Brain Stem Reflexes: Probing Human Trigeminal Nociception

Jens Ellrich

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 thepons 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. Nociceptive-specific (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).

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 inner-vate 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
pulses (1–3 ms), generated by an infrared laser, that selectively activate Aδ- and C-fiber nociceptors in hairy skin as shown by microneurography (2). The MIR was evoked by electrical and laser stimulation applied to the mental nerve area (7) (Fig. 1). The electrically-evoked and laser-evoked SPs consisted of an early SP1 and a late SP2. The difference in onset latencies between corresponding electrically and laser-evoked SPs was ~40 ms. Although electrical stimuli directly excite nerve fibers, it takes the transduction time to excite nociceptive terminals by laser heat energy. This nociceptor activation time was determined from microelectroneurographic recordings to be ~40 ms (2). The mean difference in onset latencies between laser-evoked and electrically evoked SP closely matches this nociceptor activation time to a laser heat pulse. Apart from the difference in latencies, the reflex pattern of the laser-evoked MIR is very similar to that evoked by electrical stimulation. Because laser stimuli exclusively activate nociceptors (2), the laser-evoked MIR, consisting of SP1 and SP2, is certainly nociceptive in origin. But can SP1 and SP2 also be evoked by tactile stimuli? The electrical thresholds of SP1 and SP2, expressed as multiples of the detection threshold (I<sub>θ</sub>) in the mental nerve area, were 7.7·I<sub>θ</sub> and 4.6·I<sub>θ</sub> respectively (7).

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 SNi or the pontine ISVT, and WDR interneurons mediating the medullary SP2 are probably located in the 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 supraborbital nerve evokes the trigeminofacial 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 (6, 11). R1 and R2 can be elicited by innocuous mechanical or electrical stimuli, indicating mediation by Aβ-afferents (8, 11). 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:

---

**FIGURE 1.** Masseter inhibitory reflex (MIR) evoked by an electrical stimulus (top) and a laser heat pulse (bottom). Subject adjusted EMG activity of masseter muscle to at least 90% of maximum strength by clenching the teeth, controlled by visual feedback. Electrical stimulus (200-μs duration) was percutaneously applied by surface electrodes at mental foramen. Painful heat pulse was applied to mental nerve area by a Th:YAG laser that emitted infrared light of 2-μm wavelength and 3-ms duration. Both stimuli elicited a MIR, suppression period (SP) of which was divided into an early SP1 and a late SP2. Considering nociceptor activation time of ~40 ms, onset latencies of electrically-evoked and laser-evoked SPs correspond very well (7).
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).
Acute and chronic pain in the trigeminal system presumably
results from long-term changes in the trigeminal nociceptive
system. According to the investigation of measuring cranial
nerve activity, meningeal and facial afferents onto trigeminal
brainstem neurons: an electrophysiological study in rat and man.


Ellrich, J., O. K. Andersen, R.-D. Treede, and L. Arendt-Nielsen. Conver-
gence of nociceptive and non-nociceptive input onto the medullary dor-


Ellrich, J., and H. C. Hopf. The R3 component of the blink reflex: norma-
tive data and application in spinal lesions. Electroenceph. Clin. Neuro-

Ellrich, J., H. C. Hopf, and R.-D. Treede. Nociceptive masseter inhibitory
reflexes evoked by laser radiant heat and electrical stimuli. Brain Res. 764:

Ellrich, J., and R.-D. Treede. Characterization of blink reflex interneurons
by activation of diffuse noxious inhibitory controls system in man. Brain

Ellrich, J., R.-D. Treede. Convergence of nociceptive and non-noci-
ceptive input onto spinal reflex pathways to the tibialis anterior muscle in

Hagbarth, K.-E., and B. L. Finer. The plasticity of human withdrawal reflexes

Kimura, J. The blink reflex. In: Electrodiagnosis in Diseases of Nerve and

In: Motor Control Mechanisms in Health and Disease, edited by J. E.

Shults, R. C. Nociceptive neural organization in the trigeminal nuclei. In:
The Initial Processing of Pain and its Descending Control: Spinal and

Valls-Solé, J., N. Vilà, V. Olbach, R. Alvarez, L. E. González, and A.
Chamorro. Brain stem reflexes in patients with Wallenberg’s syndrome:
correlation with clinical and magnetic resonance imaging (MRI) findings.

Woolf, C. J. Evidence for a central component of post-injury pain hyper-