plasmin inhibition, except for a slight increase in the heart after 3 months administration at the higher dose. The reported results show that an anabolic steroid can affect vascular plasminogen activators without apparent effect on plasmin inhibitors.

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Evidence that endogenous vasopressin plays a protective role in circulatory shock. Role for reticuloendothelial system using Brattleboro rats

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Summary. Experiments performed on male Wistar, Long Evans and Brattleboro rats indicate that the latter strain of animals, lacking vasopressin in their posterior pituitaries, are extremely sensitive to hemorrhagic and bowel ischemic shock. Mild forms of both hemorrhagic and bowel ischemic shock, as produced in Wistar or Long Evans rats, results in marked hypotension, hemoconcentration and blockade of the reticuloendothelial system (RES) in Brattleboro animals of similar sex, age and weight. These direct findings indicate that release of endogenous vasopressin in shock syndromes may be critical in maintenance of circulatory homeostasis and RES function.

Several lines of investigation have revealed that hemorrhage, fluid loss and trauma are strong stimuli for the release of vasopressin from the pituitary glands of rats, cats and dogs[2]. This naturally occurring pituitary hormone is a potent constrictor of vascular smooth muscle cells[3], including arterioles and precapillary sphincters in the microcirculation[3,4]. It is not, however, known whether the release of vasopressin in circulatory shock is necessary for survival, since all of the previous experiments were done by indirect approaches (e.g., infusions of exogenous vasopressin)[5].

During the past decade, evidence has been gathered which suggests that tolerance to various types of circulatory shock, trauma and surgery is associated with the functional capacity of the phagocytic cells of the reticuloendothelial system (RES)[6]. Substances which depress the phagocytic powers of RE cells increase mortality, while materials which stimulate RE cell phagocytic activity is, in most instances, associated with increased tolerance to many forms of circulatory shock, trauma and systemic stress. Infusion of some vasopressin molecules into animals subjected to circulatory shock can enhance RES phagocytic activity and induce permanent survival[7].

In view of the importance of RE cells in host defense, and the question as to whether a lack of circulating vasopressin in shock alters RES function, the present experiments were undertaken. We now report here that Brattleboro rats with hereditary hypothalamic diabetes insipidus (lacking pituitary vasopressin) are exquisitely sensitive to the lethal effects of 2 different forms of circulatory shock when compared to rats of the parent strain (i.e., Long Evans) or normal age-matched Wistar rats. In addition, our findings indicate that circulatory shock induces a complete failure of RES phagocytic function in Brattleboro but not in normal (vasopressin-containing) rats.

Methods. 3 different groups of young, adult male rats (Brattleboro, Long Evans, Wistar strains, 230±40 g) were utilized. Prior to induction of circulatory shock, each Brattleboro rat was administered 3 ml of water, 100 g b.wt

Table 1. Exacerbation of mortality after shock in Brattleboro rats

Rat strain	Hemorrhage Survivors/ total	% Survival	Bowel ischemia Survivors/ total	% Survival
Wistar	16/24	75	16/20	80
Long Evans	12/18	67	14/20	70
Brattleboro	1/12	8*	1/10	10*

* Significantly different from Wistar and Long Evans ($p < 0.01$).

intragastrically. This was based on previous metabolic cage experiments and was done to insure that the animals remained adequately hydrated during the subsequent anesthesia and surgery. The Wistar and Long Evans rats were administered 1 ml/100 g b.wt, intragastrically. 30 min after the administration of the water, the rats were lightly anesthetized, i.m., with pentobarbital sodium (3.5 mg/100 g) and subjected to either hemorrhage (3% bleeding by b.wt via femoral arterial cannulation) or bowel ischemic shock. The techniques utilized here, as well as the procedure for assessing the presence of shock, were similar to those described previously[8]. Briefly, in the case of hemorrhage, the cannulated femoral arteries were connected to calibrated bleed-out reinfusion devices containing heparin-treated Ringer's solution and in tandem with conventional mercury manometers. The animals were bled via the femoral arteries over a 30-min period to a fixed 3% by b.wt. The blood was withheld from the latter animals for 60 min. At the conclusion of this hypotensive period, the shed blood was reinfused (intra arterially) over a 30-min period. Blood pressure monitoring was continued after transfusion for 20–30 min. The cannulas were then removed and the wounds sutured. The animals were then placed back in their cages, allowed food and water ad libitum, and carefully monitored for survival for 7 days. For induction of bowel ischemia shock, we laparotomized the anesthetized animals and utilized a 30-min temporary occlusion of the superior mesenteric artery. Serial arterial microhematocrits (i.e., every 15 min) and mean arterial blood pressures were determined in selected animals. These cardiovascular parameters were monitored for at least 2 h after release of the temporary superior mesenteric arterial occlusion. The cannulas were then removed and the wounds sutured. These animals were also observed for 7 days for survival. The statistical validity of the survival data was assessed by means of the χ^2-test. Mean blood pressures ($\pm$SEM) and hematocrits ($\pm$SEM) were compared for statistical significance by means of Student's t-test.

