

# **BOTULINUM TOXIN**

## **MECHANISMS OF ACTION**

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**Germany**

**structure**

**molecular mechanisms of action**

**action on striate muscles**

**action on the spinal stretch reflex**

**action on the autonomic nervous system**

**action on the central nervous system**

**action on pain**

# BOTULINUM TOXIN STRUCTURE

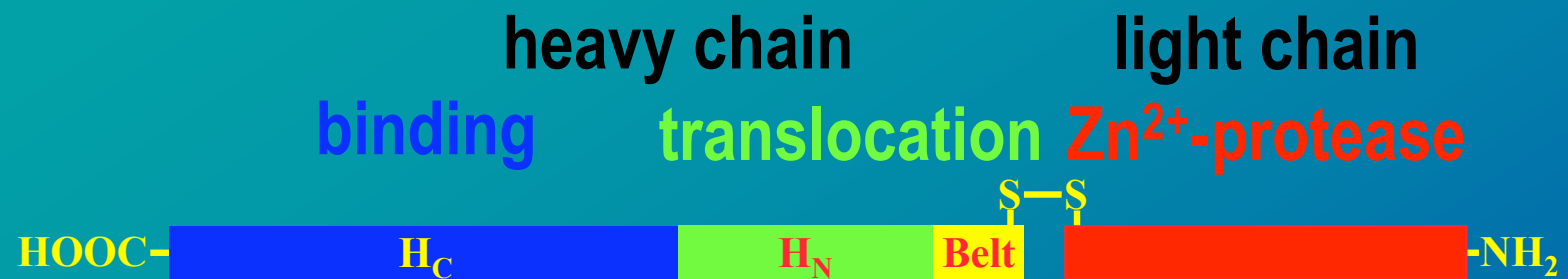
# BOTULINUM NEUROTOXIN AMINOACID SEQUENCE

M-P-F-V-N-K-Q-F-N-Y-K-D-P-V-N-G-V-D-I-A-Y-I-K-I-P-N-A-G-Q-M-Q-P-V-K-A-F-K-I-H-N-K-I-W-V-I-P-E-R-D-T- (50)  
F-T-N-P-E-E-G-D-L-N-P-P-P-E-A-K-Q-V-P-V-S-Y-Y-D-S-T-Y-L-S-T-D-N-E-K-D-N-Y-L-K-G-V-T-K-L-F-E-R-I-Y-S- (100)  
T-D-L-G-R-M-L-L-T-S-I-V-R-G-I-P-F-W-G-G-S-T-I-D-T-E-L-K-V-I-D-T-N-C-I-N-V-I-Q-P-D-G-S-Y-R-S-E-E-L-N- (150)  
L-V-I-I-G-P-S-A-D-I-I-Q-F-E-C-K-S-F-G-H-E-V-L-N-L-T-R-N-G-Y-G-S-T-Q-Y-I-R-F-S-P-D-F-T-F-G-F-E-E-S-L- (200)  
E-V-D-T-N-P-L-L-G-A-G-K-F-A-T-D-P-A-V-T-L-A-H-E-L-I-H-A-G-H-R-L-Y-G-I-A-I-N-P-N-R-V-F-K-V-N-T-N-A-Y- (250)  
Y-E-M-S-G-L-E-V-S-F-E-E-L-R-T-F-G-G-H-D-A-K-F-I-D-S-L-Q-E-N-E-F-R-L-Y-Y-N-K-F-K-D-I-A-S-T-L-N-K-A- (300)  
K-S-I-V-G-T-T-A-S-L-Q-Y-M-K-N-V-F-K-E-K-Y-L-L-S-E-D-T-S-G-K-F-S-V-D-K-L-K-F-D-K-L-Y-K-M-L-T-E-I-Y-T- (350)  
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G-F-H-Q-F-N-N-I-A-K-L-V-A-S-N-W-Y-N-R-Q-I-E-R-S-S-R-T-L-G-C-S-W-E-F-I-P-V-D-D-G-W-G-E-R-P-L\* (1296)

