Increased group I metabotropic glutamate receptor activity in paraventricular nucleus supports elevated sympathetic vasomotor tone in hypertension

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Li DP, Pan HL. Increased group I metabotropic glutamate receptor activity in paraventricular nucleus supports elevated sympathetic vasomotor tone in hypertension. Am J Physiol Regul Integr Comp Physiol 299: R552–R561, 2010. First published June 2, 2010; doi:10.1152/ajpregu.00195.2010.—The sympathetic nerve activity is elevated in cardiovascular diseases such as hypertension. Enhanced glutamatergic inputs in the paraventricular nucleus (PVN) of the hypothalamus contribute to heightened sympathetic outflow in spontaneously hypertensive rats (SHR). We determined the role of group I metabotropic glutamate receptors (mGluR) in the PVN in the control of sympathetic vasomotor tone in hypertension. Lumbar sympathetic nerve activity (LSNA), arterial blood pressure (ABP), and heart rate (HR) were recorded in anesthetized SHR and Wistar-Kyoto (WKY) rats. Bilateral microinjection of 2-methyl-6-(phenylethynyl)pyridine hydrochloride (MPEP), a selective mGluR5 receptor antagonist, or (S)-(−)-α-amino-4-carboxy-2-methylbenzeneacetic acid (LY367385), a selective mGluR1 receptor antagonist, into the PVN had no significant effect on LSNA and ABP in WKY rats. Strikingly, MPEP and LY367385 dose dependently decreased LSNA, ABP, and HR in SHR. The MPEP-induced decreases in LSNA and ABP were significantly greater than those inhibited by LY367385 in SHR. Furthermore, bilateral microinjection of (S)-3,5-dihydroxyphenylglycine (S-DHPG), a selective group I mGluR agonist, into the PVN caused a similar dose-dependent increase in LSNA, ABP, and HR in both groups. S-DHPG-induced responses were attenuated by MPEP or LY367385 alone and were abolished by a combination of MPEP and LY367385 in WKY rats and SHR. In addition, microinjection of the NMDA receptor antagonist attenuated the sympatoexcitatory responses induced by S-DHPG in both WKY rats and SHR. Collectively, this study provides important new evidence that the resting sympathetic vasomotor tone is maintained by tonic activation of group I mGluRs in the PVN in hypertension. Activation of NMDA receptors are involved in the sympatoexcitatory effect of group I mGluRs in the PVN.

We have shown that increased glutamatergic inputs to PVN presynaptic neurons contribute to the elevated sympathetic vasomotor tone in spontaneously hypertensive rats (SHR) (16, 19). For example, blocking ionotropic glutamate receptors in the PVN decreases the excitability of PVN presynaptic neurons and sympathetic outflow in SHR but not in normotensive Wistar-Kyoto (WKY) rats (16, 19). In addition to the fast-acting ionotropic receptors, glutamate also acts on G protein-coupled metabotropic glutamate receptors (mGluRs). Eight mGluR subtypes have been cloned and are classified into three groups based on their sequence homology and signal transduction pathways (8). Group I mGluRs (mGluR1 and -5) are coupled to Gq/11 proteins to activate PLC, mobilize intracellular Ca2+, and subsequently modulate various ion channels and increases cell excitability and neurotransmitter release (8, 15, 24, 25, 28). Group II (mGluR2 and -3) and III mGluRs (mGluR4, -6, -7, and -8) mGluRs are predominantly located on presynaptic terminals to decrease neurotransmitter release through Gi/o protein signaling (6, 8, 28). On the other hand, activation of group I mGluRs increases neuronal excitability through their coupling to Gq/11 proteins and PLC (21). Both mGluR1 and mGluR5 are selectively expressed in several brain regions, including the PVN (22, 34). Because group I mGluRs are often activated under the conditions in which synaptic glutamate release is increased (8, 13, 28), we reasoned that group I mGluRs in the PVN could be activated by endogenous glutamate and be involved in increased glutamatergic input in the PVN in hypertension. However, the functional significance of group I mGluRs in the PVN in the control of sympathetic vasomotor tone in hypertension has not been investigated previously.

