Spinal cord GABA receptors modulate the exercise pressor reflex in decerebrate rats

Han-Jun Wang, Wei Wang, Kaushik P. Patel, George J. Rozanski, and Irving H. Zucker

Department of Cellular and Integrative Physiology, University of Nebraska Medical Center, Omaha, Nebraska

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Wang HJ, Wang W, Patel KP, Rozanski GJ, Zucker IH. Spinal cord GABA receptors modulate the exercise pressor reflex in decerebrate rats. Am J Physiol Regul Integr Comp Physiol 305: R42–R49, 2013.—Neurotransmitters and neuromodulators released by contraction-activated skeletal muscle afferents into the dorsal horn of the spinal cord initiate the central component of the exercise pressor reflex (EPR). Whether γ-aminobutyric acid (GABA), a major inhibitory neurotransmitter within the mammalian central nervous system, is involved in the modulation of the EPR at the level of dorsal horn remains to be determined. We performed local microinjection of either the GABA(A) antagonist bicuculline or the GABA(B) antagonist CGP 52432 into the ipsilateral L4/L5 dorsal horns to investigate the effect of GABA receptor blockade on the pressor response to either static contraction induced by stimulation of the peripheral end of L4/L5 ventral roots, passive stretch, or hindlimb arterial injection of capsaicin (0.1 μg/0.2 ml) in decerebrate rats. Microinjection of either bicuculline (1 mM, 100 nl) or CGP 52432 (10 mM, 100 nl) into the L4/5 dorsal horns significantly increased the pressor and cardiovascular responses to all stimuli. Microinjection of either bicuculline or CGP 52432 into the L5 dorsal horn significantly increased the pressor and cardiovascular responses to static microinjection of α-glutamate (10 mM, 100 nl) into this spinal segment. The disinhibitory effect of both GABA receptor antagonists on the EPR was abolished by microinjection of the broad-spectrum glutamate receptor antagonist kynurenate (10 mM/100 nl). These data suggest that 1) GABA exerts a tonic inhibition of the EPR at the level of dorsal horn; and 2) that an interaction between glutamatergic and GABAergic inputs exist at the level of dorsal horn, contributing to spinal control of the EPR.

Exercise; neurotransmitter; sympathetic nerve activity; blood pressure; decerebration

DURING EXERCISE the sympathetic nervous system is activated, which results in an increase in arterial pressure (AP), heart rate (HR), and peripheral vasoconstriction, especially in nonexercising tissues. Two theories have been postulated to explain the increase in cardiovascular function during exercise: central command and the exercise pressor reflex (EPR). Central command is a mechanism whereby neural motor and sympathetic activation occur in parallel, i.e., a volitional signal from the motor cortex or subcortical nuclei, responsible for recruiting motor units, activating cardiovascular control areas in the brainstem to modulate sympathetic, and parasympathetic activity during exercise. It has been suggested that this system is linked to skeletal muscle metabolic needs via parallel rostral brain activation of motor and autonomic centers. These autonomic adjustments elicit changes in HR and AP proportional to the intensity of exercise (7, 9). The EPR is a peripheral neural reflex originating in skeletal muscle that also contributes to the regulation of the cardiovascular system during physical activity. It relays information to the central nervous system with regard to metabolic demand and the mechanical activity of exercising muscles (24). Activation of this reflex is mediated by stimulation of group III (predominantly mechanically sensitive Aδ fibers) and IV (predominantly metabolically sensitive C fibers) afferents. The dorsal horn of the spinal cord serves as the first synapse for afferent fibers from skeletal muscle. Neurotransmitters and neuromodulators released by contraction-activated group III and IV muscle afferents into this region initiate the central component of the EPR.

