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Spinal anaesthesia indirectly depresses cortical activity associated with electrical stimulation of the reticular formation

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Background. Neuraxial blockade reduces the requirements for sedation and general anaesthesia. We investigated whether lidocaine spinal anaesthesia affected cortical activity as determined by EEG desynchronization that occurs following electrical stimulation of the midbrain reticular formation (MRF).

Methods. Six goats were anaesthetized with isoflurane, and cervical laminectomy performed to permit spinal application of lidocaine. The EEG was recorded before, during and after focal electrical stimulation (0.1, 0.2, 0.3 and 0.4 mA) in the MRF while keeping the isoflurane concentration constant.

Results. During lidocaine spinal anaesthesia, the spectral edge frequency (SEF) after MRF electrical stimulation (13.6 (SD 1.0) Hz, averaged across all stimulus currents) was less than the SEF during control and recovery periods (18.6 (3.6) Hz and 17.2 (2.2) Hz, respectively; $P<0.05$). Bispectral index values were similarly affected: 69 (10) at control compared with 55 (6) during the spinal block ($P<0.05$).

Conclusions. These results suggest that lidocaine spinal anaesthesia blocks ascending somatosensory transmission to mildly depress the excitability of reticulo–thalamo–cortical arousal mechanisms.

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Neuraxial blockade is commonly used to abolish sensations elicited by noxious stimuli, particularly those occurring during a surgical procedure. Patients often receive sedation during these procedures, and occasionally the neuraxial block is combined with a general anaesthetic. Recent human and animal studies have documented that neuraxial blockade reduces sedative requirements and the concentration of sevoflurane needed to achieve a bispectral (BIS) value of 50.[1–4] The presumed underlying physiological mechanism is that the spinal anaesthetic blocks ascending somatosensory drive onto reticulo–thalamo–cortical projection pathways, thereby reducing their excitability and hence decreasing the arousal level of the brain. This change in cortical arousability might reduce anaesthetic requirements for blockade of memory and consciousness. One measure of cortical activity is the EEG. The EEG changes in a predictable way as anaesthetic concentration is increased, and includes a reduction in evoked responses to somatosensory input. Stimulation of the midbrain reticular formation (MRF) can 'desynchronize' the EEG, such that it changes from a high-amplitude, low-frequency to a low-amplitude, high-frequency pattern, approaching that observed in the state of consciousness.[5] We have recently used a differential anaesthetic delivery method in goats to investigate the indirect effects of isoflurane action in the torso (and hence spinal cord) on the efficacy of electrical MRF stimulation to alter the EEG.[6] We found that MRF stimulation was more likely to desynchronize the EEG when the torso isoflurane concentration was low as compared with when it was high.[6] In the present study we hypothesized that spinal lidocaine, by blocking ascending somatosensory transmission, would similarly reduce the efficacy (i.e. raise

the current threshold) of MRF stimulation to desynchronize the EEG.

Methods

This study was approved by the University of California, Davis Animal Care and Use committee. Goats were chosen as the experimental species to enable comparison with our earlier study.[6] Six female goats weighing 51 (SD 8) kg were anaesthetized with isoflurane via mask, intubated and mechanically ventilated. An i.v. catheter was inserted into a forelimb vein for infusion of lactated Ringer's solution. Rectal temperature was measured and maintained at 37.8 (0.8) °C. A craniotomy was performed to permit insertion of stimulating electrodes. A cervical laminectomy was performed and the dura incised, exposing the upper cervical spinal cord. Following surgery, pancuronium 0.15–0.2 mg kg^{-1} was administered i.v. and repeated every 2–3 h. End-tidal carbon dioxide was maintained at 34 (5) mm Hg and PA_{O_2} was periodically measured to ensure values greater than 200 mm Hg.