In the present study, we determined the function of mGluR1 and mGluR5 in the PVN in the maintenance of sympathetic vasomotor tone using SHR as an animal model of essential hypertension. Because NMDA receptors may mediate the excitatory effect of group I mGluRs in the central nervous system (3, 5, 13), we also determined the role of NMDA receptors in the excitatory effect of group I mGluRs in the PVN in the control of sympathetic outflow in SHR. Our study provides novel information that increased group I mGluR activity in the PVN is critically involved in the support of the elevated sympathetic outflow in hypertension. NMDA receptors contribute to the excitatory effect of group I mGluRs in the PVN.

MATERIALS AND METHODS

Animals. Experiments were carried out on age-matched (12- to 14-wk-old, 300–380 g) male WKY rats and SHR (Taconic, Germantown, NY). The procedures and protocols were approved by the Animal Care and Use Committee of The University of Texas M. D. Anderson Cancer Center and conformed to the National Institutes of
Health “Guide for the Care and Use of Laboratory Animals.” We measured blood pressure in all the WKY rats and SHR using a noninvasive tail-cuff system (model 29-SSP; IITC Life Science, Woodland Hills, CA). Blood pressure was measured every day for at least 1 wk before the final experiment. In the SHR, blood pressure started to increase at the age of 8 wk and reached a stable hypertensive level at 13 wk of age (16, 18).

Lumbar sympathetic nerve activity and ABP recording. Rats were initially anesthetized using 2% isoflurane in O2, and a mixture of α-chloralose (60–75 mg/kg) and urethane (800 mg/kg) was intraperitoneally injected; then the isoflurane was discontinued. The depth of anesthesia was confirmed for adequacy before surgery by the absence of both corneal reflexes and paw withdrawal response to a noxious pinch. The trachea was cannulated for mechanical ventilation using a rodent ventilator (CWE, Airdmore, PA) with 100% O2. Expired CO2 concentration was monitored with a CO2 analyzer (Capstar 100; CWE) and maintained at 4–5% by adjusting the ventilation rate (~60 breaths/min) or tidal volume (~2.5 ml) throughout the experiment. ABP was monitored by a pressure transducer (model PT30; Grass Instruments, Quincy, MA) through a catheter placed into the left femoral artery. Heart rate (HR) was counted by triggering from the pulsatile blood pressure. The right femoral vein was cannulated for intravenous administration of drugs. Supplemental doses of α-chloralose and urethane were administered as necessary to maintain an adequate depth of anesthesia.

A small branch of the left lumbar postganglionic sympathetic nerve was isolated under an operating microscope through a retroperitoneal incision. The lumbar sympathetic nerve was cut distally to ensure that afferent activity was not recorded (16). The nerve was then immersed in mineral oil and placed on a stainless steel recording electrode. The nerve signal was amplified (gain of 20,000–30,000) and band-pass filtered (100–3,000 Hz) by an alternating current amplifier (model P511; Grass Instruments), and the LSNA was monitored through an audio amplifier (Grass Instruments). The LSNA and ABP were recorded using an 1401-PLUS analog-to-digital converter and Spike2 system (Cambridge Electronic Design, Cambridge, UK). Background electrical noise was determined by a complete suppression of LSNA with administration of phentolamine (20 μg/kg iv) before euthanasia and 5 min after the rats were euthanized by an overdose of pentobarbital sodium (200 mg/kg iv) at the end of each experiment. Respective electrical noise levels measured with these two methods were similar and were subtracted from the integrated values of LSNA, and the percent change in LSNA from the baseline was calculated.

