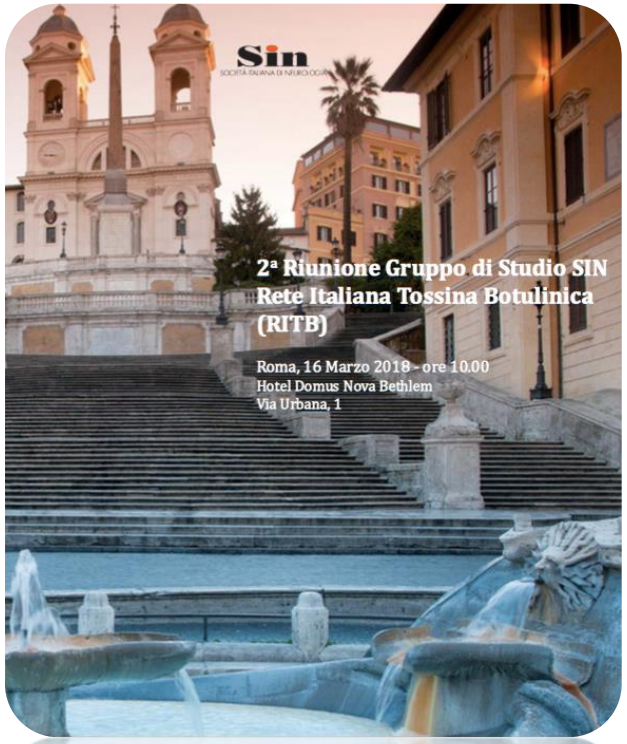


LA RICERCA SULLA TOSSINA BOTULINICA: UNA STORIA MOLTO ITALIANA

Valeria Tugnoli
U.O.C. di Neurologia
D.A.I. Neuroscienze-Riabilitazione – Ferrara

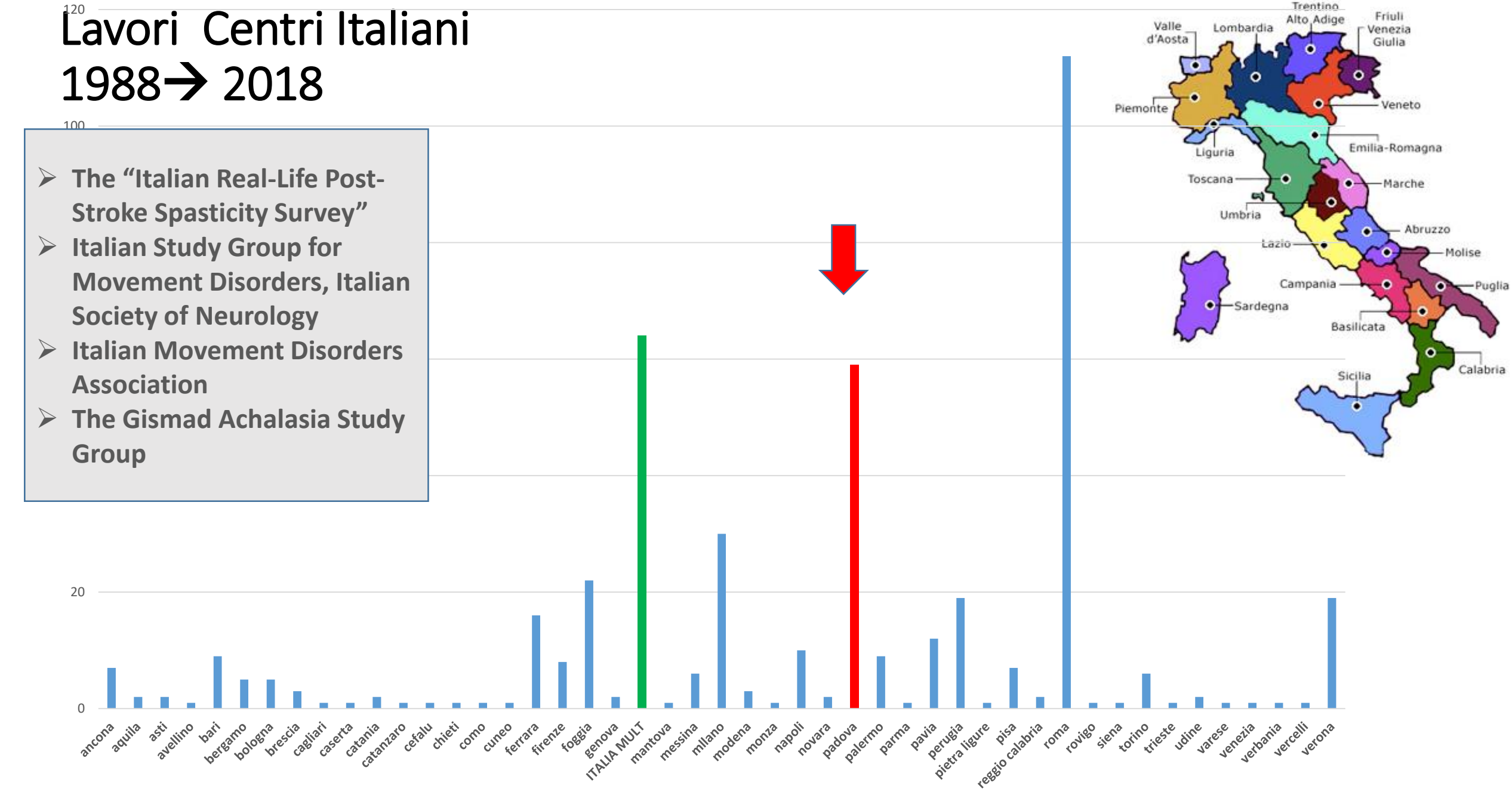
Roma 16 marzo 2018

PUBMED→ Botulinum Toxin World/Italy

Until a few years ago, the field of the study of BoNTs in general seemed to have reached a kind of steady state, with a small number of basic science papers and an overflow of thousands of clinical papers per year

Lavori Centri Italiani 1988→ 2018

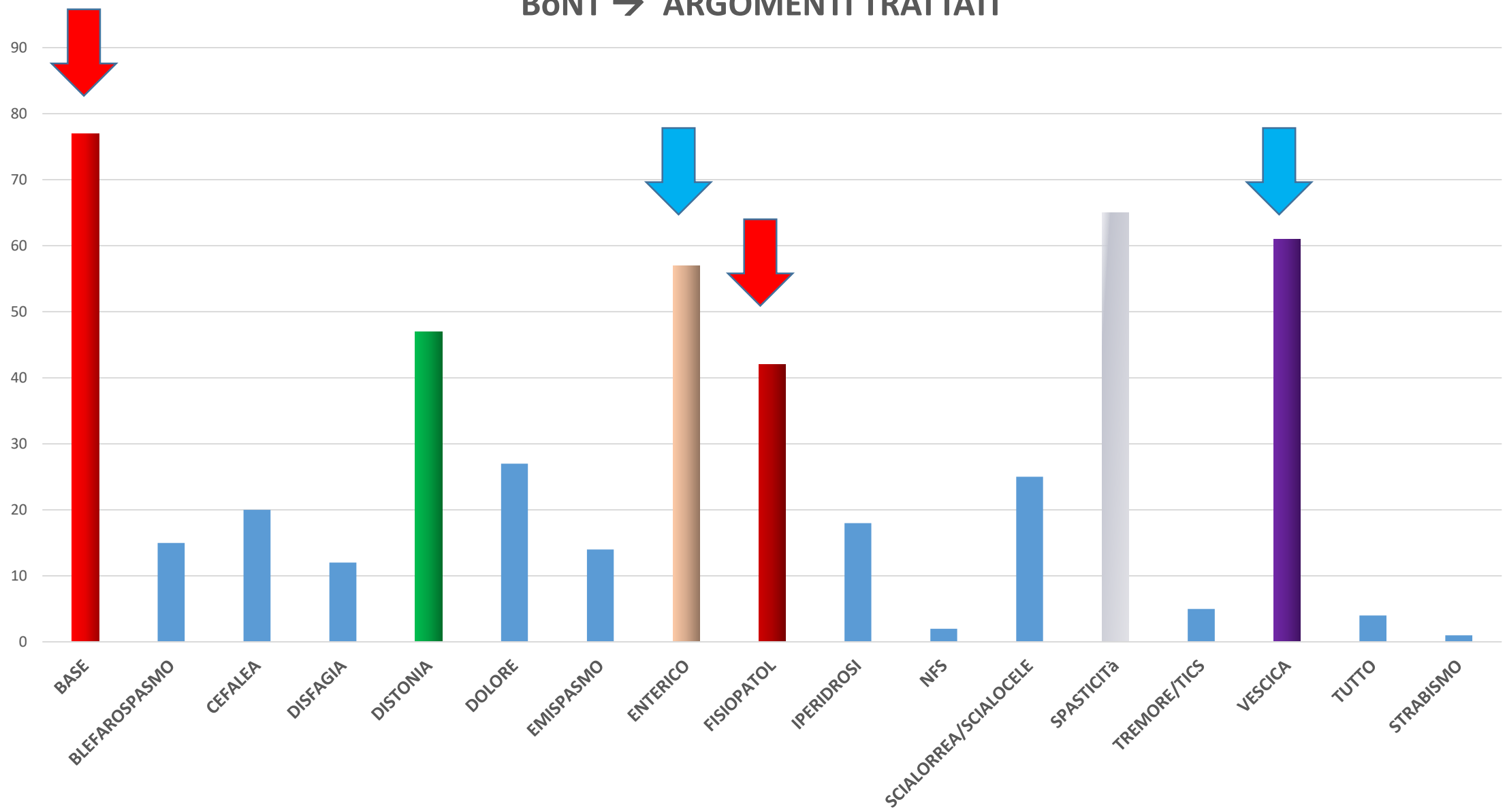
- The “Italian Real-Life Post-Stroke Spasticity Survey”
- Italian Study Group for Movement Disorders, Italian Society of Neurology
- Italian Movement Disorders Association
- The Gismad Achalasia Study Group



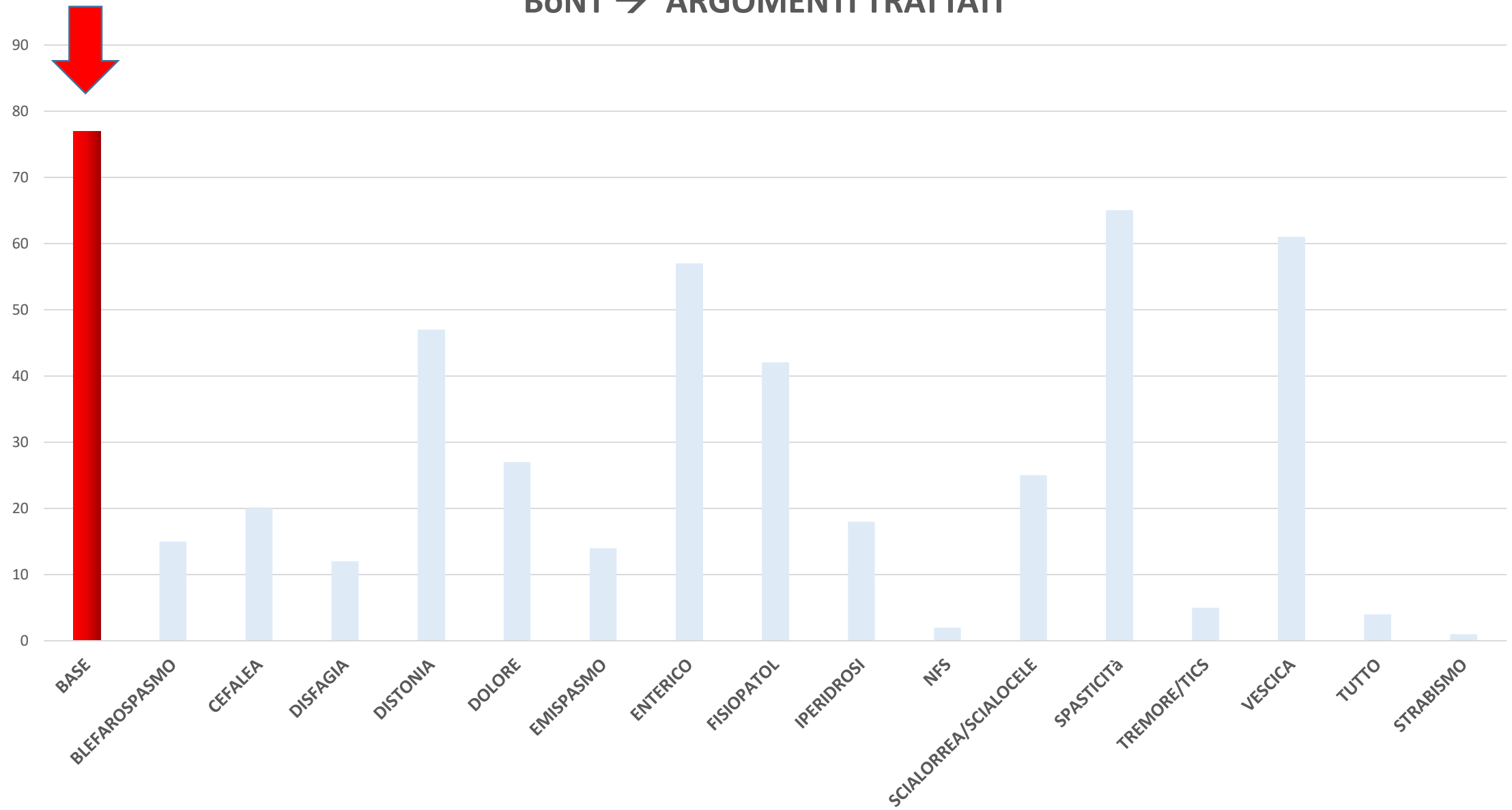
Study Groups

- Berardelli A et al. Guidelines for the therapeutic use of botulinum toxin in movement disorders. **Italian Study Group for Movent Disorders, Italian Society of Neurology**. Ital J Neurol Sci 1997 Oct;18(5):261-9
- Annese V. Comparison of two different formulations of botulinum toxin A for the treatment of oesophageal achalasia. The **GISMAD Achalasia Study Group**. Aliment Pharmacol Ther 1999 Oct;13(10):1347-50
- Annese V. A multicentre randomised study of intrasphincteric botulinum toxin in patients with oesophageal achalasia. **GISMAD Achalasia Study Group**. Gut 2000 May;46(5):597-600.
- Zappia M et al. Treatment of essential tremor: a systematic review of evidence and recommendations from the **Italian Movement Disorders Association**. J.Neurol 2013 Mar;260(3):714-40
- Picelli A et al. The **Italian real-life post-stroke spasticity survey**: unmet needs in the management of spasticity with botulinum toxin type A. Functional Neurology 2017; 32(2): 89-96

