The 5-Hydroxytryptamine1A Receptor Agonist, (+)-8-Hydroxy-2-(di-n-propylamino)-tetralin, Increases Cardiac Output and Renal Perfusion in Rats Subjected to Hypovolemic Shock

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ABSTRACT

The 5-hydroxytryptamine1A receptor agonist, (+)-8-hydroxy-2-(di-n-propylamino)-tetralin (8-OH-DPAT), raises blood pressure (BP) and venous tone in rats subjected to hemorrhagic shock. Here, BP, ascending aortic blood flow [i.e., estimate of cardiac output (CO)] and venous blood gases were measured to determine the hemodynamic effects of 8-OH-DPAT (30 nmol/kg i.v., n = 10), saline (n = 10), or an equipressor infusion of epinephrine (n = 10) in unanesthetized rats subjected to hemorrhagic shock (25 min of hypotensive hemorrhage, ~50 mm Hg). Renal and iliac blood flow were measured in separate groups of similarly hemorrhaged rats given the same dose of 8-OH-DPAT (n = 7) or saline (n = 6). Compared with saline treatment, 8-OH-DPAT produced a sustained rise in BP (+32 ± 4 versus +9 ± 2 mm Hg, 15 min after injection, P < 0.01) and CO (+27 ± 5 versus +4 ± 6 ml/min/kg, P < 0.01) but did not affect total peripheral resistance (TPR). Infusion of epinephrine reduced CO (−12 ± 6 ml/min/kg, P < 0.01) and dramatically increased TPR [+0.37 ± 0.11 versus +0.05 ± 0.05 log (mm Hg/ml/min/kg), P < 0.01]. 8-OH-DPAT increased renal conductance (+7 ± 1 versus +4 ± 1 µl/min/mm Hg, P < 0.01) but did not significantly affect iliac conductance. 8-OH-DPAT attenuated further development of acidosis compared with either saline or epinephrine (−5.6 ± 1.6 versus −13.0 ± 2.0 versus −11.3 ± 2.6 mmol/liter base excess 45 min after start of hemorrhage, both P < 0.01 versus 8-OH-DPAT). These data demonstrate that 8-OH-DPAT improves hemodynamics during circulatory shock, in part, through renal vasodilation and mobilizing of blood stores.

Treatment for hemorrhagic shock involves massive and rapid infusion of replacement fluid, which, if not sufficient to restore adequate perfusion, is supplemented by inotropic drugs to raise cardiac output or vasoconstrictor agents to raise perfusion pressure to vital organs (Kreis and Baue, 1984b). Inotropic and/or vasoconstrictor agents currently used in clinical practice can further exacerbate ischemia. As such, they are only recommended for use after adequate volume restitution has been achieved (Meier-Hellmann et al., 1997; Tabrizchi, 1998). The success of therapy is highly dependent upon the severity and duration of ischemia experienced before intervention (Blaisdell, 1989). Appropriate treatment requires bulky fluids, specialized equipment to administer and monitor inotropic or vasoconstrictor effects, and trained personnel to provide therapy. Consequently, appropriate treatment is often delayed until transport to an emergency facility becomes available. Therefore, novel, less cumbersome therapeutic regimens that can be administered rapidly and easily by first responders are needed to reduce the duration of ischemia and thus improve therapeutic outcomes.

Our previous studies have shown that a single bolus injection of a 5-HT1A receptor agonist can produce a sustained, sympathetic-dependent elevation in arterial pressure in rats subjected to hypotensive hemorrhage (Scrogin et al., 2000; Scrogin, 2003; Osei-Owusu and Scrogin, 2004). More recent work indicates that the pressor effect of the relatively selective 5-HT1A receptor agonist, 8-OH-DPAT, is due, in large part, to a sympathetic-dependent increase in venous tone (Tiniakov and Scrogin, 2006). Increased venous tone should lead to increased venous return in the absence of a change in right atrial pressure. Thus, 8-OH-DPAT would be predicted to increase perfusion in animals subjected to shock. 8-OH-DPAT is also recognized to stimulate release of epinephrine and therefore could have significant beneficial inotropic effects in hypotensive shock (Bagdy et al., 1989b). However,
the ability of 8-OH-DPAT to increase sympathetic drive to arterial beds during shock, combined with the potential vasconstrictor effects of epinephrine release, could contribute to exacerbation of ischemia and metabolic acidosis. Currently, the hemodynamic effects of 8-OH-DPAT in hypovolemic shock are not known.