PVN microinjections. For PVN microinjections, rats were placed in a stereotactic frame (Kopf Instruments, Tujunga, CA). The dorsal surface of the skull was exposed, and a small hole was drilled to expose the brain. A glass microinjection pipette (tip diameter 20–30 μm) was advanced into the PVN. The stereotactic coordinates used were as follows: 1.6–2.0 mm caudal to the bregma, 0.5 mm lateral to the midline, and 7.0–7.5 mm ventral to the dura (16, 18, 35). We identified the pressor region of the PVN as described previously (16, 35). Briefly, the injection sites of the PVN were first verified by the depressor responses to microinjection of 5.0 nmol GABA (20 nl, 250 mM). The microinjection of drugs was done by using a calibrated microinjection system (Nanoject II; Drummond Scientific, Broomall, PA) and monitored using an operating microscope. GABA microinjections were separated by a 10- to 15-min interval to allow recovery of the depressor response. The PVN vasomotor site was considered to have been located when GABA injection decreased mean ABP by at least 10 mmHg, and the stereotactic coordinates at which the prior GABA microinjection elicited the greatest depressor responses were used in the same rat for the subsequent microinjection of drugs. In total, up to six microinjections of GABA in the PVN were performed in each rat. After microinjection of the drugs, the glass pipette was left in place for 1 to 2 min to ensure adequate delivery of the drug to the injection site. The pipette was then withdrawn and immediately placed at the respective stereotactic coordinates for injection into the contralateral PVN (16, 35).

(S)-3,5-dihydroxyphenylglycine (S-DHPG), (S)-(−)-α-amino-4-carboxy-2-methylbenzeneacetic acid (LY367385), 2-methyl-6-(phenethyl)pyridine hydrochloride (MPEP), and 2-amino-5-phosphonopentanoic acid (AP5) were obtained from Ascent Scientific (Princeton, NJ). DHPG and AP5 were dissolved in saline (pH adjusted to 7.25). MPEP and LY367385 were dissolved in DMSO (final concentration of 0.05% vol/vol) and diluted to final concentrations by saline. We used variable concentrations of antagonists with the same volume (50 nl) to determine the dose-response effect starting from the lowest concentration in an ascending manner. We performed microinjection of multiple concentrations of a single agent in the dose-dependent experiments. Following injection of one concentration of the drug, the pipette was withdrawn and loaded with a different concentration of the drug solution. The pipette was then repositioned in the PVN using the identical stereotactic coordinates. Microinjection of the next dose of DHPG, MPEP, LY367385, and AP5 was performed 40–45 min after the previous injection and when the LSNA, ABP, and HR returned to the baseline level. The following concentrations of the drugs were used: 10–100 nmol DHPG, 1–10 nmol MPEP, 10–100 nmol LY367385, and 0.16–1.4 nmol AP5. The microinjection doses for S-DHPG (11, 29), MPEP (20, 26, 33), LY367385 (10, 11), and AP5 (7, 16) were selected from previous studies and determined in our preliminary experiments.

The location of the pipette tip and diffusion of the injectate in the PVN were examined and confirmed histologically in all rats. The drug solutions contained 5% rhodamine-labeled fluorescent microspheres (0.04 μm; Molecular Probes, Eugene, OR) to allow us to estimate drug dispersion throughout the PVN and its surrounding area (16). At the completion of the experiment, the rat brain was removed rapidly and fixed in 10% buffered formalin solution overnight. Frozen coronal sections (40-μm thick) were cut on a freezing microtome and mounted on slides. Rhodamine-labeled fluorescent regions were identified using an epifluorescence microscope and plotted on standardized sections from the Paxinos and Watson atlas (27). Rats were not included for data analysis if they had one misplaced microinjection outside the PVN.

