Role of spinal NMDA and non-NMDA receptors in the pressor reflex response to abdominal ischemia


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Gee, B. Y., S. C. Tjen-A-Looi, J. M. Hill, P. S. Chahal, and J. C. Longhurst. Role of spinal NMDA and non-NMDA receptors in the pressor reflex response to abdominal ischemia. Am J Physiol Regulatory Integrative Comp Physiol 282: R850–R857, 2002; 10.1152/ajpregu.00297.2001.—Abdominal ischemia induces a pressor reflex caused mainly by C-fiber afferent stimulation. Because excitatory amino acids, such as glutamate, bind to N-methyl-D-aspartate (NMDA) and non-NMDA [dl-α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA)] receptors and serve as important spinal neurotransmitters, we hypothesized that both receptors play a role in the activation of visceral afferent nerves during the abdominal ischemia pressor reflex (5, 6, 11, 12, 21, 22, 28, 30, 36–38). However, the spinal receptors that relay afferent nerve activity during abdominal ischemia have been little studied.

Glutamate, the principal excitatory amino acid of the central nervous system (CNS) (10), and the receptors to which glutamate binds, the N-methyl-D-aspartate (NMDA) receptor and the non-NMDA dl-α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor (23), are widely distributed throughout the CNS. In the spinal cord, localization of glutamate and its receptors in afferent and efferent pathways has suggested a role for glutamate as a spinal neurotransmitter. Glutamate has been found in spinal primary afferent terminals of rats (9) and in laminae I and II of the dorsal horn of cats (25). Additionally, sympathetic premotor neurons that originate from the rostral ventral lateral medulla (rVLM) contain glutamate (26).

Multiple studies point to glutamate as a neurotransmitter involved in the spinal transmission of afferent and efferent arms of reflex arcs. First, spinal NMDA receptors have been shown to be involved in processing nociceptive information evoked by stimulation of somatic and viscerosomatic afferent fibers (20). Second, dorsal horn NMDA (1) and non-NMDA (AMPA) (1, 15) receptors have been found to play a role in spinal transmission of the afferent arm of the muscle contraction-evoked pressor response. Third, both subtypes of glutamatergic receptors have been shown to in-

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volved in the spinal transmission of the arterial baroreflex. Specifically, NMDA receptors are important in mediating baroreflex-evoked vasoconstriction, while NMDA and non-NMDA receptors are important in mediating baroreflex changes in heart rate (41).

These lines of evidence, which implicate glutamate as a neurotransmitter in the spinal processing of peripheral reflexes, prompted us to speculate that glutamate and its receptors are important in the spinal transmission of the pressor reflex evoked by abdominal ischemia. Therefore, we tested the hypothesis that, in anesthetized cats, the pressor response evoked by abdominal ischemia would be reduced by intrathecal injection of an NMDA or a non-NMDA (AMPA) receptor antagonist onto the thoracic spinal cord compared with the pressor response to abdominal ischemia before the intrathecal injection of the antagonists.

Previous studies (1, 32) have noted that anesthetics such as ketamine and α-chloralose can mask the contribution of spinal sensory NMDA and, to a lesser extent, spinal sensory AMPA receptors. Because the use of decerebrate, unanesthetized cats circumvents this problem (1, 32), we tested our hypothesis in this preparation.

Glutamatergic receptors mediate not only sensory input to the spinal cord but also sympathetic outflow from the spinal cord (2, 24). To determine whether the effects of these antagonists on the pressor response to abdominal ischemia can be explained by their actions on spinal efferent pathways, we investigated the effects of thoracic intrathecal injection of NMDA and non-NMDA (AMPA) receptor antagonists on the pressor responses evoked by stimulation of the rVLM.

