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Increases in Spinal Cerebrospinal Fluid Potassium Concentration Do Not Increase Isoflurane Minimum Alveolar Concentration in Rats

Dimitry Shnayderman, BS^{*}, Michael J. Laster, DVM^{*}, Edmond I Eger II, MD^{*}, Irene Oh, BS^{*}, Yi Zhang, MD^{*}, Steven L. Jinks, PhD[†], Joseph F. Antognini, MD[‡], and Douglas E. Raines, MD[‡]

^{*} Department of Anesthesia and Perioperative Care, University of California, San Francisco, California;

[†] Department of Anesthesiology and Pain Medicine, University of California, Davis, California

[‡] Department of Anesthesia and Critical Care, The Massachusetts General Hospital, Boston, Massachusetts

Abstract

BACKGROUND—Previous studies demonstrated that MAC for isoflurane directly correlates with the concentration of Na⁺ in cerebrospinal fluid surrounding the spinal cord, the primary site for mediation of the immobility produced by inhaled anesthetics. If this correlation resulted from increased irritability of the cord, then infusion of increased concentrations of potassium (K⁺) might be predicted to act similarly. However, an absence of effect of K⁺ might be interpreted to indicate that K⁺ channels do not mediate the immobility produced by inhaled anesthetics whereas Na⁺ channels remain as potential mediators. Accordingly, in the present study, we examined the effect of altering intrathecal concentrations of K⁺ on MAC.

METHODS—In rats prepared with chronic indwelling intrathecal catheters, we infused solutions deficient in K⁺ and with an excess of K⁺ into the lumbar space and measured MAC for isoflurane 24 h before, during, and 24 h after infusion. Rats similarly prepared were tested for the effect of altered osmolality on MAC (accomplished by infusion of mannitol) and for the penetration of Na⁺ into the cord.

RESULTS—MAC of isoflurane never significantly increased with increasing concentrations of K⁺ infused intrathecally. At infused concentrations exceeding 12 times the normal concentration of KCl, i.e., 29 mEq/L, rats moved spontaneously at isoflurane concentrations just below, and sometimes at MAC, but the average MAC in these rats did not exceed their control MAC. At the largest infused concentration (58.1 mEq/L), MAC significantly decreased and did not subsequently return to normal (i.e., such large concentrations produced injury). Infusions of lower concentrations of K⁺ had no effect on MAC. Infusion of osmotically equivalent solutions of mannitol did not affect MAC. Na⁺ infused intrathecally measurably penetrated the spinal cord.

CONCLUSIONS—The results do not support a mediation or modulation of MAC by K⁺ channels.

Potassium (K⁺) channels may be important direct or indirect mediators of the capacity of inhaled anesthetics to produce immobility.¹ Several studies find that anesthetics enhance K⁺ channel conductance, thereby increasing K⁺ efflux from neuronal cells and causing hyperpolarization.^{2–4} Such an action provides a plausible explanation for anesthesia. In one

Address correspondence and reprint requests to Dr. Eger, Department of Anesthesia, S-455, University of California, San Francisco, CA 94143-0464. Address e-mail to E-mail: egere@anesthesia.ucsf.edu.

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study,⁵ changes in cerebrospinal fluid K^+ concentrations in dogs did not cause changes in MAC (the minimum alveolar concentration of inhaled anesthetic required to prevent movement in response to a noxious stimulus in 50% of subjects). However, the change in central nervous system K^+ concentration was not limited to the spinal cord but also affected the brain, which limits the implication of the finding. This is relevant because of the importance of the cord as the primary mediator of the immobility produced by inhaled anesthetics.⁶ More importantly, the change in cerebrospinal fluid K^+ was 0.2 mEq/L, only 5% of the normal extracellular K^+ concentration.

The present study tested the effect of intrathecally infused K^+ at various concentrations on isoflurane MAC in rats. We reasoned that if isoflurane acted by enhancing K^+ channel conductance, then increasing extracellular K^+ concentrations (to reduce the magnitudes of the resulting increase in K^+ efflux and hyperpolarization) would increase MAC. Similarly, we predicted that reducing extracellular K^+ concentrations would decrease MAC. As controls, we also tested whether changes in intrathecal osmolarity would affect MAC, and whether Na^+ infused intrathecally would penetrate the spinal cord. We chose to study Na^+ penetration because we had no capacity to measure K^+ increases accurately. Although we might produce substantial changes in extracellular K^+ , these would represent only a small fraction of the total (primarily intracellular) K^+ , and thus would not accurately describe the actual changes in extracellular K^+ . We investigated the possibility of using the stable isotope $^{41}K^+$, but we found it difficult to analyze by mass spectrometry because of an overlapping peak. Cowards that we are, we were not interested in working with the radioisotope of K^+ .

