Effects of Nitrous Oxide on the Somatosensory Evoked Response in Cats

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The effect of nitrous oxide on the activity of the somatosensory system was studied in cats with brain electrodes implanted chronically. The electrodes were implanted in the primary somatosensory cortex, cortical somatosensory radiation, medial lemniscus and midbrain reticular formation. Alterations in the excitability of the primary sensory pathway were assessed by the changes of the input to and output from these brain areas: the response in the medial lemniscus to the stimulation of the skin represented the input to the thalamic relay nucleus and the response recorded in the cortical sensory radiation represented the output from the thalamic relay nucleus. The concentrations of nitrous oxide studied were 50% and 75% in oxygen, and the drug effect was concentration-related. The cortical response to peripheral stimulation was suppressed in amplitude by more than 40% of the control with 75% nitrous oxide, and the response in the cortical radiation was suppressed by 20% of the control with the same dose of nitrous oxide. The response in the cortical radiation to stimulation of the mdeial lemniscus was suppressed by 20% of the control and the postsynaptic component of the cortical response to the stimulation of the medial lemniscus was suppressed by more than 50% of the control. The multi-unit activity of the brainstem reticular formation was enhanced by nitrous oxide in a dose related manner. The excitability of the thalamic relay nucleus and the primary somatosensory cortex was suppressed by natural slow wave sleep when the reticular multi-unit activity was suppressed, and they were enhanced by paradoxical phase of sleep when the reticular multi-unit activity was enhanced. These findings indicated that the degree of suppression of excitability by nitrous oxide is similar in both the thalamic relay nucleus and sensory cortex, and its action on the brain stem reticular formation is different from that on the primary sensory system. The suppression of sensory functions shown in the present study provides a certain clue to the understanding of the neural basis that though nitrous oxide does not produce deep surgical anesthesia, it does induce potent analgesia and sedation during surgery. (Key words: nitrous oxide, EEG, depth recording, multi-unit activity, somatosensory evoked response, specific sensory path, thalamus)

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There is a general agreement that nitrous oxide reduces the long latency non-specific somatosensory evoked responses in the brain stem reticular formation[1–6]. In contrast, a review of the literature revealed that there are a number of opinions on its effect on the so-called specific somatosensory evoked response in the cerebral cortex. Miyata[5] observed that nitrous oxide suppressed the early component of the somatic-induced response in the primary sensory area of the cerebral cortex, leaving the re-

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sponse in the ventrobasal thalamus unaffected, and postulated that the response was suppressed not in the thalamic relay but in the transmission within the cortical structure. In contrast, some suppression in the ventrobasal thalamic nucleus has also been reported[1,7–15]. It has been reported that the transmission property of thalamic relay nuclei are under modulation by the activity of the reticular core and its activation facilitates the activity of the thalamic relay nucleus in unanesthetized freely moving cats[16–18]. Mori and Winters[19]reported enhancement rather than suppression of the ongoing multi-cellular activity of reticular core by nitrous oxide. These results indicate that there is a possibility of the paradoxical nature of nitrous oxide: it activates cell firing of the reticular core while it suppresses the transmission property of the thalamic relay nuclei. The present study attempts to quantitatively measure the changes induced by nitrous oxide in the activity of the afferent transmission system at each step: the dorsal column nucleus, the ventrobasal thalamic nucleus and the primary sensory cortex. Our goal is to identify the site of action of nitrous oxide in suppressing the sensory functions.