Dressler D: Botulinum Toxin Therapy

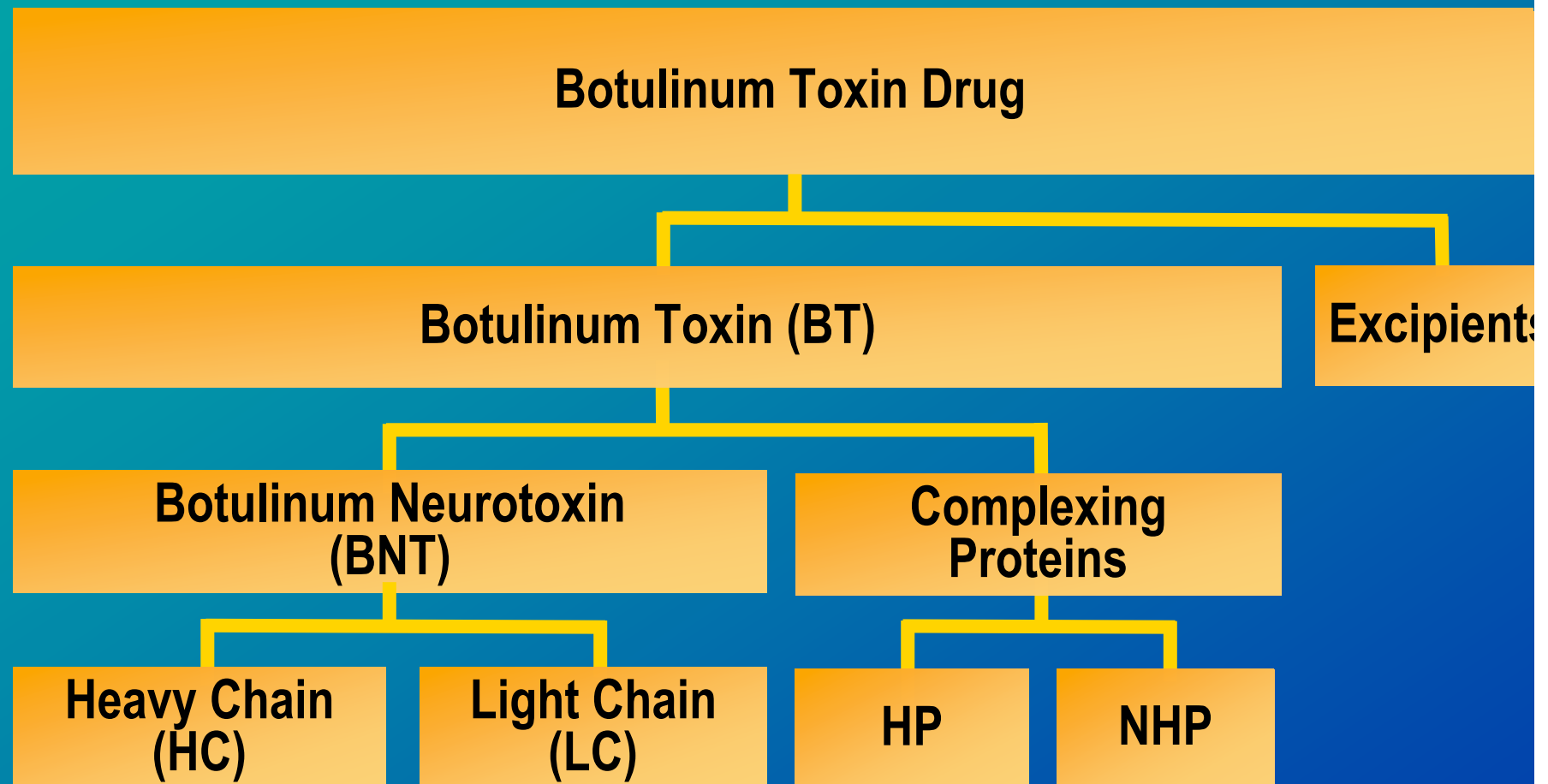
Thieme, Stuttgart, 2000

# BOTULINUM TOXIN 3D STRUCTURE



# BOTULINUM TOXIN

## CONTENT OF THERAPEUTIC PREPARATIONS



# BOTULINUM TOXIN

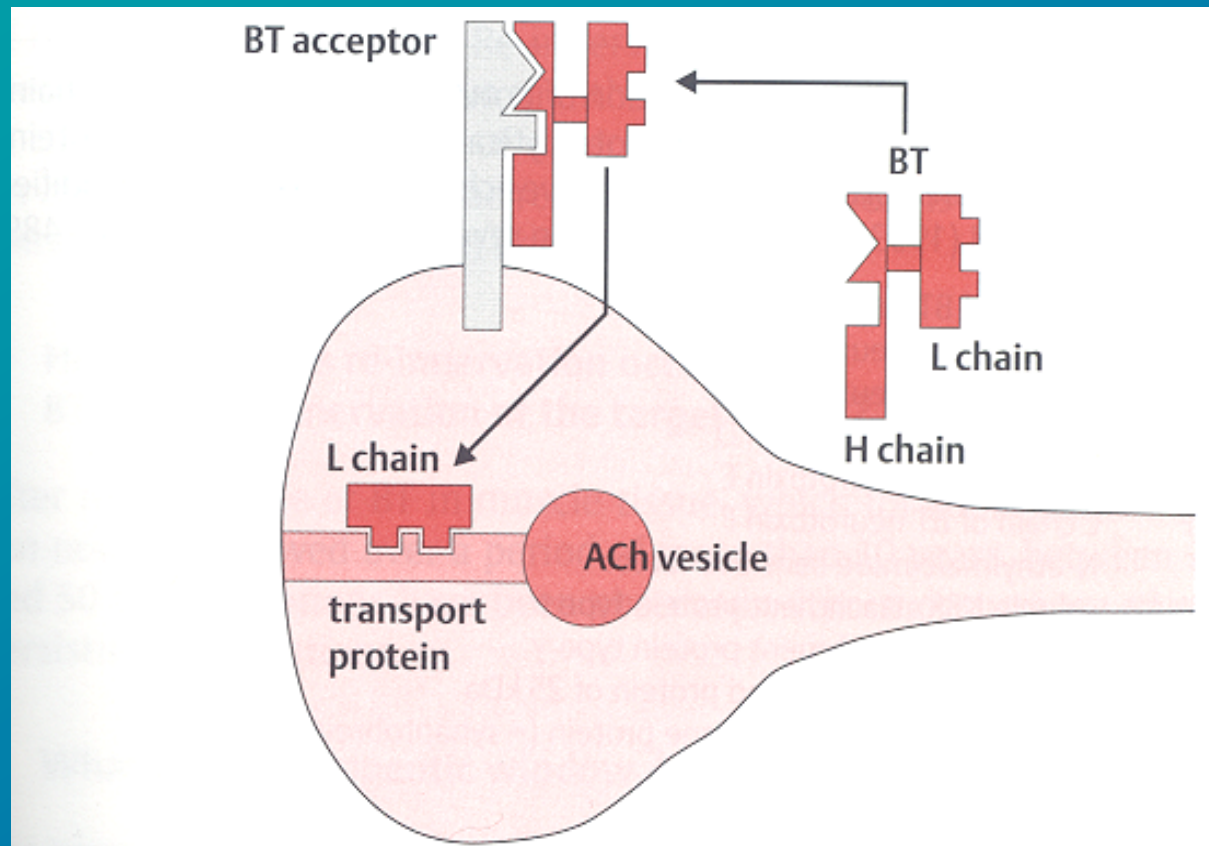