**METHODS**

**General and Surgical Preparation**

The surgical and experimental protocols were approved by the Institutional Animal Care and Use Committee at the University of California at Davis and Irvine. All experiments were performed on adult cats (n = 35) of both sexes (2.3–5.4 kg). Of these, 19 were initially anesthetized with ketamine (30 mg/kg im) and maintained under anesthesia with α-chloralose (Sigma Chemical, St. Louis, MO; 40–60 mg/kg iv). The depth of anesthesia was assessed by the cat’s response to a paw pinch, the presence of an eye reflex, and/or the presence of abnormal respiration patterns; additional doses of α-chloralose were given as needed. A separate group of cats (n = 16) was placed in a Kopf stereotaxic head holder and decerebrated under inhalation of oxygen and halothane anesthesia according to the method of Shik et al. (35). Neural tissue rostral to a transverse cut at the midscolicular level was removed. Before decerebration, the right and left common carotid arteries were occluded to prevent excessive bleeding into the cranium. Dexamethasone sodium phosphate (American Regent Laboratories, Shirley, NY; 1.0 ml of 4 mg/ml solution iv) was administered to reduce edema and swelling of the cranial contents. After decerebration, the animals were paralyzed with vecuronium bromide (Organon, West Orange, NJ; 0.25 ml of 1 mg/ml solution iv, supplemented as necessary), and the inhalant anesthetic was discontinued. Halothane was discontinued for ≥2 h before commencement of experimental protocols.

All cats underwent the following surgical procedures. The femoral vein was cannulated for administration of drugs and fluids. The femoral artery also was cannulated, and the arterial catheter was connected to a transducer (model P23 ID, Statham, Valley View, OH) for measurement of systemic arterial blood pressure. Intubation was performed so that the animal’s respiratory rate and volume could be controlled mechanically with a respirator (Harvard pump, model 661, Ealing, South Natick, MA). Arterial blood gases were measured regularly (approximately every 30 min) with a blood gas analyzer (model ABL-3, Radiometer, Copenhagen, Denmark) and were maintained within normal physiological limits (pH 7.35–7.45, 28–35 mmHg Pco2, >100 mmHg Po2, 18–22 mM HCO3).

The abdominal cavity was opened through a ventral midline incision to locate and prepare the celiac and superior mesenteric arteries for occlusion. After short portions (2–4 mm) of the two arteries were isolated, a snare occluder was placed around each vessel. Care was taken to protect the nerve plexus surrounding each vessel from damage. The inferior mesenteric artery also was ligated to reduce collateral blood flow into the region at risk. Gauze sponges soaked in saline were used to cover exposed viscera and to keep abdominal organs moist. The abdominal cavity then was closed temporarily with two towel clamps, and the cat was turned onto its ventral side for preparation for injectate administration into the subdural space of the spinal cord.

Spinal afferents from the abdominal area were reached by insertion of an intrathecal catheter (PE-50 tubing) through the spinal cord dura mater near C1 into the subarachnoid space. The tip of the catheter was advanced caudally and positioned at the thoracic level of the cord, where the spinal afferent nerves of interest are located. Spinal processes were used as landmarks to aid in positioning the catheter at T7–T9. The exact location of the catheter tip was verified visually postmortem in each cat. Drugs (NMDA or AMPA receptor antagonists), saline vehicles, and dye injections (for postmortem catheter tip identification) were administered through a 1.0-ml syringe (Monoject, St. Louis, MO) attached to the intrathecal catheter. Resin-reinforced vinyl polysiloxane (type 1, low viscosity, Jeneric/Penton) was used to hold the catheter in place at the cervical level. The upper thorax of the cat was elevated above the level of the stomach to limit rostral spread of intrathecally administered injectates toward cardiac efferents (T2–T5). The cat was monitored until arterial blood pressure stabilized before continuation of the experimental protocols.

