Botulinum toxin: mechanism of action

- Clinical benefits of botulinum toxin (BT) injections depend primarily on the toxin's peripheral action
- General assumption is that effects of BT remain localized to the injection site
- Degree of muscle paralysis depends on BT dosage

**However... observations from clinical practice**

- BT peripheral action depends also on the state of the injected muscle - BT is preferentially uptaken by the most active muscle fibers "autofocusing"
- Remote effects in the non-injected muscles
- Clinical benefit may be out of proportion of BT induced weakness
- No or loss of clinical benefit despite weakness of injected muscles
- Long-term effect of BT

**CENTRAL ACTION OF BT?**

Possible mechanisms for central action of BT

1. Reduction of Ia afferent input
   - Changes in reciprocal inhibition
   - Changes in excitability and sensormotor integration at cortical level
2. Retrograde transport to the spinal cord and transcytosis to other neurons
3. Changes in gene expression in α motoneuron
4. Hematogeneous spread (unlikely)

From Caleo M. et al. 2009

BT peripheral action depends on the state of the injected muscle

- Animal experiments suggest that the toxin is preferentially taken up by the most active muscle fibers "autofocusing" (Hughes and Whaler, 1962)
- In hemi facial spasm, injections of BT to OO muscle: moderate muscle paralysis, but complete loss of ephaptic response (Glocker, 1995) → preferential uptake of BT by hyperactive synapses involved in ephaptic transmission

- Injection of BT in both EDB: the effect of the induced neuromuscular blockade was greater on the side that received peripheral nerve stimulation (Eleopra, 1997)
BT peripheral action depends on the state of the injected muscle-dystonia

However...

- Electrical activation of OD does not improve effectiveness of BT in blepharospasm (Conte, 2010): calling effect?

Remote effects in the non-injected muscles

- When BT was injected to one side in patients with blepharospasm (Girlada, 1996)
  - Clinical benefit was bilateral
  - CMAP and SFEMG changes were present on both sides

- In adductor spasmodic dysphonia with unilateral thyroarytenoid muscle injections of BT-A (Bielamowicz and Ludlow, 2000)
  - EMG bursts were reduced bilaterally (thus also in the non-injected muscles)
  - Improvement in speech symptoms as a result of changes in a central pathophysiological mechanism?

Clinical benefit out of proportion of weakness- central effect of BT

BT peripheral action depends on the state of the injected muscle-spasticity

- Nerve stimulation improve BT effect in spastic paraparesis (Frasson, 2005)

Central effect of BT- effect on inhibition
Central effect of BT - effect on intracortical inhibition

- Healthy controls
- Dystonia before BT
- Dystonia 1 month after BT
- Dystonia 3 months after BT

Adapted from Gilio, 2000

DYSTONIA – PATHOPYSIOLOGY

ABNORMAL (ENHANCED) CORTICAL PLASTICITY

- Patients with primary dystonia have enhanced response to different experimental plasticity protocols (Quartarone, 2003; Quartarone, 2008).
- Focal limb dystonia is typically triggered by a period of intensive training of a particular movement - a clinical feature that may link the role of maladaptive plasticity to development of dystonic symptoms.
- In monkey, overtraining in specific hand movements trigger the symptoms that resemble human dystonia (Byl, 1996).
- The idea is that overtraining itself triggers functional changes in sensory and motor cortices, leading to abnormal sensorimotor integration that somehow results in dystonic symptoms.

Central effect of BT - effect on cortical plasticity as assessed by motor mapping studies with TMS

- The corticomotor representation of upper limb muscles in writer’s cramp are distorted and displaced, but this can be temporarily reversed following botulinum toxin injection (Byrnes, 1998)
- Reversible reorganisation of corticomotor representation of the hand in cervical dystonia (Thickbroom, 2003)

Sensorimotor cortical plasticity as assessed by PAS protocol

Paired Associative Stimulation – PAS

Stefan, 2000

Sensorimotor cortical plasticity in dystonia, as assessed by PAS protocol

- In susceptible individuals an excessive tendency to form association between sensory input and motor output may lead to dystonia (musician’s dystonia, writer’s cramp)

Kojović, 2011

Central effect of BT - effect on sensorimotor cortical plasticity in dystonia

BT injections reduce response to PAS in parallel with clinical improvement - contribution to clinical benefit?