## MOLECULAR MECHANISMS

### OF ACTION

# BOTULINUM TOXIN

## MOLECULAR MECHANISMS OF ACTION

### EXTRACELLULAR



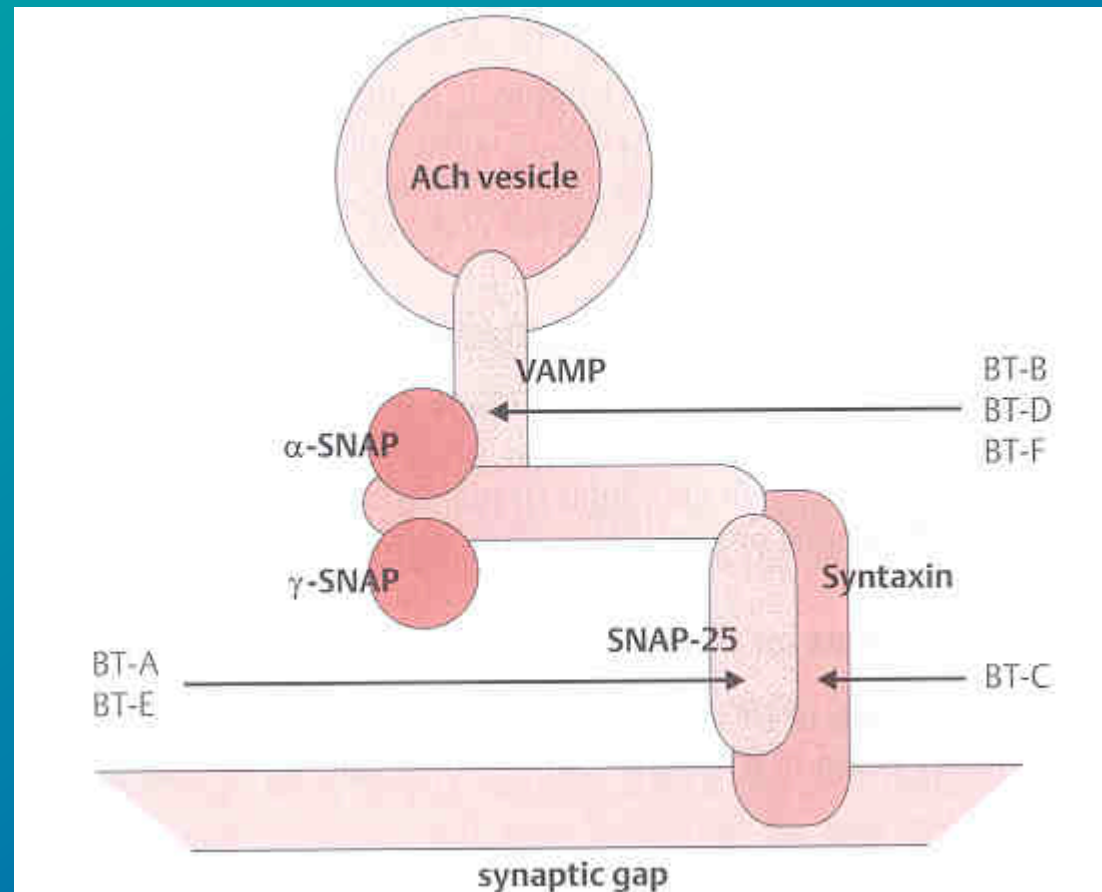
Dressler D: Botulinum Toxin Therapy  
Thieme, Stuttgart, 2000