**Experimental Protocols**

Three protocols involving thoracic intrathecal injection of glutamatergic receptor antagonists were used to investigate the role of glutamate receptors. **Protocol 1** assessed the influence of intrathecal injection of glutamatergic receptor antagonists on the pressor response to abdominal ischemia in anesthetized cats, and **protocol 2** assessed the same response in decerebrate cats. **Protocol 3** evaluated the pressor response during stimulation of the rVLM in anesthetized and decerebrate groups.
Protocol 1: effect of thoracic intrathecal injection of glutamatergic receptor antagonists on the reflex pressor response to abdominal ischemia in anesthetized cats. The purpose of protocol 1 was to determine whether NMDA and/or AMPA (non-NMDA) receptors play a role in the pressor reflex response to abdominal ischemia. Arterial blood pressure was recorded continuously on a chart recorder (model TA 4000B, Gould, Cleveland, OH), and after stabilization, recordings were taken for a 10-min period to establish baseline values. The blood pressure response to abdominal ischemia, which was induced by constricting loop snares around the celiac and superior mesenteric arteries, was recorded for 20 min or after the arterial pressure response reached a plateau, depending on which event occurred first. A 30-min recovery period ensued, during which blood pressure returned to preischemia baseline levels.

The NMDA receptor antagonist dl-α-amino-3-hydroxy-5-methylisoxazole-4-propionate (±AP-5, 25 mM, n = 4), the AMPA receptor antagonist 6-nitro-T-sulfamylbenzyl/3-amino-5-phosphonic acid (NBQX disodium, 4.0 mM, n = 6), or the vehicle (0.9% saline) was injected onto the thoracic spinal cord through the intrathecal cannula. The NMDA and non-NMDA receptor antagonists have been found to be selective to their receptors. Chiž et al. (7) have shown the selectivity of NBQX for AMPA receptors, and ±AP-5 has been used by West and Huang (41) to demonstrate spinal transmission and cardiovascular responses. The injectate volume was 0.40 ml (0.25 ml of injectate followed by a 0.15-ml saline flush) and was administered over a 10-min period; hence, the injection rate was 0.01 ml every 15 s. Because the catheter volume was 0.25 ml, 0.15 ml of the drug actually was delivered to the thoracic spinal cord. After 30 min were allowed for the antagonist to penetrate into the spinal cord, baseline blood pressure was recorded for 10 min. Then a second period of abdominal ischemia was induced, and blood pressure was recorded.

In animals that did not exhibit a pressor reflex response to abdominal ischemia, bradykinin (1–10 mg/ml) was applied to the surface of the gallbladder to determine whether the animal was capable of manifesting a reflex response. Cats that did not exhibit a pressor response to bradykinin were deemed nonresponsive. These cats, those that exhibited a pressor response of <15 mmHg, and those that had an unstable blood pressure were excluded from the study.

Protocol 2: effect of thoracic intrathecal injection of glutamatergic receptor antagonists on the reflex pressor response to abdominal ischemia in decerebrate cats. The purpose of protocol 2 was to determine whether ketamine and α-chloralose mask the function of glutamatergic receptors. The pressor response to abdominal ischemia was assessed before and after intrathecal injection of the glutamate receptor antagonist ±AP-5 (25.0 mM, n = 5). Decerebrate cats were used in protocol 2 to circumvent the problem of anesthetic blockade of neurotransmission. We wanted to focus our attention on the effects of intrathecal injection of the NMDA receptor antagonist ±AP-5 on the abdominal ischemia pressor reflex. Four animals were studied after intrathecal injection of the saline vehicle between two periods of ischemia in decerebrate cats as controls.

Protocol 3: effect of thoracic intrathecal injection of glutamatergic receptor antagonist on the pressor response to rVLM stimulation in anesthetized and decerebrate cats. Protocol 3 determined the influence of glutamatergic receptor blockade on sympathetic preganglionic neurons. We positioned the cats in a Kopf stereotaxic head holder. The dorsal surface of the medulla was exposed through a partial craniotomy, which involved removing the occipital bone and the atlanto-occipital membrane. The obex was used as a landmark to locate the rVLM, and the tip of a bipolar metal electrode (25 mm tip diameter; FHC, Bowdoinham, ME) was placed at a 20° angle and 2.70–3.4 mm lateral (left side) to the obex. An electrical current (100–500 μA, 0.5-ms duration at 80 Hz for 10 s) was passed through the tip of the electrode, and the final location of the electrode tip was at a depth of 6.88–7.52 mm from the dorsal medullary surface.

