

SEMINARS

These papers, similar to the Lectures to State Branches, are included in the Journal to avail others outside the State of origin of the material being presented to the particular teaching department. They have been segregated from the Lectures section because of their theoretical nature. The material is selected on the grounds that it is suitable background information for current clinical trends.

The determinants of neuro-muscular activity

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Neuromuscular activity is a central factor in orthodontic diagnosis, and in what the orthodontist can achieve with treatment. This discussion will begin with an outline of the components involved, and the general anatomy and physiology concerned, before relating the particular patterns of neuromuscular activity of interest in orthodontics.

EMBRYOLOGY

Muscles develop from condensations of mesodermal mesenchyme that differentiate into myoblasts, which continue to divide until about the middle of foetal life. Myoblasts then fuse to form multinucleated myotubes that synthesize the contractile proteins actin and myosin. Myotubes become muscle fibres (myocytes). Neuromuscular contacts are made by most maturing myotubes, but this poly-neural innervation is often temporary, with subsequent reduction of innervation to produce variably sized muscular motor units. In late foetal life and postnatally, muscle growth occurs by increase in size (hypertrophy) of individual muscle fibres.

The facial, masticatory, and laryngopharyngeal muscles arise from the mesodermal cores of the branchial arches. A postbranchial muscle mass combines with the cervical somites to give rise to the Trapezius and Sternomastoid muscles. The myotomes of the occipital somites migrate ventrally as the hypoglossal cord to provide the muscles of the tongue, supplied by the hypoglossal nerve.

The branchiomeric mesenchyme of the first branchial arch gives rise to the muscles of mastication, and to the Mylohyoid and the anterior belly of Digastric. The mandibular nerve supplies this arch.

The second arch mesenchyme provides the muscles of facial expression, and the posterior belly of Digastric, Stylohyoid, and Stapedius, supplied by the facial nerve.

The branchiomeric mesenchyme of the third, fourth, and fifth/sixth arches merges into the palatofaucial, pharyngeal, and laryngeal muscle groups, supplied by the glossopharyngeal and vagus nerves. The Geniohyoid and infrahyoid muscles are of upper cervical somitic origin, supplied by C1 and C2.

PHYSIOLOGY

Each myofibril is composed of individual units called sarcomeres. These units are a product of the differential refractivity of the muscular components which produce the classical Z line, I band, A band, I band, Z line appearance seen microscopically. (see diagram Huxley (1956) page 249 in Samson Wright)

The proteins active in the muscle contractile mechanism are actin, myosin, tropomyosin and troponin.

Neuromuscular transmission.

The motor nerves to skeletal muscle are cholinergic in nature, synapsing at the motor end plate. Acetylcholine is released from the presynaptic vesicles on nerve impulse. Sodium and Calcium ions inflow causes an end plate potential. When a level of 30-40 mV is reached, a

propagated muscle action potential causes contraction. Acetylcholine (ACh) is removed from the motor end plate by destruction, by acetylcholine-esterase.

Neuromuscular transmission may be blocked by inhibition of ACh release, a pre-synaptic block, as caused by botulinum toxin, or by post-synaptic block.

Post-synaptic neuromuscular blocking agents of clinical significance work by competition, or depolarization. Tubocurarine competes with ACh by attaching to the motor end plate receptors. Suxamethonium causes paralysis by persistent depolarization of the end plate.

Myasthenia Gravis is a condition producing skeletal muscle weakness and fatigue. Muscles supplied by the cranial nerves are most affected. There is a marked reduction in the amount of ACh in the synaptic vesicles, and muscle contractions are not sustained. The motor end plates are also less sensitive. The anticholinesterase Neostigmine relieves the symptoms. The thymus is involved in 80% of cases, and thymectomy cures these patients. Myasthenia gravis is one contraindication for Librium (chlordiazepoxide) which is used by some practitioners for bandings.

THE NERVOUS SYSTEM

The following section is a description of the components of the nervous system which, in total, regulate neuromuscular activity.

The Monosynaptic reflex arc is the simplest feedback system, whereby an afferent nerve from a muscle, via the dorsal root ganglion in the spinal cord segment involved, synapses with an anterior horn cell to stimulate the motor neurone to the muscle.