BoNT → ARGOMENTI TRATTATI



BoNT → ARGOMENTI TRATTATI



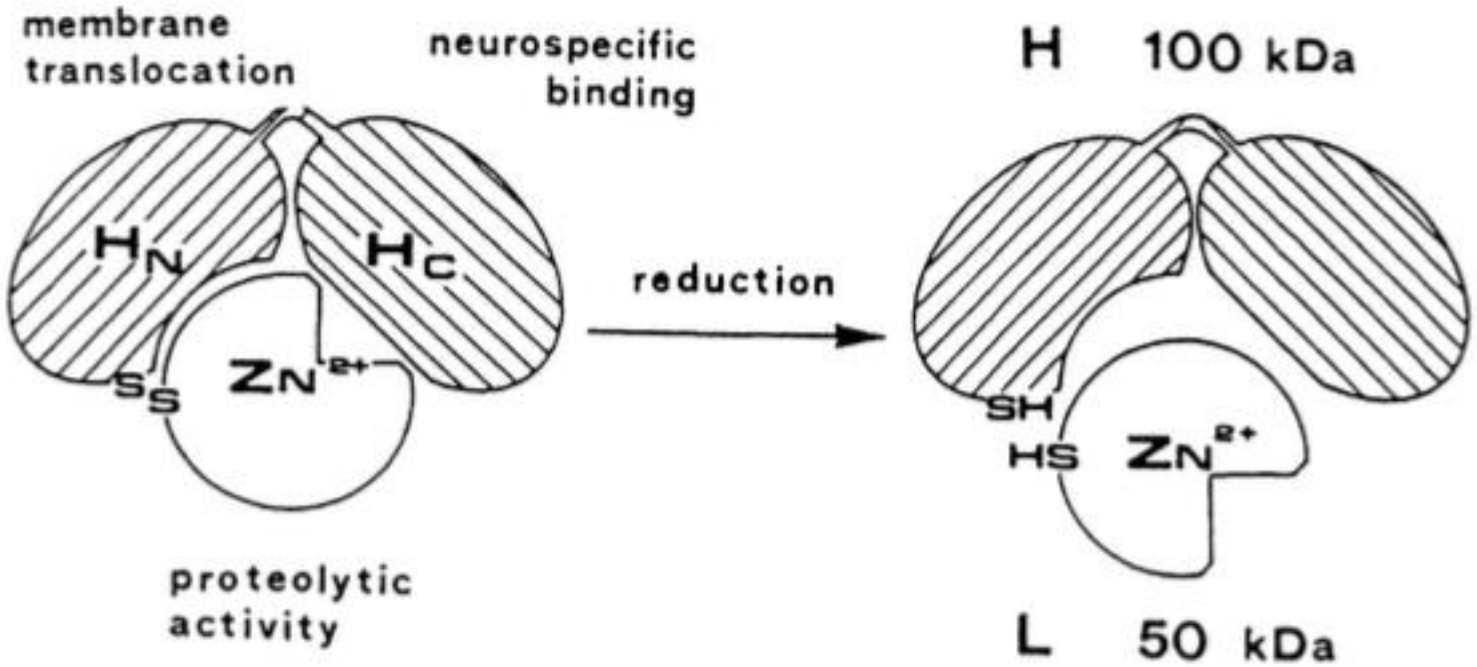
THE JOURNAL OF BIOLOGICAL CHEMISTRY

Vol. 267, No. 33, Issue of November 25, pp. 23479-23483, 1992
Printed in U.S.A.

Botulinum Neurotoxins Are Zinc Proteins*

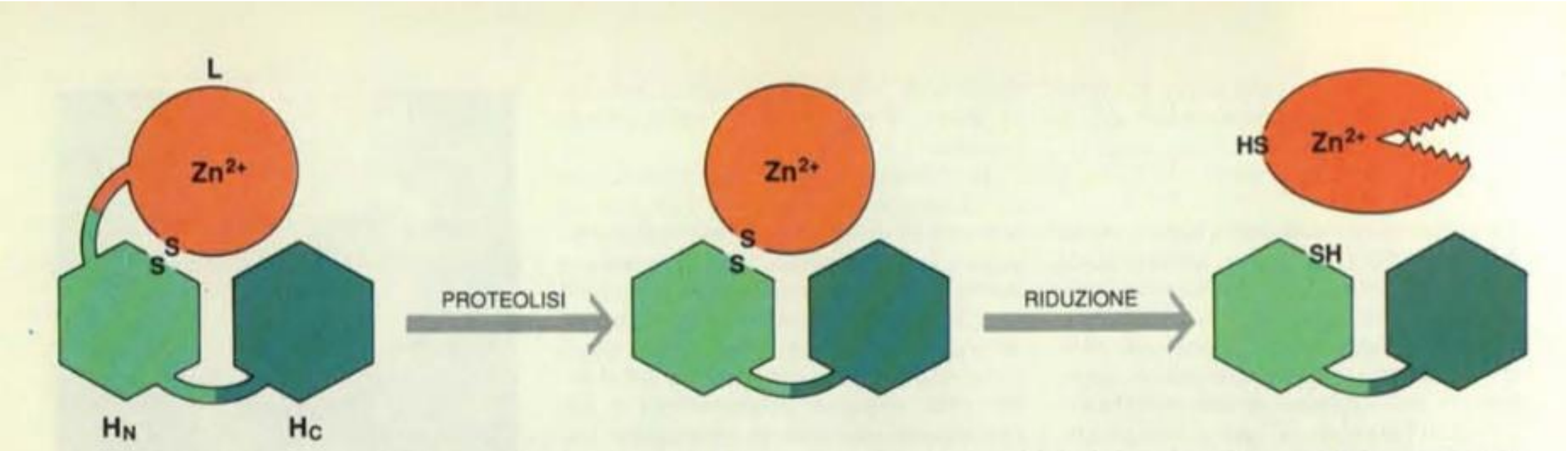
(Received for publication, May 11, 1992)

Giampietro Schiavo‡, Ornella Rossetto‡§, Annalisa Santucci¶, Bibhuti R. DasGupta‖, and Cesare Montecucco‡



un atomo di zinco per molecola di tossina legato alla catena *L* attraverso le due istidine del segmento centrale conservato

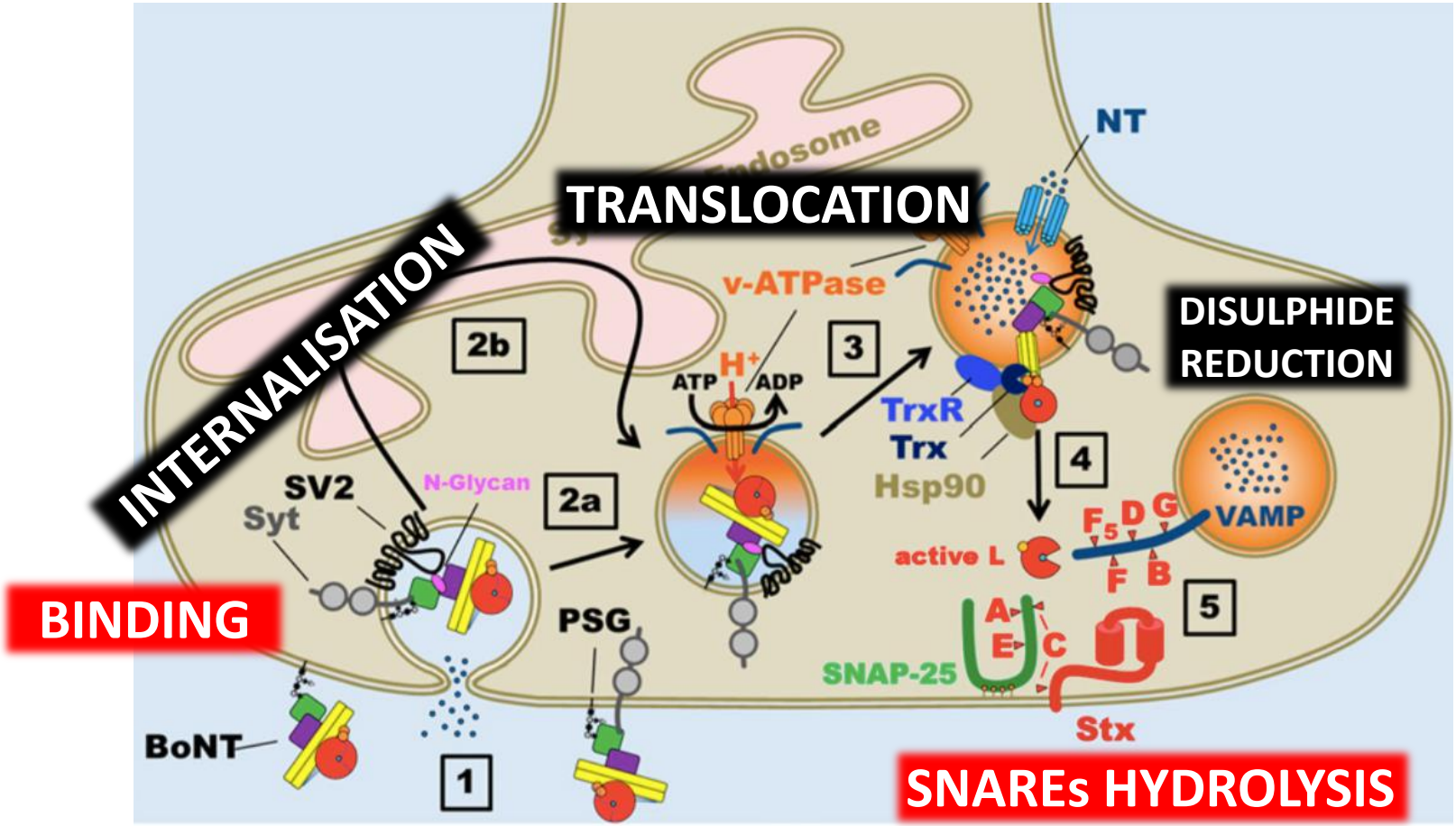
the zinc-endopeptidase activity of botulinum neurotoxins



Double anchorage to the membrane and intact inter-chain disulfide bond are required for the low pH induced entry of tetanus and botulinum neurotoxins into neurons

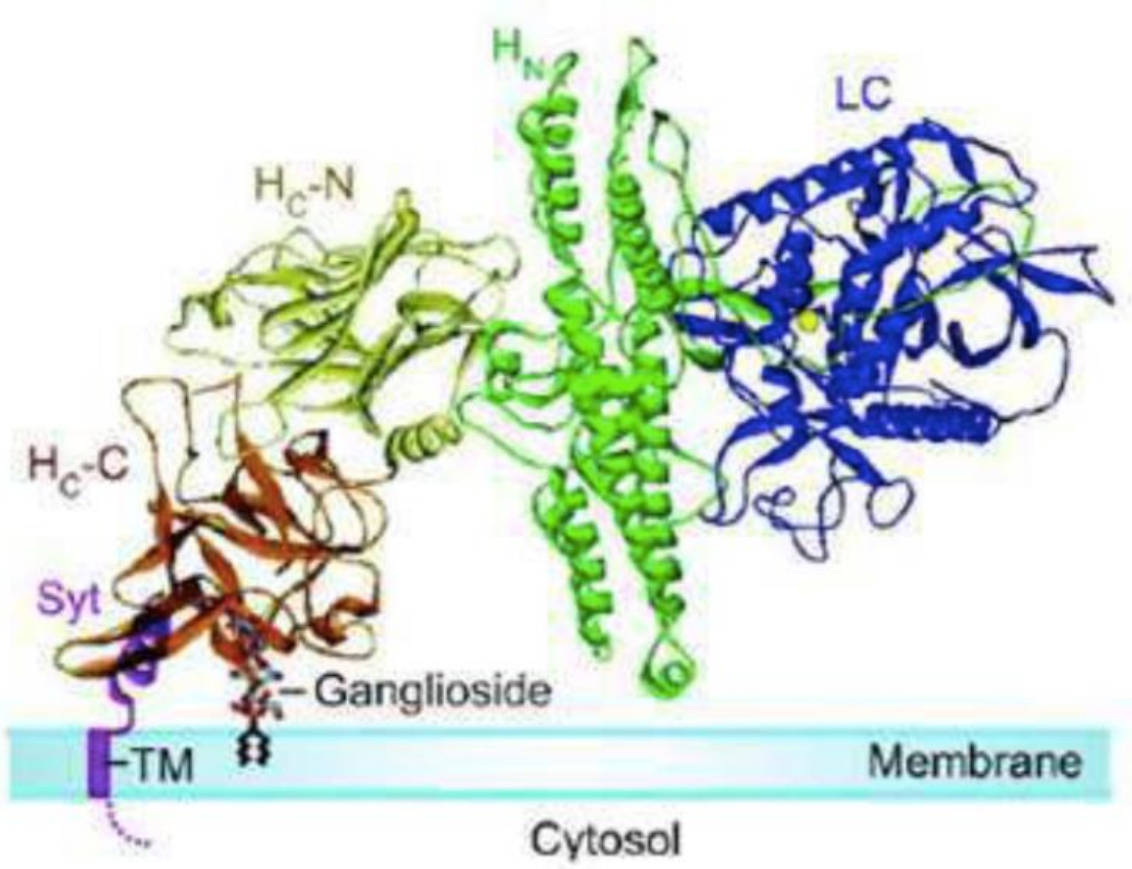
Pirazzini M., Rossetto O., Bolognese P., Shone C.C. and Montecucco C.
Cellular Microbiology. 2011

Model → bacterial toxins with intracellular activity enter cells via a four-step mechanism



Recettori: modello di doppio recettore lipidico-proteico (Montecucco, C et al. 2004)

- BoNTs bind the axon terminals of skeletal and autonomic peripheral neurons via a ***unique double receptor binding mode,*** with the two receptors binding sites located in HC
- HC-C mediates the neurospecific binding of the toxin to the presynaptic membrane via two independent receptors: a **polysialoganglioside (PSG)** and the luminal domain of a **synaptic vesicles (SV) membrane protein**
- There appears to be no interaction or mutual interference between the two receptors binding sites.
- A binding is preliminary to the following step of internalization inside the nerve.



