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AMPA Receptor Competitive Antagonism Reduces Halothane MAC in Rats

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Various subtypes of receptors have been identified for glutamate, an excitatory neurotransmitter. Previous studies have shown that antagonism of glutamate at the NMDA receptors reduces minimum alveolar concentration (MAC) for volatile anesthetics. NBQX (2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(f)quinoxaline) is a selective antagonist at the glutamatergic AMPA receptor. The purpose of this experiment was to determine whether AMPA receptor antagonism influences halothane MAC in the rat. Sprague-Dawley rats were anesthetized with halothane in 50% O_2/balance N_2, tracheally intubated and the lungs were mechanically ventilated. Increasing doses of NBQX were intravenously infused in three groups while the control group was infused with vehicle (D_5W). Halothane MAC was then determined by the tail-clamp method. Halothane MAC was log-linearly related to plasma NBQX concentrations (MAC = −0.125 (ln plasma concentration NBQX) + 1.035, r^2 = 0.77). A maximal 58% reduction of halothane MAC was achieved with an NBQX loading dose of 42 mg/kg followed by a continuous infusion rate of 36 $mg \cdot kg^{-1} \cdot h^{-1}$ (control = 1.02 ± 0.07%; NBQX = 0.43 ± 0.12%; $P < .01$). Larger doses of NBQX were not possible because of the poor aqueous solubility of this compound. In a separate experiment, awake rats were randomly assigned to groups based on the dose of NBQX infused. Pa_{CO_2} and mean arterial pressure were measured at time 0 and at 5 and 30 min after start of NBQX infusion. The infusion was then stopped. Time until recovery of the righting reflex was recorded. Pa_{CO_2} values were unchanged by the lower doses of NBQX, but were increased by the largest dose of NBQX infused (control = 37.3 ± 2.1 mmHg; NBQX = 50.1 ± 12 mmHg; $P < .01$). Mean arterial pressure was not affected by any dose of NBQX. The righting reflex was impaired in the high-dose NBQX group only. We conclude that competitive antagonism of glutamatergic neurotransmission at the AMPA receptor reduces halothane MAC in the rat. (Key words: Anesthetic, intravenous: NBQX. Anesthetic, volatile: halothane. Neurotransmitter: AMPA, glutamate. Receptors: glutamate.)

GLUTAMATE IS A ubiquitous neurotransmitter in the central nervous system.[1] This excitatory amino acid, while critical to normal cerebral function, also has been associated with several pathologic processes including cerebral ischemia, head injury, and Huntington's disease.[2,3] As a result, the physiology and pharmacology of glutamatergic neurotransmission has been the subject of recent intense investigation.

There are several recognized subtypes of glutamate receptors, each having unique neurophysiologic properties. These receptors are named according to known specific agonists including N-methyl-D-aspartate (NMDA), α-amino-3-hyroxy-5-methyl-4-isoxazole propionic acid (AMPA), and kainate.[4,5] Accordingly, an increasing number of receptor specific antagonists of glutamatergic neurotransmission have been identified.[4,6]

Previous investigations have demonstrated that pharmacologic antagonism of excitatory neurotransmission at the NMDA receptor can produce anesthesia. For example, both competitive and non-competitive antagonism of glutamatergic neurotransmission at the NMDA receptor have been shown to reduce the minimum alveolar concentration (MAC) for volatile anesthetic agents.[7,8] In addition, ketamine, at least in part, is thought to cause anesthesia by noncompetitive antagonism at the NMDA receptor.[9]

Until recently, only antagonists acting at the NMDA receptor site have been available for investigation. However, a highly specific competitive AMPA receptor antagonist has now been identified, 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(f)quinoxaline (NBQX).[10,11] To date, glutamatergic antagonism of the AMPA receptor has been unexplored as a potential mechanism for providing anesthesia. The identification of NBQX offers a unique opportunity to pursue this possibility. The purpose of the following investigation was to: 1) determine whether AMPA receptor antagonism reduces the MAC of halothane in the rat and 2) obtain preliminary information regarding the respiratory and hemodynamic effects of AMPA receptor antagonism.

Materials and Methods

These studies were approved by the University of Iowa Animal Care and Use Committee.