5-HT$_{1A}$ receptor agonists readily cross the blood-brain barrier, and, when present at high enough concentrations, can bind to several types of serotonergic and nonserotonergic receptors (Sethy and Francis, 1988; Bonaventure et al., 2004). Thus, the mechanisms that govern the cardiovascular effects of 8-OH-DPAT and other 5-HT$_{1A}$ receptor agonists are complex and involve both central and peripheral $\alpha$-adrenergic, 5-HT$_{1A}$, possibly 5-HT$_7$, and probably dopamine receptors (Yu et al., 1996; Ramage, 2001; Bonaventure et al., 2004; Hedlund et al., 2004). Responses to 8-OH-DPAT are also dependent upon the volume status of the animal. For instance, our previous studies indicated that the pressor effect of 8-OH-DPAT in acutely hemorrhaged animals is primarily mediated by central activation of the sympathetic system, our previous studies indicated that the pressor effect of 8-OH-DPAT in acutely hemorrhaged animals is primarily mediated by central activation of the sympathetic system, most likely through 5-HT$_{1A}$ receptors (Scrogin, 2003; Osei-Owusu and Scrogin, 2004). However, the pressor response to 8-OH-DPAT observed in animals subjected to more severe hemorrhagic shock are also due, in large part, to direct vascular $\alpha_1$-adrenergic receptor activation (Tiniakov and Scrogin, 2006). In contrast, a similar dose of 8-OH-DPAT causes hypotension and inhibition of renal sympathetic drive in the anesthetized, euvolemic cat (Ramage et al., 1992). As such, the hemodynamic effects of 8-OH-DPAT cannot be easily predicted.

Given our previous data indicating that 8-OH-DPAT increases venous tone in animals with hemorrhagic shock, we tested the hypothesis that 8-OH-DPAT increases perfusion pressure when administered during hypovolemic shock, primarily by increasing cardiac output. It was further predicted that 5-HT$_{1A}$ receptor agonist administration would increase perfusion of the kidney but decrease perfusion of the hind limbs, the latter of which is highly sensitive to sympathetically-mediated vasoconstriction. Finally, it was hypothesized that increased perfusion would attenuate the development of acidosis, resulting in an overall favorable effect of the 5-HT$_{1A}$ receptor agonist on hemodynamics and acid-base balance.

Materials and Methods

Animals

Male Sprague-Dawley rats weighing 310 to 360 g (Harlan, Indianapolis, IN) were housed 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 experimental protocols were approved by the institutional animal care and use committee and conducted in accordance with the Principles of Laboratory Animal Care as adopted and promulgated by the National Institutes of Health (publication 85-23, revised 1985).

Surgery

Ascending Aorta Flow Probe and Vascular Catheter Implantation. One week before the experiment, rats were given the antisialogogue, glycopyrrolate (4.0 mg/kg i.p.), and anesthetized with sodium pentobarbital (60 mg/kg i.p.). They were then intubated and artificially ventilated with room air to enable placement of an ultrasonic transit-time flow probe (model 3SB; Transonic Systems Inc., Ithaca, NY) around the ascending aorta. The probe was placed through an incision in the third intercostal space. The probe cable was tunneled s.c. and externalized at the nape of the neck. The thoracic incision was closed in layers, and the lungs were reinfated with negative pressure. All rats received ampicillin (150 mg/kg i.m.) 1, 24, and 48 h later.

One day before the experiment, rats were reanesthetized (sodium pentobarbital, 60 mg/kg i.p.) and indwelling bilateral femoral arterial and unilateral femoral venous catheters were placed to enable simultaneous measurement of arterial pressure, arterial blood withdrawal, and drug injection. Silastic tubing (outside diameter, 0.037 in.) was inserted in the femoral vein and advanced into the thoracic vena cava to enable sampling of venous blood for determination of blood gases. All catheters were exteriorized at the nape of the neck.

