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Eyelid Anatomy and the Pathophysiology of Blinking
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Glossary
Blepharospasm – A dystonic muscle contraction disorder characterized by forceful, bilateral, and uncontrolled closure of the eyelids.
Hemifacial spasm – A muscle contraction disorder characterized by forceful uncontrolled contraction of the facial muscles on one side of the face.
Levator palpebrae superioris muscle – A skeletal muscle innervated by cranial motor nerve 3 whose primary function is elevation of the upper eyelid.
Müller’s muscle – A smooth muscle that runs from the inferior surface of the tendon of the levator palpebrae superioris to insert into the tarsal plate. It receives sympathetic nervous system innervation.
Omnipause neurons – Part of the brainstem neural circuit that controls saccades. These neurons fire during fixation and cease firing before and during saccadic movements. Stimulation of omnipause neurons interrupts saccades.
Orbicularis oculi muscle – A circumferential muscle of facial expression innervated by the facial nerve that lies just deep to the skin within both eyelids as well as the surrounding bones of the orbital margin. Its main function is closure of the eyelid.
Paresis – Partial paralysis of a skeletal muscle resulting in muscle weakness.
Retractor bulbi muscle – Skeletal muscles innervated by cranial nerve 6 whose function is to retract the eyeball into the orbit causing movement of the nictitating membrane over the surface of the eye.
Saccades – Rapid eye movements that redirect the line of sight so that the image of interest falls on the fovea of the retina.
Vergence – The coordinated movements of both eyes in opposite directions in order to maintain binocular vision.

Organization of the Eyelid System
To understand the neural control of eyelids, the basis of neurological diseases affecting eyelid control, and how the eyelids protect the eye, think about the evolutionary origins of eyelids. For fish, a class of vertebrates without eyelids, eye protection primarily requires avoiding objects hitting and damaging the cornea. To avoid objects hitting the eyeball, fish retract their eyes into the orbit by co-contracting their extraocular muscles. Thus, cornea protection was initially linked to neural circuits whose primary goal was to move the eye. When vertebrates moved onto the land, the development of eyelids was a critical step in reducing the dehydrating effects of air on the cornea. Although goblet cells, lacrimal and meibomian glands produce the fluids to coat the corneal surface, it is blinking of the eyelid that spreads the tears to restore the tear film, which maintains corneal hydration. In addition, blinking removes small objects from the surface of the eye and provides some protection from objects getting into the eye. Although blinking is essential for maintaining the cornea, lid closure has the undesirable side effect of blocking vision. Thus, an eyelid control system must generate blinks that minimally disrupt vision while adequately protecting the cornea. The nervous system deals with this constraint by developing fast eyelid closure and opening without carefully controlling absolute eyelid position. The other restriction on the nervous system’s management of the eyelids is that they must move synchronously with vertical eye movements to avoid blocking vision. Overcoming this problem requires the nervous system to control eyelid position accurately. The eyelid control system accomplishes this feat by linking itself to the eye movement system. The melding of the eyelid system with the eye movement system reveals itself first in the anatomical organization of the eyelids.

Only four forces act on the upper eyelid (Figures 1(a) and 2). (1) The phasically active orbicularis oculi (OO) muscle actively closes the eyelid. The ipsilateral facial (VII) nucleus innervates the OO muscle. (2) The tonically active levator palpebrae superioris (LP) muscle actively elevates the upper eyelid. LP innervation arises from the oculomotor (III) nucleus. (3) Raising the eyelid stretches the superior transverse (Whitnall’s) ligament and the lateral and medial canthal tendons to create a passive downward force. Thus, the lowest energy state for the eyelid is closed. (4) Müller’s smooth muscle (Figure 2), which bridges the belly and the tendon of the LP, raises the eyelid approximately 1.5 mm with sympathetic activation. Post-ganglionic nerves from the superior cervical ganglion innervate Müller’s muscle. The interaction between the first three forces (OO, LP, and passive downward forces) enables
the eyelids to blink rapidly yet accurately match the vertical position of the eyeball.