EXPERIMENT 1

Male Sprague Dawley rats (Harlan, Indianapolis, IN), at 13–14 weeks of age, were allowed access to food and water until the time of the experiment. All animals were

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weighed and then anesthetized with 3–4% halothane in 50% O_2/balance N_2. Following tracheal intubation the lungs were mechanically ventilated so as to achieve normocapnia. The delivered halothane concentration was adjusted to 1.3% in 50% O_2/balance N_2. Right femoral arterial and venous catheters were placed *via* surgical incision. Rectal temperature was servoregulated at 37°C by surface heating or cooling. Electroencephalographic activity (EEG) was monitored from needle electrodes inserted into the temporalis bilaterally and a reference electrode inserted into the midline of the scalp (Grass Model 8–10c, Quincy, MA). Following preparation, the inspired halothane concentration was adjusted to 1.3% and a 20-min stabilization interval was allowed. Baseline MAP, heart rate (HR), and EEG patterns were then recorded.

Animals were assigned randomly to one of four groups (n = 6 per group) according to the dose of NBQX administered.

Control: An iv bolus of 2 ml/kg 5% dextrose in water (over 2 min) was followed by a continuous iv infusion of 5% dextrose in water at a rate of 1.4 ml/hr;
$NBQX_1$: NBQX bolus = 4.0 mg/kg (1.3 ml/kg) iv; infusion rate = 3.6 $mg \cdot kg^{-1} \cdot h^{-1}$;
$NBQX_2$: NBQX bolus = 12.5 mg/kg (4.2 ml/kg) iv; infusion rate = 11.0 $mg \cdot kg^{-1} \cdot h^{-1}$;
$NBQX_3$: NBQX bolus = 42.0 mg/kg (14.0 ml/kg) iv; infusion rate = 36.0 $mg \cdot kg^{-1} \cdot h^{-1}$.

The sodium salt of NBQX (Novo Nordisk A/S, Måløv, Denmark) was prepared as a 0.3% solution (3 mg/ml dissolved in 5% dextrose in water) buffered to a pH of 8.4 with NaOH. The bolus was given over 2 min followed immediately by the continuous infusion. Mean arterial pressure, HR, and EEG were recorded prior to drug administration and at 5 and 30 min after onset of drug administration. In addition, 30 min after onset of infusion, 1 ml of venous blood was drawn for chromatographic determination of plasma NBQX concentration, assayed according to a previously described technique.[12]

Thirty minutes after onset of the continuous infusion, the MAC for halothane was determined starting with an end-tidal concentration of 1.3%.[13] A painful stimulus was obtained by application of a rubbershod 10-inch hemostat clamped to the proximal 2 cm of the tail. The clamp was applied for a total of 60 s, during which time the hemostat was continually rotated across its long axis to simulate a wagging motion of the tail. Any purposeful movement occurring during application of the hemostat was considered a positive response.

In the absence of movement, the inspired halothane concentration was reduced by approximately 20% (*e.g.*, to 1.1%). After 20 min of ventilation at the new inspired halothane concentration, MAP, HR, EEG, and end-tidal halothane concentration were recorded. The stimulus was then repeated. If the animal failed to respond, the inspired halothane concentration was decreased again by 20% and the sequence was repeated until purposeful movement was observed. The value of the lowest end-tidal concentration at which the rat did not move and that end-tidal value at which movement was observed were averaged and recorded.

End-tidal halothane concentrations were determined as follows. A catheter (Intramedic Polyethylene Tubing PE-50) was permanently positioned at the distal tip of the endotracheal tube. Small aliquots (~1 ml for each ventilatory cycle) of expiratory gas were withdrawn into a glass syringe for a total of 35 ml. The aspirated gas was then introduced into an Ohmeda 5330 Agent Monitor (Louisville, CO) for analysis. The monitor was calibrated with known standards at the beginning of each experimental day.

Experiment 2

Rats were weighed and given pentobarbital (50 mg/kg ip). After local subcutaneous infiltration with 1% lidocaine, catheters (Intramedic Polyethylene tubing PE-50) were placed in the right femoral artery and vein *via* surgical incision and filled with heparinized saline. The catheters were capped, tunneled subcutaneously, and exteriorized at the nape of the neck. The wounds were closed with suture. The animal was then allowed to awaken and recover for 24 h.

Each rat was then placed in a plexiglass cylindrical restrainer (Kent Scientific, Litchfield, CT). The arterial catheter allowed continuous recording of MAP and sampling of blood for determination of arterial blood gases/pH (Instrumentation Laboratory 1306 ph/Blood Gas Analyzer). The venous catheter was used for drug infusion. The animals were assigned randomly to one of four groups (n = 6 per group). Vehicle and drug infusion regimens for the four groups (control, $NBQX_1$, $NBQX_2$, and $NBQX_3$) were identical to those described in experiment 1.

