Endothelin-A receptors and NO mediate decrease in arterial pressure during recovery from restraint

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Yip, Avery W. C., and Teresa L. Krukoff. Endothelin-A receptors and NO mediate decrease in arterial pressure during recovery from restraint. Am J Physiol Regulatory Integrative Comp Physiol 282: R881–R889, 2002; 10.1152/ajpregu.00308.2001.—We investigated the role of central endothelin-A (ET\textsubscript{A}) receptors and nitric oxide (NO) in regulating arterial pressure during restraint stress and recovery from stress. Rats received intracerebroventricular (icv) injections of the ET\textsubscript{A} receptor antagonist BQ123 (24 μg/kg) and were then subjected to two restraint-rest cycles (1 h of restraint and 1 h of rest/cycle). Although mean arterial pressure (MAP) values in BQ123-treated and control rats increased at the onset of restraint and remained elevated during restraint, MAP values in BQ123-treated rats were consistently greater than in control rats. During rest periods, MAP values in control rats decreased to below baseline levels, whereas those in BQ123-treated rats remained significantly higher. NO content was decreased in the brain stems of BQ123-treated compared with control rats after the 4-h protocol. Injections (icv) of the NO synthase (NOS) inhibitor N\textsuperscript{G}-nitro-L-arginine (L-NNA) eliminated the decreases in MAP values during rest periods in both BQ123-treated and control rats. Inhibition of neuronal NOS with icv injection of 7-nitroindazole sodium salt resulted in MAP values intermediate between control rats and rats receiving L-NNA. These results support the hypothesis that endothelin acts through ET\textsubscript{A} receptors in the brain, possibly via release of NO, to decrease arterial pressure during restraint and recovery from restraint.

First identified as a potent, endothelium-derived vasoconstricting factor (11), endothelin (ET)-1 (39) and its isoforms (15) act through at least two distinct receptors, ET\textsubscript{A} and ET\textsubscript{B} (1, 32), to regulate the physiological activities of several organ systems. In blood vessels, ET\textsubscript{A} receptors on vascular smooth muscle cells mediate the pressor response that is observed after intravenous injections of ET-1 (39). ET\textsubscript{B} receptors on endothelial cells also mediate the initial depressor response that is seen after intravenous (iv) administration of ET-1 primarily through the release of nitric oxide (NO) (12).

Although it is known that endothelin and its receptors are expressed in the central nervous system (5, 13, 16), the role of endothelin in the brain is not yet fully understood. In contrast to its peripheral effects, centrally administered ET-1 elicits an initial increase and a subsequent sustained decrease in blood pressure in urethane-anesthetized animals (6, 7, 9, 29, 31). The pressor and depressor effects are both mediated by changes in central output of the sympathetic nervous system: neither response was observed in rats whose spinal cords were severed at the cervical level (7), and peripheral administration of adrenergic and/or ganglionic blockers prevented the pressure changes (27, 38). Furthermore, the changes in arterial pressure in response to intracerebroventricular (icv) injection of ET-1 were shown to be mediated by ET\textsubscript{A} receptors: pretreatment with the ET\textsubscript{A} antagonist BQ123 (14) also eliminated these effects (7). Together these findings suggest that centrally administered ET-1 acts on central autonomic neurons via ET\textsubscript{A} receptors to modulate sympathetic outflow. In support of these observations, central administration of the ET\textsubscript{A} agonist sarafotoxin 6b produced a similar pattern of pressor and depressor responses in urethane-anesthetized rats that was attenuated with icv BQ123 (23). In other studies, low doses of ET-1 applied to the fourth cerebroventricle of ventilated rats (9, 10, 26, 34) or administered intrathecally (8) produced decreases in arterial pressure and heart rate. On the other hand, microinjection of ET-1 into the nucleus of the tractus solitarius (NTS) or area postrema (AP) has produced pressor (2, 4) and depressor responses (9, 26).

