Animal Model Explains the Origins of the Cranial Dystonia Benign Essential Blepharospasm

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Schicatano, Edward J., Michele A. Basso, and Craig Evinger. Animal model explains the origins of the cranial dystonia benign essential blepharospasm. J. Neurophysiol. 77: 2842 ± 2846, 1997. spasm that exhibits many of the characteristics of BEB. The current study demonstrates that combining two mild alterations to the rat trigeminal reflex blink system reproduces the symptoms of benign essential blepharospasm, a cranial dystonia characterized by uncontrollable spasms of blinking. The first modification, a small striatal dopamine depletion, reduces the tonic inhibition of trigeminal reflex blink circuits. The second alteration, a slight weakening of the lid-closing orbicularis oculi muscle, begins an adaptive increase in the drive on trigeminal sensory-motor blink circuits that initiates blepharospasm. By themselves, neither of these modifications causes spasms of lid closure, but combined, they induce bilateral forceful blinking and spasms of lid closure. A two-factor model based on these rodent experiments may explain the development of benign essential blepharospasm in humans. The first factor, a subclinical loss of striatal dopamine, creates a permissive environment within the trigeminal blink circuits. The second factor, an external ophthalmic insult, precipitates benign essential blepharospasm. This two-factor model may also be applicable to the genesis of other cranial dystonias.

METHODS
All experiments were performed with strict adherence to all Federal, State, and University regulations governing the use of animals. Male Sprague-Dawley rats underwent one of three procedures: 1) a complete (>90%) unilateral 6-hydroxydopamine (6-OHDA) lesion (n = 5); 2) a unilateral lesion of the zygomatic branch of the facial nerve (n = 4); and 3) a small (<30%) unilateral 6-OHDA lesion followed by a unilateral zygomatic branch lesion (n = 5).

Under general anesthesia and aseptic conditions, all rats were prepared for bilateral chronic recording of the lid-closing orbicularis oculi muscle electromyogram (OEmg) and electrical stimulation of the supraorbital branch of the trigeminal nerve (SO) (see Evinger et al. 1993 for details). In the same surgery, rats in group 1 received a unilateral 6-OHDA injection to completely destroy the dopamine-containing cells in one substantia nigra pars compacta (see Basso et al. 1993 for details). Rats in group 3 were given a small, unilateral 6-OHDA injection to produce minimal destruction of compacta neurons. At least 20 days after the OEmg and SO electrodes were implanted, the rats in groups 2 and 3 were anesthetized and the zygomatic branch of the facial nerve contralateral to the 6-OHDA injection was sectioned to weaken the orbicularis oculi. After rats recovered from the surgery, the minimal trigeminal threshold stimulus for evoking SO reflex blinks was established and the excitability of trigeminal reflex blink excitability was quantified by comparing the magnitude of the OEmg response to the second stimulus (test response) with the magnitude of the OEmg response evoked by the first stimulus (condition response). Thirty-five to 50 days after the facial nerve transection, animals were deeply anesthetized and transecally perfused. Coronal sections of the brains were cut and reacted immuno-histochemically with an antibody to tyrosine hydroxylase to identify dopamine-containing neurons in the substantia nigra pars compacta (see Basso et al. 1993 for details).

RESULTS
As demonstrated previously (Basso et al. 1993), 6-OHDA lesions that destroyed >90% of the dopamine-containing neurons in one substantia nigra pars compacta increased the R2 test/R2 condition ratio from normal values of <1 to values of 4–7.5, extreme trigeminal reflex blink hyperexcitability. The dopamine loss reduces tonic inhibition of the trigeminal sensory-motor transformation in blink circuits following a subclinical basal ganglia dysfunction produces blepharospasm that exhibits many of the characteristics of BEB.