Axonal transport — Axoplasm flows; centrifugal flow may be slow (1mm/day) to carry protein components essential for growth or regeneration of the axon, or fast (10-20cm/day) carrying enzymes for the manufacture of transmitters.

The Stretch reflex in muscles is monosynaptic. This is the basis for muscle tone. The more common arcs, however, are polysynaptic. Here incoming afferents synapse with intercalary (internuncial) neurones, which synapse with others which finally modify the motor neurones involved in the arc. The reflex arc forms the functional unit of the Central Nervous System.

Direct Inhibition.

The stretch reflex causes muscle contraction in the agonist muscle via a monosynaptic arc. Simultaneously, a disynaptic arc causes relaxation in the antagonist muscle. Afferents from the muscle spindle travel along collaterals which synaptically excite special neurones of the neighbouring "intermediate nucleus of Cajal". These discharge along short axons to liberate inhibitory transmitter at the antagonist motoneurone. Renshaw cells and motoneurone inhibition.

Renshaw cells, neurones situated in the ventral horn of the spinal cord, are stimulated by collaterals from axons of discharging motoneurones. The axons of the Renshaw cells act to inhibit the relevant motoneurones, thereby curbing their discharge. Golgi tendon organs, to be discussed later, excite interneurone cells, which release an inhibitory transmitter on the agonist motoneurone. All the above inhibitions are Post-synaptic. Incoming axons deliver an inhibitory chemical which hyper-polarizes the sub-synaptic membrane.

Pre-synaptic Inhibition.

In this process, afferent fibres from a muscle produce depolarization of the pre-synaptic terminal via interneurons, which causes less transmitter to be released. Eccles (1984) classified the interneurons as "D" cells, present in the dorsal horn. Barbiturates greatly accentuate pre-synaptic inhibition.

Receptors.

Receptors which respond to external changes are called Exteroceptors. These include cutaneous receptors, responding to touch, temperature, injury and also the senses of sight, hearing, smell and taste. Interoceptors respond to changes within the body itself, and include proprioceptors, visceroreceptors (e.g. baroreceptors and nociceptors) and chemoceptors.

Cutaneous Receptors.

- (1) Tactile corpuscles of Meissner are ellipsoidal structures which occur in groups in cutaneous papillae. They occur in high density in sensitive places (lips, fingertips etc.) and at the base of hair follicles. They are rapidly adapting, hence we do not feel clothing once it has been put on.
- (2) Pacinian Corpuscles are large, onion-shaped receptors present in subcutaneous tissues and near tendons and joints. They respond to deformation caused by firm pressures and are quickly adapting.
- (3) End Bulbs of Krause are spherical, but otherwise resemble the tactile corpuscles. They are mechanoreceptors, found in the conjunctiva, papilla of the lips and tongue, the skin of the genitalia, and on the sheaths of nerves.
- (4) The Organ of Ruffini in the dermis, is supplied by a large, myelinated axon. It is probably a mechanoreceptor.
- (5) Free unencapsulated nerve endings respond to noxious stimuli. They subserve sensations of touch and temperature, as well as pain.

Proprioceptors

- (1) Muscle Spindles
- (2) Golgi Tendon Organs
- (3) Joint Receptors
- (4) Vestibular Receptors

Joint Receptors

These are mainly Pacinian and Golgi type, which are situated in the tendons of the joint. Ruffini end organs are found in the joint capsule. Three types of response have been observed:

- (1) Golgi end organs in ligaments discharge relative to the position of the joint. They are slowly adapting and relatively insensitive to movement.
- (2) Ruffini end organs respond to movements, but are quickly adapting and so do not give much information regarding position.
- (3) Pacinian corpuscles in ligaments are very sensitive to quick movement or vibration. Skoglund (1973) suggests they may be "acceleration detectors".

Afferents from joint receptors relay in the spinal cord and then travel in the posterior columns, relaying in the thalamus to contralateral sensory cortical areas I and II, and ipsilateral sensory area II, within 15 msec.

Cutaneous sensibility

Dorsal root fibres subserving pain and temperature are very small myelinated or unmyelinated fibres. The sensory endings of nociceptive fibres are unmyelinated naked nerve terminals. On entering the cord, the fibres branch extensively and run several segments up and down the cord in the most lateral part of the posterior horn (Lissauer's tract) before synapsing in the apical zone of the posterior horn. Second order axons cross the midline and ascend as the lateral spinothalamic tract. Before reaching the thalamus, these fibres are joined by those from the gracile and cuneate nuclei to form the medial lemniscus.

