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Central effects of botulinum Toxin A
Recovery of spinal inhibition after botulinum toxin A in stroke patients

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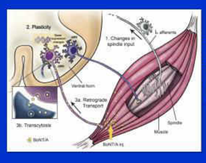
BoNT/A: Action mechanisms

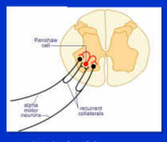
- Most poisonous proteins > flaccid paralysis > death
- **Peripheral** actions: prevents exocytosis (Ach release) > blocks neuromuscular junctions
- **Central** actions: direct and indirect mechanisms

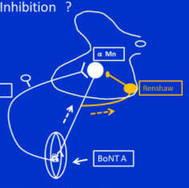


1. Intrafusal fibers: blocks γ MN inputs > changes in spindle inputs
2. Plasticity at muscular (muscle fibre type) and MN levels (membrane properties)
3a. Retrograde transport of active toxin
3b. Transcytosis blocking afferent inputs to motoneurones
...in animal models

Colins M et al J Neurochem 2003

First central target : Renshaw cells
Recurrent Inhibition ?





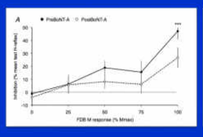
In animal models :

- BoNT/A => retrograde and anterograde transport of the active toxin
L.Restani , F. Antonucci,, E. Gianfranceschi L., C. Rossi , O. Rossetto , M. Caleo , J Neuroscience 2011
- ↘ Recurrent Inhibition
Wiegand H & Wolthoser HH , Naunyn Schmiedebergs Arch Pharmacol 1977 ...

In humans ...

- ✓ Recurrent inhibition investigated in stroke patients
- ✓ Heteronymous recurrent inhibition method
- ✓ ↘ Recurrent inhibition

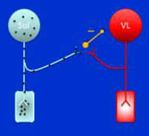
Marchand-Pauvert V, Aymard C, Giboin LS, Dominici F, Rossi A, Mazzocchio R. J Physiology, 2013



RI depressed 1 month after BoNT/A muscular injection

Possible mechanisms

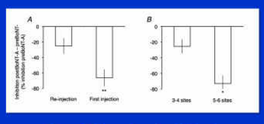
BoNT/A retrograde transport
↘ synapses Renshaw cells - VL motoneurones



Marchand-Pauvert V, Aymard C, Giboin LS, Dominici F, Rossi A, Mazzocchio R. J Physiol. 2013;591:1017-29

BoNT/A – induced Recurrent Inhibition depression

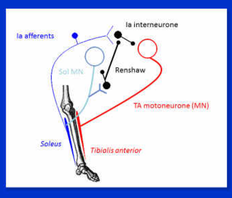
a tool for quantitative evaluation of BoNT/A effect



More efficient after the 1st injection
Dose effect

Marchand-Pauvert V, Aymard C, Giboin LS, Dominici F, Rossi A, Mazzocchio R. J Physiol. 2013;591:1017-29.

Diffuse central effect ?



Effects on Ia reciprocal inhibition

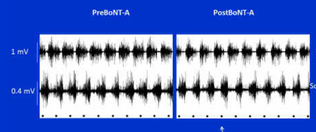
✓ Stroke patients : abnormal muscle synergies and co-activation of antagonistic muscles.
✓Reciprocal inhibition between antagonists : after stroke (Yanagisawa and al., 1976; Crone et al., 2003)
✓ In healthy subjects : reciprocal inhibition is modulated during the gait and *may help to inactivate antagonistic motoneurones in the appropriate phases of the walking cycle . Depression of the inhibition in the opposite phases may help to ensure an inhindered activation of the motoneurones by descending and segmental excitatory inputs (Petersen et al., 1999).*
✓ Reciprocal inhibition in ankle dorsiflexors investigated, triceps surae being mostly injected in stroke patients.
✓ Changes in afferents inputs from an injected muscle => activity of motoneurones supplying a non-injected muscle.
✓ Ia inhibitory interneurones mediating reciprocal inhibition between ankle muscles controlled by Renshaw cells (Baret et al., 2003).
✓Spastic cocontractions of non-injected antagonistic muscle reduced at elbow level after BoNT-A (Gracies et al., 2009; Vinti et al., 2012).

Schematic diagram of the spinal connections
Open circles represent spinal motoneurones innervating soleus (Sol) and tibialis anterior (TA). Orange and red filled circles represent, respectively, group Ia interneurons mediating reciprocal inhibition from Sol to TA, and Renshaw cells activated by recurrent collaterals of Sol motoneurons, and which control group Ia interneurons inhibiting TA motoneurons. White line and open circle represent the muscle spindle group Ia afferents from Sol and TA, mediating H reflex. TA sensory and motor axons run into the DPN, and those of Sol in PTN. BoNT-A was injected in triceps surae including Sol. Orange dotted line indicates the putative retrograde transport of BoNT-A. PTN, posterior tibial nerve; DPN, deep peroneal nerve; H reflex, Hoffmann reflex; BoNT-A, botulinum neurotoxin A.