INTRODUCTION

Focal dystonias are involuntary muscle contractions of a single group of muscles that produce abnormal postures and movements. Although one of the more prevalent neurological disorders affecting people ≥50 yr of age, the neurological basis for focal dystonias is poorly understood. Focal dystonias could be motor program disorders resulting from basal ganglia dysfunction, sensory impairment, or an inability to retrieve appropriate motor programs from a sensory input (e.g., Jankovic 1988; Kaji et al. 1995a,b). In this latter interpretation, a focal dystonia develops from a disruption of the transformation of sensory magnitude to motor drive.

Benign essential blepharospasm (BEB) is a focal cranial dystonia characterized by sustained, involuntary spasms of eyelid closure. BEB typically appears in the 5th–7th decades of life, beginning with ophthalmologic symptoms, such as dry eye and/or eye irritation associated with frequent blinking. Blinks become more forceful and transform into involuntary spasms of lid closure. In addition to spasms of lid closure, patients also exhibit hyperexcitable trigeminal reflex blinks. Although the presence of hyperexcitable reflex blinks with BEB implies an alteration in the trigeminal sensory-motor system, most studies propose that basal ganglia dysfunction underlies BEB (e.g., Berardelli et al. 1985; Carella 1994; Elston et al. 1988; Granadas et al. 1988; Jankovic 1988). In rats, we show that a disruption of the trigeminal
A: schematic circuit linking a basal ganglia output nucleus, the substantia nigra pars reticulata (SNr), to the superior colliculus (SC), the nucleus raphe magnus (NRM), and the reflex blink circuits within the spinal trigeminal complex (V-RB). B: spasm of lid closure in a rat with complete (~90%) destruction of dopamine containing neurons in the right substantia nigra pars compacta. Stimulation of the left supraorbital branch of the trigeminal nerve (LSO Stim) initiated the spasm. The 2 records show the rectified orbicularis oculi electromyographic (OOemg) activity on the left (L OOemg) and right (R OOemg) during the spasm (top traces) and the reflex response at the onset of the spasm (inset).

Blink circuits (Fig. 1A). Complete unilateral 6-OHDA lesions also produced reflex spasms of lid closure triggered by SO stimuli (Fig. 1B). Just as occurs in some humans with severe Parkinson’s disease, spasms of lid closure occurred in response to trigeminal stimuli but did not occur spontaneously (e.g., Hotson and Bowman 1991). In contrast, 6-OHDA lesions that destroyed ~30% of the nigral dopamine containing neurons in one substantia nigra slightly increased trigeminal reflex blink excitability to values of ~1 (Fig. 3D, ▲), but did not result in reflex-evoked or spontaneous spasms of lid closure.

Weakening the orbicularis oculi muscle also elevated trigeminal reflex blink excitability, but did not result in reflex induced or spontaneous spasms of lid closure. After VIIth nerve transection, trigeminal reflex blink excitability increased gradually over 1 wk to reach a level that remained constant (Fig. 2) for periods of up to 70 days. In addition to the increased excitability, the threshold for SO evoked OOemg activity of the ipsilateral and contralateral orbicularis oculi decreased in the 1st wk by a mean of 30 ± 3% (mean ± SE; t-test, P < 0.01). In contrast, the threshold for evoking ipsilateral and consensual reflex blinks through the SO nerve contralateral to the weakened orbicularis oculi did not change (6 ± 3%, mean ± SE; t-test, P > 0.49).

