**Suppression by traumatic brain injury of spontaneous hemodynamic recovery from hemorrhagic shock in rats**

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The effects of brain trauma on cardiovascular and endocrine responses to hemorrhage were investigated. Forty anesthetized rats were randomly assigned to one of four groups of 10 rats each: a control group (Group C); a group with induction of hemorrhage at 16.2 ml/kg/10 min (Group H); a group with fluid-percussion brain injury at a peak pressure of 1.7 atm and an impulse duration of 25 msec (Group T); and a group receiving hemorrhagic shock following brain trauma (Group TH). Group C and T rats showed no significant alterations in cardiovascular function. At the end of hemorrhage there were no significant differences between Groups TH and H in the nadirs of mean arterial blood pressure (MABP) (mean values ± standard error of the mean: 42 ± 2 vs. 40 ± 4 mm Hg) and stroke volume index (SVI) (0.61 ± 0.11 vs. 0.66 ± 0.10 ml/bt/kg); however, 1 hour post-hemorrhage recovery was blunted in Group TH compared to Group H (MABP 56 ± 4 vs. 65 ± 3 mm Hg; cardiac index 182 ± 15 vs. 220 ± 15 ml/min/kg; and SVI 0.71 ± 0.06 vs. 0.81 ± 0.06 ml/bt/kg). Since the two groups showed no significant differences in heart rate, preload (central venous pressure), and afterload (systemic vascular resistance), the reduced cardiac index recovery in Group TH is believed due to the attenuation of cardiac contractile performance. The Group TH preparation potentiated hormonal responses to hemorrhage with significantly higher epinephrine and aldosterone levels than in Group H. Brain trauma enhanced the norepinephrine response to hemorrhage, even at an injury level that by itself did not result in an increase in this hormone. Group TH rats also had significantly lower blood pH and HCO₃ levels. The data suggest that brain trauma suppresses MABP and cardiac index recovery after hemorrhage mainly by inhibiting cardiac contractile performance, probably due to high catecholamine levels and severe metabolic acidosis.

**KEY WORDS**  
brain injury  
fluid-percussion injury  
hemorrhagic shock  
catecholamine  
aldosterone  
rat

Brain trauma and hemorrhagic shock are frequently seen together in cases of multiple trauma. Overall, 13% to 15% of head-injured patients present in shock varying in degree of severity; arterial hypotension is often used as a predictor of negative outcome from closed head injury. The coexistence of brain injury and circulatory shock is potentially lethal. Severe head injury results in a 45% mortality rate; shock in association with severe head injury significantly increases the mortality to 83%. Analysis of data from the Traumatic Coma Data Bank showed that shock occurred prior to admission in 33% of 581 severely brain-injured patients, and resulted in a 30% increase in the frequency of death or vegetative survival.

Hemorrhagic shock and brain trauma have been studied separately for many years. A wealth of literature describes clinical or experimental studies of the consequences of hemorrhagic shock on the brain, as well as the role of the brain in the pathogenesis of shock. In most of these studies, however, the brain is intact before the initiation of shock. Specific studies investigating cardiovascular and endocrine responses to hemorrhagic shock when the brain is traumatized, as occurs frequently in the clinical situation, have not been reported. Therefore, how brain trauma modifies the systemic response to hemorrhage is not understood. The present study was designed to investigate the effects of brain trauma on cardiovascular and endocrine responses to hemorrhagic shock.

**Materials and Methods**

The experimental studies described in this report were reviewed and approved by the Institutional Review Committee/Animal Care and Use Committee at Letterman Army Institute of Research. In conducting the research described here, the authors adhered to the National Institutes of Health "Guide for the Care and Use of Laboratory Animals."
Effects of brain trauma on hemorrhage

For this study, 120 male Sprague-Dawley rats were used: 40 (weighing 405 ± 8 gm) in the experiments, and 80 as blood donors. Anesthesia was induced in a halothane chamber for 1 to 2 minutes and maintained initially by an intramuscular injection (1.3 ml/kg body weight) of a mixture of ketamine hydrochloride (50 mg/ml) and xylazine (10 mg/ml). This was supplemented with a 0.65-ml/kg injection 1 hour later. After another hour, a continuous intravenous infusion of the mixture was started at 0.2 ml/kg/hr and maintained throughout the experiment.

