

Fed, but not Fasted, Adrenalectomized Rats Survive the Stress of Hemorrhage and Hypovolemia*

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ABSTRACT. We have recently shown that conscious adrenalectomized rats exhibit nearly normal recovery of arterial blood pressure during the 5 h after hemorrhage. In those experiments, it appeared that a previous reduction in food intake might have compromised the recovery of blood pressure and increased mortality. These experiments were designed to test in conscious sham-adrenalectomized (control) and adrenalectomized rats prepared with indwelling arterial and venous cannulae 1) the effects of a 20- to 24-h fast (compared to rats fed *ad libitum*) on the mobilization of plasma substrates and recovery of arterial blood pressure after a 15 ml/kg·5 min hemorrhage, and 2) vascular responsiveness to pressor agents in fed or fasted groups before or 2 h after hemorrhage. In all rats hemorrhage resulted in decreased arterial pressure and heart rate. Arterial pressure recovered to near normal in both fed and fasted control groups and in the fed adrenalectomized rats, and all of these rats survived for 24 h after stress. By contrast, in the fasted adrenalectomized rats, arterial pressure recovered only during the first 1.5–2 h and then failed, resulting in 100% mortality by 3–5 h. Compared to the other three groups, in which substrate levels either increased or remained fairly stable, plasma glucose and β -hydroxybutyrate concentrations fell steadily from 1.5–2 h after hemorrhage until death occurred in the fasted adrenalectomized rats. Basal ACTH concentrations were elevated com-

pared to control values in both adrenalectomized groups (fed and fasted). Hemorrhage caused increases in plasma ACTH in all groups; the magnitude of the responses did not differ among the groups. The dilution of Evans' blue dye after hemorrhage (used as an index of fluid movement into the vascular space) was not different in control and adrenalectomized rats (either fed or fasted). There were no differences in pressor responses to phenylephrine, vasopressin, or angiotensin-II between the fed and fasted conditions in the control rats either before or after hemorrhage. There was a fasting-associated decrease in vascular responsiveness to vasopressin, but normal responsiveness to phenylephrine and angiotensin-II, in the adrenalectomized rats both before and after hemorrhage. We conclude that 1) since fed adrenalectomized rats all survived the stress, adrenal hormones are not required for survival unless fasting is a prior condition; 2) vascular responsiveness to phenylephrine and angiotensin-II is not altered by fasting and is, therefore, probably not the proximate cause of cardiovascular system failure; and 3) from these data we cannot distinguish between a failure in substrate supply and a failure in some component of the cardiovascular system, other than vascular responsiveness, that results in death after hemorrhage in fasted adrenalectomized rats. (*Endocrinology* 127: 759–765, 1990)

IT IS ABUNDANTLY clear that adrenalectomized rats that are maintained on saline to drink may succumb from stresses that do not cause death in rats with adrenal glands. Moreover, the proximate causes of death have been suggested to result from either a deficit in the responsiveness of the cardiovascular system to catecholamines (1, 2) or a lack of mobilizable substrate (3). In 1936, Selye (4) observed that adrenalectomized rats maintained on saline to drink lived through stresses when they were fed, but died of the same stresses if they were

fasted before imposition of the stressor.

We have recently reported that bilaterally adrenalectomized rats studied under conscious unstressed conditions exhibit nearly normal responses in mean arterial blood pressure (MABP) and heart rate (HR) to phenylephrine and nitroglycerin compared to sham-adrenalectomized controls (5). Moreover, when chronically prepared unstressed adrenalectomized rats were exposed to 15 ml/kg hemorrhage and hypovolemia, arterial blood pressure was restored normally, and the restitution of blood volume was complete by 5 h. The adrenalectomized animals appeared to be protected by the exaggerated responses that occurred in other vasoactive hormones, such as arginine vasopressin, oxytocin, norepinephrine, and plasma renin concentration (6). However, in those experiments, three of the seven adrenalectomized rats died within 24 h of the hemorrhage, whereas none of the sham-adrenalectomized rats died. Review of the records of the adrenalectomized rats in that study showed that

Received April 12, 1990.

