Buspirone Raises Blood Pressure through Activation of Sympathetic Nervous System and by Direct Activation of $\alpha_1$-adrenergic Receptors Following Severe Hemorrhage*

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Abbreviations

ANOVA, analysis of variance

BP, blood pressure

HR, heart rate

RSNA, renal sympathetic nerve activity

5-HT1A, 5-hydroxytryptamine 1A receptor

8-OH-DPAT, 8-hydroxy-2-(di-n-propylamino)tetralin

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Abstract

Serotonin 5-HT1A receptor agonists reverse the hypotensive and sympathoinhibitory responses to severe hemorrhage in rats. To determine if 5-HT1A receptor-mediated pressor responses in hypovolemic animals are due to sympathoexcitation and/or direct vasoconstriction, blood pressure (BP), heart rate (HR) and renal sympathetic nerve activity (RSNA) responses to the partial 5-HT1A receptor agonist, buspirone, or the more selective, full 5-HT1A-receptor agonist (+)-8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) were compared in intact and ganglionic blocked, hemorrhaged Sprague-Dawley rats. Buspirone produced dose-dependent increases in BP (110 ± 4**, 86±4**, 65±7 mmHg), HR (369 ± 10**, 337±14, 277±16 bpm) and RSNA (114 ±36**, 34±21, -23±25 %Baseline for 0.2, 0.1 and 0 mg/kg, **p<0.01 vs. 0 mg/kg 3 min after injection). Ganglionic blockade with hexamethonium chloride blocked the pressor effect of 9.9 µg/kg 8-OH-DPAT and attenuated, but did not block, the pressor response to 0.2 mg/kg Bus (85±7 vs. 46±6 mmHg for buspirone + ganglionic blockade vs. saline + ganglionic blockade; p<0.01). In subsequent tests, rats treated with the selective α1-adrenergic receptor antagonist, prazosin (25 µg/kg), continued to show extensive tachycardic (+73±26 bpm) and sympathoexcitatory (128±55 % baseline) responses to 0.2 mg/kg buspirone. Ganglionic blockade combined with prazosin completely blocked all responses to buspirone. Buspirone (0.2 mg/kg) produced significant bradycardic (-89±12 bpm, p<0.01) and sympathoinhibitory (-72±7 %baseline, p<0.01) responses in euvoletic rats 3 min after injection. It is concluded that the pressor effect of buspirone is unique to hypovolemic animals and, is mediated by sympathetic activation as well as
direct activation of vascular α1-adrenergic receptors.
Progressive blood loss produces a biphasic cardiovascular response consisting of an initial phase in which compensatory increases in sympathetic-mediated vascular resistance offsets the fall in cardiac output and thereby maintains blood pressure. With continued blood loss, sympathetic activity suddenly falls leading to a significant reduction in perfusion pressure (Evans et al., 1992; Scrogin, 2003). If low perfusion pressure persists circulatory shock ensues. The current first line therapy for circulatory shock includes massive volume infusion to help re-establish cardiac output. However, if sympathetic-mediated vasoconstriction is suppressed, such volume restitution may not be sufficient to provide adequate perfusion of vital organs. Efforts to raise perfusion pressure with exogenous vasoactive peptides and catecholamines have been controversial since such treatment can exacerbate end organ ischemia by promoting excessive constriction in arterial vascular beds (Greenway and Lawson, 1966; Martel et al., 2002).

An alternative therapy includes the use of agents that raise endogenous sympathetic tone, such as low volume hypertonic saline injection (Mazzoni et al., 1988; Seki et al., 1997). The rise in sympathetic activity elicited by hypertonic saline is associated with elevations in indexes of venous tone and cardiac output (Rocha e Silva et al., 1987; Seki et al., 1997). These findings suggest that endogenous elevations in sympathetic activity may increase central venous return resulting in a more favorable hemodynamic profile than the use of direct vasoconstrictors alone.