The methods for recording EEG and stimulating the MRF have been described previously[6] and are reiterated in brief here. The head was secured in a stereotaxic frame and a bipolar stimulating electrode (Frederick Haer, Inc., Bowdoinham, ME, USA) was stereotaxically positioned in the MRF (0–3 mm rostral to interaural line, 5–7 mm lateral to midline, 30–32 mm below surface of the cortex). The bifrontal EEG was monitored using platinum needle electrodes inserted into the periosteum overlying the frontal bones. The EEG was amplified (Model 8–10E, Grass Instruments, Quincy, MA, USA), filtered (0.3–35 Hz) and digitized using a commercial program (PolyViewPro, Astro-Med, West Warwick, RI, USA). In addition, we monitored the bifrontal EEG using an Aspect-1000 BIS monitor (Aspect Medical Systems, Newton, MA, USA). Processed EEG data (BIS, spectral edge frequency (SEF) 95% (SEF_{95})) were downloaded to a personal computer. These data represented averages of 5-s epochs. The BIS and SEF correlate with anaesthetic depth in the goat.[7]

The MRF stimulation paradigm consisted of a 2-s train of 0.1-ms pulses delivered at 300 Hz, at intervals of 2–4 min. The current intensities were 0.1, 0.2, 0.3 and 0.4 mA. The isoflurane concentration was adjusted to permit EEG desynchronization and this varied from animal to animal (mean 1.7%, range 1.5–2%), but once we established that EEG desynchronization could be produced in an animal the isoflurane concentration was held constant.

The EEG data were collected for the 1-min periods before and after the onset of electrical stimulation. The BIS monitor used a rolling average with a 15-s delay. We analysed the EEG data for the 30-s periods immediately preceding and following onset of the electrical stimulus. We averaged the six 5-s epochs to determine the average value for each period. We waited 2–4 min between stimuli to permit the EEG to return to baseline. After collection of control data, lidocaine 4% was microinjected into the upper cervical cord (approximate C2 level). In brief, several passes were made into each quadrant with a 30g needle attached to a microsyringe (Hamilton) and a total of 25 μl was injected (approximately 6 μl in each quadrant).[8] We then placed lidocaine 4%, 2 ml over the cord, followed by iced saline, which was replaced periodically. These three techniques were used to ensure an adequate spinal block. This was manifested by an expected decrease in mean arterial pressure (MAP), which was treated by administration of warm crystalloid and occasional phenylephrine. The MAP was 99 (27) mm Hg before the block and 66 (14) mm Hg when MRF stimulation was performed during the block. A cloth tie placed around the dura surrounding the spinal cord prevented lidocaine and saline from travelling rostrally to the brainstem and brain. In some animals the efficacy of the lidocaine/cold spinal block was verified by an absence of EEG desynchronization in response to noxious stimulation of a fore or hind foot that had elicited EEG desynchronization before the lidocaine block. The MRF stimulation paradigm was repeated 10–15 min after instillation of the lidocaine and iced saline, after which the iced saline and lidocaine were removed to permit recovery. The MRF stimulation was repeated 1–2 h after the spinal block to document recovery. In one animal we repeated the MRF stimulation paradigm before and after administration of nitroprusside (titrated to MAP 45–55 mm Hg) to determine if hypotension might affect the EEG response, while in another goat we microinjected cerebrospinal fluid (CSF) intraspinally to determine if the microinjection technique itself affected the response. In two animals the spinal cord was anaesthetized again with lidocaine and iced saline, the cord frozen with dry ice, followed by complete transection with scissors. The MRF stimulation was then repeated. This ensured complete deafferentation below the spinal cord transection.

