Gating of trigemino-facial reflex from low-threshold trigeminal and extratrigeminal cutaneous fibres in humans

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Abstract

Changes in the size of the test components (R1 and R2) of the trigemino-facial reflex were studied after electrical subliminal conditioning stimulation were applied to the trigeminal, median and sural nerves. After conditioning activation of the trigeminal nerve (below the reflex threshold), the early R1 reflex component showed phasic facilitation, peaking at about 50 ms of interstimulus delay, followed by a long-lasting inhibition recovering at 300–400 ms. The same conditioning stimulation resulted in a monotonic inhibition of the late R2, starting at 15–20 ms, with a maximum at 100–150 ms and lasting 300–400 ms. Intensity threshold for both the R1 and R2 changes ranged from 0.90 to 0.95 times the perception threshold. A similar longlasting inhibition of the R2 reflex response was also seen after conditioning stimulation applied to low-threshold cutaneous afferents of the median and sural nerves. The minimum effective conditioning-test interval was 25–30 ms and 40–45 ms respectively and lasted 600–700 ms. By contrast the early R1 reflex response exhibited a slight long-lasting facilitation with a time course similar to that of the R2 inhibition. The threshold intensity to obtain facilitation of the R1 and inhibition of the R2 test responses after conditioning volley in the median and sural nerves was similar and ranged from 0.9 to 1.2 times the perception threshold. These results demonstrate that low-threshold cutaneous afferents from trigeminal and limb nerves exert powerful control on trigeminal reflex pathways, probably via a common neural substrate. There is evidence that, in addition to any post-synaptic mechanism which might be operating, presynaptic control is a primary factor contributing to these changes.

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The trigemino-facial reflex has been largely used as a test reflex for studying the organisation and integrity of brainstem reflex circuits. The reflex response of the orbicularis oculi muscles to unilateral electrical stimulation of the first trigeminal (TR) branch shows two main components: an early and brief component (R1) and a later prolonged component (R2).^{1–3} Under appropriate experimental conditions a third reflex component (R3) can also

be constantly obtained.⁴ Many physiological studies suggest that the short and long latency components arise from different but parallel neural pathways.^{5–12}

Since the original description by Kimura,¹³ the paired shock technique has been largely employed to study the recovery cycle of the TR reflex components, both in physiological and pathological conditions.^{14–22} In all these studies conditioning stimuli were above the threshold for reflex responses. This caused difficulties in interpretation of the results: a) at conditioning-test intervals shorter than 80–100 ms the reflex response evoked by the conditioning stimulus overlaps the test reflex, obscuring the effect of the conditioning volley on the latter; b) when the motor neurons are fired in the conditioning reflex response, a long lasting depression of their excitability, due to post-spike after-hyperpolarisation, can be expected; c) in addition to any direct effect produced by the conditioning stimulus, there may also be those due to afferent reactivation during muscular contraction; d) finally, using high intensity conditioning stimuli, no conclusion can be reached on the type of afferent fibres responsible for the effects observed on test responses.

In this study, graded subliminal conditioning stimuli were applied to TR afferents and the respective effects on the early R1 and late R2 components of the trigemino-facial reflex were evaluated. The same TR reflex components were also studied after conditioning activation of low threshold cutaneous afferents arising from median (MN) and sural (SR) nerves.

Methods

The experiments were performed on 5 adult volunteers (30–37 years), all of whom gave informed consent to the experimental procedure which was approved by the local Ethical Committee. In two cases the experiments were repeated 3 and 4 times. The subjects were comfortably seated in an armchair. Electromyographic activity from the orbicularis oculi muscles was recorded by surface electrodes set on the lower lid.

1) Conditioning stimulation

Single pulses of 0.1–0.5 ms duration were given through bipolar surface electrodes, the cathode being proximal to three different nerves: the TR, the MN and SR nerves. Since it was not possible to record the incoming volley, stimulus strength was expressed in multiples (x) of the perception (P) threshold

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(Th). In all cases conditioning strength was kept below the Th for reflex responses. According to the ascending method of limits,²³ stimuli were increased in 0.25 mA steps and the reflex Th was the intensity value at which a response was evoked by approximately 50% of the stimuli. The ascending procedure was also used to estimate the subjective PTh, the value of which was verified several times during each experimental session. Branch I of the TR nerve was stimulated at the supraorbital foramen (supraorbital nerve) and branch III at the mental foramen (mandibular nerve). The MN nerve was stimulated at the second and third digits (in one case also at wrist level). The SR nerve was stimulated at the lateral malleolus.