Instrumentation and Hemodynamic Measurements

Following craniotomy, a No. 1 French thermistor microprobe (0.41 mm in diameter) was inserted into the ascending aorta through the right brachial artery to monitor blood temperature and to measure cardiac output using the thermodilution technique. The craniotomy procedures and fluid-perfusion injury device have been described in detail elsewhere. Polyethylene tubing (PE-50) was inserted into both femoral arteries to monitor mean arterial blood pressure (MABP) and heart rate, and to obtain blood samples as well as withdraw blood for hemorrhage. A PE-50 tube was inserted into the thoracic posterior vena cava through the left femoral vein to measure central venous pressure (CVP) and to inject saline (0.2 ml, at room temperature) with a microinjector for cardiac output measurements. Two other catheters were inserted into the right femoral vein for continuous infusion of anesthetic agents, and the introduction of donor blood. Blood temperature was maintained at 37.2° ± 0.2°C with a heating pad. In total, 1.6 ml of buffered heparinized solution (30 ml normal saline, 1 ml 8.4% sodium bicarbonate, 5 ml distilled water, and 4000 U heparin sodium) was used to flush the catheters throughout the surgery and the entire experiment. Cardiac index (CI), stroke volume index (SVI), and systemic vascular resistance index were calculated with standard formulas.

Experimental Protocol

After completing the instrumentation, 30 minutes were allowed for cardiovascular stabilization. Thirty-five minutes prior to initiation of experimental manipulations, 3.3 ml of arterial blood was sampled, then replaced with an equal volume of donor blood. After hemodynamic status had stabilized, the animals were randomly assigned to four groups of 10 each: a control group (Group C), and groups receiving hemorrhage shock alone (Group H), brain trauma alone (Group T), or brain trauma combined with hemorrhage shock (Group TH). Baseline hemodynamic measurements were obtained immediately before the fluid percussion or sham fluid percussion, which was followed 30 seconds later by a 10-minute hemorrhage or sham hemorrhage. The posttreatment hemodynamic data were obtained at 5 and 10 minutes after the beginning, and at 15, 40, and 60 minutes after the end of hemorrhage or sham hemorrhage. Posttreatment blood samples were collected at 15 and 60 minutes after the end of the hemorrhage or sham hemorrhage. The end of hemorrhage or sham hemorrhage was defined as time zero (T 0, in minutes).

Group C animals were prepared with instrumentation as described above; they were then connected to the trauma device at T = −10.5 for 30 seconds, but were not injured. These rats served as controls for the effects of the experimental procedures. At the end of the experiment, they were sacrificed by intravenous administration of 1 ml 20% Nembutal (pentobarbital). All of the experimental rats were treated as those in Group C but with additional manipulation. Group H rats were subjected to a 10-minute hemorrhage beginning at T = −10 and induced by constant withdrawal of blood (16 ml/kg/10 min) from the arterial cannula using a peristaltic pump. This amount of blood accounts for about 26% of a rat’s total blood volume. The rats in Group T were subjected to a fluid-perfusion brain injury at T = −10.5, then 30 seconds later, detached from the trauma device. The injury level was set at 1.7 atm, and impact duration was held constant at 25 msec. Group TH rats were subjected to the same brain trauma as the Group T rats, followed 30 seconds later by the same hemorrhage as administered in Group H.

