Enhanced γ-Aminobutyric Acid–Mediated Responses in Nucleus Tractus Solitarius of Hypertensive Rats

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Previous studies demonstrated that stimulation of type B γ-aminobutyric acid (GABAB) receptors but not type A (GABA<sub>A</sub>) receptors in the nucleus tractus solitarius of spontaneously hypertensive rats elicited a larger increase in arterial pressure compared with control rats of the Wistar-Kyoto strain. The present studies extended that observation by examining the cardiovascular response to injection into the nucleus tractus solitarius of a selective GABA<sub>B</sub> receptor antagonist, CGP 35348, in these strains as well as examining the cardiovascular responses to stimulation or blockade of GABA<sub>A</sub> receptors in the nucleus tractus solitarius in another model of hypertension, the rat treated with deoxycorticosterone acetate and salt. In both groups of hypertensive rats the pressor response to injection into the nucleus tractus solitarius of the GABA uptake blocking drug nipecotic acid was significantly greater compared with control rats (P<.01 in each model). Similarly, in both models of hypertension, the depressor response elicited by blockade of GABA<sub>B</sub> receptors in the nucleus tractus solitarius by injection of CGP 35348 was approximately 75% greater compared with control rats (P<.05 in each model). These results suggest that alterations in GABAB-mediated neural transmission in the nucleus tractus solitarius may contribute to the elevated arterial pressure observed in these models of hypertension. (Hypertension. 1993;22:819-825.)

KEY WORDS • GABA • rats, inbred SHR • nipecotic acids • glutamates • acetylcholine

The spontaneously hypertensive rat (SHR) of the Okamoto strain is a frequently used experimental model of hypertension. Although the cause of hypertension in the SHR is unknown, many studies suggest that the central nervous system may be involved in the expression of elevated arterial pressure (AP) in these animals. These studies report differences in SHR in the level or turnover of specific neurotransmitters in specific brain regions or differences in cardiovascular response to some treatment that influences central neural function. For example, in SHR altered catecholaminergic function in regions of the hypothalamus and brain stem associated with cardiovascular regulation have been noted compared with Wistar-Kyoto (WKY) rats, the normotensive control strain from which the SHR was derived.

The nucleus tractus solitarius (NTS), the region of the brain stem in which primary baroreceptor afferents terminate, has been implicated in the pathogenesis of hypertension in the SHR. This area of the brain is critically important in the normal regulation of AP, and several studies have suggested that neurochemical differences within the NTS may be involved in the elevated AP in SHR. For example, several laboratories have reported an alteration in NTS content or release of catecholamines in SHR compared with WKY rats, and responses of NTS neurons to catecholamines appear different in SHR. In addition, the levels of certain neuroactive amino acids in the NTS have been reported to be different in SHR; glutamate levels are elevated and β-alanine levels are decreased.

Another approach to this issue has been to compare the effects on AP of manipulating neural transmission within the NTS in SHR and WKY rats. Specifically, the depressor response elicited by microinjection of glutamate, an amino acid that excites virtually all neurons, into the NTS has been reported to be slightly attenuated when the responses are covariately adjusted for baseline AP, although the maximal decrease in AP appears to be the same in SHR and WKY rats. In contrast, the depressor response elicited by microinjection of acetylcholine into the NTS is slightly potentiated in SHR.

We have previously reported that γ-aminobutyric acid (GABA)–mediated neural transmission in the NTS is altered in the SHR in a manner consistent with its contributing to the elevated blood pressure in this strain. Specifically, the pressor response to stimulation of type B GABA (GABA<sub>B</sub>) receptors in the NTS by microinjection of baclofen was exaggerated in SHR, whereas the pressor response to stimulation of type A GABA (GABA<sub>A</sub>) receptors by microinjection of muscimol was not different. Consistent with this observation, Singh and Ticku reported an increase in the number of GABA<sub>B</sub> receptors in the region of the NTS in SHR. The present study was designed to extend those observations by (1) examining the effect of microinjecting an antagonist of GABA<sub>A</sub> receptors into the NTS in...
SHR and WKY rats and (2) comparing the effects of drugs that act on GABA_\textsubscript{B} receptors in another model of hypertension, the rat treated with deoxycorticosterone acetate (DOCA) and salt.

