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Animal Models of Focal Dystonia

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Summary: Animal models indicate that the abnormal movements of focal dystonia result from disordered sensorimotor integration. Sensorimotor integration involves a comparison of sensory information resulting from a movement with the sensory information expected from the movement. Unanticipated sensory signals identified by sensorimotor processing serve as signals to modify the ongoing movement or the planning for subsequent movements. Normally, this process is an effective mechanism to modify neural commands for ongoing movement or for movement planning. Animal models of the focal dystonias spasmodic torticollis, writer's cramp, and benign essential blepharospasm reveal different dysfunctions of sensorimotor integration through which dystonia can arise. Animal models of spasmodic torticollis demonstrate that modifications in a variety of regions are capable of creating abnormal head postures. These data indicate that disruption of neural signals in one structure may mutate the activity pattern of other elements of the neural circuits for movement. The animal model of writer's cramp demonstrates the importance of abnormal sensory processing in generating dystonic movements. Animal models of blepharospasm illustrate how disrupting motor adaptation can produce dystonia. Together, these models show mechanisms by which disruptions in sensorimotor integration can create dystonic movements. **Key Words:** Spasmodic torticollis, writer's cramp, blepharospasm, sensorimotor integration, dystonia, animal models.

Dystonia is a syndrome characterized by sustained muscle contractions that cause twisting movements or abnormal postures. Although there is a genetic component to dystonia, primary dystonia typically does not result from a clear brain abnormality or lesion. When dystonia involves two or more body segments, it is classified as generalized dystonia. Involvement of only one side of the body is hemidystonia and dystonia affecting only one segment of the body is segmental dystonia. Although some forms of dystonia affect many parts of the body, the syndrome can be limited to a single body part in focal dystonia. Focal dystonias include the uncontrollable spasms of eyelid closure with blepharospasm, the involuntary rotation of the head into abnormal postures with cervical dystonia or spasmodic torticollis, and the spasms of the laryngeal muscles with spasmodic dysphonia. In addition to these focal dystonias, there are occupational dystonias that only appear with one action of the affected body part such as writing with writer's cramp, or embrasure with musician's dystonia in horn players.[1–13] The focus of the current review is the contribution of animal models of focal dystonia to understanding the neural basis of dystonia.

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There are at least two possible ways to consider generalized and focal dystonia. One hypothesis is that the neural basis for the two syndromes is different. The second position is that generalized and focal dystonia are two ends of a continuum. There is significant support for this latter position. Irrespective of genetic etiology, the form and location of dystonia exhibited by an individual correlates with the age of onset.[14] Dystonia appearing in children typically begins with the legs and progresses to generalized dystonia. In contrast, the focal dystonia blepharospasm affecting the eyelids usually begins after age 50. To evaluate focal dystonia, it is valuable to first review the neural changes with generalized dystonia.

The best-characterized genetic mutation associated with generalized dystonia is a deletion in the DYT1 gene. Most DYT1 mutations that produce torsion dystonia result from a 3-bp deletion (GAG).[15] The TorsinA protein encoded by the DYT1 gene is a member of the AAA+ superfamily of ATPases that appears to function in the nuclear envelope. The mutated gene product may disrupt association of the cytoskeleton with the nucleus.[16–20] This genetic disorder is autosomal dominant with low penetrance, so that the phenotypic expression varies from severe generalized dystonia to no manifestation of the syndrome.[14,21,22]

A DYT1 mutation alters the activity of several brain regions, modifies analysis of sensory information, and

affects explicit motor learning in humans. Based on positron emission tomography (PET) scans, Eidelberg and colleagues[23–25] identified a torsion dystonia-related change in the pattern of brain activity. There was abnormal glucose utilization in the posterior putamen/globus pallidus, cerebellum, and supplementary motor area in patients with primary torsion dystonia produced by the DYT1 deletion. This increased metabolism was not the result of dystonic movement because the hypermetabolism was present even when the subjects slept without making movements. The pattern of altered brain metabolism was even present in individuals with the DYT1 mutation who were not symptomatic. The brain regions exhibiting this pattern of abnormal activity have high levels of TorsinA and TorsinB expression.[26–28] Although TorsinA expression is also high in areas not associated with primary torsion dystonia, the combination of abnormal activity and DYT1 expression suggest that modifications in the activity of a specific set of brain circuits may participate in creating dystonic movements.

