The Serotonin 5-Hydroxytryptaphan$_{1A}$ Receptor Agonist, (+)8-Hydroxy-2-(di-n-propylamino)-tetralin, Stimulates Sympathetic-Dependent Increases in Venous Tone during Hypovolemic Shock

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ABSTRACT
Adjuvant treatment of hypovolemic shock with vasoconstrictors is controversial due to their propensity to raise arterial resistance and exacerbate ischemia. A more advantageous therapeutic approach would use agents that also promote venoconstriction to augment perfusion pressure through increased venous return. Recent studies indicate that 5-hydroxytryptophan (5-HT)$_{1A}$ receptor agonists increase blood pressure by stimulating sympathetic drive when administered after acute hypotensive hemorrhage. Given that venous tone is highly dependent upon sympathetic activation of $\alpha_2$-adrenergic receptors, we hypothesized that the 5-HT$_{1A}$ receptor agonist, (+)8-hydroxy-2-(di-n-propylamino)-tetralin (8-OH-DPAT), would increase venous tone in rats subject to hypovolemic shock through sympathetic activation of $\alpha_2$-adrenergic receptors. Systemic administration of 8-OH-DPAT produced a sustained rise in blood pressure (+4.2 ± 0.7 mm Hg, $P < 0.01$ versus saline) and mean circulatory filling pressure (+$4.2 \pm 0.7$ mm Hg, $P < 0.01$ versus saline) in conscious rats subjected to hypovolemic shock. An equipressor infusion of epinephrine failed to influence mean circulatory filling pressure (MCFP). Ganglionic blockade, $\alpha_1$-, or peripheral $\alpha_2$-adrenergic receptor blockade prevented the rise in MCFP observed with 8-OH-DPAT, but only $\alpha_1$-adrenergic receptor blockade diminished the pressor effect of the drug ($P < 0.01$). 8-OH-DPAT raises blood pressure in rats in hypovolemic shock through both direct vascular activation and sympathetic activation of $\alpha_1$-adrenergic receptors. The sympathoexcitatory effect of 8-OH-DPAT contributes to elevated venous tone through concurrent activation of both $\alpha_1$- and $\alpha_2$-adrenergic receptors. The data suggest that 5-HT$_{1A}$ receptor agonists may provide an advantageous alternative to currently therapeutic interventions used to raise perfusion pressure in hypovolemic shock.

Progressive and severe blood loss elicits a complex series of autonomic responses that help to maintain or restore arterial blood pressure. During the initial phase of blood loss, arterial baroreflex-mediated increases in sympathetic drive help to maintain arterial pressure. If blood loss continues, these compensatory responses suddenly abate resulting in a syncopeal-like episode characterized by low sympathetic activity and bradycardia (Schadt and Ludbrook, 1991). It is speculated that this latter phase may provide adaptive means to increase cardiac filling and to help maintain cerebral perfusion (Oberg and Thoren, 1970; van Lieshout et al., 2003). If hypotension persists, arterial baroreflex activity slowly recovers and progressive increases in sympathetic drive and tachycardia develop. The clinical features of this third phase of hemorrhage are commonly observed in patients who arrive in the emergency room after traumatic blood loss. Interventions at this stage must be rapid to prevent patients from progressing to a fourth, mostly irreversible stage of shock characterized by insensitivity to vasoconstrictors and high capillary permeability, both of which contribute to further maldistribution of blood volume and eventually death.

Rapid reinfusion of volume is a universally accepted treatment of hypovolemic shock. However, the type of resuscita-
tion fluid used, as well as the amount and rate of reinfusion, remain controversial. Also controversial is the choice of vasoconstrictor adjuvants used to help raise perfusion pressure. Epinephrine and other sympathomimetic agents are commonly given to support blood pressure during severe hypotensive shock when volume alone is insufficient to maintain pressure. However, catecholamine use is fraught with complications related to excessive vasoconstriction and exacerbation of ischemia as well as generation of arrhythmias (Meier-Hellmann et al., 1997). More recent evidence indicates that vasopressin and vasopressin analogs may be good alternatives to maintain arterial blood pressure in various types of shock (Cam et al., 2004). Although vasopressin is a highly potent arterial vasoconstrictor, it has virtually no vasoconstrictor effects on the venous vasculature (Warner, 1990). Theoretically, pressor agents that promote venous return and cardiac filling would provide a more favorable hemodynamic response than agents that act primarily by increasing arterial resistance. However, little is known about the venoconstrictor effects of pressor agents in hypovolemic shock.