We have found that the selective 5-HT1A-receptor agonist, 8-OH-DPAT, when administered after the onset of the sympatholytic stage of hemorrhage, also rapidly re-establishes sympathetic drive and blood pressure in conscious rats (Scrogin, 2003).
HT1A-receptor agonists have additional effects that may provide an advantage over hypertonic saline use during volume resuscitation. For instance, systemically administered 5-HT1A-receptor agonists can readily cross the blood brain barrier and act on thermoregulatory centers to reduce body temperature (Blier et al., 2002). Recent work indicates that mild hypothermia reduces reperfusion injury following resuscitation from hypovolemic shock (Takasu et al., 2003; Takasu et al., 2002). 5-HT1A-receptor agonists also stimulate the release of adrenocorticotropin-releasing hormone which may be beneficial in limiting reperfusion injury following resuscitation (Guarini et al., 1990; Vicentic et al., 1998).

Currently, it is not known whether the pressor effect of 5-HT1A-receptor agonists initiated during hypovolemia is due to sympathetic activation per se or whether such drugs also act directly on vascular receptors to promote vasoconstriction. Several 5-HT1A-receptor agonists are recognized to have significant agonist activity on $\alpha_1$-adrenergic receptors (Castillo et al., 1993). Of these, buspirone is the sole 5-HT1A agonist currently approved for clinical use in the US. Buspirone belongs to the azapirone family. Like other azapirones, buspirone is a partial agonist with high affinity for 5-HT1A receptors ($pK_i = 8.03$) (Peroutka, 1985; McCall et al., 1994). Buspirone rapidly penetrates the brain to interact with central 5-HT1A receptors as demonstrated by ex-vivo receptor binding studies (Sethy and Francis, 1988; Yocca, 1990).

Thus, buspirone has potential as an adjunct to volume resuscitation in the treatment of hypovolemic shock. However, the drug is not highly specific and has additional antagonist activity at dopamine D2 receptors (Andronati et al., 1999; Protai et al., 1998). Buspirone decreases dopamine D1 receptor-mediated responses in vivo,
suggesting that it may also have D1 receptor antagonist properties (Protais et al., 1998). Moreover, buspirone has partial agonist activity at $\alpha_1$-adrenergic receptors (Castillo et al., 1993; Castillo et al., 1995; Ogawa et al., 1995). The partial $\alpha_1$-adrenergic agonist activity of buspirone could potentially interfere with its 5-HT1A-mediated pressor effect, if 5-HT1A-receptor activation does indeed raise pressure through sympathetic activation. Since buspirone does not elicit a full agonist response at $\alpha_1$-adrenergic receptors, its occupation of such receptors could interfere with its own ability to stimulate sympathetic-mediated vascular resistance when the numbers of remaining unoccupied vascular $\alpha_1$-adrenergic receptors is low. Therefore, in the present study, we determined whether buspirone also elicits pressor effects in hemorrhaged rats as does the more specific, full 5-HT1A-receptor agonist, 8-OH-DPAT. In addition, we determined whether the pressor effects of 5-HT1A-receptor agonists in hemorrhaged rats are due to increased sympathetic drive or a direct interaction with vascular $\alpha_1$-adrenergic receptors.
Methods

Animals

Male Sprague Dawley rats weighing between 350 and 400g (Harlan, Indianapolis, ID) were given ad libitum access to food and water and acclimated to the housing facility for at least 1 wk prior to surgery. The facility was maintained at a constant temperature of 22±2°C with a light/dark cycle of 12:12 hrs. All experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the US National Institutes of Health.