Materials and Methods

Animal preparation

Fourteen adult cats of either sex, weighing 2.8–4.1 kg, were used. Brain electrodes were implanted under pentobarbital anesthesia 3–5 weeks prior to the experiment. The structures from which the electrical activities were recorded were the primary somatosensory cortex (SI), the cortical radiation of the primary sensory projection (Sub-SI), the medial lemniscus (LM), and the midbrain reticular formation. The cortical surface electrodes consisted of stainless steel screws, 1.5 mm in diameter, which were inserted to reach the dura. A reference electrode was placed in the frontal bone. The subcortical electrodes were side-by-side stainless steel wires, 0.2 mm diameter. With the exception of the tips, the electrodes were insulated with eposyliteresin and the tips had 0.5- to 1.0-mm vertical separation. All leads were soldered to a small socket that was fixed to the skull with dental cement. The evoked responses in the deep structures were obtained between one of the parallel wires and the reference. The position of the electrodes in the primary sensory pathway was selected at the place where the typical and maximum response was produced by the stimulations given at the site and/or the sites peripheral to the recording site, eg., the Sub-SI electrode was guided while the stimulation was being given to either or both the LM, and that of the LM was guided while the forepaw skin was stimulated. The best electrode position for stimulation was not always suitable for recording the response induced by stimulation at the site peripheral to the recording site. Furthermore, the best recording site of the SI response to the Sub-SI stimulation was not the best recording site of the SI response to stimulation of the forepaw. Thus, only suitable recording and stimulation electrodes were used and the data were collected from these electrodes only. The electrode positions thus selected were A:27, L:13 for the SI; A:18, L:9, H:+6 for the Sub-SI; A:1, L:4, H:–4 for the LM according to the stereotaxic coordinates by Snider and Niemer (1961)[20]. An allowance of 1.0–1.5 mm on the three coordinates was made according to the size of cats. A similar wire electrode was inserted in the midbrain reticular formation (A:2; L:3; H:–2) for recording multi-unit activity. All brain electrodes were fixed to the skull with dental cement, and the wound margin was sutured.

Administration of nitrous oxide

The cats were anesthetized with 3% halothane in oxygen in a transparent anesthesia box. When the animal became unconscious and the respiration was depressed considerably, the trachea was intubated, and alcuronium (10 mg im) was administered. Next the tube was connected to a mechanical ventilator (Acoma AR100) administering a tidal volume of 10–13 $ml \cdot kg^{-1}$ at a rate of 20 min^{-1}. The end-tidal CO_2 was maintained in the range of 28–32 mmHg by adjusting the ventilation volume, utilizing an infrared CO_2 analyzer (Cavitron® PN-20N).

The rectal temperature was maintained at 37–39°C, using a warm water blanket and heating lamp. One hour later, when the cortical EEG showed a mixture of spindle-bursts and slow waves of sleep type and the pupils were thin-slit and did not respond to the electric shocks to produce evoked responses, the drug study was started. The assessment of drug effects, 50% and 75% nitrous oxide in oxygen, was performed at 30 to 40 min of administration when their effects were maximum[19,21,22].

Studies of CNS electrical activities

Peripheral stimulation, consisting of square pulses of 0.1 ms duration and 0.5–2 V in intensity was given through bipolar electrodes inserted into the subcutaneous tissue of the forepaw. The central somatic pathways were stimulated through the bipolar electrodes which were also used for recording. The stimuli consisted of square pulses of 0.1 ms duration and 1–8 V in intensity. The intensities of peripheral and central stimulations were adjusted 2–3 times the threshold to produce short latency response, which were subthreshold to induce EEG arousal response as described in free-moving cats previously[17,18]. The threshold values were determined during the control period when the EEG showed high voltage slow waves of sleep type typical of paralyzed unanesthetized cats ventilated mechanically in a warm environment[23,24]. The intensity of stimulation thus determined was usually 2–3 times the threshold to yield short latency response. The rate of stimulation was controlled manually to produce random interstimulus intervals of 1–3 s. Ten responses were summed using a signal processor (Sanei 7S06A). The resulting traces were recorded on an X-Y plotter (Watanabe WX442). Intervals of time of more than 10 min were attempted to elapse between the trials of recording evoked response so that arousal effects by electric stimulation should not summate.

The EEG activities were recorded using a polygraph (Nihonkoden), the high-cut filter was set at "off" and the low-cut filter at the time constant of 0.1 s. Ten traces of the evoked response were averaged using a computer (Sanei Signal Processor 7S06A). The analysis time ranged from 10 to 100 ms according to the response examined. The traces were recorded using an X-Y plotter (Watanabe WX442).

The multi-unit activity was obtained according to the method reported by Mori et al.[25]. The depth electrodes, described above, picked up the discharge of a population of units included in a sphere of approximately 1 mm radius around the tip of electrode[26]. As this activity was superimposed on the slow oscillation of field potential, the so-called EEG, it was passed through a high-pass filter. The filter was designed with a frequency response peaking at 1300 Hz with 5 db attenuation at 900 and 3500 Hz and 40 db attenuation at 400 and 8000 Hz. The filtered activity was rectified, smoothed with the time constant of 50 ms and recorded on a slow-moving DC recorder (Sanei Rectigraph 8s) with a paper speed of 10 $mm \cdot min^{-1}$. Calibration of this activity was not practical as the output depended on the electrode impedance as well as the level of neuronal activity. The noise level of the recording system was assessed by measuring the difference between the output voltages produced by connecting the imput terminals together and placing a 10 kΩ resistor between them. With this method the signal-to-noise ratio exceeded 10 in all the studies.