Weakening the orbicularis oculi muscle 20 days after a small (<30%) unilateral 6-OHDA lesion produced a dramatic increase in trigeminal reflex blink excitability and led to bilateral reflex-evoked (Fig. 3) and spontaneous spasms of lid closure. Within 24–48 h after a facial nerve transection in unilaterally 6-OHDA-lesioned rats, trigeminal reflex blink excitability increased. On the basis of the excitability determined at the 50-ms interstimulus interval, the trigeminal reflex blink excitability produced by combining the weak 6-OHDA and facial nerve lesions increased by a factor of 4 over the excitability increase caused by the small 6-OHDA lesion alone, and by a factor of 3.5 relative to rats that received orbicularis oculi weakening alone (Fig. 3D). In the same time period after the nerve lesion, the threshold for SO evoked ipsilateral and contralateral OOemg activity decreased by a mean of 68 ± 4% (t-test, P < 0.001), slightly more than twice the decrease caused by orbicularis oculi weakening alone. The SO threshold for evoking ipsilateral
and contralateral OOemg activity decreased by 17% (t-test; \( P < 0.13 \)) contralateral to the weakened orbicularis oculi muscle. Combining the orbicularis oculi weakening with the small 6-OHDA lesion caused a mean 3.1-fold increase in the slope of the relationship between SO stimulus magnitude and the size of the evoked blink relative to the 6-OHDA lesion alone (Fig. 3E), and a mean 2.3-fold increase over orbicularis oculi weakening alone. Reflex blepharospasm also became apparent within 1–2 days after the facial nerve lesion (Fig. 3C), and frequent, forceful blinking and spontaneous spasms of lid closure were present 7–10 days after orbicularis oculi weakening. These BEB characteristics remained until the rats were killed >35 days later.

**DISCUSSION**

Both dopamine depletion and orbicularis oculi weakening increase the excitability of trigeminal reflex blinks by modifying trigeminal sensory-motor blink circuits. The basal ganglia modulates the excitability of trigeminal reflex blinks via the substantia nigra pars reticulata inhibition of the superior colliculus. The superior colliculus excites tonically active, serotonergic neurons in the nucleus raphe magnus, which in turn inhibit reflex blink circuits within the spinal trigeminal complex (Fig. 1A) (Basso and Evinger 1996; Basso et al. 1996). Dopamine depletion increases nigral inhibition of the superior colliculus, which reduces the nucleus raphe magnus inhibition of trigeminal reflex blink circuits.

Orbicularis oculi weakening increases the excitability of SO evoked blinks and decreases the threshold for evoking blinks on the side ipsilateral to the orbicularis oculi weakening. The changes in threshold indicate an adaptive increase in the ability of trigeminal sensory stimuli to engage motor activity, i.e., motor learning (Evinger and Manning 1988). These changes have the effect of elevating the slope of the relationship between stimulus magnitude and evoked blink size to SO stimuli ipsilateral to the weakened orbicularis oculi. If orbicularis oculi weakening produced a general increase in blink excitability or an increase in the axotomized facial nucleus, then the threshold for eliciting a trigeminal blink should have decreased for the OOemg response ipsilateral to the nerve cut regardless of which SO nerve was
FIG. 3. Effect of combining a small 6-hydroxydopamine (6-OHDA) lesion with weakening of the orbicularis oculi on trigeminal reflex blink excitability. A: after a small (<35%) unilateral 6-OHDA lesion, the response to the 2nd stimulus to the SO (arrowhead) was unaffected by the occurrence of the 1st stimulus and reflex blink evoked 100 ms earlier. B: 20 days after weakening of the orbicularis oculi muscle of the rat shown in A, the trigeminal reflex blink was extremely hyperexcitable. Records in A and B are averages of 5 rectified OOemg responses. C: 21 days after orbicularis oculi weakening, an SO stimulus produced prolonged spasms of lid closure. Single rectified record. D: R2 test response magnitude/R2 condition response magnitude as a function of interstimulus interval before lesioning (●, Pre), after a small 6-OHDA lesion (●, 6-OHDA), and 20 days after orbicularis oculi weakening in addition to the 6-OHDA lesion (●, BLEPH). Each point is the mean of ≥10 responses from each of 5 rats. E: change in the slope of the line relating OOemg activity with stimulus intensity. Slope was established by calculating the change in ADU units of OOemg activity (ADU) as a function of SO stimulus current (µA). Slope increased for all 5 rats from the small 6-OHDA lesion condition (6-OHDA) to the small 6-OHDA lesion combined with orbicularis oculi weakening (BLEPH).
stimulated. Thus these data argue that orbicularis oculi weakening primarily modified trigeminal sensory-motor circuits ipsilateral to the facial nerve transection.

