INHIBITION OF THALAMIC AND HYPOTHALAMIC
SOMATOSENSORY EVOKED POTENTIALS BY STIMULATION
OF SUBSTANTIA NIGRA AND ITS MODIFICATION
BY MORPHINE AND METHOTRIMEPRAZINE
(LEVOMEPROMAZONE)

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Accepted February 2, 1976

Abstract—A brief electrical stimulation of the substantia nigra induced a marked and
long lasting inhibition of the somatosensory evoked potentials recorded from the
centrum medianum of the thalamus (CM) and posterior hypothalamic area (PHA)
following sciatic stimulation in unanesthetized rabbits. The nigral inhibitory effect on
CM was prolonged by the administration of morphine (4 mg/kg i.v.) but not influenced
by that of methotrimeprazine (2-4 mg/kg i.v.). In contrast, the nigral inhibitory effect
on PHA was enhanced by the injection of methotrimeprazine (2 mg/kg i.v.), but not
changed by that of morphine (4 mg/kg i.v.). These results indicate that the inhibitory
system originating from the substantia nigra operates on the somatosensory trans-
missions from the peripheral nerve to the thalamus and hypothalamus, and that mor-
phine or methotrimeprazine in small doses induces a selective potentiation of the nigral
inhibitory influence on the thalamus or hypothalamus, respectively.

It has been generally accepted that the caudate nucleus and substantia nigra participate
in the control of motor performance as components of the extrapyramidal system. Several
authors (1-3), however, demonstrated that a conditioning stimulus applied to the caudate
nucleus inhibited the somatosensory evoked potential recorded from the thalamus. These
data suggest that the caudate nucleus plays a certain role in both the motor and sensory
systems. Since the existence of intimate fiber connections between the substantia nigra and
caudate nucleus is well acknowledged, whether or not the substantia nigra also controls
somatosensory mechanisms is worthy of investigation.

Kuromi et al. (3) have reported that the caudate-induced inhibition of the somatosensory
input into the thalamus was enhanced by morphine but depressed by methotrimeprazine
(levomepromazine), a phenothiazine derivative possessing analgesic action, in unanesthetized
rabbits.

In the present experiments, the effect of a conditioning nigral stimulation on the soma-
tosensory evoked potentials recorded from the thalamus and hypothalamus was observed
in unanesthetized rabbits, and the influences of morphine and methotrimeprazine on the
conditioning effect were then investigated.

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MATERIALS AND METHODS

The present experiments were performed on 21 albino rabbits of both sexes, weighing 2.5 to 3.0 kg. Surgical procedures, including cannulation of the endotracheal tube and placement of electrodes, were performed under ether anesthesia. The rabbits were placed in a stereotaxic apparatus, immobilized with gallamine triethiodide (Flaxedil, 2-3 mg/kg i.m.), and artificially ventilated. Subcortical electrodes were placed stereotaxically according to coordinates from the rabbit brain atlas of Sawyer et al. (4). A local anesthetic, lidocaine, was repeatedly applied to wound edges and pressure points throughout the entire experiments. An interval of at least 2 hr elapsed between the discontinuance of ether and the beginning of the experiment.

For a test stimulation, the sciatic nerve was stimulated with single rectangular pulse (duration: 0.1 msec, intensity: 14-16 volts) every 10 sec. In most experiments, the evoked potential was recorded from either the centrum medianum of the thalamus (P: 5.0, L: 1.5-2.0, H: -2.5--3.5) contralateral to the stimulated sciatic nerve, through a concentric bipolar stainless-steel electrode insulated except for the tip. In 4 rabbits, however, the evoked potentials were recorded from both sites in an individual preparation. These evoked potentials were amplified and displayed on an oscilloscope (Nihonkohden's VC-7). The potentials following 10 successive stimulations were averaged by means of an averaging data processor (Nihonkohden's ATAC-201), and then the averaged pattern was photographed.

For a conditioning stimulation, the substantia nigra (P: 7.0-7.5, L: 4.5-5.5, H: -4.0--5.0), contralateral to the diencephalon explored, was stimulated with a single shock or with a train of 2-5 rectangular pulses (duration: 1.0 msec, intensity: 1-2 volts) at a frequency of 200 Hz, using the same type of electrode as in the previous experiments (3). The time interval between conditioning and test stimuli was measured from the first pulse of the conditioning volley. The position of subcortical electrodes was histologically checked at the termination of each experiment.

Materials used were morphine hydrochloride and methotrimeprazine (levomepromazine) hydrochloride. Both drugs were injected intravenously. Drug doses given are in terms of the salts. An individual rabbit was administered only one dose of either drug.