Other fibres subserving touch relay in the dorsal horn to give rise to second order fibres and cross to the

opposite side to ascend as the ventral or anterior spinothalamic tracts. These are also incorporated in the medial lemniscus. This tract is of less importance as tactile sensation is also conveyed by tracts in the dorsal columns.

Position Sense

(a) Conscious sense of position, vibration, and deep pressure is carried by axons of joint receptors and Pacinian corpuscles. From the cervical region, the fibres terminate in the cuneate nucleus of the medulla. Second order fibres sweep vertically across the midline (internal arcuate fibres) to form the medial lemniscus.

(b) Unconscious proprioception. The afferents are from muscle spindles and tendon end organs. They ascend in the dorsal spinocerebellar tract to the anterior lobe of the cerebellum.

THE BRAIN STEM

The brain stem contains the nuclei of cranial nerves XII, XI, X, and IX.

The hypoglossal nerve (XII) supplies the muscles of the tongue.

The accessory nerve (XI) supplies the Sternomastoid and Trapezius.

The vagus nerve (X) supplies the muscles of the larynx and heart.

The glossopharyngeal nerve (IX) supplies the muscles of the pharynx.

The facial nerve (VII) is arranged similarly to the above, but its nucleus is in the pons. It supplies the muscles of facial expression. Autonomic fibres arise in the dorsal nucleus. The motor nucleus is in line with the nucleus ambiguus. In lesions of the pyramidal tract (supranuclear lesions) voluntary movements of the face are lost, but emotional movements (frowning, smiling) are retained.

The Midbrain

This consists of the superior and inferior colliculi, and the cerebral peduncles.

The motor nucleus of the trigeminal nerve (V) lies at the side of the grey matter bounding the aqueductus cerebri and fourth ventricle in the lower midbrain and upper pons. The afferent fibres are derived from the semilunar (Gasserian) ganglion and end in a mass of grey matter lying lateral to the motor nucleus. Long descending fibres are given off which form the spinal tract to the upper cervical region of the cord. From the sensory nuclei a relay of fibres cross the midline to join the medial lemniscus.

Ascending paths in the brain stem

(1) The Medial Lemniscus conveys impulses in the dorsal columns from joint receptors, touch receptors, Pacinian corpuscles and other sources.

(2) The Spinothalamic Tract. Fibres from touch receptors rejoin those in the medial lemniscus.

(3) The Spinocerebellar Tracts convey impulses from muscle and tendon receptors and also cutaneous afferent fibres.

(4) The Cranial Nuclei. Afferents from the face travel via the Vth nerve to the sensory nucleus in the pons, and in the descending root of the upper cervical spinal cord. Fibres of the ophthalmic, maxillary and mandibular divisions travel in the descending root, but the order of the termination is reversed, with the ophthalmic division ending in the lowest part.

MUSCLE TONE

Muscle tone is a state of "partial tetanus" maintained by asynchronous impulses from motor nerves. Tone is a reflex to muscle spindle afferents which excite alpha-motoneurons supplying the muscle containing the spindle. It is a monosynaptic reflex arc. Supraspinal pathways modify the arc reflex. Midcollicular transection of the brainstem (decerebrate preparation) leads to exaggerated muscle tone. The stretch reflex is the most prominent in the anti-gravity muscles. Spindles are not

stimulated by voluntary effort because intrafusal motor nerve fibres, gamma fibres, cause contraction of intrafusal muscle to influence the central part of the spindle, which contains the large afferent nerve endings.

The Muscle Spindle

This is a fusiform structure, several millimetres long, located in parallel with muscle fibres. Each spindle contains 2-12 intrafusal fibres. Primary, annulo-spiral, afferents innervate the central equatorial region of each intrafusal fibre. They are fast, large diameter fibres. Secondary, slower afferent fibres are in polar positions.

POSTURAL REFLEXES

The following reflexes are found in decerebrate animal preparations.

- (1) Stretch Reflexes
- (2) Positive Supporting Reaction

Here all the muscles of the limbs reflexly contract, extensors and flexors, to form a solid rigid pillar. It is seen after removal of the anterior lobe of the cerebellum.