**Methods**

These experiments were conducted on adult male SHR and WKY rats (16 to 20 weeks of age) (Taconic Farms, Germantown, NY) and DOCA-salt hypertensive rats and normotensive control rats of a Sprague-Dawley strain (Zivic-Miller, Allison Park, Pa). Rats were housed singly in wire mesh cages in a temperature-controlled room on a 12-hour light/dark cycle with food and tap water available ad libitum for at least 1 week before use in experiments. All animal protocols were in strict accordance with the *Guide for the Care and Use of Laboratory Animals* (National Institutes of Health, Bethesda, Md) and were approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh.

To produce DOCA-salt hypertension, we subjected rats weighing 160 to 180 g to right unilateral nephrectomy while anesthetized with pentobarbital sodium (50 mg/kg IP). Immediately after nephrectomy, a pellet containing 50 mg of DOCA (Innovative Research Products) was placed subcutaneously in the back of the neck. The drinking water was replaced with 0.9% saline for the first 2 weeks after nephrectomy and then was switched to 0.45% saline. Rats were used 3 to 4 weeks after nephrectomy. Control rats consisted of heminephrectomized rats not treated with either DOCA or salt.

For injections of drugs into the NTS, rats were initially anesthetized with halothane (2% in 100% oxygen administered through a cone placed over the nose). A cannula (PE-50 tubing filled with heparinized saline) was inserted into the right femoral artery for recording of AP and heart rate (HR). A second cannula was placed in the right femoral vein for administration of drugs. The trachea was cannulated and rats were artificially ventilated with 2% halothane in 100% oxygen followed by the administration of a muscle relaxant (d-tubocurarine, 0.5 mg/kg IV, supplemented hourly with 0.2 mg/kg IV). Rats were placed in a stereotaxic instrument with the incisor bar positioned 11 mm below the interaural line. The dorsal surface of the medulla was exposed by limited craniotomy, and with the aid of a surgical microscope, the area postrema was visualized. α-Chloralose was administered (60 mg/kg IV, supplemented hourly with 20 mg/kg IV) and the halothane terminated. Rats were ventilated with 100% oxygen throughout the remainder of the experiment.

Animals were left to stabilize for at least 20 minutes before the start of the experiment. Drug injections were made into the NTS using single- or double-barreled glass micropipettes pulled to an outer diameter of 40 to 50 μm and beveled to approximately 45°. The tip of the micropipette was positioned 0.5 mm rostral to the caudal tip of the area postrema, 0.5 mm lateral from the midline, and 0.5 mm deep to the surface of the brain stem for injection into the NTS. All drugs were dissolved in artificial cerebrospinal fluid and injected in a 100-N volume over a period of several seconds using a PicoPump (WPI, New Haven, Conn). The volume of drug injected was carefully monitored by watching the movement of the fluid meniscus in the calibrated micropipette. For bilateral injections, the drug was initially injected on one side, the pipette withdrawn and repositioned on the contralateral side, and the second injection made; thus, injections were made approximately 1 minute apart. Doses refer to the amount injected into each NTS.

In most experiments, animals received unilateral electrolytic lesions of one NTS, as described previously, at least 20 minutes before injection of drugs into the contralateral, intact NTS. This was done to ensure that reflex pathways mediated through the contralateral NTS did not blunt the responses elicited by unilateral injection into the NTS.

In experiments examining the dose-response relation for glutamate-evoked changes in AP and HR, each rat received unilateral injections of each of three doses of glutamate (30, 100, and 300 pmol) in ascending order, with at least 5 minutes between injections. A single-barreled pipette was used for these injections, so after each injection the pipette was removed from the NTS, filled, and reinserted. After the glutamate injections, the depressor and bradycardic responses to an injection of 440 pmol acetylcholine were also examined.

At the conclusion of the study, 100 nL of 1% Fast Green was injected into the NTS using the same micropipette previously used for drug injections. The animal was then decapitated and the brain stem rapidly removed and frozen in isopentane on dry ice. Brain stems were subsequently cut into 40-μm sections with a cryostat, and sections were mounted on glass microscope slides. Sections were stained with cresyl violet or thionin. Only animals in which microinjection sites and lesions were centered in the medial subnucleus of the NTS at the level of the area postrema were included in the data analysis.

CGP 35348 was generously donated by CIBA-GEIGY, Basel, Switzerland, and γ-vinylGABA (GVG) was a gift from Merrell-Dow, Strasbourg, France. All other drugs were purchased from Sigma Chemical Co, St Louis, Mo.