Blood Sample Measurement

Blood gases and pH were measured with a blood gas analyzer; red blood cells, hemoglobin, and hematocrit with a cell counter; and blood glucose with a glucometer.* The blood samples for hormonal measurements were collected in ice-cooled plastic tubes and divided among tubes containing ethylenediaminetetra-acetic acid (EDTA) to determine adrenocorticotropic hormone (ACTH) levels, heparin sodium to measure corticosterone, aldosterone levels, and sodium metabisulfate and EDTA to determine norepinephrine and epinephrine levels. These blood samples were centrifuged at 5000 G for 10 minutes at 4°C and stored at −70°C until assayed. Corticosterone, aldosterone, and ACTH levels were measured using commercial radioimmunoassay kits. Norepinephrine and epinephrine levels were measured with an electrochemical detector following high-performance liquid chromatography.

Statistical Analysis

A two-way analysis of variance was performed on each variable to determine group and time effect. Whenever the F statistic was significant, or a significant interaction between group and time existed, Newman-Keul’s test was performed to locate the intergroup difference. Dunnett’s test was used to compare the posttreatment values to the baseline value within each

* Blood gas analyzer manufactured by Instrumentation Laboratory, Lexington, Massachusetts; cell counter manufactured by Baker Instrument Co., Allentown, Pennsylvania; and glucometer, Model 5550, manufactured by Miles Laboratories, Inc., Elkhart, Indiana.
FIG. 1. Results in Group C (control), Group H (hemorrhage), Group T (trauma), and Group TH (hemorrhage and trauma), showing the effects of brain trauma on the mean arterial blood pressure (MABP) and cardiac index (CI) response to hemorrhage. Brain trauma caused no difference in the decline in MABP during the hemorrhage, but resulted in significantly lower MABP and CI over the post-hemorrhage recovery period. Values are means, bars indicate standard error of the mean. Asterisks = p ≤ 0.05 (vs. baseline); daggers = p < 0.05 (Group H vs. TH).

FIG. 2. Results in Group C (control), Group H (hemorrhage), Group T (trauma), and Group TH (hemorrhage and trauma), showing the effects of brain trauma on the heart rate, and stroke volume index (SVI) responses to hemorrhage. Brain trauma resulted in less reduction in heart rate, but presented no difference in the decline in SVI during hemorrhage. One hour after the hemorrhage, brain trauma showed a substantially suppressed SVI (p = 0.08) with no effect on heart rate (p = 0.74). Values are means, bars indicate standard error of the mean. Asterisks = p ≤ 0.05 (vs. baseline); dagger = p < 0.05 (Group H vs. TH).

TABLE 1
Changes in preload and afterload*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Mins Before or After Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-10 (baseline)</td>
</tr>
<tr>
<td>central venous pressure (mm Hg)</td>
<td>C</td>
<td>2.5 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>2.8 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>2.7 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>TH</td>
<td>2.3 ± 0.3</td>
</tr>
<tr>
<td>systemic vascular resistance</td>
<td>C</td>
<td>19.0 ± 2</td>
</tr>
<tr>
<td>index (resistance unit index)</td>
<td>T</td>
<td>19.7 ± 1</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>18.7 ± 1</td>
</tr>
<tr>
<td></td>
<td>TH</td>
<td>18.5 ± 1</td>
</tr>
</tbody>
</table>

* Group C = control; Group H = hemorrhage; Group T = brain trauma; Group TH = combined injury. There were no significant differences between Groups C and T, or between Groups H and TH. Values are means ± standard errors of the means.

† Significance: p < 0.05 (vs. baseline).
Effects of brain trauma on hemorrhage

A difference of $p \leq 0.05$ was considered significant for all tests.

**Results**

No significant differences were found in body weight or temperature among the four groups in the amount of shed blood between Groups H and TH (mean ± standard error of the mean: 16.2 ± 0.2 vs. 16.2 ± 0.1 ml/kg), nor in the brain trauma impact levels between Groups T and TH (1.73 ± 0.04 vs. 1.74 ± 0.07 atm).