# BOTULINUM TOXIN

## MOLECULAR MECHANISMS OF ACTION

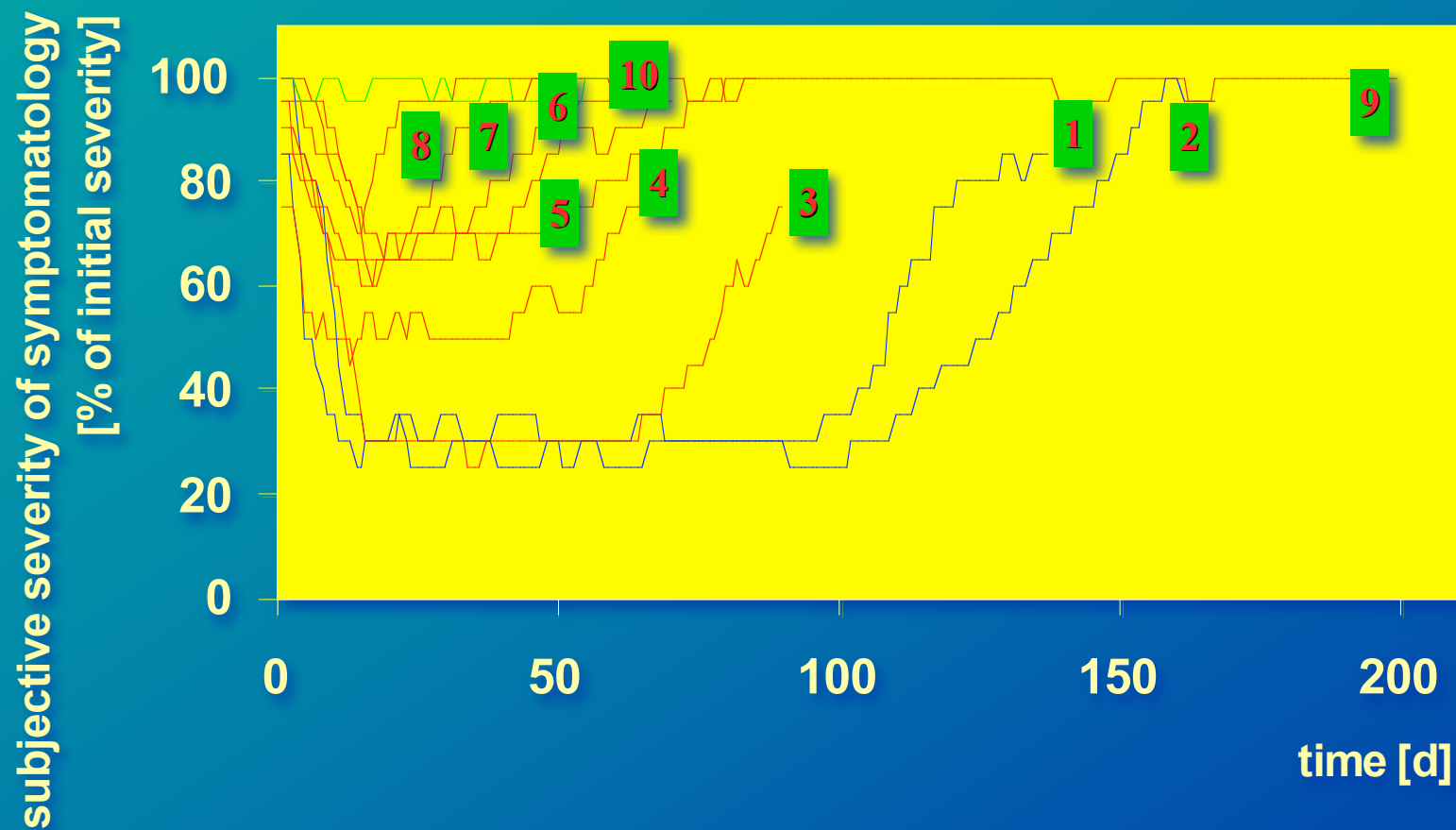
### INTRACELLULAR



# **BOTULINUM TOXIN**

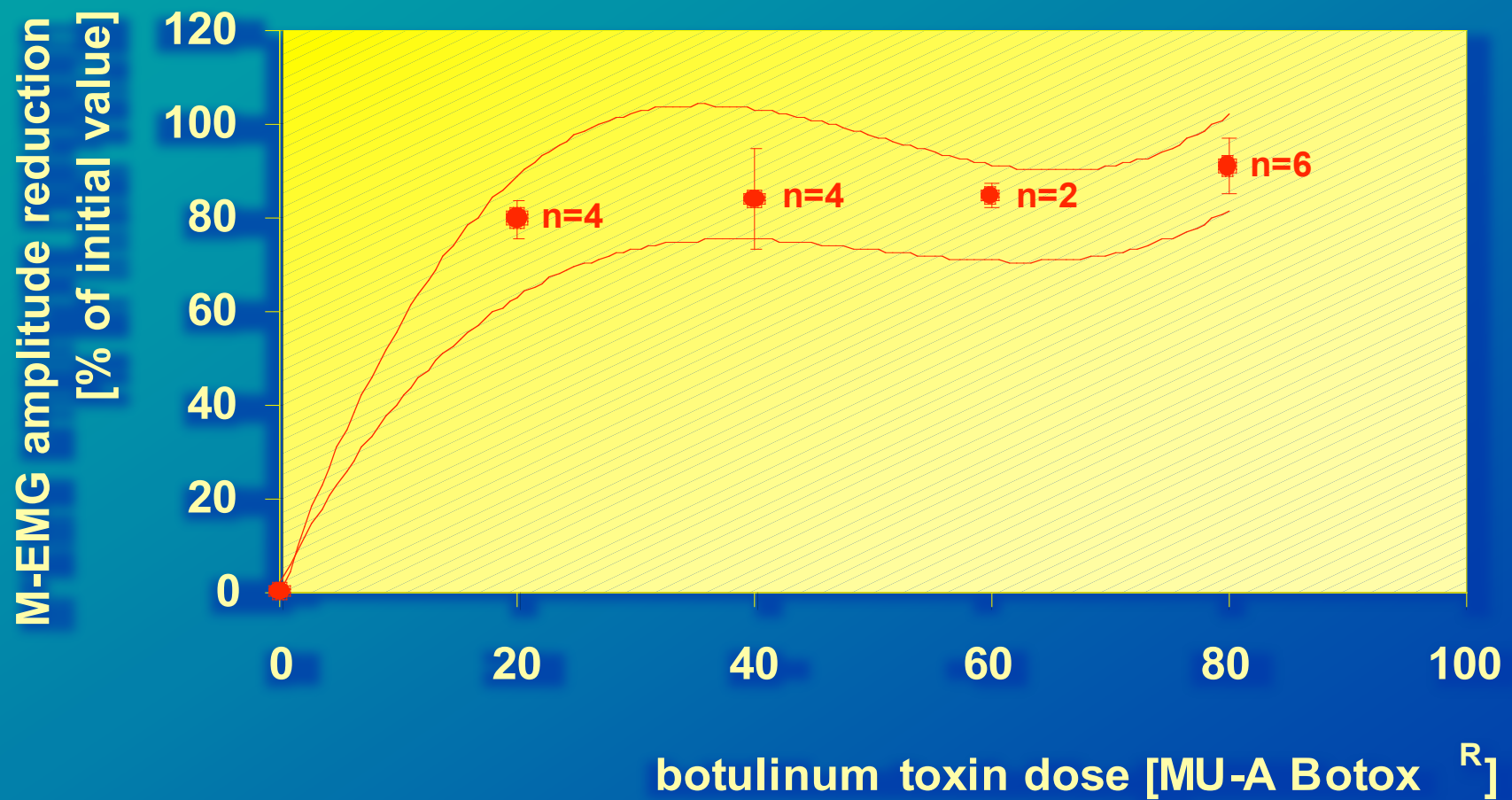
## **ACTION ON STRIATE MUSCLES**

# BOTULINUM TOXIN ACTION ON STRIATE