2) Test stimulation

The R1 and R2 responses of the trigemino-facial reflex were evoked by test stimuli (0.1–0.5 ms duration) applied by surface electrodes to the supraorbital nerve.

Since the aim of this study was primarily to give a description of the excitability changes of the trigemino-facial reflex, it was important, as a first step, to verify whether the size of the test reflex itself could affect its susceptibility to the conditioning volley. The amount of facilitation of the R1 and inhibition of the R2 reflex components of different size were then tested during a constant conditioning input. Conditioning stimulation was applied to the MN nerve (conditioning-test interval 200 ms, intensity $1.1 \times PTh$) and the size of the test responses was systematically varied by chang-

ing the strength of the test stimulus to the supraorbital nerve. Figure 1 shows a representative example of the effect evoked by the same conditioning stimulus on R1 and R2 responses of small (A) and large size (B). It is apparent that the facilitation of R1 response is much more evident when the size of the test reflex is small. Figure 2 gives a detailed description of the susceptibility changes of R1 and R2 responses in relation to their control size. The amount of R1 facilitation and R2 inhibition (expressed as a percentage of their control values) is plotted against the size of the test reflex (as a percentage of its maximum value) giving a two-part curve: 1) at low reflex amplitude (below 50% of their maximum value) the susceptibility to the conditioning volley was high for both R1 and R2 reflexes; 2) with increasing unconditioned reflex size, the amount of the R2 depression remained almost constant, the curves exhibiting a plateau. On the contrary, when the size of the R1 response approached its maximum value (above 70–80%), no facilitatory event was apparent, suggesting saturation of the response. Accordingly the intensity of the test stimulus was adjusted to evoke an R1 response 50–70% of its maximum size. This allowed: a) acceptably stable responses; b) sufficient margin to observe any phenomena of facilitation; c) an R2 response within the plateau phase of the curve. To disclose better the time course of the R1 facilitation, the size of the test response was occasionally adjusted to its lower value (20–30% of its maximum value). This resulted in a large scatter of the data points necessitating several trials before the temporal profile of facilitation could be unambiguously recognized.

3) General experimental procedure

The stimulus sequences were regularly alternated as follows: 1) control test reflexes alone; 2) test stimulus preceded by conditioning stimulation. Two groups of experiments were performed: 1) keeping the strength of the conditioning stimulus constant (below reflex threshold), the conditioning-test interval was randomly varied from 10 to 400–900 ms; 2) keeping the conditioning-test interval constant, the strength of the conditioning stimulus was randomly varied from 0.7–0.8 to $1.2–1.5 \times PTh$. The sequence, unconditioned-conditioned responses, was repeated 10–15 times for each conditioning-test interval and for each conditioning stimulus strength. Stimuli were given at intervals of 15–20 s, delivered by constant-current stimulator. The EMG signals were fed from the oscilloscope to a full wave rectifier and further to an averager and integrator. The digital integral values of R1 and R2 conditioned reflex components were measured and expressed as a percentage of their unconditioned values.

Results

To obtain a valid comparison between the effects of different cutaneous conditioning stimuli on TR reflex responses, all the data

Figure 1 Example of the R1 facilitation and R2 inhibition induced by the same conditioning stimulus to the median nerve ($1.1 \times PTh$; 200 ms conditioning-test interval) when different control sizes were used. Note the large facilitation on R1 response when the conditioning stimulus was applied on a reflex test of small amplitude (A); the same conditioning volley failed to evoke such effect when applied on a test reflex the size of which was kept near its maximum value (B).