**Hemodynamic Response**

At baseline the four groups did not differ with respect to hemodynamic variables (Figs. 1 and 2 and Table 1). In Groups C and T, hemodynamic status remained stable over the entire experiment. In both hemorrhage groups, however, there were significant changes in hemodynamics. The MABP, CI, heart rate, SVI, and CVP levels declined significantly during the 10-minute hemorrhage in both groups, then gradually increased after the hemorrhage. At the end of the hemorrhage (T 0), there were no significant differences between Groups H and TH in MABP (40 ± 4 vs. 42 ± 2 mm Hg), SVI (0.61 ± 0.11 vs. 0.66 ± 0.10 ml/bt/kg), and CVP (1.9 ± 0.3 vs. 1.7 ± 0.3 mm Hg). However, Group TH rats had significantly high heart rate (197 ± 16 vs. 187 ± 18 bt/min, $p < 0.05$) and CI (120 ± 12 vs. 102 ± 13 ml/min/kg, $p < 0.10$). The recovery profile of these variables, however, was contrary to the above pattern. At T 60, Group TH, compared to Group H, had significantly lower MABP (56 ± 4 vs. 65 ± 3 mm Hg, $p < 0.05$) and CI (182 ± 15 vs. 220 ± 15 ml/min/kg, $p < 0.05$) as well as substantially lower SVI (0.71 ± 0.06 vs. 0.81 ± 0.06 ml/bt/kg, $p = 0.08$); no significant differences were found in heart rate ($p = 0.74$) or CVP ($p = 0.12$). The patterns of systemic vascular resistance index response to the hemorrhage were opposite to those of the above variables; no significant differences were found between the two hemorrhage groups over the entire period with virtually the same values in Groups TH and H at T 60 (18.58 ± 1.35 vs. 18.12 ± 1.72 resistance unit index). Over the 1-hour observation period, the hemodynamic compensation gains, as expressed by the ratio of recovery to residual decrement, were significantly higher in Group H than in Group TH (0.87 ± 0.21 vs. 0.47 ± 0.13 for MABP and 1.46 ± 0.26 vs. 0.79 ± 0.40 for CI at T 60).

**Plasma Hormone Level Response**

Initially, none of the hormone levels differed significantly among the four groups (Figs. 3 and 4). Group C showed no significant change over time for plasma levels of epinephrine, norepinephrine, ACTH, corticosterone, or aldosterone. Brain trauma led to significant increases in plasma levels of epinephrine at T 60, and aldosterone at T 15 and T 60. Both groups with hemorrhage (Groups H and TH) had consistent increases in all plasma hormone levels measured. In Group H, epinephrine, ACTH, corticosterone, and aldosterone levels were significantly higher than the respective baseline and control group values. Group TH had greater increases than Group H in all hormone levels measured. At T 15, significant differences in epinephrine and aldosterone were observed between Groups TH and H. The elevation in the norepinephrine level was not significant in Group H, but was significant in Group TH at T 60. Changes in blood gas levels, glucose, and hematologic are shown in Tables 2 and 3.

**Discussion**

**Hemodynamics**

This study demonstrates that brain trauma suppresses the hemodynamic recovery from hemorrhagic hypotension. In almost every animal, MABP, CI, SVI, heart rate, and CVP decreased following the initiation of hemorrhage, then gradually returned toward baseline.
levels after the termination of hemorrhage. There were no significant differences in the nadirs of MABP and SVI at the end of hemorrhage between Groups H and TH, but the recoveries of MABP, CI, and SVI differed between the two groups. One hour after the hemorrhage, Group TH had significantly lower MABP and CI, and substantially lower SVI than Group H. The diminished MABP recovery in brain-injured animals with hemorrhage is believed to be caused solely by the damaged CI recovery, as the systemic vascular resistance index, or afterload, was virtually the same in both groups with hemorrhage. In addition, heart rate and preload (CVP) were not significantly different between Groups H and TH. This hemodynamic profile clearly indicates that the reduced cardiac contractility may be the major reason for this diminished cardiac performance in response to hemorrhage in brain-injured animals.