We have shown that the 5-HT1A receptor agonist (+)-8-hydroxy-2-(di-n-propylamino)-tetralin (8-OH-DPAT) produces a potent sympathoexcitatory response in conscious rats when administered during the syncopal phase of blood loss (Scroggin, 2003; Osei-Owusu and Scroggin, 2004b). Preliminary data also indicate that 8-OH-DPAT is an effective pressor agent when administered to rats in hypovolemic shock (Henze et al., 2005). Venous tone is regulated largely by sympathetic drive (Pang, 2001). Therefore, we tested the hypothesis that 8-OH-DPAT increases arterial pressure during hypovolemic shock, in part, by stimulating sympathetic-mediated increases in venous tone through adrenergic receptor activation.

**Materials and Methods**

**Animals**

Male Sprague-Dawley rats weighing 310 to 360 g (Harlan, Indianapolis, IN) were maintained in the institutional animal facility under standard conditions (22 ± 2°C ambient temperature, 12:12 h light/dark cycle) with water and food provided ad libitum. 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**

Four days prior to experiments, rats were anesthetized with sodium pentobarbital (60 mg/kg intraperitoneally; Sigma-Aldrich, St. Louis, MO) and instrumented with bilateral femoral arterial and venous catheters for measurement of arterial pressure, arterial blood withdrawal, and drug injections, respectively. Silastic tubing (o.d. 0.037 inches) was inserted into the thoracic vena cava via the femoral vein for measurement of central venous pressure. A saline-filled inflatable balloon-tipped catheter (Vesta, Inc., Franklin, WI) was inserted into the right atrium via the jugular vein to allow brief cessation of circulation for measurement of mean circulatory filling pressure (MCFP), an indirect measure of venous tone. All catheters were tunneled under the skin to exit at the nape of a neck.

**Experimental Protocols**

**Hemorrhage Procedure.** On the day of the experiment, animals were connected to the recording instrumentation while resting unrestrained in their home cage. Two measurements of baseline MCFP were taken 20 and 10 min prior to initiation of hemorrhage according to methods developed by Yamamoto et al. (1980). Hemorrhage was initiated using a modified Wigger’s model. Blood was withdrawn at a rate of 3.2 ml/kg/min for 6 min, after which the rate was reduced to 0.53 ml/kg/min for an additional 4 min. Over the following 15 min, small amounts of blood (0.1–0.25 ml) were withdrawn or infused manually to maintain mean arterial pressure (MAP) at 50 mm Hg. All blood volume manipulations were terminated 25 min after initiation of hemorrhage, after which blood pressure was allowed to fluctuate. MCFP measurements were performed 20, 30, 40, 50, and 60 min after initiation of blood withdrawal.

**Study 1.** Animals were randomly assigned to one of three experimental groups, all of which were given saline (150 μl i.v.) 15 min after the initiation of blood withdrawal to control for volume of drug injections used in later protocols. Ten minutes later, immediately after the termination of blood withdrawal, animals were given 8-OH-DPAT (9.85 μg/kg/150 μl i.v.; Sigma), 15 min after the initiation of hemorrhage, followed 10 min later by either saline or 8-OH-DPAT (9.85 μg/kg/150 μl i.v.).

**Study 2.** Rats were subject to the hemorrhage protocol described above but were given the autonomic ganglionic blocker, hexamethonium chloride (30 mg/kg i.v.; Sigma), 15 min after the initiation of hemorrhage, followed 10 min later by either saline or 8-OH-DPAT (9.85 μg/kg/150 μl i.v.).

**Study 3.** Rats were treated as in study 2 but were pretreated with the α1-adrenergic receptor blocker, prazosin (25 μg/kg i.v.; Sigma), rather than hexamethonium.

**Study 4.** Rats were treated as in study 2 except they were pretreated with peripherally acting α2-adrenergic receptor blocker, L-659,066 (100 μg/kg i.v.; Merck & Co., Inc., Rahway, NJ), rather than hexamethonium.

**Data Acquisition and Analysis.** During all experiments, arterial and central venous pressures (CVPs) were recorded continuously on a Macintosh G4 PowerBook computer using PowerLab data acquisition software (Chart version 5.2.1; ADInstruments, Grand Junction, CO). Heart rate was calculated online using peak-to-peak detection of the arterial pulse pressure wave. Mean arterial pressure, heart rate (HR), and CVP were averaged within subject over 20-s segments and averaged within groups at 5-min intervals.