RESULTS

Inhibition of somatosensory evoked potentials of the centrum medianum of the thalamus and the posterior hypothalamic area by nigral stimulation

Evoked potentials following stimulation of the sciatic nerve were recorded from the centrum medianum of the thalamus (CM) and the posterior hypothalamic area (PHA) contralateral to the stimulated nerve, using bipolar electrodes. The evoked potentials in both sites consisted of 3 components (Fig. 1), the first upward, the second sharp downward and the third upward components, and the onset-latencies of their first components were 15-20 msec in CM and 20-40 msec in PHA. These evoked potentials were used as test responses.

Conditioning stimuli applied to the substantia nigra at varying time intervals before
FIG. 1. Changes in the nigral inhibitory effects on the somatosensory evoked potentials recorded from the posterior hypothalamic area (A and B rows) and the centrum medianum of the thalamus (C and D rows) following sciatic nerve stimulation. Parameters of the conditioning stimuli were changed. In A and C rows, the number of pulses in a train was changed at a given voltage (2 volts). In B and D rows, the voltage was changed at a given number of pulses (5 pulses). The first photograph in each row (A-D) shows unconditioned response and the others conditioned responses. Each photograph shows an averaged pattern of the responses following 10 successive stimulations. Calibration; 0.1 mV. Time scale; 250 msec. Note that a marked inhibition occurs at 1–2 volts with 3–5 pulses.

the test stimuli inhibited the test responses particularly their second downward components. For that reason, the conditioning effect was represented as a percentage of the amplitude (from the base line to the peak) of the second component of the conditioned response to that of the unconditioned response. The inhibition of the somatosensory evoked potentials by the conditioning stimulation with a critical intensity (2 volts) was slight following single shock to the substantia nigra but became more prominent by increasing the number of pulses in a given volley and reached its maximum at 5 pulses (Fig. 1A and C). A threshold voltage for inducing the inhibition was 1 to 2 volts with a train of five pulses (Fig. 1B and D). The time-course of the inhibition was determined by systematically varying the interval between conditioning (2 volts; a train of five pulses) and test stimuli. The nigra-induced inhibition in both CM and PHA occurred at a time interval within 50 msec and reached its maximum at that of 50 or 100 msec, and then declined gradually and could be no longer detected at that of over 600–800 msec in most cases (Fig. 2A and B).
The conditioning stimulation applied to the substantia nigra consistently produced a marked inhibition. In contrast, conditioning stimulation applied to the structure surrounding substantia nigra such as the medial geniculate body, lateral reticular formation, basis pedunculi or medial lemniscus did not cause notable inhibition. These facts indicate that the inhibition of the diencephalic somatosensory response by nigral stimulation is not attributed to a propagation of stimulation current to the surrounding structures.

Effects of methotrimeprazine and morphine on the nigral-induced inhibition of the somatosensory thalamic evoked potential

When 2 or 4 mg/kg of methotrimeprazine was administered into 5 rabbits respectively, the conditioning effect of nigral stimulation on somatosensory thalamic response was not markedly influenced up to 2 hr after dosing; at intervals of 100 and 400 msec, the ratios of the amplitude of the second component of conditioned response to that of unconditioned response were 40.7 ± 10% (mean ± S.E.) and 85.7 ± 14% in the control (Fig. 3A solid line) and 55.1 ± 7.2% and 76.0 ± 4.0% at 60 min after the administration of 4 mg/kg of the drug (Fig. 3A broken line), respectively.

In contrast, the injection of 4 mg/kg of morphine in 5 experiments significantly prolonged the duration of the maximum inhibitory effect induced by the nigral stimulation, but did not augment the degree of the maximum inhibition; at intervals of 100 and 400 msec, the ratios were 26.0 ± 3.2% and 91.0 ± 14% in the control (Fig. 3B solid line) and 34.0 ± 7.3% and 41.0 ± 9.8% at 30 min after the injection (Fig. 3B broken line), the difference between the ratios at an interval of 400 msec being significant (Student’s t test, p<0.05). This effect of morphine lasted for about 90 min. Very little change was observed in the unconditioned response with either drug.

Effects of methotrimeprazine and morphine on the nigral-induced inhibition of somatosensory hypothalamic evoked potential

The administration of methotrimeprazine, in a dose of 2 mg/kg, enhanced the extent
Fig. 3. Effect of methotrimeprazine (A) or morphine (B) on the nigral inhibition of the somatosensory response in the centrum medianum of the thalamus. The ordinate gives percentage of the amplitude of conditioned response to that of unconditioned response. The abscissa gives time-interval between conditioning and test stimuli. Solid lines; control. Broken line in A; 60 min after the injection of 4 mg/kg of methotrimeprazine. Broken line in B; 30 min after the administration of 4 mg/kg of morphine. Each point shows a mean value of 5 experiments except for two points at an interval of 600 msec in A which were mean values of 2 experiments. The vertical bars represent the standard error (S.E.). A symbol (*) indicates a significant difference between a pair of mean values at a given interval (Student's t test, p<0.05). Note that morphine, but not methotrimeprazine, prolonged the inhibitory influence of nigral stimulation on the thalamus.