Figure 2 Susceptibility to a constant conditioning stimulus of the R1 (open circles) and R2 (filled circles) test responses of different sizes. Conditioning stimulation as in fig 1. The amount of the effects on the conditioned responses was plotted against the control reflexes size. Each symbol is the mean of ten measurements. Vertical bars 1 SD of mean.

illustrated here are from the same subject. Although the amount of facilitation and/or inhibition caused by the various conditioning stimuli was variable from one subject to another, qualitatively similar results were obtained in all cases.

The time course of the R1 and R2 responses when preceded by subliminal supraorbital nerve stimulation ($1.0 \times PTh$) is shown in fig 3. The early R1 response showed a facilitatory phase between 30 and 60 ms, followed by a long lasting inhibition which was maximal for a conditioning-test interval of 100–150 ms. The

Figure 3 Time course of the effects of a conditioning stimulus applied to the ipsilateral supraorbital nerve ($1.0 \times PTh$) on R1 (open circles) and R2 (filled circles) test reflex responses. The size of the conditioned R1 and R2 responses is expressed as a percentage of their unconditioned values. Each symbol is the mean of ten responses. Vertical bars 1 SD of mean.

Figure 4 Effect of changing the strength of conditioning stimuli applied to the ipsilateral supraorbital nerve on R1 (open circles) and R2 (filled circles) test responses. The conditioning-test interval was kept constant at 50 ms (on the left) and 100 ms (on the right). Each symbol is the mean of ten responses. Vertical bars 1 SD of mean.

size of the conditioned response recovered to near its control value within 300–400 ms. The same conditioning stimulation resulted in a monotonic long-lasting inhibition of the late R2 response. The minimum effective conditioning-test interval was 15–20 ms. The test response was maximally depressed for an interval of 100–150 ms and returned to its control level for intervals of 300–400 ms. A comparable time course was obtained for the contralateral R2 response. Very similar effects on the R1 and R2 responses from the orbicularis oculi muscle were also obtained when the conditioning stimulus ($1.0 \times PTh$) was applied to the ipsilateral mental nerve (not illustrated). In an attempt to determine the Th of these changes and whether the same afferent fibres were responsible for both excitatory and inhibitory variations in the test reflexes, a conditioning stimulus of increasing strength was applied at 50 ms (corresponding to the increasing phase of the R1 and the decreasing phase of R2) and 100 ms (corresponding to the inhibition of both responses) of interstimulus delay (fig 4). With a delay of 50 ms, increasing the strength of the TR nerve stimulation resulted in a progressive increase in R1 and decrease in R2, both appearing at $0.9 \times PTh$. When the interstimulus delay was fixed at 100 ms the depression of both R1 and R2 responses was also apparent at a conditioning strength of $0.9 \times PTh$ [mean (SD) 0.92 (0.02); range 0.90 – $0.95 \times PTh$]. That the Th values were identical suggests that these changes are contingent upon the same low-threshold afferent fibres. Figure 5 illustrates the results obtained when the conditioning stimulus was applied to the MN nerve fibres arising from the fingers ($1.0 \times PTh$). At interstimulus interval longer than 25–30 ms, the R1 component showed a first facilitatory peak followed by a subsequent long lasting facilitation which recovered at 500–600 ms. A similar but opposite time course was shown by the R2 reflex response. In the same subject the conditioning

Figure 5 Time course of the effects of a conditioning stimulus applied to the MN nerve ($1.0 \times PTh$ to ipsilateral II-III digit) on R1 (open circles) and R2 (filled circles) test reflex responses. The size of the conditioned R1 and R2 responses is expressed as a percentage of their unconditioned values. Each symbol is the mean of ten responses. Vertical bars 1 SD of mean.