In addition to dystonic movements, individuals with primary torsion dystonia also exhibit deficiencies in sensory processing.[29–31] Primarily, these deficits are in temporal processing. Dystonic patients require significantly longer intervals between stimuli than do control subjects to distinguish whether two somatosensory or two visual stimuli occur asynchronously. Pairing a visual and a somatosensory stimulus exacerbates the difference between controls and individuals with generalized dystonia in their ability to identify temporal differences.[30] Aglioti et al.[30] hypothesize that these deficits represent basal ganglia dysfunction. Nevertheless, the evidence that the cerebellum plays a role in temporal processing suggests that the somatosensory processing difficulties may also arise from cerebellar dysfunction.[32–35] This interpretation is consistent with the data showing that both the basal ganglia and the cerebellum exhibit abnormal activity levels with generalized dystonia.[23–25]

In addition to altered brain and sensory activity, individuals with the DYT1 deletion who do not have dystonic movements manifest deficits in motor learning. Ghilardi and colleagues[36] show that these individuals exhibit normal implicit motor learning but have difficulties with explicit motor learning tasks. The authors hypothesize that this motor learning deficit in DYT1 carriers results from failures of spatial working memory.

Generalized dystonia only occurs in 30–40% of individuals with the DYT1 deletion. Individuals with the DYT1 mutation but who do not exhibit dystonic movements show changes in brain metabolism similar to dystonic patients. The existence of comparable brain alterations in dystonic and nondystonic individuals with the same gene mutation demonstrates that the DYT1 mutation alone is insufficient to produce generalized dystonia.[6] There must be additional factors, environmental or genetic, that lead to the expression of dystonia. Studies of the focal dystonia, benign essential blepharospasm, indicate that dystonia arises from the combination of a predisposing factor, probably genetic, and a second precipitating event, such as motor adaptation to cornea irritation.[9,37] Applying the hypothesis for the development of benign essential blepharospasm to generalized dystonia may explain why some individuals with the DYT1 deletion exhibit generalized dystonia, but others do not.

Animal models of focal dystonia enable us to dissect out the multiple components that combine to cause dystonia. It is easier to investigate these factors in focal dystonia than generalized dystonia because focal dystonic movements occur on a background of normal movement. Currently, there are animal models of the focal dystonias spasmodic torticollis, writer's cramp, and benign essential blepharospasm. Each of these animal models provides different information about dystonia. Animal models of spasmodic torticollis identify different brain regions, each of which is capable of creating abnormal head postures. The animal model of writer's cramp demonstrates the importance of abnormal sensory processing in creating dystonic movements. Animal models of blepharospasm explore how disrupting motor adaptation can produce dystonia. Together, the models illustrate a valuable way to think about how transformations of sensorimotor integration can create dystonic movements.

SPASMODIC TORTICOLLIS

Spasmodic torticollis, or cervical dystonia, is a sustained involuntary muscle contraction that rotates the head into an abnormal posture.[13,38–41] The muscle contractions appear to reflect reduced inhibition in the motor and somatosensory cortex that lead to excessive muscle activation.[1,42,43] In addition, the overactivity of neck muscles alters motor cortex so that the representation of neck muscles appears to displace the adjacent hand representation.[44] Similar to patients with generalized dystonia,[23–25,45] individuals with spasmodic torticollis exhibit increased metabolism in the basal ganglia, thalamus, premotor-motor cortex, and cerebellum.[23–25] Patients with cervical dystonia also exhibit sensory abnormalities similar to those present in generalized dystonia. There is a reduction in the ability to recognize temporal asynchrony of pairs of spatial stimuli with cervical dystonia, but the ability to identify visual stimuli asynchrony is normal.[43] Similarly, the perception of vibration induced illusion of movement is subnormal in patients with spasmodic torticollis.[46] One striking aspect of the sensory changes that occur with cervical dystonia is that approximately 70% of the patients have a sensory trick that alleviates the dystonic posture.[31] For example, touching the cheek reduces agonist EMG activity in the dystonic muscle by

48%.[47] The slower and smaller than normal interaction between the vestibulo-collic reflexes and voluntary movements demonstrates reflex dysfunction in spasmodic torticollis.[48]

Animal models of cervical dystonia recreate the primary symptom of the focal dystonia, sustained abnormal head posture. The data from these studies identify brain regions whose modification reproduces the neck movements of spasmodic torticollis.