Once a repeatable pressor response of >25 mmHg to rVLM stimulation was evoked, 4.0 mM NBQX disodium was injected intrathecally in anesthetized cats (n = 4), and 25.0 mM ±AP-5 (n = 4) or the saline vehicle (n = 3) was injected intrathecally in decerebrate cats. After 30 min to allow the antagonist to penetrate the spinal cord, the pressor response was reassessed using the same parameters for stimulation. The pressor response to rVLM stimulation after intrathecal injection of NMDA receptor antagonists was not determined in anesthetized cats, because results from protocol 1 showed that blockade of NMDA receptors did not affect the abdominal ischemia pressor reflex for these animals. At the end of each experiment, the stimulation site was lesioned to allow anatomic localization. Throughout the periods in which the pressor responses to rVLM stimulation were determined, arterial blood pressure was recorded continuously on a chart recorder. Animals that did not exhibit a pressor response of >25 mmHg to electrical stimulation of the rVLM were excluded from the study.

At the end of each protocol, capsaicin (200 mg/ml, 0.20 ml) was injected into the femoral artery to confirm the presence of a pressor reflex and to demonstrate a viable preparation (33).

Verification of Intrathecal Injection and rVLM Stimulation Sites

The position of the catheter tip was confirmed at the end of each experiment by injection of 0.25 ml of 2% Chicago sky blue dye (Sigma Chemical) followed by 0.15 ml of saline into the subdural spine. Then a postmortem laminectomy was performed to determine the location of the catheter tip. If the catheter tip was not positioned between T7 and T8, the animal was eliminated.

After rVLM stimulation, the medulla was removed and placed in a fixative solution consisting of 40 g of paraformaldehyde and 10 g of sucrose per liter of water for ≥24 h. Then the brain was mounted and stored at −70°C for ≥24 h before it was sectioned. The brain was sliced in 80-μm sections on a freezing microtome cryostat (International Equipment) and was mounted on poly-l-lysine-coated microscope slides. A neutral red stain was utilized to improve histological identification of the stimulation site. Thus stimulation sites in the rVLM were verified histologically and by observing a pressor reflex of ≥25-mmHg increase in blood pressure.

Drugs

The intrathecal injectates included the NMDA receptor antagonists ±AP-5 (Sigma Chemical) and the AMPA receptor antagonist NBQX disodium (Research Biochemicals International). These antagonists are highly selective and potent for their respective receptors (8, 41). Although other studies have used regular NBQX (1, 40), we used NBQX disodium, because it is more water soluble. Intravenous injectates included bradykinin (Sigma Chemical) and capsaicin (Sigma Chemical). All drugs were reconstituted in normal saline (0.9%) and diluted to achieve desired concentrations. Stock solutions of each drug were stored at −70°C.
RESULTS

Protocol 1: Effect of Thoracic Intrathecal Injection of Glutamatergic Receptor Antagonists on the Reflex Pressor Response to Abdominal Ischemia in Anesthetized Cats

In six cats, intrathecal administration of the AMPA receptor antagonist NBQX disodium significantly attenuated the pressor response to abdominal ischemia (29 ± 5 to 16 ± 4 mmHg, P < 0.05; Fig. 1Ba). However, intrathecal injection of the NMDA receptor antagonist AP-5 (n = 4) failed to modify the abdominal ischemia pressor response (P > 0.05). MAP before and after intrathecal injection of AP-5 increased by 33 ± 9 and 33 ± 7 mmHg, respectively (Fig. 1Bb). In five cats, intrathecal administration of the saline vehicle did not affect the pressor response during abdominal ischemia (27 ± 4 to 25 ± 3 mmHg, P > 0.05; Fig. 1Ba).

