Buspirone Raises Blood Pressure through Activation of Sympathetic Nervous System and by Direct Activation of α1-Adrenergic Receptors after Severe Hemorrhage

Patrick Osei-Owusu and Karie E. Scrogin
Department of Pharmacology and Experimental Therapeutics, Loyola University Chicago, Stritch School of Medicine, Maywood, Illinois
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ABSTRACT

5-Hydroxytryptamine 1A (5-HT1A) receptor agonists reverse the hypotensive and sympathoinhibitory responses to severe hemorrhage in rats. To determine whether 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 mm Hg), HR (369 ± 10**, 337 ± 14, 277 ± 16 beats per minute (bpm)), and RSNA (114 ± 36**, 34 ± 21, −23 ± 25% baseline for 0.2, 0.1, and 0 mg/kg; **p < 0.01 versus 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 buspirone (85 ± 7 versus 46 ± 6 mm Hg for buspirone + ganglionic blockade versus 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 euvolemic 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 replacement of vital organs. Efforts to raise perfusion pressure with exogenous vasoactive peptides and catecholamines have been controversial because 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-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT), when administered after the onset of the sympatholytic stage of hemorrhage, produces a pressor response. This effect is unique to hypovolemic animals and is mediated by direct activation of vascular α1-adrenergic receptors.

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ABBREVIATIONS: 5-HT1A, 5-hydroxytryptamine 1A receptor; 8-OH-DPAT, 8-hydroxy-2-(di-n-propylamino)tetralin; BP, blood pressure; HR, heart rate; RSNA, renal sympathetic nerve activity; PE, polyethylene; MAP, mean arterial pressure; ANOVA, analysis of variance; bpm, beats per minute; WAY-100,635, [O-methyl-5-HT]-N-[2-(4-[2-methoxyphenyl]-1-piperazinyl)ethyl]-N-(2-pyridyl)jicyclohexanecarboxamide trihydrochloride.
hemorrhage, also rapidly reestablishes sympathetic drive and blood pressure in conscious rats (Scrogin, 2003). 5-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 after resuscitation from hypovolemic shock (Takasu et al., 2002; Takasu et al., 2003). 5-HT1A receptor agonists also stimulate the release of adrenocorticotropic-releasing hormone, which may be beneficial in limiting reperfusion injury after resuscitation (Gaurini 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 α1-adrenergic receptors (Castillo et al., 1993). Of these, buspirone is the sole 5-HT1A agonist currently approved for clinical use in the United States. Buspirone belongs to the azapirone family. Like other azapirones, buspirone is a partial agonist with high affinity for 5-HT1A receptors (pKᵢ = 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 (Protais et al., 1998; Andronati et al., 1999). 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 α1-adrenergic receptors (Castillo et al., 1993, 1995; Ogawa et al., 1995). The partial α1-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. Because buspirone does not elicit a full agonist response at α1-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 α1-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 α1-adrenergic receptors.

Materials and Methods

Animals. Male Sprague-Dawley rats weighing between 350 and 400 g (Harlan, Indianapolis, IN) were given ad libitum access to food and water and acclimated to the housing facility for at least 1 week before surgery. The facility was maintained at a constant temperature of 22 ± 2°C with a light/dark cycle of 12:12 h. All experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the 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 h 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 of mean arterial pressure, arterial blood withdrawal, and drug injection, respectively. During the same surgery, a stainless steel, Teflon-coated (bare diameter = 0.005 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 version 3.6.1; ADInstruments, Grand Junction, CO). The arterial pressure was measured with a disposable pressure transducer (Abbott Laboratories, North Chicago, IL) and a PowerLab bridge amplifier (ADInstruments). Heart rate was calculated on line using peak-to-peak detection of the pulse pressure wave. Sympathetic activity was sampled (4000 Hz), amplified (10–20,000×), and filtered (1–3000 Hz) with a PowerLab Bioamplifier (ADInstruments). 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 after 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 (percentage of baseline) to basal nerve activity determined over a 10-min period directly before 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. Before the experiment, the animals were connected to the recording instrumentation and withdrawal pump while resting unrestrained in their home cage. The i.v. 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, whereas the second was connected to the blood pressure transducer. The recording electrode as well as the arterial and venous tubing was 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 h before the hemorrhage. Arterial pressure, HR, and RSNA were recorded continuously beginning 20 min before the hemorrhage and ending 20 min after 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 mean arterial pressure (MAP), HR, and RSNA after withdrawal of approximately 11.2 ml/kg 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 whether 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 1 min later. To determine whether 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 before 0.2 mg/kg buspirone. In a separate experiment, hexamethonium (30 mg/kg i.v.) and prazosin were administered 6 min after hemorrhage, followed 1 min later by buspirone (0.2 mg/kg i.v.) or saline. To determine the effect of buspirone in euvoletic animals, 0.2 mg/kg 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 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 two-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 euvoletic animals.