Renal and Iliac Flow Probe Implantation. Five days before the experiment, a separate group of rats was anesthetized with ketamine and xylazine (100 and 7 mg/kg i.p.). The left renal and iliac arteries were exposed and isolated through a midline laparotomy using care not to disrupt innervation of the vasculature. Ultrasonic transit-time flow probes (model 1RB; Transonic Systems Inc.) were placed around each vessel. The probe cables were passed through the right flank muscles, tunneled s.c., and exteriorized at the nape of the neck. Rats were given ampicillin (150 mg/kg i.m.) after surgery and were allowed to recover in their home cage for 4 days.

One day before the experiment, animals were reanesthetized with ketamine and xylazine (100 and 7 mg/kg i.p.) for placement of unilateral venous and bilateral femoral arterial catheters to enable drug injection, blood withdrawal, and direct measurement of arterial blood pressure. The catheters were tunneled s.c. and externalized at the nape of the neck. Rats were allowed to recover overnight in their home cage.

Data Acquisition

During all experiments, arterial pressure, heart rate (HR), and ascending aorta blood flow [cardiac output (CO)] or renal and iliac blood flow were recorded continuously on a Macintosh G4 PowerBook computer using PowerLab data acquisition software (Chart version 5.2.1; ADInstruments, Grand Junction, CO). Arterial pressure was measured with a disposable pressure transducer (Abbott Laboratories, North Chicago, IL) connected to a PowerLab bridge amplifier (ADInstruments). Cardiac output and renal and iliac blood flows were measured using a Transonic small animal blood flowmeter (model T206; Transonic Systems Inc.).

Heart rate was calculated online using peak-to-peak detection of the pulse pressure wave. Renal (RC) and iliac (IC) conductances, stroke volume (SV), and total peripheral resistance (TPR) were calculated from measured flow, arterial pressure, and HR data. Values for CO were normalized to body weight.

Hematocrit and plasma protein concentration were determined from arterial blood samples. Blood gases were determined from central venous blood using an i-STAT 1 Analyzer (i-STAT Corporation, East Windsor, NJ).

Experimental Protocols

On the day of the experiment, all tubing and flow probe cables were passed through an overhead swivel to enable sampling while the animals rested unrestrained in their home cage. After at least 30 min of habituation, baseline hemodynamic recordings were started 5 min before hemorrhage. Hemodynamic parameters were recorded continuously throughout the remainder of the experiment. Blood was withdrawn at a rate of 3.2 ml/kg/min for 6 min, after which the withdrawal rate was reduced to 0.53 ml/kg/min for an additional 4 min. Thereafter, small amounts of blood (~0.1–0.25 ml) were manually withdrawn periodically over the next 20 min to maintain mean arterial pressure (MAP) at 50 mm Hg. All blood volume manipulations were terminated 30 min after initiation of hemorrhage.

In the first study, animals were randomly assigned to one of three groups. Thirty minutes after the start of blood withdrawal, animals...
received a bolus injection of isotonic saline (150 \mu l i.v.) or 8-OH-DPAT (30 nmol/kg i.v.) or an infusion of epinephrine titrated to mimic the pressor effect of 8-OH-DPAT (~1.5 \mu g/min i.v.). Fifteen minutes after initiation of drug treatment, shed blood was reinfused (0.53 ml/kg/min). After reinfusion, the animals were disconnected from the recording instrumentation and allowed to recover overnight. Twenty-four hours later, hemodynamic parameters were again recorded for 2 to 5 min after sufficient habituation. Animals were then euthanized with an overdose of sodium pentobarbital (200 mg/kg i.v.). The choice of 8-OH-DPAT dose used in these studies was based on evidence demonstrating it to be the half-maximal dose necessary to delay the rapid hypotensive response to blood loss in unanesthetized rats (Scrogin et al., 2000). The same dose has since been proven to produce reliable and significant increases in blood pressure in rats subjected to either acute hemorrhage or hemorrhage sufficient to produce circulatory shock (Osei-Owusu and Scrogin, 2004; Tiniakov and Scrogin, 2006).