Surgery

A renal sympathetic nerve recording electrode and vascular catheters were implanted as described previously (Scrogin et al., 2002). Briefly, 24 hrs before the experiment, bilateral femoral arterial catheters and a unilateral femoral venous catheter (PE-50 heat-welded to a length of PE-10) were implanted into the anesthetized rats (sodium pentobarbital, 65 mg/kg, i.p.) to enable direct measurement and of mean arterial pressure, arterial blood withdrawal and drug injection respectively. During the same surgery a stainless steel, Teflon-coated (bare di =.005 in., A-M Systems, Inc., Everett, WA) bipolar renal nerve recording electrode was implanted through a left flank incision. The electrode connector was externalized subcutaneously along with the vascular catheters at the nape of the neck. Once viability of the nerve was determined, the preparation was embedded in lightweight dental silicon (Bisico S4i, Bisico, Bielefeld, Germany). The flank incision was sutured closed in two layers with the electrode leads coiled within the subcutaneous space. The rats were allowed to recover overnight in their home cage.
Data Acquisition

During all experiments, arterial pressure, heart rate (HR) and renal sympathetic nerve activity (RSNA) were recorded continuously on a Macintosh G4 Powerbook computer using PowerLab data acquisition software (Chart v. 3.6.1, ADinstruments, Grand Junction, CO). The arterial pressure was measured with a disposable pressure transducer (Abbott Labs, North Chicago, IL) and a PowerLab bridge amplifier (ADinstruments, Grand Junction, CO). Heart rate was calculated on line using peak-to-peak detection of the pulse pressure wave. Sympathetic activity was sampled (4,000 Hz), amplified (10-20,000x) and filtered (1-3000 Hz) with a PowerLab Bioamplifier (ADinstruments, Grand Junction, CO). The recorded neurogram was full-wave rectified and integrated off line over 20 ms time bins. The background noise in the electrode recording was determined at the end of each experiment by measuring the remaining signal following injection of the ganglionic blocker, hexamethonium chloride (30 mg/kg, i.v.). Background noise was subtracted from nerve activity values to provide a measurement of RSNA. All measurements of RSNA were normalized (% baseline) to basal nerve activity determined over a 10 min period directly prior to hemorrhage. Only data from animals with greater than a 2:1 signal to noise ratio in their nerve recording signal were included in the study.

Experimental Design

Prior to the experiment the animals were connected to the recording instrumentation and withdrawal pump while resting unrestrained in their home cage. The iv catheters were flushed and connected to PE tubing filled with appropriate doses of drug or vehicle. One arterial line was connected to a withdrawal syringe pump while the
second was connected to the blood pressure transducer. The recording electrode as well as the arterial and venous tubing were connected to the recording amplifiers via 2 ft long connections to enable undisturbed recordings while the animal rested in its home cage. The rat was then allowed to rest undisturbed for at least 2 hrs prior to the hemorrhage. Arterial pressure, HR and RSNA were recorded continuously beginning 20 min prior to the hemorrhage and ending 20 min following hemorrhage termination. Controlled blood withdrawal was initiated at a rate of 3.2 ml/min/kg for 6 min after which the speed was reduced to 0.53 ml/min/kg for an additional 4 min. In preliminary test, this procedure was found to produce a consistent fall in MAP, HR and RSNA after withdrawal of approximately 11.2 ml/kg of blood or approximately 14 % of estimated blood volume. The subsequent change to the lower rate of withdrawal was sufficient to maintain bradycardic and sympatholytic responses until hemorrhage termination.

In the first experiment, 0, 0.1, or 0.2 mg/kg buspirone in 5 µl of saline was injected 7 min after the initiation of blood withdrawal. To determine if the blood pressure effects of buspirone or 8-OH-DPAT were due to sympathetic activation, saline or 30 mg/kg hexamethonium chloride was given 6 min after initiation of hemorrhage, i.e., after pressure had fallen to its nadir, followed by 0.2 mg/kg buspirone or 30 nmol/kg (9.9 µg/kg) 8-OH-DPAT one min later. To determine if buspirone’s pressor effects were related to activation of α1-adrenergic receptors, the selective α1-adrenergic receptor antagonist prazosin (25 µg/kg) was given 6 min after initiation of hemorrhage, 1 min prior to 0.2 mg/kg buspirone. In a separate experiment, hexamethonium (30 mg/kg, iv) and prazosin were administered 6 min after hemorrhage, followed 1 min later by buspirone (0.2 mg/kg, iv) or saline. To determine the effect of buspirone in euvolemic
animals, 0.2 mg/kg of buspirone was given without prior hemorrhage. At the end of each experiment, except in those experiments in which ganglionic blockade was given as part of the protocol, hexamethonium (30 mg/kg, i.v.) was administered in order to assess the signal to noise ratio of the recording preparation.