Data analysis. Values are presented as means ± SE. The mean ABP was derived from the pulsatile arterial blood pressure and calculated as the diastolic pressure plus one-third of the pulse pressure. Sympathetic nerve signals were rectified and integrated off-line. The background noise was subtracted using the level obtained after the rats were euthanized with an overdose of pentobarbital sodium. Control values were obtained by averaging the signal over a 60-s period immediately before each injection. Response values following each intervention were averaged over 30 s when the maximal responses occurred. To compare the responses of the ABP, LSNA, and HR to the agonist and antagonist microinjected within the group, a repeated-measures ANOVA with Dunnett’s post hoc test was performed. A two-way ANOVA with Bonferroni’s post hoc test was used to compare responses between WKY rats and SHR groups. P < 0.05 was considered statistically significant.

RESULTS

This study was carried out using a total of 86 rats, including 42 WKY rats and 44 SHR. The mean ABP in conscious rats measured by the noninvasive tail-cuff technique was 153.5 ± 15.5 mmHg for SHR, which was significantly higher than that in WKY rats (95.2 ± 11.4 mmHg, P < 0.05). After completion of all surgical procedures and establishment of stable anesthesia, the SHR displayed a significantly higher mean ABP (135.6 ± 5.8 mmHg) than the WKY rats did (85.1 ± 4.4 mmHg). Also, the HR was significantly higher in SHR (359.4 ± 7.9 beats/min) than that in WKY rats (310.2 ± 8.6 beats/min).
In all rats included in the data analysis, the area of the fluorescent microsphere spread was 0.20–0.40 mm around the injection site. The spread of the dye did not penetrate to the third ventricular ependymal lining and was not consistently observed in a nucleus outside of the PVN. The distribution of microinjection sites within the PVN was not different between WKY rats and SHR (Fig. 1). Micropipette misplacement occurred in five WKY rats and six SHR. These data from these rats were not included in the data analysis.

**Effects of microinjection of S-DHPG into the PVN on ABP, LSNA, and HR in WKY rats and SHR.** We first determined the effects of activation of group I mGluRs in the PVN on sympathetic vasomotor tone in WKY rats and SHR. Bilateral microinjection of the group I mGluR agonist S-DHPG (11, 29) (5.0–50.0 nmol/50 nl) into the PVN significantly increased ABP, LSNA, and HR in a dose-dependent manner in WKY rats \((n = 6)\). The onset latency of ABP, LSNA, and HR in response to S-DHPG injection was 0.6 ± 0.2 min, and the peak response appeared 5.2 ± 0.6 min after S-DHPG microinjection. The increases in the ABP and LSNA elicited by S-DHPG microinjections were slightly enhanced in SHR \((n = 7)\). The ABP and LSNA returned to the baseline levels 20–25 min after S-DHPG injection. The mean recovery time for ABP, LSNA, and HR was not significantly different between WKY rats and SHR. Repeated injection of S-DHPG produced a reproducible effect on LSNA, ABP, and HR (data not shown).

To determine the effect of activation of mGluR5 or mGluR1 on the sympathetic vasomotor tone, S-DHPG was injected into the PVN in combination with MPEP or LY367385. This approach was used because there is no highly selective agonists for mGluR1 or mGluR5. Microinjection of S-DHPG (25.0 nmol/50 nl) significantly increased ABP, LSNA, and HR in WKY rats. The increase in the magnitude of ABP, RSNA, and HR was not significantly different between WKY rats and SHR. Coinjection of LY367385 (25.0 nmol) and S-DHPG still significantly increased ABP, LSNA, and HR in eight WKY rats. However, the increase in ABP, LSNA, and HR was smaller than the increase induced by S-DHPG alone. Furthermore, coinjection of MPEP (5.0 nmol) and S-DHPG (25.0 nmol) only slightly increased ABP, LSNA, and HR in these WKY rats (Fig. 4).

In seven SHR, microinjection of both LY367385 (25.0 nmol) and S-DHPG (25.0 nmol) slightly increased ABP, LSNA, and HR. Interestingly, coinjection of MPEP (5.0 nmol) and S-DHPG (25.0 nmol) only slightly increased ABP, LSNA, and HR in these WKY rats (Fig. 4).