FEBS Letters 583 (2009) 2321–2325

ELSEVIER

FEBS Letters

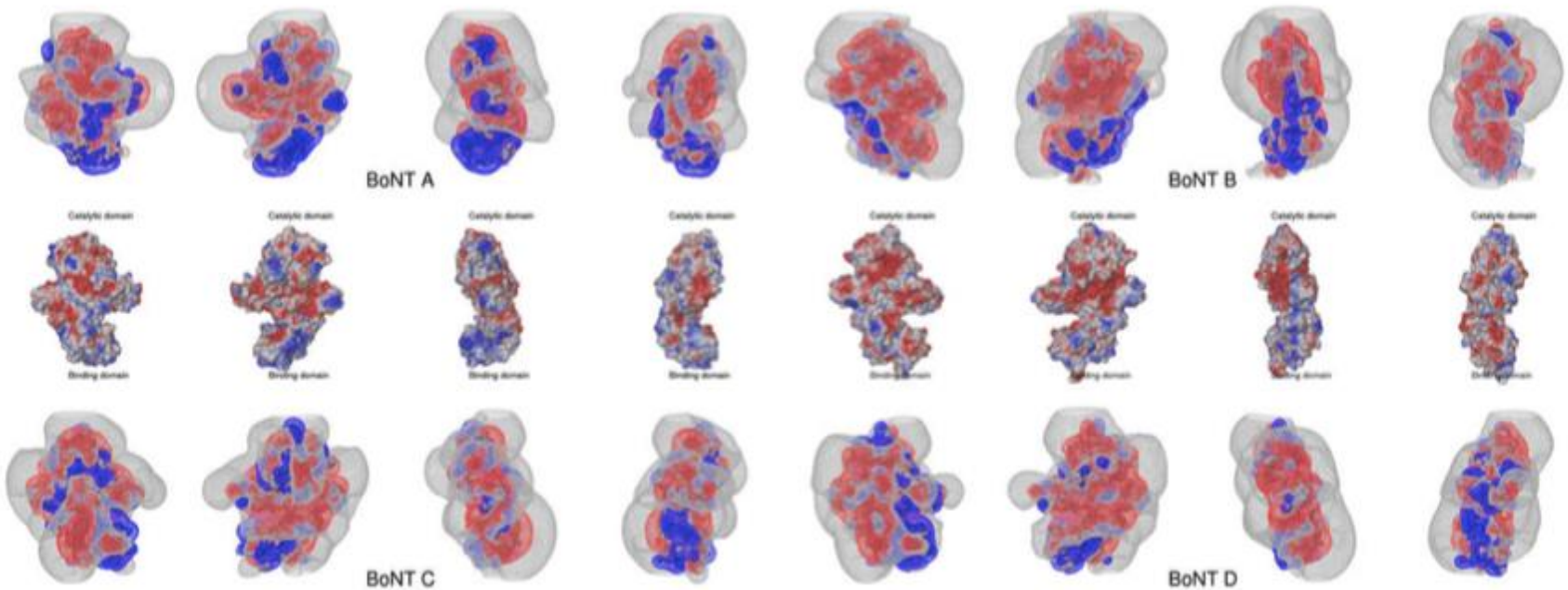
journal homepage: www.FEBSLetters.org

Hypothesis

Electric dipole reorientation in the interaction of botulinum neurotoxins with neuronal membranes

Federico Fogolari [a,1], Silvio C.E. Tosatto [b,1], Lucia Muraro [c], Cesare Montecucco [c,*]

- these neurotoxins possess an electric dipole with the positive pole on receptor binding domain Hc-C and that (2) on approaching the negatively charged presynaptic membrane, they reorient themselves and hit the membrane surface with Hc-C; this electrostatic effect would contribute efficient binding.

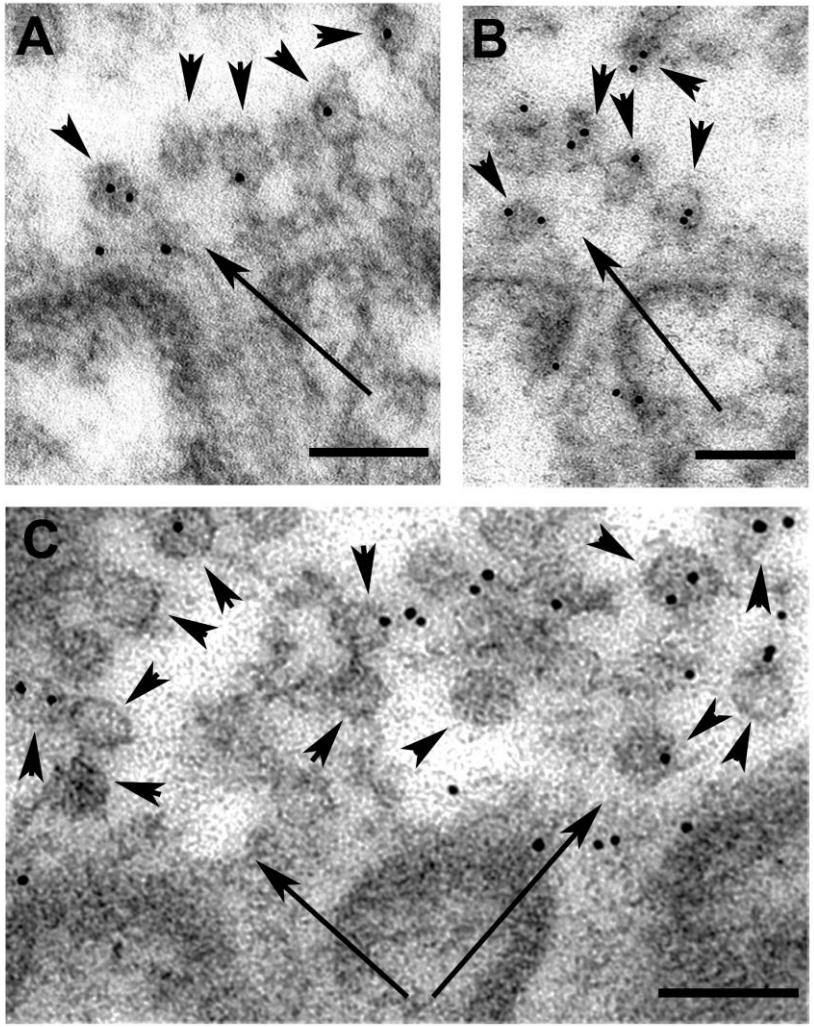


INTERNALISATION

Molecular Neurobiology 2013

Botulinum Neurotoxin Type A is Internalized and Translocated from Small Synaptic Vesicles at the Neuromuscular Junction

Cesare Colasante, Ornella Rossetto, Laura Morbiato, Marco Pirazzini Jordi Molgó & Cesare Montecucco



Immuno EM with gold-labelled Ab ***anti GFP-HC/A***

1-2 molecules of toxin per Synaptic Vesicle

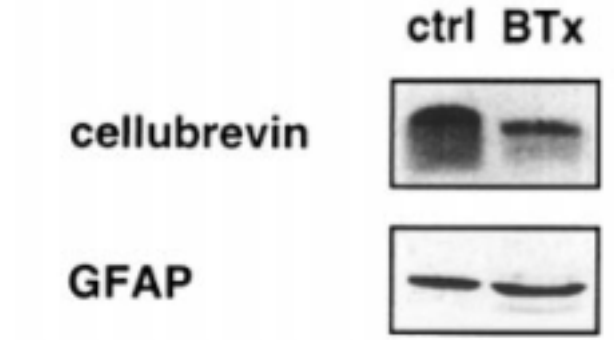
The toxin endocytosis is temperature dependent. It doesn't occur below 18° C
NO ice after toxin injection

The translocation of the L chain is mediated by ONE-TWO molecules of BoNT/A

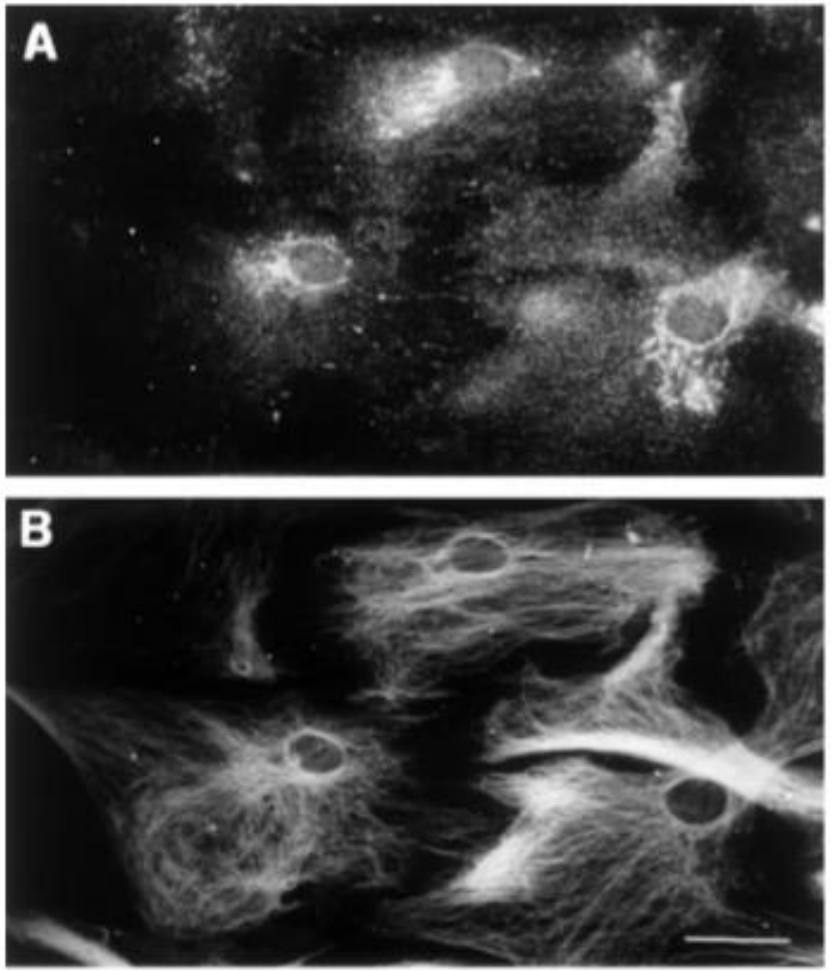
Internalization and Proteolytic Action of Botulinum Toxins in CNS Neurons and Astrocytes

Claudia Verderio, Silvia Coco, *Ornella Rossetto, *Cesare Montecucco, and Michela Matteoli

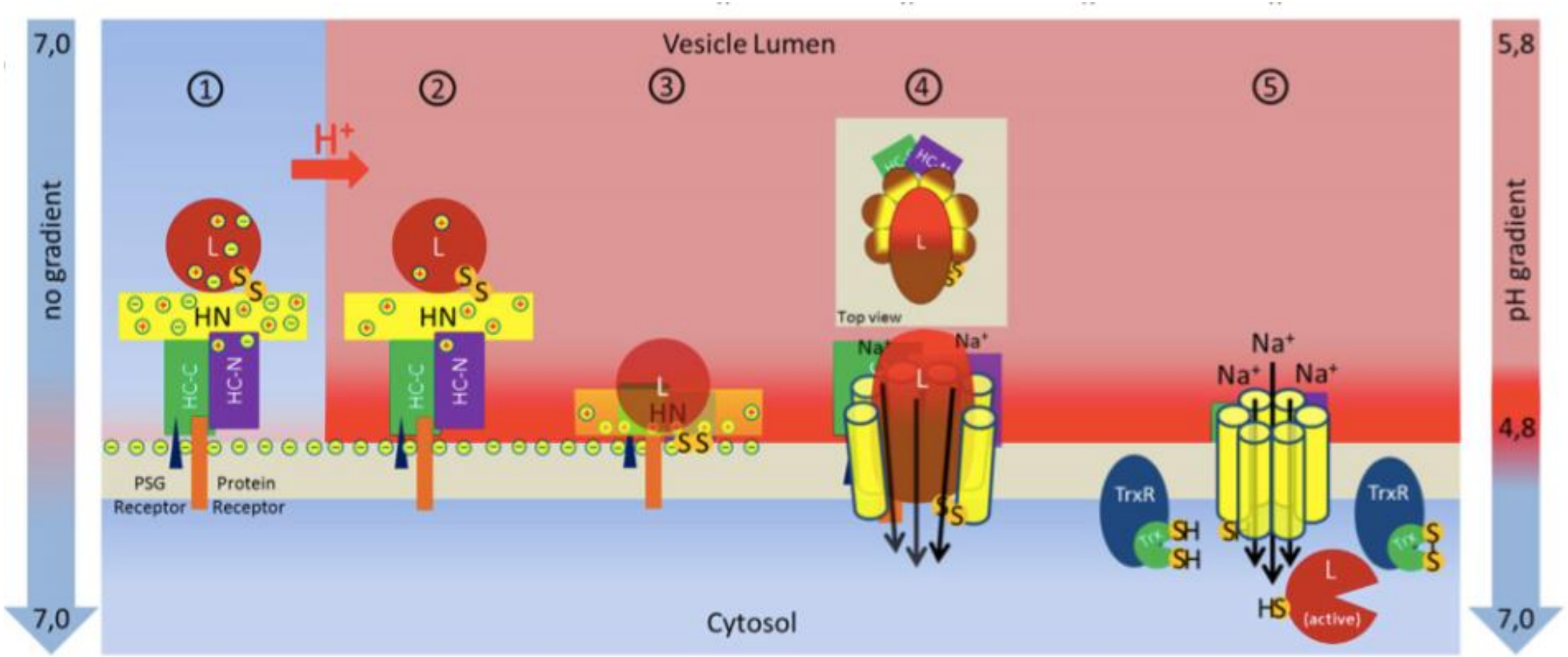
*CNR Cellular and Molecular Pharmacology and "B. Ceccarelli" Centers, Department of Pharmacology, University of Milan, Milan, and *Department of Biological Sciences, Center CNR Biomembrane, University of Padua, Padua, Italy*

