EFFECT OF FENTANYL, A NARCOTIC ANALGESIC, ON TWO COMPONENTS OF THE JAW OPENING REFLEX

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Abstract—An action of fentanyl, a short-acting narcotic, on the reflex discharge in the digastric nerve induced by the inferior alveolar nerve stimulation was investigated in α-chloralose anesthetized cats. In the ipsilateral digastric reflex discharge, there were an early phase induced by stimulus exciting Aα fibers and a late phase appearing when Aβ fibers were also stimulated. Following dorso-lateral cordotomy at the obex level, an isolation of the spinal trigeminal nucleus caudalis, a total area in the digastric reflex discharge decreased, while its first peak amplitude was little affected, indicating a disappearance of the late phase and a preservation of the early phase. Fentanyl depressed both the total discharge area and the first peak amplitude. After dorso-lateral cordotomy, the depression of the area decreased considerably, whereas that of the amplitude decreased slightly. Results indicate that fentanyl depressed both the early phase which is activated by the Aα fiber stimulation, not via the subnucleus caudalis and the late phase which is activated by the Aβ fiber stimulation via the subnucleus caudalis or its surroundings. The latter action would be related to the analgesic action of fentanyl.

It is known that the jaw opening in the cat, as seen by digastric muscle contraction, can be reflexly elicited by the excitation of the second or third branches of the trigeminal nerve (1-7). Responsible afferent limbs are low threshold afferents of Group II range size (Aα) (1, 3, 4, 7) and those of Group III (Aβ) (2, 5-7). Analgesics such as morphine increased the threshold for this reflex to the stimulation of tooth pulp, which consists exclusively of Aγ-α fibers in cats (8), and this action was implicated in drug action to alleviate the pain, though direct proof on an analgesic effect has not been demonstrated (2).

Following unilateral hemisection at C1 level, which is known to cause ipsilateral facial analgesia in man (Sjöqvist operation) (9), Riblet and Mitchell (10) found that the tooth pulp threshold on the ipsilateral side for eliciting the jaw opening reflex in the cat elevated and concurrently, morphine became less effective, and suggested that morphine may exert its depressant effect through actions on the subnucleus caudalis of the spinal trigeminal nucleus. However, the digastric reflex discharge induced by the inferior alveolar nerve stimulation was not totally affected by the transection of the spinal tract and the spinal tract nucleus at the level of the obex (11). Therefore, it is likely that the digastric reflexes induced by volleys in different afferent fiber components pass through different pathways and have different drug sensibilities within the brain stem and upper spinal cord.

In the present investigation, we studied an action of a narcotic on the trigeminal sys-
tem, by analysing the digastric reflex discharges induced by the stimulation of different fiber components in the inferior alveolar nerve. As a short acting narcotic, fentanyl citrate (N-(1-phenethyl-4-piperidinyl) propionanilide dihydrogen citrate) (12) was used, since it could be injected several times in a single experiment.

Results indicate that the digastric reflex discharge to the inferior alveolar nerve stimulation may be divided into two components: an early phase activated by volleys in rapidly conducting myelinated fibers, not via the subnucleus caudalis and a late phase excited by volleys in slowly conducting myelinated fibers, via the subnucleus caudalis or its surroundings. Fentanyl depressed both phases. It was suggested that the effect of fentanyl on the latter may be related to its analgesic action.

MATERIALS AND METHODS

Experiments were performed on 26 adult cats. Ether anesthesia was maintained briefly during cannulation of the trachea, femoral artery and femoral vein. The ether was then discontinued, and animals were anesthetized with α-chloralose (50 mg/kg i.v.), paralyzed with gallamine triethiodide (Teisan) and artificially respired. Animals anesthetized only by α-chloralose (80 mg/kg i.p.) without ether induction were also used. Rectal temperature was maintained at 37–38°C. Arterial blood pressure was monitored during the course of the observations.

