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Does the Brain Influence Somatic Responses to Noxious Stimuli during Isoflurane Anesthesia?

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Background: **Recent evidence suggests that anesthetic action within the spinal cord is important in suppressing somatic responses to painful stimuli. Whether the brain influences this response is not clear. This study was designed to test the hypothesis that the brain affects anesthetic requirements.**

Methods: **Six goats were anesthetized with isoflurane. After tracheal intubation and femoral arterial cannulation, bilateral neck dissections were performed to isolate the external carotid arteries and external jugular veins. The occipital arteries were ligated bilaterally. Control isoflurane requirements as defined by the minimum alveolar concentration (MAC) were determined by using a dew-claw clamp as a painful stimulus. Cranial venous blood was drained into a bubble oxygenator in which an isoflurane vaporizer was placed in line with the gas flow, and arterial blood was infused into a carotid artery with a roller pump. This arrangement permitted selective control of the delivery of anesthetic to the head and to the systemic circulation. Isoflurane concentration in the arterial blood delivered to the head was estimated from the isoflurane concentration in the oxygenator exhaust. While isoflurane concentration in the head was maintained at approximately 0.2–0.3%, MAC for the body was determined. After return to the native circulation, MAC was determined again.**

Results: **During bypass with cranial isoflurane concentration at 0.2–0.3%, all animals showed varying, intermittent degrees of light anesthesia, including spontaneous head movement, chewing, swallowing, and eye opening. Isoflurane MAC was 1.4 ± 0.2% (mean ± SD) at baseline, decreased to 0.8 ± 0.1% during bypass ($P < 0.05$), and increased to 1.2 ± 0.2% after bypass (P not significant compared with baseline).**

Conclusions: **These results verify the importance of volatile anesthetic action at an extracranial site *vis à vis* purposeful movement in response to a noxious stimulus. Furthermore, the results confirm that the brain affects anesthetic requirements. (Key words: Anesthesia: mechanisms. Anesthetics, volatile: isoflurane. Brain, isolation: nociception. Potency: minimum alveolar concentration.)**

THE MECHANISM by which volatile anesthetics block purposeful movement in response to noxious stimuli is unknown. Some authors have postulated that anesthesia occurs as the result of suppressed excitation, enhanced inhibition, or both.[1,2] Recent evidence suggests that the spinal cord is an important site of anesthetic action with regard to somatic responses. We have shown that preferential delivery of isoflurane to the brain, with a low isoflurane concentration in the torso, dramatically increases cerebral anesthetic requirements.[3] These results suggest that the spinal cord (and perhaps the periphery) is an important site of anesthetic action. Furthermore, Rampil *et al.* have performed studies in rats that corroborate our findings.[4,5] Rats that underwent precollicular decerebration or spinal cord transection had no change in isoflurane minimum alveolar concentration (MAC) when compared with control values. Rampil concluded that, at least in rats, the brain does not influence anesthetic requirements[5]; however, stimulation of periaqueductal gray matter in humans[6] or ablation of discrete brain stem neurons in rats[7] can alter MAC.

The unique cerebral circulation of the goat as previously described[3,8] allowed us to investigate the effect of preferentially anesthetizing the body while maintaining a low isoflurane concentration in the brain. Thus, we were able to test the hypothesis that the brain affects anesthetic requirements.

Materials and Methods

This study was approved by the Animal Care and Use Committee of the University of California–Davis. Six goats weighing 43–88 kg were anesthetized with isoflurane and oxygen *via* mask. After tracheal intubation the lungs were ventilated and a tube was passed into

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the stomach *via* the esophagus to drain rumen contents. The femoral artery was catheterized for measurement of mean arterial pressure and withdrawal of blood for blood gas analysis and hematocrit. Core and head temperatures were measured with thermistors placed in the cranial vena cava and nasopharynx, respectively. The temperatures were matched to within 1°C and maintained at 37.9 ± 0.7°C with a heating lamp and the oxygenator heat exchanger during bypass. The carotid arteries and external jugular veins were isolated and the occipital arteries were ligated.

