Effect of nitrous oxide on myogenic motor evoked potentials during hypothermia in rabbits anaesthetized with ketamine/ fentanyl/propofol

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Background. A number of authors have reported that anaesthetics suppress myogenic motor evoked potentials (MEPs). However, the influence of hypothermia on these effects is unknown. Therefore we investigated the effects of hypothermia on nitrous oxide-induced suppression of myogenic MEPs.

Methods. Twenty-two rabbits anaesthetized with ketamine, fentanyl and propofol were randomly allocated to one of three groups, with oesophageal temperatures of 40°C (n=8), 35°C (n=7) and 30°C (n=7). Myogenic MEPs in response to electrical stimulation of the motor cortex with a train of five pulses were recorded from the soleus muscle. Following the control recording, nitrous oxide was administered at concentrations of 30%, 50%, and 70% in random order, and MEPs were recorded. Control MEP amplitudes and percentage of control MEP amplitudes (%MEP amplitude) during the administration of nitrous oxide were compared between the three groups.

Results. Control MEP amplitudes were similar between the three groups. Nitrous oxide suppressed MEPs in a dose-dependent manner in all groups. During the administration of nitrous oxide, % MEP amplitudes at 35°C and 30°C (hypothermia) were significantly lower than those at 40°C (normothermia).

Conclusion. These results suggest that nitrous oxide-induced suppression of MEPs may be augmented during hypothermia.

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Materials and methods

The study was approved by the Animal Experiment Committee of Nara Medical University. Twenty-two male New Zealand White rabbits weighing 2–3 kg were used in this study. They were housed and maintained on a 12 h light–dark cycle with free access to food and water.

Rabbits were given ketamine 50 mg kg⁻¹ i.m., and a 24-gauge catheter was inserted in the right ear vein. Thereafter, a continuous infusion of ketamine 17 mg kg⁻¹ h⁻¹ and fentanyl 33 kg⁻¹ h⁻¹ in lactated Ringer solution at a rate of 3 ml h⁻¹ was initiated. Another 24-gauge catheter was placed in the left ear vein for the administration of propofol. The trachea was intubated via a tracheostomy and the lungs were ventilated mechanically. The left femoral artery was exposed and cannulated for arterial pressure monitoring and blood gas analysis. Blood gases, pH, and haematocrit were measured periodically with a blood gas analyser (GEM premier, Mallinckrodt, Ann Arbor, MI, USA). Oesophageal temperature and right soleus muscle temperature were monitored continuously with a thermometer (Mon-a-Therm, Mallinckrodt, St Louis, MO, USA).

The rabbit was turned prone and the head was fixed in a stereotactic frame. The scalp was reflected laterally and the calvaria exposed. Two small craniotomies were performed with an air drill. A point 0.5 mm lateral to the sagittal suture was 0.5 mm lateral to the sagittal suture at the level of the lambdoid suture. The hemisphere was chosen as the anodal stimulating site. 15 A point 0.5 mm lateral to the sagittal suture at the level of 14.5 mm rostral from the lambdoid suture on the right hemisphere was chosen as the anodal stimulating site. 15

Table 1 Physiological variables and blood gas analysis before administration of nitrous oxide. Data are expressed as mean (SD). *P<0.05 vs normothermia (40°C)

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<td>Mean arterial pressure (mm Hg)</td>
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When preparation was complete, animals were randomly allocated to one of three groups according to oesophageal temperature: the oesophageal temperature was maintained at 40°C in group 1 (n=8), at 35°C in group 2 (n=7), and at 30°C in group 3 (n=7). Cooling was achieved by wrapping the animal in a water blanket. In all groups, a bolus of propofol 10 mg kg⁻¹ was administered followed by a continuous infusion at 0.8 mg kg⁻¹ min⁻¹. Thirty min after the bolus injection of propofol, control MEPs in response to train-of-five pulses were recorded. Peak-to-peak amplitude was determined from the average of three individual responses, and the amplitudes were converted to percentages of the control MEP amplitude (%MEP amplitude). The interval between each stimulation was set at 30–60 s. When control MEPs had been recorded, nitrous oxide was administered at concentrations of 30%, 50% and 70%. The order was randomized to eliminate time-course bias. At least 10 min was allowed to elapse between each target concentration, and the end-tidal concentration of nitrous oxide was confirmed by a gas analyser. MEPs were recorded at each concentration of nitrous oxide. When recordings at the three different concentrations of nitrous oxide had been made, administration of nitrous oxide was discontinued. Following confirmation that the end-tidal concentration of nitrous oxide was 0%, MEPs were recorded again. During the experimental periods, a bolus administration of phenylephrine was used if arterial pressure decreased by more than 20% of control. At the end of the experiment the animals were killed by an injection of potassium chloride, which caused cardiac arrest.

Statistical analysis

All values are expressed as mean (SD). Repeated-measures analysis of variance was used to compare physiological variables and amplitudes at each concentration of nitrous oxide within each group, followed by Fischer’s protected least significant difference test. Factorial analysis of variance was used to compare physiological variables and amplitudes at each concentration of nitrous oxide within each group, followed by Fischer’s protected least significant difference test. Results were considered significant when P<0.05.