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* This work was supported in part by USPHS Grant DK-28172, NASA NCC 2-354, and ONR N00014-88-K-0059.

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‡ Supported by the American Heart Association, California Affiliate, Student Research Program, 1988 and 1989.

the three rats that died had lost body weight, whereas the four that lived had gained weight slowly, suggesting that there might be an interaction between food intake and stress that accounted for the death of these rats.

The present studies were performed to test the effects of a 20- to 24-h fast on the mobilization of substrates in response to hemorrhage and sustained hypovolemia in otherwise healthy chronically prepared adrenalectomized and sham-adrenalectomized control rats. Other studies tested vascular responsiveness to pressor agents in fed and fasted adrenalectomized and sham-adrenalectomized rats, both under control conditions and 2 h after hemorrhage. Some of the results of these experiments have been reported in abstract form (7, 8) and in a symposium paper (9).

Materials and Methods

Adult male Sprague-Dawley rats (Holtzman, Madison, WI), weighing between 280–400 g, were housed in hanging basket cages in a light (12 h on)-, temperature-, and humidity-controlled room and were allowed food and drink *ad libitum* until the day before hemorrhage. Under pentobarbital anesthesia, rats were provided with indwelling femoral arterial and venous cannulae that exited from the top of the cage through a spring fastened to a sc anchor between the scapulae (10). Three days later the animals were weighed and either adrenalectomized or sham-adrenalectomized under ether anesthesia; thereafter, the rats were given saline (0.5%) to drink. Fluid intake was measured daily. Four days after adrenal surgery, rats were weighed, and then half of the animals in each group had food, but not drinking fluid, removed. The studies were designed so that equal numbers of sham-adrenalectomized control and adrenalectomized rats were studied on each day. The experiments were approved by the University of California-San Francisco committee on animal research.

Exp 1

On the morning of the sixth day after adrenal surgery, within 1 h of lights on, after injection of Evans' blue dye and collection of a control sample, hemorrhage (15 ml/kg·5 min) was performed. Additional 2.5 ml blood samples were withdrawn at 0.3, 1, 1.5, 2, 3, and 5 h for measurement of Evans' blue dye, protein, hormones, and energy substrates in plasma. Red blood cells mixed with an equivalent volume of saline were reinfused as each sample was collected after the initial hemorrhage volume was removed. Additional 0.2 ml blood samples were collected 10, 45, and 180 min after hemorrhage for measurement of plasma substrate concentrations. The time zero measurement of these plasma constituents was derived from the blood removed at hemorrhage. No more than two rats were studied on 1 day.

These experiments were performed on conscious rats. The animals did not exhibit behavioral responses during the period of rapid hemorrhage and appeared to be oblivious to the withdrawal of blood, which was performed from the outside of the cage without handling the animals. During the first hour after

the hemorrhage, the rats lay quietly in their cages, which is typical behavior for rats in the morning. During the first hour, the rats almost certainly did not lose consciousness, since they maintained their posture and kept their weight on all four paws. In the rats that subsequently died, we found that as MABP began falling steadily after about 60 min until death occurred, the rats appeared to lose consciousness and rolled over onto their sides at some point before loss of the arterial pressure trace. There was no intervening period of excitement or evidence of convulsions before or after this apparently gradual loss of consciousness.

Exp 2

In a second set of chronically prepared conscious control and adrenalectomized rats, peak arterial blood pressure and HR responses to injected doses of phenylephrine, arginine vasopressin, and angiotensin-II were measured under resting conditions and 2 h after hemorrhage of 15 ml/kg·5 min. Experiments were performed under both fed and fasted conditions. Some rats were studied twice, once under basal conditions and once after hemorrhage 4 days later. Basal plasma volume and hormone concentrations were measured in an initial 0.5-ml blood sample that was replaced simultaneously with red blood cells and saline or plasma from the hemorrhaged blood; 0.1-ml samples were collected 20 min after hemorrhage for measurement of corticosterone in these experiments; further blood sampling was not performed. Under these restricted blood-sampling conditions, both fed and fasted adrenalectomized rats lived for 5 h after hemorrhage, allowing the measurement of blood pressure after the injection of pressor agents 2 h or more after hemorrhage. Up to eight rats were studied on 1 day.