In other experiments, phagocytic indices (or K-values) were determined prior to shock (controls) and 3 h after bleeding or release of the superior mesenteric arterial occlusion in all 3 groups of anesthetized, shocked animals. The phagocytic indices were determined from the rate of blood clearance of colloidal carbon, 4 mg/100 g b.wt, suspended in calf-skin gelatin, as described previously[8,9]. The phagocytic indices were calculated according to the expression

$$K = \frac{\log C_1 - \log C_2}{T_2 - T_1}$$

where C_1 and C_2 represent the blood carbon concentrations at times T_1 and T_2, respectively. The means and SEM's were calculated and statistically analyzed using Student's t-test.

Results. The data in table 1 demonstrate that Brattleboro rats are extremely sensitive to the loss of blood and/or fluid. The quantitative survival data clearly show that these animals are at least 7 times more susceptible to blood and fluid loss than are normal Long Evans or Wistar control rats of the same age, weight and sex. The mild forms of shock, used here, lower arterial blood pressure only 20–30 mm Hg 60 min post-shock in the control rats, but result in marked hypotension in the Brattleboro strain (table 2). In addition, the results in table 2 indicate that the hematocrit values 60 min post-shock in both the Wistar and Long Evans rats exhibit hemodilution, while those of the Brattleboro animals exhibit hemoconcentration. Although RES phagocytic function prior to induction of hemorrhage or bowel ischemia is not different in the 3 different strains of rats, virtually no colloidal carbon is cleared by the RES in Brattleboro rats 3 h post-hemorrhage or bowel ischemia (table 2). The 30–50% depression of RES phagocytic function observed in Wistar and Long Evans control rats post-shock (table 2) is in concert with previous findings[6–9].

Discussion. The present experiments support the idea that the release of endogenous vasopressin, from the posterior pituitary gland, into the circulation during shock syndromes is probably an intrinsic, homeostatic regulator of vascular tone. In addition, our findings suggest that RES function in shock syndromes may also be due to an intrinsic regulation by vasopressin. Although mild hemorrhagic or bowel ischemic episodes in normal rats (i.e., Long Evans or Wistars) result in only slight depression in mean arterial blood pressure and reticuloendothelial phagocytic function, rats devoid of endogenous vasopressin (i.e., Brattleboro strain) become markedly hypotensive and fail to demonstrate any perceptible ability to clear particulate matter from their bloodstreams in response to similar mild shock episodes. The hematocrit patterns noted here in normal animals, containing vasopressin in their posterior pituitary glands, seem to closely parallel what would be expected in mild forms of shock, i.e., a hemodilution, characteristic of vascular compensation. However, Brattleboro rats, lacking endogenous vasopressin, exhibit progressive hemoconcentration, which is characteristic of circulatory decompensation. An inability of an animal's peripheral vasculature to undergo compensatory vasoconstriction after bleeding and/or fluid loss (e.g., in case of animal lacking endogenous vasopres-

Table 2. Mean arterial blood pressures, arterial hematocrits and reticuloendothelial system phagocytic function in Wistar, Long Evans and Brattleboro rats after mild hemorrhage and bowel ischemia*

Rat strain	Hemorrhage			Bowel ischemia		
	Mean blood pressure (mm Hg $\pm$ SEM)	Hct (% $\pm$ SEM)	K value (mean $\pm$ SEM)	Mean blood pressure (mm Hg $\pm$ SEM)	Hct (% $\pm$ SEM)	K value (mean $\pm$ SEM)
Wistar						
Control	122 $\pm$ 6	42.2 $\pm$ 2.2	0.043 $\pm$ 0.005	124 $\pm$ 6	41.8 $\pm$ 1.6	0.046 $\pm$ 0.004
Post-shock	95 $\pm$ 4**	36.0 $\pm$ 1.6**	0.025 $\pm$ 0.004**	92 $\pm$ 5**	37.3 $\pm$ 1.4**	0.033 $\pm$ 0.005**
Long Evans						
Control	120 $\pm$ 7	43.0 $\pm$ 1.8	0.048 $\pm$ 0.006	118 $\pm$ 5	42.2 $\pm$ 1.4	0.045 $\pm$ 0.003
Post-shock	97 $\pm$ 4**	35.5 $\pm$ 1.9**	0.027 $\pm$ 0.007**	90 $\pm$ 6**	36.4 $\pm$ 1.8**	0.031 $\pm$ 0.005**
Brattleboro						
Control	128 $\pm$ 6	44.2 $\pm$ 2.5	0.045 $\pm$ 0.006	126 $\pm$ 7	43.5 $\pm$ 1.5	0.051 $\pm$ 0.005
Post-shock	30 $\pm$ 6***	52.5 $\pm$ 2.2***	0.002 $\pm$ 0.002***	32 $\pm$ 8***	50.8 $\pm$ 2.1***	0.001 $\pm$ 0.001***