Results

As expected, hemorrhage produced a biphasic response (Fig. 1). Within-group analysis of the first 7 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 3rd min (9.6 ml/kg) of blood with-
Buspirone produced a dose-dependent acceleration of blood pressure recovery that began immediately after injection of the drug (Fig. 1). The 0.2 mg/kg dose of drug produced a full recovery of blood pressure within 3 min of injection, whereas the 0.1 mg/kg dose produced an intermediate recovery of blood pressure within 3 min of injection, whereas the 0.05 mg/kg dose did not fully recover over the duration of the recording period. Autonomic blockade also attenuated the recovery of blood pressure after termination of blood withdrawal, particularly in the latter stage of recovery (Fig. 2). During the recorded recovery period, hexamethonium-treated rats never fully regained baseline pressure, as did saline-treated controls (Fig. 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 (Fig. 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 agonist 8-OH-DPAT (Fig. 3).

Prazosin blocked the initial rapid rise in pressure normally observed with buspirone administration (Fig. 4). However, buspirone continued to produce a modest acceleration of blood pressure recovery in rats pretreated 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 it 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 Fig. 5, which depicts the effects of buspirone in an individual prazosin-treated animal. Blockade of both ganglionic transmission and α1-adrenergic receptors completely prevented the blood pressure and heart rate responses to buspirone in hemorrhaged rats (Fig. 6).

Administration of the 0.2 mg/kg dose of buspirone in euolemic rats resulted in a mild and transient, but nonsignificant hypotensive response (Fig. 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 United States (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 after 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 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 because many are reported to exacerbate tissue injury in ischemia-sensitive vascular beds at doses that provide sufficient recovery of arterial pressure (Kellum and Finsky, 2002). It is clear that current strategies for treatment of hypovolemic shock are not adequate in many situations. Consequently, new therapies are sought that can improve patient outcomes.

Previous studies have shown that the nonselective 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 adrenocorticotropic hormone, both of which have been found to have beneficial effects in suppressing reperfusion injury after resuscitation from hypovolemic shock (Guarini et al., 1990; Vicentic et al., 1998; Blier et al., 2002; Takasu et al., 2002). Together, these stud-
lies 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) whether buspirone also has significant pressor effects in animals subjected to hypotensive hemorrhage, and 2) whether 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, whereas 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 seems to be mediated by direct activation of vascular α1-adrenergic receptors because combined treatment with hexamethonium and prazosin completely prevented the pressor effect of the drug. Although 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 before hemorrhage, the selective 5-HT1A receptor antagonist WAY-100635 completely reversed the ability of the full 5-HT1A receptor agonist 8-OH-DPAT to prolong the sympathoexcitatory response to hemorrhage. WAY-100635 also dose dependently reversed the ability of the nonselective 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 euvoletic animals. The sympathoinhibitory effect of 5-HT1A agonists is 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 (Bokker and Williams, 1989). Indeed, the sympathoinhibitory response to systemic 5-HT1A receptor agonist administration in euvoletic animals is likely due to activation of postsynaptic 5-HT1A receptors expressed by bulbospinal neurons of the rostral ventrolateral medulla that normally provide tonic excitatory input to preganglionic sympathetic neurons (Nosjean and Guyenet, 1991; Bago et al., 1999). 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 rostral ventrolateral medulla premotor neurons or some other population of presympathetic neurons during severe hypovolemia. This view assumes that such 5-HT1A-sensitive inhibitory input is negligible in euvoletic 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 after buspirone administration in hypovolemic prazosin-treated rats coincided in time with the onset of buspirone-mediated sympathoinhibition in euvoletic 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 seemed somewhat exaggerated after α1-adrenergic blockade, as evidenced by the large increases in heart rate and sympathetic activity after 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 sympathethic activity and heart rate in rabbits hemorhaged 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 restablishing perfusion pressure because 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 because 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 sympathetically-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 hypovolemic through direct stimulation of vascular α1-adrenergic receptors and elevations of endogenous sympathetic drive. Although 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.

References


Address correspondence to: Dr. Karie Scrogin, Department of Pharmacology and Experimental Therapeutics, Loyola University Chicago, Stritch School of Medicine, Maywood, IL 60153. E-mail: kscrog@lumc.edu