Figure 6 Effect of changing the strength of conditioning stimuli applied to the MN nerve (ipsilateral II–III digit) (on the left) and SR nerve (on the right) on R1 (open circles) and R2 (filled circles) test reflex responses. Conditioning–test interval was kept constant at 200 ms. Each symbol is the mean of ten responses. Vertical bars 1 SD of mean.

stimulation was also applied to the MN nerve at the wrist. The intensity was set at the motor threshold ($2.5 \times \text{PTh}$ in this case) to ensure that, in addition to the cutaneous volley, a large fraction of muscular afferents was also activated. Virtually identical results were obtained, although the recovery phase of the R2 response remained incomplete (60–70% of its control size) up to 900–1000 ms. Figure 6 (left panel) shows the effects of increasing conditioning stimuli applied to the second and third digits, at 200 ms of interstimulus delay. Both the R1 facilitation and R2 inhibition became apparent at $1.0 \times \text{PTh}$ [mean (SD) 0.96 (0.03); range 0.9 – $1.0 \times \text{PTh}$]. A similar time course of both these reflex responses was obtained when the conditioning stimulation was applied to the SR nerve at the ankle (not illustrated). A slight long lasting monotonic facilitation of the R1 response and a deep long lasting monotonic inhibition of the R2 response started at intervals of 40–45 ms and recovered within 700–800 ms. None of the cases showed an early facilitatory peak of the R1 component. Increasing conditioning stimulus strength (200 ms interstimulus interval), both the inhibitory effect on R1 and the facilitatory effect on R2 were apparent at $1 \times \text{PTh}$ (right panel fig 6) [mean (SD) 1.04 (0.09); range 0.95 – $1.20 \times \text{PTh}$].

The mean (SD) Th values for the unconditioned R1 and R2 test responses were respectively $2.27 \times \text{PTh}$ [(0.7); range 1.55 – 3.3] and $1.46 \times \text{PTh}$ [(0.5); range 1 – 2.45]; the absolute mean (SD) value of PTh was 1.15 mA [(0.5), range 0.5 – 2 mA].

Discussion

A single perception threshold conditioning stimulus to the TR, MN and SR nerves modified the excitability of neural pathways mediating the early R1 and late R2 components of the trigemino-facial reflex. Two main factors suggest that these effects depend on the activation of large cutaneous afferent fibres: a)

in all cases the threshold of the effects was very low (0.9 – $1.2 \times \text{PTh}$), suggesting that only low-threshold afferent fibres were activated; b) when the stimulus was applied to the median nerve, similar effects were observed for stimulation at the wrist (which is supposed to activate both muscular and cutaneous afferents) and for selective stimulation of the cutaneous afferents from the fingers.

Activation of low-threshold TR or limb cutaneous afferent fibres produced a monotonic long-lasting depression of the R2 reflex component. Following activation of TR nerve, this inhibition was apparent at a conditioning–test interval of 15–20 ms, reached a maximum at 100 ms and lasted 300–400 ms.

When the conditioning stimulus was applied to the MN and SR nerve afferents, the inhibition had a longer latency (25–30 ms and 40–45 ms respectively) and lasted 500–600 ms. The greater afferent delay due to the distance between the site of application of the stimulus and the brainstem in which interactions between conditioning and test volleys are presumed to occur (see below), can explain the later onset of inhibition. In addition, the time dispersion of the arrival of action potentials in the afferent fibres from MD and SR nerves must be rather large with the long conductance distances that are involved. This time dispersion of the conditioning spikes could be an additional contributory factor responsible for the longer time course of the R2 inhibition with respect to that observed after TR stimulation.

The almost identical temporal trajectory of the R2 inhibition originating from TR, MN and SR nerves suggests a common mechanism. It has been shown in animal studies that impulses in the TR fibres or in ascending and descending pathways in relation to the TR complex, can depress the TR second order neuron response evoked by stimulation of the TR afferent fibres.^{24–29} For the ascending pathways it has been shown in animals that stimulation of the posterior columns or the superficial radial and sciatic nerves is effective in producing depression in the TR nuclei.^{24–27,30} Ascending influences from limb afferents on TR reflex responses have also been observed in humans.¹⁷ Neural elements of the medullary and upper spinal cord reticular formation may be a possible common final pathway of these inhibitory interactions.^{27–31,32}

Much evidence exists that presynaptic depolarisation of the TR primary afferents largely contributes to the inhibition observed within TR nuclei.^{24–25,28–30,33–35} It is now generally accepted that this depression is caused by an increase in conductance of the primary afferent terminals brought about by axo-axonal TR synapses,²⁹ resulting in reduced transmitter release.^{36–37} In addition to any post-synaptic inhibitory mechanism which might be operating, we believe that presynaptic inhibition was also the primary factor contributing to the inhibition of the R2 reflex component. Two main arguments favour this possibility: a) the time course of this inhibition is identical to the time course of presynaptic inhibition described

in animals and human spinal cord;³⁸ b) there is a surprising identity between the time course of the R2 inhibition observed here, and that of the TR primary afferent depolarisation seen in the cat.^{24 27 29}