**Effects of microinjection of MPEP into the PVN on LSNA and ABP in WKY rats and SHR.** To determine the role of mGluR5 in the PVN in the control of sympathetic vasomotor tone, we examined the effect of microinjection of MPEP, a highly selective antagonist for mGluR5 (20, 26, 33), into the PVN on ABP, LSNA, and HR in WKY rats and SHR. Bilateral microinjection of MPEP (1.0–10.0 nmol/50 nl) into the PVN...
had no significant effect on the ABP, LSNA, and HR in WKY rats \((n = 7)\). However, bilateral microinjection of MPEP decreased the ABP, LSNA, and HR in seven SHR in a dose-dependent manner (Figs. 5 and 6). The latency of the response of the ABP, LSNA, and HR to MPEP injection was \(0.45 \pm 0.1\) min. The maximal reductions in the ABP, LSNA, and HR in response to the highest dose of MPEP microinjection were \(30.7 \pm 2.7\) mmHg, \(24.2 \pm 4.3\)%, and \(40.7 \pm 7.6\) beats/min, respectively. The peak responses of the ABP, LSNA, and HR occurred at \(3.3\) min after MPEP microinjection in SHR. All variables gradually returned to the control levels. The recovery times for the ABP, LSNA, and HR were similar (\(21.7 \pm 4.0\) min for the ABP, \(22.8 \pm 2.1\) min for the LSNA, and \(22.0 \pm 2.7\) min for the HR).

**Fig. 2.** Effect of microinjection of group I metabotropic glutamate receptors (mGluRs) agonist \((S)-3,5\)-dihydroxyphenylglycine \((S\text{-DHPG})\) into the PVN on ABP, integrated lumbar sympathetic nerve activity \(\text{(Int-LSNA)}\), and heart rate \(\text{(HR)}\) in WKY rats and SHR. Original tracings showing responses of the LSNA, ABP, and HR to bilateral microinjection of different doses of \(S\text{-DHPG}\) \((5.0–50.0\ \text{nmol/50 nl})\) into the PVN in 1 WKY rat and 1 SHR.

**Fig. 3.** Effect of activation of group I mGluRs in the PVN on the LSNA, ABP \(\text{[mean blood pressure \text{(MBP)}]}\), and HR in WKY rats and SHR. \(A–C\): summary data showing responses of the ABP, LSNA, and HR during the control \((C)\), microinjection of different doses of \(S\text{-DHPG}\) \((5.0–50.0\ \text{nmol/50 nmol})\) into the PVN, and recovery period \((R)\) in WKY rats and SHR. \(A1–C1\): summary data showing the relative changes in the LSNA, ABP, and HR after microinjection of \(S\text{-DHPG}\) into the PVN in WKY rats and SHR. *\(P < 0.05\) compared with vehicle \((V)\) injection \(\text{(repeated-measures ANOVA with Dunnett’s post hoc test)}\); #\(P < 0.05\) compared with values in WKY rats with the same dose of \(S\text{-DHPG}\) \(\text{(2-way ANOVA with Bonferroni post hoc test)}\).
Effects of microinjection of LY367385 into the PVN on LSNA and ABP in WKY rats and SHR. We next determined the mGluR1 function in the PVN in the regulation of the ABP, LSNA, and HR in WKY rats and SHR. Bilateral microinjection of the selective mGluR1 receptor antagonist LY367385 (10, 11) (5.0–50.0 nmol/50 nl) into the PVN in WKY rats and SHR had no significant effect on the ABP, LSNA, and HR (n = 6). In contrast, bilateral microinjection of LY367385 (5.0–50.0 nmol/50 nl) into the PVN in WKY rats and SHR had no significant effect on the ABP, LSNA, and HR (n = 6).
nmol/50 nl) dose-dependently reduced the ABP, LSNA, and HR in SHR (Fig. 7, A and B). The latency of the response of the ABP, LSNA, and HR to LY367385 injection was 0.39 ± 0.2 min. The peak responses of the ABP, LSNA, and HR occurred about 3.6 min after LY367385 injection. The recovery times for the ABP, LSNA, and HR were 18.6 ± 1.6 min, 20.5 ± 1.6 min, and 18.4 ± 2.6 min, respectively.