The digastric nerves of one or both sides which innervate the anterior belly of digastric muscle were exposed. This nerve was cut at the medial bone at its angular process and the distal end was ligated with cotton thread and tied to the distal electrode for reflex recording. Collar-type bipolar electrodes consisting of a pair of silver wires separated by about 5 mm or bipolar platinum wire electrodes were used as recording electrodes. Nerves were covered with warmed liquid paraffin or a solid paraffin-vaseline mixture to prevent them from drying. Uni- or bilateral inferior alveolar nerves in the mandibular canals were exposed by removing parts of the mandibular bones near the proximal and distal ends. In the proximal end, a pair of thin stainless steel wires were inserted directly into the nerve trunk (interpolar distance, 2-3 mm) and used for stimulation. The exposed nerve, together with the electrodes, was covered with dental cement. In the distal end, the inferior alveolar nerve was carefully removed from the bony mandible, placed on the collar-type recording electrodes, and covered with a solid paraffin-vaseline mixture. A distance between two pairs of the electrodes was from 15 to 18 mm.

As for the spinal transection, a dorso-lateral cordotomy and complete spinal transection were carried out at the level of the obex, using fine-pointed scissors. The dorso-lateral cordotomy means the transection of the area containing the spinal tract, the spinal tract nucleus and a part of lateral reticular formation. The extent of each cordotomy was determined histologically in Nissl stained serial sections of the brain.

The inferior alveolar nerve was stimulated by a single monophasic square pulse of 0.02 msec duration, generated by an electronic stimulator (MSE-40, Nihon Kohden) and passed through an isolating unit (MSE-JM, Nihon Kohden). The stimulation was re-
peated at the frequency of 0.3-1 Hz. The stimulus intensity was set at supramaximal level, except for cases studying the effect of stimulus intensity changes. The discharge in digastric nerve was amplified through DC amplifier and then displayed on an oscilloscope (RM 565, Tektronix) for photographing. The signals were simultaneously introduced to an averaging computer (CAT 400B) through DC amplifier, and superimposed traces of 30 to 50 responses were displayed on the oscilloscope for photographing. A total area of digastric reflex discharge was measured by weighing a tracing paper (Tracer A-300, Somar) which was cut out along a potential trace magnified by 10 times using an enlarger. Their weights were between 50 and 500 mg in the control responses.

The drugs used were fentanyl citrate (Janssen) and levallorphan tartrate (Lorfan®, Takeda). Fentanyl was dissolved in 0.9% saline (40 μg/ml) and administered by slow intravenous injection.

RESULTS

Two components of the jaw opening reflex

A single shock stimulation of the inferior alveolar nerve induced reflex discharges in the bilateral digastric nerves (Fig. 1). With a stimulus intensity of 1.3 times the nerve threshold (N.T.; 0.36 V, 0.02 msec), the ipsilateral digastric discharge appeared with a latency of 5.0 msec (Fig. 1-B). The lowest intensity necessary for inducing the contralateral digastric discharge was 1.6 × N.T. (Fig. 1-C). With this intensity, the ipsilateral digastric discharge greatly increased in size and its latency shortened to 3.4 ± 0.5 msec (Mean ± S.D., N = 18), ranging from 2.8 to 4.3 msec.

![Fig. 1](image-url)

Fig. 1. Ipsi- and contralateral digastric reflex discharges induced by stimulation of the inferior alveolar nerve. For each of A–E, 1 and 2 indicate the digastric reflex discharges ipsi- and contralateral to the stimulating side, respectively, and 3 represents compound action potentials recorded from the inferior alveolar nerve 15 mm caudal to the stimulating electrode. Stimulus intensities of inferior alveolar nerve are expressed as multiples of nerve threshold (× N.T.); A: nerve threshold, B: threshold for the ipsilateral digastric reflex discharge, C: threshold for the contralateral digastric reflex discharge, D: responses by supramaximal stimulation of Aα fibers, E: responses by stimulation of Aα plus Aδ fibers. In E, the late discharge related to activity in the slowly conducting myelinated fibers in the inferior alveolar nerve appeared in the bilateral digastric nerves.
When the Aα potential in the distal alveolar nerve (peak conduction velocity, about 60 m/sec) reached its maximum (3.9 × N.T.), the first peaks in bilateral digastric discharges reached nearly the maximal amplitudes (Fig. 1-D). The fourth peak in the ipsilateral digastric nerve appeared with an onset latency of 8.5 msec following the three peaks, in response to volleys containing Aδ fiber activity (under 25 m/sec) (Fig. 1-E). This fourth potential was therefore considered to be due to activation of Aδ fibers. Averaging the data obtained in 18 preparations of 14 animals, the digastric reflex discharge induced by volleys of Aδ fibers began at 9.3 ± 1.5 msec and persisted for up to 13.8 ± 3.4 msec. A duration of Aδ component in the digastric discharge was therefore 4.5 ± 2.4 msec. When an excitatory volley had a Aδ fiber component, the duration of the contralateral digastric nerve discharge was also prolonged (Fig. 1-E).