Data Analysis

Blood pressure, heart rate and RSNA (where applicable) were averaged over 1 min time bins for analysis. A 2-way analysis of variance (ANOVA) with repeated measures was used to assess the dose effect of buspirone over time in hemorrhaged-rats directly before drug or vehicle injection (7 min after initiation of hemorrhage) and 10, 15, 20, 25, and 30 min after the start of blood withdrawal. Tukey/Kramer post-hoc tests were used to compare group means at each time point. Three-way ANOVAs with repeated measures was used to assess the effect of ganglionic blockade on pressor and HR responses to buspirone or 8-OH-DPAT in hemorrhaged animals over time using the same time points. One-way ANOVAs with repeated measures and Tukey/Kramer post-hoc tests were used to determine within group effects of the first 7 min of blood withdrawal as well as within group effects of buspirone in euvolemic animals.
Results

As expected, hemorrhage produced a biphasic response (Figure 1). Within group analysis of the first seven min of data pooled across buspirone dose groups was performed to assess changes over time from the start of hemorrhage to the time of injection. As in our previous studies, blood pressure was well maintained during the initial phase of hemorrhage and then fell precipitously after the third min (9.6 ml/kg) of blood withdrawal to a nadir of 56 ± 3 mmHg after 7 min (19.7 ml/kg) of blood withdrawal. During the initial 3 min of hemorrhage, heart rate rose 30 ± 6 bpm (p<0.05 vs. pre-hemorrhage baseline). During the same time period sympathetic activity almost doubled to 93± 16 % of baseline (p<0.01). The blood pressure fall was paralleled by a large fall in heart rate of –126 ± 40 bpm. Sympathetic activity also declined back to baseline levels.

Buspirone produced a dose-dependent acceleration of blood pressure recovery that began immediately after injection of the drug (Figure 1). The 0.2 mg/kg dose of drug produced a full recovery of blood pressure within 3 min of injection while the 0.1 mg/kg dose produced an intermediate recovery of pressure. Both doses of buspirone produced a similar rapid rise in heart rate that was maximal within 1 min of injection. Heart rate subsequently declined in both groups. However, in rats treated with the larger dose of buspirone, HR remained significantly elevated above that of saline-treated rats by 3 min after injection (p<0.01). Both doses of buspirone also rapidly raised sympathetic activity within the first minute of injection. The 0.2 mg/kg dose of buspirone produced a
sustained elevation in sympathetic activity that was significantly greater than saline-treated rats 3 min after injection ($p<0.05$). In contrast, the lower dose of buspirone produced only a transient rise in sympathetic activity that subsequently fell to levels similar to that of control animals 3 min after injection.