MCFP was determined by initiating circulatory arrest by brief (~5 s) inflation of the balloon catheter. During balloon inflation, central venous pressure increased to a plateau level (VPP), whereas MAP fluctuated. MCFP measurements were performed 20, 30, 40, 50, and 60 min after the initiation of hemorrhage.

Two and three-way ANOVAs with repeated measures were used to determine effects of autonomic manipulations and 8-OH-DPAT or epinephrine treatment over time (from 25–60 min after start of hemorrhage) on hemodynamic parameters where appropriate. Separate one- and two-way ANOVAs were used to assess effects of pressor agents on MCFP or the effects of hexamethonium, prazosin, or L-659,066 treatment on MCFP responses to 8-OH-DPAT over time (from 20–60 min after start of hemorrhage). Significant main effects and interactions were followed up with Tukey/Kramer post hoc tests. Total blood loss was pooled across pretreatment groups. Total blood loss and change in hematocrit were analyzed by two-way ANOVA followed by Tukey/Kramer post hoc tests. Change in plasma protein and hematocrit of the two groups treated with L-659,066 were excluded from the ANOVA due to excessive variability.
Results

Statistical analyses showed no differences in hemodynamic responses to hemorrhage prior to drug treatment in any of the groups. Thus, BP, HR, and CVP data obtained prior to drug administration were pooled across groups for clarity of presentation and to assess the hemodynamic profile during the initial blood withdrawal period.

**Hemodynamic Effect of 8-OH-DPAT in Circulatory Shock.** The initial blood withdrawal (22.4 ml/kg) over the first 10 min of hemorrhage caused a precipitous drop in MAP (−70.4 ± 3.5 mm Hg), HR (−138 ± 23 beats per minute), and CVP (−1.5 ± 0.5 mm Hg). An additional 12.2 ± 1.0 ml/kg blood was withdrawn over the following 15 min to maintain MAP at 50 mm Hg. Heart rate reached a nadir 10 min after initiation of blood withdrawal but then began to rise steadily and stabilized near baseline by the end of blood withdrawal. Changes in CVP paralleled changes in MAP (Fig. 1).

Following termination of hemorrhage, 8-OH-DPAT administration caused a rapid rise in MAP that persisted throughout the 35-min posthemorrhage recording period. Heart rate and CVP were not affected by 8-OH-DPAT. Continuous infusion of epinephrine, titrated to match the pressor effect of 8-OH-DPAT, caused a distinct tachycardia during the early part of the infusion (Fig. 1).

Balloon inflation prior to hemorrhage caused a large rise in CVP. In subsequent tests after blood loss, the rise in CVP was markedly attenuated and remained low throughout the posthemorrhage period in saline-treated rats. The rise in CVP during balloon inflation was exaggerated in hemorrhaged rats given 8-OH-DPAT (data not shown). This resulted in a significant elevation of MCFP that lasted throughout the recovery period. Epinephrine infusion had no effect on MCFP (Fig. 2).

**Effect of Autonomic Blockade on Hemodynamic Responses to 8-OH-DPAT.** Ganglionic blockade caused an immediate drop in pressure below the target MAP of 50 mm Hg (data not shown). This was quickly rectified by reinfusion of a small amount of shed blood. As a result, the total blood withdrawal needed to sustain hypotension was reduced in rats given hexamethonium (Table 1). Ganglionic blockade had a slight but nonsignificant tachycardic effect and did not influence CVP (data not shown).

Ganglionic blockade attenuated recovery of blood pressure following termination of hemorrhage. However, the immediate pressor response to 8-OH-DPAT was similar in intact and ganglionic-blocked rats compared with their respective control groups (Fig. 3, compare light- and dark-gray shaded areas). With time, the pressor response diminished in ganglionic-blocked animals (darker gray) but grew larger in intact animals (light gray). An overall ANOVA revealed a significant interaction among ganglionic blockade, 8-OH-DPAT treatment, and time (P < 0.01). Subsequent two-way ANOVAs performed at each time point showed significant interactions between ganglionic blockade and 8-OH-DPAT 50 and 55 min after the start of hemorrhage due to the waning pressor effect of 8-OH-DPAT after ganglionic blockade and the persistent pressor effect in intact animals. Heart rate and CVP were not significantly affected by 8-OH-DPAT in either intact or ganglionic-blocked rats (data not shown).