In contrast with the monotonic inhibition of R2, the early R1 reflex component undergoes more complex variations. When the test stimulus applied to the supraorbital nerve was preceded by a conditioning stimulus to the TR fibres, (branch I or III) a facilitatory phase, having a maximum between 40 and 50 ms, was observed, cut off by a subsequent long-lasting inhibition which paralleled the time course of the R2 depression (fig 2). In the cat, a facilitatory phase, with a maximum at about 30 ms, has been observed on facial motor neurons following stimulation of trigeminal afferents.³⁹ A similar motor neuronal facilitation may account for the present results. Since the latency of this phase appears to coincide with the time at which the R2 component is expected, this facilitation may be produced by the subliminal activation, brought about by the conditioning volley, of the R2 reflex pathway inducing EPSPs on facial motor neurons. Indeed, since the Th of the R2 response is very close to the PTh (that is below the Th of the R1 reflex), it is conceivable that the same low-threshold afferent fibres activated by the subliminal conditioning stimulus are also responsible (when adequate spatial and/or temporal summation takes place) for the late R2 response. In the cat this short latency excitatory phase is followed by a period of reduced responsiveness of motor neurons lasting 30–100 ms.³⁹ Because of the experimental condition used, that inhibition may be partially due to motor neurone after-hyperpolarisation following the conditioning reflex response: when the motor neurone is fired in the conditioning volley the subsequent after-hyperpolarisation depresses its excitability and prevents it from firing again. This, however, seems unlikely to account for our case, since the conditioning stimulus was constantly kept below the motor Th, thus ruling out any post-spike after-hyperpolarisation. As shown in fig 3, the temporal profile of the R1 depression parallels that of the R2 component, except for a later onset, probably masked by the preceding facilitation. By a process of analogy, therefore, the most obvious possibility is that it is presynaptic in origin.

When the conditioning stimulus was applied to the MN and SR afferents, the R1 component showed a slight long-lasting facilitation with a time course similar to that of the R2 inhibition (fig 5). Most or all of the presynaptic inhibitory pathways are capable of exerting not only transient but also tonic inhibitory influences on the primary afferent terminals. Temporary removal of tonic presynaptic depolarisation would lead to transitory disinhibition, which could be recorded as facilitation. For example, removal of tonic presynaptic inhibition on Ia fibres restores the monosynaptic excitatory post-synaptic potential to its control height.⁴⁰

Electrophysiological evidence also exists in favour of a tonic presynaptic action on TR

primary afferents.^{29 35 41 42} In view of this and of the evidence that R1 facilitation has a time course very similar to that of R2 inhibition, one of the possibilities is that this long-lasting facilitation is due to a transient reduction in tonic presynaptic control acting on the TR afferents responsible for R1 reflex. However, a prerequisite for such a theory is that TR primary afferents for the R1 response are different from those responsible for the R2 component. The difference between R1 and R2 Th values observed here (see Results Section) and in previous studies²³ suggests that the R1 component is contingent upon TR afferents smaller (less excitable fibres) than those projecting onto the R2 pathway.

Close observation of fig 5 shows that the facilitation of R1 appears to have an early peak which roughly coincides with the phase of short latency facilitation observed after TR stimulation (fig 3). Similarly, this phase of facilitation may be due to the subliminal activation of facial motor neurons induced by the conditioning stimulation of the MN nerve. It has been shown that MN afferents access facial motor neurons generating, under appropriate condition, a reflex response in the facial muscles.⁴³ This interpretation is indirectly sustained by evidence that the same facilitatory peak does not appear for stimulation of the SR nerve, which never evokes facial reflex responses even at high stimulus intensity.

