discussed. Because reduction of α-DTX binding by brain tissue indicates the degeneration of synaptic terminals and connections enriched with K_V1 channels, α-DTX binding

has been used as a direct biomarker for detecting the integrity of synaptic connections and neural circuits. In Alzheimer's disease, for example, α-DTX has been applied to detect the extent of synaptic loss in hippocampal tissue (Cochran 1998). Using a similar approach, age-related changes in synaptic density have been shown in the rat brain (Cochran and Pratt 1997). DTXs have been also instrumental in targeting and functional validation of the unique juxta-paranodal expression of K_V1 channels in demyelinated axons (Nashmi and Fehlings 2001; Devaux et al. 2004; Bagchi et al. 2014). In denuded axons of optic nerves, for instance, it was shown that α-DTX restores the functionality of demyelinated nerves by blocking of $K_V1.1$ subunits displaced into nodal and intermodal regions. Finally, through the use of DTXs and synthetic blockers of K_V1 channels, demyelination-related remodeling of K_V1 with emergence of a novel $K_V1.1$ homotetramer has been shown in optic nerve axons, which might be of major relevance for diagnosis and treatment of multiple sclerosis and other axonal disorders associated with myelin loss (Bagchi et al. 2014; Al-Sabi et al. 2017).

Taken together, the advances in DTX research demonstrate the major assistance of this unique family of neurotoxins for understanding the biology and functions of K_V1 channels with their role in neuron and synaptic physiology. The high affinity binding of DTXs to presynaptic K_V channels also present considerable potentials as a bio-marker for quantifying synaptic density in the central nervous system, with possible application in diagnostics of neurodegenerative disease affecting the integrity of the brain connectome. Despite major developments, there is further need in research to take full advantage of DTXs and their synthetic analogs for preclinical use as potent synaptic enhancers and biomarkers with the potential for clinical translation.

SUMMARY AND FUTURE DIRECTIONS

Amoung contemporary biomarker and therapeutic discoveries, there is a growing trend towards developing new paradigms and approaches to replace the blockbuster-based models of pharma industry. Impressive recent advances with antibody-based therapies have greatly contributed towards the increasing recognition that bio-molecules and particularly short peptides can be potent and highly promising leads for innovative therapies. Neurotoxic peptides present an enormous and largely untapped resource of pharmacological leads, with major potential for bio-marker and drug discovery. Over countless years of evolution, a vast spectrum of potent and highly specific peptides and proteins have been developed and fine-tuned by microbes, plants and animals as part of their defensive or offensive system. In light of the critical importance of neuronal functions for animal adaptation and survival, it is hardly surprising that many highly potent biological toxins and pathogens become specialised for targeting presynaptic functions, which play a major role in neuronal integration and motor functions. Indeed, the dynamic and complex processes involving interaction of supramolecular scaffolds driving transmitter release at presynaptic terminals present a highly attractive and vulnerable target. Throughout this review, we presented a concise summary of the biology and function of several well-characterized neurotoxins that target the presynaptic release machinery

(**FIG. 8**). We discussed their shared features as well as the differences and highlighted numerous unique characteristics which present major interest for basic and translational neurosciences. As it emerges, the extraordinary wealth of neurotoxins produced from bacteria to vertebrates, present an invaluable research tool as well as potential leads for developing new drugs affecting transmitter release machinery and a wide range of neuronal regulatory mechanisms. Despite their vast natural diversity and origin, neurotoxins acting at the presynaptic terminals appear to converge on a few selected processes and functions. At the core of the extraordinary efficacy of neurotoxins and their selectivity for specific functional processes, render neurotoxins that target presynaptic functions, a unique source of new bio-therapeutics. Notwithstanding the safety concerns and methodical challenges, an increasing number of peptides derived from bacterial toxins and animal venoms targeting synaptic functions have passed the test of time as bio-therapeutic candidates, contributing assertively in pre-clinical studies of animal models, thus paving a new way for their future clinical usage.