Following data collection, a lesion was made at the MRF stimulation site by passing direct current through the stimulating electrode, and the animal was killed using additional isoflurane and i.v. potassium chloride. The brain was removed, fixed in formalin, and cut into 50-μm frozen sections to microscopically verify the MRF lesion site. Technical problems prevented us from recovering sites in all animals; however, the coordinates used have, in previous studies, consistently placed electrodes in the MRF.[6 9]

Data are expressed as mean (SD). An 'area under the curve' analysis was used to evaluate SEF_{95} and BIS values (before and after stimulation) at each anaesthetic condition (control, spinal block, recovery).[6 10 11] For example, for each experimental condition (i.e. control pre-spinal lidocaine; during spinal block, and recovery), the SEF values after MRF stimulation at each current intensity were summed and compared with the summed SEF values in the absence of MRF stimulation. These values were compared across experimental conditions using ANOVA followed by a Student–Newman–Keuls *post-hoc* test.

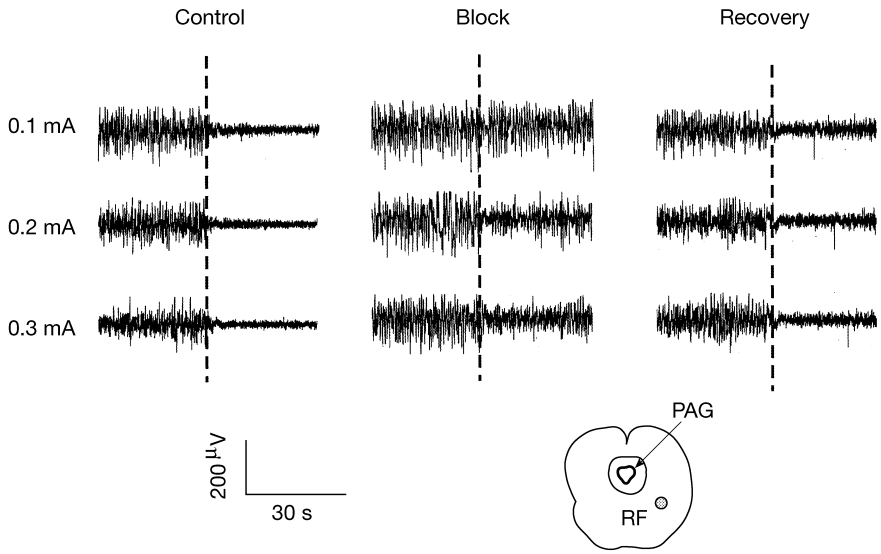

Fig 1 These individual examples of the EEG at different stimulating currents (0.1–0.3 mA) and during different anaesthetic conditions demonstrate that lidocaine spinal anaesthesia affected the propensity for EEG desynchronization. Before application of spinal lidocaine (control), the EEG was easily desynchronized by electrical stimulation of the MRF (2-s duration, dotted line) while during a spinal block EEG desynchronization was more difficult to achieve. The recovery EEG again showed significant desynchronization at the lowest electrical current. The inset shows the stimulating site. RF, reticular formation; PAG, periaqueductal gray.

$P<0.05$ was considered significant. We chose to sum data points across stimulation currents primarily because we were interested in changes in overall sensitivity rather than changes at a specific stimulation current. We also analysed whether MAP correlated with the evoked BIS and SEF values for control, spinal block and recovery periods combined. In brief, evoked BIS values at each stimulus current were summed and correlated with the MAP at which the values were obtained. A similar analysis was performed for SEF.

Results

Before spinal anaesthetic block, electrical stimulation of the MRF resulted in EEG desynchronization which was manifest as increases in BIS and SEF (Figs 1 and 2). A measurable desynchronization often occurred at the lowest stimulating current (0.1 mA) and became more pronounced as the stimulating current was increased. During spinal anaesthetic block, MRF stimulation was less efficacious in eliciting EEG desynchronization. Significant increases in the BIS and SEF were not observed until the MRF stimulation current was at 0.3–0.4 mA, and the magnitude of change was lower. Recovery occurred 1–2 h after the spinal block was initiated.

