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Botulinum Neurotoxin, an Example of Successful Translational Research

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One of the major problems in medicine is the difficulties in translating preclinical research into successful clinical studies and new therapies. It is evident that understanding the molecular mechanisms of action of a drug may open the doors to clinical applications. Botulinum neurotoxin is an excellent example of such a transition where elucidation of its paralyzing mechanism has allowed actual treatment of a series of neurological disorders through its muscle relaxation effects.

The potential of neurotoxins as therapeutic agents is based on a pharmacological concept named "hormesis" which posits beneficial effects of toxins at very low concentrations [1]. This concept is specifically confirmed by the use of botulinum neurotoxin in various disorders or conditions elaborated below. Botulinum is a potent neurotoxin which is produced by anaerobic bacteria such as Clostridium botulinum, Clostridium argentinensis, Clostridium barati, and Clostridium butyrricum [2]. Botulism is a disease induced by the presence of this neurotoxin in food contaminated with any of these bacteria. Botulinum neurotoxins can be classified as metalloproteases that cleave vesicle-associated membrane proteins. These neurotoxins have the ability to cause paralysis as a consequence of inhibition of neurotransmitter release, particularly that of acetylcholine (ACh) at peripheral cholinergic nerve terminals including the autonomic ganglia and skeletal muscle [3-8]. Although different forms of botulisms (depending on the type of bacteria) exist, all induce paralysis primarily via their action at the autonomic ganglia and the neuromuscular junction.

Botulinum neurotoxin was first used in 1980 as an alternative treatment to strabismus surgery based on the observation that the local intramuscular injection of very low doses of this neurotoxin resulted in local but reversible paralysis of the injected muscle [9]. The success of this therapeutic action opened the door for neurologist and other specialists to use botulinum neurotoxin in different conditions where a reversible controlled paralysis was desireable. These conditions included strabismus and nistagmus in opthalmology [10] and focal dystonia, characterized by involuntary muscle contractions causing repetitive twisting movements, pain and abnormal postures [11-14]. Local injection of botulinum neurotoxin relaxes the muscle and provides the patient a period of time free of involuntary muscle contractions [15, 16]. The focal dystonias treated with botulinum neurotoxin include blepharospasma, lingual dystonia, cervical dystonia (torticollis, anterocollis, laterocollis), occupational dystonias (writer's cramps, musician's cramps), oromandibular dystonia and laryngeal dysphonia [17-22]. Botulinum neurotoxin is also useful in treating nondystonic disorders such as tremors in parkinsonism, tics, Bruxism and hemifacial spasm [23, 24]. Interestingly, a variety of diseases such as: spasticity associated with pain, partial absence of voluntary movement, partial or mild paralysis (usually described as muscle weakness) and muscle hyperactivity, may also respond to botulinum toxin. Thus, botilinum toxin has been used in multiple sclerosis, cerebral stroke, spinal cord injury, traumatic brain injury, and infantile cerebral palsy [25, 26]. A common aim of treatment in all these conditions is to decrease motor overactivity and improve movement without worsening the weakness [8]. In addition to dystonias and spasticity, a number of hypersecretory disorders such as hyperhidrosis, sialorrhea, chronic rhinorrhea as well as smooth muscle hyperactivities in gastrointestinal and urologic disorders may also be treated with botulinum toxin [27, 28]. Recently, use of this drug in patients with spinal cord lesions of different types, lower urinary tract symptoms due to benign prostatic hyperplasia, detrusor sphincter dyssynergia and detrusor overactivity [29-31], Bruxism, temporomandibular disorder, prostatic pain, myofascial pain syndromes, migraine headache, low back pain, tension and different types of neurophatic pain syndromes [23, 32-35], gastroenterology and proctologic disorders such as achalasia and chronic anal fissure [36, 37] has also been advocated.

Curiously, the use of botulinum neurotoxin has not been restricted to pathologies. Indeed, cosmetic application of this drug is one its major uses [38, 39]. Thus, around 50% of botulinum neurotoxin A1 produced is consumed in aesthetic medicine as it tends to reduce wrinkles in skin areas of the face and the neck [40].

Although more than 40 botulinum neurotoxins have been extracted from clostridial bacteria, only two of these are commercially available for clinical use. Botulinum neurotoxin family include several pharmacologically distinct proteins with similar multi-domain structure at the molecular level, but distinct pharmacological properties. Next generation botulinum neurotoxins will likely be derived through protein engineering providing recombinant forms with enhanced therapeutic efficacy. The clinical success of these drugs will also depend on new formulation and delivery [35, 41, 42].

In summary, diligence in understanding the mechanism of action of a drug or a novel compound and keeping an eye on its potential application in certain diseases can greatly facilitate translational outcomes.

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