Data are expressed as mean±SEM; variables were compared between normotensive and hypertensive rats by *t* test. Dose-response data for glutamate were analyzed by two-way analysis of variance (group×dose) followed when appropriate by the Newman-Keuls test (SYSTAT, Systat Inc, Evanston, Ill).

**Results**

**Spontaneously Hypertensive Rats**

After destruction of the contralateral NTS, unilateral injection of nipecotic acid (NIP) (10 nmol, a maximally effective dose10,14) into the NTS increased AP, as previously reported in Sprague-Dawley rats.13 The pressor response elicited by injection of NIP into the NTS was larger in SHR compared with control WKY rats (Fig 1), as expected based on the effects of bilateral injections of NIP in these strains.10 NIP produced a small but statistically significant increase in HR, which was not different between the two strains (see legend of Fig 1). Twenty minutes after the end of the NIP-evoked pressor response, the GABA\textsubscript{B} receptor antagonist CGP 35348 (5 nmol, a maximally effective dose15) was injected into the NTS. This drug elicited a decrease in AP that was 75% greater in SHR compared with WKY rats (Fig 1). This drug did not significantly alter HR in either strain (P>.1 compared with sham injection). Similar results were obtained with unilateral injections of CGP 35348 into the
In a separate group of WKY rats and SHR with unilateral NTS lesions, the pressor response elicited by injection into the NTS of another indirectly acting GABA agonist, GVG, was examined. GVG (25 nmol) injected into the NTS elicited a pressor response that was significantly greater in SHR compared with WKY rats (Table 1). The magnitudes of the pressor effects elicited by NIP and GVG were not significantly different in either strain (compare data in Table 1 and Fig 1, P > .1 in each strain). CGP 35348 (5 nmol) injected into the same site 4 to 5 minutes after GVG completely reversed the GVG-evoked pressor response in each strain (Table 1), as previously shown in Sprague-Dawley rats.

To examine the effect of stimulation of neurons in the NTS on AP and HR, we injected glutamate unilaterally into the NTS in SHR and WKY rats in which the contralateral NTS was intact. Glutamate injected into the NTS elicited dose-dependent decreases in AP and HR in both strains (Fig 2). The glutamate-evoked pressor response was not significantly different between SHR and WKY rats. However, compared with WKY rats, the glutamate-evoked bradycardia was significantly smaller in SHR (Fig 2). Similar to glutamate-evoked responses, acetylcholine injected into the NTS elicited a depressor response that was not different between strains, whereas the bradycardic response to acetylcholine injection was significantly smaller in SHR compared with WKY rats (see legend to Fig 2).

**DOCA-Salt Hypertensive Rats**

Bilateral injection of NIP into the NTS of control uninephrectomized rats increased AP approximately 40 mm Hg (Table 2), in agreement with previous observations in intact Sprague-Dawley rats. The same treatment produced a significantly greater pressor response in DOCA-salt hypertensive rats (Table 2). After destruction of the contralateral NTS in a different group of DOCA-salt and control rats, unilateral injection of NIP increased AP, and this response was larger in DOCA-salt hypertensive rats than in control rats (Fig 3). The pressor response elicited by unilateral injection of NIP in rats in which the contralateral NTS was...
Fig 2. Line graphs show effect of glutamate injected into the nucleus tractus solitarius (NTS) on mean arterial pressure (MAP) and heart rate (HR) in spontaneously hypertensive rats (SHR) and Wistar-Kyoto (WKY) rats. Groups of chloralose-anesthetized SHR (○, n=6) and WKY rats (△, n=8) received unilateral injections into the NTS of 30, 100, and 300 pmol glutamate (contralateral NTS intact). Each rat received each dose in ascending order. Values are maximal fall in MAP and HR that occurred within 30 seconds of injection; all responses lasted for less than 2 minutes. Baseline MAP measured just before the first injection was 140±4 and 170±9 mm Hg; baseline HR was 338±10 and 351±13 beats per minute (bpm) for WKY and SHR rats, respectively. Baseline values did not change significantly during the course of the experiment. The two higher doses of glutamate significantly decreased MAP and HR in each rat strain (P<.05); the 10 pmol dose elicited statistically significant changes from baseline values only in WKY rats. After the last glutamate injection, the response to injection of acetylcholine (440 pmol) was also tested. Acetylcholine elicited a transient decrease in MAP (−42±8 and −39±12 mm Hg in WKY rats and SHR, respectively; P>.05 between strains) and HR (−38±15 and −19±2 bpm in WKY rats and SHR, respectively; P<.05). *Significantly different from WKY rats.