Although it is clear that activation of ET\textsubscript{A} receptors affects sympathetic output from the brain, the role(s) of this endothelin receptor subtype in mediating physiological responses during the homeostatic instability of psychological stress was unknown. To test the hypothesis that ET\textsubscript{A} receptors mediate changes in arterial pressure during stress and/or recovery from stress, experiments were designed using a model of restraint stress that elevates sympathetic activity. We measured the mean arterial pressure (MAP) for rats subjected to two restraint-rest cycles (1 h of restraint and 1 h of...
rest/cycle; see Ref. 22), and the role of central ET<sub>Α</sub> receptors in each phase was investigated using icv injections of BQ123 to block these receptors. Furthermore, because central NO regulates sympathetic output to the periphery (17, 18), we investigated the effects of ET<sub>Α</sub> receptor blockade on NO content in the hypothalamus and brain stem of restrained rats. Finally, the NO synthase (NOS) blocker N<sup>ω</sup>-nitro-L-arginine (L-NNA) and the neuronal NOS (nNOS) blocker 7-nitroindazole sodium salt (7-NI) were used to block NO production in the brain to determine whether NO mediates the decrease in arterial pressure after restraint.

**METHODS**

**Animals**

Male Sprague-Dawley rats (body wt 200–300 g) were purchased from the Biological Sciences Animal Centre, University of Alberta. They were housed 2 rats/cage on a 12:12-h light-dark schedule (lights on at 0700) at a temperature of 21°C. The rats were given food and water ad libitum. All protocols used in these experiments were approved by the University of Alberta Animal Welfare Committee.

**Instrumentation**

Rats were anesthetized with Somnotol pentobarbital sodium (60 mg/kg ip; MTC Pharmaceuticals, Cambridge, ON) and received sterile Ethacillin penicillin G procaine (30,000 U im; Rogar/STB, London, ON), atropine sulfate (25 μg sc; Ormond Veterinary Supply, Ancaster, ON), and Buprenex injectable buprenorphine hydrochloride (15 μg im; Reckitt & Colman Pharmaceutical, Richmond, VA).

Indwelling 22-gauge C313G ivc guide cannulae (Plastic One, Roanoke, VA) were implanted in rats as described previously (40). An internal 28-gauge C313I cannula (Plastic One) was connected to an Accu-Rated pump tube (Fisher Scientific, Nepean, ON), and a bubble was made at the cannula end of the tubing (using a Hamilton microsyringe) so that outflow of cerebrospinal fluid (CSF) could be observed by withdrawing it with the microsyringe (40). The internal cannula was inserted into the guide cannula, and accurate cannula placement was confirmed by 1) movement of the bubble and outflow of CSF; 2) observance of a rise in blood pressure of at least 10 mmHg after injection of angiotensin II (5 pmol icv; Bachem California, Torrance, CA) immediately after surgery; and 3) visual inspection of tissue sections for the tract left by the guide cannula. With the internal cannula removed, the guide cannula was secured to the skull using three screws and orthodontic resin (L. D. Chalk, Milford, DE) and was closed with a C313DC dummy cannula (Plastic One).

As described in our previous studies (20, 21, 40), a midline abdominal incision was made and the descending aorta and inferior vena cava were exposed. Polyethylene tubing (PE-10, 0.011 ID, 0.024 OD; Fisher Scientific) and a Silastic catheter (0.02 ID, 0.037 OD; Fred A. Dungey, Scarborough, ON) were inserted into the aorta and vena cava, respectively, and sutured to the posterior abdominal wall. The free ends of the arterial and venous catheters were passed under the skin and externalized at the nape of the neck with 27- and 23-gauge stainless steel tubing, respectively (Small Parts, Miami Lake, FL). The arterial line was closed with polyvinylpyrrolidone, and both lines were capped with Silastic tubing.

Rats were allowed to recover and were handled daily after surgery. Experiments were performed 5–7 days after surgery. On the day of the experiment, the arterial line of each rat was connected to a transducer for continuous recording of arterial blood pressure. A baseline pressure was established for 30 min before the start of the experiment. MAP values (in mmHg) were calculated for every 5-min interval, and each pressure for each rat was expressed as a percentage of its own baseline MAP.

**Experimental Design**

**Controls:** ET<sub>Α</sub> receptor blockade in urethane-anesthetized rats with selective antagonist BQ123. The effectiveness of icv injection of BQ123 in blocking the rise in MAP after icv administration of ET-1 was assessed. Because icv injection of ET-1 in conscious animals causes barrel-rolling behavior (28), animals were anesthetized with urethane (1 g/kg; Sigma Chemical, St. Louis, MO). Using concentrations determined in previous studies (7, 23, 29), rats received icv injections of BQ123 (24 μg/kg dissolved in 10 μl of saline: American Peptide, Sunnyvale, CA) and/or ET-1 (200 ng dissolved in 10 μl of saline; American Peptide). Rats were divided into four groups: group 1, ET-1 injected at time 0; group 2, BQ123 injected at time 0 and ET-1 administered 15 min later; group 3, BQ123 injected at time 0 and ET-1 administered 120 min later; and group 4, BQ123 injected at time 0 and ET-1 administered 240 min later.