* N = 8–12 different animals for each group. All post-shock values recorded here are at 60 min post hemorrhage or post release of the superior mesenteric arterial occlusion. ** Significantly different from paired controls ($p < 0.01$). *** Significantly different from all other values ($p < 0.001$).

sin) would, at least in theory, result in marked hypotension, progressive hemoconcentration and marked RES phagocytic depression, all of which we see take place in Brattleboro rats subjected to only mild episodes of hemorrhage and intestinal ischemia.

A loss of RES phagocytic function, as seen in the present studies using Brattleboro rats subjected to mild blood and/or fluid loss, is known to result in a failure to inactivate pathogenic microorganisms, blood borne tissue mediators, endotoxins, metabolites and/or other noxious tissue products released in shock[6,7,9]. In addition, severe depression, or a loss of RES function is known to be associated with depressed microcirculatory blood flow, tissue ischemia and rupture of lysosomal membranes, thereby releasing hydrolytic enzymes into the circulation[6]. The fact that previous experiments have clearly demonstrated that vasopressins, when administered to normal animals subjected to severe forms of the same types of shock used here, can either restore or enhance RES phagocytic function[7] lends support to the concept that endogenous, released vasopressin probably aids in the maintenance of RES function after mild blood and/or fluid loss.

In conclusion, our current observations provide strong, direct evidence for a role for endogenous vasopressin in the compensatory phase of the shock syndrome and in homeostatic regulation of the RES after shock and trauma.

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Effects of propafenone on TEA-induced action potentials in vascular smooth muscle of canine coronary arteries[1]

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Summary. The Ca^{++}-dependent, TEA-induced action potential is blocked by propafenone in a dose-dependent manner. Such results suggests that in coronary arterial smooth muscle one mechanism of action of propafenone is to inhibit Ca^{++} inward current.

Propafenone has recently been demonstrated to possess antiarrhythmic properties in a significant number of individuals with ectopic beats and tachycardias of atrial or ventricular origin[2]. It also has been shown that propafenone has negative inotrophic actions in that it reduces systolic time intervals[3], transiently reduces cardiac function[2], and prolongs the refractory period[4]. Such negative inotrophic actions of this drug have been attributed, in part, to a decrease in Ca^{++} inward current[4].

Propafenone also induces a dose dependent increase in coronary blood flow in dogs and guinea-pigs, and relaxes strips of bovine coronary arteries[4,5]. Such findings suggest that propafenone may have similar action on coronary arteries and cardiac tissue in inhibiting Ca^{++} inward current necessary for excitation-contraction coupling.

Recently, Harder et al.[6] have demonstrated that in vascular smooth muscle (VSM) from canine coronary arteries tetraethylammonium ion (TEA) induces Ca^{++} dependent action potentials upon electrical stimulation. These TEA-induced action potentials are blocked by known Ca^{++} antagonists such as verapamil and Mn^{++}.

It is the purpose of the present study to determine the effect of propafenone on the Ca^{++} dependent action potential in the VSM of canine coronary arteries since it may serve as a useful tool in the study of Ca^{++} inward current in the cells.

Materials and methods. Mongrel dogs were anesthetized with sodium pentabarbital (30 mg/kg, i.v.) after which the hearts were rapidly removed. The left main coronary artery was cannulated and perfused with cold oxygenated Ringers' solution. Coronary arteries (1.0 mm outside diameters) were removed and slit down the longitudinal axis, allowing microelectrode penetration from the intimal sur-

Summary of membrane potential, action potential amplitude and maximal rate of rise measurements in canine coronary arterial smooth muscle in the presence of 10 mM TEA (±1 SEM)

Condition	E_m (mV)	Amplitude (mV)	$+\dot{V}_{max}$ (V/sec)	N**
Control	48±1.0	54±1	6.8±0.7	9/5
Propafenone (10^{-6} M)	47±0.7	27±1.1*	2.9±1.4*	9/5
Propafenone (10^{-5} M)	45±1.0*	0	0	10/6

* Significantly less than control at $p<0.05$. ** Numerator refers to the number of cells impaled, denominator refers to the number of arteries.