Early studies reported that disrupting dopamine in the striatum produced head asymmetry that resembled torticollis.[49–52] Malouin and Bédard[52] showed that unilateral electrolytic lesions of the lateral substantia nigra pars reticulata (SNr) produced a sustained contralateral head turn in cats. Electrolytic lesions of the medial forebrain bundle as well as 6-OHDA lesions to deprive the striatum of dopamine caused persistent ipsilateral head turn and reduced head mobility. Disruption of caudate functioning appeared to be the cause of the head asymmetry because injections of dopamine and thyrotropin-releasing hormone into the caudate produced head asymmetry but did not affect head motility.[51] Although unilateral dopamine depletion of the striatum caused head and postural asymmetries, it is unclear that this modification related directly to human torticollis. The head asymmetry in this animal model required an 80–90% depletion of dopamine, which produced hemi-Parkinsonism. The effect of these dopamine lesions was probably more a head position bias than a dystonic posture.[53] Nevertheless, these studies demonstrated that abnormalities in basal ganglia activity could play a role in imposing an abnormal head position.

The observation that neuroleptic drug treatment of typical antipsychotics could elicit acute dystonia and other extrapyramidal side effects[54–61] is the basis for another animal model of cervical dystonia. Antipsychotic drugs that cause acute dystonia typically have a strong affinity for σ receptors. The σ receptor is a novel opioid receptor that is naloxone insensitive and steroselective for (+) enantiomers of benzomorphans.[61] Expression of the receptor is highest in the substantia nigra pars compacta, red nucleus, cerebellum, and many cranial motor nuclei.[62–64] In alert rats, microinjection of σ receptor ligands into the red nucleus produces a marked rotation of the head about the saggital axis, such that the side of the head ipsilateral to the injection rotates upward. This dystonic head posture begins within 10 min of the injection, peaks approximately 20 min after the injection and disappears within 60–90 min.[65] Although some data suggest that both σ_1 and σ_2 receptors play a role in acute human dystonia,[66] microinjection of σ ligands into the rat red nucleus shows that activation of the σ_2, but not the σ_1, receptor causes neck dystonia.[67] The mechanism through which σ agonists injected into the red nucleus produce neck dystonia is unclear. Early studies report that iontophoretic application of σ agonists that cause neck dystonia inhibit red nucleus neurons.[68,69] In contrast, the same investigator finds in a later study that σ agonists that cause head torsion in rats prolong burst duration of red nucleus neurons in the *in vitro* turtle brainstem preparation.[70] Regardless of the physiological actions of σ agonists, however, the data from red nucleus microinjections demonstrate that altering the activity of one of the cerebellum's interfaces with the rest of the brain can acutely cause torticollis-like head postures.

The interstitial nucleus of Cajal (INC) in the midbrain was also identified as a site that might play a role in torticollis in the middle of the previous century. An early study demonstrated that stimulation of the INC produced rotation toward the side of stimulation.[71,72] There were even attempts to eliminate torticollis with stereotaxic lesions of this region in humans.[73,74] A recent study in nonhuman primates created an animal model of cervical dystonia by showing that altering INC activity disrupted sensorimotor integration of head information.[75] As with the early study,[71] Klier et al.[75] found that microstimulation of INC produced ipsiversive head rotations. Microinjection of muscimol into the INC produced prolonged contraversive torsional head shifts that matched those found in humans with torticollis.[76] Klier et al.[75] interpreted their data as showing that the INC is a neural integrator for torsional head position in which the nuclei on each side of the midbrain establish opposite directions of head rotation. As appears to occur for eye movements, a head position neural integrator would convert a signal to turn the head into neural activity appropriate to hold the head in the new position following the movement. If the INC misinterpreted sensory inputs, or there was an imbalance between the two nuclei, then a dystonic head posture would occur. Consistent with this primate model of torticollis, humans with midbrain damage involving the INC exhibited cervical dystonia.[77,78]

Although the animal models of cervical dystonia do not address the basis for the development of the dystonia, they demonstrate that modifying the activity of at least three brain regions can cause a torticollis-like head posture. Two of these regions, the basal ganglia and the cerebellum, are regions that show elevated glucose uptake in generalized[23–25] and cervical dystonia.[79] These data indicate that disrupting any component of an interconnected set of brain regions can cause dystonic head movements. Disruptions of INC activity also causes cervical dystonia-like head postures. This region appears to convert efference copy information about the intended head movement into a signal to hold the head in the new position. Altering INC activity appears to be equivalent to the brain misrepresenting the intended or actual head movement, a derangement of sensorimotor integration. The animal model of writer's cramp further illustrates

the importance of disordered sensory signals from a movement in the generation of focal dystonia.