MUSCLES DURATION OF ACTION

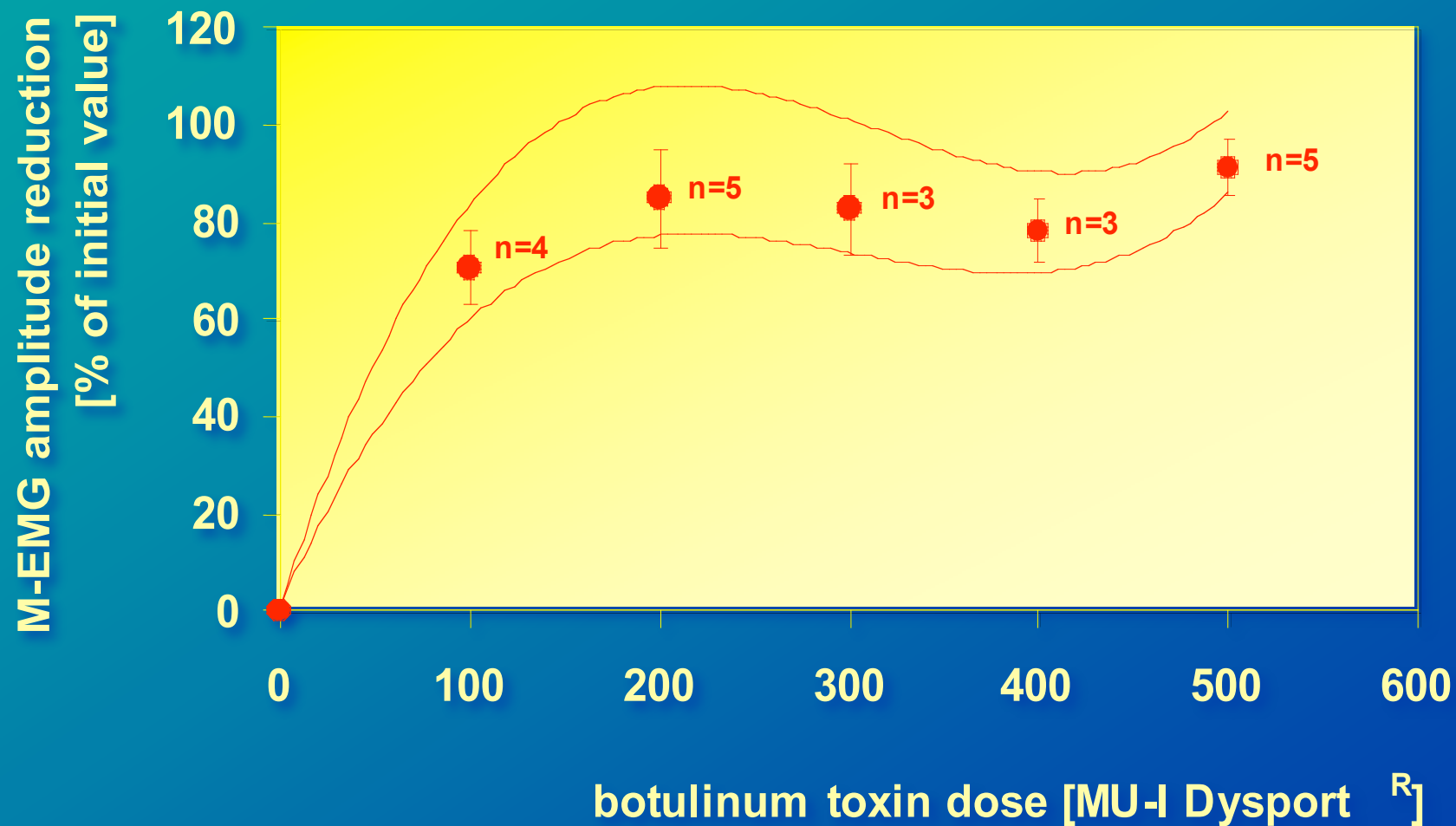


cervical dystonia  
complete secondary therapy failure

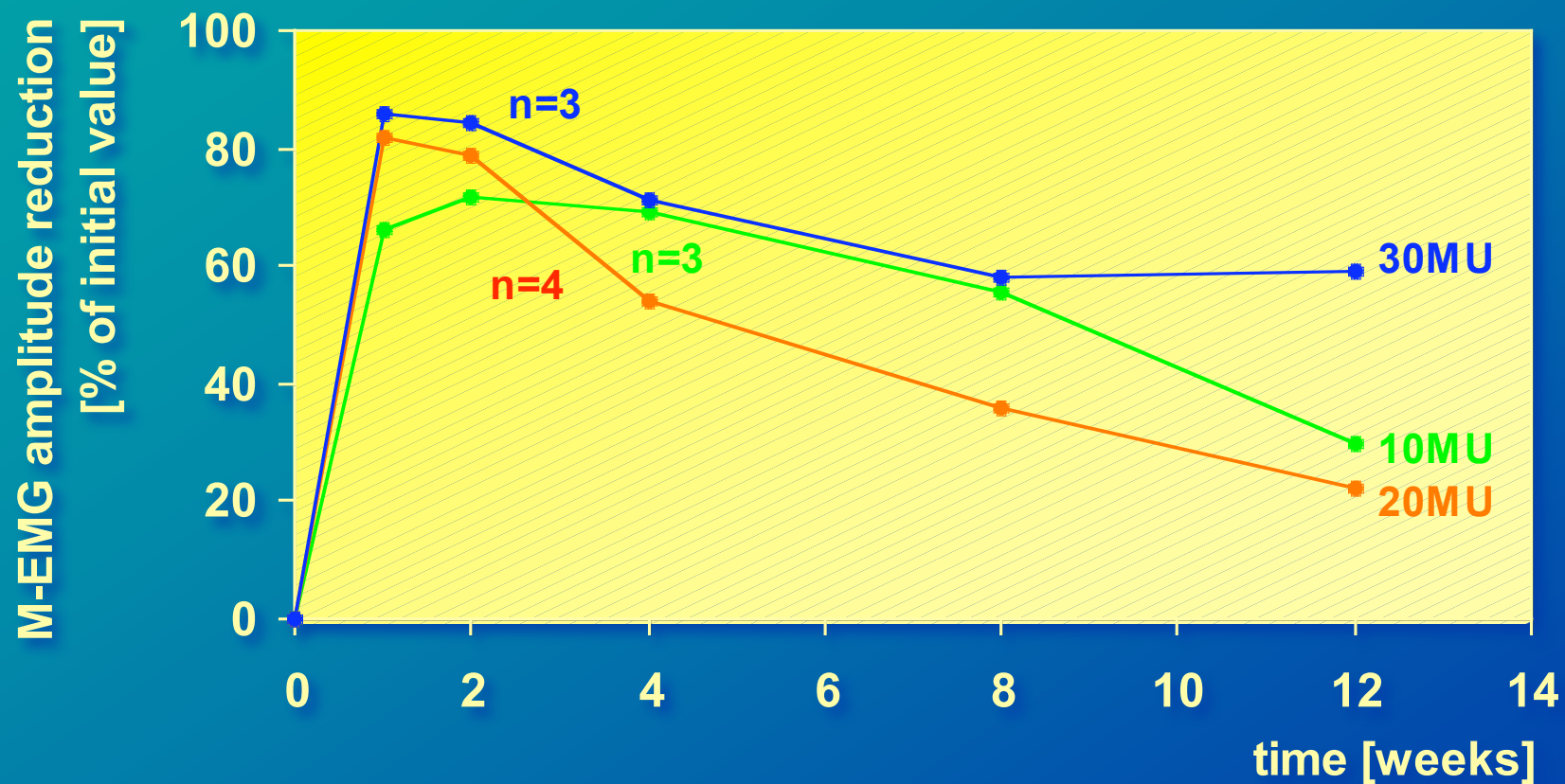
# BOTULINUM TOXIN ACTION ON STRIATE MUSCLES DOSE-EFFECT CORRELATION/BOTOX<sup>®</sup>