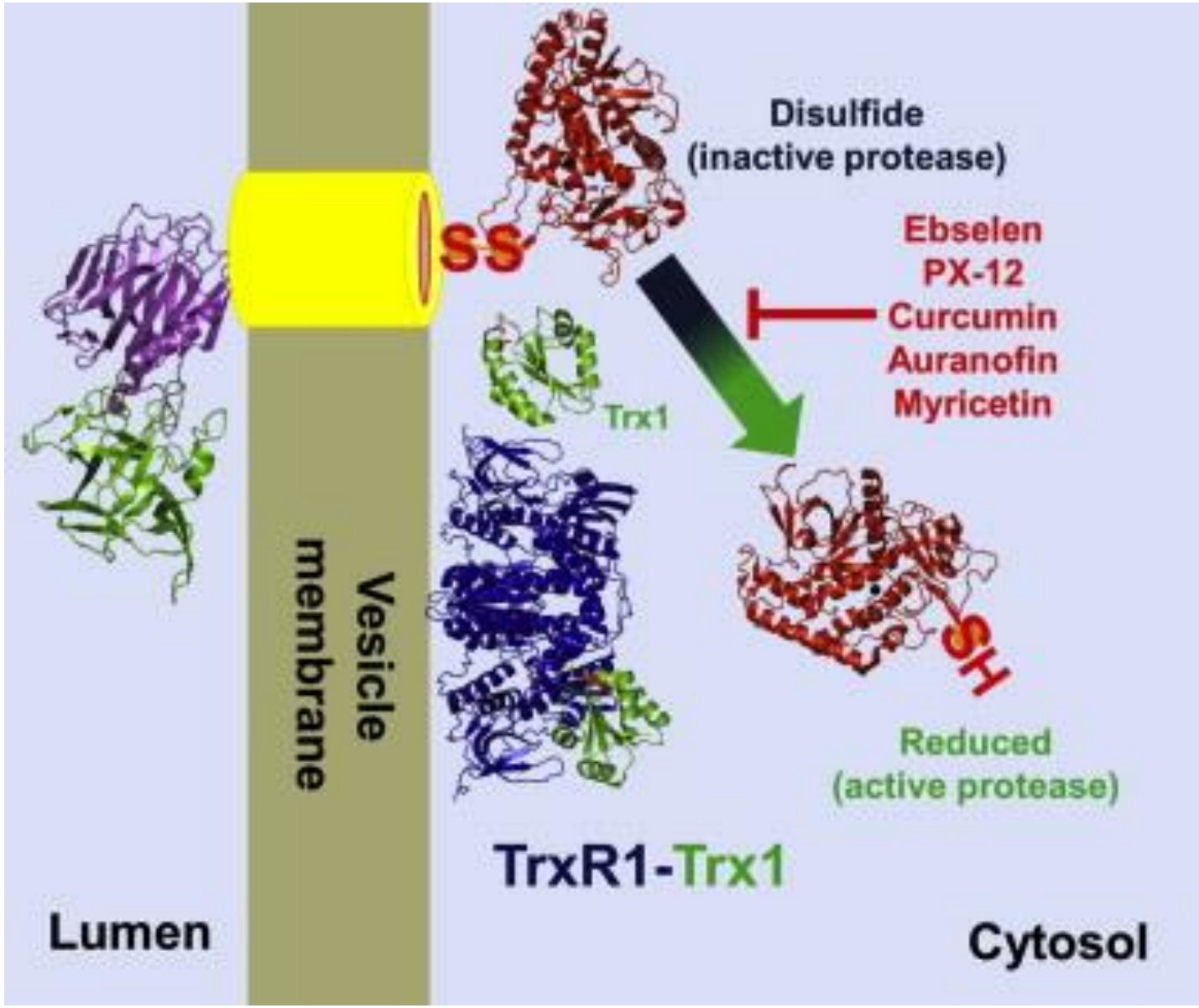


- botulinum toxins also exploit endocytosis to enter ***cultured astrocytes***, where they partially cleave cellubrevin, a ubiquitous synaptobrevin/VAMP isoform.



the membrane translocation of the clostridial neurotoxins.



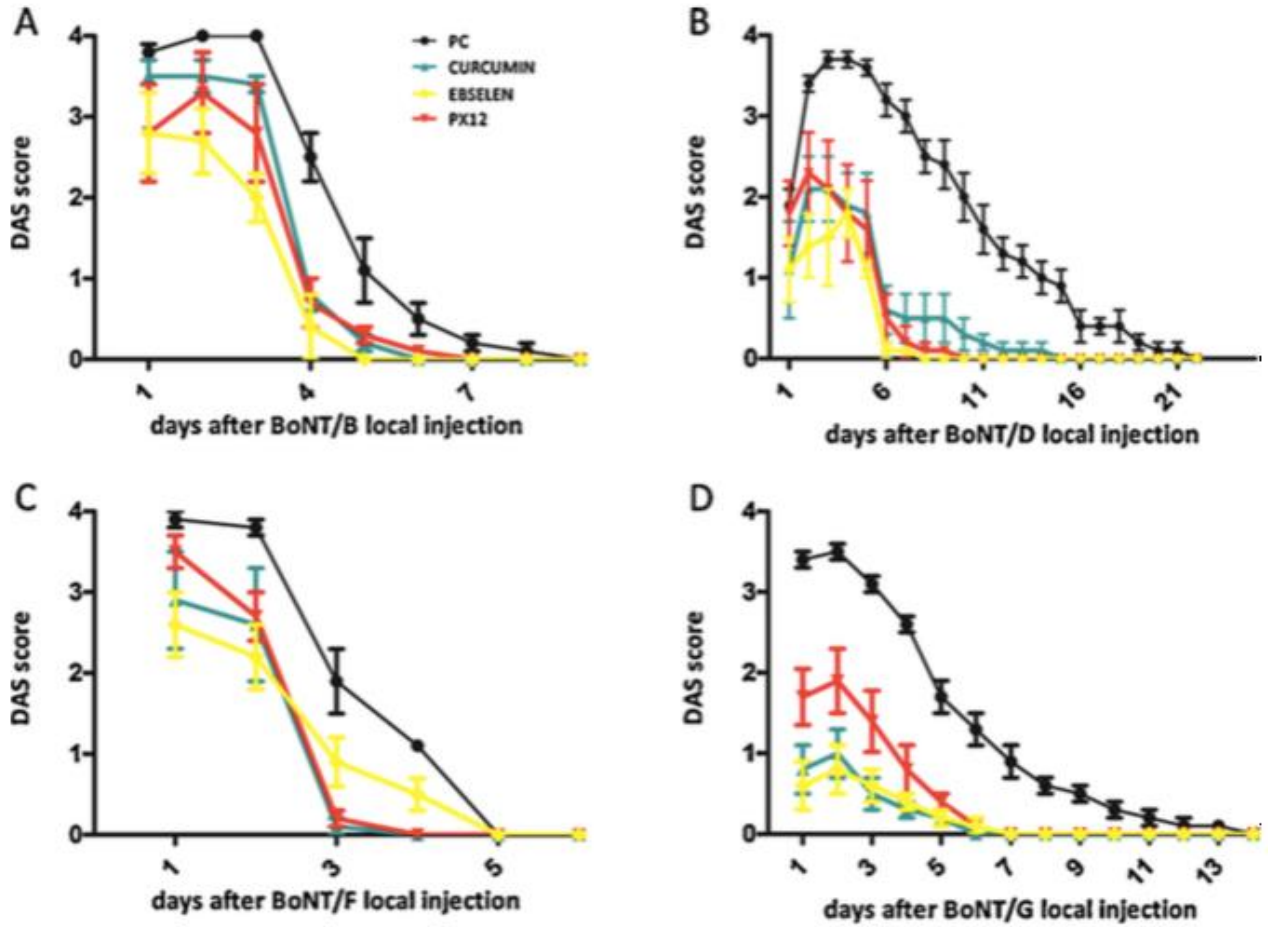


Pirazzini et al., *FEBS Lett.,* 2013
Pirazzini et al. *Cell Reports,* 2014
Zanetti et al., *Biochem. Pharmacol*., 2015

Inhibition of botulinum neurotoxins interchain disulfide bond reduction prevents the peripheral neuroparalysis of botulism

Giulia Zanetti[a,1], Domenico Azarnia Tehran[a,1], Marcon Pirazzini[a], Thomas Binz[c], Clifford C. Shone[d], Silvia Fillo[e], Florigio Lista[e], Ornella Rossetto[a], Cesare Montecucco[a,b,*]

Biochemical Pharmacology 98 (2015) 522–5



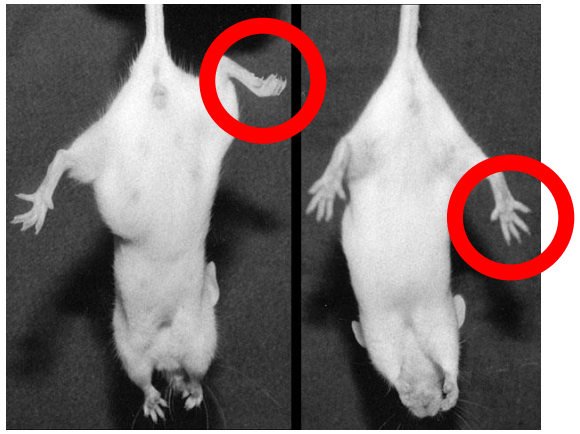
- Thioredoxin and Thioredoxin Reductase Inhibitors Prevent the Local Paralysis and Death Induced by BoNT/A
- Auranofin, as a possible basis for the design of novel inhibitors of these neurotoxins.

FEBS Letters 587 (2013) 150–155

Thethioredoxin reductase-thioredoxin system is involved in the entry of tetanus and botulinum neurotoxins in the cytosol of nerve terminals

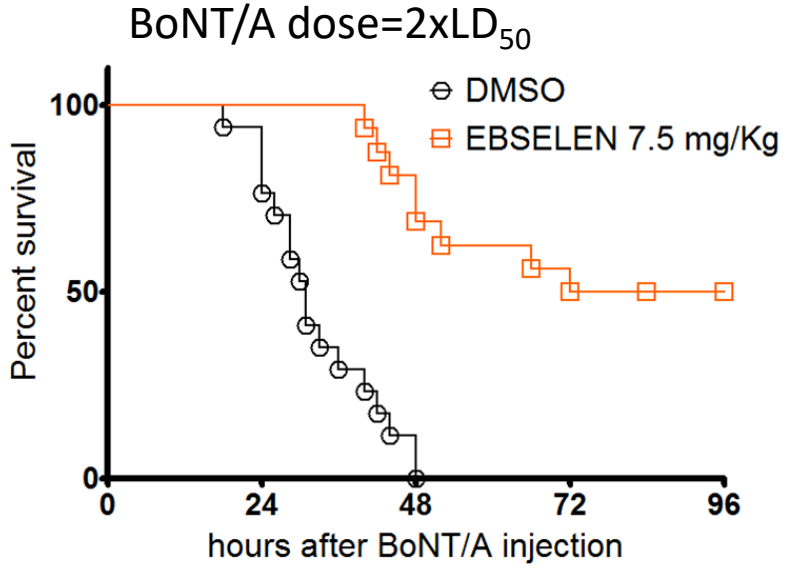
Marco Pirazzini a, Fulvio Bordin a, Ornella Rossetto a, Clifford C. Shone b, Thomas Binz c, Cesare Montecucco a,⇑

TrxR-Trx inhibitors reduce BoNTs paralysis duration

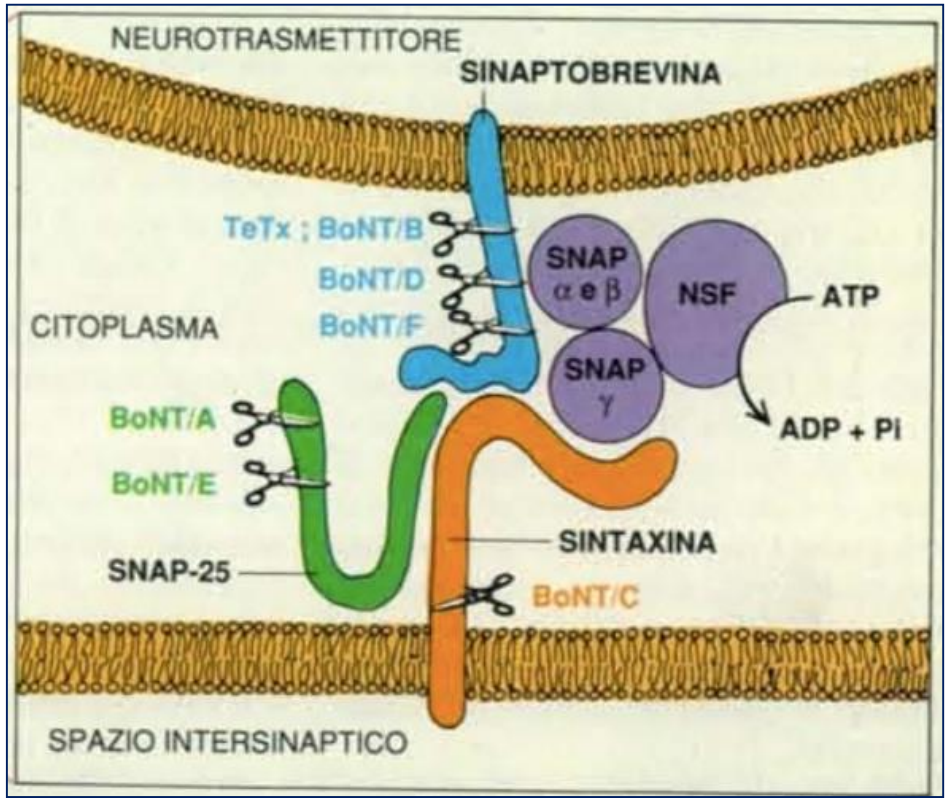


DAS-ASSAY

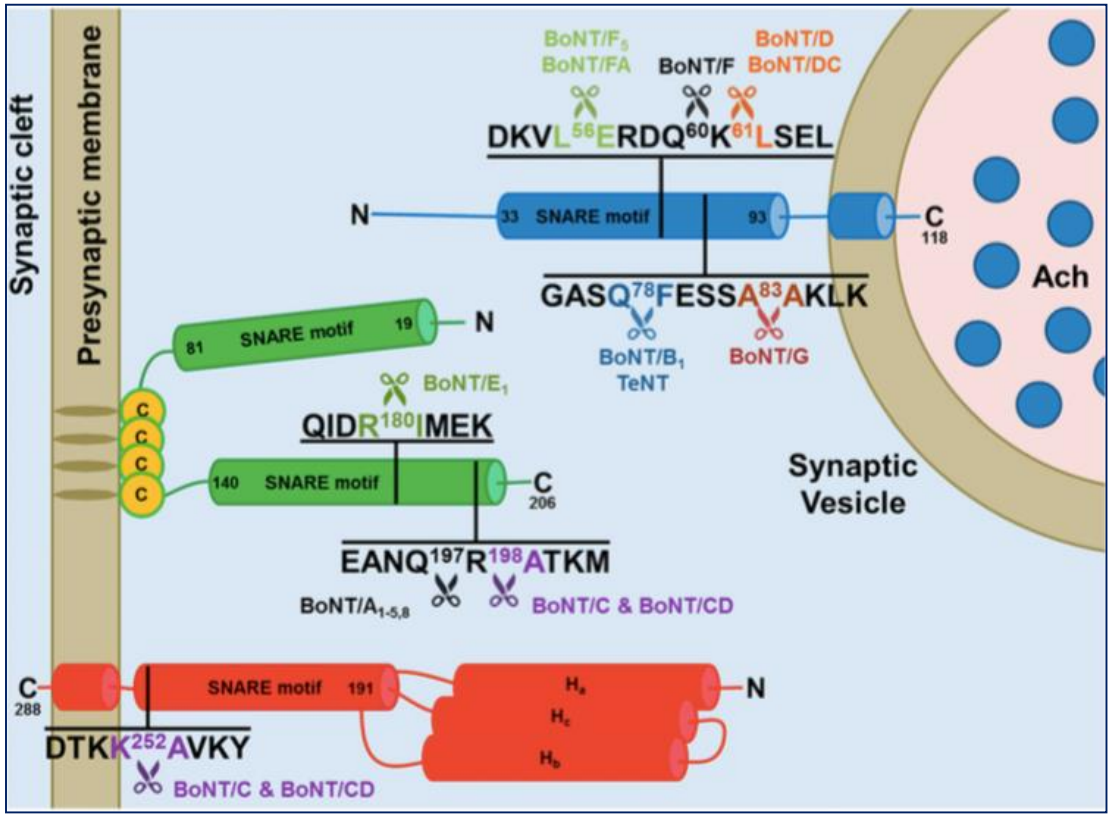
Ebselen protects mice *in vivo*



Mouse Lethality Assay



SCHIAVO G., BENFENATI F., POULAIN B., ROSSETTO O., POLVERINO DE LAURETO P., DASGUPTA 13. R. e MONTECUCCO C.,
Tetanus and Botulinum B Neurotoxins block Neurotransmitter Release by Proteolytic Cleavage of Synaptobrevin in «Nature», 359, pp. 832-835, 1992