FOCAL HAND DYSTONIA

Most focal hand dystonias are task specific in that they primarily occur when an individual performs a certain task such as writing.[13,38–40] Although there is no evidence for brain lesions causing focal hand dystonias, brain function changes significantly with hand dystonia. Reduced inhibition of motor cortex occurs with writer's cramp.[39,80] Consistent with these physiological studies, individuals with writer's cramp exhibit reduced GABA levels in cortex.[81] As with many forms of dystonia, increased excitability or reduced inhibition is present at spinal and brainstem levels with writer's cramp.[31,82–84] PET imaging reveals a decrease in D2 receptors or receptor binding in the putamen with writer's cramp.[85] One of the most striking aspects of hand dystonia is that the somatosensory cortex loses its crisp organization with hand dystonia. The hand representation is disordered both for the cortex receiving input from the affected hand[86–91] and for the cortex receiving input from the unaffected hand.[89] Associated with the disordered somatosensory cortex organization, individuals with writer's cramp exhibit deficits in somatosensory perception similar to those occurring with torticollis.[92–94]

Based on their animal model, Byl, Merzenich, and colleagues[95–102] propose the "sensorimotor learning" hypothesis of focal hand dystonia. This hypothesis emerges from the observation that somatosensory representations in cortex are plastic and can be modified by Hebb-like processes.[103–113] For example, if a neuron receives nearly simultaneous inputs from a weak and a strong sensory synapse, the weak synapse will gain in strength. In the normal primary somatosensory cortex, area 3b, there is a precise differentiation of the representation of the fingers. Receptive fields are small and do not include more than one finger. These receptive field properties, however, are modifiable. As an individual practices a hand movement, the movement becomes more efficient and stereotyped. This stereotyped movement causes near simultaneous activation of multiple sensory inputs to somatosensory cortex. If individuals repetitively perform tasks that simultaneously activate multiple somatosensory regions, somatosensory cortex receptive fields can dedifferentiate by responding to previously ineffective sites on the skin. This change occurs as pyramidal neurons receive simultaneous inputs from different skin regions and fingers on already active neurons.[114] Normally, inhibitory processes prevent cortical networks from being re-excited by an input for several hundred milliseconds after the arrival of the first stimulus. In focal dystonia, however, the magnitude and duration of inhibitory processes decrease,[42] which facilitates this abnormal linking of somatosensory signals. As cortical somatosensory receptive fields dedifferentiate, the "sensorimotor learning" hypothesis posits that individuals become less able to integrate sensory and motor signals that makes movement dystonic. In a variation on this theme, Sanger and Merzernich[102] propose that an increased gain produced by abnormal linking of different somatosensory responses causes focal dystonia.

Byl and colleagues[95–97,115,116] required owl monkeys to perform repetitive hand movements to receive rewards. Before beginning the task and again after the monkeys developed dystonic hand movements, the investigators measured area 3b receptive fields for the hand. In one task,[96,97,115] two monkeys were required to hold on to a hand piece molded to fit the hand. While the monkey gripped the hand piece, it opened and closed by 6.4 mm one to nine times. If the monkey maintained its grip by keeping all of its fingers on the hand piece, the monkey received a reward. The monkeys performed 300 trials per day in which they received 1100-3000 opening and closings of the hand in a 1- to 2-h period. Training occurred 5 or 6 days a week over a 12- to 25-week period. Both monkeys developed hand dystonia so that fingers pulled away from the hand piece as the monkey attempted to grasp it. In another study,[116] the investigators made another three monkeys perform repetitive squeezing of a hand piece for reward. Two of the monkeys developed hand dystonia within 5 or 24 weeks. The third monkey began with a hand squeezing strategy, but switched to a variable arm pulling procedure in the second week of training. This animal did not develop dystonic hand movements within 24 weeks of training. The dystonic movements in these monkeys did not result from inflammation of the tendons or hand caused by repetitive hand movements.[116] The change in hand representation in the somatosensory cortex that accompanied hand dystonia in these monkeys, however, was dramatic. Receptive field size was 10–20 times larger than normal and receptive fields frequently included more than one distal digit. As occurred with human writer's cramp,[89] monkeys also showed enlarged receptive fields in the cortex receiving inputs from the hand not used in the task.[115]