Measurements

Arterial blood pressure and HR were measured before and after hemorrhage via the arterial cannula, using a Statham pressure transducer connected to Grass amplifiers and a tachograph (Grass Instruments, Quincy, MA). Vascular refilling after hemorrhage was estimated by measuring the dilution of Evans' blue dye, which was injected iv before hemorrhage. The concentration of dye was determined 0, 0.3, 1, 1.5, 2, and 5 h after hemorrhage and was corrected for the loss of Evans' blue from the vascular space with time. The loss of Evans' blue was measured in the absence of hemorrhage in a separate experiment in eight adrenalectomized and eight sham-adrenalectomized chronically cannulated rats in which 1 mg dye was injected iv, and the concentration of dye was determined at the times given above. Plasma protein concentration was measured using a hand protometer (National Diagnostic Corp., Somerville, NJ). Plasma glucose was measured by the glucose-oxidase technique (Beckman Glucose Analyzer II, Palo Alto, CA). Plasma lactate, β -hydroxybutyrate, and alanine concentrations were measured using methods previously described (11). Plasma ACTH and corticosterone concentrations were measured by RIA, as previously described (12, 13). The limit of detection for ACTH was 8 pg/ml; inter- and intraassay coefficients of variation were 8.5% and 9%, respectively. The limit of detection for corticosterone was 0.1 μ g/dl; inter- and intraas-

say coefficients of variation were 1.0 and 2.4%, respectively. Data were analyzed for statistical significance using one-way analysis of variance (ANOVA) for response over time and two-way ANOVA, corrected for repeated measures, to compare responses between groups. Newman-Keuls multiple range test was used to compare means after ANOVA. Significance was accepted at $P < 0.05$.

Results

Exp 1

All fed adrenalectomized rats and both fed and fasted controls lived through the hemorrhage and subsequent 24 h. By contrast, all fasted adrenalectomized rats died within 24 h of the hemorrhage, most of them between 2.5–3.5 h after the hemorrhage volume was removed. The responses of MABP and HR in both fed and fasted adrenalectomized and control rats are shown in Fig. 1. Fed adrenalectomized rats restored and maintained MABP well compared to sham-operated animals. By

contrast, the fasted adrenalectomized rats did not sustain MABP, demonstrating a slow decline until death occurred, even though the initial return of MABP resembled that in the fasted controls during the first hour. Initial HR was elevated in both groups of adrenalectomized rats compared to that in the controls, and after the reflex bradycardia occasioned by hemorrhage ceased, the elevated HR was sustained for several hours in the adrenalectomized rats compared to values in controls.

The dilution of Evans' blue dye (which reflects both the return of fluid into the vascular system via Starling forces across the capillaries and successive dilution of plasma protein by the repeated removal of plasma and replacement with saline) did not differ between adrenalectomized rats and controls under either fed or fasted conditions (Fig. 2, *left and right*). The initial concentration of Evans' blue dye was slightly greater in the fasted than the fed rats, reflecting the decrease in blood volume that occurs with a 20- to 24-h fast (6).