Fig 3. Bar graph shows effect of nipecotic acid and CGP 35348 injected into the nucleus tractus solitarius (NTS) on mean arterial pressure (MAP) in deoxycorticosterone (DOC)-salt hypertensive rats. Groups of chloralose-anesthetized DOC-salt hypertensive rats (n=10) and normotensive control rats (n=13) with unilateral lesions of the NTS received injections of nipecotic acid (10 nmol) into the intact NTS. Approximately 20 minutes later, CGP 35348 (5 nmol) was injected into the same site. Results are expressed as maximal change from baseline occurring within 3 minutes of injection. Baseline MAP values taken just before injection of nipecotic acid were 188±6 and 139±3 mm Hg for DOCA-salt and control rats, respectively; baseline values just before injection of CGP 35348 were not significantly different from these values. Nipetic acid elicited a significant increase in MAP in both groups, and CGP 35348 elicited a significant decrease (P<.01). Nipetic acid elicited a significant increase in heart rate that was not different between groups (DOC-salt: +16±4 beats per minute from baseline of 327±13; control: +16±3 beats per minute from baseline of 323±8). CGP 35348 did not significantly alter heart rate (DOC-salt: −1±2 beats per minute; control: −6±2 beats per minute). *Significant difference between groups, P<.05. NTS lesions elicited a decrease in AP that was significantly larger in the hypertensive rats (Fig 3). CGP 35348 did not significantly alter HR in either the hypertensive or normotensive rats. GVG (25 nmol) injected into the NTS of DOCA-salt hypertensive rats with unilateral NTS lesions increased AP to the same extent as NIP, and this GVG-evoked pressor response was completely reversed by injection of CGP 35348 into the same site 3

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<tr>
<th>Group</th>
<th>Mean Arterial Pressure, mm Hg</th>
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<td>118±4</td>
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<td>Control (n=10)</td>
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<td>DOCA-salt (n=8)</td>
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bpm indicates beats per minute; and DOCA, deoxycorticosterone acetate. Arterial pressure and heart rate were measured in groups of chloralose-anesthetized DOCA-salt and control normotensive rats that received bilateral injections of nipecotic acid (10 nmol) into the nucleus tractus solitarius. Baseline values refer to values just before drug injection; change with nipecotic acid is expressed as maximal increase that occurred within 3 minutes of injection.

*Significant increase from baseline (P<.01).

*Significant difference from control group (P<.05).
minutes later (baseline MAP, 189±12 mm Hg; change with GVG, +56±5 mm Hg; change with CGP 35348, −59±6 mm Hg; n=5). The magnitude of the GVG-evoked pressor response in DOCA-salt hypertensive rats was not significantly different from the response elicited by NIP (P>0.1; see Fig 3).

To examine the effect of stimulation of neurons in the NTS on AP and HR, we injected glutamate unilaterally into the NTS in DOCA-salt hypertensive rats and control rats in which the contralateral NTS was intact. Glutamate injected into the NTS elicited dose-dependent decreases in AP and HR in both groups (Fig 4), and these responses were not significantly different between groups except at the highest dose tested (300 pmol), where the depressor response was greater in the hypertensive rats. Acetylcholine (440 pmol) injected into the NTS elicited depressor responses that were similar to those elicited by 300 pmol glutamate, where the depressor response was significantly larger in DOCA-salt hypertensive rats compared with control rats (see legend to Fig 4). In contrast, the bradycardic response to acetylcholine was significantly attenuated in DOCA-salt hypertensive rats compared with control rats (see legend to Fig 4).

Discussion

These results demonstrate a difference in GABA-mediated neural transmission within the NTS in two models of experimental hypertension—the SHR and the DOCA-salt hypertensive rat. Injection of a specific GABA<sub>B</sub> receptor antagonist into the NTS produced a decrease in AP that was larger in the hypertensive rats than in the normotensive control rats. Similarly, injection of NIP or GVG, drugs that elicit pressor responses by increasing the action of endogenous GABA on GABA<sub>B</sub> receptors in the NTS, elicited larger pressor responses in the hypertensive rats.