The dramatic transformation in somatosensory cortex representation of the hand in human writer's cramp could cause the syndrome or simply reflect the altered sensory signals produced by the dystonic movements.[117] Although the monkey model of hand dystonia cannot distinguish between these two possibilities, the sensorimotor learning hypothesis argues that the dedifferentiation of somatosensory cortex causes hand dystonia. The animal model studies support this interpretation because somatosensory cortex was normal before training but dedifferentiated with the development of dystonic hand movements. It is surprising, however, that monkeys can

develop focal hand dystonia with only 216,000 occurrences of the hand piece opening and closing. Before developing a task-related focal dystonia, a human experiences many more repetitions of a movement than the monkeys. For example, writer's cramp usually appears around age 38,[14] after the individual has written for at least 32 years. Moreover, the majority of individuals never develop writer's cramp in a lifetime of writing. Although these observations from humans indicate the necessity of a predisposing factor in the development of writer's cramp, the animal model demonstrates that a disruption of the sensory processing from a movement is a critical component of this focal dystonia.

BLEPHAROSPASM

The dystonic movements of blepharospasm are involuntary spasms of bilateral eyelid closure.[9,37] In addition to lid spasms, subjects exhibit an increased spontaneous blink rate that may result from the increased excitability of the trigeminal system that is a constituent of blepharospasm.[118–120] This focal dystonia typically appears later in life than any other dystonia, usually after age 50.[7,9,37,121,122] PET and functional magnetic resonance imaging studies of blepharospasm patients reveal hyperactivity of brain regions typical of other forms of dystonia, frontal cortex, striatum, thalamus, and cerebellum.[123–127] There appear to be three general categories of blepharospasm: 1) benign essential blepharospasm, an idiopathic focal dystonia; 2) reflex blepharospasm, a syndrome associated with dopamine depletion; and 3) Bell's palsy associated blepharospasm, a syndrome concomitant with facial palsy. There are animal models that reproduce reflex blepharospasm and benign essential blepharospasm.

The evidence linking blepharospasm to basal ganglia dysfunction[9,85,123–125] led investigators to modify dopamine levels to model reflex blepharospasm in animals. The blink system is exquisitely sensitive to dopamine levels. The excitability of trigeminal reflex blinks increases as dopamine is lost with normal aging.[128] Elevated dopamine levels increase the rate of spontaneous blinking.[129–135] Despite this increased blink rate, elevated dopamine levels or systemic treatment with apomorphine, a D_2/D_1 receptor agonist, reduces trigeminal reflex blink excitability and the speed of lid closure.[136–138] Conversely, destroying the majority of nigral dopamine neurons with catecholamine-specific toxins such as 6-OHDA, or as a result of Parkinson's disease, dramatically decreases the spontaneous blink rate but increases the excitability of trigeminal reflex blinks.[139–148] This elevated trigeminal excitability can be sufficient for a strong trigeminal stimulus such as touching the cornea to cause involuntary spasms of lid closure in humans[149–151] and rats.[140]

In addition to the reflex blepharospasm in rats caused by 6-OHDA lesions of the substantia nigra pars compacta,[140] systemic injection of the catecholamine depleting compound, Ro 4-1284, produced a reserpine syndrome in mice and rats that included lid closures described as blepharospasm.[152] The characteristics of blepharospasm in this study, however, were unclear. A later study[153] reported that Ro 4-1284 increased blink rate from a predrug rate of 0.34 blinks/min to 1.42 blinks/min after 10 days of Ro 4-1284 treatment. Although these results appear to conflict with previous observations that dopamine reduction depresses the spontaneous blink rate, it is unclear whether the investigators measured spontaneous blinks or increased reflex blinking from elevated trigeminal excitability caused by dopamine depletion.

