Brain Stem Reflexes: Probing Human Trigeminal Nociception

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Although many people suffer from orofacial pain and headache, objective methods for investigation of trigeminal nociception in humans have been lacking. Trigeminal brainstem reflexes such as the masseter inhibitory reflex and the blink reflex are mediated by central multireceptive neurons that are also involved in trigeminal nociception. Therefore, these trigeminal reflexes are suitable models for probing pontine and medullary pain processing.

The trigeminal nerve supplies the skin of the face, the lips, the tooth pulp, the oral and nasal cavities, the mucosa of sinuses, the cornea, and the meninges. All of these structures are often involved in pathological processes causing pain. Trigeminal afferents project via the trigeminal ganglion to the mesencephalic nucleus, the principal sensory nucleus (PSN), the interstitial nucleus of the spinal trigeminal tract (ISVT), and the spinal trigeminal nucleus (STN) (13). The STN, extending from the pontis to the upper cervical spinal cord, is divided into three subnuclei: subnucleus oralis (SNo), interpolaris (SNi), and caudalis (SNC). On the basis of the responsiveness to mechanical stimuli applied to the skin, neurons within these nuclei have been classified into three groups. Low-threshold mechanoreceptive (LTM) neurons and wide dynamic range (WDR) neurons respond to light tactile stimuli, but only WDR neurons increase their discharge rate as the mechanical stimulus intensity is increased into the noxious range. Nociceptivespecific (NS) neurons do not respond to tactile input but only to noxious stimuli. Nociceptive neurons (WDR and NS) have been localized in the ISVT and in all subnuclei of the STN, indicating an involvement in trigeminal pain processing (13). From animal experiments and from studies in patients with circumscribed brain stem lesions, it is well known that nociceptive processing within the trigeminal system takes place mainly within the medullary SNi and SNC of the STN (13, 14).

Sensorimotor processing in the spinal cord has been investigated for decades by applying cutaneousmuscular reflexes in humans and animals (10, 15). Reflexes in the biceps femoris and the tibialis anterior muscles evoked by electrical stimulation at the foot were especially applied to examine nociceptive processing in the spinal cord (1, 9). We learned a lot about central sensitization, convergence of nociceptive and tactile input, the mechanisms of referred pain, hyperalgesia, and allodynia in humans and animals by applying these reflex models (1, 9, 15). The results of studies on spinal nociception cannot be applied to the trigeminal system because several features of the trigeminal system are unique and quite different from the spinal cord. Innervation density of the cornea and perioral skin is extremely high. Compared with spinal dermatomes, the main branches of the trigeminal nerve innervate remarkably well-defined and restricted regions of the face. Tissues supplied by the trigeminal nerve are associated with a relatively high incidence of pathology, and the nociceptive neural organization in the trigeminal nuclei is much more complex than in the spinal dorsal horn. To find a similar potent model to investigate trigeminal nociception in humans, the involvement of the masseter inhibitory reflex (MIR) and the blink reflex (BR) in nociceptive processing was investigated. For decades, these trigeminal reflexes have been applied in topodiagnosis of small brain stem lesions in clinical neurology (11, 12, 14). From reflex patterns in patients with solitary and circumscribed brain stem lesions, it is known which trigeminal nuclei are part of the reflex arcs, but it remained unclear whether nociceptive neurons are involved in MIR and BR in humans. If, however, nociceptive neurons take part in these reflexes, trigeminal nociception can be probed by applying MIR and BR in humans.

The Masseter Inhibitory Reflex

The MIR is a trigemino-trigeminal reflex in humans that was first described by Hoffmann and Tönnies in 1948. Electrical stimulation of the mental nerve elicits two bilateral suppression periods (SP) of voluntary masseter muscle activity, with onset latencies of 10–15 ms for the early SP1 and 40–55 ms for the late SP2 (12). In patients with circumscribed solitary lesions of the midpons, SP1 is affected, whereas SP2 is abolished by medullary lesions (12, 14). In the cat, a monosynaptic mas- seter reflex was evoked by stimulation in the trigeminal mesencephalic nucleus. It could be suppressed by conditioning stimuli applied to the inferior dental nerve or the masseteric nerve. This suppression consisted of an early and a late phase. A transection of the brain stem at the level of the obex more or less abolished the late inhibitory phase, whereas the early component remained unchanged. Thus the trigeminal interneurons mediating SP1 are probably located within the PSN, the SNo, or the pontine part of the ISVT; SP2 interneurons probably belong to the SNI, the SNC, or the medullary part of the ISVT. Because of the two distinct reflex arcs for the pontine SP1 and the medullary SP2, the MIR has become a potent tool in topodiagnosis of small brain stem lesions (12, 14). If nociceptive neurons are involved in the MIR reflex arc, it should be possible to elicit the MIR by selective activation of nociceptors in human skin. Such stimuli are brief radiant heat
In 30% of the volunteers, the SP1 threshold was equal to pain threshold or exceeded it. The SP1 threshold is clearly sufficient to activate nociceptive Aδ-afferents, but there are reports about innocuous mechanical stimuli applied to intraoral and perioral sites that also evoked an SP1. The SP2 threshold, which has always been below the pain threshold, is nearly supramaximal for Aβ-afferents but barely reaches the Aδ-fiber threshold. Therefore, the SP1 is probably nociceptive in origin, but a contribution of tactile afferents certainly cannot be excluded, whereas the SP2 can probably be evoked by low-threshold mechanoreceptive input. Thus both components, SP1 and SP2, can be evoked by nociceptive afferent input, and there is some evidence that the SP2 in particular can also be elicited by nonnociceptive afferent input. Considering the similar reflex pattern and onset latencies of laser-evoked and electrically evoked MIR, it can be assumed that both reflexes share the same nociceptive interneurons: NS or WDR interneurons mediating the pontine SP1 may be located in the SNc or the pontine ISVT, and WDR interneurons mediating the medullary SP2 are probably located in the SNi or SNC or the medullary ISVT.