The responses of plasma ACTH and corticosterone to

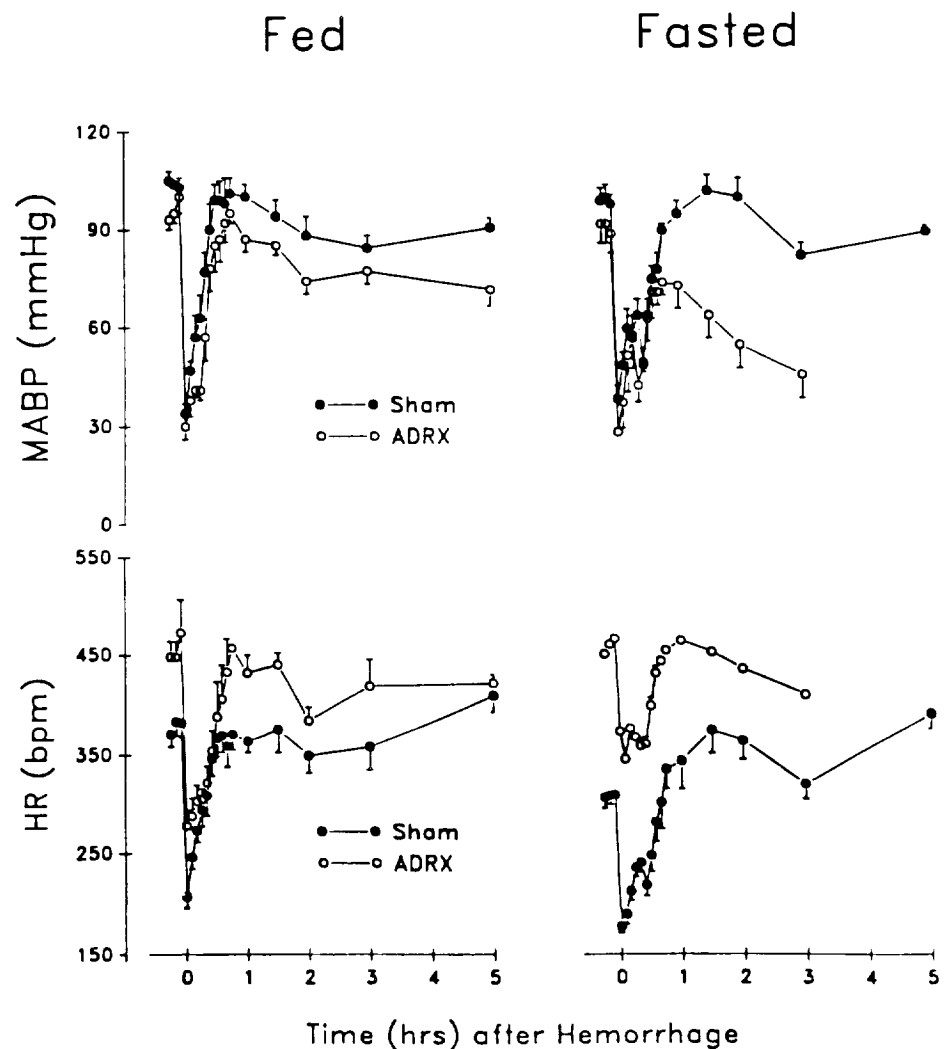


FIG. 1. The responses of MABP and HR to 15 ml/kg · 5 min hemorrhage in conscious fed and 20- to 24-h fasted sham-adrenalectomized (Sham) and adrenalectomized (ADRX) rats. There was a significant difference (by two-way ANOVA) between the Sham and ADRX groups for the responses of MABP and HR (for both fed and fasted treatments). Values represent the mean \pm SE (six rats per group).