Evidence suggests that transmission at the level of the dorsal horn is mainly mediated by excitatory amino acids (e.g., glutamate) (1, 11, 13, 14, 51). A series of studies by Wilson and colleagues (12–14) demonstrated that 1) static contraction increased glutamate release in the dorsal horn of anesthetized cats; and 2) microdialysis of both glutamatergic N-methyl-D-aspartate (NMDA) receptor and non-NMDA-sensitive receptor antagonists into the dorsal horn attenuated the pressor and tachycardiac responses to either static contraction or passive stretch (a pure mechanical stimulus) in anesthetized cats. In addition, a parallel study by Adreani et al. (1) demonstrated that intrathecal blockade of both NMDA and non-NMDA receptors attenuated the EPR in decerebrate cats. On the other hand, γ-aminobutyric acid (GABA) is widely accepted as a major inhibitory neurotransmitter within the mammalian central nervous system (CNS). Like glutamate, the highest concentration of GABA is in the dorsal grey (laminae I–III) (8, 22, 32, 40). A previous study by Wilson et al. (49) reported that dorsal horn administration of the GABA(A) agonist muscimol abolished the EPR in anesthetized cats, indicating that the exogenous activation of GABA(A) receptors in the dorsal horn can inhibit the EPR. However, whether GABAergic neurons in the dorsal horn exert tonic control of the EPR remains unclear. Therefore, the first goal of the current study was to determine the role of the endogenous spinal GABAergic system in modulating the EPR at the level of the dorsal horn. Furthermore, we determined the role of spinal GABAergic neurons in modulating the mechanoreflex and metaboreflex, respectively. Finally, we also investigated whether an interaction between spinal glutamatergic and GABAergic systems exists at the level of dorsal horn thereby contributing to the spinal control of the EPR. We hypothesize that 1) endogenous GABA in the dorsal horn exerts a tonic inhibition of the EPR via GABA(A) and/or GABA(B) receptors and 2) an interaction between glutamatergic and GABAergic inputs at the level of dorsal horn contributes to spinal control of the EPR.

METHODS

Experiments were performed on male Sprague-Dawley rats weighing 370 to 450 g. These experiments were approved by the Institutional Animal Care and Use Committee of the University of Nebraska Medical Center and were carried out under the guidelines of the...
National Institutes of Health Guide for the Care and Use of Laboratory Animals.

General Surgical Preparation

Rats were initially anesthetized with isoflurane (5% in O2; Halocarbon, River Edge, NY). A jugular vein and the trachea were cannulated. After tracheal cannulation, the lungs were ventilated with an anesthetic mixture of 2–3% isoflurane and O2. The right carotid artery was cannulated for measurement of AP, mean arterial pressure (MAP), and HR. Body temperature was maintained between 37°C and 38°C by a heating pad.

Decerebration

Previous studies (34) have shown that the EPR is compromised by anesthesia, which is especially a concern in rats. However, after decerebration, the effects of anesthesia on the EPR are largely abolished. Therefore, a decerebrate rat model was used in the present studies. The decerebration procedure was performed as described by us and others (34, 44, 45). Briefly, under isoflurane anesthesia, decerebration was performed precollicularly. A minimum recovery period of 1.25 h was employed postdecerebration before data collection began.

Activation of the EPR, Mechanoreflex, and Metaboreflex

To activate both mechanically and metabolically sensitive skeletal muscle afferent fibers, static hindlimb contraction was induced by electrical stimulation of the ventral roots. A laminectomy exposing the lower lumbar portions of the spinal cord (L2–L6) was performed and electrically induced static muscle contraction of the triceps surae was achieved by stimulating the peripheral end of L4/L5 ventral roots for 30 s. Constant-current stimulation was used at three times motor threshold (defined as the minimum current required to produce a muscle twitch) with a pulse duration of 0.1 ms at 40 Hz. All muscles of the hindlimb undergoing study were denervated except for the triceps surae muscle.

Previous studies had reported that passive stretch, a pure mechanical stimulus, was used to selectively activate mechanically sensitive intramuscular afferents (group III) in decerebrate rats (34, 36). Therefore, in animals in which ventral root stimulation was performed, preferential activation of the mechanoreflex was achieved by passively stretching the triceps surae muscles using a calibrated rack and pinion system (Harvard Apparatus). Care was taken to match the peak tension developed in response to electrical stimulation during the passive stretch experiments.

It has been reported that the capsaicin-sensitive receptor (transient receptor potential vanilloid 1, TRPV1) is localized primarily to metabolically sensitive afferent fibers (group IV) in skeletal muscle (33, 38). As a result, the exogenous chemical capsaicin can be used to preferentially activate these fibers. In the current study, we used hindlimb arterial bolus injections of capsaicin (0.1 μg/0.2 ml) to predominately activate group IV afferent neurons associated with the muscle metaboreflex (21). Briefly, a catheter was placed in the right iliac artery with its tip advanced to the abdominal aortic bifurcation, ensuring that capsaicin was delivered to the left hindlimb through the left iliac artery. To limit drug delivery to the left hindlimb, the common iliac vein was reversibly ligated by a vascular occluder (Harvard). On injection of drug, the vein was occluded for 2 min to trap the injectate in the leg.