Protocol 2: Effect of Thoracic Intrathecal Injection of Glutamatergic Receptor Antagonists on the Reflex Pressor Response to Abdominal Ischemia in Decerebrate Cats

In five cats, intrathecal injection of the NMDA receptor antagonist AP-5 significantly attenuated the pressor response to abdominal ischemia (36 ± 3 to 25 ± 4 mmHg, P < 0.05; Fig. 2Bb). In the control group of decerebrate cats (n = 4), changes in MAP during the first (before intrathecal injection of vehicle) and second (after intrathecal injection of vehicle) periods of abdominal ischemia were not significantly different. Changes in MAP were 43 ± 7 and 51 ± 6 mmHg, respectively (P > 0.05; Fig. 2Ba).

Protocol 3: Effect of Thoracic Intrathecal Injection of Glutamatergic Receptor Antagonist on the Pressor Response to rVLM Stimulation in Anesthetized and Decerebrate Cats

We found that the intrathecal injection of the saline vehicle or glutamatergic receptor antagonists had no

Baseline blood pressure was the average mean arterial pressure (MAP) recorded during a 10-min period immediately before induction of abdominal ischemia. The blood pressure response to abdominal ischemia is bimodal. The initial increase in blood pressure is attributed to the immediate mechanical diversion of blood flow and volume into high-resistive circuits consequent to snaring the celiac and superior mesenteric arteries (17, 33). This increase in blood pressure typically is followed by a transient drop in blood pressure, the nadir. Then there is a secondary and more gradual increase in blood pressure, which is caused by an abdominal reflex response. Thus we measured the reflex increase in MAP evoked by ischemia as the difference between the nadir and the secondary increase in blood pressure, as we have reported in past studies (17, 33). The pressor response to stimulation of the rVLM was the difference between baseline and peak MAP achieved during rVLM stimulation.

The software package SigmaStat (Jandel Scientific, San Rafael, CA) was used to analyze the data, expressed as means ± SE. A Student’s paired t-test determined statistical significance. When appropriate, a one-way repeated-measures ANOVA and a Student-Newman-Keuls post hoc test were used to determine statistical significance. The criterion for significance was P = 0.05.

RESULTS

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<td>Arterial Blood Pressure (mmHg)</td>
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<td>Mean Arterial Pressure (mmHg)</td>
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effect on the pressor response induced by electrical stimulation of the rVLM. Thus, in four anesthetized cats, the intrathecal administration of NBQX disodium did not attenuate the pressor response to rVLM stimulation (Table 1). Similarly, in four decerebrate cats, intrathecal administration of AP-5 also did not attenuate the pressor response to rVLM stimulation (Table 1). Control experiments involving injection of the saline vehicle were performed in three decerebrate cats (Table 1). Histological analysis confirmed that the electrode was located in the rVLM in each instance (Fig. 3). The locations of the rVLM stimulation sites were 2.6–2.9 mm lateral of the midline, 2.2–3.0 mm rostral to the obex, and 1.9–2.0 mm dorsal to the ventral surface.

**DISCUSSION**

The purpose of our experiments was to determine whether glutamatergic receptors play a role in the spinal transmission of the pressor reflex evoked by abdominal ischemia. We measured the pressor responses to abdominal ischemia before and after intrathecal injection of glutamatergic receptor antagonists onto the lower thoracic spinal cord. We showed that these pressor responses were attenuated by NMDA and AMPA receptor blockade. The present study indi-

![Fig. 2. A: arterial blood pressure responses to occlusion of celiac and superior mesenteric arteries before (left) and after (right) intrathecal injection of saline (a) and NMDA receptor antagonist (±AP-5) (b) in decerebrate cats. Intrathecal injection of the saline vehicle did not affect the abdominal ischemia pressor reflex (a). Spinal NMDA receptor blockade reduced the pressor reflex rise by 41.7% in this animal (b); the change in mean arterial blood pressure before and after intrathecal injection was 60.0 and 35.0 mmHg, respectively. First arrow, vascular occlusion; second arrow, reperfusion. B: comparison of arterial blood pressure responses (means ± SE) to occlusion of celiac and superior mesenteric arteries before and after intrathecal injection of saline (a, n = 4) and ±AP-5 (b, n = 5) in decerebrate cats. Values below histograms represent 10 min of baseline mean arterial pressure values recorded immediately before occlusion. *P < 0.05 vs. before injectate.