Brain injuries may impair cardiac function.11,18,22 This impairment may be caused not only by structural damage to the brain per se, but also by systemic response to brain trauma. In a study by Cruickshank, et al.,1 of 30 patients with severe head injury, 28 demonstrated an elevation in the myocardial isoenzyme (CK-MB), which implies ongoing myocardial cell injury. Clifton, et al.,4 noted the presence of subendocardial hemorrhage in 50% of autopsies performed on a group of patients who died of severe brain injury. This disclosure is similar to the pathological findings in animals infused with high levels of catecholamines.26 Our catecholamine data are consistent with this theory; they showed that rats had a much stronger catecholamine response to hemorrhage after a brain injury than to hemorrhage alone. Myocardial damage and subsequent decreased contractility induced by massive catecholamine release have been considered the major cause of circulatory collapse after severe brain trauma.21,27 These changes might also account for the compromised ability to compensate for systemic hemorrhage in brain trauma victims.

Factors other than massive catecholamine release may also contribute to myocardial dysfunction. Severe acidosis has been shown to decrease myocardial contractility.6,11 Our data showed that Group TH rats had a much lower blood pH than any other group, and this acidosis might be in part responsible for that group’s
diminished compensatory capacity. Other systemic humoral factors, especially the release of various opioid peptides, have been implicated as possible causes for the cardiac dysfunction observed in traumatic brain injury.14,16

**Catecholamines**

It has been well recognized that brain trauma activates the sympathetic nervous system with subsequent catecholamine release.2,7,30 Our data demonstrated that fluid percussion significantly increased the plasma concentration of epinephrine but not norepinephrine. Severity of injury and timing of sampling may be responsible for the lack of a demonstrated norepinephrine response, although species difference may be another cause. No report on the catecholamine changes following brain trauma in rats is available. In a cat fluid-percussion model, Rosner, *et al.*,27 revealed a linear relationship in logarithmic values of the original data between injury level and peak catecholamine concentration when the injury severity was between 0.6 and 4.5 atm. The injury level in our investigation (1.7 atm) is considered low, and at low levels of concussion there is only a minimal release of catecholamines.27 In our study this seemed to occur with norepinephrine response to the brain trauma.

Plasma epinephrine and norepinephrine levels have been reported to rise about 500- and 100-fold, respectively, by 10 seconds after a severe (2.83 atm) fluid-percussion injury in cats.27 These values fell logarithmically for the first 1000 seconds. By 17 minutes, the catecholamine levels had declined to two to three times the baseline values. This pattern is similar to our epinephrine value at T 15 although our data did not show an increase in norepinephrine level after brain trauma. If our animal model had been large enough to allow us to take more frequent samples, especially in the immediate postinjury period, we would have demonstrated more remarkable changes in catecholamine levels in response to the percussion on the brain.

Despite a less striking catecholamine response to brain trauma alone, our study showed that catecholamine responses to hemorrhage were significantly enhanced by the presence of brain trauma. Hemorrhage alone did not significantly increase epinephrine levels after 15 minutes, but hemorrhage associated with brain trauma did; the difference between the two levels was significant. Hemorrhage alone caused significant increases in plasma epinephrine levels, but not in norepinephrine level, at 60 minutes after the hemorrhage; however, when hemorrhage was preceded by a brain trauma, both epinephrine and norepinephrine levels were significantly increased after the hemorrhage. This indicates that the norepinephrine responses to hemorrhage may be significantly enhanced by a brain trauma at an injury level that alone does not result in significant changes in plasma norepinephrine levels.

**Aldosterone**

Our study showed both a significant increase in plasma aldosterone level after brain trauma and a potentiated response of plasma aldosterone level to hemorrhage in the presence of a superimposed brain trauma. The production and release of aldosterone by the adrenal zona glomerulosa are mainly controlled by the renin-angiotensin system,25,31 which is stimulated by sympathetic activation.24,25,31,32 Although we did not measure the renin-angiotensin system, it is reasonable to propose that the high catecholamine levels might be the major factor contributing to the elevation in plasma aldosterone level following the brain trauma in our experiment. An increase in aldosterone level triggered by brain trauma is of clinical significance, because mineralocorticoid excess can result in sodium retention, thus prompting the formation of cerebral edema.