METHODS

Materials

Isoflurane was donated by Baxter Healthcare Corp. (New Providence, NJ).

Studies of MAC in Rats

With approval of the Committee on Animal Research of the University of California, Davis (studies of intrathecal potassium and of altered intrathecal osmolarity), and the Committee on Animal Research of the University of California, San Francisco (studies of diffusion of Na^+ into the spinal cord), we studied 98 male, 12–15 wk-old, Long-Evans rats weighing 300–450 g obtained from Charles River Laboratories (Hollister, CA). Six rats died during study and two were discarded for logistical reasons, leaving 90 rats for which results are presented. Each animal was caged with up to as many as two additional rats before insertion of catheters, and was housed singly thereafter. All had continuous access to standard rat chow and tap water before study.

Effect of Lumbar Intrathecal Infusions of Solutions Containing Lower and Higher Concentrations of K^+ (49 Rats)

Figure 1 summarizes the experimental design. On day 1, rats were anesthetized with isoflurane, and a 32-gauge polyurethane catheter (Micor Inc., Allison Park, PA) was placed through the atlanto-occipital membrane using the method described by Yaksh and Rudy.⁷ The catheter was threaded caudally 6–8 cm towards the lumbar sac, the length depending on the size of the rat. The proximal end of the catheter was drawn through the external auditory meatus and sutured in place, and the wound was infiltrated with 0.25% bupivacaine. Rats recovered from anesthesia and surgery for 24 h before study.

Rats were studied in groups of up to eight placed in individual clear plastic cylinders. Each cylinder received approximately 1 L/min oxygen containing approximately 2% isoflurane. An infusion of artificial cerebrospinal fluid (aCSF) was begun immediately after induction of

anesthesia at 4 $\mu\text{L}/\text{min}$ via the previously placed intrathecal catheter. The aCSF contained: NaCl 126.6 mM; NaHCO_3 27.4 mM; KCl 2.4 mM; KH_2PO_4 0.50 mM; NaSO_4 0.49 mM; CaCl_2 1.10 mM; MgCl_2 0.83 mM; and glucose 5.49 mM. The pH was adjusted to 7.3 by addition of a small amount of NaOH. Total osmolarity was approximately 330 mOsm. A rectal temperature probe was inserted. The isoflurane concentration was decreased to 1.0%–1.2% and sustained at this concentration for 50 min, after which the tail was clamped and moved by rolling the clamp at 1–2 Hz for up to 1 min (less if the rat moved). After certifying that movement had occurred, the isoflurane concentration was increased by approximately 0.15%–0.2% and, after a 30-min period of equilibration, the tail clamp was again applied and movement or lack of movement determined. Isoflurane partial pressures were monitored using an infrared analyzer (Datascope, Helsinki, Finland). Immediately after determination of the response to tail clamp, a sample of gas was obtained from one of the chambers and analyzed for isoflurane by gas chromatography. This process continued until all rats failed to move in response to application of the tail clamp. MAC was calculated as the average of the largest concentration that permitted movement and the smallest concentration that suppressed movement. This value was designated MAC0. Anesthetic administration was then discontinued, and the rats recovered.

The next day, the rats again were anesthetized with isoflurane and MAC redetermined (MAC1). However, on this day, one or two of the rats received an infusion of aCSF (the control group). The other six or seven rats received an infusion of a solution containing a decreased or an increased concentration of KCl (the experimental group). A decreased concentration was produced by removing the 2.4 mM of KCl. An increased concentration was produced by adding 4, 8, 12, 16, and 24 times the normal KCl (the largest K^+ concentration was 58.1 mEq/L as opposed to the normal of 2.9 mEq/L). When the concentration of K^+ was increased by eight-fold or more, the aCSF given the control group was altered by addition of sufficient mannitol to produce an osmolarity equal to that produced by the addition of KCl in the experimental group. Anesthetic administration was then discontinued and the rats recovered. The investigator making the determination of MAC was blinded to the contents of the infusions.