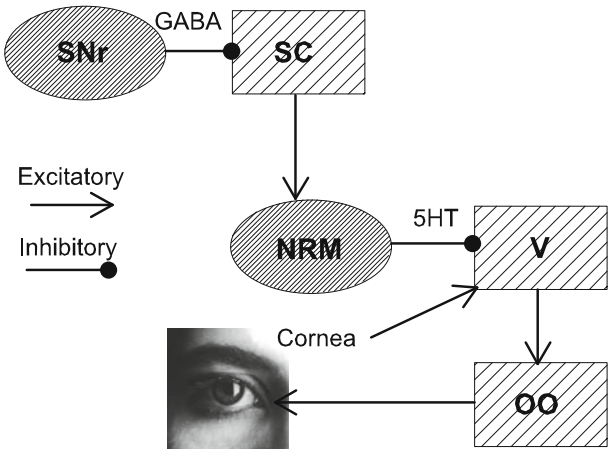

FIG. 1. Schematic of the circuit through which the basal ganglia modulates trigeminal reflex blink excitability from Basso et al.[155] NRM = nucleus raphe magnus; OO = orbicularis oculi motoneurons in the facial nucleus; SC = superior colliculus; V = spinal trigeminal complex.

Although the circuits through which dopamine modulates spontaneous blink rate are unknown, Basso and colleagues[154,155] have determined how the basal ganglia regulate trigeminal reflex blink excitability (FIG. 1). This circuit accounts for the reflex blepharospasm resulting from dopamine depletion. GABAergic (GABA) SNr inhibit neurons in the intermediate layers of the superior colliculus (SC). These neurons excite a small group of neurons in the nucleus raphe magnus (NRM). These serotonergic (5HT) nucleus raphe magnus neurons inhibit trigeminal reflex blink circuits (V), which innervate the lid closing, orbicularis oculi motoneurons (OO). The dopamine depletion of Parkinson's disease increases substantia nigra pars reticulata inhibition of superior colliculus neurons.[156] The consequent reduction of nucleus raphe magnus neuron excitation from the superior colliculus decreases inhibition of the trigeminal blink circuit, thereby increasing its excitability. Conversely, elevating basal ganglia dopamine levels causes an increase in nucleus raphe magnus inhibition of the blink circuits that reduces trigeminal blink excitability.

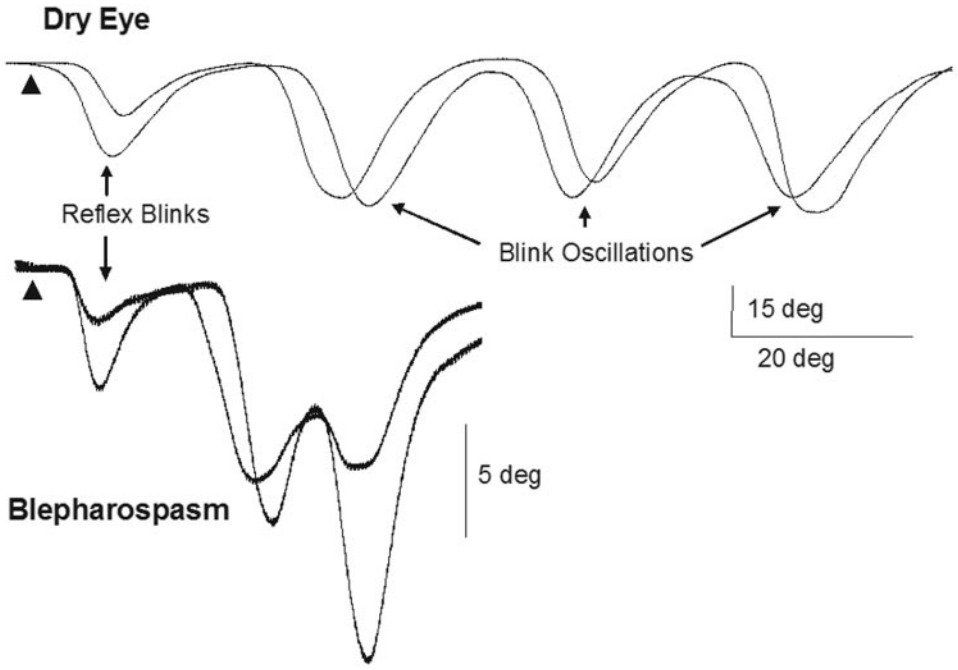

FIG. 2. Reflex blinks and blink oscillations (dry eye) and spasm of lid closure (blepharospasm) elicited by stimulation of the supraorbital branch of the trigeminal nerve (▲). Top traces are two consecutive trials from a human subject with dry eye. Bottom traces are two consecutive trials from a human subject with benign essential blepharospasm. Each trace is a single trial. The spasms of lid closure with blepharospasm appear to be blink oscillations with a very short interblink interval.