The Blink Reflex

In 1896, Overend was the first to describe a reflex of the orbicularis oculi muscles evoked by a gentle tap on the forehead: the blink reflex (BR). Electrical stimulation of the supraorbital nerve evokes the trigeminal facial BR, consisting of an early R1 component on the ipsilateral side with an onset latency of 11 ms and two bilateral components, R2 at 33 ms and R3 at 84 ms (5, 11). R1 and R2 can be elicited by innocuous mechanical or electrical stimuli, indicating mediation by Aβ-afferents (8, 10). The interneurons are probably located in the PSN for the R1 and in the medullary STN for the R2 (11, 14). The R3 can be evoked by strong electrical stimuli, but especially in the beginning of an experimental series or when the stimulus is surprisingly applied, low intensities are also effective. The R3 can not be elicited when the stimulus is announced (5, 6). Thus this reflex response is very likely part of the startle reaction. The location of R2 reflex interneurons in the medullary STN was confirmed by reflex studies in patients with circumscribed brain stem lesions. A unilateral ischemic lesion in the dorsolateral medulla, the so-called Wallenberg syndrome, caused an abnormal R2 in >90% of the patients, whereas the R1 remained unchanged. Stimulation on the healthy side elicited a normal reflex pattern (11, 14). To investigate whether selective activation of trigeminal nociceptive afferents also elicits a BR, a heat pulse of an infrared laser causing a pricking painful sensation was applied to the forehead. This noxious phasic stimulus elicited a bilateral BR with an onset latency of 70 ms (5) (Fig. 2). Considering the nociceptor activation time, the onset latencies of the electrically evoked R2 and the laser-evoked BR also called R2 correspond very well. It is noteworthy that this component was the earliest one; a component corresponding to the electrically evoked R1 was never elicited by painful heat. Nociceptive and nociceptive afferent input can elicit the R2. Thus two reflex arcs are conceivable:
1) the electrically or mechanically activated low-threshold mechanoreceptive afferent input (Aβ) projecting onto low-threshold mechanoreceptive neurons and the heat-evoked nociceptive input (Aδ) projecting onto nociceptive-specific neurons (in this case, the nonnociceptive and the nociceptive R2 were mediated by different interneurons) or 2) both inputs converging onto common WDR interneurons, i.e., both reflexes share the same interneurons. To differentiate between these two possible reflex arcs, it was tested whether the R2 is modulated by activation of the diffuse noxious inhibitory control system (DNIC) and whether there is spatial summation between nociceptive and tactile afferent input. Nociceptive afferent input from anywhere on the body activates nociceptive neurons in the subnucleus reticularis dorsalis of the brain stem, causing inhibition of WDR neurons in the spinal cord and the trigeminal system. Thus, if the R2 is mediated by WDR neurons, it should be suppressed by remote painful stimuli (DNIC). Actually, the BR elicited by weak electrical stimuli was modulated by painful conditioning heat applied to the extremities. The R2 was inhibited and the R1 remained unchanged (8) (Fig. 3). This inhibition of the R2 by remote painful heat (DNIC) indicates not only an involvement of WDR neurons in the generation of the electrically evoked Aβ-fiber-mediated R2 but also a convergence of Aβ- and Aδ-afferents onto common WDR neurons within the medullary STN. Because the R1 was not affected by DNIC, it is probably not mediated by WDR neurons but by pontine LTM neurons. This concept was confirmed by the following study. Applying painful radiant heat and weak electrical stimuli simultaneously to the forehead, the R2 was increased, whereas the R1 remained unchanged (4) (Fig. 3). The results suggest that both afferent inputs, electrically evoked Aβ-input and heat-evoked Aδ-input, facilitated the R2 reflex by spatial summation. These data confirm the mediation of the R2 by WDR neurons and of the R1 by LTM neurons (Fig. 4).
simultaneous occurrence of R1 and R2 components may help to differentiate nonnociceptive from nociceptive processes within the trigeminal system.

In summary, there is evidence that nociceptive neurons, probably WDR neurons, are involved in the MIR and the BR. Trigeminal nociception can therefore be investigated by applying these brain stem reflexes. Trigeminal nociceptive processing within the pons can be investigated by the SP1 component of the MIR and within the medulla oblongata by applying the SP2 of the MIR and the R2 component of the BR. The BR in particular seems to be a very tempting model for investigation of trigeminal nociception. According to the investigation of spinal nociception by cutaneomuscular reflexes, the pathophysiological mechanisms of central sensitization, hyperalgesia, allodynia, and referred pain can be investigated in the trigeminal system by using the BR. In a recent study, convergence of meningeal and facial input on the STN, probably a condition for referred pain, was demonstrated in healthy volunteers by facilitation of the R2 component of the BR by raising intracranial pressure (3). The next step is to apply these brain stem reflexes in patients suffering from orofacial pain. Acute and chronic pain in the trigeminal system presumably modulates the pattern of the brain stem reflexes in a facilitating or inhibiting manner. Actually, the R2 component of the BR seems to be facilitated during a migraine attack compared with the reflex in the headache-free interval (unpublished observations). Last but not least, these reflexes are probably suitable models to test analgesic drug effects on trigeminal nociception.

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References