On the third day, the rats again were anesthetized with isoflurane and the process of MAC determination repeated (MAC2). On this day, all rats received only an infusion of aCSF. The rats again were allowed to recover and were examined for gross abnormalities in hindlimb function.

Thus, these measurements supplied two control assessments. The change in MAC with treatment could be compared with the MAC in the same rat when given aCSF, and the change in MAC with treatment could be compared with the MAC in a comparable group of rats given aCSF. Injury from treatment could be assessed by noting whether a gross abnormality in motor function, particularly of the hindlimbs, was evident after the third anesthetic, and whether MAC2 differed from MAC0 in the experimental group more than in the control group.

Effect of Lumbar Intrathecal Infusions of Hyperosmotic Solutions (23 Rats)

We further studied the issue of the effect of osmolarity on isoflurane MAC by additional studies of rats allocated to receive intrathecal infusions of osmolarity increased by the addition of mannitol (K^+ normal). These were done to certify that any changes in MAC were not caused by changes in osmolarity rather than changes in K^+ . These added numbers to the rats for whom such studies had already been done as described earlier. Blinding was maintained by studying rats receiving various osmolar concentrations in the same group (i.e., again the person determining MAC1 did not know the contents of the infusate).

Determination of Movement of Sodium into the Spinal Cord (18 Rats)

The preceding studies assume that at least some fraction of K^+ penetrates the spinal cord. An absence of penetration would explain an absence of an effect of infusion of larger K^+ concentrations. However, measurement and interpretation of changes in cord K^+ consequent to infusion of increased K^+ may be confounded by the fact that most K^+ is intracellular and the concentration we seek to measure is extracellular. In addition, we might significantly increase extracellular K^+ but that would represent only a small fraction of the total K^+ , and the difference would be difficult to measure accurately (the difference of two large numbers).

Accordingly, we measured the change in cord Na^+ (Na^+ as a surrogate for K^+). This allowed a more sensitive measure of extracellular penetration, since most Na^+ is extracellular. Groups of six rats prepared as above with intrathecal catheters received infusions of a low concentration of Na^+ (28.5 mEq/L), normal aCSF, or a high concentration of Na^+ (192.5 mEq/L), concentrations used in our previous study of the determination of Na^+ infusion on isoflurane MAC.⁸ After 2 h of infusion at 4 μ L/min, the lower cord and the brain were removed, briefly dipped in distilled water, blotted, weighed, homogenized in a determined volume of distilled water, and the concentration of Na^+ measured with a Na^+ -sensitive electrode. The Na^+ concentration in the cord and brain were calculated, considering the weights and known dilutions.

Gas Chromatographic Analysis

We used a Gow-Mac 580 flame ionization detector gas chromatograph (Gow-Mac Instrument Corp., Bridgewater, NJ) to analyze isoflurane concentrations. The 4.6-m-long, 0.22-cm (ID) column was packed with SF-96. The column temperature was 107°C with the detector maintained at a temperature approximately 50°C higher. The carrier gas flow was nitrogen at a flow of 16 mL/min. The detector received 35 mL/min hydrogen and 250 mL/min air. Primary standards were prepared for isoflurane and the linearity of the response of the chromatograph determined. We commonly used secondary (cylinder) isoflurane standards referenced to the primary standards.

Statistical Analyses

Mean values and standard deviations were determined for the MAC determinations. A one-way analysis of variance with Fisher's protected least significant difference was done to determine whether infusion of altered K^+ concentrations significantly affected MAC and whether one or more groups differed significantly. We accepted a value of $P < 0.05$ as significant.

RESULTS

No group of rats demonstrated a significantly increased MAC associated with an alteration in infused K^+ (Table 1, P Fig. 2; < 0.0004). MAC1/MAC0 did not correlate with the concentration of K^+ in the intrathecal infusate (Table 1, P Fig. 2), except that the results for the infusion of the highest concentration (24 times control KCl, or 58.1 mEq/L) showed a significant decrease in MAC (< 0.005 for all comparisons), and rats given 16 times the control KCl had MAC decreases that significantly exceeded those for rats given aCSF ($P < 0.02$) and 8 times control KCl ($P < 0.01$). The results for MAC2/MAC0 also differed significantly among groups ($P < 0.005$). Most of the significance resulted from the groups given 24 times control [significantly different ($P < 0.05$) from rats given 0, aCSF, 8, and 16 times control KCl], a finding indicative of residual injury at the largest infused concentration. We also found that intrathecal infusion of hyperosmotic solutions did not change MAC1/MAC0 ($P = 0.46$) or MAC2/MAC0 ($P = 0.53$), suggesting that the changes seen at the largest concentrations of infused KCl were not due to an increase in osmolarity (Fig. 3).