Microinjection Into L4/L5 Dorsal Horn

An additional laminectomy (T11–L2) was performed to expose the dorsal horn of the spinal segment in which the L4/L5 dorsal roots enter for the microinjection experiments. Dorsal horn microinjections were made from a four-barrel micropipette and performed by a four-channel pressure injector (PM2000B, World Precision Instruments). The procedure for microinjection in the dorsal horn of the spinal cord was similar to that performed in brain nuclei such as the rostral ventrolateral medulla (RVLM), as described by our previous studies (47). Briefly, a four-barrel micropipette (20 to 30 μm diameter) was placed in the dorsal horn of the spinal segment in which the L4/L5 dorsal roots enter. The coordinates of the dorsal horn in this study ranged from 0.5–0.8 mm lateral to the midline of spinal cord and 0.3–0.5 mm from the dorsal surface of spinal cord. The dorsal horn was also functionally identified by a pressor response to injection of l-glutamate (1 nmol, Sigma-Aldrich, St. Louis, MO). Injections were made over a 15-s period, and a 100-nl injection volume was measured by observing the movement of the fluid meniscus along a reticule in the microscope.

The GABA_A antagonist l-bicuculline methiodide (Bic, 0.1 and 1 mM, Sigma-Aldrich), the GABA_B antagonist CGP 53432 (CGP, 1 and 10 mM, Fisher Scientific, Pittsburgh, PA), l-glutamate (10 mM, Sigma-Aldrich), and kynurenate (Kyn, 10 mM, Sigma-Aldrich) were dissolved in artificial cerebrospinal fluid. In the case of Kyn, pH was adjusted to 7.4–7.6 with 1 M NaOH. The time interval between L4 and L5 segment injections was within 2 min. One barrel of a multibarrel pipette was filled with 2% Pontamine sky blue to mark the injection site (Fig. 1). The dose-dependent effects of the GABA_A antagonist Bic and the GABA_B antagonist CGP on the EPR were first determined at the onset of the study and then the effective doses of Bic (1 mM/100 nl) and CGP (10 mM/100 nl) were used to investigate the

![Fig. 1. A histological example showing a microinjection site in the superficial L5 dorsal horn of rats: A: a schematic figure showing the microinjection site (black dot). B: an original digital picture for the microinjection site filled with 2% Pontamine sky blue. Red arrows in B point to the injection site. Scale bar represents 200 μm.](http://ajpregu.physiology.org/)
interaction between spinal glutamatergic and GABAergic systems that modulate the EPR at the level of the dorsal horn. The dose of the glutamatergic antagonist Kyn (10 mM/100 nl) was determined in a preliminary study showing effective blockade of the EPR at the level of dorsal horn.

**Experimental Protocols**

**Protocol 1.** This protocol was designed to determine whether GABAergic neurons in the dorsal horn exert tonic control of the EPR. The pressor and cardioaccelerator responses to a 30-s static contraction induced by electrical stimulation of L4/L5 ventral roots were measured before and 5 min after microinjection of either the GABAA antagonist Bic or the GABAB antagonist CGP into the ipsilateral L4/L5 dorsal horns. The dose-dependent effect of both GABA antagonists on the EPR was also determined in this protocol.

**Protocol 2.** This protocol investigated the effects of both GABAA and GABAB antagonists on the mechanoreflex and metaboreflex, respectively. The pressor and cardioaccelerator responses to either passive stretch or hindlimb injection of capsaicin were compared before and 5 min after microinjection of both GABA antagonists into the ipsilateral L4/L5 dorsal horns.

**Protocol 3.** This protocol determined whether an interaction between spinal glutamatergic and GABAergic inputs at the level of dorsal horn contributes to the spinal control of the EPR. Compared with microinjection of either the GABAA antagonist Bic or the GABAB antagonist CGP alone in protocol 1 experiments, we added an additional group in which microinjection of either of the GABA antagonists in combination with Kyn was performed to investigate whether this treatment attenuated the disinhibition of the EPR by microinjection of GABA antagonists alone. In addition, the cardiovascular response to direct microinjection of l-glutamate (10 mM, 100 nl) into the dorsal horn was measured before and 5 min after microinjection of GABA antagonists into the ipsilateral L4 or L5 dorsal horns in decerebrate rats.