In these reflex responses, fine unmyelinated afferent fibers may not be involved, because the length of the alveolar nerve from the stimulating electrode to the entry into the brain was more than 30 mm, so that volleys in C fibers (about 1 m/sec) need more than 30 msec to arrive the medulla.

**Fentanyl effect in intact animals**

Figure 2 illustrates effects of fentanyl upon the digastric reflex discharges evoked by supramaximal stimulation of the ipsi- and contralateral inferior alveolar nerves. Responses of top row represent control in α-chloralose animals. By fentanyl injection (40 μg/kg), an onset latency of ipsilateral digastric discharge was prolonged from 3.4 ± 0.5 to 3.8 ± 0.5 msec, its first peak amplitude was depressed by 33.3 ± 4.7%, and a total duration of the discharge shortened from 10.9 ± 2.6 to 8.1 ± 1.9 msec. If a total area of the potential

![Fig. 2. Influences of fentanyl administrations, spinal transection at the obex level, and levallorphan on the digastric reflex discharges to the supramaximal stimulation of the inferior alveolar nerves. These results are quantitatively presented in Figs. 3-5.](image-url)
FENTANYL AND JAW OPENING REFLEX

Fig. 3. Influences of fentanyl and cordotomy on the digastric reflex discharges induced by the supramaximal stimulation of the inferior alveolar nerves. Comparison of their effects on first peak amplitudes (abscissa) and total areas (ordinate) of the digastric reflex discharges. Oblique lines in graphs represent the same values of both, thin crosses on the line are points at which both are 100%. Each circle or cross indicates a maximal effect expressed as percentage of control value in each experiment. Solid and broken lines are averages of circles and crosses, respectively. In the lower row, ipsilateral cordotomy means the ipsilateral dorso-lateral cordotomy at the obex level and bilateral cordotomy, the complete spinal section at the same level. Note that fentanyl depressed both measures, and the cordotomy decreased only the total discharge area in the ipsilateral digastric discharges.

was measured, the area became smaller by 28.4±3.5% (averages of 10 animals). All of these changes caused by fentanyl were significant at the level of P=0.01. These results indicate that fentanyl depressed the early phase (from its actions upon the first peak amplitude and the onset latency) as well as the late phase (from its action upon the total duration) of the digastric reflex discharge. This was also supported by upper left graph in Fig. 3, where it was illustrated that fentanyl (20 and 40 µg/kg) depressed, to the same extent, both the first peak amplitude which represents the early phase and the total discharge area which contains the early and late phases of the digastric reflex discharge.

Time courses of fentanyl effect on the total area of the discharge are illustrated in Fig. 4. A maximal depression by fentanyl, 20 µg/kg, occurred within 5 minutes after the injection. Thereafter, the discharge gradually recovered and returned to the control values in about 30 min. In dose of 40 µg/kg, fentanyl effect was more potent and longer-
Fentanyl depressed the total area and the amplitude of the first peak of digastric reflex discharge caused by volleys in the contralateral inferior alveolar nerve as potent as those from the ipsilateral one (Figs. 3 and 4).

After fentanyl administration, a new discharge appeared in the digastric nerve at 15-30 msec after the inferior alveolar nerve stimulation in 8 of 15 animals. This discharge was easily abolished by Nembutal®, 2-5 mg/kg, or by the complete spinal section at the obex level.