Our results with limb stimulation seem compatible with those of Bulou *et al*,¹⁷ who used the radial and SR as conditioning nerves (see fig 3). Their observations become clearer as a result of this study: first, it demonstrates that large cutaneous afferents make a major contribution to these TR reflex changes; second, in view of the similarity of the reflex changes produced, TR and limb afferents appear to operate via a common neural substrate. A similar conclusion was also reached by Rimpel *et al*⁴⁴ who observed almost identical effects of acoustic and visual stimuli on TR test responses.

Figure 7 shows a schematic model of hypothetical presynaptic control of the pathways mediating the R1 and R2 reflex components. A conditioning volley in low threshold TR afferents (Ltta) subliminally activates the pathway responsible for the R2 component, causing an increase in the discharge of presynaptic interneurons X and Z acting on the afferent fibres of both the R1 (Htta) and R2 (Ltta) responses. This is translated into a parallel depression of these reflex responses (fig 3). Incidentally, subliminal activation of the R2 pathway could evoke excitatory post-synaptic potentials in the motor neurons, possibly responsible for the first facilitatory phase observed on the R1 component. Low threshold afferent fibres from limb nerves (Llta) converge on the interneuron Z but not on X. The increased activity of the Z interneuron depresses the R2 pathway, consequently reducing the firing onto presynaptic interneuron X acting on the R1 Htta. This causes disinhibition of these afferents and a consequent facilitation of the R1 component (fig 5).

Figure 7 A hypothetical model illustrating presynaptic control onto the pathways mediating the R1 and R2 components of the trigemino-facial reflex. Htta: High threshold trigeminal afferents; Ltta: Low threshold trigeminal afferents; Ltla: Low threshold limb afferents; X and Z: last interneurons of putative pathways acting presynaptically on TR primary afferents; R1: reflex pathway mediating the R1 component; R2: reflex pathway mediating the R2 component.

Although our experiments were unable to identify with certainty the neural substrate of the R1 and R2 changes, it is plausible to conclude that presynaptic action from low-threshold cutaneous afferents on TR terminals is a major contributory factor. The possibility of facilitating or depressing cutaneous transmission at presynaptic level could certainly constitute a powerful means of reducing and selecting peripheral information pertinent to sensory and/or motor processing. For example, "trigemino-trigeminal" and "extratrigemino-trigeminal" inhibitory influences can optimise spatial contrast, respectively within the same receptive field and between different sensory channels, to facilitate the localisation of the stimulus.

A final comment is required on the observation that even a stimulus strength below the subjective PTh is sometimes effective in producing changes in the trigemino-facial reflexes. One possibility is that these low-Th cutaneous afferent fibres do not access the cerebral cortex. However, the evidence in the cat that even the activation of single fibre (from Pacinian corpuscles) is able to generate a corticofugal evoked response⁴⁵ argues against this possibility. Sensory perception should not be regarded as depending exclusively on the peripheral afferents activated but also on the temporal and spatial gradients of the applied stimulus.

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Neurological stamp

Niels Stensen (or Steno) 1648–86

Niels Stensen was still a student when he discovered in 1661 the excretory duct of the parotid gland in sheep. This was later identified in humans by Sylvius. Stensen was the first to identify the heart as a muscle and to recognise the congenital cardiac defects later known as the tetralogy of Fallot. Stensen identified the cerebral grey and white matter and argued that it was idle to speculate about cerebral function when so little was known about its structure. He disagreed with the views of Willis on the location of certain higher functions such as memory, and of Descartes who considered the pineal gland to be the location of the soul that existed only in humans. Stensen showed that the pineal gland existed in other animals. He opposed the views of Borelli who believed that increased muscle bulk noted on contraction was due to a fermentation process generated by a discharge of liquid from the nerves.

Stensen was one of the founders of geology and he wrote important works on the production of strata, fossils and other geological formations. Brought up a Lutheran, Stensen converted to Catholicism in 1667 and gave up the study of science after he was ordained a bishop in 1677. He was one of the greatest intellects of his time, but died in extreme poverty.

Denmark honoured him with this stamp in 1969 on the 300th anniversary of the publication of his geological work *On Solid Bodies* (Stanley Gibbons 507, Scott 462).

L F HAAS