PIRAZZINI M, ROSSETTO O, ELEOPRA R, and MONTECUCCO C

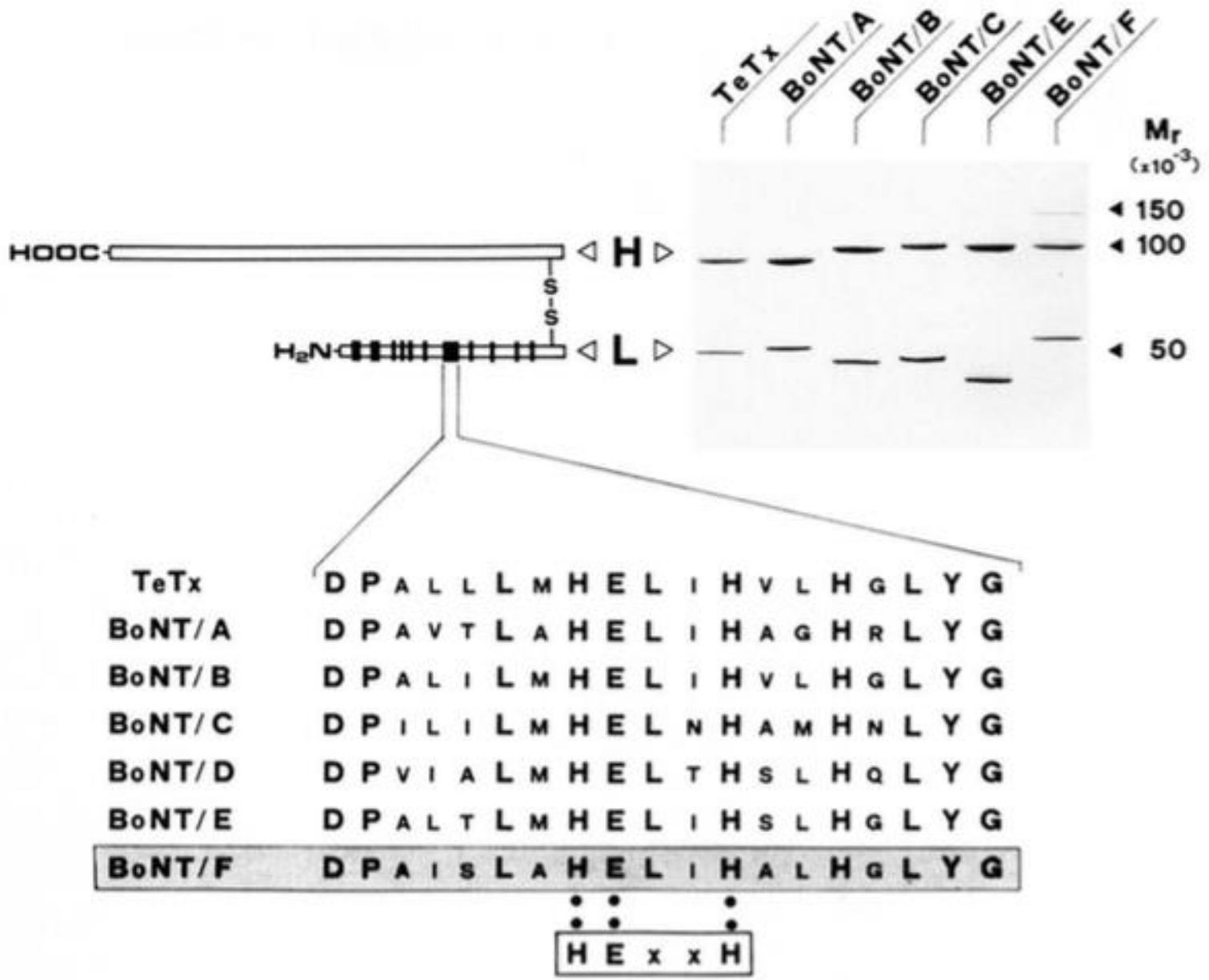
Botulinum Neurotoxins: Biology, Pharmacology, and Toxicology Pharmacol Rev 69:200–235, April 2017

Botulinum Neurotoxin Serotype F Is a Zinc Endopeptidase Specific for VAMP/Synaptobrevin*

(Received for publication, February

Giampietro Schiavo‡, Clifford C. Shone§,
Ornella Rossetto‡, Frances C. G. Alexander
Cesare Montecucco‡

Le forbicine nascono così!!!

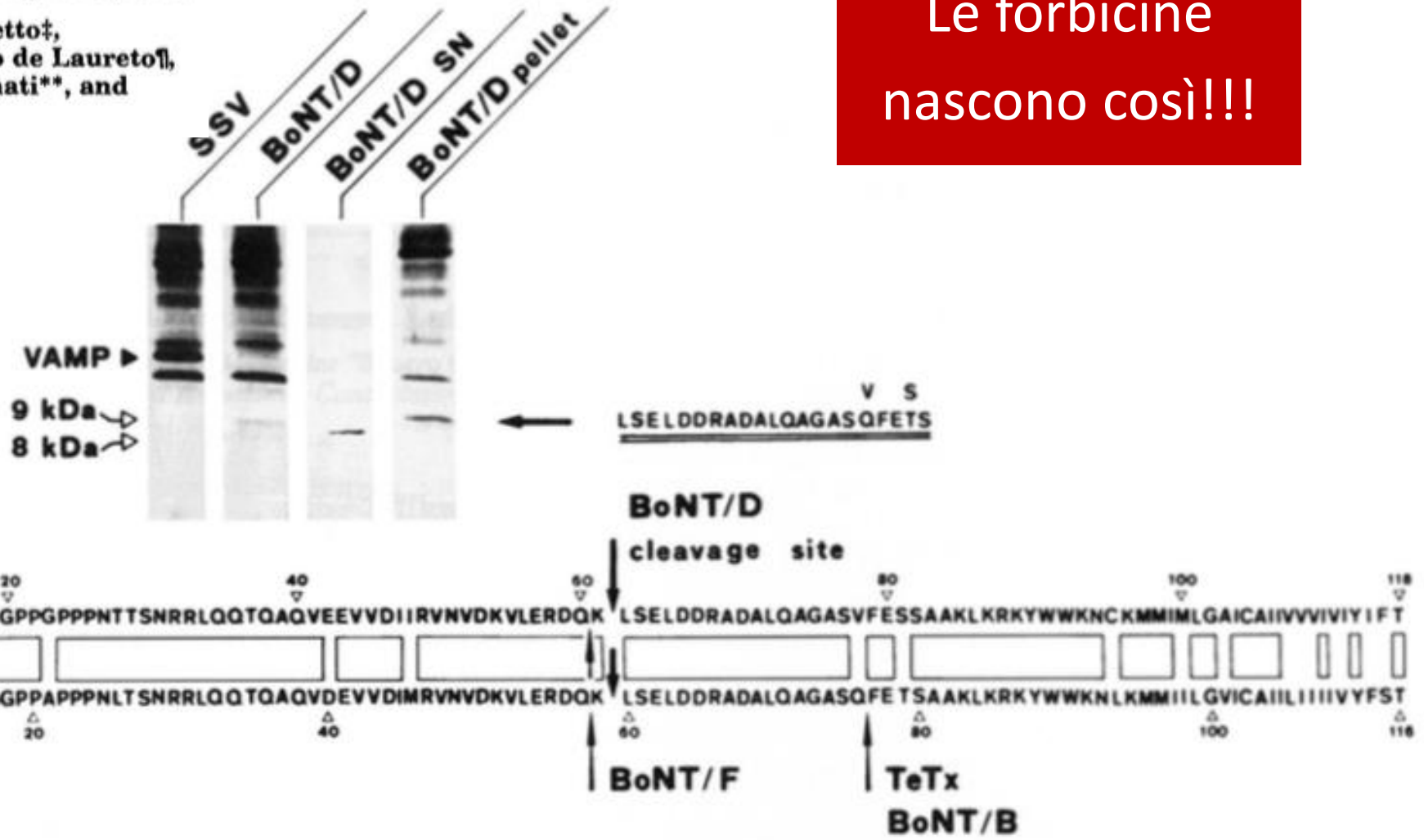


Identification of the Nerve Terminal Targets of Botulinum Neurotoxin Serotypes A, D, and E*

(Received for publication, August 12, 1993)

Giampietro Schiavo‡, Ornella Rossetto‡, Stefan Catsicas§, Patrizia Polverino de Laureto¶, Bibhuti R. DasGupta‖, Fabio Benfenati**, and Cesare Montecucco‡

Le forbicine nascono così!!!

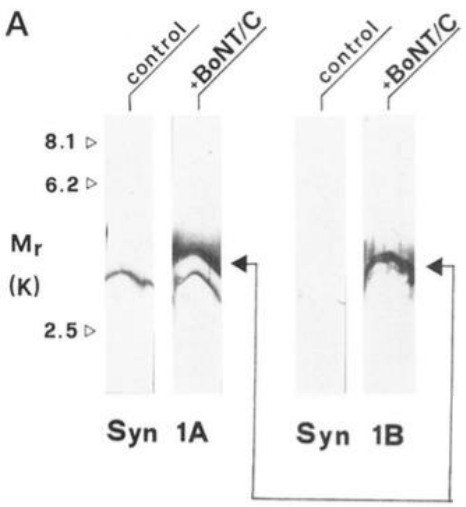


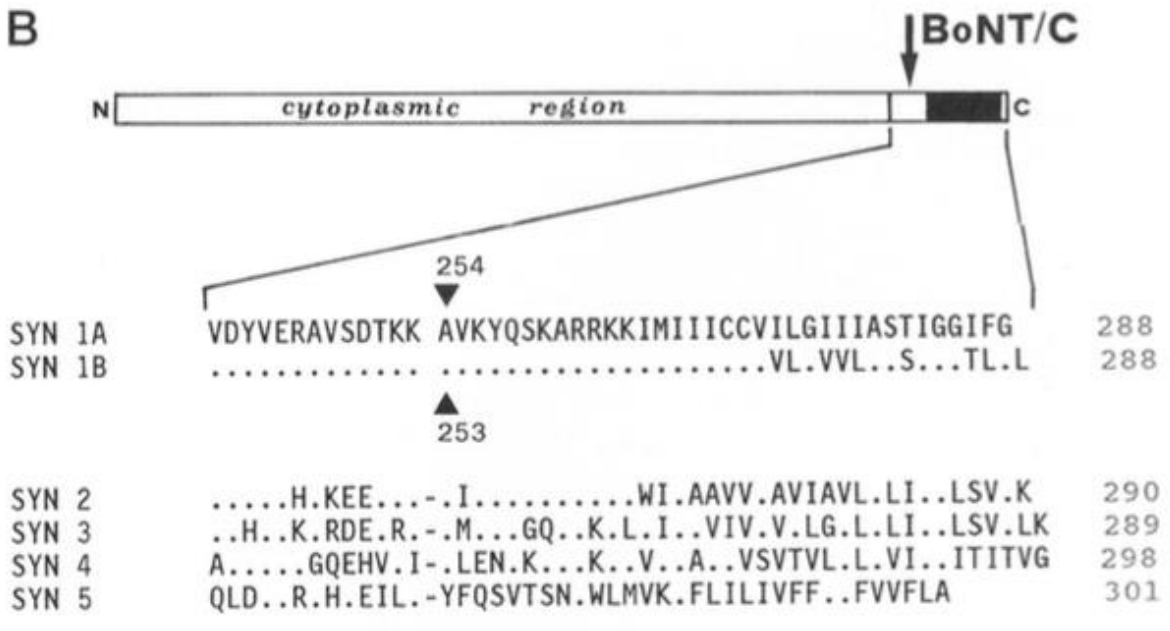
THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 270, No. 18, Issue of May 5, pp. 10566–10570, 1995
Printed in U.S.A.

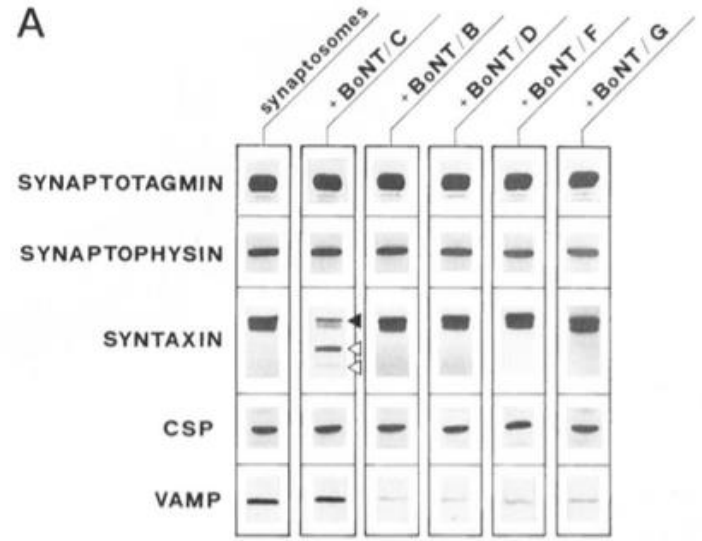
Botulinum Neurotoxin Type C Cleaves a Single Lys-Ala Bond within the Carboxyl-terminal Region of Syntaxins*

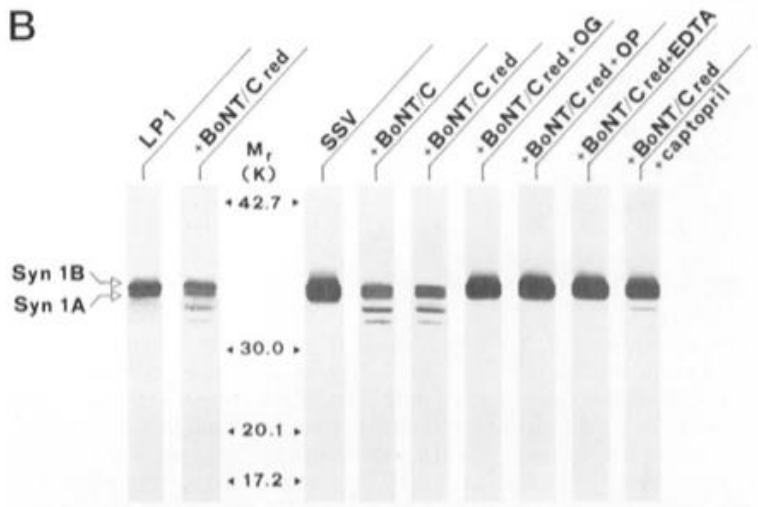
Schiavo G. et al 1995

Le forbicine nascono così!!!