(3) An example is the crossed extensor reflex. Impulses from one leg reflexly produce extension of the opposite limb.

- (4) Attitudinal Reflexes

Posture can be adjusted in accordance with:

- (a) alterations of position of the head in space. Here afferents come from otolith organ of the vestibule, (tonic labyrinthine reflex).
- (b) changing position of the head relative to the trunk. Additional afferents come from the neck muscles, (tonic neck reflexes).

Tonic Neck Reflexes

The receptors are Pacinian corpuscles in the cervical joints, especially the atlanto-occipital joint, and also neck muscle spindles. Various movements of the head produce reflex tonicity in the limb muscles, for support and other purposes. Centres for the reflexes are in the cervical spinal cord.

Tonic Labyrinthine Reflexes

These are due to alterations in the position of the head relative to the horizontal plane. Receptors are in the otolith organ. The centres are in the vestibular and reticular nuclei. Maximum tone is elicited in the anti-gravity muscles when the animal is in the supine position.

The vestibular apparatus is stimulated by gravity, and rotation movements. The function is to indicate head movement, and to transmit impulses to cranial nuclei III, IV, and VI which supply the eye muscles, which compensate for this head movement. As a result, the position of the eyes is held approximately constant, allowing visual fixation on moving objects.

The Reticular Formation

This is an interlacing network of fibre bundles in the brain stem, which sends both inhibitory and facilitatory fibres to spinal neurones. In decerebrate animals the result is exaggerated muscle reflex and exaltation of stretch reflexes.

THE CEREBELLUM

The Flocculo-nodular lobe controls body posture by maintaining equilibrium or steadiness.

The Anterior lobe:

- (1) Receives tactile and proprioceptive impulses.
- (2) Modifies muscle tone and stretch reflexes. Stimulation of the anterior lobe may inhibit tone in the extensor muscles. Anterior lobe activity depresses gamma efferents to intrafusal fibres, but also forms a link between the alpha and gamma systems responsible for muscle tone.

The Neocerebellum (most of the cerebellar hemispheres) These connect with the opposite cerebral hemisphere, and the upper brainstem. Cerebral/cerebellar connections mutually influence one another's activities.

The function of the cerebellum is as a comparator

of a servo-mechanism. It receives both a representation of the cortico-spinal activity which is transmitted to the muscles, and almost simultaneously a representation of the result in terms of muscle movement from the proprioceptors of the muscles. Information from the eyes and ears is compared. Cerebellar lesions cause disturbances of posture, and disturbances of voluntary movement, including speech.

THE THALAMUS

This also is a sensory relay station, where ascending sensory fibres synapse and are projected to the primary cortical sensory areas

CEREBRAL CORTEX

The Sensory cortex — parietal lobes. This is concerned with:

- (1) Differences in relative intensity of different stimuli.
- (2) Recognition of spatial relationships — tactile localization and discrimination; small joint displacements.
- (3) Appreciation of similarity and difference in external objects brought in contact with the body.
- (4) Stereogenesis — the synthesis of sensations within the cortex and comparison with previous sensory "memories".

MASTICATION AND SWALLOWING

In the foregoing material, an attempt has been made to present the components and mechanisms by which neuromuscular activity is controlled in the human body. Of specific interest in orthodontics are the mechanisms whereby the processes of mastication and swallowing are controlled.

Hannam (1975) reviewed material on periodontal mechano-receptors, and cited particularly the work of Griffin and Malor (1972). The periodontal ligament contains simple and compound receptors. Simple receptors are composed of a myelinated fibre which coils and loses its myelin sheath, and divides into many smaller unmyelinated terminals. Compound receptors are composed of three or more myelinated fibres which lose their sheaths and encircle one another with terminal branches. The periodontal ligament has rapid and slowly adapting fibres. Hannam postulated that single units are rapid and the complex ones are slower and monitor changes in periodontal tension. The cell bodies of first order peripheral periodontal neurones are located in two sites — the Gasserian ganglion, and the mesencephalic nucleus of the Vth nerve. Periodontal neurones with cell bodies in the mesencephalic nucleus are responsible for reflex activity within the muscles of mastication, since they synapse with motor neurones in the motor nucleus of the Vth nerve. Mechano-sensitive nerve endings are present in the gingival tissue, the ligament, and periosteum. In the gingiva, Krause-like and Meissner-like endings are seen in papillary and sub — papillary regions. There are also unencapsulated whorls. The periosteum contains mainly Golgi and Massoni type receptors, and some complex unencapsulated. These are very similar to receptors in joint capsules.