Under control conditions before spinal block, SEF_{95} after MRF electrical stimulation was greater than after MRF stimulation in the presence of spinal block (18.6 (3.6) Hz *vs* 13.6 (1.0) Hz, summed and averaged across all stimulus currents; $P<0.05$). Similarly, BIS was significantly greater before spinal block than during spinal block (69 (10) *vs* 55 (6), $P<0.05$). The mean post-stimulation SEF_{95} and BIS values (summed across all current intensities) were lower during spinal block than control (pre-block) and recovery (post-block) conditions (Fig. 2). Moreover, the current threshold to elicit increased SEF_{95} or BIS (Fig. 2) tended to be lower (≈0.1 mA) during the pre-block condition compared with the period during spinal blockade (0.3–0.4 mA). The spinal block appeared to be effective, as demonstrated by the lack of EEG response to noxious stimulation (Fig. 3). In another animal in which CSF instead of lidocaine was injected intraspinally, EEG responses to MRF stimulation were unaffected (Fig. 3). Complete transection of the spinal cord yielded results similar to lidocaine block (Fig. 3). Nitroprusside-induced hypotension (MAP ≈50 mm Hg) only slightly reduced the evoked BIS response (averaged over the 0.2, 0.3 and 0.4 mA currents), from 68 to 64. The latter value was well above the average evoked BIS value (53) for the same current intensities during spinal block. The summed evoked BIS and SEF values did not correlate with MAP ($r^2=0.06$ for the BIS–MAP, $r^2=0.08$ for the SEF–MAP; $P>0.05$).

Discussion

We found that spinal cord anaesthesia using lidocaine indirectly affected the EEG desynchronization response to electrical stimulation of the MRF. This suggests that the arousal state of the brain is altered during spinal anaesthesia and that sedative and anaesthetic requirements (to depress brain arousal) will be lower during a spinal anaesthetic.

The present findings are consistent with our recent report using differential delivery of isoflurane to the cranial and torso (and hence spinal) circulation in goats.[6] In this latter

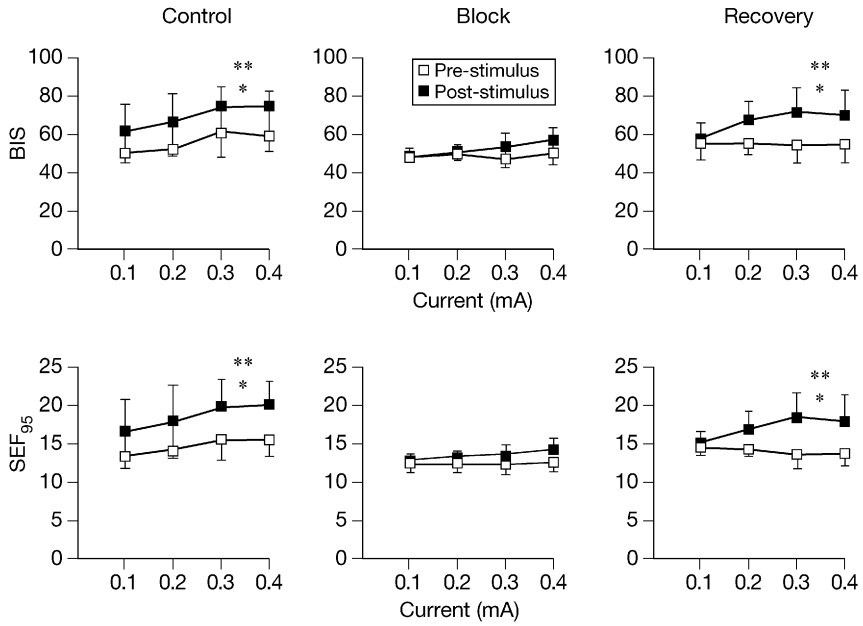

Fig 2 Spectral edge frequency (SEF_{95}) and bispectral index (BIS) values before and after electrical stimulation plotted at each electrical current applied to the midbrain reticular formation during control, lidocaine spinal block and recovery conditions. The isoflurane concentration was 1.7 (0.2)%. The electrical current during the control and recovery periods was associated with EEG desychronization, as seen in the greater BIS and SEF values (*P<0.05 compared with pre-stimulus curve; **P<0.05 compared with curve during spinal block). Data are mean (SD).