# BOTULINUM TOXIN ACTION ON STRIATE MUSCLES DOSE-EFFECT CORRELATION/DYSPORT®



# BOTULINUM TOXIN ACTION ON STRIATE MUSCLES DOSE-DURATION CORRELATION



# BOTULINUM TOXIN

## ACTION ON STRIATE MUSCLES

### MUSCLE ATROPHY

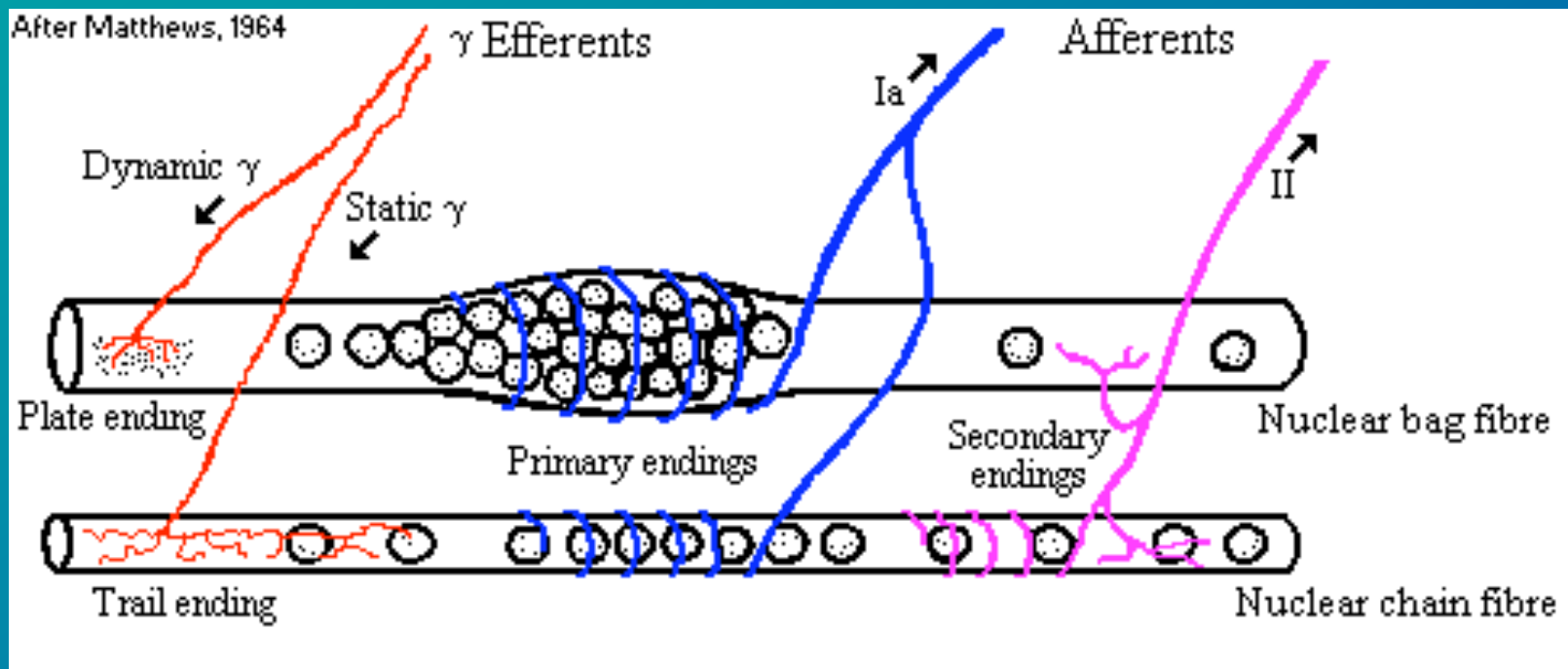
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**muscle diameter reduction due to paresis**  
**normalisation in hypertrophy possible**  
**hypotrophy possible**