The characteristic rapid eyelid closure of a blink followed by lid opening at approximately half the speed of lid closure follows directly from the anatomical organization of the eyelid (Figures 1(b)–1(d)). A blink begins with relaxation of the tonically active LP muscle. LP relaxation releases the passive downward forces to initiate lid closure. The phasically active OO muscle discharge combines with the passive downward forces to lower the eyelid rapidly. As the OO muscle relaxes, the LP muscle slowly resumes its tonic discharge. This LP contraction raises the upper eyelid. Eyelid elevation is slower than lid closure because the LP muscle must work against the passive downward forces. The point at which the tonically active LP force matches the passive downward force created by tendon and ligament stretching determines final lid position. This anatomical organization is conserved so that the pattern of blinking is similar among mammals (Figures 1(c) and 1(d)).

In contrast to the interactions between the OO and LP muscles and passive downward forces with blinking, the coordination of eyelid motion with vertical eye movement arises from the antagonistic interactions between the LP muscle and the passive downward forces. The linkage with eye movements occurs because the LP behaves like the superior rectus muscle, which rotates the eye upward. Embryologically, the LP muscle arises from the superior rectus muscle, and LP motor neurons are always adjacent to superior rectus motor neurons in the oculomotor nucleus. LP and superior rectus motor neurons exhibit similar patterns of activity except during a blink. The tonic firing frequency of superior rectus and LP motor neurons correlates with vertical eye position. With an upward saccadic eye movement, superior rectus and LP motor neurons generate a burst of action potentials followed by an increased tonic firing frequency that holds the eye in the new elevated position. A downward saccade results from a cessation of tonic activity followed by a lower frequency tonic discharge to hold the eye in the

**Figure 1** Forces acting on the eyelid and mammalian blinking. (a) Opening the eye stretches the levator palpebrae (LP) aponeurosis (APO), the superior transverse ligament (Whitnall’s ligament, WL), and the medial and lateral canthal tendons (CT) to create passive downward forces. The lowest energy state for the eyelid system is closed. (b) Lid (Pos) lowering during a blink results from a transient relaxation of the LP followed by a phasic activation of the orbicularis oculi (OO) muscle. Raising the eyelid occurs as the LP resumes its tonic activity following the completion of OO activity. Gray indicates LP activity and black indicates OO activity. (c, d) Individual examples of a reflex blink evoked by stimulation of the supraorbital branch of the trigeminal nerve (SO ▲) for a human (c) and a guinea pig (d). R1 is the short latency response and R2 is the long latency response seen after nerve stimulation. Abbreviations: OOemg, orbicularis oculi EMG; Pos, upper eyelid position.
depressed position. When the LP motor neurons transiently cease discharging during a downward saccadic eye movement, unopposed passive downward forces lower the eyelid. When the LP motor neuron resumes its activity at a lower tonic firing frequency, the new balance point between passive downward forces and active upward LP muscle force establishes the final eyelid position. With an upward eye movement, the increased LP motor neuron firing frequency pulls the eyelid upward until the LP muscle and passive downward forces match. Although it seems counter-intuitive that passive downward forces rather than the OO muscle act as the antagonist to the LP muscle with eye movements, it is clear that the OO does not participate in eyelid movement with vertical saccades. For example, individuals with OO denervation created by seventh nerve palsy exhibit nearly normal saccadic lid movements with vertical saccades but abnormally slow blinks.

Further evidence of the evolutionary linkage of blinking with the oculomotor system is that blinks frequently occur with saccadic eye movements. These gaze-evoked blinks most commonly accompany large saccades to visual targets that do not have a strong behavioral significance. The advantage of combining blinks with saccades is that visual suppression occurs during both blinks and saccades. A gaze-evoked blink refreshes the tear film, but does not produce more loss of vision than the saccadic eye movement. The evolutionary linkage also appears in the eye movements associated with blinking, blink-evoked eye movements. When looking straight ahead, there is an adducting and downward rotation of the eye with each blink. Nevertheless, the state of the eyelid system determines the trajectory of blink-evoked eye movements. These movements exhibit an upward trajectory in both eyes and are smaller than normal in individuals with a unilateral seventh nerve palsy. Eyeball retraction is also a component of these blink-evoked eye movements. For mammals, the eyeball retraction with blinking results from extraocular muscle co-contraction and contraction of the retractor bulbi muscle. This accessory extraocular muscle is innervated by motor neurons in the accessory abducens nucleus that send their axons to the orbit as part of the VIth nerve. Extraocular muscle co-contraction with blinking in mammals appears to reflect the evolutionary origins of the eyelid control system from eye retraction of fish. Despite blink-evoked eye movements accompanying all blinks, neither gaze-evoked nor reflex blinks occurring with a saccade prevent the eye from achieving its desired endpoint. With a simultaneous blink and saccade, the eyes follow a complex trajectory instead of the nearly straight path of a saccadic eye movement alone. This complex
trajectory results in a significantly slower saccade than when the saccade occurs alone.