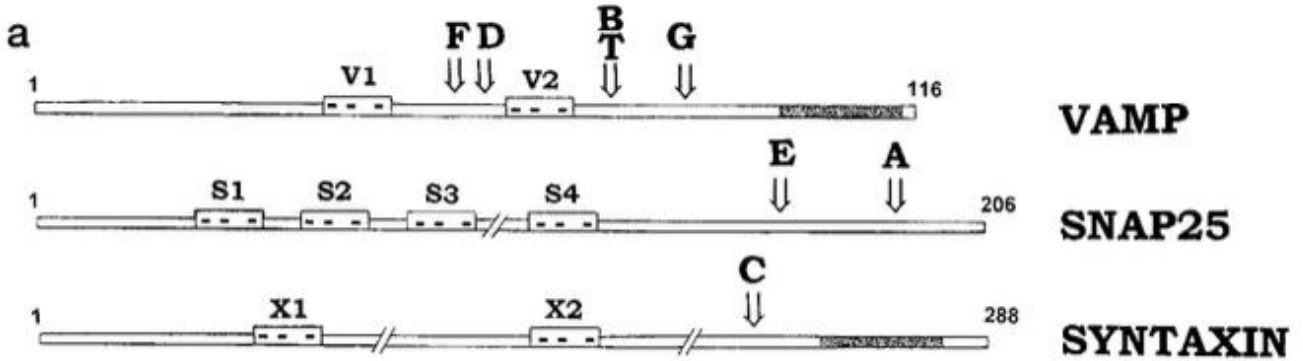
THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 271, No. 34, Issue of August 23, pp. 20353–20358, 1996
Printed in U.S.A.

Structural Determinants of the Specificity for Synaptic Vesicle-associated Membrane Protein/Synaptobrevin of Tetanus and Botulinum Type B and G Neurotoxins*

(Received for publication, February 29, 1996, and in revised form, May 21, 1996)

Rossella Pellizzari‡, Ornella Rossetto‡, Luisa Lozzi§, Silvia Giovedi'‡, Eric Johnson¶, Clifford C. Shone‖, and Cesare Montecucco‡**

Le forbicine nascono così!!!



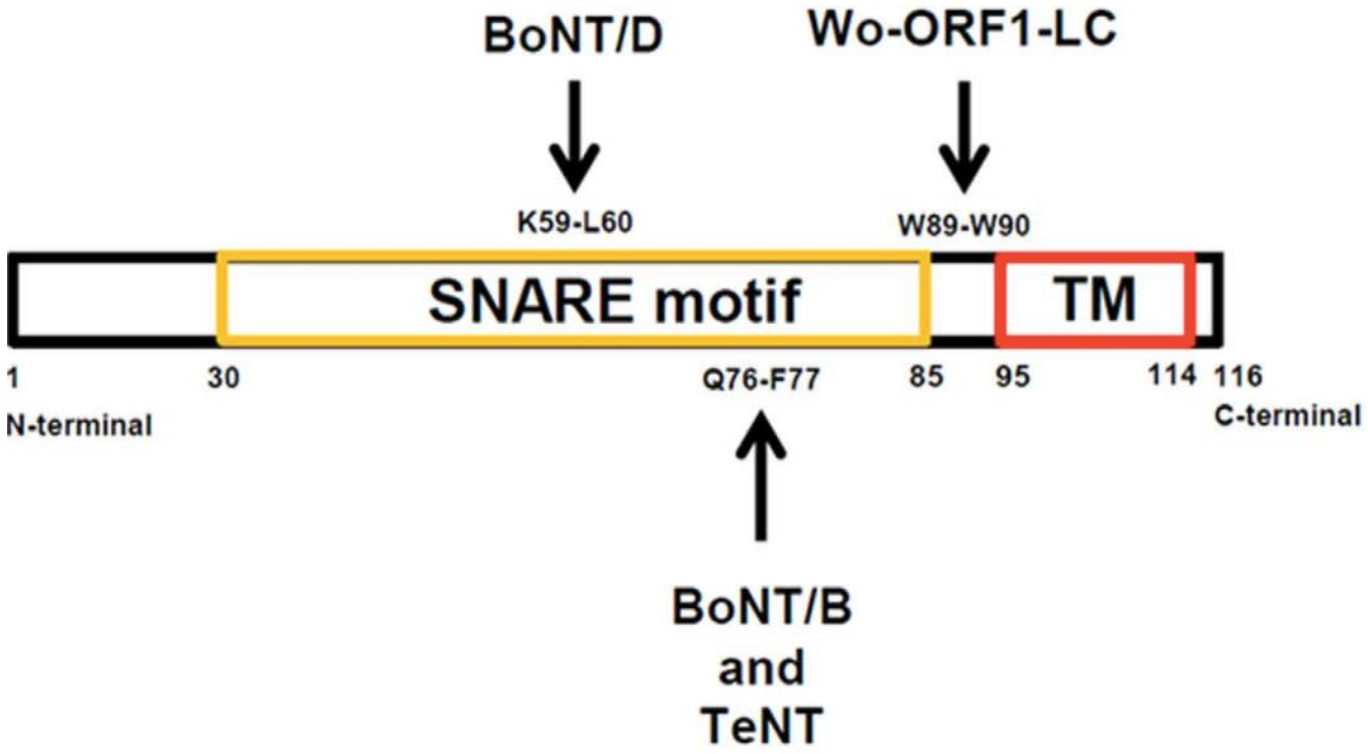
b

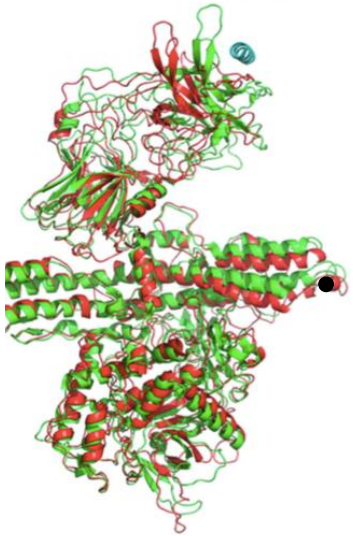
V1	38Q	V	D	E	V	V	D	I	M	R 47
V2	62E	L	D	D	R	A	D	A	L	Q 71
S1	21L	A	D	E	S	L	E	S	T	R 30
S2	35L	V	E	E	S	K	D	A	G	I 44
S3	49M	L	D	E	Q	G	E	Q	L	E 58
S4	145E	M	D	E	N	L	E	Q	V	S 154
X1	29F	M	D	E	F	F	E	Q	V	E 38
X2	164E	L	E	D	M	M	L	E	S	G 173

x	h	-	-	x	h	-	x	h	p

The first non Clostridial botulinum-like toxin cleaves VAMP within the juxtamembrane domain

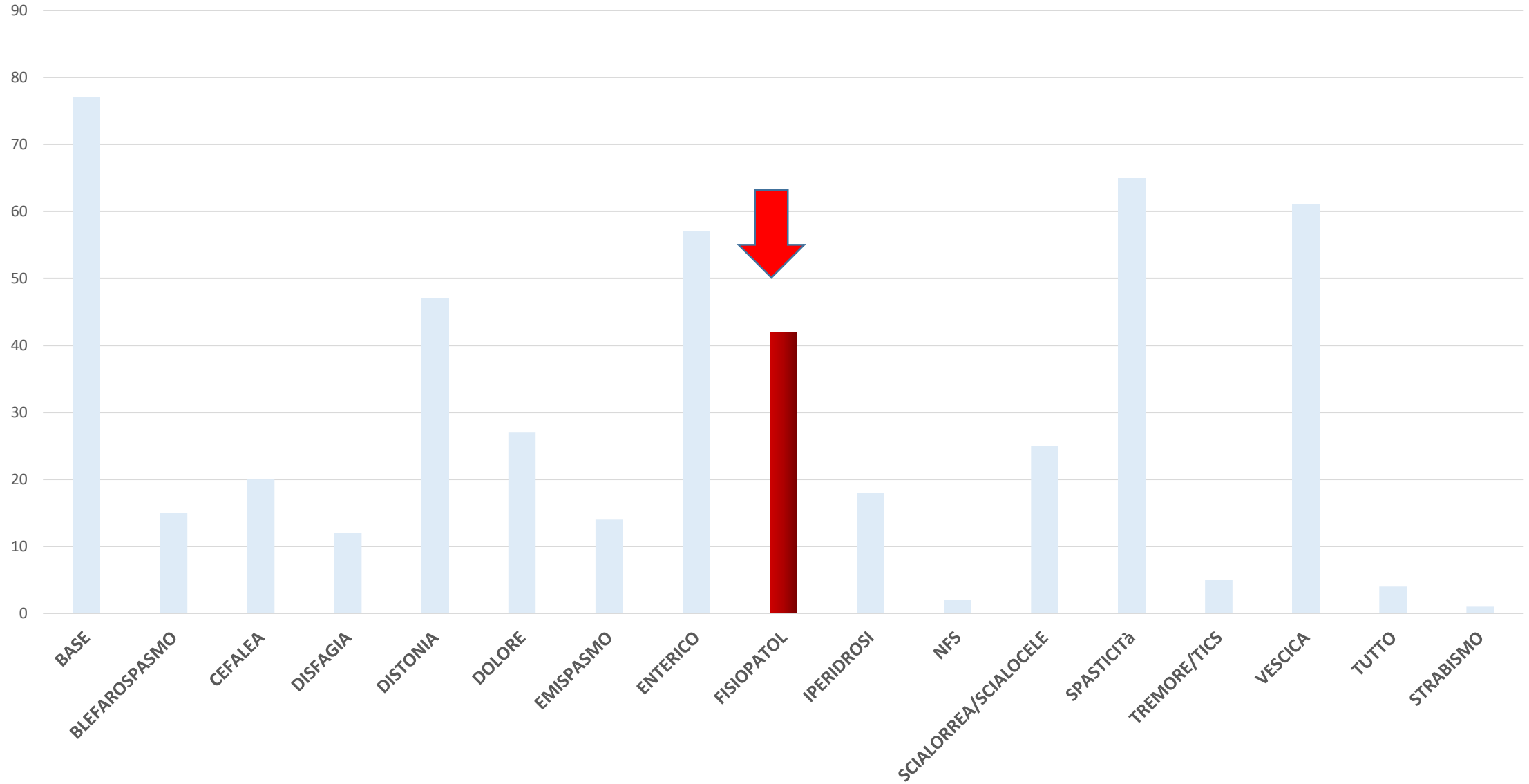
Irene Zornetta[1,*], Domenico Azarnia Tehran[1,*], Giorgio Arrigoni[1,2,*], Fabrizio Anniballi[3], Luca Bano[4], Oneda Leka[1], Giuseppe Zanotti[1], Thomas Binz[5] & Cesare Montecucco[1]





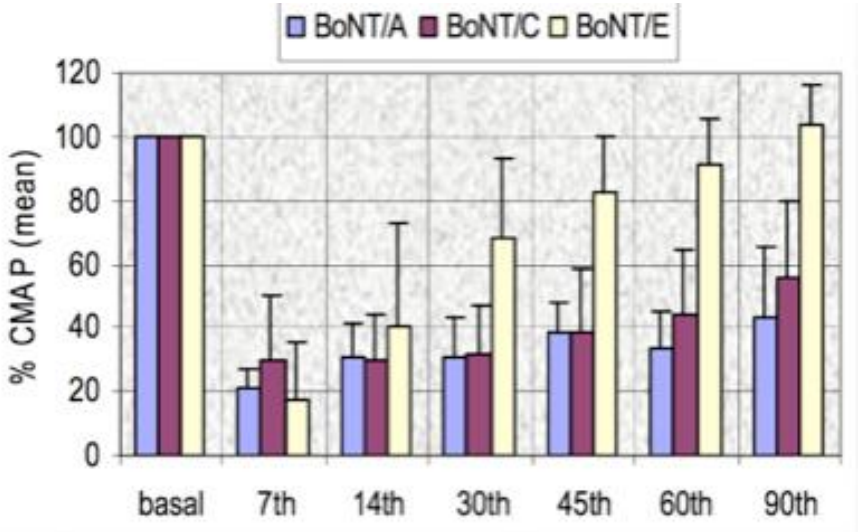
- We found that the purified *Weissella* metalloprotease cleaves VAMP at a single site untouched by the other VAMP-specific BoNTs.
- This site is a unique Trp-Trp peptide bond located within the juxtamembrane segment of VAMP which is essential for neurotransmitter release.
- the first non-Clostridial BoNT-like metalloprotease that cleaves VAMP at a novel and relevant site and we propose to label it BoNT/Wo.

