Pathophysiology of focal dystonia

why do people get cranial dystonia or blepharospasm?

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Presentation at the Benign Essential Blepharospasm Research Foundation Symposium
held at University of California, San Diego
August 10, 2013
Disclosure

- All material presented is independent of and unrelated to industry
Summary of talk

- Dystonia pathophysiology is an active area of research
- Pathophysiology can be understood at different levels: genes, brain circuits, and motor behavior
- Understanding pathophysiology leads to development of novel therapies

- Dystonia is heterogeneous
- Not all dystonia is the same (even if it can look similar)
- Not all treatments work equally for all dystonia patients
- Can we tailor better treatments for patients?
Why do I have dystonia?

sustained muscle contractions, frequently causing appearance of twisting, repetitive, or patterned movements or postures (Fahn 1988)

Supportive signs of dystonia

1. sustained abnormal postures
2. task-specificity (action-specificity)
3. movement overflow (excess movements)
4. sensory trick (geste antagoniste)

Non-specific

1. worse with stress and fatigue, better with sleep
# Dystonia classification

## Anatomic distribution
- focal dystonia
- blepharospasm
- oromandibular dystonia
- spasmodic dysphonia
- cervical dystonia
- Meige syndrome
- writer’s cramp
- limb dystonia
- segmental dystonia
- multifocal dystonia
- generalized dystonia

## Age of onset
- early-onset (<= 26 yo)
- late-onset (> 26 yo)

## Cause
- primary dystonia (pure dystonia)
- secondary dystonia
  - dystonia-plus syndromes*
  - heredo-degenerative dystonia
  - identified secondary etiologies

*plus = plus other movement disorders

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Geyer and Bressman, Lancet 2006
Dystonia - many causes, similar appearance

Jinnah et al, Dystonia Coalition, MDS 2011
Dystonia - anatomy and circuits
Pathophysiology of dystonia I: Loss of inhibition

- May account for excess muscle contraction and motor overflow seen clinically
- Can be demonstrated in cortical, subcortical, and spinal circuits are reduced (intracortical circuits, blink reflex, reciprocal inhibition)
- Abnormalities can exist in limb muscles distant from dystonia and are not always specific (Quartarone et al 2008, 2010)
Blink reflex
Blink reflex
Blink reflex

**superimposed EMG traces**

- Right OO emg (0.1 mV)
  - Time (sec): 0.05 to 0.2
  - Peak R2

- Left OO emg (0.1 mV)
  - Time (sec): 0.05 to 0.2
  - Peak R1 and R2

**rectified and averaged EMG traces**

- Right OO emg (0.1 mV)
  - Time (sec): 0.05 to 0.2
  - Rectified R2

- Left OO emg (0.1 mV)
  - Time (sec): 0.05 to 0.2
  - Rectified R1 and R2
Paired-pulse supraorbital nerve stimulation tends to show disinhibition in blepharospasm patients
Paired-pulse supraorbital nerve stimulation tends to show disinhibition in blepharospasm patients.
Blepharospasm patient

Control subject
Loss of inhibition

• In majority of studies, blink reflex recovery (BRR) shows loss of an inhibitory circuit in the blink reflex.
  • Suggests blepharospasm patients have an increased excitability of this brainstem blink circuit
  • Relates to tendency for a given stimulus to induce a reflex blink
  • May contribute to excess blinking or sustained eye closure
• May distinguish certain forms of blepharospasm from atypical forms (Schwingenschuh et al 2011)
Dystonia pathophysiology II: Sensory processing abnormalities

- Sensory afferent information directs goal-directed movement
- Sensory abnormalities often present in blepharospasm: dry eye, photophobia
- May account for sensory tricks (geste antagoniste)

Hallett, Ann Neurol 1995
Dystonia pathophysiology II: abnormal plasticity

Exaggerated plasticity is suggested by overuse phenomena (e.g. musician's cramp)

Excess plasticity may contribute to disinhibition and/or sensorimotor integration abnormalities
Plasticity

• Plasticity
  – Capacity for change in response to an experience
  – Long-term potentiation (LTP) & long-term depression (LTD)
    • forms of plasticity recognized by relatively long-lasting changes in a neural circuit
    • Balance of LTP and LTD thought required for adequate learning and forgetting
  – Plasticity can be beneficial (adaptive) or maladaptive
    • adaptive plasticity - supports changes that aid a goal-directed behavior
    • maladaptive plasticity - generates changes that interfere with goal-directed behavior
Spike-timing plasticity

- A and B represent a standard neuron connection (like a blink reflex)
- Strength of connect between A and B
  - increases if Z fires in sync with A
  - weakens if Z first out-of-sync with A
Spike-timing conditioning of blink reflexes can produce LTP-like and LTD-like responses.

Mao & Evinger 2001
Spike-timing conditioning of blink reflexes shows exaggerated LTP-like response in blepharospasm

Mao & Evinger 2001

Dystonia - putting it together
sensory inputs
sensory states
(trigeminal, auditory, visual, pain)

LOCAL BRAINSTEM BLINK CIRCUIT

Brainstem afferent input

LTD(-)/LTP(+)

Blink GAIN

BLINK of eyelids

Brainstem efferent output

DURING

BEFORE
Example systems-level model of blepharospasm

- Reduced midbrain dopamine increases blink reflex excitability
- Weakening of orb. oculi muscle then

Schicatano, Basso & Evinger 1997
sensory inputs
sensory states
(trigeminal, auditory, visual, pain)

Brainstem afferent input

Blink GAIN

Brainstem efferent output

Basal ganglia & prefrontal ctx

Cerebellum

HABITUATION

GAIN ADAPTATION & CONDITIONING

LOCAL BRAINSTEM BLINK CIRCUIT

BLINK of eyelids

LTD(-)/LTP(+)

(-)habituate

(+)=dishabituate

(+)=adapt/inc gain [decondition/dec gain (-)]
Treatments based on dystonia pathophysiology

- Reduce excess excitability (improve inhibition)
  - *Neuromodulatory protocols (see below)*
  - botulinum toxin
- Improve sensorimotor integration (via afferent inputs)
  - Sensory perceptual training (Zeuner et al 2002)
  - Tinted glasses (Herz and Yen 2005), novel tear films (Hallett et al 2008)
- Address abnormal pattern induced by abnormal plasticity
  - Re-training protocols (sensory training, immobilization)
  - *Neuromodulatory protocols*
    - low-frequency rTMS
      inhibitory theta-burst TMS,
      cathodal TDCS (Kranz et al 2009, 2010)
    - trigeminal nerve stimulation

Priori et al, Neurol 2001
Take home

• Pathophysiology of blepharospasm (focal dystonia) can be understood at many levels: genetic, circuits, or systems

• Circuits: Blepharospasm neurophysiology shows
  • Loss of inhibition,
  • Abnormal sensory processing,
  • Excess plasticity

• Systems related to blepharospasm (focal dystonia) implicate
  • Increased excitability and plasticity of the blink reflex
  • Influences from the basal ganglia (dopamine system)
  • Possible influences from the cerebellum

• Therapies based on neurophysiology are being developed and studied
  • Novel rehabilitation training programs (sensorimotor tuning)
  • Methods to reduce or balance excess plasticity