Following a 15-min interval for acclimation to the restraining apparatus, baseline MAP, Pa_{O_2}, Pa_{CO_2}, and pH_a were determined. The designated bolus and infusion regimen was then initiated. So as to reflect the temporal events occurring in experiment 1, respective iv infusions were continued for 30 min. At 5- and 30-min intervals after onset of infusion, MAP, Pa_{O_2}, Pa_{CO_2}, and pH_a determinations were repeated. The infusion was then discontinued. The animal was removed from the restraining apparatus and was placed on its side in a cage and observed. The interval required for spontaneous recovery of the righting reflex was recorded.

TABLE 1. Physiologic Values for Experiment 1

	Control (n = 6)	$NBQX_1$ (n = 6)	$NBQX_2$ (n = 6)	$NBQX_3$ (n = 6)
Baseline				
MAP (mmHg)	109 ± 12	114 ± 3	102 ± 20	103 ± 6
HR (beats/min)	338 ± 24	322 ± 30	324 ± 10	320 ± 21
5 min postbolus				
MAP (mmHg)	100 ± 19	105 ± 8	87 ± 13	82 ± 14
HR (beats/min)	328 ± 30*	305 ± 25†	292 ± 31	264 ± 20
30 min postbolus				
MAP (mmHg)	81 ± 20	89 ± 19	98 ± 17	89 ± 11
HR (beats/min)	299 ± 26	290 ± 25	306 ± 17	276 ± 8
*p*Ha	7.40 ± .05	7.44 ± .04	7.45 ± .02	7.42 ± .03
Pa_{CO_2} (mmHg)	37.9 ± 2.5	36.9 ± 2.1	35.5 ± 2.4	37.8 ± 2.8
Pa_{O_2} (mmHg)	157 ± 23	146 ± 18	165 ± 10	168 ± 19
Rectal temperature (° C)	37.2 ± 0.4	37.2 ± 0.2	37.0 ± 0.3	36.9 ± 0.2
Body weight (g)	303 ± 17	318 ± 16	294 ± 28	300 ± 20

All values are means ± SD.
NBQX = 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(f)quinoxaline; MAP = mean arterial pressure; HR = heart rate.

* Control *versus* $NBQX_3$.
† $NBQX_1$ *versus* $NBQX_3$, where $P < .01$.

Data were analyzed by one-way analysis of variance. *Post hoc* testing was performed to identify between-group differences when indicated by a significant F ratio by use of the Fisher PLSD test. Statistical significance was assumed when $P < .05$. Values are mean ± SD.

Results

EXPERIMENT 1

Physiologic data are presented in table 1. Baseline body weight, MAP, and HR were similar between groups. Mean arterial pressure, HR, pH_a, Pa_{CO_2}, Pa_{O_2}, and rectal temperature were similar between groups when measured 30 min after onset of infusion.

The MAC for halothane in the control group was 1.02 ± 0.07%. The MAC for halothane was not significantly affected by the lowest dosage of NBQX ($NBQX_1$ = 0.95 ± 0.12 vol %). However, larger doses of NBQX caused substantial reductions in the end-tidal halothane concentrations at which a purposeful response to tail clamp was observed ($NBQX_2$ = 0.67 ± 0.12%; $P < .01$). The maximum dose of NBQX administered resulted in a 58% reduction in halothane MAC ($NBQX_3$ = 0.43 ± 0.21%; $P < .01$).

As expected, plasma concentrations of NBQX increased with larger doses of the drug ($NBQX_1$ = 2.98 ± 0.46; $NBQX_2$ = 13.50 ± 3.37; $NBQX_3$ = 143.97 ± 35.32 μg/ml; $P < .001$). Because variances for plasma concentrations in the respective groups appeared different, a test for inhomogeneity of variance (Bartlett's test) was performed confirming this observation.[14] Accordingly, plasma concentrations were normalized by transformation to natural logarithmic values. A regression analysis was performed on the transformed plasma concentrations as a function of halothane MAC resulting in an r^2 value of 0.77 ($y = -0.125x + 1.035$; fig. 1).