**Data Acquisition and Statistical Analysis**

MAP, HR, and muscle tension were acquired using PowerLab software (AD Instruments). Baseline values were determined by analyzing at least 30 s of data before muscle contraction, stretch, or capsaicin injection. The peak response was determined in the period of the greatest change (1 s average) from baseline. The tension-time index (TTI, expressed in kg × s) was calculated by integrating the area between the tension trace and the baseline level. Peak developed tension was calculated by subtracting the resting tension from the peak tension and is expressed in grams. All values are expressed as means ± SE. Differences between groups were determined by a two-way ANOVA followed by a Tukey post hoc test. Changes in MAP, HR, TTI, and peak developed tension before and after spinal administration of chemicals were determined by paired t-test. \( P < 0.05 \) was considered statistically significant.

**RESULTS**

**Effect of Microinjection of GABA Receptor Antagonists Into the Spinal Cord**

After decerebration, baseline MAP and HR were maintained at physiological levels in all animals (Table 1). Microinjection of the GABAA antagonist Bic (1 mM) into the L4/L5 dorsal horn caused a small transient increase in baseline blood pressure (−6–10 mmHg), which quickly returned to baseline levels within 1 min. As shown in Figs. 2 and 3, microinjection of either Bic or CGP into the ipsilateral L4/L5 dorsal horn dose dependently enhanced the pressor response to static contraction induced by electrical stimulation of L4/L5 ventral roots, indicating that both GABAA and GABAB receptors in the dorsal horn of the spinal cord are involved in the tonic inhibition of the EPR in the normal state.

**Effect of Microinjection of GABA Receptor Antagonists Into the Spinal Cord on the Mechanoreflex and Metaboreflex**

To investigate the effects of both GABAA and GABAB antagonists on the mechanoreflex and metaboreflex, the pressor and cardioaccelerator responses to either passive stretch (a purely mechanical stimulus) or hindlimb injection of capsaicin were compared before and after microinjection of both GABA antagonists into the ipsilateral L4/L5 dorsal horns. As shown in Fig. 4, microinjection of either Bic (1 mM/100 nl) or CGP (10 mM/100 nl) into the ipsilateral L4/L5 dorsal horn significantly enhanced the pressor and cardioaccelerator responses to passive stretch or hindlimb arterial injection of capsaicin (0.1 μg/0.2 ml), indicating that GABA receptors play an inhibitory role in the modulation of both the mechanoreflex and the metaboreflex.

### Table 1. Basal mean arterial pressure and heart rate before and 5 min after microinjection of drugs into the L4/L5 dorsal horn in decerebrated rats

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<tr>
<th></th>
<th>MAP, mmHg</th>
<th>HR, beats/min</th>
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<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Vehicle (n = 7)</td>
<td>108.2 ± 3.4</td>
<td>108.1 ± 3.5</td>
</tr>
<tr>
<td>Bic</td>
<td>91.6 ± 4.4</td>
<td>91.9 ± 4.4</td>
</tr>
<tr>
<td>0.1 mM (n = 5)</td>
<td>100.2 ± 2.4</td>
<td>102.1 ± 2.4</td>
</tr>
<tr>
<td>1 mM (n = 14)</td>
<td>111.7 ± 3.7</td>
<td>110.2 ± 3.6</td>
</tr>
<tr>
<td>CGP</td>
<td>97.1 ± 4.1</td>
<td>97.2 ± 4.1</td>
</tr>
<tr>
<td>Kyn</td>
<td>99.1 ± 6.1</td>
<td>99.1 ± 6.1</td>
</tr>
<tr>
<td>10 mM (n = 7)</td>
<td>89.6 ± 6.4</td>
<td>90.1 ± 6.4</td>
</tr>
<tr>
<td>Kyn + Bic (n = 7)</td>
<td>104.7 ± 4.4</td>
<td>103.0 ± 4.4</td>
</tr>
<tr>
<td>Kyn + CGP (n = 7)</td>
<td>104.7 ± 4.4</td>
<td>103.0 ± 4.4</td>
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</table>

Values are means ±; n = number of rats. MAP, mean arterial pressure; HR, heart rate. Kyn, kynurenate. In both bicuculline (Bic; 1 mM) and CGP 52432 (CGP; 10 mM) groups, 7 rats were used to perform static contraction whereas the other 7 rats were used to perform passive stretch and administration of capsaicin.
Effect of Microinjection of GABA Receptor Antagonists on the Glutamatergic Input of the EPR at the Level of the Dorsal Horn