Arterial blood samples (50 \mu l) were taken 10 min after initiation of blood withdrawal and again 15 min after drug treatment for determination of hematocrit and plasma protein concentration. Venous blood was withdrawn and again 15 min after drug treatment for determination of which received either isotonic saline (150 \mu l i.v.) or 8-OH-DPAT (i.v.) 30 min after the start of hemorrhage. Rats were euthanized with pentobarbital (200 mg/kg i.v.) after completion of blood reinfusion. 

**Data Analysis**

Cardiovascular parameters were averaged over 1-min segments. Data are presented as 1-min averages over the first 10 min and then as the 1-min average at 5-min intervals. One-way within-group repeated-measures analyses were performed on pooled data before drug injection to determine differences from baseline (time 0). Two-way analyses of variance with repeated measures at 5-min intervals from the start of treatment until blood reinfusion 15 min later. Similar analyses were used to determine the effects of drug treatment on hemodynamic parameters at 5-min intervals from the start of treatment until blood withdrawal. Blood withdrawal was then ‘habituated’ (Figs. 1 and 2). Cardiac output tended to increase slightly during the rapid onset of hypotension but then fell rapidly in parallel with pressure. Heart rate remained stable throughout the remainder of hemorrhage. Heart rate rose, although not significantly, during the initial 3 min of hemorrhage and then fell rapidly in parallel with pressure. Heart rate remained low during the initial phase of maintained hypotension but then began to rise slowly back to the prehemorrhage baseline beginning 15 min after the start of blood withdrawal. Blood withdrawal caused a progressive decrease in CO from the start of hemorrhage (Figs. 1 and 2). Cardiac output fell in parallel with pressure. Heart rate remained low during the initial phase of maintained hypotension but then began to rise slowly back to the prehemorrhage baseline beginning 15 min after the start of blood withdrawal. Blood withdrawal caused a progressive decrease in CO from the start of hemorrhage (Figs. 1 and 2). Cardiac output tended to increase slightly during the rapid onset of hypotension but then continued to fall during the period of controlled hypotension (Figs. 1 and 2). Stroke volume fell in parallel with CO. With continued hypotension, SV declined further, reaching its nadir at the end of blood withdrawal (Fig. 2). Total peripheral resistance rose during the initial 4 min of blood withdrawal but declined with the rapid fall in MAP and HR. It then rose progressively throughout the period of controlled hypotension (Fig. 2).

8-OH-DPAT injection caused a prominent and persistent pressor response (P < 0.01) but did not affect HR. The small
rise in HR observed with epinephrine infusion was not significant (Fig. 2). 8-OH-DPAT administration also caused a progressive rise in CO (+54 ± 15%, 15 min after injection) and SV (+52 ± 11%). Saline had no appreciable effect on CO or SV, whereas both parameters tended to decrease with epinephrine infusion (Figs. 1 and 2). Consequently, CO remained significantly higher after 8-OH-DPAT treatment than after either saline or epinephrine treatment for the duration of the recording period (P < 0.01). Stroke volume was also significantly higher in 8-OH-DPAT-treated rats throughout the recording period (P < 0.01) compared with those given an epinephrine infusion. Within-group variability of TPR was greater in the epinephrine-treated group than in either the saline- or 8-OH-DPAT-treated groups. Therefore, analyses of TPR were performed on data transformed by taking the log of the original data multiplied by a factor of 10 to avoid negative log values. Epinephrine infusion produced a progressive and substantial increase in TPR (+37.2 ± 9.7%, 15 min after injection) that was higher than the increase with either saline (+5.1 ± 4.8%, P < 0.01) or 8-OH-DPAT (+4.1 ± 2.1%, P < 0.01) throughout the 15-min postinjection period (Figs. 1 and 2).

Immediately after the infusion of shed blood was begun, MAP rose rapidly and stabilized near baseline levels within 15 min for all groups (data not shown). This increase was accompanied by relatively slow increases in CO and SV that reached baseline values 45 to 50 min after the start of blood transfusion. Similarly, HR and TPR normalized within 35 to 50 min in all groups. Group differences were eliminated by the end of the reinfusion. This rise in mean pressure coincided with the rapid fall in pressure. Conduction declined further with continued hypotension. 8-OH-DPAT administration increased RC by 288 ± 66% of preinjection values, whereas saline raised RC by 136 ± 38% (P < 0.01). A similar rise in IC followed 8-OH-DPAT administration (198 ± 79%). However, the rise was not different from that with saline (85 ± 71%). Reinfusion of shed blood caused a steady increase in RC and IC to near baseline levels, although values were not significantly different between groups by the end of the reinfusion.