**Comparison of the inhibitory effects of MPEP and LY367385 in the PVN in WKY rats and SHR.** To assess the relative importance of mGluR1 and mGluR5 subtypes in the
PVN in the control of ABP, LSNA, and HR in SHR, we microinjected a single effective dose of MPEP or LY367385 alone and in combination in separate WKY rats and SHR. The order of MPEP and LY367386 microinjection was randomized. Bilateral microinjection of 5.0 nmol MPEP alone or in combination with 25.0 nmol LY367385 did not significantly change ABP, LSNA, and HR in WKY rats. Microinjection of MPEP (5.0 nmol/50 nl) alone into the PVN decreased ABP, LSNA, and HR in SHR (n = 8). In response to microinjection of LY367385 (25.0 nmol) alone, the reduction of ABP, LSNA, and HR were considerably less than those injected with MPEP in these rats (Fig. 7C). Microinjection of a combination of 5.0 nmol MPEP and 25.0 nmol LY367385 caused a larger reduction in ABP, LSNA, and HR compared with microinjection of MPEP or LY367385 alone (Fig. 7C).

Effects of microinjection of S-DHPG and AP5 into the PVN on LSNA, ABP, and HR in WKY rats and SHR. Previous studies suggest that activation of group I mGluRs enhances NMDA receptor function (3, 5, 13). Furthermore, NMDA receptor activity is increased in the PVN in SHR (16, 19). Therefore, we determined the role of NMDA receptors in the sympathoexcitatory response to activation of group I mGluRs in the PVN in WKY rats and SHR. Microinjection of S-DHPG (25.0 nmol) caused similar increases in ABP, LSNA, and HR in WKY rats and SHR (Fig. 8). After ABP, LSNA, and HR returned to the basal level, subsequent injection of AP5 (1.4 nmol/50 nl) did not significantly change ABP, LSNA, and HR in SHR.

Fig. 8. Effect of microinjection of S-DHPG and 2-amino-5-phosphonopentanoic acid (AP5) into the PVN. A and B: raw tracings show responses of the LSNA, ABP, and HR to bilateral microinjection of S-DHPG (5.0–50.0 nmol/50 nl), AP5 (1.4 nmol/50 nl), and S-DHPG + AP5 into the PVN in 1 WKY (A) and 1 SHR (B). Note that AP5 decreased the basal LSNA, ABP, and HR in SHR but not in WKY rats. Also, AP5 reduced the response of LSNA, ABP, and HR to S-DHPG. C: summary data showing changes of ABP, LSNA, and HR elicited by microinjection of S-DHPG (25 nmol/50 nl), AP5 (1.4 nmol/50 nl), and AP5 + S-DHPG into the PVN in WKY rats and SHR. *P < 0.05 compared with values of S-DHPG alone (repeated-measures ANOVA with Dunnett’s post hoc test). #P < 0.05 compared with the corresponding value in WKY rats (2-way ANOVA with Bonferroni post hoc test).
not significantly change ABP, LSNA, and HR in WKY rats but caused a large reduction in ABP, LSNA, and HR (Fig. 8). Coinjection of S-DHPG and AP5 produced significantly smaller increases in ABP, LSNA, and HR compared with the effect of S-DHPG alone in SHR and WKY rats. The stimulatory effect of S-DHPG plus AP5 on ABP, LSNA, and HR was significantly less in SHR than in WKY rats (Fig. 8).