Arterial pressures were recorded for the duration of the experiment and continued for 30 min after ET-1 administration. After each experiment, rats were given an overdose of pentobarbital sodium.

These experiments confirmed that pretreatment with icv injection of BQ123 for 15 min was sufficient to prevent the icv ET-1 pressor response and demonstrated (see Results) that BQ123 is effective in blocking the ET-1 pressor response for at least 4 h.

**Effect of BQ123 on MAP during restraint stress and recovery.** Rats received icv injections of BQ123 (24 μg/kg dissolled in 10 μl of saline). Control rats received the same amount of vehicle (saline). Fifteen minutes after BQ123 or vehicle injections, rats were individually restrained in hemicylindrical, well-ventilated Plexiglas tubes (19, 22, 41) according to a 4-h restraint-stress protocol of alternating 1-h sessions of restraint and rest (22). Rats were returned to their home cages during the rest periods. MAP was recorded for the duration of the experiment. At the end of the experiment, rats were given an overdose of pentobarbital sodium.

**Effect of BQ123 on MAP during restraint stress and recovery.** Rats received icv injections of BQ123 (24 μg/kg dissolled in 10 μl of saline). Control rats received the same amount of vehicle (saline). Fifteen minutes after BQ123 or vehicle injections, rats were individually restrained (alternating 1-h sessions of restraint and rest) as described (see Effect of BQ123 on MAP during restraint stress and recovery). At the end of the experiment (4 h), animals were decapitated with a rat guillotine. The hypothalamus and brain stem were microdissected from each brain at 4°C.
homogenized in 750 µl of PBS (pH 7.2), and centrifuged at 11,000 g for 20 min. The supernatant was centrifuged at 53,000 g for 15 min, and the final supernatant was frozen for a nitrate-nitrite (NOx) colorimetric assay (see NOx Colorimetric Assay) (40).

Effect of NOS inhibition on MAP during restraint stress and recovery. Rats received icv injections of BQ123 (24 µg/kg dissolved in 10 µl of saline) or vehicle alone. At the same time, rats also received icv injections of L-NNA (88 µg/kg dissolved in 10 µl of saline; Calbiochem, La Jolla, CA), 7-NI (74 µg/kg dissolved in 10 µl of saline; Calbiochem), or vehicle alone as we have previously described (40). L-NNA is an inhibitor of nNOS and endothelial NOS (eNOS) when used at the concentrations employed in this study and inhibits inducible NOS only at much higher concentrations (30). Fifteen minutes after the injections, rats were individually restrained (alternating 1-h sessions of restraint and rest) as described. Immediately before the second hour of restraint, rats were given a second injection of L-NNA, 7-NI, or vehicle to ensure continued inhibition of NO production (40). Rats were divided into six groups: group 1, controls (saline + saline administration); group 2, eNOS and nNOS inhibition (saline + L-NNA administration); group 3, nNOS inhibition (saline + 7-NI administration); group 4, ETA antagonism (BQ123 + saline administration); group 5, ETA antagonism and eNOS and nNOS inhibition (BQ123 + L-NNA administration); and group 6, ETA antagonism and nNOS inhibition (BQ123 + 7-NI administration). Blood pressure was recorded for the duration of the experiment. At the end of the experiment (4 h), rats were given an overdose of pentobarbital sodium.

NOx Colorimetric Assay

Levels of NOx in the hypothalamus and brain stem were measured using a NOx colorimetric assay kit (Cayman Chemical, Ann Arbor, MI) as we have described (40). Frozen supernatant samples were brought to room temperature, filtered with a 30-kDa cutoff filter (Millipore, Bedford, MA), and 80 µl of eluant were incubated with 10 µl of enzyme cofactor mixture and 10 µl of nitrate reductase mixture for 3 h at room temperature. After incubation, 50 µl each of Griess reagents R1 and R2 were added, and the color reaction was allowed to develop for 10 min at room temperature. The absorbance was read at 540 nm using a microplate reader (MTX Lab System, McLean, VA).