Study in freely moving state

The drug effect was studied in a cat able to move about freely. The control evoked responses were recorded while the cat was placed in the room air. A subthreshold intensity of stimulation was used as in the case of paralyzed cats. The stimulation was given to the medial lemniscus and the responses were recorded in the cortex. Nitrous oxide was administered in a trasparent anesthesia box, 20 × 30 × 50 cm in size, the concentrations that were studied were 50 and 75% nitrous oxide in oxygen. The drug effects were compared with the effects of slow wave sleep and paradoxical phase of sleep. The intracerebral stimulation parameters were identical with those used in the study of paralyzed state.

Table 1. SEP induced by peripheral stimulation

	L.M		Cort. Rad (Sub-SI)		SI	
	M ± S.E.(%)	α	M ± S.E.(%)	α	M ± S.E.(%)	α
50%	100.4 ± 2.8	n.s.	85.9 ± 1.2	< 0.001	79.0 ± 8.0	< 0.001
75%	96.4 ± 2.3	n.s.	80.1 ± 2.3	< 0.001	56.5 ± 6.9	< 0.001

LM: medial lemniscus
Cort. Rad (Sub-SI): somatosensory cortical radiation
SI: primary sensory cortex

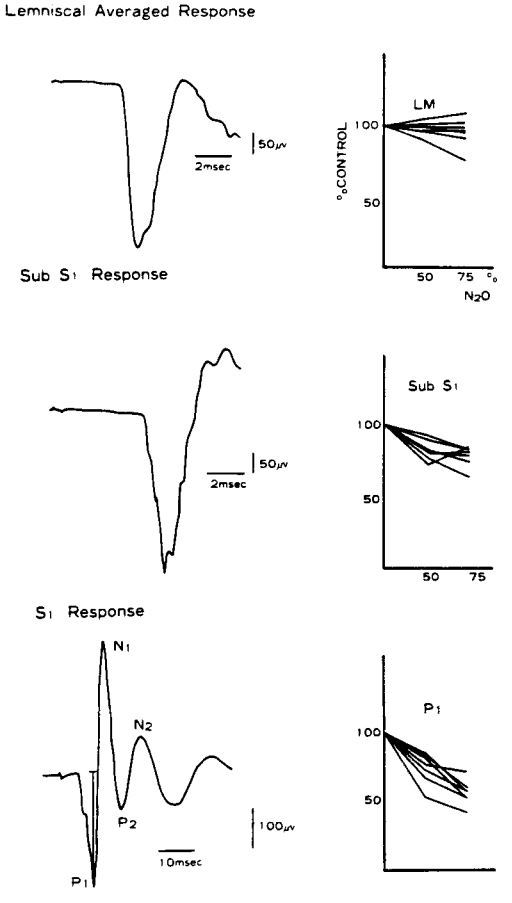

Fig. 1. Effect of nitrous oxide on the somatosensory evoked responses in the afferent sensory pathway. The stimulation was given to the skin of the contralateral forepaw. The upper left figure represents the response recorded at the medial lemniscus (LM), the middle left figure is that recorded at the cortical radiation (Sub-SI), and the lower left figure is that recorded at the primary sensory cortex. The right figures show the changes induced by nitrous oxide (50 and 75% in oxygen). See text for further explanation.

Care of animal

The strict criteria for animal experimentation proposed by Venes et al.[13] and modified in our laboratory were followed. These criteria are as follows: 1) electric stimulation to the peripheral nerves, which can be in the range of A delta and C, should be such as to prevent summating effects which occur at frequencies greater than 3 s^{-1}; 2) an interval of time, which in this laboratory study was set at at least 10 min, should elapse between the trials of recording the evoked response, so that there is no summation of arousal effects; 3) the animal should be free of extraneous noxious stimulation during the whole course of study; 4) the ongoing EEG should show the sleep pattern of high voltage slow waves which is induced by the administration of muscle relaxants[23] and the warm environment[24]; 5) it must be confirmed that the pupils are thin-slit and do not respond to the peripheral electric stimulation.