We have previously reported that bilateral injections of baclofen, a directly acting GABA<sub>B</sub> agonist, into the NTS elicited a larger pressor response in SHR than in WKY rats. This difference in pressor responses also occurred with injections of the GABA<sub>A</sub>-selective GABA<sub>B</sub>-antagonist NIP but not with the GABA<sub>A</sub>-agonist muscimol. Additional studies in Sprague-Dawley rats have demonstrated that the pressor response elicited by injection into the NTS of NIP and other indirectly acting GABA agonists was due to a potentiation of the action of GABA at GABA<sub>B</sub> receptors. These present studies confirm our previous studies using NIP and extends the study by demonstrating that blockade of GABA<sub>B</sub> receptors in the NTS elicits a decrease in AP that is greater in SHR than WKY rats. In addition, these studies show that the pressor response elicited by indirectly acting GABA agonists injected into the NTS of SHR is completely reversed by a GABA<sub>B</sub> receptor antagonist, as previously shown in normotensive Sprague-Dawley rats. Thus, it appears that enhanced tonic stimulation of GABA<sub>B</sub> receptors in the NTS contributes to the elevated AP in SHR. These results are consistent with the previous observation by Singh and Ticku that there are more GABA<sub>B</sub> receptors in the region of the NTS in SHR compared with WKY rats. Furthermore, the present studies demonstrate that drugs acting on GABA<sub>B</sub> receptors in the NTS elicit greater cardiovascular responses in rats made hypertensive by treatment with DOCA and salt.

When the responses to injections of drugs into the NTS between normotensive and hypertensive rats are compared, the analysis is confounded by the differences in baseline AP and possible differences in vascular reactivity. The data presented here were analyzed as absolute changes from baseline; this approach was chosen because treatments that would nonspecifically excite (eg, glutamate) or inhibit (eg, muscimol) neurons in the NTS elicit the same absolute maximal changes in AP in SHR and WKY rats. Furthermore, stimulation of central sympathetic vasomotor outflow by injection of glutamate into the rostral ventrolateral medulla elicits the same increase in AP in these two strains when the data are expressed as absolute change in AP. Similar results are also observed with sympathomimetic drugs such as phenylephrine and tyramine. In addition, when the increases in AP and splanchnic sympathetic nerve activity elicited by electrical stimulation of the ventromedial hypothalamus in SHR and WKY rats are compared, it is clear that the increase in AP expressed per unit increase in nerve activity is not exaggerated. (Even so, sympathetic nerve activity recorded from a single nerve may not be a good measure of sympathetic vasomotor outflow, because it
WKY rats, and this larger response was correlated with a larger decrease in adrenal but not splanchnic nerve activity.) Together, these results indicate that when centrally evoked changes in AP between SHR and WKY rats are compared, the relevant variable is absolute change in AP.

However, because some evoked decreases in AP, such as those elicited by inhibition of neural function in the rostral ventrolateral medulla, may differ between SHR and WKY rats as a result of differences in baseline AP,

changes that occurred in AP should be expressed as change relative to baseline. Thus, the depressor response elicited by a maximally effective dose of a general neuronal excitant such as glutamate or the response elicited by a dose of glutamate that in control rats elicits a response similar to that of the test drug. Because the absolute changes in mean AP elicited by various doses of glutamate are the same in SHR and WKY rats (Fig 2), such an analysis would indicate that CGP 35348 elicited a larger response in SHR. In contrast to CGP 35348, the responses elicited by acetylcholine were comparable to those elicited by glutamate, and thus the lesser bradycardic response elicited in SHR compared with WKY rats would be expected based on the responses to stimulation of the NTS with glutamate. It is worth noting that Talman and Lewis\(^9\) have previously examined the effects of glutamate and acetylcholine injected into the NTS on AP and HR, and their data are somewhat different from those reported here, although the two sets of data are not directly comparable because all of the results presented by Talman and Lewis\(^9\) had been covaried adjusted for baseline values.