**Discussion**

Here, we show that the relatively selective 5-HT1A receptor agonist, 8-OH-DPAT, increases perfusion pressure by increasing cardiac output in rats subjected to hemorrhagic shock without prior volume restitution. Indeed, a relatively small rise in cardiac output was able to stimulate a significant elevation in blood pressure because of the prevailing vasoconstrictor responses that developed during the course of hemorrhage before drug administration. This rise in mean pressure coincided with improved renal perfusion and acid-base balance. In contrast, epinephrine raised blood pressure exclusively by increasing total peripheral resistance and had no beneficial effect on metabolic acidosis.

Recent work indicates that the sympathetic response to 8-OH-DPAT observed in hypovolemia is, in part, dependent upon an intact arterial baroreflex and may reflect a reversal of the abrupt baroreflex inhibition that occurs during the syncopeal phase of hemorrhage (Osei-Owusu and Scrogin, 2006). The syncopeal response to rapid blood loss appears quite similar in hemodynamic character to neurogenic syncope provoked by head-up tilt in humans (Secher et al., 1994). The syncopeal response to head-up tilt is associated with a sudden loss of venous tone. Therefore, we predicted that the reversal of the syncopeal phase of hemorrhage with 8-OH-DPAT would coincide with recovery of venous tone and thus

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Blood loss, hematocrit, and plasma protein</th>
<th>Hematocrit</th>
<th>Plasma Protein</th>
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<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Total Blood Loss</td>
<td>10 min</td>
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<td></td>
<td>% b.wt.</td>
<td>%</td>
<td>g/100 ml</td>
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<tr>
<td>Saline (n = 10)</td>
<td>4.2 ± 0.1</td>
<td>34.7 ± 0.7</td>
<td>25.5 ± 0.9*</td>
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<tr>
<td>8-OH-DPAT (n = 10)</td>
<td>4.2 ± 0.1</td>
<td>34.9 ± 0.5</td>
<td>30.0 ± 0.9*</td>
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<tr>
<td>Epinephrine (n = 10)</td>
<td>4.2 ± 0.1</td>
<td>35.9 ± 0.7</td>
<td>30.3 ± 0.5*</td>
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* P < 0.01 within-group versus 10-min value.

**Effects of Renal and Iliac Conductance.** During the first 10 min of blood withdrawal, decreases in MAP and HR were paralleled by rapid reductions in renal and iliac conductances, both of which reached their nadir 30 min after the start of hemorrhage (9.5 ± 2.9 and 9.0 ± 10.3% prehemorrhage baseline for RC and IC, respectively) (Figs. 3 and 4). The fall in IC started at the onset of blood withdrawal, whereas decreases in RC paralleled the biphasic fall in blood pressure. During the rapid fall in pressure, the progressive fall in IC was interrupted by a transient increase in conductance that coincided with the rapid fall in pressure. Conductance declined further with continued hypotension. 8-OH-DPAT administration increased RC by 288 ± 66% of preinjection values, whereas saline raised RC by 136 ± 38% (P < 0.01). A similar rise in IC followed 8-OH-DPAT administration (198 ± 79%). However, the rise was not different from that with saline (85 ± 71%). Reinfusion of shed blood caused a steady increase in RC and IC to near baseline levels, although values were not significantly different between groups by the end of the reinfusion.
venous return. Evidence from the present study supports these findings by demonstrating that 8-OH-DPAT promotes increased cardiac output.