The development of reflex blepharospasm rather than benign essential blepharospasm with nigral dopamine depletion does not rule out a role for dopamine in the development of this focal dystonia. Recent genetic evidence from patients with benign essential blepharospasm shows a modification in the gene for the D_5 receptor.[157,158] Future animal studies need to explore the function of the D_5 receptor in blinking.

Schicatano and colleagues[159] created a two-component model of benign essential blepharospasm based on the explanation usually put forth for the development of human blepharospasm. Dystonia arises from the combination of a permissive condition and a precipitating event.[9,37] Benign essential blepharospasm patients frequently come to the clinic with an initial complaint of dry eye.[119] Therefore, Schicatano and colleagues [120] reasoned that cornea irritation might be the precipitating event for the development of benign essential blepharospasm. The normal adaptive response to dry eye or eye irritation is to increase trigeminal reflex blink excitability and to generate additional large amplitude blinks in response to a trigeminal reflex blink stimulus. These additional blinks are called blink oscillations (FIG. 2). Because blink oscillations with dry eye occur with a constant interblink interval, the investigators proposed that the spasms of lid closure of blepharospasm were an exaggeration of the normally compensatory process evoked by dry eye or eye irritation. To create the permissive component of benign essential blepharospasm that would allow an exaggerated response to dry eye, the investigators produced a small, unilateral lesion of substantia nigra pars compacta dopaminergic neurons. By itself, this small 6-OHDA lesion of dopamine neurons slightly increased trigeminal reflex blink excitability but did not generate reflex blepharospasm or spasms of lid closure. To create the precipitating factor, the zygomatic branch of the facial nerve was crushed to transiently eliminate approximately 30% of the orbicularis oculi innervation. By itself, this procedure induced a mild dry eye, which slightly increased trigeminal reflex blink excitability and resulted in the development of blink oscillations similar to that seen in human dry eye. Combining the two procedures, however, dramatically elevated trigeminal reflex blink excitability, increased spontaneous blinking, and caused long-lasting spasms of lid closure similar to benign essential blepharospasm. These blepharospasm-like characteristics continued after the facial nerve regained full function and eliminated the dry eye. Thus, this animal model recreated many of the characteristics of the focal dystonia benign essential blepharospasm.

As occurs in focal dystonia[40,93,160] and generalized dystonia,[29,30,160] the animal model of benign essential blepharospasm[159] creates dysfunctional sensorimotor integration in which the nervous system either misinterprets sensory signals or misrepresents the desired movement. Sensorimotor integration continuously adjusts the eyelid system to maintain cornea integrity. These adjustments, motor adaptations, result from interactions among

the activity of cornea afferents, sensory inputs from the eyelid movement, and a model of the sensory signals anticipated from the eyelid movement. Altering any component of this triad transforms the signals of the other two components. For example, reducing eyelid motility increases afferent input from the cornea because of dry eye and produces an unexpectedly small sensory signal from the attempted eyelid movement relative to the intended eyelid movement. This change in the sensory signals revises the inputs to the eyelid motor circuits in an attempt to reduce cornea afferent input and generate a blink equivalent to the expected lid movement through long-term potentiation- and long-term depression-like modifications of trigeminal blink circuits.[161] The increased cornea afferent input also transforms the trigeminal reflex blink circuit from a single response circuit into a damped oscillator (FIG. 2).[120]

