fellow at the Rudolf Buchheim Institute of Pharmacology and Toxicology, again under the supervision of Prof. Habermann. In 1981 he spent 12 months at the National Institutes of Health, Bethesda, MD, and was trained in electrophysiology. Returning to the laboratory of Prof. Habermann, he studied the mode of action of tetanus toxin, first by making antibodies and then by developing electrophysiological methods. He received his Habilitation in 1986. Since 1986, he has been Professor and Vice-Chairman of Toxicology at the Medical School of Hannover, Germany. He directs a research group working on the binding characteristics of botulinum toxins. On September 30, 2011, he will begin his retirement. He has more than 80 publications in the field and is an inventor on four issued or pending patents. He wrote several reviews and chapters in textbooks of pharmacology and toxicology. Since 2008 and currently, he is Chief Executive Officer of Toxogen GmbH, a spin-off of the Hannover Medical School. The company works on methods for the detection and quantification of botulinum toxins, has developed a test for the quantification of anti-botulinum-toxin antibodies in human sera, and performs research on protein-based peripheral muscle relaxants.

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Central nervous system effects of botulinum neurotoxins

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It is generally assumed that the effects of botulinum neurotoxins (BoNTs) remain localized to the injection site. However, studies have provided evidence for central actions of the widely-used BoNT/A. Here we review these data and discuss the mechanisms by which BoNT/A may affect central circuits. We have used detection of cleaved SNAP-25 as an assay of BoNT/A trafficking. We have also used electron microscopy and calcium imaging to demonstrate effects of BoNT/A at distant synapses.

Our results demonstrate retrograde axonal transport and transcytosis of catalytically-active BoNT/A. There is evidence that intramuscular injection of BoNT/A results in central nervous system effects. These findings have been usually ascribed to plastic rearrangements subsequent to the peripheral blockade. The finding of a retrograde transport of catalytically-active BoNT/A suggests that BoNT/A may also have direct central effects.

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Retrograde transport of proteins in the central nervous system

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Axonal transport is an essential process for neuron survival and homeostasis. However, this pathway also acts as a portal for the entry and dissemination in the nervous system of virulence factors and pathogens, such as tetanus toxin and several neurotropic viruses (Nat Rev Microbiol 2008;8:645). To identify novel participants in the regulation of this pathway, we have established siRNA screens using the binding fragment of tetanus toxin (TeNT HC) in embryonal stem cell (ES)-derived motor neurons.

TeNT HC enters motor neurons at the neuromuscular junction and is targeted to the soma located in the spinal cord. Its entry determines its sorting to axonal carriers shared with neurotrophins and their receptors. This route requires specific small GTPases and relies on Rab7 activity for long-range axonal transport powered by dynein (Neuron 2006;19:293). Mutations in dynein and Rab7 have been shown to be associated with motor neuron disease and peripheral neuropathies in humans, suggesting the possibility that mutations in other components of these pathways may predispose to or determine these pathologies. To identify novel regulators of the retrograde transport pathway of TeNT HC, we have used a library of siRNAs directed against genes involved in endocytosis and membrane traffic. Positive and negative regulators of axonal retrograde transport were identified, and candidates were validated using secondary screens with in vitro and in vivo assays (PNAS USA 2010;107:20523; Hum Mol Genet 2011;20:1776) that monitored the axonal dynamics of TeNT HC and botulinum neurotoxins A and E.

Our study demonstrates that siRNA approaches represent a powerful tool for investigating traffic events in neurons and for discovering novel participants in the axonal transport process.

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Peripheral cholinergic specificity of botulinum type A neurotoxin

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Botulinum neurotoxin type A (BoNT/A) binds to a polysialoganglioside and to a luminal segment of the integral synaptic vesicle protein SV2 in the presynaptic membrane. It is then endocytosed into peripheral cholinergic nerve terminals, where it cleaves SNAP-25, an essential protein for neurotransmitter release. This mechanism is the basis of its large use in human therapy and cosmetology. The order of the binding to the two BoNT/A receptors is at present not known. In the present work we have investigated the neurospecific binding of BoNT/A at motor nerve terminals of the neuromuscular junction (NMJ). BoNT/A binding domain coupled to Enhanced Green Fluorescent Protein (BoNT/A-Hc-EGFP) was produced and injected into the sternocleidomastoid muscle of anesthetized mice. Animals were sacrificed 5–10 min after the injection of the fusion protein. In addition, in vitro experiments were performed with frog Cutaneous pectoris nerve-muscle preparations, some of which were stimulated through their motor nerves.