Statistics

The values obtained during the nonanesthetized state served as control in each experiment, and the changes induced by nitrous oxide were expressed as a percent of control, mean ± SEM. The statistical method used was analysis of variance with Newman-Keuls test.

Results

1. Control EEG

The control cortical EEG of the unanesthetized state maintained a mixture of 10–14 Hz spindle bursts and 0.5–4 Hz high voltage slow waves, which was similar to the EEG of slow wave sleep. The electric stimulation of both the forepaw and the intracerebral struc-

Table 2. SEP induced by medial lemniscus stimulation

	Cort. Rad (Sub-SI)		SI							
			C1		C3		C4		C5	
	M ± S.E. (%)	α	M ± S.E. (%)	α	M ± S.E. (%)	α	M ± S.E. (%)	α	M ± S.E. (%)	α
50%	78.0 ± 5.4	<0.01	82.1 ± 5.5	<0.05	64.2 ± 4.3	<0.001	35.0 ± 5.1	<0.001	48.1 ± 7.5	<0.001
75%	80.1 ± 6.6	<0.01	78.0 ± 6.1	<0.01	48.1 ± 5.0	<0.001	12.3 ± 3.7	<0.001	40.3 ± 4.8	<0.001

Cort. Rad (Sub-SI): somatosensory radiation.
SI: primary sensory cortex.
C1, C3, C4 and C5: Component 1, 3, 4 and 5 of the evoked potential.

tures induced evoked responses in the EEG but did not produce arousal reactions in the EEG. The pupils also did not respond to the electric shocks.

2. *Effects of nitrous oxide on the reticular multi-unit activity*

The reticular multi-unit activity was enhanced by 17.4 ± 5.0% (m ± sem) ($P < 0.05$) following the administration of 50% nitrous oxide for 30 min, and by 28.6 ± 16.2% following 75% nitrous oxide for 30 min.

3. *SEP induced by peripheral stimulation*

The results are summarized in table 1.

The medial lemniscus (LM)

The LM response consisted of a sharp positive deflection followed by a small negative deflection (fig. 1). The latent period for the rising phase of the initial positive deflection was 3.58 ms, and that for the peak was 5 ms. The suppression by nitrous oxide, 50% and 75%, was not significant.

The somatosensory cortical radiation (Sub-SI)

The Sub-SI response consisted of a sharp positive deflection followed by a slow negative component (fig. 1). The latent period for the rising phase of the initial positive deflection was 4.95 ms, indicating the delay by 1.3 ms in the thalamic relay. Nitrous oxide significantly suppressed the thalamic relay in a dose related manner.

The primary sensory cortex (SI)

The SI response consisted of four deflections of positive (P_1), negative (N_1), positive (P_2) and negative (N_2) components (fig. 1). The latent period for the rising phase of the initial positive deflection was 4.9 ms, which coincided with that of the somatosensory cortical radiation. The latent periods for the peaks of each deflections were 8–12 ms (P_1), 12–14 ms (N_1), 15–18 ms (P_2), and 20–24 ms (N_2). Nitrous oxide suppressed the amplitudes of all these peaks, but the measurement was done only for the initial positive component, which was suppressed significantly in a dose related manner.

4. *SEP induced by stimulation at the medial lemniscus*

The results are summarized in table 2.

Somatosensory cortical radiation (Sub-SI)

The response in the cortical radiation to stimulation of the LM consisted of two successive positive deflections followed by a negative deflection. The initial positive deflection was small in amplitude, and the latent period for the rising phase was negligible, indicating that this component was induced by activation of fibers bypassing the thalamic relay nucleus. The second positive deflection was greater in amplitude and the latent period for the rising phase was approximately 1 ms, which corresponded with the latent period for thalamic relay in the peripheral stimulation study. Nitrous oxide of both concentrations had no effect on the initial small positive component, while it significantly suppressed the second positive component in a dose related manner (table 2 and fig. 2).