To determine whether an interaction between spinal glutamatergic and GABAergic inputs at the level of dorsal horn contributes to the spinal control of the EPR, we compared cardiovascular responses to direct microinjection of L-glutamate (10 mM, 100 nl) into the dorsal horn before and after microinjection of GABA_A and GABA_B antagonists into the ipsilateral L5 dorsal horns in decerebrated rats. As shown in Fig. 5, direct microinjection of L-glutamate (10 mM, 100 nl) into the L5 dorsal horn caused significant pressor and cardioaccelerator responses, which were exaggerated by pretreatment with either Bic or CGP.

Furthermore, microinjection of either GABA antagonist in combination with Kyn was performed to investigate whether this treatment could attenuate the disinhibition of the EPR by microinjection of GABA antagonists into spinal cord alone. As shown in Fig. 6, microinjection of Kyn alone into the L4/L5 dorsal horn attenuated the EPR, whereas microinjection of either GABA receptor antagonist alone enhanced the EPR. After microinjection of either GABA antagonist with Kyn, the disinhibition of the EPR by microinjection of GABA antagonists was completely abolished.

Muscle Tension Produced by Static Contraction or Passive Stretch

In the present study, muscle peak developed tension induced by static contraction or passive stretch ranged from 620 to 850 g in all groups. There was no significant difference in TTI during either static contraction or passive stretch between groups (Table 2).

DISCUSSION

A previous study by Wilson et al. (49) reported that dorsal horn administration of the GABA_A agonist muscimol abolished the EPR in anesthetized cats, indicating that the exogenous activation of GABA_A receptors in the dorsal horn can inhibit the EPR. Compared with the previous study by Wilson et al. (49), the present study provides four innovative findings that significantly advances our current knowledge concerning the spinal control of the EPR. First, we show that GABA is an endogenous transmitter at the level of the dorsal horn that tonically modulates the expression of the EPR in an unanesthetized decerebrate preparation. Second, compared with the study of Wilson et al. (49), the current study demonstrated that both the mechanoreflex and metaboreflex are tonically controlled by endogenous spinal GABA activity. Third, the current study demonstrated that both GABA_A and GABA_B receptors...
There is abundant evidence to indicate that a synapse in the dorsal horn is involved in mediating the EPR (11, 48, 51). Several neurotransmitters or neuromodulators have been reported to be involved in the modulation of the EPR at the level of the dorsal horn. Administration of antagonists to excitatory amino acid (EAA) receptors into this region attenuates the pressor reflex (11, 13, 51). Consistent with these studies are the data from Hand et al. (11) showing that static muscle contraction increases the release of the EAA glutamate and aspartate into the dorsal horn of cats. In addition, it has been demonstrated that blockade of neurokinin-1 receptors in the dorsal horn reduces the EPR (52). Substance P is the endogenous ligand for neurokinin-1 receptors, and previous work has demonstrated that static contraction causes the release of this neuropeptide in the dorsal horn (50). In addition to EAA and substance P, several inhibitory neuromodulators and their respective receptors have also been reported to modulate the EPR at the level of the dorsal horn. These include acetylcholine, α2-adrenergic receptors, opiates, vasopressin, and oxytocin (2, 16–18, 25, 28, 39). Nevertheless, the role of GABA, a major inhibitory neurotransmitter in the CNS, in modulating the EPR in the spinal cord remains to be determined. A previous study reported that dorsal horn administration of the GABAA agonist muscimol abolished the EPR in anesthetized cats (49), indicating that exogenous activation of GABAA receptors in the dorsal horn can inhibit the EPR in the normal state. However, whether endogenous spinal GABAergic activity in the dorsal horn exerts a tonic control of the EPR has never been investigated. This hypothesis has been confirmed by our current data demonstrating that microinjection of GABA receptor antagonists into the dorsal horn enhanced the EPR in decerebrate rats.