BoNT → ARGOMENTI TRATTATI



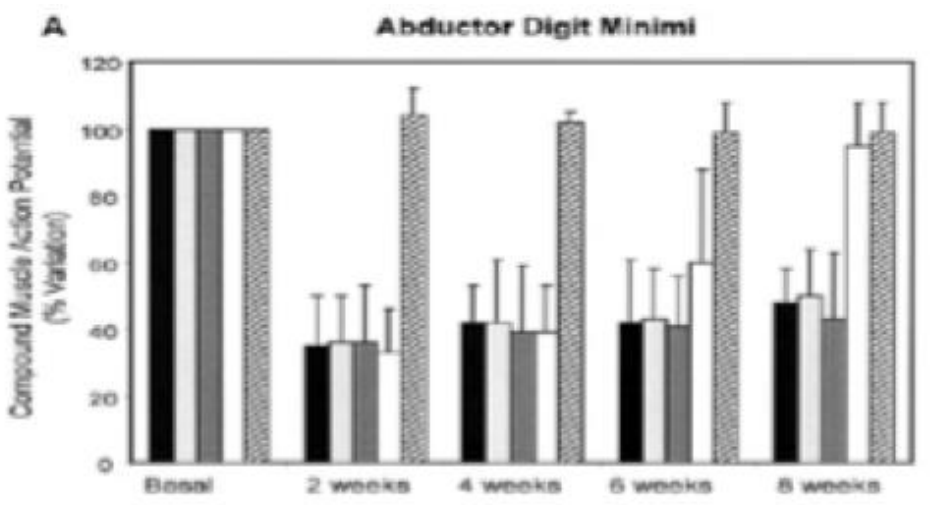
Different time course of recovery after poisoning with botulinum neurotoxin serotypes A and E in human. Eleopra, R., Tugnoli, V., Rossetto, O., De Grandis, D., Montecucco, C. (1998) Neurosci. Lett. 256 (3), 135–138S

- cMAP m.EDB



- cMAP m.ADM

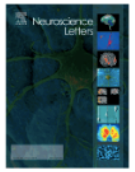
Eleopra et al 2004



ELSEVIER

Neuroscience Letters

Volume 224, Issue 2, 14 March 1997, Pages 91-94



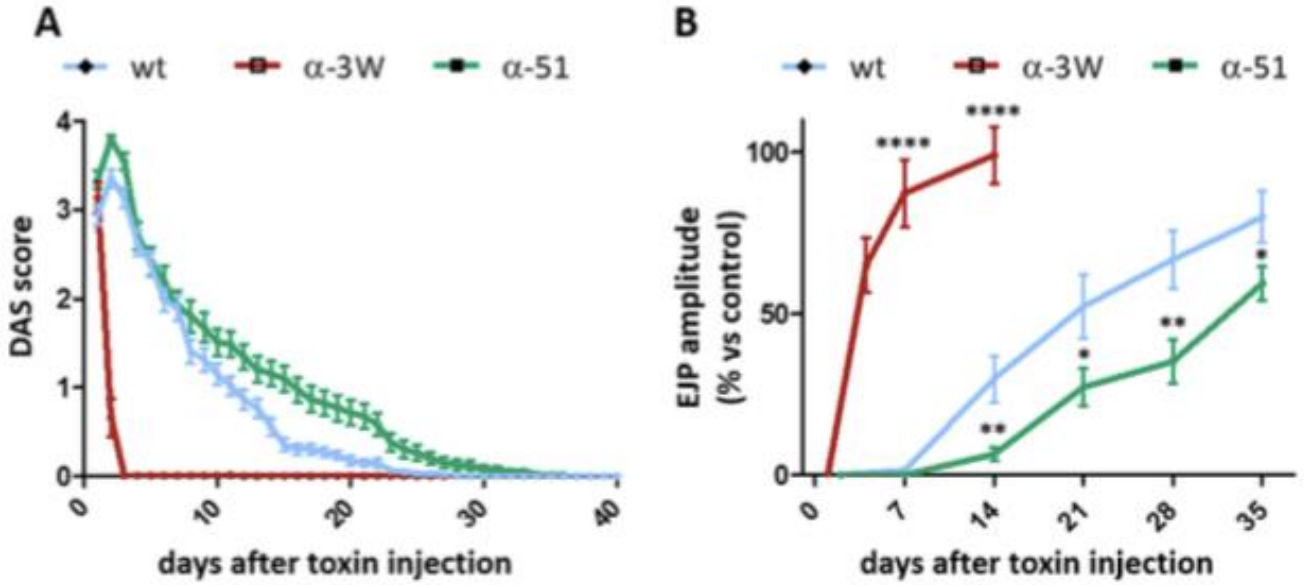
Botulinum neurotoxin serotype C: a novel effective botulinum toxin therapy in human

Roberto Eleopraa, Valeria Tugnolia, Ornella Rossettob, Cesare Montecuccob, Domenico De Grandisa

Diverse Tossine

Botulinum neurotoxin C mutants reveal different effects of syntaxin or SNAP-25 proteolysis on neuromuscular transmissio

Giulia Zanetti[1], Stefan Sikorra[2], Andreas Rummel[3], Nadja Krez[3], Elisa Duregotti[1], Samuele Negro[1], Tina Henke[2], Ornella Rossetto[1], Thomas Binz[2], Marco Pirazzini[1]*



- Two **triple mutants** of BoNT/C, namely **BoNT/C α-51** and **BoNT/C α-3W,** were reported to selectively cleave **syntaxin** + **SNAP-25**, although to a lesser extent than wild type BoNT/C
- Local injection of BoNT/C α-51 persistently impairs neuromuscular junction activity: initial phase in which SNAP-25 cleavage causes a complete blockade of neurotransmission; second phase of incomplete impairment ascribable to syntaxin cleavage.
- In light of this evidence → A possible clinical use of **BoNT/C α-51** as a botulinum neurotoxin endowed with a **wide safety margin and a long lasting effect.**

Botulinum toxin therapy: distant effects on neuromuscular transmission and autonomic nervous system

(*J Neurol Neurosurg Psychiatry* 1992;55:844–845)

Paolo Girlanda, Giuseppe Vita, Carmelo Nicolosi, Sonia Milone, Corrado Messina

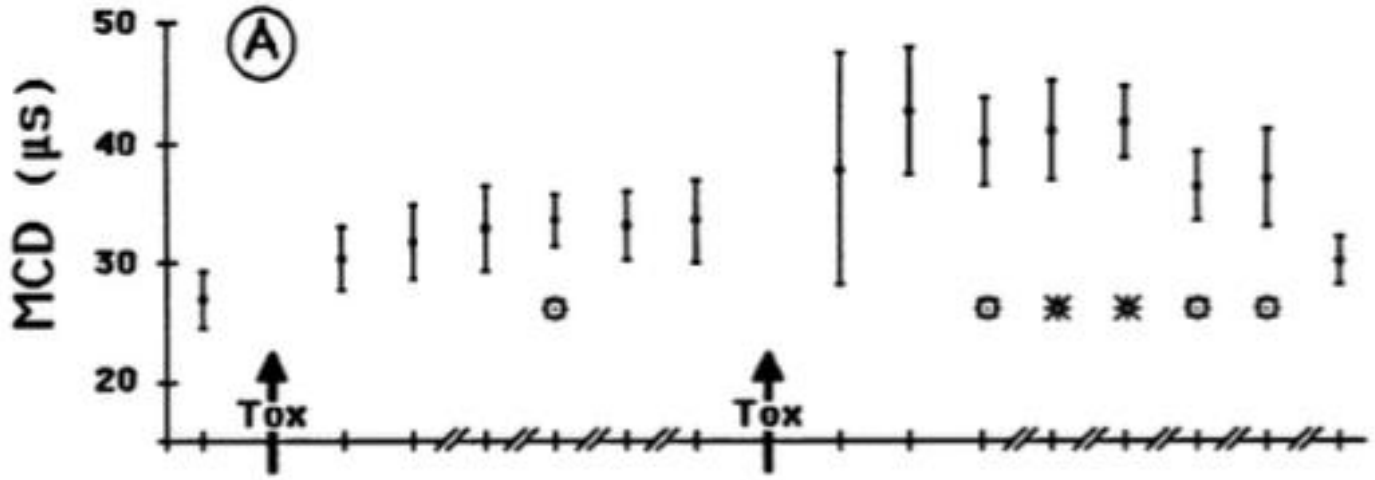
Movement Disorders
Vol. 11, No. 1, 1996, pp. 27–31

Unilateral Injection of Botulinum Toxin in Blepharospasm: Single Fiber Electromyography and Blink Reflex Study

P. Girlanda, A. Quartarone, S. Sinicropi, C. Nicolosi, and C. Messina

- 3 pts blepharospasm, 1 hemifacial spasm (20 U), 1 spasmodic torticollis (65 U)
- mild abnormalities in cardiovascular reflexes
- Jitter, fiber density

Diffusione



Neurology®

April 01, 1996; 46 (4) BRIEF COMMUNICATION

Botulinum toxin treatment in the facial muscles of humans

Evidence of an action in untreated near muscles by peripheral local diffusion

Roberto Eleopra, Valeria Tugnoli, Luisa Caniatti and Domenico De Grandis

Neurotoxicity Research, 2006, VOL. 9(2,3). pp. 141-144

No Clinical or Neurophysiological Evidence of Botulinum Toxin Diffusion to Non-Injected Muscles in Patients with Hemifacial Spasm

C. LORENZANO, S. BAGNATO, F. GILIO, G. FABBRINI and A. BERARDELLI*

Long-Distance Retrograde Effects of Botulinum Neurotoxin A

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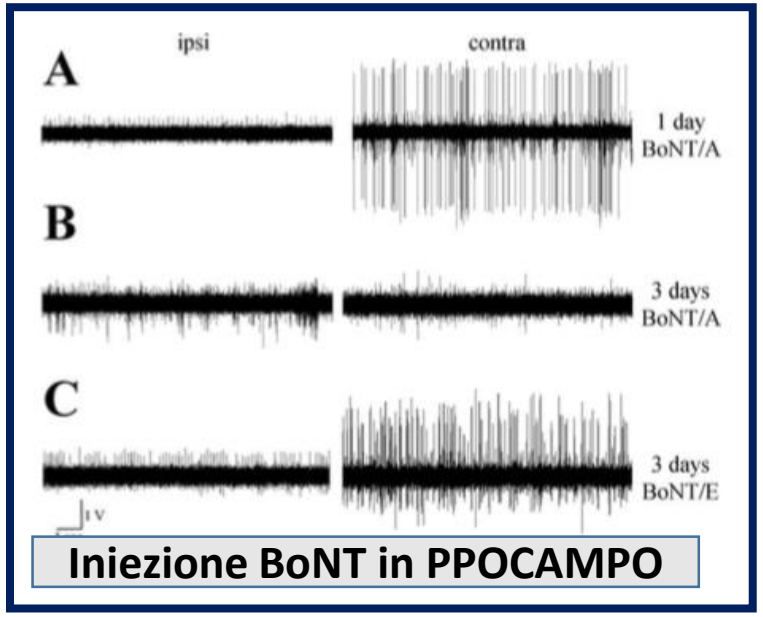
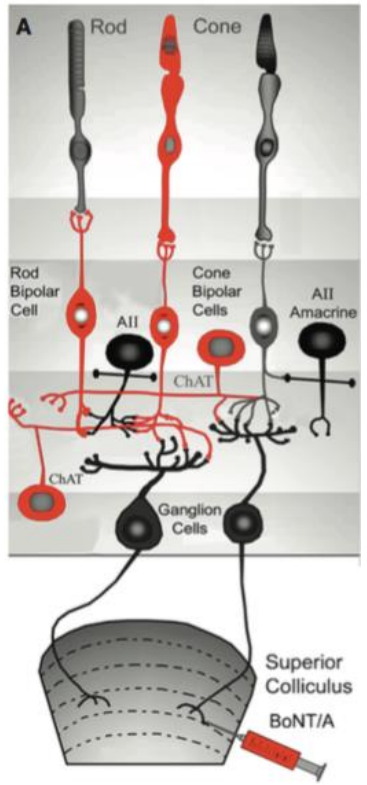
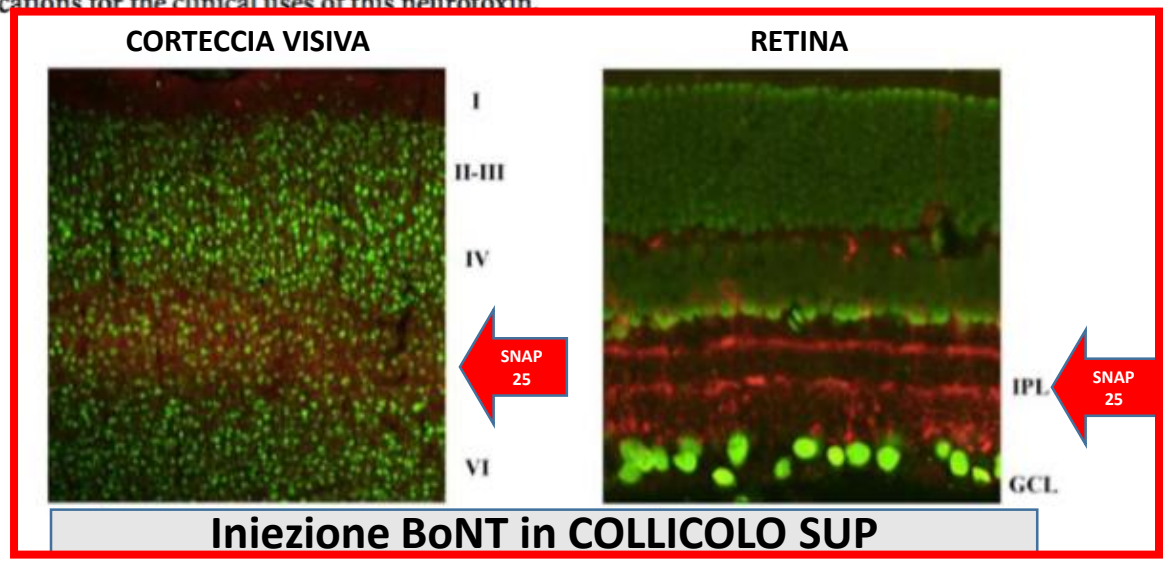
Botulinum neurotoxins (designated BoNT/A–BoNT/G) are bacterial enzymes that block neurotransmitter release by cleaving essential components of the vesicle fusion machinery. BoNT/A, which cleaves SNAP-25 (synaptosomal-associated protein of 25 kDa), is extensively exploited in clinical medicine to treat neuromuscular pathologies, facial wrinkles, and various types of pain. It is widely assumed that BoNT/A remains at the synaptic terminal and its effects are confined to the injection site. Here we demonstrate that catalytically active BoNT/A is retrogradely transported by central neurons and motoneurons and is then transcytosed to afferent synapses, in which it cleaves SNAP-25. SNAP-25 cleavage by BoNT/A was observed in the contralateral hemisphere after unilateral BoNT/A delivery to the hippocampus. Appearance of cleaved SNAP-25 resulted in blockade of hippocampal activity in the untreated hemisphere. Injections of BoNT/A into the optic tectum led to the appearance of BoNT/A-truncated SNAP-25 in synaptic terminals within the retina. Cleaved SNAP-25 also appeared in the facial nucleus after injection of the toxin into rat whisker muscles. Experiments excluded passive spread of the toxin and demonstrated axonal migration and neuronal transcytosis of BoNT/A. These findings reveal a novel pathway of BoNT/A trafficking in neurons and have important implications for the clinical uses of this neurotoxin.