Nerve terminal examination by confocal microscopy revealed that BoNT/A-Hc-EGFP was detected exclusively in nerve terminals of the NMJ, and immunostaining with GT1b-2a monoclonal antibody, which specifically recognizes the polysialoganglioside GT1b, was closely similar to that obtained with BoNT/A-Hc-EGFP. Following nerve stimulation, the fluorescent BoNT/A-Hc-EGFP redistributed with extensive localization by the active zones. Electron microscopy with gold-labelled anti-EGFP antibodies confirmed that in nerve-stimulated muscles, BoNT/A is localized close to the active zones. The present findings open a novel and interesting possibility: that polysialogangliosides microdomains may actively redistribute on the membrane plane toward active zones upon nerve stimulation, thus bringing the toxin to the site of endocytosis.

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Mechanism of action of botulinum neurotoxin in hyperhidrosis

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Botulinum toxin is a very potent agent that blocks cholinergic transmission in sudomotor fibers. This blockade leads to a marked reduction of sweat secretion in hyperhidrosis, as shown in several randomized controlled trials and in open-label studies. However, the exact mode of action, the effect of botulinum toxin on the morphology of sweat glands, and the transmitters other than acetylcholine that may be blocked by botulinum toxin, are not yet fully understood.

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Botulinum toxin for detrusor overactivity

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Extensive evidence exists to indicate the response of detrusor overactivity (DO) to botulinum toxin. Numerous case series and now controlled trials have indicated the feasibility and efficacy of the use of botulinum toxin for detrusor overactivity arising from both neurogenic and idiopathic causations. Areas of controversy continue to exist regarding optimal dosing for the specific type of overactive bladder, appropriate administration technique and optimization of therapeutic delivery. Currently, botulinum toxin is being used in off-label indications for both neurogenic and non-neurogenic detrusor overactivity (overactive bladder). Adverse events that include increased post-void residual volume result in the possible need for bladder catheterization, as well as in an increased risk of urinary tract infection. Further information is needed for purposes of assessing alternative delivery techniques and ideal patient populations for administration of toxin.

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Researchers have shown how Botox -- also known as Botulinum neurotoxin serotype A -- is transported via our nerves back to the central nervous system. Botox -- best known for its ability to smooth wrinkles -- has been extremely useful for the treatment of over-active muscles and spasticity as it promotes local and long-term paralysis. "While no side-effects of using Botox medically have been found yet, finding out how this highly active toxin travels to the central nervous system is vital because this pathway is also hijacked by other pathogens such as West Nile or Rabies viruses. "A detailed understanding of this pathway is likely to lead to new treatments for some of these diseases." Botulinum neurotoxin Type A (BoNT/A) is an effective treatment for several movement disorders, including spasticity and dystonia. BoNT/A acts by cleaving synaptosomal-associated protein of 25 kDa (SNAP-25) at the neuromuscular junction, thus blocking synaptic transmission and weakening overactive muscles. SIGNIFICANCE STATEMENT Botulinum neurotoxins are among the most potent toxins known. Despite this, their specific and reversible action prompted their use in clinical practice to treat several neuromuscular pathologies (dystonia, spasticity, muscle spasms) characterized by hyperexcitability of peripheral nerve terminals or even in nonpathological applications (i.e., cosmetic use). Central Effects of Botulinum Neurotoxin - Evidence from Human Studies. January 2019. Toxins 11(1). For more than three decades, Botulinum neurotoxin (BoNT) has been used to treat a variety of clinical conditions such as spastic or dystonic disorders by inducing a temporary paralysis of the injected muscle as the desired clinical effect. BoNT is known to primarily act at the neuromuscular junction resulting in a biochemical denervation of the treated muscle. Author Summary Botulinum neurotoxins are the most toxic molecules known to mankind, and as a result, are currently listed among the top bio-threats. However, their ability to bind specifically to neurons and their inhibitory effects on regulated secretion prompted their clinical use in pathologies characterised by increased muscular tone, such as dystonia and various forms of spasticity, or abnormal secretion, such as drooling and excessive sweating, to cite a few. Our results show that axonal retrograde transport is a common pathway for the dissemination in the central nervous system of pathogens and virulence factors important for human and animal health. Botulinum toxin type A and B are considered cosmetic when used to improve appearance, or in the absence of physiological functional impairment that would be improved by their use. Most Oxford Certificates of Coverage (COCs) exclude benefit coverage for cosmetic services. Some plans may exclude benefit coverage for medical and surgical treatment of excessive sweating (hyperhidrosis).