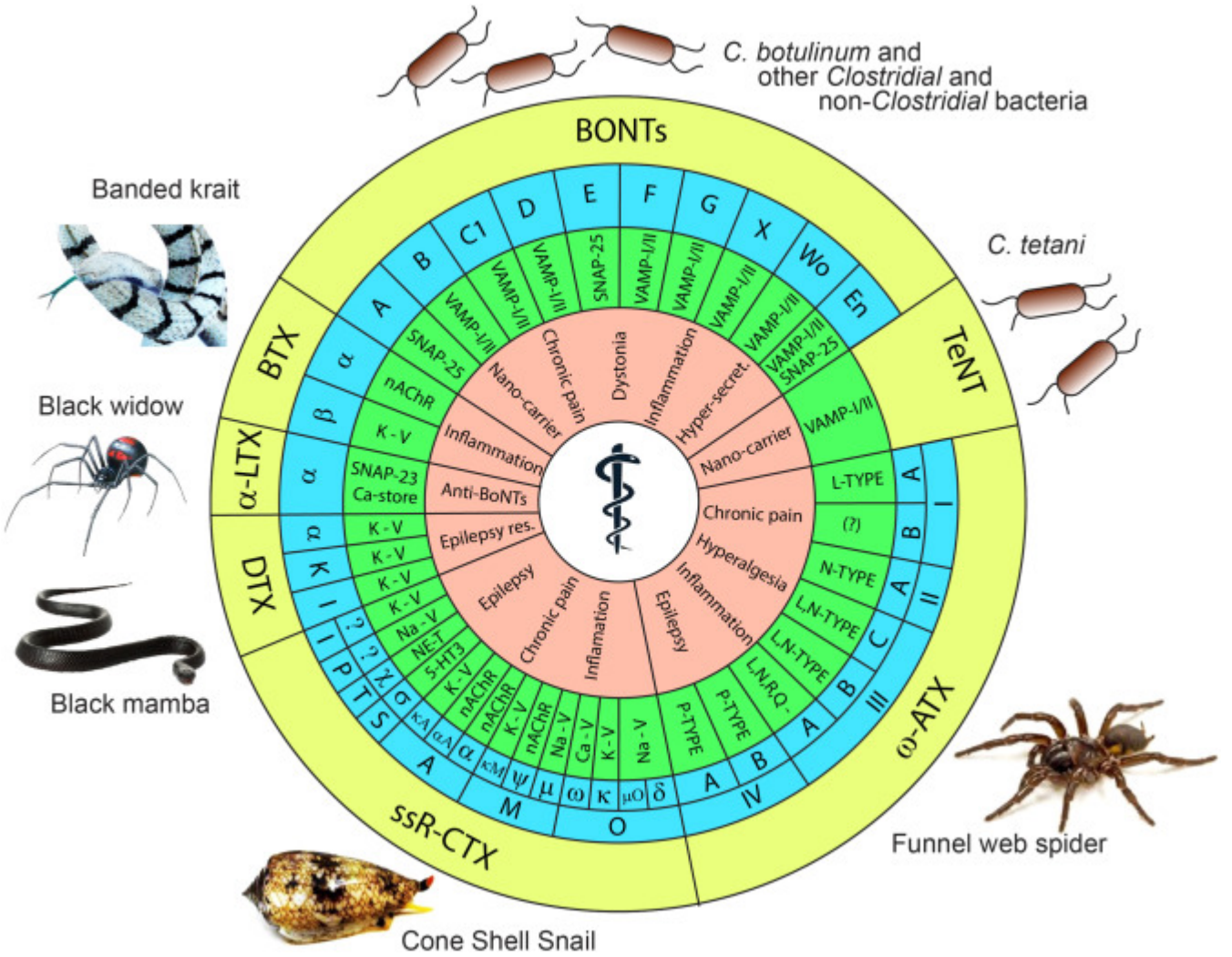

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Figure 8. Summary diagram illustrating major presynaptic neurotoxins, with their molecular targets and areas for potential clinical use. The details of biology and therapeutic utility are discussed throughout this review.

BOX – 1:

Autoimmune disorders targeting presynaptic functions and causing neuromuscular paralysis

While mechanistically different from the paralysis caused by presynaptic neurotoxins, several autoantibodies targeting axons and nerve terminals can also cause acute or long-lasting weakness of neuromuscular synapses and motor deficit. Indeed, neuromuscular junction has been recognized as a veritable hot spot of several autoimmune diseases, which include myasthenia gravis (MG), Lambert-Eaton myasthenic syndrome (LEMS), acquired neuromyotonia (NMT) and Guillain-Barré syndrome (GBS). In case of MG, autoantibodies target the neuronal post-synaptic (and also pre-synaptic) acetylcholine receptors (AChR), while LEMS is caused by autoimmune response against presynaptic voltage-gated calcium and potassium channels. The NMT and GBS, on the other hand, are associated with anti-ganglioside antibodies, which cause acute inflammatory neuropathies, leading to impaired axonal conductivity and neuromuscular weakness (Lang and Vincent 2009).