**Conclusions**

Traumatic brain injury at a moderate level does not affect MAP reduction during a fixed-volume hemorrhage, but suppresses post-hemorrhage recovery of MAP and CI, despite the fact that the brain trauma alone does not alter hemodynamic function. This suppression of hemodynamic recovery from hemorrhage is due principally to alteration in cardiac rather than peripheral vascular function. The damaged cardiac function may be due to a reduction in contractile performance and not to a chronotropic effect. Catecholamine responses to hemorrhage are significantly

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**TABLE 3**

*Changes in blood glucose and hematology*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Baseline</th>
<th>Mins After Hemorrhage 15</th>
<th>Mins After Hemorrhage 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>glucose (mg/dl)</td>
<td>C</td>
<td>169 ± 21</td>
<td>124 ± 16</td>
<td>127 ± 15</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>162 ± 11</td>
<td>159 ± 17†</td>
<td>149 ± 17‡</td>
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<td></td>
<td>H</td>
<td>183 ± 13</td>
<td>270 ± 24‡</td>
<td>201 ± 25</td>
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<td></td>
<td>TH</td>
<td>164 ± 18</td>
<td>287 ± 22†</td>
<td>224 ± 21†‡</td>
</tr>
<tr>
<td>hematocrit (%)</td>
<td>C</td>
<td>43.0 ± 1.2</td>
<td>42.8 ± 1.5</td>
<td>41.1 ± 3.2</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>42.1 ± 1.5</td>
<td>43.4 ± 1.7</td>
<td>39.9 ± 3.1</td>
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<tr>
<td></td>
<td>H</td>
<td>43.3 ± 0.5</td>
<td>33.4 ± 2.1†</td>
<td>35.5 ± 1.5†</td>
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<td></td>
<td>TH</td>
<td>40.4 ± 2.3</td>
<td>35.1 ± 1.0†</td>
<td>34.0 ± 1.8†</td>
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<td>hemoglobin (gm/dl)</td>
<td>C</td>
<td>15.4 ± 0.4</td>
<td>15.4 ± 0.6</td>
<td>14.7 ± 1.1</td>
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<tr>
<td></td>
<td>T</td>
<td>15.1 ± 0.6</td>
<td>15.5 ± 0.6</td>
<td>14.2 ± 1.0</td>
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<tr>
<td></td>
<td>H</td>
<td>16.0 ± 0.3</td>
<td>12.3 ± 0.8†</td>
<td>12.8 ± 0.6†</td>
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<td>TH</td>
<td>14.7 ± 0.8</td>
<td>12.4 ± 0.3†</td>
<td>11.9 ± 0.6†</td>
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<tr>
<td>red blood cells (10⁶/dl)</td>
<td>C</td>
<td>7.8 ± 0.2</td>
<td>7.9 ± 0.3</td>
<td>7.5 ± 0.6</td>
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<tr>
<td></td>
<td>H</td>
<td>8.0 ± 0.1</td>
<td>6.1 ± 0.4†</td>
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<tr>
<td></td>
<td>TH</td>
<td>7.4 ± 0.4</td>
<td>6.4 ± 0.2†</td>
<td>6.3 ± 0.4†</td>
</tr>
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</table>

*Group C = control; Group H = hemorrhage; Group T = brain injury; Group TH = combined injury. Values are means ± standard errors of the mean.
† Significance: p < 0.05 (vs. baseline).
‡ Significance: p < 0.05 (Group C vs. Group T or Group H vs. TH).
enhanced in the presence of brain trauma and may bear primary responsibility for the suppressed cardiac performance. Brain trauma also leads to significant increases in plasma aldosterone levels in the absence of a concomitant rise in plasma ACTH or corticosterone levels, and amplifies the aldosterone response to hemorrhage.

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