Results

Mean arterial pressure, heart rate, blood gases and haematocrit before administration of nitrous oxide are shown in Table 1. There were no significant differences in mean arterial pressure, pH, P_O2, and P_CO2 between the three groups. Heart rate was significantly lower at 35°C and
Table 2 Amplitudes of motor evoked potentials before the administration of nitrous oxide. Data are expressed as mean (sd). There were no significant differences between the groups.

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<th>Amplitude (mV)</th>
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<tr>
<td>40°C (n=8)</td>
<td>4.0 (2.1)</td>
</tr>
<tr>
<td>35°C (n=7)</td>
<td>4.5 (1.5)</td>
</tr>
<tr>
<td>30°C (n=7)</td>
<td>4.7 (3.4)</td>
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Discussion

The results show that nitrous oxide suppressed MEPs in a dose-dependent manner in normothermic rabbits anaesthetized with ketamine, fentanyl and propofol. A reduction of core temperature to 35°C or 30°C did not significantly affect the MEP amplitude before administration of nitrous oxide. However, MEP amplitude during the administration of nitrous oxide were significantly lower during hypothermia (35°C and 30°C) than during normothermia. These results suggest that nitrous oxide-induced suppression of MEPs may be augmented during hypothermia.

Nitrous oxide has been shown to be a potent suppressor of MEPs in response to transcranial electrical and magnetic stimulation in humans and experimental animal models. Zentner and colleagues investigated the effects of 10–70% nitrous oxide on MEPs in response to electrical stimulation of the motor cortex in rabbits. They demonstrated a major suppressive effect of high nitrous oxide doses on MEP amplitudes. With 50% nitrous oxide, MEP amplitudes were suppressed to 14% of baseline values. The results of our previous study also showed that nitrous oxide significantly reduced the amplitudes of MEPs in response to single-pulse and multi-pulse stimulation in a dose-dependent manner in rabbits anaesthetized with ketamine, fentanyl and propofol. These findings are compatible with the results obtained in the present study.

There have been few reports detailing the effect of hypothermia on MEPs. Oro and Haghighi investigated the effects of systemic hypothermia on spinal neurogenic MEPs recorded from the epidural space at L1–2 in rats anaesthetized with pentobarbital. They demonstrated that amplitudes of spinal MEPs in response to a
single stimulation were significantly reduced with a decrease in core temperature, and no spinal MEPs were detectable below 28°C. Meylaerts and colleagues31 investigated the influence of regional spinal cord hypothermia on myogenic MEPs in response to transcranial electrical stimulation with a train-of-five pulses in pigs anaesthetized with ketamine, sufentanil and nitrous oxide. Progressive cooling resulted in an increase in MEP amplitude at 28–30°C and was followed by a progressive decrease. In the present study, although control MEP amplitudes in the hypothermic groups tended to be higher than those in the normothermic group, these differences were not statistically significant. However, configurational differences in the responses were evident at 40°C, 35°C, and 30°C. The influence of hypothermia on MEPs requires further study.

To the best of our knowledge, this is the first report of the effects of hypothermia on anaesthetic-induced suppression of MEPs. Data in the present study suggest that nitrous oxide-induced suppression of MEPs was greater during hypothermia than during normothermia. The mechanisms by which nitrous oxide-induced suppression of MEPs is augmented under hypothermia are unknown. One possible explanation is that sensitivity of myogenic MEPs to nitrous oxide might be increased during hypothermia. Antognini and colleagues31 demonstrated that hypothermia decreased the minimum alveolar anaesthetic concentration (MAC) of nitrous oxide in rats. MAC of nitrous oxide was 1.9 atm during normothermia but was reduced to 1.6 atm at 30°C. It was suggested that this reduction in MAC was related to the effects of hypothermia on the solubility of nitrous oxide in the lipid membrane. Hypothermia-induced changes in synaptic transmission might have been responsible. During moderate hypothermia, MEP amplitudes may increase because longer duration of action potentials can increase the release of neurotransmitter in the synaptic space.30 In fact, MEP amplitudes in the hypothermic groups, although not statistically significant, tended to be higher than those in the normothermic group. This hypothermia-induced hyperresponsiveness might influence the nitrous oxide-induced suppression of MEPs. Another possibility is that hypothermia-induced changes in background anaesthetic concentration might influence these results. Leslie and colleagues32 demonstrated that a temperature reduction of 3°C increased blood propofol concentration by 30% during a constant rate infusion. The results in our previous study have shown that the dosage of propofol as a background anaesthetic can affect nitrous oxide-induced suppression of MEPs in response to multi-pulse stimulation.15 These premises are, however, speculative. Further study would be required to clarify this mechanism.

In summary, the effects of hypothermia on nitrous oxide-induced suppression of MEPs to transcranial multi-pulse stimulation were investigated in rabbits anaesthetized with ketamine, fentanyl and propofol. A reduction of core temperature to 35°C or 30°C did not significantly affect the MEP amplitudes. However, the suppressive efficacy of nitrous oxide on MEPs was greater during hypothermia (35 and 30°C) than during normothermia. These results suggest that MEP monitoring is feasible during 30°C hypothermia. Nitrous oxide should be used carefully as a supplemental anaesthetic during intraoperative MEP monitoring, because of its marked suppressive effects on MEPs during hypothermia.

References


Marsala M, Vanicky I, Yaksh TL. Effect of graded hypothermia (27 degrees to 34 degrees C) on behavioral function, histopathology, and spinal blood flow after spinal ischemia in rat. Stroke 1994; 25: 2038–46