Isoflurane MAC was determined as previously described.[3] Alveolar samples were withdrawn from a catheter the tip of which was near the carina and analyzed with a calibrated Datex 254 agent analyzer (Tewksbury, MA). The end-tidal isoflurane concentration was stabilized for 15–20 min and a large clamp was applied to a forelimb dew claw and moved vigorously for 1 min. A simple reflex withdrawal of the extremity was considered negative. Only gross purposeful movement of the head or another extremity was considered positive. Coughing, straining, chewing, and swallowing were also considered negative responses. When a response was equivocal, the stimulus was applied again. On a few occasions, the clamp was applied to the ear, because this appeared to be supramaximal in a few animals; however, only the response to the dew-claw clamp was used for MAC determinations during bypass. End-tidal isoflurane concentration was increased or decreased 0.2% depending upon the response, maintained for 15–20 min, and the dew-claw clamp was reapplied. The isoflurane MAC was the average of the two concentrations that just permitted and just prevented movement, respectively.

Once control MAC was determined, heparin (4 mg/kg) was administered and a Y-cannula was placed into an external jugular vein such that cranial venous blood could be alternatively drained to the body or to the bypass unit.[3,8] A cannula was placed into a carotid artery for infusion of oxygenator blood, and a cannula was placed into the remaining external jugular vein to drain additional cranial venous blood during bypass. Lactated Ringer's solution (2–3 l) was administered, and an oxygenator (B10, Baxter, Irvine, CA) was primed with approximately 500 ml of blood drained from the goat. Gas (95% oxygen–5% carbon dioxide at 3–4 l/min) was administered *via* the oxygenator with an isoflurane vaporizer placed in line. The oxygenator exhaust was sampled with a calibrated agent analyzer (254, Datex) in an airtight fashion and the isoflurane concentration in the arterial blood was estimated from the isoflurane concentration in the exhaust.[8,9] Cranial bypass was initiated with flows of approximately 5–11 $ml \cdot kg^{-1} \cdot min^{-1}$ after temporary ligation of the carotid artery. Isoflurane concentration in the exhaust was then decreased to approximately 0.2–0.3% and isoflurane concentration in the body was maintained. Glucose was infused at 10–20 mg/min into the oxygenator blood. Isoflurane MAC was measured from the body as before. During this period the isoflurane concentration in the oxygenator exhaust was maintained at 0.2–0.3%. In two animals, insufficient venous return required periodic transfusion of blood (200 ml) from the body to the bypass unit. After determination of isoflurane MAC, the carotid artery ligature was removed, the native circulation reestablished, and bypass terminated. Isoflurane MAC was redetermined. Arterial blood gases, glucose and hematocrit were determined before, during, and after bypass. Blood gas analysis, glucose and hematocrit were also determined on the oxygenator blood.

Data are presented as mean ± SD. Changes in anesthetic requirement were evaluated with repeated measures analysis of variance; $P < 0.05$ was considered significant.

Results

Control isoflurane MAC was 1.4 ± 0.2% (table 1). During bypass with cranial isoflurane = 0.2–0.3%, body isoflurane MAC was 0.8 ± 0.1% ($P < 0.05$ compared with control). After return to the native circulation, isoflurane MAC was 1.2 ± 0.2% (P not significant compared with control). In one animal, postbypass MAC could not be determined because of hypoxemia caused

Table 1. Isoflurane Minimum Alveolar Concentration

Goat No.	Control	Bypass	Postbypass
1	1.3	0.8	1.1
2	1.5	0.7	1.2
3	1.5	0.8	1.0
4	1.3	0.7	—
5	1.0	1.0	1.4
6	1.5	1.0	1.4
Mean ± SD	1.4 ± 0.2	0.8 ± 0.1*	1.2 ± 0.2

Control = value obtained before bypass; Bypass = value obtained during bypass with head isoflurane = 0.2–0.3%; postbypass = value obtained after bypass (obtained in five goats).