The neural basis of generating dystonic spasms of eyelid closure is unknown. Data from animal and human studies, however, suggest that the cerebellum may be crucial in this process. The cerebellum is essential for eyelid adaptation to reduced eyelid motility.[162] Interpositus neurons of the cerebellum activate lid closing, orbicularis oculi motoneurons via the red nucleus[163–165] and also modulate trigeminal complex neuronal activity.[166] Thus, the cerebellum participates in sensorimotor processing and modulates blink circuits. There is abundant evidence from animal studies that the cerebellum is important in generalized dystonia.[167–171] Low-dose injection of kainic acid into the mouse cerebellum causes a transient generalized dystonia including spasms of lid closure. These dystonic postures result from glutamatergic modifications of Purkinje cell discharge because transgenic mice lacking Purkinje cells do not exhibit dystonic posturing following kainic acid injections into the vermis[169] (see Hess and colleagues[170] in this issue). In a genetically dystonic rat (dt), deep cerebellar nucleus neurons exhibit a bursting rather than a tonic discharge pattern and removal of the cerebellum eliminates dystonic posturing.[167,171,172] This bursting discharge pattern parallels the activity of the orbicularis oculi muscle during eyelid spasms. The cerebellum may modulate the excitability of the facial nucleus and/or interact with other neural structures to create an oscillatory pattern in reflex blink circuits that can convert into spasms of lid closure in the presence of a permissive condition, such as sensorimotor dysfunction.

IMPLICATIONS OF ANIMAL MODELS OF FOCAL DYSTONIA

Human data suggest that dystonia may be a continuum of syndromes from generalized to focal dystonias. Regardless of genetic background, the type of dystonia depends upon the age of development.[6,14] In generalized dystonia appearing in children, the dystonic movements begin in the legs, whereas cranial dystonias appear after age 50 and do not progress to generalized dystonia. Most imaging studies in both generalized and focal dystonias report that the same brain regions exhibit increased glucose uptake or blood flow.[23,80,85,89,123–125,127,173,174] In virtually all cases of primary dystonia, there is dysfunction of the thalamus, frontal cortex, cerebellum, and basal ganglia, particularly the striatum. These altered activity patterns at least partially reflect a reduction in cortical inhibition.[42,117] Finally, abnormalities in sensory processing accompany all forms of dystonia.[29,31] Animal models reinforce these clinical observations. Generalized dystonia in the genetically dt rat results exclusively from modifications in the cerebellum.[167,170,172,175] In contrast, generalized dystonia in the genetically dystonic hamster dt(sz) appear primarily to create basal ganglia dysfunction.[176–186] These generalized dystonia models imply that disruption anywhere in the sensorimotor circuit can produce dystonia. For example, microinjection of σ receptor agonists into the red nucleus causes cervical dystonia.[66,70] Modification of basal ganglia function enables the development of blepharospasm.[159] Thus, animal models of dystonia reveal that disruption in a variety of brain regions can cause dystonia. Alterations in sensory processing are concomitant with these motor system transformations. Indeed, data from the animal model of hand dystonia suggest that degradation of the hand representation in somatosensory cortex alone is sufficient to produce dystonic hand movements.[98] These types of data point to the conclusion that dystonia results from a disruption of sensorimotor integration.

Sensorimotor integration may be a comparison of sensory information resulting from a movement with the sensory information expected from the movement. Inherent to this concept is the postulation that the nervous system has learned the sensations that a specific motor command should generate. Based on this knowledge, unanticipated sensory signals identified by sensorimotor processing can serve as signals to modify the ongoing movement or subsequent movements. Normally, this process provides an effective and unconscious way to adapt neural commands to internal or external changes in the movement environment. Several lines of evidence suggest that the cerebellum plays an important role in this process.[187–191] Nevertheless, sensorimotor integration for complicated actions such as hand movements probably engages multiple brain regions such as motor cortex areas, basal ganglia, somatosensory cortex, and cerebellum. Disruption of neural signals in any structure could mutate the activity pattern in all of the others. For example, if the basal ganglia fails to suppress competing motor commands of a specific movement,[192,193] then sensorimotor integration should recognize the unanticipated sensory signals from the movement and attempt to

compensate for them. If sensorimotor processing is abnormal in dystonia, the brain will not identify the movement as anomalous. Dedifferentiation of the hand representation of somatosensory cortex can provide unanticipated sensory information from a normal movement. The attempt to correct this illusory error may produce dystonic hand movements. Disruptions of primary motor cortex can create motor commands in which the movement does not match the anticipated sensory consequences. Animal models of focal dystonia provide powerful tools to analyze these complex interactions. Understanding modifications in sensorimotor processing in focal dystonia may help establish how genetic mutations combine with the environment to create generalized dystonia.

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