The primary sensory cortex (SI)

The SI response induced by stimulation of the LM consisted of four successive positive deflections which were followed by a large negative deflection (fig. 2). The first positive deflection had no latent period for the ris-

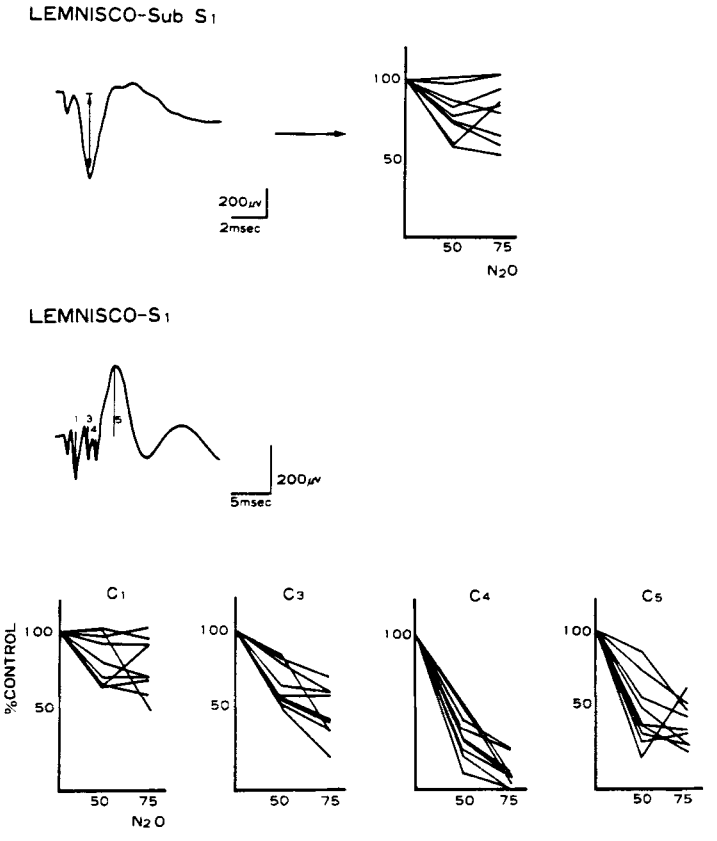

Fig. 2. Effect of nitrous oxide on the somatosensory evoked responses induced by stimulation of the medial lemniscus. The upper figures (LEMNISCO-Sub SI) show the responses recorded at the cortical radiation, and the lower figures (LEMNISCO-SI) are those recorded at the primary sensory cortex. Component 2 is lacking in the LEMNISCO-SI potential. See text for further explanation.

Table 3. SEP induced by Sub-SI stimulation

	C1		C2		C3		C4		C5	
	M ± S.E. (%)	α	M ± S.E. (%)	α	M ± S.E. (%)	α	M ± S.E. (%)	α	M ± S.E. (%)	α
50%	99.9 ± 1.8	n.s.	112.3 ± 12.0	n.s.	93.7 ± 4.4	n.s.I	72.5 ± 7.8	<0.05	81.9 ± 6.7	n.s.
75%	98.1 ± 2.7	n.s.	96.5 ± 10.6	n.s.	79.8 ± 4.2	<0.005	41.3 ± 11.8	<0.001	62.0 ± 5.3	<0.005

C1, C2, C3, C4 and C5: Component 1, 2, 3, 4 and 5 of the evoked potential.

ing phase and was affected little by nitrous oxide, indicating that this component was derived from the activation of fibers bypassing the thalamic relay nucleus. This response was similar in waveform to that produced by the stimulation of the somatosensory cortical radiation except that the latter had small positive deflection "2". These components were numbered from the second deflection 1, 3 and 4 for the positive deflections and 5 for the negative deflection in order to fit the response induced by the stimulation of the somatosensory cortical radiation. All these deflections were significantly suppressed by nitrous oxide in a dose related manner (fig. 2).

5. SEP induced by stimulation at somatosensory cortical radiation

The results are summarized in table 3. The SI response induced by the stimulation of the Sub-SI consisted of four successive positive deflections followed by a large negative deflection (fig. 3). The amplitude of each deflection was measured from the beginning of the deflection to the peak. The effects of nitrous oxide on component 1 was little and the changes were not significant. The effects of nitrous oxide on compo-