Table 1. Effects of saline vehicle, NMDA receptor antagonist (±AP-5), and AMPA receptor antagonist (NBQX disodium) on the pressor response to rVLM stimulation in anesthetized and decerebrate cats

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<td>Saline vehicle (decerebrate)</td>
<td>3</td>
<td>72 ± 18</td>
<td>78 ± 21</td>
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<td>±AP-5 (decerebrate)</td>
<td>4</td>
<td>56 ± 12</td>
<td>54 ± 12</td>
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<td>NBQX disodium (anesthetized)</td>
<td>4</td>
<td>33 ± 2</td>
<td>38 ± 5</td>
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Values are means ± SE, expressed as changes (mmHg) in mean arterial blood pressure (MAP) during rostral ventral lateral medulla (rVLM) stimulation (difference between MAP at the peak and MAP at baseline) before and after intrathecal injection of the antagonist. n, Number of cats; NMDA, N-methyl-D-aspartate; ±AP-5, dl-2-amino-5-phosphopentanoate; AMPA, dl-α-amino-3-hydroxy-5-methylisoxazole-4-propionate; NBQX disodium, 6-nitro-7-sulfamlybenzo(f)quinoxaline-2,3-dione.

![Fig. 3. Composite of histologically verified stimulation sites in rostral ventral lateral medulla of planes 2.2–3.0 mm rostral to the obex in 4 cats. All stimulation sites are located on the left side of the medulla. +, each site; ION, nucleus of the inferior olive; SSP, alaminar spinal trigeminal nucleus.]
cates that NMDA and AMPA receptors mediate the spinal transmission of the abdominal ischemia pressor reflex.

Our findings suggest that although glutamatergic receptors are involved in the spinal transmission of this ischemia-induced pressor reflex, activation of these receptors is not the sole explanation for the spinal transmission of the afferent arm of this reflex arc. We showed that the blockade of NMDA or AMPA receptors attenuated the reflex blood pressure response to abdominal ischemia. However, the reflex blood pressure response to abdominal ischemia could not be abolished, in part, because nonglutamate receptors also may be involved in the spinal transmission of the afferent arm of this reflex arc. The localization of multiple neuropeptides (18, 19) in the spinal terminals of A-δ and C-fibers, which comprise the afferent arm of this reflex arc, supports this explanation. Additionally, one previous study from this laboratory, in which the intrathecal injection of a neurokinin type 1 receptor antagonist attenuated the reflex pressor response to the topical application of bradykinin to the gallbladder (28), suggests a role for the neuropeptide substance P in the spinal transmission of the reflex pressor response to abdominal ischemia. Thus we speculate that the full expression of the pressor response to abdominal ischemia requires the activation of receptors activated by glutamate and other neuropeptides. We showed that NMDA receptor blockade reduced the reflex blood pressure response to abdominal ischemia in decerebrate, but not in anesthetized, cats. We attribute these different findings in the decerebrate and anesthetized animal models to α-chloralose and ketamine. First, α-chloralose exerts antagonistic-like effects on NMDA receptors (32). Also, α-chloralose depresses dorsal horn cell responsiveness to iontophoretic application of NMDA (32). Furthermore, in the presence of α-chloralose, noxious inputs to dorsal horn cells are not attenuated by NMDA receptor antagonists; without α-chloralose, these inputs are attenuated by NMDA receptor antagonists (32). Moreover, the exercise pressor reflex is not attenuated after the intrathecal injection of NMDA receptor antagonists onto the lumbar spinal cord of cats anesthetized with α-chloralose (15). However, this exercise pressor reflex is attenuated by NMDA receptor antagonists in decerebrate cats (1). Second, ketamine is a noncompetitive NMDA receptor antagonist (15, 16, 32) with an approximate half-life of 1 h (31). Even though the initiation of our experimental protocol occurred ≥3 h after the final ketamine injection, we do not know whether dorsal horn NMDA receptors were occupied by ketamine. Taken together, the use of ketamine and α-chloralose in our anesthetized cat model is a likely explanation for the discrepant findings between decerebrate and anesthetized cats.