Interpretation of the data obtained in DOCA-salt hypertensive rats is less straightforward than data from SHR and WKY rats for several reasons: (1) Changes in AP elicited by injections into the NTS of drugs that act on GABA\(_B\) receptors are greater in DOCA-salt hypertensive rats compared with control rats when data are expressed as absolute change in AP but not when expressed as percent change from baseline; (2) the depressor response evoked by injection of 300 pmol glutamate into the NTS is greater in DOCA-salt hypertensive rats than in control rats, but this difference is not observed with smaller doses of glutamate; and (3) there are less published data comparing centrally evoked responses in DOCA-salt hypertensive and control rats. Still, the similarity of the responses elicited by both NIP and CGP 35348 in DOCA-salt hypertensive rats and SHR suggests that similar changes in GABA\(_B\) receptor function may occur in both models of hypertension.

The interpretation of the present results also depends on the specificity of the drugs used in this study. The action of NIP as a specific competitive antagonist of GABA uptake has been well studied,\(^25,26\) and it is likely that GVG injected into the NTS elicits a pressor response via a similar action,\(^16\) although this drug is also an effective inhibitor of the GABA metabolizing enzyme GABA transaminase. We have previously demonstrated that the pressor response elicited by injections of NIP or GVG into the NTS of normotensive Sprague-Dawley rats results from increased stimulation of GABA\(_B\) receptors in this area,\(^12,16,17\) and the present studies suggest that this is also the case in SHR and DOCA-salt hypertensive rats. The GABA\(_B\) antagonist used in these studies, CGP 35348, is a relatively new drug and therefore has not been as thoroughly studied. Still, all of the available data suggest that CGP 35348 is an effective and selective competitive GABA\(_B\) receptor antagonist.\(^27,28\) Recent studies characterizing the cardiovascular responses elicited by injection of CGP 35348 into the NTS of Sprague-Dawley rats indicate that this drug produces a decrease in AP specifically by blocking GABA\(_B\) receptors.\(^15\) Dose-response data show that the dose used in the present studies (5 nmol) is supramaximal for decreasing AP and blocking the pressor response elicited by injection of a maximally effective dose of the GABA\(_B\) receptor agonist baclofen.\(^15\) The demonstration that CGP 35348 (5 nmol) injected into the NTS totally reversed the GVG-evoked pressor response in SHR and DOCA-salt hypertensive rats suggests that this dose of CGP 35348 is also effective at blocking GABA\(_B\) receptors in these rats as well. We have also examined the response of another drug reported to be an antagonist at GABA\(_B\) receptors, 2-hydroxysaclofen.\(^29\) However, when a dose of 2-hydroxysaclofen (2 nmol) that blocks the actions of baclofen is injected into the NTS, a pressor response is observed;\(^29\) this is consistent with the action of this drug as a poor partial agonist at GABA\(_B\) receptors\(^10,13\) or as an antagonist at some subtype of GABA\(_B\) receptor.\(^32-34\) Interestingly, the pressor response elicited by injection into the NTS of 2 nmol 2-hydroxysaclofen is potentiated in SHR compared with WKY rats (unpublished observation).

The similar potentiation of the cardiovascular responses elicited by stimulation or blockade of GABA\(_B\) receptors in the NTS of SHR and DOCA-salt hypertensive rats compared with the appropriate control rats suggests that a common mechanism may underlie the response in both models of hypertension. One possible explanation is that the potentiated responses to drugs acting on GABA\(_B\) receptors result from the hypertension. Because the alteration in GABA\(_B\)-mediated neural transmission that occurs in the hypertensive rats would seem to act to maintain elevated AP, this explanation would suggest that hypertension results in central neural changes that contribute to the maintenance of hypertension. Another possibility is that changes in GABA\(_B\)-mediated neural transmission precede the development of hypertension and contribute to it. In both SHR and DOCA-salt hypertensive rats there is a centrally mediated attenuation of the baroreceptor reflex\(^25,26\) that has been shown to precede the development of hypertension in DOCA-salt treated rats.\(^24\) Because enhanced GABA\(_B\)-mediated neural transmission in the NTS acts to atten-
uate the baroreceptor reflex, it is conceivable that an alteration in \(GABA_{B}\)-mediated transmission in the NTS precedes the development of hypertension, resulting in an attenuation of the baroreceptor reflex and therefore possibly contributing to the increase in AP.

In summary, these data demonstrate that in two models of experimental hypertension there is a potentiation of the cardiovascular responses to administration of the NTS of both agonists and antagonists of the \(GABA_{B}\) receptors. This change in \(GABA_{B}\)-mediated neural transmission may contribute to the pathogenesis of hypertension in these models.

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