study,[6] electrical MRF stimulation elicited EEG desynchronization (assessed by increased SEF and BIS values) at significantly lower current intensities when the isoflurane concentration delivered to the torso was low (~0.3%) compared with when it was high (~1.2%). Thus, two different means of inducing spinal anaesthesia result in a reduced efficacy to elicit cortical activation by MRF stimulation. This indirect, spinally mediated reduction in the excitability of reticulo–thalamo–cortical 'arousal' mechanisms may partly account for our finding that increased torso concentrations of volatile or injected anaesthetic agents blunt cortical EEG desynchronization in response to peripheral noxious stimuli.[9 12 13]

Previous studies have shown that neuraxial blockade using local anaesthetics has indirect effects on sedative requirements. Ben-David and colleagues[1] found that midazolam requirements were decreased in patients receiving spinal anaesthesia. In rats recieving spinal bupivicaine, less thiopental was required for sedation and for blocking responses to noxious stimuli applied above the level of the block.[2] Spinal anaesthesia appears to have sedative effects.[3] In humans, epidural lidocaine anaesthesia decreased the concentration of sevoflurane required to achieve a BIS value of 50.[4] Thus, blocking ascending somatosensory transmission appears to reduce reticulo–thalamo–cortical arousability, consistent with reduced anaesthetic requirements to achieve unconsciousness.

We propose the following mechanism by which spinal anaesthesia affects the excitability of reticulo–thalamo–cortical arousal systems. First, local anaesthetics such as lidocaine block the sodium channel and thereby prevent propagation of action potentials along the axon. The spinal anaesthetic would therefore be expected to reduce ascending transmission of impulses from spinal cord neurones to the brainstem reticular formation and other supraspinal centres. This would presumably lead to reduced synaptic release of excitatory neurotransmitters such as glutamate. Previous studies from our laboratory[14 15] and others[16] have shown that a variety of anaesthetic agents reduce both spontaneous and evoked responses of nociceptive and non-nociceptive dorsal horn neurones. Importantly, systemic administration of thiopental was recently shown to significantly depress the spontaneous firing of spinoreticular and dorsal spinocerebellar tract neurones identified by antidromic stimulation.[17] Furthermore, such a reduction in ascending spinoreticular activity presumably reduces the excitability of target neurones in the brainstem reticular formation. Consistent with this, using differential isoflurane delivery in goats we have shown that excitatory responses of neurones in the MRF[9] or medial thalamus[12] to noxious stimuli were significantly greater when the torso isoflurane concentration was 0.3% than when it was 1.2%. Moreover, differential delivery of propofol to the torso significantly depressed nociceptive responses of MRF neurones.[13] These findings suggest that a reduction in ascending somatosensory traffic by spinal anaesthetics decreases the excitability of MRF and medial thalamic neurones, while increased ascending traffic increases their excitability. We speculate that excitatory afferent input onto MRF neurones maintains them in a relatively depolarized and hence more excitable