(Quartarone, 2003; Weise, 2006; Edwards 2006)
Central effect of BT- effect on sensorimotor cortical plasticity in dystonia

- The longer was the time elapsed since the last injection -> the more pronounced was the rPAS response

Central effect of BT- effect on SSEPs in dystonia and spasticity

- Cervical dystonia: reduction in the amplitude of P22/N30 precentral component after treatment with BT + in parallel with clinical improvement (Kanowsky, 1998) changes in cortical excitability secondary to BT induced modulation of spindle afferent input
- But in writer’s cramp: no changes in cortical SSEPs before and after BT treatment (Contarino, 2007)
- Spasticity: An improvement of cortical SEPs associated with reduction of spasticity in cerebral palsy (Park, 2002; Frascarelli, 2011)

Loss of clinical benefit despite weakness of injected muscles

- Some patient with CD report return of symptoms at the time when injected muscles are still paralysed (Gelb, 1989)
- In some patients there is no clinical improvement despite EMG detected changes in muscle activity pattern after BT injections (Gelb, 1991)
- Loss of clinical benefit in patients who were initially good responders

ABNORMAL NECK POSTURE PRODUCED BY ACTIVITY OF DIFFERENT MUSCLES??

Loss of clinical benefit despite weakness of injected muscles

- ADVANTAGE OF BT TREATMENT could be in preventing central motor adaptation due to its temporary paralysing effect
- Relevance of changing pattern of injection on repeated treatment sessions?
- Combination of BT injections with repeated session of rTMS?

Long-term effect of BT in dystonia

- Long-term remission of idiopathic cervical dystonia after BT treatment in 6/30 patients (Giladi, 2000)
- The possibility that BT might have induced early remission in those patients who would otherwise develop spontaneous remission (10-20%).
- Gamma motor neuron paralysis induced by BT may change afferent input from injected muscles and act as ‘continuous sensory trick’ -> ‘reorganization’ in the BG and/or sensorimotor cortex -> correction of the basic pathophysiological process which causes cervical dystonia
- The role of combining BT injections with repeated session of rTMS?
Long-term effect of BT in spasticity

- Early treatment of spasticity may (theoretically) brake a cycle of spasticity → muscle shortening → fibrosis → contractures
- Cosgrove et al. (1994) - BT injection in gastrocnemius muscle of hereditary spastic infant rats before they developed spasticity prevented shortening of muscle in adult rats
- Window of opportunity in children, but studies are lacking
- Effect on BT on recurrent (Renshaw) inhibition (Marchand-Pauvert, 2014) → possibility of long-term effect by modulating maladaptive spinal cord plasticity in stroke patients

CONCLUSIONS

- Clinical benefits of BT injections depend mainly on the toxin’s peripheral action
- However, this seems not to be the whole story
- Central action of BT
  - may account for remote effects of BT
  - may contribute to clinical improvement after injections
  - May underlie long-term effects of treatment

Research issues arising from practice and possible clinical relevance of feedback information

- How to improve the response to BT?
- How to obtain clinical effect with a lower BT dose?
- Insight into pathophysiology of disease

BT research issues: relevance for understanding the pathophysiology of dystonia

- Dystonia is an abnormality of sensory-motor network
- Change of afferent input caused by BT injections result in upstream changes that may affect different nodes of the network
- Abnormalities in inhibition and plasticity in dystonia are not predetermined fixed aberrations, but reflect dynamic functional reorganization influenced by inputs from another nodes in the network

THANK YOU FOR YOUR ATTENTION