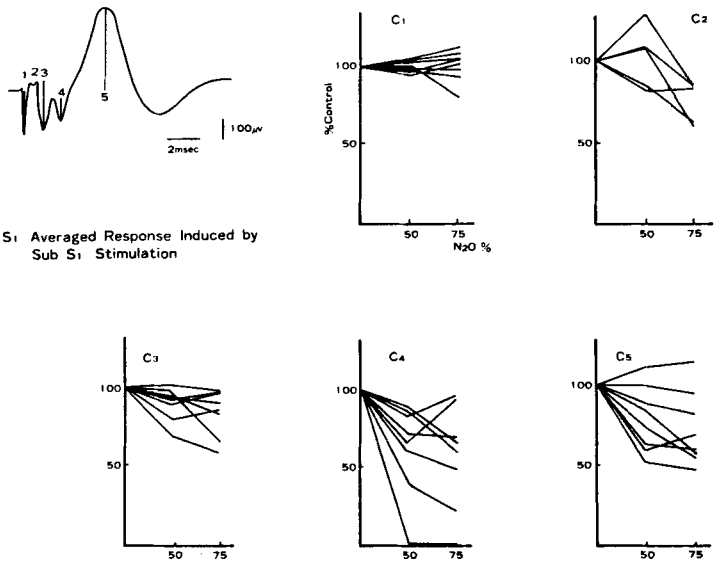

Fig. 3. Effect of nitrous oxide on the cortical responses to radiation stimulation. The component 2 was not always measurable and was assessed in 5 cats. See text for further explanation.

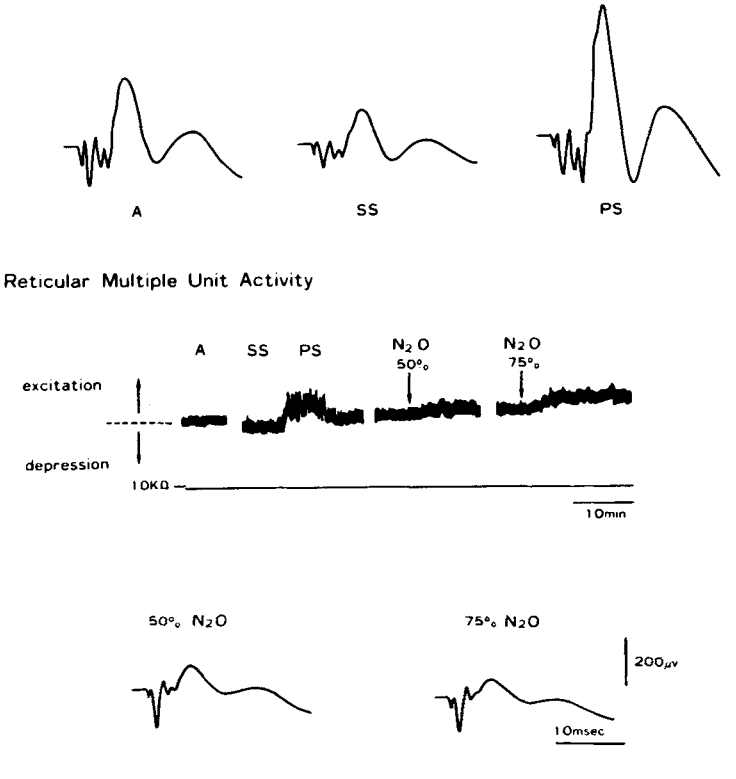

Fig. 4. Effect of sleep and nitrous oxide on the cortical responses to radiation stimulation and midbrain reticular multi-unit activity. A: awake, SS: show wave sleep, and PS: paradoxical phase of sleep. The multi-unit activity is shown in an integrated form: the upper deflection represents an increase in the cellular firing, and the lower deflection a decrease. The maximum activity in the non-anesthetized state was recorded during paradoxical phase of sleep and the minimum activity during slow wave sleep. See text for further explanation. Similarly, the maximum response was obtained during paradoxical phase of sleep, and the minimum response during slow wave sleep. Nitrous oxide enhanced the reticular multi-unit activity and suppressed the evoked response in a dose-related manner. See text for further detail.

nent 2 were variable and not significant. The suppressive effects on components 3–5 were all significant.

6. SEP induced by medial lemniscus stimulation in a cat able to move about freely

The response had a configuration identical to that recorded in paralyzed states (fig.

4). All deflections except the initial positive one increased in amplitude by paradoxical phase of sleep, and were suppressed by slow wave sleep. All deflections were suppressed by nitrous oxide administration. The degree of suppression by nitrous oxide was greater than that produced by slow wave sleep. The reticular multiunit activity was enhanced in a dose-related manner by nitrous oxide.