The linkage between blinking and saccadic eye movements indicates that blinking interacts with the brainstem circuits that generate saccadic eye movements. This interaction is apparent when reflex blinks increase the speed of saccadic eye movements in individuals with abnormally slow saccades, initiate saccade oscillations, and alter the speed of vergence eye movements where the eyes are moving in opposite directions. The neurophysiological mechanism that may underlie these effects is the activity of omnipause neurons, which control fixation, and are associated with reflex blinks. Tonically active omnipause neurons gate saccadic eye movements. Omnipause neurons cease discharging immediately before and during all saccadic eye movements and reflex blinks. Microstimulation of omnipause neurons blocks reflex blinks as well as saccadic eye movements. The evolutionary origins of eyelid control functionally intertwine blinking and saccadic eye movements so that blinks frequently occur with saccadic eye movements, blinking modifies the trajectory of eye movements, and blinking and saccadic eye movements utilize some of the same brainstem neuronal circuits.

**Modifiability of the Blink System**

In order to respond to challenges to the eyelid's protective function, the neural control of blinking exhibits significant adaptive plasticity. The most common challenge to the protective function of blinking is the development of dry eye. Cornea irritation created by tear film inadequacy rapidly initiates several changes. First, the trigeminal system becomes more excitable, so that a given blink-evoking stimulus elicits a bigger blink than before cornea irritation. In addition to increased blink excitability, the trigeminal reflex blink circuit begins to ‘oscillate’ in response to a blink-evoking stimulus (Figure 3). In this condition, a single stimulus evokes a reflex blink followed by blink oscillations, one or more additional large blinks. Blink oscillations occur at a constant interblink interval. These modifications compensate for dry eye in at least two ways. The reduced threshold for evoking a blink produces more frequent blinking so that blinks can occur before significant disruptions of the tear film. The larger blinks increase the amount of meibum released over the tear film. Increasing the thickness of the oily meibum layer superficial to the aqueous layer reduces aqueous evaporation. Disruptions of these normally adaptive mechanisms may underlie neurological disorders involving the eyelids, benign essential blepharospasm (BEB) and hemifacial spasm (HFS).

We have an outline of the neural basis for these adaptive modifications of the blink reflex initiated by eye irritation. The adaptive changes occur in trigeminal blink circuits, but not at OO motor neurons or reticular neurons receiving bilateral trigeminal inputs. If just one eye experiences irritation, stimulating the ophthalmic branch of the trigeminal nerve on the irritated side elicits adaptive blink modifications in both eyelids. Stimulating the contralateral trigeminal nerve associated with the unaffected eye, however, elicits normal, unadapted blinks in both eyes. Consistent with this result, spinal trigeminal neurons in the corneal-evoked blink circuit discharge before blink oscillations, and this discharge correlates with the pattern of OO activity producing the blink oscillation. Although the adaptive processes clearly involve the trigeminal system, the cerebellum is also essential for blink adaptation. Blink-related neurons in the cerebellum are active with blink adaptation, and lesioning the cerebellum blocks this form of motor learning. A hypothesis for the function of this brainstem–cerebellum circuit is that the cerebellum recognizes an error signal produced by eye irritation and then initiates modifications in spinal trigeminal blink circuits to compensate for the eye irritation. These adaptive modifications in the trigeminal blink circuits may involve long-term potentiation (LTP)- and long-term depression (LTD)-like processes.

**Figure 3** Stimulating the supraorbital branch of the trigeminal nerve (SO ▲) evokes a reflex blink followed by additional blinks with a constant interblink interval, blink oscillations. Each upper eyelid position trace is a record from a single trial from an individual with dry eye.
As discussed in the next section, the cerebellum appears to be an important element in creating the symptoms of dystonic movement disorders such as BEB.