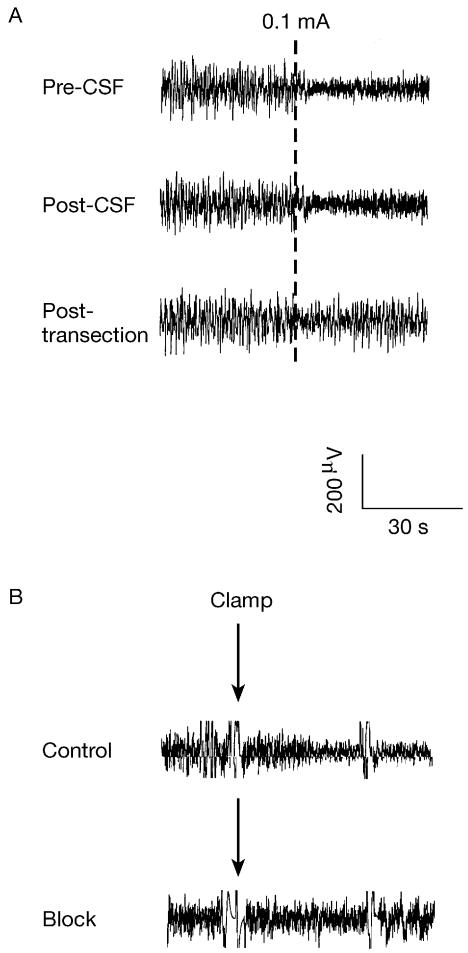

Fig 3 (A) Microinjection of cerebrospinal fluid (CSF) into the spinal cord did not affect the EEG response to midbrain reticular formation electrical stimulation (0.1 mA at dotted line). Transecting the spinal cord, however, did decrease the response to MRF stimulation. (B) A clamp applied to the forelimb before spinal block evoked EEG desynchronization while no such response occurred during spinal block. The large wide swings in the EEG just before and during clamp application are artefacts.

state, raising the probability that they will fire action potentials when subjected to intracranial electrical stimulation. Reduced afferent input via spinal anaesthesia would reduce the excitability of MRF cells, lowering their probability of firing. A further requirement of our proposed mechanism is that at least some of the MRF and medial thalamic neurones that receive input from spinal neurones participate in neural systems involved in regulating activity in cortical and subcortical neurones (the 'ascending reticular activating system').[18] These cortical and subcortical neurones would thereby be more sensitive to anaesthetics such as isoflurane. The exact mechanism by which general anaesthetics produce their effects is unknown. However, effects at the gamma-aminobutyric acid receptor are thought to be important, at least as regards amnesia and loss of consciousness, although effects at other receptors (e.g. glutamate receptors) might be involved.[19] The present report, combined with other animal studies[2] and studies in humans,[1 3 4] strongly suggest that neuraxial blockade reduces sedative and anaesthetic requirements by 'deafferentation' (i.e. decreased ascending sensory input into the brain). This has important clinical implications, as anaesthetists should expect to reduce anaesthetic and sedative drug doses during neuraxial blockade, unless the blockade involves lower dermatomes alone. In this latter setting the neuraxial blockade might have less effect on sedative requirements, as sensory information from higher dermatomes would be expected to reach the brain and increase arousal.

We performed intraspinal microinjections in addition to topical application of lidocaine because deeper fibre tracts that transmit ascending somatosensory information might have been otherwise variably affected by topical application alone.[20] We cannot exclude the possibility that some ascending somatosensory information reached the brain, although responses to noxious stimulation appeared to be abolished (Fig. 3B). Furthermore, the hypotension that followed spinal block might have contributed to the effect on evoked responses, but the minimal effect of nitroprusside-induced hypotension suggests that hypotension could not account for all of the effects on the EEG response to MRF stimulation. Finally, MAP did not correlate with evoked BIS or SEF, indicating that changes in MAP were not a major factor in our results.

We do not believe that local effects of lidocaine or iced saline on blood vessels are likely to be important factors. The goat has a unique cerebral circulation in that the vertebral arteries do not contribute to cerebral circulation. In fact, blood normally flows from the brain and brainstem to the spinal cord via the basilar artery.[21] In addition, any lidocaine entering the venous system would be transported to the systemic circulation where it would be greatly diluted. It seems unlikely that any lidocaine would be transported to the brainstem via the local venous system.

In summary, we found that spinal lidocaine anaesthesia decreased cortical activity, as measured by EEG changes induced by electrical stimulation of the reticular formation. This effect is consistent with other studies suggesting that spinal anaesthesia decreases sedative and anaesthetic requirements.

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