Previous studies indicated that venoconstriction is, in part, responsible for the rise in venous return (Tiniakov and Scroggin, 2006). However, additional studies suggested that 8-OH-DPAT may also increase cardiac output by virtue of its ability to stimulate epinephrine release (Bagdy et al., 1989a,b). An effect of 8-OH-DPAT on ventilation may also have contributed to the increased venous return by promoting more vigorous intrathoracic pump activity. Indeed, a relatively large dose of 8-OH-DPAT (250 μg/kg i.p.) was found to produce fairly prolonged (>20 min) increases in tidal volume as well as respiratory rate in unanesthetized rats (Teng et al., 2003). However, our preliminary studies indicate that the same dose of 8-OH-DPAT as used in the present study produced only a transient (1–2 min) rise in ventilatory rate in acutely hemorrhaged rats (Scroggin and Ruszaj, 2006). Thus, the mechanical benefit probably only contributed to the initial increase in cardiac output observed in the present study.

Surprisingly, 8-OH-DPAT did not increase peripheral resistance. Given the susceptibility of the hind limb vasculature to sympathetic-mediated vasoconstriction, it was also surprising that IC did not fall further after 8-OH-DPAT injection (Duanmu et al., 1999). The very low IC observed just before 8-OH-DPAT injection suggests that there may have been very limited reserve for further sympathetic-mediated arterial constriction of the hind limbs. Alternatively, it is possible that 5-HT1A agonists produce a patterned sympathetic response in hypovolemic animals that does not include increased output to the hind limb vasculature.

Renal conductance remained stable during the early phase of hemorrhage but fell as hemorrhage progressed. The fall in RC that occurs with progressive hemorrhage is thought to result primarily from a rise in vasoconstrictor hormones rather than from direct effects of increased sympathetic drive (Al-Omar Azzawi and Shirley, 1984; Koyama et al., 1993). Although the renal vasculature itself may be less susceptible to sympathetic-mediated vasoconstriction in euvoidic animals, hypovolemic shock results in a large increase in renin release and thus in angiotensin II-mediated renal constriction, which is presumed to be mediated, at least in part, by increased renal sympathetic drive (Simchon et al., 1985). As such, it was surprising that 8-OH-DPAT increased RC, given the presumed high level of background renal sympathetic drive and the additional renal sympathoexcitatory effect of the drug during shock.

Several reports have previously documented increases in RC after 5-HT1A receptor agonist administration in euvoidic animals. However, these findings were attributed to centrally mediated withdrawal of renal sympathetic tone (Ramage et al., 1988; Ramage and Wilkinson, 1989). Given that 8-OH-DPAT produces a paradoxical renal sympatho-

![Fig. 2. MAP, HR, CO, SV, and TPR during hemorrhage (pooled across groups), during subsequent injection of 8-OH-DPAT (30 nmol/kg) or saline or an equipressor infusion of epinephrine, and after reinfusion of shed blood. Values are means ± S.E. Group numbers are shown in parentheses. #, no within-group difference from baseline for pooled data. □ and ■, within-group difference from baseline (P < 0.05 and P < 0.01, respectively). **, P < 0.01, 8-OH-DPAT versus saline; ++, P < 0.01, epinephrine versus saline; ##, P < 0.01, 8-OH-DPAT versus epinephrine. Values after reinfusion of shed blood are shown at 90 min.](https://aspetjournalsonline.org/doi/fig/10.1124/jpet.106.119115)
citation during hypovolemia, it is more likely that a local vascular effect of the drug mediated the increase in RC shown here. Limited evidence has demonstrated a direct renal arterial dilatory effect of 8-OH-DPAT and other 5-HT₁A receptor agonists (Eltz et al., 1991; Verbeuren et al., 1991). Studies in isolated renal arteries suggest that 5-HT₁A receptors elicit renal vasodilation via a nitric oxide-dependent mechanism (Verbeuren, 1993). Interestingly, the L-enantiomer of 8-OH-DPAT also has significant affinity and functional agonist activity at dopamine D₂ receptors. The R-enantiomer used in these studies also shows some affinity for these receptors, although to a much lesser degree (Yu et al., 1996). In vitro and in vivo studies indicate that activation of postsynaptic D₂ dopamine receptors localized on sympathetic nerve terminals of the renal vasculature reduces norepinephrine release (Rump et al., 1993b). In vivo, this phenomenon culminates in renal vasodilation during sympathetic stimulation in the rabbit (Szabo et al., 1992). Whether this mechanism regulates renal function in rats remains controversial (Rump et al., 1993a).