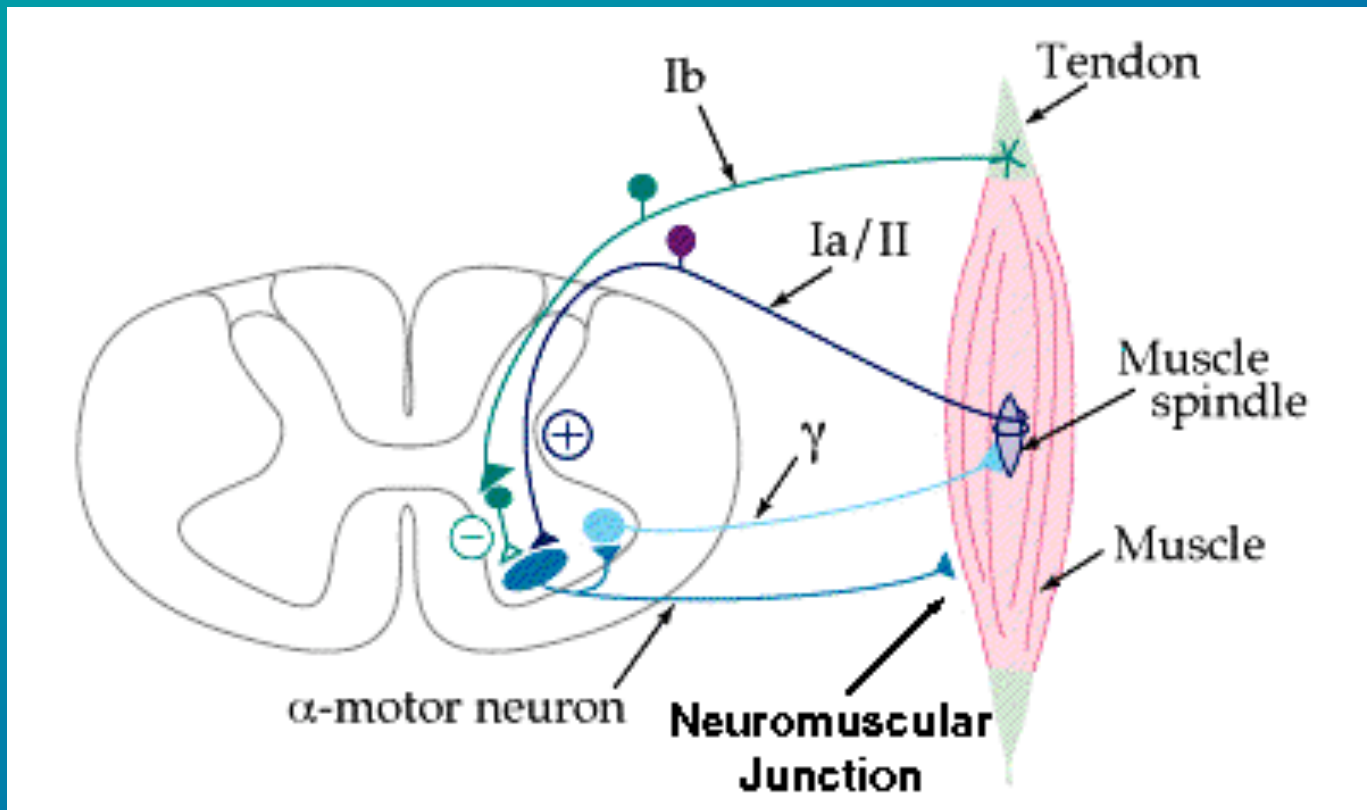
# **BOTULINUM TOXIN ACTION ON THE SPINAL STRETCH REFLEX**



# BOTULINUM TOXIN ACTION ON THE SPINAL STRETCH REFLEX MUSCLE SPINDLE ORGANS



# BOTULINUM TOXIN ACTION ON THE SPINAL STRETCH REFLEX PATHWAYS



# Ia/II MUSCLE SPINDLE AFFERENCES AND DYSTONIA

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**feedback mechanisms in laryngeal dystonia**

**Ludlow et al. 1990, Zwirner et al. 1992**

**vibration increases writer's cramp**

**Kaji et al. 1995**

**muscle afferent block improves writer's cramp  
and oromandibular dystonia**

**Kaji et al. 1995**

# BOTULINUM TOXIN

## ACTION ON THE SPINAL STRETCH REFLEX

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**muscle spindle organ**

**atrophy (Rosales et al. 1996)**

**blockade of gamma activation (Rosales et al. 1996)**

**reduction of muscle spindle Ia/II output**

**'reflex inhibition'**

**(Filippi et al. 1993, Rosales et al. 1996)**

**golgi tendon organ**

**?**

# **BOTULINUM TOXIN ACTION ON THE AUTONOMIC NERVOUS SYSTEM**

# BOTULINUM TOXIN

## ACTION ON THE AUTONOMIC NERVOUS SYSTEM

### SMOOTH MUSCLES I

distal oesophageal sphincter

sphincter ani internus

detrusor vesicae

sphincter Oдии

achalasia

AE: heart burn

anal fissures

anismus

prostate pain

detrusor overactivity

AE: voiding difficulties

sphincter Oдии dysfunction

# BOTULINUM TOXIN

## ACTION ON THE AUTONOMIC NERVOUS SYSTEM

### SMOOTH MUSCLES II

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pylorus

internal eye muscles

bowel muscles

arterioles

gastroparesis

obesity?

**AE: accommodation difficulties**

**AE: constipation**

**Raynaud phenomenon**

# BOTULINUM TOXIN

## ACTION ON THE AUTONOMIC NERVOUS SYSTEM

### EXOCRINE GLANDS

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**sweat glands**

**hyperhidrosis**

**gustatory sweating**

**lacrimal glands**

**crocodile tears**

**idiopathic hyperlacrimation**

**AE: dryness of eye**

**salivary glands**

**relative hypersalivation in**

**Parkinson's disease**

**motoneuron disease**

**paretic dysphagia**

**AE: dryness of mouth**

**prostate**

**prostate hyperplasia**



# BOTULINUM TOXIN

## ACTION ON THE AUTONOMIC NERVOUS SYSTEM

### OTHER TISSUES

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**mucosa**

**AE: dryness of mouth**

**fungal superinfection**

**heart**

**AE: heart rate variability ↓**

# BOTULINUM TOXIN

## ACTION ON THE AUTONOMIC NERVOUS SYSTEM

### MECHANISMS

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**cholinergic blockade of autonomic efferent fibres**  
similar to action on the striate neuromuscular junction  
**cholinergic blockade of autonomic afferent fibres?**