**DISCUSSION**

This is the first study to determine the physiological significance of group I mGluRs in the PVN in the control of sympathetic vasomotor tone in hypertension. We found that bilateral microinjection of specific mGluR5 or mGluR1 antagonists into the PVN dose-dependently decreased basal ABP, LSNA, and HR in SHR, but not in WKY rats. Blocking mGluR5 produced a greater decrease in ABP, LSNA, and HR than the mGluR1 antagonist in SHR. Also, we observed that activation of group I mGluRs with S-DHPG in the PVN produced comparable increases in ABP, LSNA, and HR in both WKY rats and SHR. Blocking mGluR1 or mGluR5 attenuated the sympathoexcitatory response induced by S-DHPG in WKY rats and SHR. Furthermore, we found that microinjection of the NMDA receptor antagonist AP5 into the PVN significantly attenuated the sympathoexcitatory responses to S-DHPG in WKY rats and SHR. Blocking NMDA receptors produced a greater attenuation of S-DHPG-induced responses in SHR than in WKY rats. Collectively, our study provides new functional evidence that tonic activation of group I mGluRs in the PVN contributes to the elevated sympathetic vasomotor tone in hypertension. NMDA receptors mediate sympathoexcitatory responses of group I mGluR receptors in the PVN.

It is well-known that sympathetic vasomotor tone is elevated in SHR (2, 14). However, the mechanisms for elevated sympathetic vasomotor tone in SHR are poorly understood. The PVN plays an important role in regulating autonomic and neuroendocrine functions and may be critically involved in the development or maintenance of hypertension (1, 17, 30, 31). We have shown that increased glutamatergic input in the PVN is involved in maintaining elevated sympathetic vasomotor tone in hypertension. NMDA receptors mediate sympathoexcitatory responses of group I mGluR receptors in the PVN.

Activation of group I mGluRs in the PVN can potentiate NMDA currents in the hippocampus, spinal cord dorsal horn, and hypothalamic melanin-concentrating hormone neurons (3, 5, 13). In the present study, we further determined the possible interaction between group I mGluRs and NMDA receptors in the PVN. As we reported previously (16), blockade of NMDA receptors with AP5 in the PVN profoundly decreased ABP and LSNA in SHR but not in WKY rats. Importantly, AP5 largely attenuated the sympathoexcitatory response produced by injection of S-DHPG in both WKY rats and SHR. Thus, these data suggest that activation of NMDA receptors contributes to the stimulatory effect of the group I mGluR agonist in the PVN on the sympathetic vasomotor tone. This finding is consistent with previous studies showing that blockade of NMDA receptors inhibits
cardiovascular responses to activation of group I mGluRs in the nucleus of the solitary tract (4). Furthermore, we found that after blocking NMDA receptors with AP5, stimulation of group I mGluRs with S-DHPG produced a less sympathoexcitatory response in SHR than in WKY rats. Thus, it seems that there is a greater involvement of NMDA receptors in the sympathoexcitatory response produced by group I mGluR stimulation in the PVN in SHR than in WKY rats.

**Perspectives and Significance**

Our study provides new functional evidence that group I mGluRs in the PVN play an important role in the control of the sympathetic vasomotor tone in SHR. Tonic activation of group I mGluRs in the PVN may contribute to increased glutamatergic inputs in the PVN in SHR. On the other hand, increased synaptic glutamate release can activate group I mGluRs in the PVN in hypertension. Thus, this positive-feedback mechanism may play a key role in sustained stimulation of PVN presympathetic neurons in hypertension. Because blockade of NMDA receptors largely attenuated the effect of S-DHPG on sympathetic vasomotor tone in SHR, activation of group I mGluRs in the PVN may increase glutamatergic inputs through both increased presynaptic glutamate release and augmentation of postsynaptic NMDA receptor activity. This new information is important for our understanding of the mechanisms of increased sympathoexcitatory outflow in hypertension. On the basis of the findings from our study, we speculate that group I mGluRs may represent a new target for treatment of certain types of hypertension.

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**DISCLOSURES**

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

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