Fig. 4. Effect of methotrimeprazine (A) or morphine (B) on the nigral inhibition of the somatosensory response in the posterior hypothalamic area. The ordinate gives percentage of the amplitude of conditioned response to that of unconditioned response. The abscissa gives time-interval between conditioning and test stimuli. Solid lines; control. In A, subthreshold conditioning stimuli were used. Broken line in A; 60 min after the injection of 2 mg/kg of methotrimeprazine. Broken line in B; 30 min after the administration of 4 mg/kg of morphine. Each point shows a mean value of 5 experiments except for four points at an interval of 600 msec which were mean values of 2 experiments. The vertical bars represent the standard error (S.E.). A symbol (*) indicates a significant difference between a pair of mean values at a given interval (p<0.05). Note that methotrimeprazine, but not morphine, enhanced the inhibitory influence of nigral stimulation on the hypothalamus.
and prolonged the duration of the inhibition of somatosensory hypothalamic evoked potential by nigral stimulation. Such a potentiation of the nigra-induced inhibition was also observed, even when the conditioning stimulation was too weak to produce a marked inhibition of the test response in the control; at intervals of 100 and 400 msec the ratios of the amplitude of conditioned response to that of unconditioned response were 94.5±5.1 % and 96.6±5.1 % in the control (Fig. 4A solid line) and 40.0±13 % and 79.0±5.6 % at 60 min after the administration (Fig. 4A broken line), each pair of values at both intervals of 100 and 400 msec being significantly different (p<0.05). The effect of the drug lasted for about 120 min. On the other hand, the injection of 4 mg/kg of morphine in 5 rabbits did not modify the nigra-induced inhibition of somatosensory hypothalamic response (Fig. 4B). Little change was observed in the unconditioned response with either drug.

**DISCUSSION**

Present experiments using unanesthetized rabbits have shown that a conditioning stimulation of the substantia nigra inhibited the somatosensory evoked potentials recorded from the centrum medianum of the thalamus and the posterior hypothalamic area. These results indicate that the substantia nigra is involved in the somatosensory mechanisms at the diencephalic level as well as participating in the control of motor performance. Furthermore, it was shown that the threshold voltage and the duration of the nigra-induced inhibitions on both sites were 1–2 volts with a train of five pulses and 600–800 msec after delivering such a threshold stimulus. On the other hand, those of the caudate-induced inhibition of the somatosensory thalamic response were 4–6 volts and 200 msec as shown in the previous experiments (3) using the same type of electrode and the same parameters except for the intensity used in the present experiments. These facts indicate that the inhibitory influence of nigral stimulation on the diencephalic somatosensory mechanisms is more likely to occur and is more prolonged than the influence of caudate stimulation. This discrepancy may be due to the possibility that the nigral stimulation activates not only the caudate nucleus but the other regions of basal ganglia which also have inhibitory effects of the diencephalon (1).

It was shown in the present experiments that methotrimeprazine (2 mg/kg) selectively enhanced the nigra-induced inhibition on the posterior hypothalamic area, while morphine (4 mg/kg) selectively potentiated that on the centrum medianum. The authors observed in another experiment carried out on unanesthetized rabbits (unpublished data) that methotrimeprazine (4 mg/kg) suppressed a hypothalamic evoked potential following tooth pulp stimulation but did not suppress a thalamic evoked potential following such stimulation, whereas morphine (4 mg/kg) inhibited the latter but not the former. Moreover, it has been observed that methotrimeprazine (5) and morphine (6) produced a relatively selective depression of hypothalamic and thalamic EEG arousal response, respectively. These facts suggest that one of sites of analgesic action of methotrimeprazine is at the hypothalamic level, while that of morphine is at the thalamic level and further confirm the previous suggestion that the mechanisms of analgesic action of the former are different from those of the latter (3, 5).
Furthermore, the differences in susceptibility of the nigra-induced inhibitions on the thalamus and hypothalamus to analgesics used suggest that these inhibitions do not occur along the common pathways from the stimulated peripheral nerve to the recording sites but rather within the thalamus and hypothalamus, respectively.

Satoh and Takagi (7) and Satoh et al. (8) have shown in cats and rabbits that morphine (2-4 mg/kg) enhances the descending inhibitory mechanisms of the lower brain stem which act on the spinal sensory transmission. All these data suggest that enhancement of central inhibitory systems acting on the sensory afferent systems plays a most important role in the analgesic mechanism of morphine.

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