# **BOTULINUM TOXIN ACTION ON THE CENTRAL NERVOUS SYSTEM**

# BOTULINUM TOXIN

## ACTION ON THE CENTRAL NERVOUS SYSTEM

### DIRECT EFFECTS

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#### **systemic spread**

**low for BT-A (Takamizawa et al. 1987)**

**higher for BT-B (Dressler & Benecke 2003)**

**blood-brain-barrier unpermeable for BT**

#### **retrograde axonal transport**

**slow (Wiegand et al. 1976)**

**not transsynaptic (Wiegand et al. 1976)**

# BOTULINUM TOXIN

## ACTION ON THE CENTRAL NERVOUS SYSTEM

### INDIRECT EFFECTS

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**reflex inhibition** (Filippi et al. 1993, Rosales et al. 1996)

**BT-induced normalisation of abnormal reciprocal inhibition**  
**in upper limb dystonia** (Priori et al. 1995)

**BT-induced normalisation of abnormal intracortical inhibition**  
**(Gilio et al. 2000)**

**BT-induced normalisation of abnormal SEP** (Dressler et al.

# BOTULINUM TOXIN ACTION ON PAIN

# **BOTULINUM TOXIN ACTION ON PAIN PHENOMENA**

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**pain reduction in muscle hyperactivity syndromes  
effect of muscle relaxation?  
formalin pain reduction (Cui & Aoki 2000)  
no relationship to muscle relaxation**

# BOTULINUM TOXIN

## ACTION ON PAIN

### MECHANISM I

substance P release↓

rabbit iris muscles (Ishikawa et al. 2000)

rat dorsal root ganglia cells (Purkiss et al. 2000)

glutamate release↓

rat dorsal horn (Cui et al. 2002)

noradrenaline release↓

rat PC12 cells (Shone & Melling 1992)

calcitonin gene related peptide (CGRP) release↓

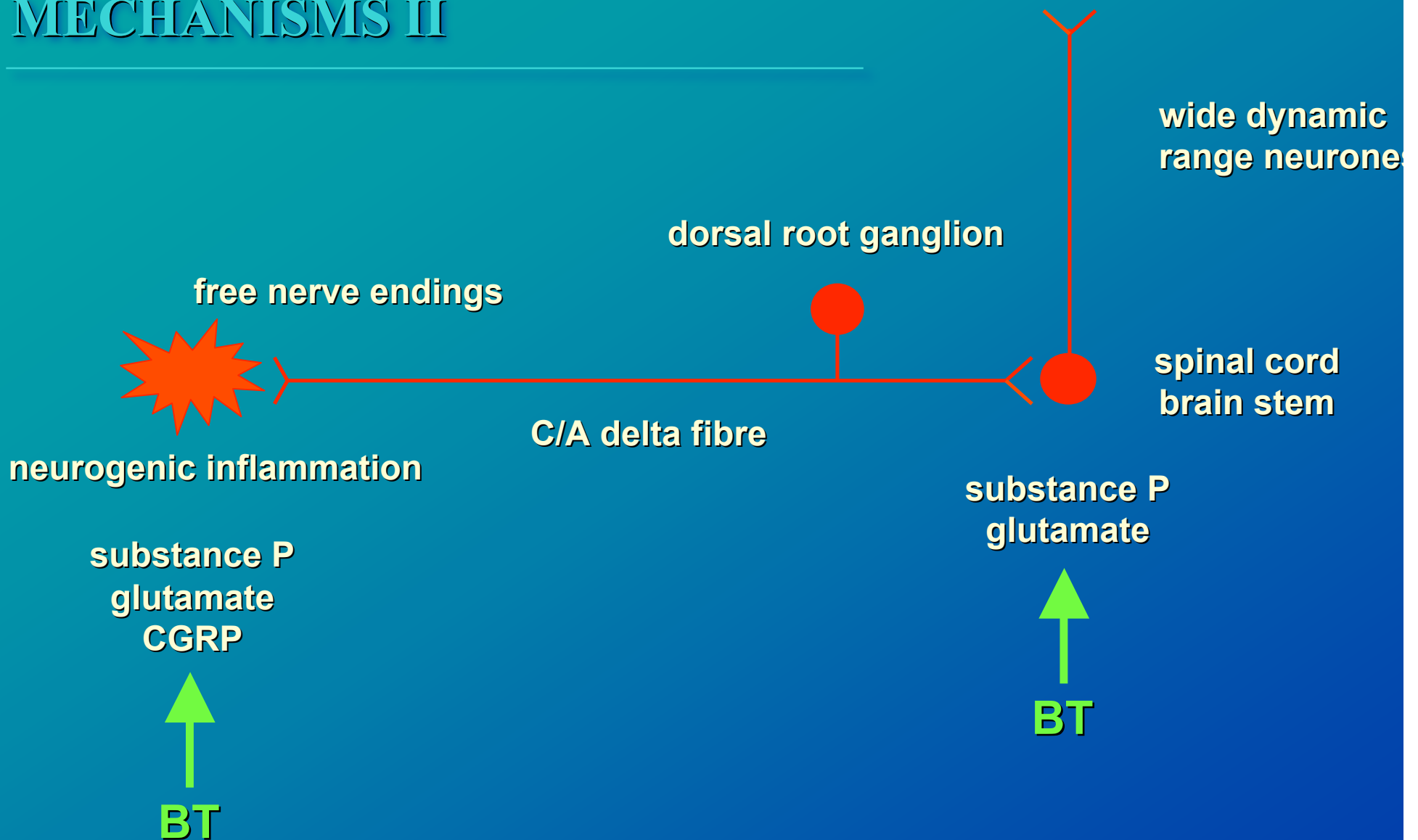
autonomic vascular nerve terminals (Morris et al. 2000)

reflex inhibition

analgetic effect?



# BOTULINUM TOXIN ACTION ON PAIN MECHANISMS II



# SUMMARY

# BOTULINUM TOXIN MECHANISMS OF ACTION SUMMARY

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**botulinum toxin acts on**

- **striate neuromuscular synapse**
- **autonomic efferent synapse**
- **the spinal stretch reflex**
- **the central nervous system (indirectly)**
  - stretch reflex inhibition**
  - normalisation of reciprocal inhibition**
  - normalisation of intracortical inhibition**
  - normalisation of SEP**
- **non-cholinergic transmitters**
  - analgetic effects?**

**END**