* $P < 0.05$ *versus* control.

by bleeding due to airway trauma. During bypass, when head isoflurane was 0.2–0.3%, all goats demonstrated intermittent signs of light anesthesia, with spontaneous movements such as chewing, ear twitching, swallowing, eye opening, and movements of the head and extremities. When the clamp was applied to the ear, it could not be closed to the first ratchet, because even this mild noxious stimulus initiated vigorous movement. In one goat that had purposeful spontaneous movement during bypass (in between MAC determinations), when a dew-claw clamp was applied, the initial response was negative; a positive response was obtained on a second 1-min application.

During bypass, before decreasing the brain isoflurane concentration to 0.2%, in two goats we attempted to determine MAC during bypass while the isoflurane concentration in the oxygenator was matched to that in the body. In one goat MAC decreased slightly, from 1.5 to 1.3%, whereas in the other goat, at 0.8% isoflurane (control MAC = 1.5%), there was no gross purposeful movement to dew-claw clamping. When this latter goat is excluded from the data, there is still a significant decrease in MAC during the bypass period ($1.3 \pm 0.2\%$ *vs.* $0.8 \pm 0.2\%$, $P < 0.05$). In a third goat the isoflurane concentration was kept at the lower limit, which allowed movement prebypass. When the dew-claw clamp was applied the animal demonstrated gross purposeful movement, indicating that MAC had not decreased.

Arterial blood gas, hematocrit, and glucose values are shown in table 2. Systemic mean arterial pressure during the prebypass, bypass, and postbypass periods was 92 ± 29, 77 ± 25, and 83 ± 15 mmHg, respectively. Cranial mean arterial pressure during these periods was 89 ± 29, 59 ± 13, and 80 ± 18 mmHg, respectively. Bypass time was 98 ± 32 min.

Discussion

The significant decrease in MAC observed with preferential spinal cord anesthesia was unexpected. If anything we expected MAC to increase. We speculate that our results are due to differential effects on excitatory and inhibitory pathways in the central nervous system.

The effect of anesthetic agents on cerebral and spinal cord pathways has been extensively examined,[1] with some authors noting suppression of excitation in the midbrain reticular formation[10,11] and hippocampus.[12] Variable effects on inhibition have been documented, including potentiation,[1] possibly through enhancement of inhibition *via* γ-aminobutyric acid agonist action.[13] The inhibitory and excitatory effects are mediated mainly through synaptic actions while individual neurons remain excitable.[1] Polysynaptic and monosynaptic spinal cord inhibition have been demonstrated in the ventral horn[14] and spinal motor neuron.[15] Peripheral nociceptors are sensitized by volatile anesthetics.[16] These studies demonstrate varied anesthetic effects at individual pathways and neurons, but how these effects interact remains unclear. Most studies used spinal cord transection to separate brain from spinal cord action but the results may be confounded by subsequent spinal shock.

Whether or not an animal moves in response to painful stimuli during general anesthesia likely depends on the balance of excitatory and inhibitory influences on the spinal cord. These excitatory and inhibitory effects might arise within the spinal cord or within the brain and then transmitted to the spinal cord *via* descending tracts. For example, Shimoji *et al.* found that inhibitory pathways in the spinal cord, particularly those from a supraspinal site, are very sensitive to isoflurane.[17] As noted above, differential effects on excitatory and in-

Table 2. Arterial Blood Gas, Hematocrit, and Glucose Values

	pH	Pa_{O_2} (mmHg)	Pa_{CO_2} (mmHg)	Be (mM)	Hct (%)	Glucose (mg/dl)
Prebypass	7.38 ± 0.05	409 ± 194	33 ± 3	−4 ± 4	30 ± 4	57 ± 7
Bypass systemic	7.36 ± 0.08	283 ± 181	29 ± 5	−7 ± 3	26 ± 6	70 ± 26
Cranial (arterial)	7.29 ± 0.08	571 ± 37	35 ± 2	−9 ± 5	27 ± 5	58 ± 23
Cranial (venous)	7.23 ± 0.09	96 ± 32*	41 ± 3	−9 ± 5	—	—
Postbypass	7.34 ± 0.06	291 ± 127	32 ± 6	−7 ± 3	28 ± 6	50 ± 19

Values are mean ± SD.