**Benign Essential Blepharospasm and Hemifacial Spasm**

BEB is a focal dystonia characterized by involuntary bilateral spasms of lid closure, trigeminal reflex blink hyperexcitability, and photophobia (i.e., excessive sensitivity to light). BEB frequently begins with a complaint of ocular discomfort. The available evidence indicates that BEB arises from the confluence of a predisposing and a precipitating factor. Although the predisposing factor has not been identified, the genetic basis for other forms of dystonia suggests that the predisposing factor for BEB is genetic. The precipitating factor appears to be ocular irritation. Consistent with eye irritation as the precipitating factor is that BEB characteristics appear to be an exaggeration of the normally adaptive response to dry eye.

For most individuals, the spasms of lid closure in BEB are rapid, repetitive contractions of the OO muscle. This spasm pattern is equivalent to shortening the interblink interval of the blink oscillations developed in response to dry eye (Figure 3). BEB patients exhibit trigeminal reflex blink hyperexcitability. One adaptive response to dry eye is to elevate trigeminal reflex blink excitability, although this increase accompanying dry eye is not as profound as occurs with BEB. The trigeminal hyperexcitability with BEB is sufficient to explain the photophobia. Consistent with the exaggeration of dry eye hypothesis, photophobia is present with dry eye although the light sensitivity is not as debilitating as with BEB. Thus, the exaggerated dry eye hypothesis proposes that BEB begins with the onset of dry eye or significant eye irritation. The nervous system initiates blink modifications to compensate for this irritation, but the genetic predisposition prevents the nervous system from recognizing that the adaptive changes corrected the ocular irritation. The nervous system responds by further increasing these adaptive modifications until the normally compensatory mechanisms becomes so maladaptive as to create the BEB syndrome.

Although genetic modifications probably create the predisposing environment for BEB, the genetics underlying this focal dystonia are not yet clear. Most investigators agree that there is an autosomal dominant transmission with reduced penetrance in BEB. One challenge to linking genetics to specific types of dystonia, however, is that individuals with the same genetic mutation may exhibit very different forms of dystonia. For example, individuals with the DYT1 mutation responsible for the most common form of generalized dystonia may exhibit generalized dystonia, focal dystonia, or may be asymptomatic. Individuals with generalized dystonia, focal dystonia, and asymptomatic DYT1 carriers all exhibit a similar pattern of abnormal brain activity. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) scans reveal hyperactivity in the basal ganglia, primary motor cortex, supplementary motor area, putamen, thalamus, and cerebellum. In patients with BEB, these areas are also active, but the focus of abnormal activity is in the brainstem and cerebellum. Abnormal cerebellar activity with BEB supports the hypothesis that abnormal blink adaptation involving the cerebellum is critical in the development of BEB. Consistent with the hypothesis that a genetic predisposing factor affects adaptation or motor learning, individuals with BEB exhibit exaggerated LTP-like plasticity of blink circuits relative to normal subjects.

There are two clear examples in which exaggeration of the adaptive processes initiated by eye irritation or dry eye leads to BEB. A small number of individuals with Bell's palsy develop blepharospasm. The ocular irritation produced by incomplete eye closure, the precipitating factor, initiates unadapted modifications that produce the BEB syndrome. As predicted by the exaggerated dry eye hypothesis, implanting gold weights in the paretic (weakened) eyelid, enabling nearly complete closure of the paretic eyelid, reduces eye irritation and allows a resolution of BEB signs. Combining predisposing and precipitating factors can also create a BEB-like syndrome in rats. In this model, a chemical lesion reducing approximately 30% of the dopamine neurons in the substantia nigra pars compacta elevates the excitability of the trigeminal blink reflex circuits. This increased trigeminal excitability acts as the predisposing factor. Transient eye irritation produced by crushing a facial nerve branch providing a portion of the OO innervation acts as the precipitating factor. The reduced eyelid mobility created by this procedure causes eye irritation that initiates adaptive blink modifications. Although the eye irritation resolves following nerve regrowth, rats continue to exhibit spasms of lid closure caused by repetitive bursts of OO activity and hyperexcitable trigeminal reflex blinks. Thus, the evidence indicates that BEB occurs in individuals genetically predisposed to the disorder who experience a precipitating condition, ocular irritation. The ocular irritation initiates a series of normally adaptive modifications. In the presence of the predisposing condition which creates an abnormal environment for motor learning, these modifications become exaggerated to create the signs of BEB.