Ganglionic blockade with hexamethonium completely blocked sympathetic activity. Activity remained suppressed in the saline-treated group throughout the experiment. However, rats treated with the ganglionic blocker and subsequent buspirone or 8-OH-DPAT showed a slight tendency for recovery of sympathetic activity towards the end of the recording period (Figures 2 and 3). Autonomic blockade also attenuated the recovery of blood pressure following termination of blood withdrawal, particularly in the latter stage of recovery (Figure 2). During the recorded recovery period, hexamethonium-treated rats never fully regained baseline pressure, as did saline-treated controls (Figure 2). Ganglionic blockade also produced a rapid rise in HR when given after initiation of the hypotensive phase of hemorrhage. Blockade of ganglionic transmission attenuated the initial blood pressure response to buspirone as well (Figure 2). However, buspirone continued to have a significant pressor effect despite blockade of sympathetic activity. As with saline-treated rats given hexamethonium, blood pressure of buspirone-treated rats subjected to ganglionic blockade did not fully recover over the duration of the recording period. Buspirone did not have any further tachycardic effects when given after hexamethonium. In contrast, ganglionic blockade prevented development of significant pressor and tachycardic responses to the full 5-HT1A-receptor agonists, 8-OH-DPAT (Figure 3).
Prazosin blocked the initial rapid rise in pressure normally observed with buspirone administration (Figure 4). However, buspirone continued to produce a modest acceleration of blood pressure recovery in rats pre-treated with prazosin. In contrast to buspirone’s immediate pressor effects in saline- or hexamethonium-treated rats, a significant rise in pressure in prazosin-treated rats was not apparent until several minutes after injection. The large increase in sympathetic activity produced by buspirone in prazosin-treated rats was rapid in onset, but tended to decline slightly between the 3rd and 8th min after buspirone administration. After this initial decline, activity began to rise further and remained high through the rest of the recording period. This transient reduction of the sympathetic activation is shown more clearly in Figure 5, which depicts the effects of buspirone in an individual prazosin-treated animal. Blockade of both ganglionic transmission and $\alpha_1$-adrenergic receptors completely prevented the blood pressure and heart rate responses to buspirone in hemorrhaged-rats (Figure 6).

Administration of the 0.2 mg/kg dose of buspirone in euvoletic rats resulted in a mild and transient, but non-significant hypotensive response (Figure 7). Heart rate dropped precipitously (-89 ± 12 bpm) within 5 min of buspirone injection. HR eventually recovered to baseline levels within 18 min of buspirone injection. Buspirone injection led to a sharp drop in sympathetic activity that reached a minimum of -72 ± 7% of baseline within 5 min of injection. The sympathoinhibitory response was transient and was reversed relatively rapidly.
Discussion

Trauma is the leading cause of death of young people in the U.S. (150,000/year). Most trauma deaths result either from insufficient tissue perfusion, due to excessive blood loss (i.e., shock), or the development of inflammation, infection and end organ damage following resuscitation (Sauaia et al., 1995). The current treatment for hypovolemic shock includes massive and rapid infusion of crystalloid fluids to raise cardiac output (Martel et al., 2002). A relatively small number of vasoconstrictor agents can also be used as adjuncts to volume resuscitation when use of the latter therapy alone fails to sufficiently improve cardiac output. The type and dose of vasoconstrictor agents used in hypovolemic shock remains controversial as many are reported to exacerbate tissue injury in ischemia-sensitive vascular beds at doses that provide sufficient recovery of arterial pressure (Kellum and Pinsky, 2002). It is clear that current strategies for treatment of hypovolemic shock are not adequate in many situations. Consequently, new therapies are sought which can improve patient outcomes.