Analysis

Data are expressed as means ± SE. In experiments measuring MAP values, data within each group were compared over time using one-way repeated-measures ANOVA and the Newman-Keuls post hoc test. In experiments with two groups, data from experimental animals were compared with data from control animals using the unpaired Student’s t-test. In the NOS inhibitor experiments, MAP values were compared among groups by one-way ANOVA and the Newman-Keuls post hoc test. P < 0.05 was taken to signify statistical significance.

RESULTS

Controls: ETA Receptor Blockade in Urethane-Anesthetized Rats by Selective Antagonist BQ123

In urethane-anesthetized rats, injections of ET-1 (n = 4) produced increases in MAP values of 42–45 mmHg that reached plateaus within 5 min after ET-1 injection (Fig. 1A). Although icv BQ123 injections alone produced initial increases in arterial pressure of 17–25 mmHg (Fig. 1, C and D), pretreatment with BQ123 for 15 min, 2 h, and 4 h (n = 4 in each group) prevented the increases in MAP values in response to ET-1 (Fig. 1, B, C, and D).

Controls: Effects of BQ123 in Conscious, Nonstressed Animals

MAP values for conscious, freely moving rats receiving icv BQ123 (n = 4) were not significantly different from those receiving vehicle (n = 4; Fig. 2). In both groups, icv injections elicited small (5–9 mmHg) and transient (<10 min) increases in MAP values.

Effects of BQ123 in Conscious Animals During Restraint Stress and Recovery

MAP values. At the onset of restraint, MAP values in experimental and control animals (n = 8/group, ) rose ~40 mmHg (Fig. 3). During the first hour of restraint (0–60 min), there was a tendency for MAP values in both groups of animals to decline slightly but not significantly. Although differences in MAP values between the two groups did not reach statistical significance, MAP values in rats receiving BQ123 were consistently greater than in rats receiving vehicle (Fig. 3). MAP values in both groups of animals decreased significantly from restraint levels when the animals were removed from the restraint chamber (60 min; Fig. 3). During the hour of rest (60–120 min), MAP values in animals receiving vehicle continued to decrease and leveled off below baseline values. In animals receiving BQ123, however, MAP values decreased from restraint levels and then leveled off above baseline values. MAP values in experimental animals remained significantly higher than those in control animals (Fig. 3) with an average pressure difference of ~13 mmHg.

At the onset of the second period of restraint (120 min), MAP values in both experimental and control animals rose ~35 mmHg (Fig. 3). During this second hour of restraint (120–180 min), MAP values in animals receiving vehicle tended to decrease whereas MAP values in animals receiving BQ123 did not. MAP values in experimental rats were consistently greater than in control rats. Toward the end of the restraint period, MAP values were significantly greater in experimental rats than in control rats with an average pressure difference of ~13 mmHg (Fig. 3).

MAP values in both groups of animals decreased significantly from restraint levels when the animals were removed from the restraint chamber (180 min) a second time (Fig. 3). During this second hour of rest (180–240 min), MAP values in animals receiving vehicle tended to decrease whereas MAP values in animals receiving BQ123 remained above baseline and were significantly higher than those in control animals (Fig. 3) with an average pressure difference of ~16 mmHg.

NOx assay. A significant decrease in NOx levels was found in brain stem but not hypothalamus of BQ123-
treated rats \((n = 5)\) compared with controls \((n = 7;\) Fig. 4).  

**Effects of nNOS and eNOS Inhibition on MAP Values in Conscious Animals During Restraint Stress and Recovery**

MAP values in *group 1* (control rats for injections of NOS inhibitors: saline + saline) and *group 4* (BQ123 + saline) rats \((n = 4\) group; Fig. 5) showed patterns similar to those already described for the saline and BQ123 rats, respectively.

*Effects of l-NNA.* During both hours of restraint \((0–60\) min and \(120–180\) min), MAP profiles in *group 2* rats (saline + l-NNA; \(n = 5\)) were similar to those in *group 1* (saline + saline) and *group 4* (BQ123 + saline) rats (Fig. 5). During the first \((60–120\) min) and second...
(180–240 min) hours of rest, MAP values in the group 2 (saline + l-NNA) rats remained elevated (Fig. 5) compared with group 1 (saline + saline) and group 4 (BQ123 + saline) rats, where MAP values decreased when animals were removed from restraint. MAP values in the group 2 (saline + l-NNA) rats were significantly greater than those in the group 1 (saline + saline) rats.