Iniezione BoNT in PPOCAMPO



- Trasporto retrogrado
- Transcitosi



Iniezione BoNT in COLLICOLO SUP

MUSCLE
&NERVE

ABSTRACT: Botulinum neurotoxin type-A (BoNT/A) is very effective in the therapy of a wide range of human syndromes characterized by hyperactivity of peripheral cholinergic nerve terminals. Little diffusion of this toxin from the site of injection is commonly observed, but even minor changes in this property would greatly affect the validity of the treatment. Different pharmacological formulations of BoNT/A are available, and they may have different diffusion characteristics due to protein complex size, product format, and pharmacological properties. Here we assessed the extent of diffusion of three commercial preparations of BoNT/A: Botox (Allergan), Dysport (Ipsen), and Xeomin (Merz Pharmaceuticals) using a novel and highly sensitive test based on neural cell adhesion molecule (N-CAM) expression in muscle. N-CAM is a membrane glycoprotein that accumulates on muscle fibers after denervation and is not expressed in untreated adult muscle. This allows fine monitoring of the functional diffusion of this toxin, and the sensitivity of this assay is emphasized by the use of the mouse model because of the small muscle dimensions. The results presented here indicate that there is no significant difference between Botox, Dysport, and Xeomin with respect to diffusion into adjacent muscles in the mouse leg.

Muscle Nerve **40:** 374–380, 2009

ASSAY OF DIFFUSION OF DIFFERENT BOTULINUM NEUROTOXIN TYPE A FORMULATIONS INJECTED IN THE MOUSE LEG

LUCA CARLI, PhD, CESARE MONTECUCCO, FP, and ORNELLA ROSSETTO, PhD

Azione Periferica

ELSEVIER

Clinical Neurophysiology

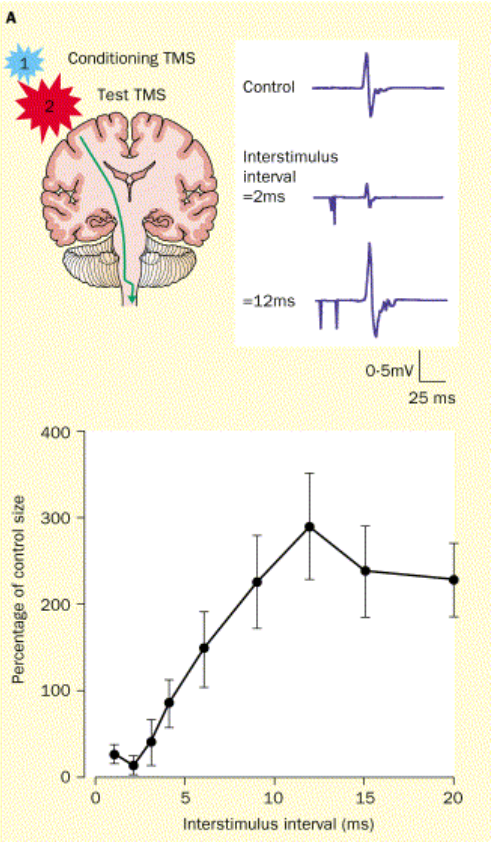
Volume 113, Issue 8, August 2002, Pages 1258-1264

Botulinum neurotoxin serotypes A and C do not affect motor units survival in humans: an electrophysiological study by motor units counting

Roberto Eleopra [a], Valeria Tugnoli [a], Rocco Quatrale [a], Ernesto Gastaldo [a], Ornella Rossetto [b], Domenico De Grandis [c], Cesare Montecucco [b]

Azione Centrale

- **Reciprocal inhibition**. Normalisation of the abnormal late phase of in patients with dystonia and essential tremor
  - Priori et al, 1995
  - Modugno et al, 1999
- Botulinum toxin changes intrafusal feedback in dystonia: a study with the **tonic vibration reflex**
  - Trompetto C et al 2006
- Effects of botulinum toxin type A on **intracortical inhibition** in patients with dystonia
  - Gilio F et al 2000



Effetti sistemici

- ***Spasticità***

Eur Neurol 2004;51:181–183
DOI: 10.1159/000077670

Acute Neuromuscular Failure Related to Long-Term Botulinum Toxin Therapy

Mario Coletti Moja[a], Ugo Dimanico[a], Tiziana Mongini[b], Valentina Cavaciocchi[a], Pier Carlo Gerbino Promis[a],

- ***Iperidrosi***

BJD British Journal of Dermatology
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Botulism-like syndrome after botulinum toxin type A injections for focal hyperhidrosis

V. Tugnoli, R. Eleopra, R. Quatrale, J.G. Capone, M. Sensi, E. Gastaldo

First published: 4 October 2002 Full publication history

Movement Disorders
Official Journal of the International Parkinson and Movement Disorder Society
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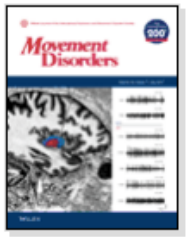
Article

The variability in the clinical effect induced by botulinum toxin type A: The role of muscle activity in humans

Dr. R. Eleopra ✉, V. Tugnoli, D. de Grandis

First published: January 1997 Full publication history

DOI: 10.1002/mds.870120115 View/save citation



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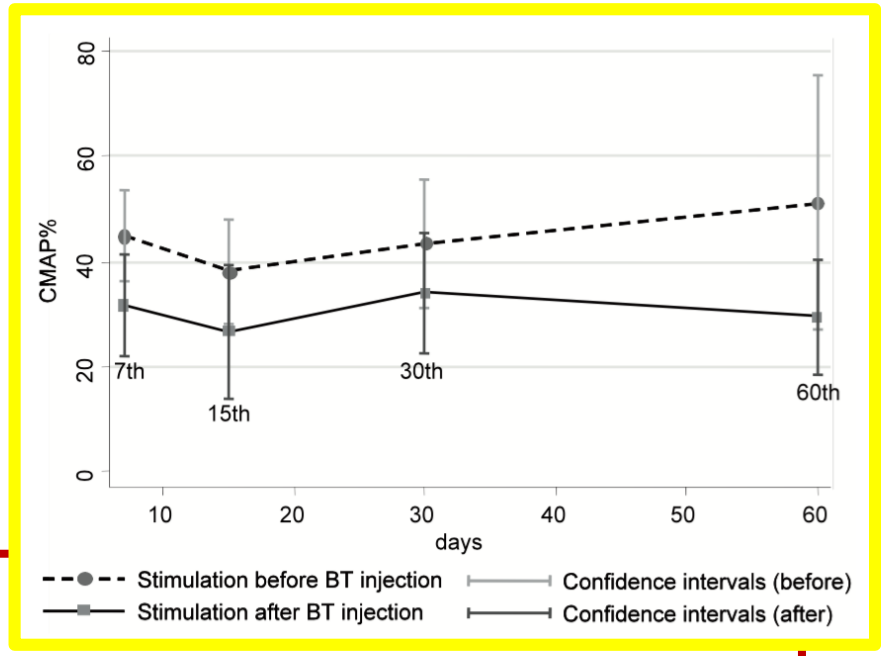
Volume 12, Issue 1
January 1997
Pages 89–94



J Rehabil Med 2011; 43: 420–423

ORIGINAL REPORT

EFFECT OF SHORT-TERM ELECTRICAL STIMULATION BEFORE AND AFTER BOTULINUM TOXIN INJECTION

Gianna Santus, MD[1], Sofia Faletti, MD[1], Ingrid Bordanzi, MD[1], Francesco Pirali, MD[2] and Domenico De Grandis, MD[1]

European Journal of Neurology 2010, **17:** 449–455

Electrical activation of the orbicularis oculi muscle does not increase the effectiveness of botulinum toxin type A in patients with blepharospasm

A. Conte[a,b], G. Fabbrini[a,b], D. Belvisi[a], L. Marsili[a], F. Di Stasio[a] and A. Berardelli[a,b]

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Ruolo dell'attività

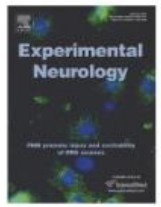
BoNT/E prevents seizure-induced activation of caspase 3 in the rat hippocampus

Manno, Ilaria; Antonucci, Flavia; Caleo, Matteo; Bozzi, Yuri

NeuroReport: April 16th, 2007 - Volume 18 - Issue 6 - p 577-580

Experimental Neurology

Volume 210, Issue 2, April 2008, Pages 388-401



Botulinum neurotoxin E (BoNT/E) reduces CA1 neuron loss and granule cell dispersion, with no effects on chronic seizures, in a mouse model of temporal lobe epilepsy

Flavia Antonucci [a], Angelo Di Garbo [b], Elena Novelli [c], Ilaria Manno [a, d], Ferdinando Sartucci [a, e], Yuri Bozzi [a] [1] ✉, Matteo Caleo [a] [1] ✉

CNR Pisa

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Manno et al. (2007) BoNT/E prevents seizure-induced activation of caspase 3 in the rat hippocampus. NeuroReport 18: 577-580.

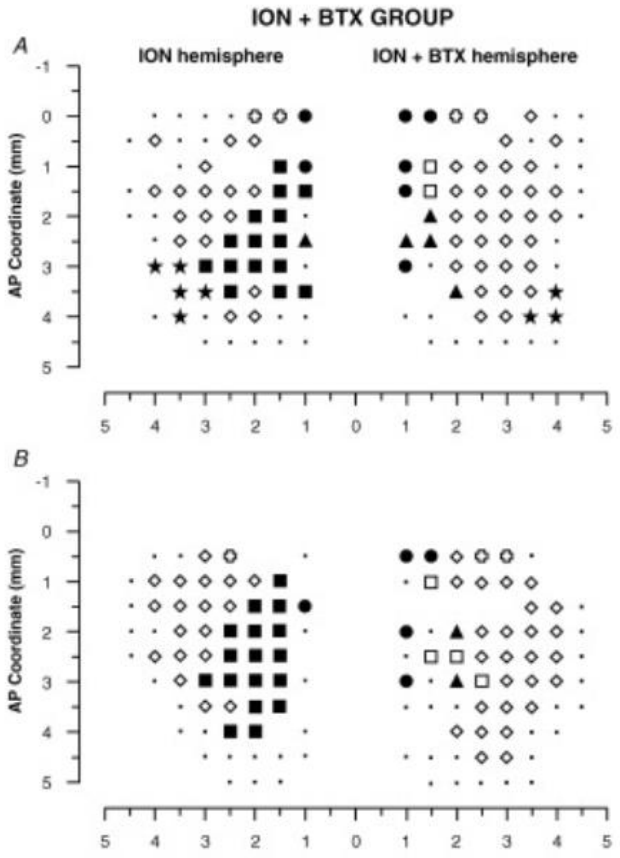
Toxins (Basel). 2015 Dec 8;7(12):5322-36. doi: 10.3390/toxins7124887.

Snake and Spider Toxins Induce a Rapid Recovery of Function of Botulinum Neurotoxin Paralysed Neuromuscular Junction.

Duregotti E[1], Zanetti G[2], Scorzeto M[3], Megighian A[4], Montecucco C[5,6], Pirazzini M[7], Rigoni M[8].

- Botulinum neurotoxins (BoNTs) and some animal neurotoxins (β-Bungarotoxin, β-Btx, from elapid snakes and α-Latrotoxin, α-Ltx, from black widow spiders) are pre-synaptic neurotoxins that paralyse motor axon terminals with similar clinical outcomes
- Their mechanism of action is different
- BoNTs induce a long-lasting paralysis without nerve terminal degeneration
- Animal neurotoxins cause an acute and complete degeneration of motor axon terminals, followed by a rapid recovery.
- The injection of animal neurotoxins in mice muscles previously paralyzed by BoNT/A or /B accelerates the recovery of neurotransmission
- By causing the complete degeneration, reabsorption, and regeneration of a paralysed nerve terminal, one could favour the recovery of function of motor axon terminal

Altered facial motor output leads to cortical reorganization



J Physiol 574.2 (2006) pp 457–476

Short-term reorganization of input-deprived motor vibrissae representation following motor disconnection in adult rats

Gianfranco Franchi and Carlo Veronesi

Dipartimento di Scienze Biomediche e Terapie Avanzate, Sezione di Fisiologia umana and Centro di Neuroscienze, Università di Ferrara, 44100 Ferrara, Italy

It has been proposed that abnormal vibrissae input to the motor cortex (M1) mediates short-term cortical reorganization after facial nerve lesion. To test this hypothesis, we cut first the infraorbital nerve (ION cut) and then the facial nerve (VII cut) in order to evaluate M1 reorganization without any aberrant, facial-nerve-lesion-induced sensory feedback. In each animal, M1 output was assessed in both hemispheres by mapping movements induced by intracortical microstimulation. M1 output was compared in different types of peripheral manipulations: (i) contralateral intact vibrissal pad (intact hemispheres), (ii) contralateral VII cut (VII hemispheres), (iii) contralateral ION cut (ION hemispheres), (iv) contralateral VII cut after contralateral ION cut (ION + VII hemispheres), (v) contralateral pad botulinum-toxin-injected after ION cut (ION + BTX hemispheres). Right and left hemispheres in untouched animals were the reference for normal M1 map (control hemispheres). Findings demonstrated that: (1) in ION hemispheres, the mean size of the vibrissae representation was not significantly different from those in intact and control hemispheres; (2) reorganization of the vibrissae movement representation clearly emerged only in hemispheres where the contralateral vibrissae pad had undergone motor output disconnection (VII cut hemispheres); (3) the persistent loss of vibrissae input did not change the M1 reorganization pattern during the first 48 h after motor paralysis (ION + VII cut and ION + BTX hemispheres). Thus, after motor paralysis, vibrissa input does not provide the gating signal necessary to trigger M1 reorganization.

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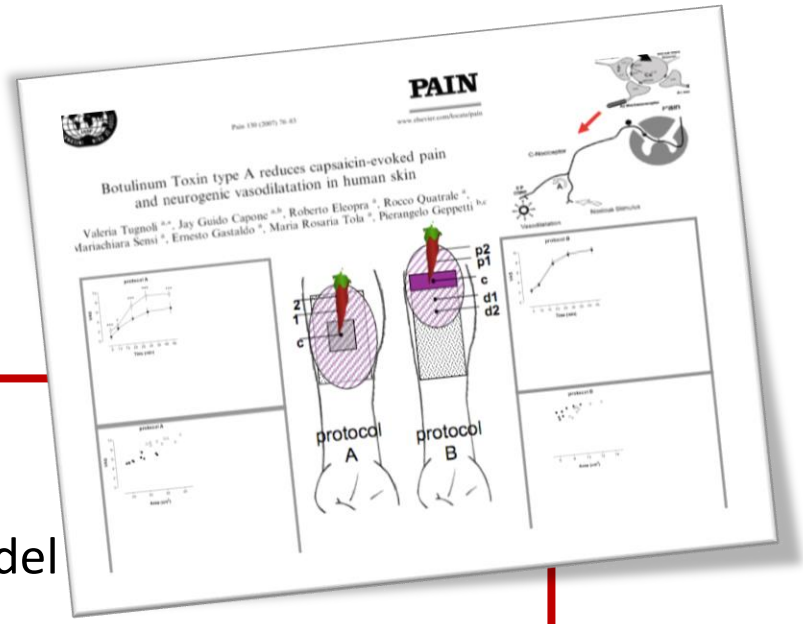
BoNT and Pain



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