Sakuda (1971) found that most periosteal receptors are of the Golgi — Massoni type — rapid acting. The rapid response attributed to the periodontium may be from the periosteum.

Hannam (1975) states that neurones with cell bodies in the Gasserian ganglion project to the main sensory and spinal nucleus of V, and may cause a reflex trigeminal motoneurone influence. The result is that there are both excitatory and inhibitory reflex effects on the jaw closing musculature.

Ahlgren (1966) analysed the masticatory mechanism using cinematography and electromyography. He found much variation in patterns, but a characteristic pattern for each child, with more complexity in the presence of malocclusion. Activity of the temporalis and masseter is low at the start of the closing phase, and

steadily increases to the finish. There is a deceleration at the end of the closing phase.

Hannam et al (1969) found transient inhibition of masseter and temporalis following tooth contact. The short latency period (12 msec) suggested reflex origin, involving periodontal receptors.

Jarabak (1954) found that EMG recordings of chewing patterns were influenced by hardness, size and resistance of food particles, and by occlusion and interocclusal space. The high interocclusal distance in a cleft palate subject produced loss of synchnonization of activity of temporalis and masseter, which was restored when a splint was inserted. Jarabak believed the temporal muscles elevated the mandible, and the masseters provided the power stroke.

Ahlgren et al (1973) compared electrical activity in masseter, orbicularis oris, and temporalis in a group of Class II division I, and Class I boys. The retrognathic group showed no difference in posterior temporalis activity (previously found by Moyers). Children with low gonial angles had higher resting activity of anterior temporalis. Posterior temporalis was most important in maintaining mandibular posture. Muscle activity was greater in the normal group in both chewing and swallowing. Lower gonial angles showed increased posterior temporalis activity and decreased masseter activity in swallowing.

Goldberg (1975) stated that rhythmic activity in motoneurons involved in chewing may be controlled to some extent by a brain stem "chewing centre", and cited the activity seen in decerebrate cats. There are many receptors in the oropharyngeal area which connect to these motoneurons. These include TMJ mechanoreceptors, intra-oral mucosa mechanoreceptors including those of the tongue, gingiva, periodontal ligament, and palate; pharyngeal and laryngeal mucosal receptors, mechanoreceptors in the lips and skin of the face, muscle proprioceptors in the facial and masticatory muscles, and specialised receptors in the tongue. The classical theory of reflex control of mastication proposed an interaction of two oral reflexes producing an excitation of depressors and inhibition of elevators. Studies by Goldberg and Nakamura (1968), and Kidokoro et al (1968), indicated the system is much more complex, with both inhibitory reflexes involving the supratrigeminal nucleus, and caudal to the trigeminal motor nucleus, plus a masseter excitatory reflex which is masked by the inhibitory ones. The net effect, however, is stimulation of digastric and inhibition of the elevators, at least in all but the first phase of jaw closure.

Kubota (1975) states that higher structures such as the neocortex, limbic cortex and hypothalamus can modulate mastication and swallowing, but little is understood of their roles. Data on microstimulation supports the view that there is a pathway from the motor cortex to the trigeminal motor nucleus responsible for contraction of the masseter and digastric muscles.

Swallowing activity normally progresses from an immature to a pattern of neuromuscular maturity. (Graber 1963, 1972; Subtelny 1965). At birth, tongue posture is with the centre depressed and periphery raised, the whole mass elongated and plunger-like. The tongue is interposed between the gum pads, and the mandible is stabilized primarily by contraction of the muscles of the VIIth nerve. In the swallow, the mandible moves forward, and the lips purse and move rhythmically and in unison. At five to six months, as the incisors begin to erupt, proprioceptive activity leads to a transitional stage in tongue pattern. As more teeth erupt, the mature, somatic pattern develops. Here, the muscles of facial expression are not used in swallowing. The muscles of mastication bring the teeth together and stabilize the jaws. The tongue remains between the confines of the dental arches, the tip approximating the incisive foramen at the moment of

deglutition. The mature swallow is usually seen by eighteen months of age.