The EEG (monitored in rats undergoing halothane MAC determination, *i.e.*, experiment 1) was also affected by the administration of NBQX in a dose-dependent manner. Typically, the loading bolus of NBQX resulted in a rapid onset of burst suppression (particularly with the higher doses) that persisted for approximately 5 min. Thereafter, the EEG showed some recovery in the $NBQX_1$ and $NBQX_2$ groups, although a marked slowing with high amplitude activity persisted throughout the continuous infusion interval. In contrast, the $NBQX_3$

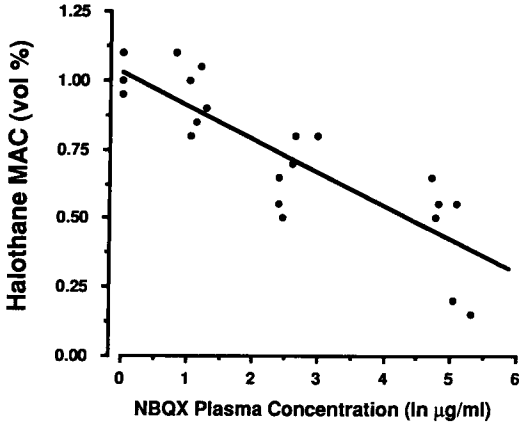

FIG. 1. Minimum alveolar concentration (MAC) for halothane as a function of the natural log of the plasma concentration of the competitive glutamate receptor antagonist 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(f)quinoxaline (NBQX). Each point depicts values for an individual rat. MAC = −0.125 (ln plasma concentration NBQX) + 1.035, r^2 = 0.77.

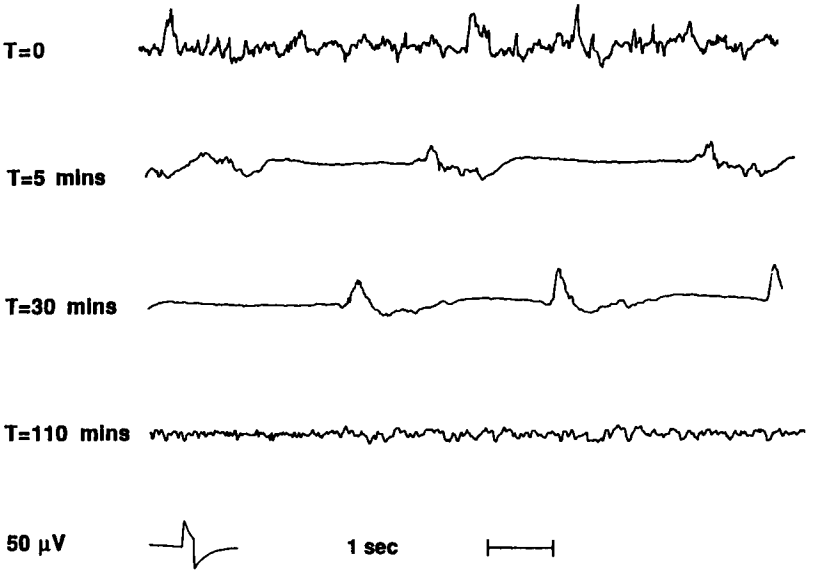

FIG. 2. Electroencephalographic activity for one rat in the $NBQX_3$ group at various intervals of the experimental protocol. T = 0: baseline (1.3% halothane end-tidal) before NBQX administration; T = 5: 5 mins after administration of NBQX bolus (42 mg/kg) and commencement of NBQX continuous infusion (36 $mg \cdot kg^{-1} \cdot h^{-1}$); T = 30: commencement of MAC determination sequence; T = 110: time at which rat exhibited purposeful response to tail clamp. NBQX = 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(f)quinoxaline.

group continued to demonstrate a pattern of burst suppression until the end-tidal halothane concentration was reduced to approximately 0.6%, whereupon recovery to slow-wave, high-amplitude activity was observed (fig. 2).

EXPERIMENT 2

Physiologic values are presented in table 2. Baseline values for MAP, pH_a, Pa_{CO_2}, Pa_{O_2}, and body weight were similar between groups. Five minutes after the start of NBQX administration, there were no significant differences between groups for MAP or Pa_{O_2}. The $NBQX_1$ and $NBQX_2$ infusion regimens had no effect on Pa_{CO_2} or pH_a 5 min after administration as compared to control values. Pa_{CO_2} values were increased and pH_a was decreased in the $NBQX_3$ group ($P < .01$). Thirty minutes after onset of infusion, MAP and Pa_{O_2} remained similar between the control, $NBQX_1$, and $NBQX_2$ groups. In contrast, hypercarbia with a resultant respiratory acidosis persisted in the $NBQX_3$ group ($P < .01$).