As the most common autoimmune disease of the NMJ, MG is an acquired condition, with over 80% cases having autoantibodies against the nAChR. When in excess, the autoantibodies cause strong reduction in the density of nAChR at NMJ via their enhanced internalization, accelerated degradation or complement-mediated damage of the post-synaptic membrane. In majority of MG cases, abnormalities of thymus glands have been documented, where production of antibodies takes place. It is thought that the expression of autoantigens in the thymic epithelial cells is responsible for the depletion of self-reactive T lymphocytes, which in turn are responsible for MG specific antibody synthesis. Although questions remain over the mechanisms the abnormal autoimmune response, these antibodies, when released in the circulatory liquids, target nAChR rich postsynaptic folds of NMJ, leading to development of the fatigable muscle weakness (Leite et al. 2008). Similar to MG, LEMS also causes proximal muscle weakness of autoimmune origin, but through targeting presynaptic voltage-gated Ca^{2+} channels. In LEMS, pathogenic antibodies against these channels have been found in over 85% of patients (Lang and Vincent 2009). In stark contrast to MG, LEMS is a prototypic paraneoplastic disorder, with the majority of cases associated with small cell lung carcinomas (SCLC). In is of interest to note that SCLC patients with clinical LEMS have shown better prognosis than patients with SCLC without neurological dysfunctions, perhaps due to the fact that the neurological symptoms assist the early tumor diagnosis (Maddison et al. 1999; Wirtz et al. 2005). Some data also suggest differences in voltage-gated Ca^{2+} channel antibodies between the tumor and non-tumor patients, with antibodies in the absence of tumors binding the extracellular domain IV of the a-1A subunit (Pellkofer et al. 2008). Future research and identification of new antibodies and analysis of the clinical history holds promise for an earlier and accurate diagnosis of SCLC in LEMS patients with improved treatment.

Unlike MG and LEMS, muscle weakness and neuromuscular paralysis in NMT and GBS are typically precipitated by an acute inflammation, which follows by autoimmune response leading to impaired axonal conductivity and disintegration of the membrane integrity at the NMJ. Known also as Isaac's syndrome, NMT is characterised by muscle twitching (myokymia), cramps, muscle stiffness and excessive sweating. In most severe cases, NMT patients also reveal additional central symptoms, which include sleep disorders, memory loss and anxiety. In ~ 40% NMT patients, antibodies to voltage-gated potassium channels are detected from the very early stages of the disease (Hart et al. 2002). For detection of the expression levels of voltage-gated potassium channels, ^{125}I-labelled DTX-based test are used, which binds to K_V1.1, 1.2 and 1.6 subunits of Shaker family channels expressed presynaptic terminals. At present, it remains unclear which subunit of potassium channel is most susceptible to the antibody and if the neurological signs depend on the channel type. Although at this stage, the aetiology of the disease remains largely unknown, the disease seems to be a multifactorial. The majority of cases seem to emerge and unfold as a self-limiting monophasic disease, while in ~ 20% cases thymic tumours have been documented (Lang and Vincent 2009). The final most studies autoimmune disorder affecting neuromuscular transmission is GBS and its variants, which are acute autoimmune-mediated neuropathies that cause demyelination of peripheral nerves and axonal damage. Typically, these conditions are precipitated by acute infection involving *Campylobacter jejuni* in the gastrointestinal tract or respiratory infection. In the acute phase of the disease, autoantibodies against gangliosides including mono-sialvc-GM1 (GBS) or poloisyalil-GD1B have been found in between 20 to 60% of patients. These antibodies can bind to the motor nerve terminal, causing changes in neurotransmitter release (Willison 2005). The levels of antibodies against GD1a/GD1b and GD1b/GT 1b in the membrane have been shown especially strongly correlating with the severe forms of GBS (Kusunoki et al. 2008). It is important to note that both, the inducing pathogens and the autoantibody isotypes may be indicative of the severity of the neurological signs and prognosis. For instance, patients with cross-reactive *C. jejuni* IgG1 and IgA anti-ganglioside antibodies typically show poor recovery to immunotherapy, whilst those having IgG1 and IgG3 with negative *C. jejuni* serology but reactive to *H. influenza*, had a better prognosis (Jacobs et al. 2008).

Overall, despite some shared targets and clinical manifestation with neurotoxins targeting presynaptic terminals, the aetiology, pathobiological mechanisms and treatment strategies autoimmune disorders targeting NMJ fundamentally differ from those induced by neurotoxins. In addition to symptomatic therapies, depending on their forms and stage, the NMJ weakness caused by autoimmune response require intense and occasionally long-term immune-suppressant therapies combined with non-steroid anti-inflammatory treatment (Skeie et al. 2006). Development of new immunosuppressive drugs are currently in trials, and proved effective in some MG cases, while autoantibodies depleting B-cells lymphocytes or combinatorial therapies have shown promises in MG and GBS preclinical trials (Skeie et al. 2006; Willison et al. 2016). Whether these approaches could be modified using humanized antibodies for clinical applications remains to be determined by future studies.

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Conflict to interest

The authors claim no conflict of interest.

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