Intrathecal 2-h infusions of solutions with a decreased Na^+ concentration decreased Na^+ concentrations in the spinal cord and infusions of increased concentrations increased cord concentrations (Fig. 4). Such intrathecal infusions had no effect on brain concentrations.

DISCUSSION

The data pictured in Figures 2 and 3 confirm previous observations⁸ that repeated measurements of MAC over days do not affect MAC. More importantly, the results do not support our hypothesis that intrathecal infusion of increased concentrations of K^+ would increase MAC. Instead, we found no change in MAC at any infused concentration of K^+ except that the largest infused concentration produced a significant decrease and injury to the cord as reflected in the failure of MAC to return to control values.

Why did no increase in MAC occur? Perhaps K^+ failed to penetrate the cord. Several observations suggest that this was not the case. First, we observed that rats receiving infusions of largest concentrations of K^+ displayed evidence of stimulation (e.g., spontaneous movement at concentrations less than MAC and pain if awakened soon after cessation of the infusion). Perhaps this reflected stimulation of nerve roots, rather than penetration of the cord, but similar observations were not made during our previous study of infusion of high and low concentrations of Na^+ ⁸ which also might have affected such nerves.

Second, intrathecal infusions of decreased and increased concentrations of Na^+ produced parallel shifts in cord concentrations of Na^+ (Fig. 4). If K^+ and Na^+ have similar capacities to diffuse into the cord, these findings for Na^+ suggest that K^+ also penetrated the cord. The counterargument might be that Na^+ primarily resides in the extracellular space, a smaller (and thus more readily filled) space than the intracellular space occupied by K^+ . That is, the intracellular space in glia and neurons provides a buffer to the infused K^+ . However, the amount of neural tissue is smaller than the volume infused. The average weight of 11 spinal cords (total cord) equaled 0.233 ± 0.085 g and the lumbar portion of the cord would be still less. In 2 h of intrathecal infusion at $4 \mu\text{L}/\text{min}$, we supplied 0.480 mL. Thus, it would appear likely that what we infused might overwhelm any buffering by neurons and glia, particularly at higher K^+ concentrations.

Third, intrathecal, but not intraventricular, infusion of Na^+ produces a concentration-dependent increase in MAC.⁸ Increases in central nervous system Na^+ produced by systemic alterations in Na^+ (where the changes in Na^+ must occur throughout the central nervous system) produce similar changes in MAC.⁵

Fourth, we have demonstrated that some anesthetic drugs [e.g., etomidate]⁹ penetrate the brain in the time frame of the present experiment. A report on intrathecal Mg^{++} injections suggests that, in rabbits, injected Mg^{++} acts on ventral horn neurons in less than an hour.¹⁰ The larger cord of the rabbit makes the diffusion distances greater than in our experimental animal, the rat.

Could the negative results be the product of a K^+ -induced increase in MAC counteracted by another effect of increased extracellular K^+ , such as reduction of action potential amplitude due to a larger proportion of Na^+ channels being in the inactivated state? This hypothesis suggests a fortuitously exact counterbalancing between excitation and depression, an unlikely result, especially over a wide range of K^+ concentrations. That is, the increase in excitation at every point would have to be matched by an exactly equal decrease at every K^+ concentration: The curves for excitation and depression would have to be *quantitative* mirror images of each other. *Qualitative* mirror images would be insufficient to explain the results. Furthermore, K^+ changes must be greater at the surface of the cord as opposed to deeper within the cord. Thus, if increasing K^+ concentrations acted on two sites (one inhibitory and one excitatory),

the more superficial site would be acted on at lower infused concentrations than the deeper one. With increasing concentrations, the more superficial site might approach a maximum response at a lower concentration than the deeper site. This, too, would make unlikely a precise counterbalancing of effects at all infused concentrations of K^+ . Thus, this possible explanation seems unlikely to provide a significant criticism.

The argument of counterbalancing effects also could be leveled at the effects of inhaled anesthetics on K^+ channels. If compensation occurs with K^+ infusion, why can it not occur in response to the increased K^+ conductance produced by inhaled anesthetics? Obviously, such a criticism might lead to the absurd conclusion that nothing inhaled anesthetics do can explain anesthesia.