Previous studies have shown that the non-selective serotonin ligand, methysergide, accelerates recovery of blood pressure in anesthetized cats subjected to hypotensive hemorrhage. The same study demonstrated improved survival among cats treated with methysergide (Elam et al., 1985). In previous work we demonstrated that both methysergide and the relatively selective 5-HT1A receptor agonist, 8-OH-DPAT, act on 5-HT1A receptors within the central nervous system to prolong the sympathoexcitatory response in conscious rats subjected to severe hemorrhage (Scrogin et al., 2000). In subsequent work, we found that systemic 8-OH-DPAT rapidly reversed the sympatholytic response to hypotensive hemorrhage when administered after...
establishment of hypotensive hemorrhage (Scrogin, 2003). In addition, 5-HT1A-receptor agonists reduce core body temperature and stimulate the release of endogenous ACTH, both of which have been found to have beneficial effects in suppressing reperfusion injury following resuscitation from hypovolemic shock (Blier et al., 2002; Guarini, Tagliavini, Bazzani, Ferrari, and Bertolini, 1990; Takasu et al., 2002; Vicentic, Li, Battaglia, and Van de Kar, 1998). Together these studies suggest that lipophilic 5-HT1A-receptor agonists have potential as adjuncts to volume resuscitation in the treatment of hypovolemic shock. Currently, the only 5-HT1A-receptor agonist approved for clinical use in the United States is buspirone, a partial 5-HT1A-receptor agonist with significant affinity for several other receptor types. Therefore, this study sought to determine 1) if buspirone also has significant pressor effects in animals subjected to hypotensive hemorrhage and 2) if the pressor effect exhibited by 5-HT1A agonists is mediated by sympathetic activation.

The present study demonstrated that buspirone dose-dependently restored blood pressure, heart rate and renal sympathetic nerve activity when administered during the hypotensive phase of hemorrhage in conscious rats. Buspirone continued to produce a significant pressor effect even after ganglionic blockade, while the more selective, full 5-HT1A-receptor agonist, 8-OH-DPAT, did not. Treatment with the selective α1-adrenergic receptor antagonist, prazosin, strongly suppressed and delayed the pressor, but not the tachycardic and sympathoexcitatory responses to buspirone. In contrast, the same dose of buspirone elicited hypotensive, bradycardic and sympathoinhibitory responses in euvolemic rats.
The data indicate that buspirone owes much of its pressor effect in hypovolemic animals to sympathetic activation. The remainder of the pressor effect appears to be mediated by direct activation of vascular $\alpha_1$-adrenergic receptors since combined treatment with hexamethonium and prazosin completely prevented the pressor effect of the drug. Though the receptor through which buspirone mediates its sympathoexcitatory effect was not determined in this study, the response is most likely mediated through activation of central 5-HT1A receptors. Previous work demonstrated that, when administered prior to hemorrhage, the selective 5-HT1A-receptor antagonist, WAY100635, completely reversed the ability of the full 5-HT1A-receptor agonist, 8-OH-DPAT, to prolong the sympathoexcitatory response to hemorrhage. WAY100635 also dose-dependently reversed the ability of the non-selective 5-HT ligand, methysergide, to delay the sympatholytic response to hemorrhage in conscious rats (Scrogin et al., 2000). The almost complete blockade of the pressor response to 8-OH-DPAT by ganglionic blockade in the present study also suggests that 5-HT1A-receptor activation raises pressure in hypovolemic animals primarily by increased sympathetic-mediated vasoconstriction.

This view is contradicted by our findings that buspirone produced a profound sympathetic inhibition in euvolemic animals. The sympathoinhibitory effect of 5-HT1A agonists are well documented (Laubie et al., 1989; Nosjean and Guyenet, 1991). 5-HT1A receptors are coupled to the Gi/Go/Gz family of inhibitory G-proteins (Albert et al., 1996; Barr et al., 1997; Barr and Manning, 1997). Activation of 5-HT1A receptors normally leads to hyperpolarization of neurons (Bobker and Williams, 1989). Indeed, the sympathoinhibitory response to systemic 5-HT1A-receptor agonist administration in
euvolemic animals is likely due to activation of post-synaptic 5-HT1A receptors expressed by bulbspinal neurons of the rostral ventrolateral medulla (rVLM) that normally provide tonic excitatory input to pre-ganglionic sympathetic neurons (Bago et al., 1999; Nosjean and Guyenet, 1991). It is possible that the atypical sympathoexcitatory response to 5-HT1A-receptor agonists observed during hemorrhage results from hyperpolarization of an alternative population of cells that provides inhibitory synaptic input to rVLM pre-motor neurons or some other population of pre-sympathetic neurons during severe hypovolemia. This view assumes that such 5-HT1A-sensitive inhibitory input is negligible in euvolemic animals, but highly active during severe hypovolemia. If this scenario is correct, then the overall cardiovascular response to systemic 5-HT1A-receptor agonist administration should depend upon the prevailing level of 5-HT1A-receptor sensitive inhibitory drive to sympathetic regulatory nuclei. Moreover, the overall response to 5-HT1A-receptor agonist administration should represent the combined sympathoexcitatory and sympathoinhibitory effects of 5-HT1A receptor activation. Interestingly, the transient dip in sympathetic activation observed following buspirone administration in hypovolemic prazosin-treated rats coincided in time with the onset of buspirone-mediated sympathoinhibition in euvolemic rats. These data support the view that opposing responses elicited by two separate populations of 5-HT1A receptors have additive effects on sympathetic drive.