Influence of cordotomy at the obex level

The dorso-lateral cordotomy at the level of the obex abolished the late phase of the reflex discharge in the ipsilateral digastric nerve induced by the ipsilateral inferior alveolar nerve stimulation, but did not influence its early phase (Fig. 2). This is quantitatively shown by a graph illustrating the relationship between a change of the first peak amplitude and that of the total discharge area (crosses in lower left graph of Fig. 3). Following the cordotomy the total discharge area was decreased by 21%, while the first peak
amplitude was little affected (2.3% decrease). There was a significant difference between the decreases of the area and the amplitude at the level of P=0.05. The influence of total spinal section at the obex level was similar to that of the ipsilateral dorso-lateral cordotomy (circles in lower left graph of Fig. 3).

On the other hand, the digastric nerve discharge to the contralateral alveolar nerve stimulation was little affected by the dorso-lateral cordotomy ipsilateral to the recording side at the obex level, but decreased remarkably after complete spinal section (lower right graph in Fig. 3).

Effect of fentanyl after the complete spinal section at the obex level

As shown in Fig. 2, after the complete spinal transection at the obex level, fentanyl depressed the first peak amplitudes in the digastric reflex discharges to the ipsi- and contralateral alveolar nerve stimulations as potently as before the cordotomy. Levallorphan, in dose of 0.5 mg/kg, antagonized this fentanyl effect. The later portion of the digastric reflex discharge was little influenced by fentanyl. This is quantitatively shown by graphs in Fig. 5 which illustrate the effect of fentanyl on the digastric reflex discharge evoked by volleys in the ipsilateral inferior alveolar nerve before and after the complete spinal section in 5 cats. The upper and lower rows indicate the effects of fentanyl on the total dis-

![Graphs showing effects of fentanyl on digastric reflex discharges](image)

**Fig. 5.** Effects of fentanyl on the ipsilateral digastric reflex discharges induced by supramaximal stimulation of the inferior alveolar nerve, before (solid lines) and after (broken lines) the complete spinal section at the obex level. Upper row shows fentanyl effect on the total discharge area and lower row shows that on the first peak amplitude. Graphs in each column were obtained from the same animal. Ordinates indicate percentage of control values. Doses of fentanyl used were 20 or 40 µg/kg. Note that following the complete spinal section, the fentanyl effect on the total discharges areas decreased considerably.
Y. NISHIJIMA & Y. SAKAI

charge area and on the first peak amplitude, respectively. After the complete spinal section, the depression of the first peak amplitude by fentanyl was slightly weaker, such as by 30% before the transection and by 23% thereafter. The decrease of the total discharge area was reduced from 24% to 10% by the complete spinal section.

DISCUSSION

Jaw opening reflex and afferent fiber components

The data presented in this study indicate that the activity in the small myelinated fibers in the inferior alveolar nerve is also responsible for the jaw opening reflex, since a stimulus which excites all of the myelinated afferent fibers of the nerve brought about more prolonged reflex discharges than a stimulus exciting only Aβ fibers. These results are consistent with the observations that the reflex jaw opening in the cat was induced not only from the lowest threshold fibers in the trigeminal nerve (Aβ fibers) (1, 3, 4), but also from Aδ fibers (6, 7) containing the tooth pulp (2, 5) which consists exclusively of the small myelinated fibers of 1–7 μ in diameter (Aγ-δ fibers) (8).

Following the dorso-lateral cordotomy at the level of the obex abolished the late phase of the ipsilateral digastric nerve discharge induced by supramaximal stimulation of the ipsilateral inferior alveolar nerve, while the early phase of the discharge and the reflex discharge from the contralateral one were not influenced. These findings seem to be in agreement with the observation of Riblet and Mitchell (10) that hemisection at the C1 level in the cat elevated the jaw jerk threshold to ipsilateral tooth pulp stimulation, but not to the contralateral one. Therefore, it is conceivable that the late phase in the digastric reflex discharge which was abolished by the dorso-lateral cordotomy in our preparations would predominantly contain the components from the smaller diameter myelinated fibers. Sumino (11) reported, however, that in Nembutal® treated cats the digastric reflex discharge was not affected by the transection of the spinal tract and the spinal tract nucleus at the level of the obex. This discrepancy may be due to differences between both the given stimulus intensities and/or between α-chloralose and Nembutal®.