Discussion

The combined use of muscle relaxants and mechanical ventilation is a safe and common technique used in humans. The induction of sleep-type EEGs by the administration of muscle relaxants[23], which reduces the muscle proprioceptive input, and that is induced by a warm environment[24] were confirmed. It is widely accepted that slow repetitive electric stimulation of the peripheral nerve is innocuous to humans through clinical experience of "train-of-four stimulation" in the post-anesthetic period[27]. It is also well-established that such repetitive peripheral and central electric stimulation do not disturb natural slow wave and rapid eye movement sleep[17,18], indicating that the stimulation is innocuous. The present study confirmed these results in that the electric stimulation of subthreshold intensity was sufficient to measure the size and configuration of the somatosensory evoked response.

The development of acute tolerance to the CNS actions of nitrous oxide has been reported from our laboratory[19,21,22]: the effects are maximal during the initial 15–30 min, but attenuate in 2–3 hours. In the present study, therefore, in order to measure its maximum actions they were evaluated at 30–40 min, i.e. before the appearance of tolerance.

The potent analgesic action of nitrous oxide is well-known. Although nitrous oxide does not produce deep surgical anesthesia, it does produce marked analgesia and sedation[28,29]. This is the basis for which nitrous oxide is used in combination with muscle relaxants for human surgical anesthesia with or without opioid supplements. In spite of such potent analgesic action, it is also known that the effect of nitrous oxide on the thalamic relay nuclei is relatively weak when it is assessed by the changes in the amplitude and form of evoked responses. In the present study the LM response represented the activity of the dorsal column nucleus, the Sub-SI response induced by LM stimulation represented that of the thalamic relay nucleus, and that of the SI induced by Sub-SI stimulation represented that of the cerebral cortex. The dorsal column nuclei receive presynaptic inhibition from the somatosensory cortices[30,31] and both facilitation and inhibition from the brain stem reticular core[31–33]. However, it has not been clarified yet in what situation such modulation functions, eg., wakefulness, the sleep cycle and in the changes of the level of vigilance. The present study indicated that the action of nitrous oxide in the dorsal column nuclei was negligible in that the suppression of activity of the dorsal column nuclei was not significant. The suppression of the thalamic relay nucleus was dose-related and the response was suppressed by approximately 10% of the control with 50% nitrous oxide and 20% of the control with 75% nitrous oxide. The suppression of the cortical evoked response induced by peripheral stimulation was also dose-related and was greater than that observed in the cortical radiation. The cortical response to peripheral stimulation was suppressed to approximately 60% of the control with 75% nitrous oxide and that of the cortical radiation to either lemniscal or peripheral stimulation was suppressed to 80% of the control by 75% nitrous oxide. These results indicate that the degree of supression by nitrous oxide was similar in both the cortical and thalamic nuclei, and the suppression of the cortical response evoked by peripheral stimulation is the sum of the suppression in both the thalamic relay nucleus and the cerebral cortex. Of the five components of cortical response to stimulation in the cortical radiation, the latter components were suppressed more than the earlier components, indicating that the greater the number of synaptic relays involved, the greater the susceptibility to anesthetics.

It is well-established that the activation

of the reticular core produces an enhancement of the activity of the thalamic relay nucleus[16–18]. The present study confirmed the activation of reticular cell activity by wakefulness and paradoxical phase of sleep, which was associated with the enhancement of evoked responses. In addition, the findings by Mori et al.[19] that nitrous oxide activates the cell firing of reticular core were also confirmed. However, the activation by nitrous oxide was not associated with enhancement of the activity of the thalamic relay nucleus, but rather suppression was noted. These findings together indicate that the direct suppressive action of nitrous oxide on the thalamic relay nucleus exceeds the indirect action through activation of the reticular neurons, which may facilitate the activity of the thalamic relay nucleus.

The suppression of nociceptive neural activity in the spinal cord dorsal horn by nitrous oxide has well been established[28,34]. The evoked responses studied in the present study deal with the early components and there is little possibility that they are related directly to the nociceptive neural information. Nevertheless, the present study indicates a certain role of suppression by nitrous oxide in the thalamic and cortical levels of nociceptive neural informations. It is concluded that nitrous oxide suppresses the efficiency of afferent transmission in both the thalamic relay nuclei and cortical sensory areas to similar degrees.

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