Perhaps the failure of increasing K^+ to alter MAC in the absence of injury to the cord indicates that K^+ channels do not mediate the immobility produced by inhaled anesthetics. Despite the plausibility of the argument for K^+ channels playing some role, the evidence against such a role is considerable. For example, although knockout of the TREK1 potassium channel increases the MAC of chloroform, desflurane, halothane, and sevoflurane,¹¹ the increase is usually small and, more importantly, it is inconsistent, varying from 7% (desflurane) to 48% (halothane), and these changes do not correlate with the *in vitro* effects of these anesthetics on the TREK1 potassium channel.⁴ Mice lacking KNCK5 or Kir3.2 potassium channels do not have an increased MAC.¹² Administration of the K^+ channel blocker 4-aminopyridine does not decrease halothane MAC in rats.¹³ Administration of the TASK-1 or TASK-3 potassium channel blocker doxapram to mice does not increase MAC.¹⁴ An increase in body temperature activates (opens) some potassium channels¹⁵ and thus should decrease MAC, but an increase in body temperature increases MAC in diverse mammals.^{16–19} Increases in pH can increase the opening of some potassium channels,²⁰ but decreases in $PaCO_2$, and thus increases in pH, do not decrease MAC.²¹ Increasing $PaCO_2$ decreases MAC rectilinearly.²² Perhaps K^+ channels are not relevant to MAC.

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Figure 1.

A schematic of the Methods used in the present study.

Figure 2.

Intrathecal infusion of K⁺ did not increase isoflurane MAC. MAC0 is the control MAC obtained during intrathecal infusion of normal artificial cerebrospinal fluid (aCSF). MAC1 is the MAC obtained during intrathecal infusion of aCSF containing the indicated concentrations of K⁺. Thus, MAC1/MAC0 indicates the fractional change in MAC produced by the altered K⁺ concentration. The largest concentration infused (58.1 mEq/L) significantly ($P < 0.001$) decreased MAC, but this decrease also was associated with injury to the cord as reflected in the failure of a subsequently determined MAC (MAC2) to return to normal.

Figure 3.

Separate control groups of rats received artificial cerebrospinal fluid (aCSF) containing a normal concentration of K^+ , but various concentrations of mannitol, concentrations that changed osmolarity as much as the studies in which K^+ had been altered. No significant changes in MAC were associated with changes in osmolarity.

Figure 4.

Intrathecal infusion of artificial cerebrospinal fluid (aCSF) containing decreased and increased concentrations of Na^+ , respectively, decreased and increased cord concentrations of Na^+ ($P < 0.002$ for the difference in cord concentrations for the infusion of increased versus decreased Na^+ concentrations) without altering cerebral Na^+ concentrations (difference not significant). Values are given as the fraction of the average value during infusion of normal aCSF. $N = 6$ for all groups.

Table 1
Effect of Decreasing and Increasing the Concentration of Intrathecally Infused K^+ on the MAC of Isoflurane

K^+ Infused (mEq/L)	N	MAC0	MAC1	MAC1/MAC0	MAC2	MAC2/MAC0
0.5	6	1.19 ± 0.13	1.15 ± 0.08	0.97 ± 0.06	1.19 ± 0.09	1.01 ± 0.06
2.9	6	1.20 ± 0.18	1.26 ± 0.22	1.06 ± 0.18	1.34 ± 0.19	1.12 ± 0.14
10.1	6	1.30 ± 0.20	1.26 ± 0.07	0.99 ± 0.16	1.22 ± 0.12	0.95 ± 0.12
19.7	8	1.19 ± 0.14	1.27 ± 0.16	1.07 ± 0.14	1.27 ± 0.15	1.07 ± 0.09
29.3	7	1.18 ± 0.13	1.12 ± 0.19	0.95 ± 0.12	1.04 ± 0.28	0.87 ± 0.19
38.9	9	1.22 ± 0.07	1.07 ± 0.13	0.88 ± 0.14	1.17 ± 0.08	0.96 ± 0.10
58.1	7	1.16 ± 0.20	0.85 ± 0.16	0.74 ± 0.11	0.93 ± 0.30	0.80 ± 0.23

Values are given as the mean ± SD. All infusions were at 4 μ L/min.