MAP values in group 5 (BQ123 + l-NNA rats; n = 5) were not significantly different from those in the group 2 (saline + l-NNA) rats (data not shown).

Effects of 7-NI. During both hours of restraint, MAP values in the group 3 (saline + 7-NI; n = 5) rats were similar to those in group 1 (saline + saline) and group 4 (BQ123 + saline) rats (Fig. 5). During the first and second hours of rest, MAP values in 7-NI rats dropped slightly from restraint levels but remained above baseline and were indistinguishable from MAP values in the group 4 (BQ123 + saline) rats. During rest periods, therefore, MAP values in the group 3 (saline + 7-NI) rats were intermediate between MAP values in the group 1 (saline + saline) and the group 2 (saline + l-NNA) rats (Fig. 5).

MAP values in group 6 (BQ123 + 7-NI) rats (n = 5) were not significantly different from those in group 3 (saline + 7-NI) rats (data not shown).

DISCUSSION

Using a novel experimental paradigm of psychological stress (two restraint-rest cycles of 1 hour of restraint and 1 hour of rest per cycle), we show that ETA receptors and NO play important roles in decreasing arterial pressure and that they are especially important in regulating arterial pressure during recovery
from psychological stress. The results lead us to speculate that ETA receptors and the NO system in the brain are activated as an animal attempts to restore homeostatic balance when a stressor has been removed. The precise location(s) of the ETA receptors responsible for these effects is/are not yet known. However, using an antibody generated against a 64-amino acid residue of the COOH-terminus of the rat ETA receptor, Kurokawa and colleagues (24) have described immunoreactive neurons in several candidate brain areas known for involvement in regulating arterial pressure; e.g., the hypothalamic paraventricular nucleus (PVN), locus ceruleus, reticular formation, and dorsal vagal complex of the medulla. In addition, involvement of blood vessels in the brain cannot be discounted as ETA receptors have been described on cultured endothelial cells from human and rat microvessels (33, 36).

**Control Experiments**

We have shown that icv-administered BQ123 effectively inhibits ETA receptors for at least 4 h by verifying that BQ123 prevents increases in MAP values in response to icv ET-1 in anesthetized rats (7). Thus we are confident that BQ123 was effective in inhibiting ETA receptors for the duration of our experiments. Furthermore, we show that in conscious rats, BQ123 itself had no effect on MAP. This finding is in agreement with a study (27) showing that icv BQ123 did not alter basal levels of sympathetic and cardiovascular activities in conscious Wistar-Kyoto rats.

**MAP Values in Control Rats During Restraint Stress and Recovery**

Not surprisingly, the onset of restraint resulted in increased MAP values in control rats because psychological stress activates the sympathetic nervous system. Consistent with another study (25), we also show that MAP values tended to decline from initial levels during each hour of restraint. To our knowledge, however, we are the first to measure changes in MAP values during recovery from restraint stress. We show that when rats under the current experimental conditions were allowed to rest, their MAP values decreased and leveled off below baseline values, which suggests that a compensatory overshoot in the decrease of arterial pressure occurs during recovery from acute restraint.

**Effects of BQ123 During Restraint Stress and Recovery**

Our results show that MAP values in both BQ123-treated and control rats increased equally at the onset...
of restraint. It has been proposed that central endothelin regulates sympathetic activity, which results in both pressor and depressor responses, and that these responses are mediated by ETA receptors (7, 23). It is interesting, then, that blockade of central ETA receptors did not affect the initial increases in MAP values in response to restraint stress. This observation suggests that the increase in arterial pressure at the onset of restraint stress may not be mediated by ETA receptors. In contrast, the physiological responses during the remainder of the restraint periods were altered by BQ123 treatment. Thus during the first restraint period, MAP values in BQ123 rats remained higher than in saline controls, and by the end of the second period of restraint, these differences reached statistical significance. Although we did not measure sympathetic output directly, these observations are consistent with the notion that central endothelin mediates decreases in sympathetic activity through ETA receptors (7).