The immature type of swallow is frequently seen in older children and adults, in cases of abnormal dento-alveolar morphology. Ballard (1962) suggested that a habit tongue thrust occurred when the degree of lip incompetence was such that the subject could not maintain the muscular effort needed for an anterior oral seal by means of circumoral contraction, and adopted another pattern.

Milne and Cleall (1970), using cinefluorography, found that when the deciduous central incisors were exfoliated, a forward tongue position was assumed in swallowing and speech. This was reversed after the permanent incisors erupted.

McNamara and Moyers (1973) studied the oral phase of deglutition in rhesus monkeys, using electromyography. They observed three patterns of activity in the masticatory muscles:

- (1) The suprahyoids fired concurrently with the superior head of lateral pterygoid, with little or no elevator activity — the teeth did not occlude.
- (2) Temporalis, masseter, and the superior head of lateral pterygoid fired concurrently with the suprahyoids — teeth in occlusion.
- (3) Elevators and lateral pterygoid activity preceded the suprahyoids.

The suprahyoid musculature initiated the swallow in a rigid time sequence, not susceptible to proprioceptive or outside feedback. The supportive musculature, however, was shown to be affected by anaesthesia and changes in head posture, and the type of bolus.

Goldberg (1976) states that swallowing and mastication involve the motoneurons of cranial nerves V, VII, IX, X, and XII. Swallowing can be stimulated by appropriate stimuli from the periphery. Once initiated, precise activity follows in the muscles innervated by the above nerves. There is a constant pattern from one swallow to the next. Motoneurons are coordinated by a "swallowing centre" in the medullary reticular formation. The hypothesis is put forward that periodontal receptor stimulation during chewing may be important in determining when a swallow will occur, by affecting the level of polarization in the terminals of those afferents mediating the triggering input. If the level of depolarization is sufficiently elevated, there is a presynaptic inhibition of swallowing, e.g. tough food produces increased periodontal receptor activity, delaying swallowing.

Tongue and mandibular posture are influenced by body posture, airway demands, and dental occlusion. Harvold (1968) fixed acrylic blocks to the dorsal region of the palatal vaults in monkeys. A lowering of the mandible was produced, and forward movement of the tongue between the maxillary and mandibular teeth to avoid discomfort. Linder-Aronson (1979), and McNamara (1981) showed that thickening of the adenoids, compromising nasal airway patency caused an increase in vertical dimension. The soft palate is held down and disrupts tongue/palate feedback. The feedback to the hypoglossal motoneurone is altered, causing genioglossal activity to hold the tongue antero-inferiorly. The tongue is held lower by altered supra — and infra-hyoid activity, and the posterior vertebral muscles cause a higher head posture.

McNamara (1973) cemented maxillary splints in rhesus monkeys which allowed for occlusion at a 2mm anterior and inferior displacement of the mandible. He found that normal neuromuscular patterns were disrupted during the first six hours. The suprahyoids were hypertonic. From days one to seven suprahyoid activity decreased, and the anterior temporalis and masseters became dominant. Lateral pterygoid activity rose to a peak at eight weeks, and trailed off to thirteen weeks.

The neuromuscular changes were first to avoid occlusal discomfort, then to posture the mandible to a comfortable occlusal position. As the morphological dental and skeletal changes occurred, the muscular patterns were able to return to normal.

There are many views as to *what constitutes an ideal static and functional occlusion*. There is a general agreement, however, that when there is a lack of harmony between opposing teeth, and with the temporomandibular joint, parafunctional muscle activity results.

Yemm (1969,1977) believes that the rest position of the mandible is passive, and he found no EMG activity of the masseter and temporalis muscles at the rest position. Most researchers, however, observe that mandibular posture is dependant on head posture and feel that there is a maintained minimum activity in the elevator muscles to balance the head posture muscles. When occlusal interferences are present, there is a range of muscle activity possible which is modified by the extent of the problem, and psychological considerations. The muscle activity can be that of a slight forward posturing to centric occlusion, with no symptoms, or there may be a great deal of hyper — activity in the muscles of mastication, and head and neck, both statically and in bruxism.

CONCLUSION

The determinants of neuromuscular activity include both local factors, and complex neural pathways at all levels of the conscious and unconscious central nervous system. The factors involved serve normally to maintain homeostasis and modulate activity with the greatest possible physiological economy. In abnormal states, however, these same mechanisms can cause harmful results.

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