The result of the dorso-lateral cordotomy at the obex level, the boundary between the subnucleus interpolaris and the subnucleus caudalis of the spinal trigeminal nucleus, indicates that the late phase of ipsilateral digastric reflex discharge is related to the spinal trigeminal nucleus caudalis or its surroundings. It is possible that dorso-lateral cordotomy would abolish the late phase at least in two ways. It would block the trigeminal input to the reflex pathway that relays to the digastric motoneurons through subnucleus caudalis or its surroundings. Or, it would also induce a decrease in transmission through the subnucleus oralis by relative depolarization of primary afferent terminals, which is caused by interruption of tonic hyperpolarizing influence from the subnucleus caudalis (13) and of hyperpolarization induced by noxious stimulation, via the subnucleus caudalis (14). However, Young and King (14) described that the measurements of excitability changes mainly reflect the events in large fibers and that there is no confirmation at present that this primary afferent hyperpolarization results in a significant facilitation
FENTANYL AND JAW OPENING REFLEX

of the firing of second-order neurons. Furthermore, the first peak amplitude in the digastric reflex discharge from the large myelinated fibers in the inferior alveolar nerve was not changed by the dorso-lateral cordotomy which also increased the excitability of the primary afferent terminals in the subnucleus oralis in our preparations. Therefore, the excitability changes of primary afferent terminals may have little direct influence on the digastric reflex discharge.

These facts and considerations led us to the following statement: the digastric reflex discharge evoked by volleys in the ipsilateral inferior alveolar nerve would be divided into two components which were composed of the early phase from the large myelinated afferent fibers through the subnucleus oralis and subnucleus interpolaris (11) and the late phase from the small myelinated fibers via the subnucleus caudalis or its surroundings.

Action of fentanyl

Fentanyl depressed the early phase as well as the late phase in the digastric reflex discharge induced by supramaximal stimulation of the ipsilateral inferior alveolar nerve. This finding seems to be in accordance with the results of Koll et al. (15) that in the ipsilateral flexion reflex of the hind limb of spinal cats, morphine, in doses of 0.5 0.6 mg/kg, produced a depression of both the Aδ- (probably nociceptive) and the Group II (non-nociceptive) reflexes. Iwata and Sakai (16), however, reported that fentanyl exerted a preferential effect on the Aδ component in the cutaneous inhibition of the monosynaptic reflex in spinal cats. This difference may reflect a different sensibility to the drug of polysynaptic EPSP and IPSP elicited in motoneurons by low threshold afferent nerve stimulation (17).

The inhibition of Group II reflex (15) and, in general, of polysynaptic spinal reflex (PSR) (18) may, at least in part, be related to some ataxia which is produced by morphine in an analgesic dose (2 and 4 mg/kg i.p.) in cats (2). Fentanyl (20 μg/kg i.p.) also disturbed the normal walking ability in cats (19). It is evident from this study that the early phase in the digastric reflex discharges is related to the large myelinated afferent fibers, and its inhibition may indicate a non-analgesic motor disturbing action of fentanyl such as the depression of the polysynaptic spinal reflexes.

It is inferred that the late phase in digastric reflex discharge corresponds to the nociceptive reflex for the following two reasons: (i) it appeared following the stimulation of Aγ plus Aδ fibers, not only Aγ fibers, in the inferior alveolar nerve. And, pain impulses are thought to be conducted by medullated A fibers at 15 to 45 m/sec (Aγ-δ fibers) and by C fibers (20); (ii) it disappeared following the dorso-lateral cordotomy at the level of the obex which, clinically, may lead to loss of temperature and pain sensibilities in the trigeminal area, while touch sensibility is preserved (9).

The effect of fentanyl on this late phase, observed in this study, may correspond to the depression of the Aδ reflex in flexion reflex (15) or the elevation of the jaw jerk threshold to tooth pulp stimulation (2) by morphine. Particularly, the latter does so, since its decrease was observed after ipsilateral hemisection at the C1 level (10).

These findings may imply an action of fentanyl in the subnucleus caudalis or its sur-
roundings. An action of morphine on the potentials in the subnucleus caudalis evoked by tooth pulp stimulation has been investigated by Mizoguchi (21) in dogs and by Kuromi et al. (22) in rabbits. The former observed depressant action of morphine and the latter described no effect of morphine. It is not evident from their results (21, 22) whether morphine acts in the subnucleus caudalis.

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