Prebypass = value obtained from systemic circulation before bypass; Bypass systemic = value obtained from systemic circulation during bypass; Cranial (arterial) = value obtained from arterial limb of bypass unit; Cranial (venous) = value obtained from venous limb of bypass unit; Postbypass = value obtained from systemic ciculation after bypass; BE = base excess; Hct = Hematocrit.

* N = 5.

hibitory neurons are well documented.[1] These effects can be seen clinically during emergence from anesthesia when patients may show varying degrees of decorticate posturing[18] or nonthermogenic shivering.[19] Likewise, increased movements during induction of anesthesia define the excitement stage and may also be explained by an imbalance of excitatory and inhibitory influences. It is unclear which pathways would be affected by these excitatory and inhibitory influences, but might include motor and sensory tracts.

As noted above, some neurons may be potentiated by inhalational anesthetics. Shimoji *et al.* found that inhibitory neurons in the midbrain reticular formation were potentiated by isoflurane and halothane, particularly at higher concentrations (3%).[11] Also, Miu and Puil found that low concentrations of isoflurane (<1%) depressed inhibitory postsynaptic potentials, but higher concentrations (1–4%) enhanced these potentials.[20] These actions could explain the results of our previous study,[3] where high cerebral isoflurane concentration, with coincident low spinal cord isoflurane concentration, prevented gross purposeful movement in response to a painful stimulus.

It is possible that our results may be explained by the effect of bypass itself, however, we have previously determined in dogs that bypass does not alter anesthetic requirements.[21] In our current study, in the animals tested, there were variable effects, with one animal showing a substantial decrease in MAC apparently due to bypass itself. Nonetheless, when this animal is excluded from the data, there is still a significant decrease in MAC. Also, all animals showed intermittent signs of awakening. At 0.2–0.3% isoflurane we could not ethically or practically lower anesthetic concentrations more because the animals might move constantly (suggesting that the animals would be conscious) and such movement would disrupt the experiment. Even if some of the decrease in MAC that we saw was due to an effect (ischemia) of the bypass, it could not explain all of the data, and our basic conclusion would be unaltered. That is, the brain influences anesthetic requirements.

Rampil *et al.* demonstrated the importance of the spinal cord to anesthetic action.[4] After precollicular decerebration, MAC remained unchanged, thus demonstrating that the cerebral cortex does not appear to be important to suppression of somatic responses to painful stimuli.[4] In a subsequent study, Rampil performed spinal cord transection in a manner that prevented spinal shock; MAC did not change, suggesting that the brain does not modulate somatic responses to noxious stimuli during general anesthesia.[5] Descending modulation occurs under different conditions. In humans, stimulation of periaqueductal gray matter has been shown to decrease anesthetic requirements.[6] In rats, ablation of the locus coeruleus causes a MAC reduction,[7] as does intracerebroventricular injection of cholinergic antagonists.[22] Nonetheless, species differences may be important, because Rampil *et al.*'s[4,5] conclusions are based on data from rats, whereas ours are based on data from goats. The lack of change in MAC observed in Rampil *et al.*'s[4,5] studies suggests that the "machinery" is present within the spinal cord to generate purposeful movement in response to a painful stimulus; however, some authors have concluded that the central nervous system "re-represents" itself at higher brain levels.[23] These higher brain structures can modulate spinal cord function.

In summary, our data suggest that the brain influences the spinal cord in relation to somatic responses to a painful stimulus. We speculate, but cannot prove, that alterations in the balance of excitatory and inhibitory neurons within the spinal cord and brain caused the observed reduction in MAC. We cannot exclude, however, the possibility that the bypass procedure itself somehow decreased anesthetic requirements. Nonetheless, this would not alter our conclusion that the brain influences anesthetic requirements.

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