NMDA and AMPA receptors are located on sympathetic preganglionic cell bodies, which ultimately mediate changes in blood pressure by altering contractility and vasomotor tone. We were concerned that if the injectate containing NMDA or AMPA receptor antagonists migrated from the lower thoracic spinal cord to the upper thoracic and cervical spinal cords, any observed attenuation of the reflex pressor response to abdominal ischemia would be due to the antagonists’ effects on the efferent, rather than the afferent, arm of this reflex arc. Two findings from this study suggest that, when injected intrathecally onto the lower thoracic cord, these antagonists did not have access to glutamatergic receptors in the upper thoracic and cervical spinal cords. First, Chicago sky blue dye injected in the same volume and through the same cannula as the glutamatergic antagonists onto the lower thoracic spinal cord did not spread to the upper thoracic and cervical spinal regions. Second, the intrathecal injection of NMDA or AMPA receptor antagonists onto the lower thoracic spinal cord did not attenuate the pressor response to electrical stimulation of the rVLM. Hill et al. (15) showed that the increase in blood pressure evoked by electrical stimulation of the rVLM is attenuated by the intrathecal injection of an NMDA antagonist onto the upper thoracic spinal cord, but not onto the lower thoracic spinal cord. Furthermore, when the NMDA antagonist was injected intrathecally onto the upper lumbar spinal cord, the investigators noted an attenuated reflex pressor response during muscular contraction, but not during stimulation of the rVLM (15). Taken together, the findings in the present and previous studies suggest that the attenuated reflex pressor response to abdominal ischemia was an antagonism of the glutamatergic receptors involved in the spinal transmission of the afferent arm, not efferent arm, of this reflex arc.

Previous studies from our laboratory suggest that abdominal ischemia induces nociceptive input to the spinal cord. For example, we have shown that most chemosensitive abdominal visceral endings are C-fibers (21), that the responses of visceral afferent C-fibers to ischemia display characteristics of visceral nociceptors (29), and that throughout the ischemic period metabolites associated with nociception are produced (21, 34, 40). Our finding that NMDA and non-NMDA receptors play a role in the spinal transmission of the afferent arm of the abdominal ischemia reflex arc not only is consistent with other studies showing that glutamatergic receptors are important for the synaptic transmission of nociceptive input to the dorsal horn of the spinal cord (4, 27, 32) but also provides the first evidence that spinal NMDA and non-NMDA receptors mediate spinal sensory neurotransmission of impulse activity from visceral afferent fibers to the CNS during abdominal ischemia.

Perspective

Abdominal ischemia activates visceral afferents, which, in turn, reflexly stimulate the cardiovascular system. This pressor reflex requires spinal transmission employing the neurotransmitter glutamate, which involves NMDA and non-NMDA receptors.
Thus the neurotransmitter glutamate appears to contribute to the first synapse of the abdominal ischemia-induced pressor reflex arc. Spinal transmission of the afferent limb of the pressor reflex arc occurs at a low thoracic level. The presence of an abdominal reflex pressor response to ischemia may be beneficial, since an increase in perfusion pressure would help maintain flow through collateral mesenteric blood vessels after vascular occlusion. In this respect, inhibitors of the ionotropic glutamatergic receptors (i.e., ketamine) potentially could impair the full manifestation of this potentially beneficial reflex and, hence, could be deleterious. Thus knowledge about the neurotransmitters of and receptors on the spinal cord is clinically relevant.

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