The decreased ability to reduce arterial pressure in rats whose ETA receptors were blocked was more apparent when the animals were removed from restraint and allowed to rest. In contrast to control rats where the resting MAP values decreased to below baseline, the MAP values in BQ123 rats remained above baseline and were significantly higher than in controls during this rest period. These results provide strong evidence that ETA receptors mediate at least part of the decrease in arterial pressure during the recovery from restraint stress.

Role of NO in the ETA-Mediated Decrease in Arterial Pressure During Recovery From Restraint

Central NO is generally believed to mediate decreases in arterial pressure and sympathetic drive during homeostatic instability (18). Using tissue homogenates, we have shown that blockade of ETA receptors with BQ123 leads to a significant decrease in the NO content in the brain stems of restrained rats. This result suggests that the ETA receptor-mediated decrease in arterial pressure that is observed in control animals during recovery from restraint is dependent at least in part on release of NO in the brain stem. This suggestion is supported by findings from two other studies. First, the depressor effect of ET-1 injection into the fourth cerebroventricle was attenuated when rats were pretreated with excitatory amino acid antagonists (10), and second, the depressor responses of the excitatory amino acid L-glutamate in the NTS have been shown to be due to release of NO (34). Therefore, the results of the present study suggest that the ETA receptor-induced decrease in arterial pressure may be partly mediated through the release of L-glutamate to increase NO production in the NTS. Another brain stem region where NO production may be affected by BQ123 is the ventrolateral medulla, because this region plays an important role in regulating arterial pressure and sympathetic activity and contains NO-producing neurons (19).

Because the PVN is a major center for integration of autonomic output and also because NO neurons are numerous in the PVN (19), it is surprising that we did not observe a difference in NO content in the hypothalamus of restrained rats that received BQ123 compared with restrained rats that received vehicle. We are not yet prepared, however, to exclude the possibility that NO neurons in the PVN are affected by the BQ123 treatment, because tissue homogenization of the entire hypothalamus used in the present study may have obscured changes in NO production in discrete groups of neurons. This issue will be addressed in future studies where cellular resolution will be obtained using in situ hybridization for constitutive NOS mRNAs.

The importance of NO in mediating the decrease in arterial pressure during recovery from restraint is illustrated by our results, which show that inhibition of central nNOS and eNOS production with L-NNA prevented the decreases in MAP values that normally occur during the rest period in both BQ123-treated and non-BQ123-treated rats. [Note that much higher concentrations of L-NNA are believed to be required to inhibit inducible NOS (30).] Inhibition of NOS with 7-NI produced MAP values that were intermediate between those of control rats and rats receiving L-NNA. As we have discussed (40), 7-NI is thought to selectively inhibit nNOS in the brain in vivo. Thus although we cannot rule out the possibility that 7-NI may have a limited inhibitory effect on eNOS, our results from using L-NNA and 7-NI suggest that NO produced by both nNOS and eNOS participates in the decrease in arterial pressure that normally occurs during recovery from psychological stress. The involvement of nNOS is in agreement with a relatively large amount of data which show that NO from this isoform decreases arterial pressure and sympathetic output from the brain during periods of homeostatic imbalance (18). Although a role for eNOS in these functions is a much more novel idea, it is not without precedent, as we have previously shown that NO from eNOS inhibits the central responses to an immune challenge (40).

Inhibition of nNOS with 7-NI produced MAP values that were indistinguishable from those in BQ123-treated rats. Together with our demonstration that NO production was reduced in brain stems of restrained rats treated with BQ123, this result suggests but does not prove that the effects on MAP values of blocking ETA receptors with BQ123 are mediated through an interaction with nNOS. This suggestion is supported by the demonstration that ETA receptors are present on neurons within many autonomic nuclei within the brain (24, 37). A more direct demonstration of interactions between central ETA receptors and NO will be the focus of future studies.

Perspectives

Increased arterial pressure is one of many protective physiological responses to psychological stress, but equally important to the survival of the animal is a return to homeostatic balance because chronically ele-
vated arterial pressure can lead to hypertension and other complications. The experiments described here show that ET\textsubscript{A} receptors and NO in the brain play important roles in reducing pressure during recovery from stress. We propose that endothelin acts on ET\textsubscript{A} receptors in autonomic centers of the brain to decrease arterial pressure as part of a general reduction in sympathetic output during recovery from stress possibly through the production of NO by nNOS.

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