MCFP is directly affected by both blood volume and venous tone (Guyton et al., 1954). Since the total volume of blood withdrawn differed among rats given various pretreatments (i.e., hexamethonium, prazosin, L-659,066, or saline), MCFP was only compared between groups subjected to similar degrees of blood withdrawal, e.g., in study 2, only 8-OH-DPAT- and saline-treated rats subjected to ganglionic blockade were compared with one another, whereas animals with intact autonomic responses were compared in a separate analysis. In contrast to intact rats, 8-OH-DPAT did not increase MCFP after ganglionic blockade (Fig. 4).

**Effect of Prazosin on 8-OH-DPAT-Mediated Hemodynamics.** Blockade of peripheral α1-adrenergic receptors exacerbated the hemorrhage-induced hypotension resulting in less blood withdrawal over the course of hemorrhage (Table 1). Prazosin also attenuated recovery of blood pressure following termination of hemorrhage and completely blocked
the pressor effect of 8-OH-DPAT (Fig. 5). Prazosin had no effect on either HR or CVP (data not shown) but blocked the ability of 8-OH-DPAT to increase MCFP (Fig. 6).

Effect of L-659,066 on 8-OH-DPAT-Mediated Hemodynamics. Blockade of peripheral $\alpha_2$-adrenergic receptors did not alter blood pressure prior to saline or 8-OH-DPAT administration. Consequently, total blood loss did not differ between rats pretreated with the $\alpha_2$-adrenergic receptor antagonist and those pretreated with saline (Table 1). However, $\alpha_2$-adrenergic receptor blockade did attenuate the recovery of blood pressure following termination of blood withdrawal and tended to accelerate decompensation in a subset of animals, leading to the increased blood pressure variability observed at the end of the recording period. The magnitude of the initial pressor response to 8-OH-DPAT was not affected by $\alpha_2$-receptor blockade. Although the blood pressure profile observed after L-659,066 clearly resembled that observed after hexamethonium, there was no significant interaction between L-659,066 and 8-OH-DPAT treatment either as a whole or over time. L-659,066 raised HR and CVP immediately after injection but did not influence the HR or CVP response to 8-OH-DPAT (Fig. 7).

L-659,066 pretreatment blocked the effect of 8-OH-DPAT on MCFP (Fig. 8). L-659,066 itself appeared to lower MCFP compared with control animals despite a similar volume of blood withdrawal during hemorrhage (compare Figs. 2 and 8). However, hematocrit and plasma protein changes were highly variable in animals treated with L-659,066. Therefore, MCFP of saline- and L-659,066-treated rats was not directly compared.

### Table 1

<table>
<thead>
<tr>
<th>Total Blood Loss (ml/kg)</th>
<th>Hematocrit Δ</th>
<th>Plasma Protein Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline + saline (10)</td>
<td>35.0 ± 0.10</td>
<td>-3.9 ± 0.9</td>
</tr>
<tr>
<td>Saline + 8-OH-DPAT (10)</td>
<td>-3.6 ± 0.9</td>
<td>-0.47 ± 0.10</td>
</tr>
<tr>
<td>Epinephrine (8)</td>
<td>-6.3 ± 1.2</td>
<td>-0.61 ± 0.06</td>
</tr>
<tr>
<td>Hex + saline (8)</td>
<td>29.6 ± 0.10</td>
<td>-5.5 ± 0.5</td>
</tr>
<tr>
<td>Hex + 8-OH-DPAT (8)</td>
<td>-5.9 ± 0.7</td>
<td>-0.60 ± 0.06</td>
</tr>
<tr>
<td>Prazosin + saline (8)</td>
<td>25.9 ± 0.10</td>
<td>-6.3 ± 1.0</td>
</tr>
<tr>
<td>Prazosin + 8-OH-DPAT (9)</td>
<td>-4.4 ± 0.7</td>
<td>-0.43 ± 0.13</td>
</tr>
<tr>
<td>L-659,066 + saline (7)</td>
<td>34.3 ± 0.04</td>
<td>-1.0 ± 1.8</td>
</tr>
<tr>
<td>L-659,066 + 8-OH-DPAT (7)</td>
<td>-1.0 ± 1.7</td>
<td>-0.04 ± 0.31</td>
</tr>
</tbody>
</table>

* $P < 0.01$ vs. saline pretreatment.

** $P < 0.01$ vs. L-659,066 pretreatment.
In the current study, 8-OH-DPAT elicited a significant pressor response when administered during hypovolemic shock. The pressor effect was mediated by a combination of direct- and sympathetic-dependent activation of \( \alpha_1 \)-adrenergic receptors. 8-OH-DPAT produced a similar initial pressor effect in the absence of ganglionic blockade suggesting that the direct vascular effect of 8-OH-DPAT predominated immediately after drug treatment. The pressor effect waned after 20 to 25 min in animals subjected to ganglionic blockade but persisted in intact animals, indicating that the sympathetic component of the pressor response elicited a lasting hemodynamic effect.