GABA acts on two receptor subtypes in the rat spinal dorsal horn: the ligand-gated Cl− channel GABAA receptor and the GTP-binding protein-coupled GABAB receptor (22). In the...
Table 2. Tension-time indexes for static contraction before and 5 min after microinjection of drugs into the L4/L5 dorsal horn in decerebrated rats

<table>
<thead>
<tr>
<th>Static Contraction (Kg/XS)</th>
<th>Passive Stretch (Kg/XS)</th>
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<tbody>
<tr>
<td><strong>Before</strong></td>
<td><strong>After</strong></td>
</tr>
<tr>
<td>Vehicle</td>
<td>14.4 ± 1.9</td>
</tr>
<tr>
<td>Bic (0.1 mM)</td>
<td>15.2 ± 2.1</td>
</tr>
<tr>
<td>Bic (1 mM)</td>
<td>15.6 ± 1.8</td>
</tr>
<tr>
<td>CGP (1 mM)</td>
<td>16.0 ± 3.0</td>
</tr>
<tr>
<td>CGP (10 mM)</td>
<td>15.8 ± 1.7</td>
</tr>
<tr>
<td>Kyn (10 mM)</td>
<td>15.5 ± 2.0</td>
</tr>
<tr>
<td>Kyn + Bic</td>
<td>16.3 ± 2.3</td>
</tr>
<tr>
<td>Kyn + CGP</td>
<td>14.8 ± 1.7</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = number of rats.
known to mediate metaboreflex function. Injection of capsaicin itself likely does not mimic the normal activation of these afferent fibers during exercise; especially considering capsaicin is not endogenously produced. Finally, we also acknowledged that capsaicin may activate pain fibers as well as those activated during exercise.

An interaction between GABAergic and glutamatergic neurons is widely observed in the CNS. For example, microinjection of glutamatergic antagonists into RVLM does not alter baseline cardiovascular parameters and sympathetic outflow in normal animals, whereas the same treatment decreases blood pressure, HR, and sympathetic activity after removing the GABAergic activity by administration of GABA receptor antagonists into this region (19, 27), indicating that glutamatergic activity in RVLM neurons is suppressed by the tonic GABA tone. In the spinal cord, the studies by Wilson and colleagues (11, 13, 14) have demonstrated the glutamatergic contribution to the genesis of the EPR at the level of dorsal horn. Our current data also suggest the spinal GABAergic control of the EPR at the level of dorsal horn. Based on the findings above, we further determined whether interaction between the spinal GABAergic and glutamatergic systems also exists in the dorsal horn and contributes to the genesis of the EPR. We provided two lines of evidence to support this hypothesis. First, the cardiovascular response to direct microinjection of glutamate into the dorsal horn was exaggerated by spinal pretreatment with the GABA antagonists. Second, we found that the net increment of the EPR by spinal microinjection of GABA antagonists alone can be abolished by simultaneous treatment with glutamatergic antagonists. These findings suggest that glutamatergic activity in dorsal horn neurons is tonically suppressed by GABAergic activity, which limits the amplitude of the EPR-induced cardiovascular response. In certain pathological states such as hypertension and chronic heart failure in which the EPR is exaggerated (26, 35–37, 43, 46), a potential loss of GABAergic tone in the spinal cord will cause enhanced glutamatergic activity in spinal neurons via presynaptic or postsynaptic mechanisms, which will likely contribute to the genesis of the exaggerated EPR in these diseases.

In conclusion, the current study first demonstrated that endogenous spinal GABA activity leads to a tonic inhibition of the EPR at the level of the dorsal horn under physiological conditions. Furthermore, our data suggest that both GABA\(_A\) and GABA\(_B\) receptors contribute to the tonic spinal GABA activity that modulates the EPR evoked by either mechanical or metabolic stimuli. Finally, our data also suggest an interaction between spinal glutamatergic and GABAergic inputs involved in the modulation of the EPR at the level of dorsal horn.

**Perspectives and Significance**

The current study identified GABA as an endogenous transmitter at the level of the dorsal horn that tonically modulates the expression of the EPR under physiological conditions. Based on our findings, administration of GABA agonists or antagonists into the spinal cord may be a useful strategy to manipulate the EPR in both experimental and clinical studies. For example, in chronic heart failure patients, an exaggerated EPR-induced sympathetic activation can potentially increase cardiovascular risk and contribute to exercise intolerance even during minor physical activity (10, 29, 35, 46). In these patients, administration of GABA agonists into the spinal cord may be a potential therapeutic strategy for preventing or slowing the progression of the exaggerated EPR. Clearly, further work is needed to translate these findings in applicable therapies.

**ACKNOWLEDGMENTS**

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**GRANTS**

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**


**REFERENCES**