HFS begins as spontaneous, unilateral spasms of eyelid closure. Over a period of weeks to months, the spasms expand to include the rest of the facial muscles on that side of the face. Another characteristic of HFS is synkinesis in which there is an involuntary activation of multiple muscles that normally do not act together. An example of synkinesis is that stimulating the supraorbital branch of the trigeminal nerve would strongly activate the mentalis muscle, as well as the OO, in HFS patients.
HFS is unilateral and involves most of the ipsilateral facial muscles in addition to the OO. There is strong evidence, however, that HFS also arises from a combination of predisposing and precipitating factors that disrupt normal motor learning.

The accepted precipitating factor for HFS is arterial compression at the root entry zone of the facial nerve. The most common blood vessels affecting the facial nerve in HFS are the anterior inferior cerebellar artery, the posterior inferior cerebellar artery, or the vertebral artery. Microsurgical decompression of the facial nerve typically reduces or eliminates the spasms and synkinesis of HFS so that spasms disappear in 64% and synkinesis in 53% of HFS patients within the first week following surgery. After 2–8 months, 90% of patients are spasm or synkinesis free. If arterial compression of the facial nerve alone is responsible for these signs of HFS, however, then decompression surgery should eliminate the spasms and synkinesis in less than 2–8 months. To understand the basis for this delay, it is important to consider what neural modifications might occur in response to pulsatile arterial compression of the facial nerve. A strong argument that facial nerve compression alone is insufficient to cause HFS is that 15–25% of the population exhibits arterial compression of the facial nerve, but do not develop HFS. This observation shows that HFS requires a predisposing factor as well as the precipitating factor, arterial compression of the facial nerve.

Pulsatile arterial compression of the facial nerve can generate many modifications in brainstem neural circuits. Compression injury to motor neuron axons effectively weakens facial muscles, which initiates adaptive modifications. Repetitive antidromic activation of facial motor neurons by pulsatile compression of axons can alter facial motor neuron excitability or motor neuron excitability may increase because of facial motor neuron axotomy, severing the facial nerve fibers. Repetitive orthodromic activation of facial muscles by pulsatile compression of motor neuron axons can lead to a reorganization of sensory trigeminal circuits. Simultaneous orthodromic (electrical impulses traveling in the normal direction) activation of muscles that normally do not act together, for example, mentalis and OO, causes trigeminal primary afferent sensory signals from mentalis and OO muscle contraction to reach second-order trigeminal neurons synchronously. This abnormal pairing of sensory inputs can restructure trigeminal receptive fields so that the second-order trigeminal neurons respond strongly to inputs from both mentalis and OO activity instead of weakly to one and strongly to the other. Pulsatile activation of the facial nerve can also augment reflex circuit excitability because of synchronous activation of circuit elements. Second-order trigeminal neurons receiving synchronous afferent inputs innervate facial motor neurons that are already depolarized by antidromic activation. This activity pattern can strengthen trigeminal inputs onto facial motor neurons in a spike timing-dependent plasticity-like manner.

It is clear that pulsatile activation of the facial nerve can produce blink modifications, but these changes should not cause HFS by themselves. The eyelid system normally modifies itself so as to perform appropriately in the face of changes in the motor system or sensory inputs. For example, creating unexpectedly large blinks by adding weights to the upper eyelids initiates a rapid reduction in the trigeminal drive onto OO motor neurons. Similarly, chronic, repetitive facial nerve stimulation, such as occurs with pulsatile facial nerve compression, reduces blink amplitude. Thus, pulsatile facial nerve compression is insufficient to cause spasms of lid closure because the blink system will modify itself to prevent spasms of lid closure. The significant number of humans not experiencing HFS, but exhibiting arterial compression of the facial nerve, further supports this interpretation. These observations indicate that HFS, like BEB, requires a predisposing factor to develop spasms. Like BEB, an autosomal-dominant genetic mutation with low penetrance may provide the predisposing condition, which disrupts normally adaptive processes to create a pathological condition.

See also: Cranial Nerves and Autonomic Innervation in the Orbit.

Further Reading