We hypothesize that the increased inhibitory output of the basal ganglia’s substantia nigra pars reticulata created a permissive condition in the trigeminal sensory-motor blink circuits that made the rats susceptible to the induction of blepharospasm. In this permissive environment, the normally adaptive increase in drive on the trigeminal sensory-motor circuits to compensate for lid weakness became too strong and altered trigeminal circuits to produce blepharospasm. Thus the transformation of sensory stimulus magnitude to motor drive continued to shift toward increased sensitivity as if its ‘set point,’ the correlation between sensory magnitude and evoked blink size, was dramatically increased or was no longer recognized in the permissive trigeminal environment. This rodent model also accounts for the characteristics of BEB in humans: 1) onset usually during the 5th–7th decades of life; 2) hyperexcitable trigeminal reflex blinks; 3) involvement of the basal ganglia; and 4) beginning usually with an ophthalmologic insult, e.g., dry eye.

The factors of aging, trigeminal reflex blink excitability, and basal ganglia dysfunction are interrelated. Decreasing striatal dopamine levels elevates trigeminal reflex blink excitability (Basso et al. 1993; Kimura 1973). Because there is progressive dopamine cell loss in the substantia nigra pars compacta with aging (e.g., Fearnley and Lees 1991), it is not surprising that trigeminal reflex blink excitability increases with age. Trigeminal reflex blink excitability escalates during normal aging, and starting in the fifth decade of life these increases become most pronounced (Evinger et al. 1995). Our model predicts that when a subclinical increase in basal ganglia output significantly reduces nucleus raphe magnus inhibition of the trigeminal complex, an individual will become susceptible to blepharospasm that can be initiated by an external ophthalmologic insult.

Ophthalmic insults, such as dry eye, can initiate adaptive increases in the drive on trigeminal blink circuits. In the case of dry eye, the nervous system changes the set point of the trigeminal blink system so that a given trigeminal stimulus now evokes a larger blink to better wet the cornea (Pita-Salorio and Quintana-Conte 1988). In otherwise normal individuals, treatment of the dry eye eliminates the excessive blinking associated with dry eye. However, when basal ganglia dysfunction creates a permissive trigeminal sensory-motor blink environment, the adaptive process initiated by the dry eye appears to lose its set point or the set point continually increases, which results in blepharospasm.

Our model may also account for development of other cranial dystonias. BEB often expands from the eyelids to involve oral structures, i.e., Meige’s syndrome. In our model, the critical basal ganglia dysfunction is an increased inhibitory drive of the nigrocollicular pathway. Because the superior colliculus mediates basal ganglia modulation of oral reflexes (e.g., Taha et al. 1982) and as well as blink reflexes, any progressive basal ganglia dysfunction will eventually create the permissive environment for a normally adaptive change in oral sensory-motor circuits to develop into an orofacial dystonia. The idea that inappropriate motor learning produces cranial dystonia may also be applicable to focal limb dystonias. Byl et al. (1996) report that repetition of stereotyped hand movements in a motor learning paradigm can produce a de-differentiation of hand representation in cortex and dystonic hand movements in monkeys.

We thank D. M. Schmidt for expert technical assistance. We also acknowledge the crucial insights gathered at symposia organized by the Essential Blepharospasm Research Foundation.

This work was supported by National Eye Institute Grant EY-07391 to C. Evinger and Parkinson’s Disease Summer Fellowships to M. A. Basso. Present address of M. A. Basso: Laboratory of Sensorimotor Research, National Eye Institute, Bethesda, MD 20892-4435.

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Received 9 October 1996; accepted in final form 22 January 1997.

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