The 5-HT1A-receptor mediated recovery of sympathetic drive remained intact and appeared somewhat exaggerated after $\alpha_1$-adrenergic blockade, as evidenced by the large increases in heart rate and sympathetic activity following buspirone administration in prazosin-treated rats. The responses were likely augmented due to the lack of blood
pressure rise and reduced stimulus for arterial baroreceptor activation. Animals with intact vasoconstrictor responses also had significant tachycardic responses to buspirone and 8-OH-DPAT indicating that the positive chronotropic effects of 5-HT1A receptor agonists persist even during the normalization of pressure. In contrast, elevation of pressure with the selective α1-adrenergic agonist, phenylephrine, suppresses sympathetic activity and heart rate in rabbits hemorrhaged to hypotension, presumably through activation of the arterial baroreceptors (Hasser and Schadt, 1992). These data indicate that 5-HT1A-receptor agonists may have a significant advantage over alternative vasoconstrictor agents in re-establishing perfusion pressure since the former may also have significant positive effects on cardiac output.

Interestingly, buspirone continued to promote a significant pressor effect in the presence of prazosin. This was not due to incomplete α1-adrenergic receptor blockade since the same dose of prazosin combined with hexamethonium completely blocked the pressor effect of buspirone. Moreover, in euvoletic rats this dose of prazosin completely blocked the pressor response to a supramaximal pressor dose of phenylephrine (3.0 µg/kg, i.v.; data not shown). The origin of the remaining pressor response could be due to a number of alternative sympathetic-mediated responses including α2-adrenergic receptor mediated venoconstriction (Nilsson, 1985; Pang and Tabrizchi, 1986), neuropeptide Y- or ATP-mediated vasoconstriction (Bradley et al., 2003) and or β-adrenergic-mediated stimulation of angiotensin II production and its direct vasoconstrictor capacity or its ability to stimulate vasopressin release (Davis and Freeman, 1976; Suzuki and Hashiba, 1986). However, it is clear that other than direct α1-
adrenergic receptor activation, buspirone’s pressor effects are dependent upon activation of the sympathetic nervous system.

Our results indicate that 5-HT1A-receptor agonists raise pressure during hypovolemia through direct stimulation of vascular \( \alpha_1 \)-adrenergic receptors and elevations of endogenous sympathetic drive. While these data suggest that 5-HT1A-receptor agonists may provide a novel alternative to current therapies in circulatory shock, it remains to be determined whether the ability to raise sympathetic tone provides a more favorable hemodynamic profile than exogenous administration of vasoactive drugs in the hypovolemic animals.
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Figure Legends:

Figure 1. Mean arterial pressure (MAP), heart rate (HR), and renal sympathetic nerve activity (RSNA) during hemorrhage (indicated by shaded box) and recovery in rats treated with buspirone (BUS, 0.1 mg/kg or 0.2 mg/kg, i.v.) or saline 7 min after initiation of hemorrhage. Values are group means ± SE. Group n are indicated in parentheses. Between-group comparisons were performed using Tukey/Kramer post hoc tests directly before injection and 10, 15, 20, 25, and 30 min after initiation of hemorrhage. **P<0.01, 0.2 mg/kg buspirone vs. saline; δδP< 0.01, 0.1 mg/kg buspirone vs. saline; ##P< 0.01, 0.1 mg/kg vs. 0.2 mg/kg buspirone.