Catecholamine infusion during hypovolemic shock can exacerbate ischemia, particularly when administered before volume resuscitation (Mills and Moyer, 1960; Mills et al., 1960). Epinephrine can improve cardiac performance during low flow states. However, its propensity to increase renal resistance and oliguria as well as afterload limit its clinical use in the earlier phases of hemorrhagic shock (Kreis and Baue, 1984a). In accord with these findings, the present study shows that epinephrine produced a substantial increase in peripheral vascular resistance when infused at a rate that produced the same pressor response as a single injection of 8-OH-DPAT. However, only mild, nonsignificant chronotropic effects were observed at this infusion rate. At the same time epinephrine infusion reduced stroke volume presumably in response to the large increase in afterload. Consequently, epinephrine actually reduced CO.

Historically, norepinephrine has been thought to be subject to the same complications as epinephrine (Mills et al., 1960; Cronin et al., 1978). More recent work indicates that norepinephrine has beneficial effects that include restoration of urine flow and creatinine clearance when used at appropriate doses (Albanese et al., 2004). However, the use of norepinephrine before volume restitution is strictly avoided because of case reports of severe necrotizing limb ischemia (Hayes et al., 1992). Moreover, the need for constant infusion and careful monitoring limits the use of norepinephrine in the field, away from emergency facilities.

Until recently, dopamine and dobutamine had been favored for use in hypovolemic shock because their inotropic effects were not accompanied by significant increases in afterload (Hamed et al., 1983; Curtis et al., 1989; Levy et al., 1993). Dopamine has the further advantage of producing a substantial increase in peripheral vascular resistance when infused at a rate that produced the same pressor response as a single injection of 8-OH-DPAT. However, only mild, nonsignificant chronotropic effects were observed at this infusion rate. At the same time epinephrine infusion reduced stroke volume presumably in response to the large increase in afterload. Consequently, epinephrine actually reduced CO.

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ever, studies suggest that dopamine may aggravate gut ischemia and exacerbate reperfusion injury (Segal et al., 1992). Moreover, the beneficial effects of dopamine are dependent upon prior volume resuscitation (Gupta et al., 2005). As with all catecholamines, both dopamine and dobutamine are rapidly metabolized, requiring constant infusion to produce a sustained effect.

8-OH-DPAT produces hemodynamic effects similar to those of dopamine, but with a significantly longer half-life. Here, we demonstrated that a single bolus dose of 8-OH-DPAT increased CO throughout the 15-min postinjection recording period. In our prior study, 8-OH-DPAT increased arterial and mean circulatory filling pressure for the duration of a 35-min postinjection recording period (Tiniakov and Scrogin, 2006). Hematocrit and plasma protein levels were not affected by drug treatment in either the previous or present studies, indicating that increases in mean circulatory filling pressure and CO were most likely the result of altered venous tone and not differences in capillary refill.

This shock model produced a mixed respiratory and metabolic acidosis by 25 min after the start of blood withdrawal. Acidosis continued to worsen during the posthemorrhage period. 8-OH-DPAT, but not epinephrine, prevented further progression of acidosis. Increased renal perfusion probably contributed to H+ secretion as indicated by elevated HCO3−, although this is difficult to determine without further data. 8-OH-DPAT also suppressed the rise in lactate levels. Surprisingly, epinephrine-treated animals also had lower lactate levels, despite having a reduced venous blood pH similar to that in saline-treated rats. It is probable that the fall in pH among epinephrine-treated animals was due, in part, to greater metabolic activity and thus greater CO2 generation in resistance vessels. The variability in pCO2 observed in the epinephrine-treated group precluded statistical verification of this possibility. Nevertheless, the treatment by time interaction found for venous pO2 and sO2 suggests a greater tissue extraction of oxygen in epinephrine-treated animals as would be expected in subjects with more metabolically active tissue.

The data presented herein indicate that a relatively selective 5-HT1A receptor agonist can have sustained beneficial effects on hemodynamics and acid-base balance in animals subjected to hemorrhagic shock without volume resuscitation. The data suggest that acute injection of a 5-HT1A receptor agonist may provide an advantageous alternative to the more cumbersome administration of inotropic and vasopressor agents currently used in hypovolemic shock.

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