After 30 min of NBQX (or vehicle) administration, rats in the control, $NBQX_1$, and $NBQX_2$ groups showed no evidence of sedation and had no impairment of the righting reflex. In contrast, all rats in the $NBQX_3$ group

TABLE 2. Physiologic Values for Experiment 2

	Control (n = 6)	$NBQX_1$ (n = 6)	$NBQX_2$ (n = 6)	$NBQX_3$ (n = 6)
Baseline				
MAP (mmHg)	122 ± 6	124 ± 19	128 ± 14	122 ± 14
*p*Ha	7.47 ± .01	7.46 ± .01	7.47 ± .01	7.46 ± .02
Pa_{CO_2} (mmHg)	37.3 ± 2.3	39.4 ± 2.3	37.0 ± 2.1	37.3 ± 2.1
Pa_{O_2} (mmHg)	87 ± 3	87 ± 8	88 ± 2	96 ± 19
5 min postbolus				
MAP (mmHg)	120 ± 8	122 ± 18	125 ± 13	123 ± 18
*p*Ha	7.46 ± .02	7.45 ± .02	7.42 ± .01	7.33 ± .07
Pa_{CO_2} (mmHg)	37.8 ± 3.0	40.2 ± 1.7	40.9 ± 3.0	49.5 ± 9.0*
Pa_{O_2} (mmHg)	89 ± 3	89 ± 3	90 ± 4	78 ± 21
30 min postbolus				
MAP (mmHg)	124 ± 8	123 ± 19	123 ± 8	123 ± 18
*p*Ha	7.47 ± .03†	7.44 ± .02	7.43 ± .02	7.34 ± .08*
Pa_{CO_2} (mmHg)	37.2 ± 1.8	39.9 ± 2.7	40.4 ± 2.5	50.1 ± 12.0*
Pa_{O_2} (mmHg)	93 ± 14	94 ± 7	99 ± 3	93 ± 18
Body weight (g)	308 ± 18	311 ± 29	312 ± 17	305 ± 15

All values are mean ± SD.
NBQX = 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(f)quinoxaline; MAP = mean arterial pressure.

* $NBQX_3$ *versus* control, $NBQX_1$, and $NBQX_2$.
† Control *versus* $NBQX_2$, where $P < .01$.

were visibly sedated and had a loss of the righting reflex. The interval necessary to allow recovery of the righting reflex in the $NBQX_3$ had considerable variability with a range of 6–222 min.

Discussion

Our interest in performing this experiment was twofold. First, the concept of specifically inhibiting excitatory neurotransmission would seem to be a reasonable mechanistic approach to defining new anesthetic agents. The recent availability of NBQX, a glutamate (AMPA) receptor antagonist, provided a unique opportunity to investigate this possibility. Second, NBQX has been demonstrated to substantially reduce ischemic brain damage.[11,15,16] Little or no effort has been made to define the sedative properties or effects on hemodynamics and respiration for this agent when administered either alone or in combination with anesthetic agents. These factors could have major implications for the clinical utility of a neuroprotective drug.

Several physiologic aspects of glutamatergic neurotransmission make it likely that some properties of anesthesia can be achieved with AMPA receptor specific antagonists. First, *via* a directly linked monovalent cationic channel, AMPA receptor agonism is associated with increased cellular conductances for both Na+ and K+ leading to the generation of excitatory post-synaptic potentials in many central neural circuits.[6,17,18] Second, AMPA receptor antagonism/agonism has been demonstrated to modulate ionic conductances at the NMDA receptor-regulated channels that are believed to be the site of action for dissociative anesthetics (*e.g.*, ketamine).[19,20] Finally, given the rich endowment of glutamatergic receptors in the dorsal horn of the spinal cord and periaqueductal gray matter,[21,22] AMPA receptor antagonism has been speculated to represent a potential mechanism for inhibiting nociception.[23]

In this experiment, the observed MAC for halothane (in the presence of a continuous infusion of the vehicle, 5% dextrose in water) was 1.02 ± 0.07%, consistent with values previously reported for the rat.[13] AMPA receptor antagonism, in a log-linear fashion, resulted in a maximal 58% reduction of halothane MAC at the highest NBQX concentration administered. Thus evidence for a substantial anesthetic effect of AMPA receptor antagonism is provided.