**Discussion**

In the current study, 8-OH-DPAT elicited a significant pressor response when administered during hypovolemic shock. The pressor effect was mediated by a combination of direct- and sympathetic-dependent activation of \( \alpha_1 \)-adrenergic receptors. 8-OH-DPAT produced a similar initial pressor effect in the absence of ganglionic blockade suggesting that the direct vascular effect of 8-OH-DPAT predominated immediately after drug treatment. The pressor effect waned...
during hemorrhage. Vascular α₂-adrenergic receptors also contributed to compensation during recovery. However, the effect was not immediate because the α₂-adrenergic antagonist, L-695,099, did not reduce the volume of blood withdrawal necessary to maintain pressure during active hemorrhage. After hemorrhage termination, blood pressure of α₂ antagonist-treated rats began to fall toward the end of the recording period. In fact, several animals pretreated with the α₂-antagonist alone tended to develop what appeared to be the beginning of irreversible decompensation prior to the end of the recording period. 8-OH-DPAT protected against this effect, suggesting that sympathetic activation of α₁-receptors may compensate for lack of α₂-receptor activation to maintain blood pressure.

8-OH-DPAT markedly elevated MCFP through an autonomic-dependent mechanism. MCFP is determined by total blood volume and overall vascular compliance. Thus, MCFP is primarily dependent on volume and venous tone since venous compliance is so much larger than arterial compliance (Guyton et al., 1954). Thus, 8-OH-DPAT mediated its effects on MCFP in hemorrhaged animals by increasing vascular blood volume, venous tone, or both. Neither the volume of blood withdrawn nor the hemorrhage-induced change in hematocrit differed between 8-OH-DPAT- and saline-treated control groups, suggesting that differences in capillary refill contributed little to the difference in MCFP. However, it cannot be ruled out that the assessment of hemodilution differences was confounded by a sympathetic-mediated increase in erythrocyte release by splenic contraction in 8-OH-DPAT-treated animals (Kuwahira et al., 1999). However, plasma protein declined to the same degree in animals treated with 8-OH-DPAT and saline, favoring the view that increases in MCFP were primarily mediated by increased venous tone.

The rise in MCFP was prevented by either α₁- or α₂-receptor blockade, suggesting that both receptor subtypes must be available for 8-OH-DPAT to increase venous tone during hypovolemic shock. In accord, previous studies have shown that treatment with either prazosin or rauwolscine produces a dose-dependent decrease in MCFP in euveolic conscious rats but only during reflex sympathetic activation (D’Oyley and Pang, 1990). Prazosin was also found to reduce MCFP in an anesthetized, open-chest dog preparation, but only during infusion of norepinephrine (Ito and Hirakawa, 1984). Selective α₁-adrenergic agonists produce little increase in MCFP when infused into intact rats, whereas norepinephrine produces a potent, dose-dependent increase in MCFP (Pang and Tabrizchi, 1986). Studies in isolated mesenteric veins confirm that activation of α₁-adrenergic receptors may be necessary to observe a venoconstrictor effect of α₂-adrenergic receptors in some vascular beds. Specifically, clonidine and other α₂-adrenergic agonists alone do not produce mesenteric venoconstriction, but yohimbine, idazoxan, or rauwolscine inhibit venoconstriction caused by norepinephrine (G. Fink, unpublished data). Taken together, the data suggest that α₁- and α₂-adrenergic receptor populations interact with one another to mediate sympathetic-dependent increases in venous tone.

Surprisingly, epinephrine did not affect MCFP despite its high affinity and agonist activity at both α₁- and α₂-adrenergic receptor subtypes. To our knowledge, the effect of epinephrine on MCFP has not previously been studied in mammals. Selective β-receptor agonists tend to increase MCFP in intact rats but produce a consistent decrease in MCFP when administered after blockade of sympathetic reflexes (Abdelrahman and Pang, 1990). Thus, the β-adrenergic properties of epinephrine may have antagonized its α-adrenergic-mediated venoconstrictor effect. Alternatively, the venoconstrictor effect of epinephrine may have been masked by a concomitant loss of circulating blood volume due to increased capillary filtration. Although not significant, the fall in hematocrit tended to be larger with epinephrine infusion arguing against a greater loss of intravascular volume in this group.