Figure 2. MAP, HR and RSNA during hemorrhage (shaded box) and recovery in rats treated with either hexamethonium (HEX, 30 mg/kg, i.v.) or saline (SAL) 6 min after initiation of hemorrhage, and either buspirone (0.2 mg/kg, i.v.) or saline 1 min later. Values are group means ± SE. Group n are indicated in parentheses. Comparisons were performed using Tukey/Kramer post hoc tests at the time of buspirone/saline injection and 10, 15, 20, 25, and 30 min after initiation of hemorrhage. **P< 0.01, SAL/BUS vs. HEX/BUS; ##P< 0.01, #P<0.05, SAL/SAL vs. HEX/SAL; δδP< 0.01, HEX/BUS vs. HEX/SAL.

Figure 3. MAP, HR and RSNA during hemorrhage (shaded box) and recovery in rats treated with either hexamethonium (HEX, 30 mg/kg, i.v.) or saline (SAL) 6 min after initiation of hemorrhage, and either (+)-8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT, 9.9 µg/kg, i.v.) or saline 1 min later. Values are group means ± SE. Group n are
indicated in parentheses. Comparisons were made using Tukey/Kramer post hoc tests at the time of 8-OH-DPAT injection and 10, 15, 20, 25 and 30 min after initiation of hemorrhage. **\(P<0.01\), *\(P<0.05\), SAL/8-OH-DPAT vs. HEX/8-OH-DPAT; \(^{\delta\delta}P<0.01\), \(^{\delta}P<0.05\), SAL/8-OH-DPAT vs. SAL/SAL; \(^{##}P<0.01\), \(^#P<0.05\), SAL/SAL vs. HEX/SAL.

Figure 4. MAP, HR and RSNA during hemorrhage (shaded box) and recovery in rats treated with prazosin (25 \(\mu\)g/kg, i.v.) at 6 min and buspirone (0.2 mg/kg, i.v.) or saline 7 min after initiation of hemorrhage. Values are group means ± SE. Group n are indicated in parentheses. For RSNA data, one rat was excluded from the buspirone-treated group due to poor electrode signal. Between-group comparisons were performed using Tukey/Kramer post hoc tests at the time of buspirone injection and 10, 15, 20, 25, and 30 min after initiation of hemorrhage. **\(P< 0.01\), *\(P< 0.05\) between group.

Figure 5. Blood pressure, HR and integrated RSNA before, during and after hemorrhage (shaded box) in an individual rat given prazosin (25 \(\mu\)g/kg, i.v.) at 6 min and buspirone (0.2 mg/kg, i.v.) 1 min later.

Figure 6. Blood pressure and HR during hemorrhage (shaded box) and recovery in rats treated with hexamethonium (HEX, 30 mg/kg, i.v.) and prazosin (PRAZ, 25 \(\mu\)g/kg, i.v.) 6 min after initiation of hemorrhage, and either buspirone (BUS, 0.2 mg/kg, i.v.) or saline (SAL) 1 min later. Values are group means ± SE. Group n are indicated in parentheses.
Figure 7. Blood Pressure, HR and RSNA of euvolemic rats treated with systemic buspirone (0.2 mg/kg, n = 5, i.v.). Values are group means ± SE. Group n = 6. Within-group comparisons were performed at 5-min intervals beginning at time 0 using Tukey/Kramer post hoc test. **P<0.01, * P< 0.05 vs. time 0.
Figure 1
Figure 2
Figure 3
Figure 7

MAP (mmHg)

HR (bpm)

RSNA (%Δbaseline)

Time (min)

Buspirone

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