NBQX was chosen to probe the potential for AMPA receptor antagonism-mediated anesthesia because it is the only currently available selective AMPA receptor antagonist. This compound, however, has poor aqueous solubility and precipitates in the renal tubules when administered in high concentrations.[§§] Hence, we were limited by the maximal dose of the dissolved agent which could be administered. For example, in the $NBQX_3$ group, the administered volume of 0.3% NBQX was ≈16 ml over 2 h. It is important to note that this volume was substantially greater than that administered in the $NBQX_2$ (≈11 ml) and $NBQX_1$ (≈4 ml) groups. The effect of this difference in volume of fluid administration on measured MAP values is not known. An additional four rats were studied with an even larger dose of NBQX (*i.e.*, 151 mg/kg bolus followed by an infusion rate of 125 $mg \cdot kg^{-1} \cdot h^{-1}$). Two of these rats showed no response to tail clamp after the halothane had been turned off for 40 min (with end-tidal halothane concentrations undetectable by the agent analyzer in either animal). The other two rats died after an abrupt, and profound, decrease in MAP, which occurred before the MAC determination could be made. These hypotensive episodes occurred within 5 min after the end of the NBQX bolus and may be attributed to either intravascular volume overload or direct toxicity. For these reasons, a ceiling effect for the drug could not be definitively achieved with respect to MAC reduction.

Other glutamate antagonists also have anesthetic properties. The non-competitive NMDA receptor antagonist, ketamine, has already been alluded to above. Similarly, the more selective non-competitive NMDA receptor antagonist, dizocilpine (MK-801), has been demonstrated to reduce halothane MAC by ≈50%.[7] Both of these drugs exhibit psychotomimetic properties that have limited their clinical application.[20,24,25] A preliminary report has indicated that psychotomimetic side effects are not inherent in AMPA receptor antagonism.[26]

In this experiment, NBQX was found to have little or no effect on MAP. In experiment 1, a trend for reduced MAP was observed immediately after bolus administration of NBQX while the end-tidal halothane concentration was 1.3% ($P < .06$). This trend, however, was completely resolved at the 30-min measurement interval. In experiment 2, there were no differences between groups for MAP at any experimental interval as a function of NBQX dose. The apparent lack of hemodynamic compromise in these spontaneously breathing rats also provides motivation for continued investigation of AMPA receptor antagonism as an approach to providing anesthesia.

In contrast, respiratory depression was observed for the largest dose administered ($NBQX_3$). In this group only, loss of righting reflex was also observed, indicating a potential interaction between AMPA receptor-mediated neurotransmission and the regulation of respiration. In experiment 2, we also investigated a limited number of rats with even larger doses of NBQX (151 mg/kg bolus

§§ Unpublished data.

followed by an infusion of 125 $mg \cdot kg^{-1} \cdot h^{-1}$), all of which exhibited abrupt obtundation, and a decrease in respiratory rate followed by hemodynamic collapse.

Of note, we observed no loss of righting reflex or hemodynamic/respiratory compromise at the lower doses evaluated. Investigations concerning the efficacy of NBQX as a neuroprotective agent in the rodent have found substantial protection against both global[11,16,27] and focal cerebral ischemia.[15] The dose of drug administered in those studies (*e.g.*, 30 mg/kg ip) was most closely approximated by our $NBQX_2$ group (12.5 mg/kg bolus and 11.0 $mg \cdot kg^{-1} \cdot h^{-1}$ iv). Utilization of a neuroprotective agent with minimal hemodynamic effects or respiratory depression at low doses is a clear advantage of receptor specific glutamate antagonism.

In conclusion, AMPA receptor antagonism of glutamatergic neurotransmission by iv NBQX administration was demonstrated to provide up to a 58% reduction in the MAC for halothane. The magnitude of MAC reduction by NBQX was similar in magnitude to that previously observed for glutamatergic antagonism at the NMDA receptor with other agents, although a ceiling effect for AMPA receptor antagonism could not be identified due to the limited solubility of NBQX in aqueous solution. Minimal hemodynamic or respiratory depression was observed as a result of NBQX administration in dosage ranges previously shown to offer neuroprotection against ischemia. In contrast, in those animals exhibiting loss of righting reflex, hypercarbia was observed. These results indicate antagonism of glutamatergic neurotransmission at the AMPA receptor offers a promising avenue for future investigations seeking to identify anesthetic agents that function by selectively antagonizing the excitatory components of the central nervous system.

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