Experimental procedures

- ✓ Test response : TA EMG
- ✓ Conditioning : PTN stimulation
- ✓ Central latency for reciprocal inhibition 1 ms, duration 10 ms
- ✓ 17 post-stroke patients (4 excluded cross talk on TA EMG)
- ✓ 13 patients with focal spasticity in ankle plantarflexors
- ✓ Excluded :
  - BoNT-A injection < 4 months
  - Alcohol or phenol blocks
  - Surgery, fixed contractures
  - Ongoing treatments unchanged

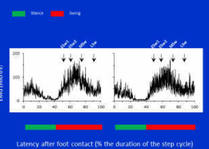
- ✓Assessment before and 1 month after BoNT-A injection (soleus, MG, LG, TP)
- ✓ Walk on a treadmill without bodyweight support
- ✓ Same speed before and after injection
- ✓ PTN stimulation => TA EMG : 4 delays: ESw1, ESw2, MSw, LSw



Soleus activity started 500 ms before foot contact, before BoNT-A , 300 ms after BoNT-A

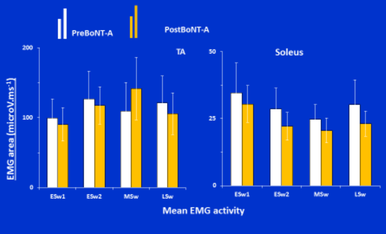
Foot contact

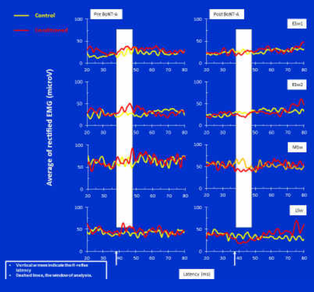
Silent period between 2 TA bursts sharper after BoNT-A

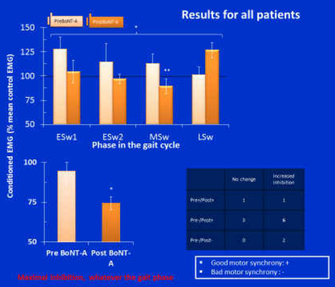


short silent period 40 % of duration cycle more pronounced after BoNT-A

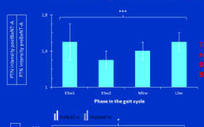
Mean background EMG activity in TA and soleus not modified in the group of 13 patients



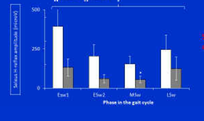




Monitoring of conditioning stimuli



Threshold for motor responses almost stable BoNT-A : 2.3 +/- 0.3 X before BoNT-A

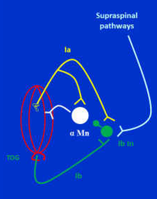


Soleus H reflex depressed after BoNT-A, then rises

Maximal inhibition whatever the gait phase

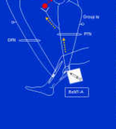
Discussion

Reciprocal facilitation during post-stroke walking



- ✓ Reciprocal inhibition of TA motoneurons is depressed and may reverse into excitation after stroke => disrupted supraspinal control ? (Crone et al.,2003) (crosstalk TA EMG excluded).
- ✓Reciprocal facilitation during post-stroke walking mediated by group Ib spinal pathways ?
- ✓ Group Ib inhibition reversed into excitation after stroke (Delwaide and Oliver, 1988)
- ✓Group Ib excitatory pathways specifically activated during walking (Marchand-Pauvert and Nielsen, 2002)
- ✓ Reciprocal inhibition of TA motoneurons unchanged in stroke patients at rest (Yanagisawa, 1976)

Recovery of reciprocal inhibition after BoNT-A



- ✓ Reciprocal facilitation depressed in ESw and reversed into inhibition in MSw after BoNT-A
- ✓ EMG influences reciprocal inhibition (Petersen et al, 1999) but no changes between recordings
- ✓ PTN stimulation ↗ (same stimuli before BoNT-A ↗ reciprocal facilitation, Yanagisawa et al., 1976)
- ✓Less recurrent inhibition => more inhibition by reciprocal group Ia interneurons
- ✓ Renshaw cells need to be blocked by toxin for effect on reciprocal inhibition of antagonistic motoneurons (Hagenah et al., 1977)
- ✓ Direct central action on spinal circuitry , involving retrograde transport along motor axons (blockade of Renshaw cells)

Enhanced reciprocal facilitation in LSw

- ✓ Co-contraction of ankle flexors and extensors in LSw just before foot contact
- ✓ Not in normal walking and post-stroke walking before BoNT-A
- ✓ No plasticity involving Renshaw cells : control Mns and reciprocal group Ia Ins only, not group Ib Ins (Pierrot-Deseilligny and Burke, 2012)
- ✓ Renshaw cells involved => similar modification in all the swing phases.
- ✓ Probably modification of peripheral inputs on group Ib Ins after BoNT-A

↘ Spindle signals
⬇
Afferent inputs
Motor outputs

Functional significance

- After BoNT- A : recovery of reciprocal inhibition between soleus and TA = better temporal pattern of their activity
- Recovery of reciprocal inhibition in TA in ESw and MSw => better timing of ankle dorsiflexor activity during walking
- Co-contraction between antagonists in LSw : block ankle position on the paretic leg for upright position.

Conclusion

BoNT-A influences spinal excitability through direct and indirect central actions :

1- Blockade of synapse between Mns and Renshaw cells => recovery of reciprocal inhibition in TA Mns.

2- Reinforcement of group Ib excitatory Ins (toxin-induced changes in peripheral inputs)

⇒ Limiting co-contraction between antagonistic muscles during the transition phase from stance to swing

⇒ Facilitating co-contraction between antagonistic muscles during the transition phase from swing to stance to block ankle joint