Presumably, a peripherally acting agent with both α₁ and α₂ agonists activity, but little β₂ activity such as norepinephrine would significantly increase venous tone during hemorrhage. As described above, norepinephrine has a potent effect on MCFP in intact animals. To our knowledge, no one has yet determined the effect of norepinephrine on MCFP in hemorrhage. Such studies are problematic because of norepinephrine’s propensity to exacerbate ischemia during hypovolemia. There were no outward signs of exacerbated ischemia in animals treated with 8-OH-DPAT. In accordance, preliminary evidence suggests that the 8-OH-DPAT does not exacerbate ischemic end-organ injury as assessed by hemorrhage-induced neutrophil activation in lung, kidney, or gut (Osei-Owusu and Scrögin, 2004a).

An increase in venous tone should result in an elevation in venous return and a rise in blood pressure if right atrial pressure is maintained. Surprisingly, neither ganglionic blockade nor α₂-receptor blockade had any apparent effect on the initial pressor response to 8-OH-DPAT despite their ability to block the 8-OH-DPAT-mediated rise in MCFP. However, it could be argued that the direct arterial vasoconstrictor effect of 8-OH-DPAT was exaggerated after ganglionic blockade due to the greater availability of adrenergic receptors. Pressor responses to norepinephrine are exaggerated in euveolic animals after ganglionic blockade (Rowe et al., 1979; Del Basso et al., 1983). The pressor response to 8-OH-DPAT-mediated sympathetic activation was also likely exaggerated during α₂-receptor blockade due to lack of α₂-adrenergic autoreceptor inhibition of catecholamine release. This view is supported by the greater HR rise observed during blood withdrawal in animals treated with L-659,066. Thus, we suspect that the rise in MCFP elicited by 8-OH-DPAT...
does indeed contribute to increased venous return via its sympathoexcitatory action.

The similarity in the blood pressure profiles of animals treated with 8-OH-DPAT following ganglionic blockade and α₂-adrenergic antagonist administration suggests that the late pressor effect of 8-OH-DPAT was mediated largely by sympathetic activation of α₂-adrenergic receptors. Animals subjected to ganglionic blockade, however, did not show the late decompensatory response seen after selective α₂-adrenergic ganglionic blockade. However, it should be recognized that rats treated with the ganglionic blocker were subjected to significantly less blood withdrawal than those treated with the α₂-receptor antagonist.

It is possible that MCFP was increased by mobilization of blood stores following 8-OH-DPAT-mediated increases in sympathetic drive. Sympathetic activation produces a prolonged, slow contraction of the spleen in rats (Kuwahira et al., 1999). The rat spleen is innervated by sympathetic nerves and expresses a high density of α₂-adrenergic receptors (Handy et al., 1993). Moreover, α₂-adrenergic receptor antagonists interfere with hypoxia-induced increases in hematocrit proposed to result from splenic contraction in the rat (Kuwahira et al., 1999). It has been proposed that the rat spleen, like that of the human, contributes to intravascular blood volume regulation primarily through diversion of cell free filtrate to the lymphatic system, most likely through reflex sympathoinhibition stimulated by cardiopulmonary stretch (Kaufman and Deng, 1993). 8-OH-DPAT could exaggerate sympathetic activation during hypovolemia, thus attenuating splenic filtration. The lack of difference in hematocrit fall after 8-OH-DPAT would argue against this view. Nevertheless, the delayed decompensatory effect of the α₂-adrenergic receptor antagonist observed in the current study may reflect blockade of a relatively slow contribution of the spleen or other splanchnic organs to venous return.

The slow rise in heart rate observed over the duration of active hemorrhage suggests that a parallel increase in sympathetic drive also occurs. Our preliminary studies indicate that renal sympathetic activity rises in parallel with heart rate in this model of hypovolemic shock (data not shown). It is tempting to speculate that 8-OH-DPAT accelerates the sympathetically-mediated fluid redistribution that normally occurs during compensation. The rapid rise in sympathetic activity appears to provide a superior hemodynamic response compared with that elicited by epinephrine infusion. Like 8-OH-DPAT, hypertonic saline resuscitation has been reported to result in an increase in blood pressure, a decrease in heart rate, and an increase in cardiac output (Handy et al., 1993). The norepinephrine response to 8-OH-DPAT may reflect blockade of a relatively slow contribution of the spleen or other splanchnic organs to venous return.

Acknowledgments

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References


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