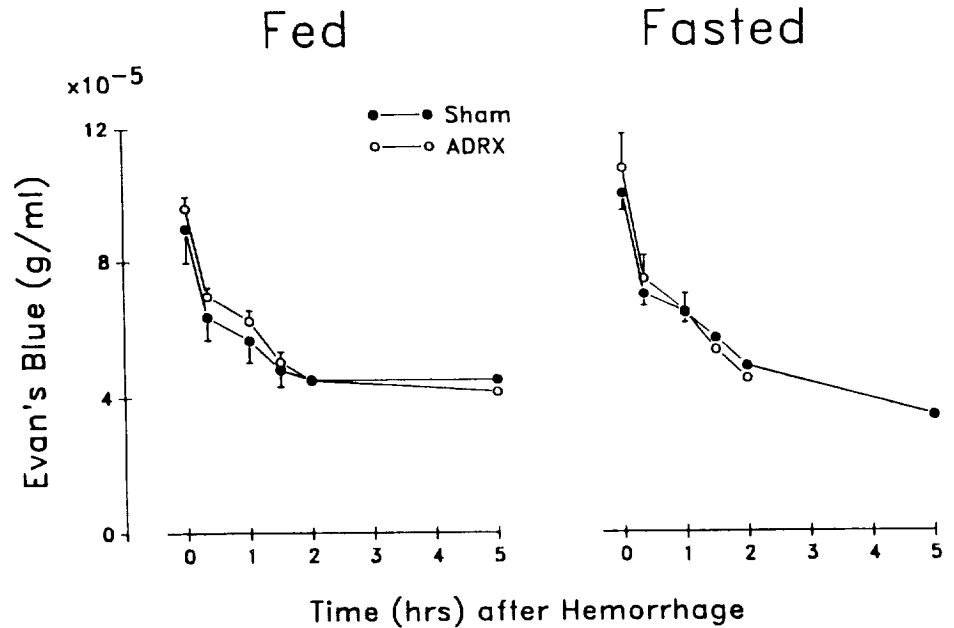


FIG. 2. The dilution of Evans' blue dye (1 mg) in plasma after 15 ml/kg·5 min hemorrhage in conscious fed and 20- to 24-h fasted sham-adrenalectomized (Sham) and adrenalectomized (ADRX) rats. There were no significant differences between groups. Values represent the mean \pm SE.

hemorrhage are shown in Fig. 3. Initial ACTH concentrations were elevated in the adrenalectomized rats compared to those in the controls (Fig. 3, *top*), and there was no corticosterone response to the hemorrhage in these groups (Fig. 3, *bottom*). By contrast, the ACTH responses to hemorrhage were significant, and the magnitudes were similar in fed and fasted adrenalectomized and control rats. The ACTH responses persisted for approximately 2 h, and hormone concentrations had returned to initial levels by 5 h in the rats that survived.

Plasma concentrations of energy substrates are shown in Fig. 4. Plasma glucose concentrations did not change after hemorrhage in fed controls (Fig. 4, *top left panel*). By contrast, in fed adrenalectomized rats, glucose concentrations fell between 1–2 h and remained at a plateau thereafter. Initial plasma glucose concentrations were decreased in both groups of fasted rats. Plasma glucose increased with time after hemorrhage in fasted control rats, so that by 5 h the levels were elevated above initial values. Plasma glucose levels fell in fasted adrenalectomized rats; there was a progressive and marked decline from 90 min until death occurred.

There was a biphasic change in plasma lactate after hemorrhage in all groups (Fig. 4, *second panel*). However, the fasted adrenalectomized group showed an exaggerated response compared to the fasted control group. Plasma β -hydroxybutyrate concentrations did not change with time after hemorrhage in the fed groups. By contrast, fasting resulted in elevated initial values of this fatty acid, and hemorrhage occasioned increased levels in the controls, but not the adrenalectomized rats (Fig. 4, *third panel, left and right*). Plasma concentrations of alanine were only marginally affected in these experi-

ments, with minor elevations occurring in the fasted adrenalectomized rats at 90 and 180 min (Fig. 4, *bottom panel, left and right*).

Exp 2

The responsiveness of MABP to injections of vasoactive agents in control and adrenalectomized rats under resting conditions revealed that fasting only changed responsiveness to vasopressin (AVP) in adrenalectomized rats (Fig. 5). Responses to phenylephrine and angiotensin-II were not affected by fasting in adrenalectomized rats, and fasting did not affect responses to any of the pressor agents in the control rats (Fig. 5). Similarly, pressor responsiveness to these vasoactive agents administered 2 h after hemorrhage was not altered in fasted control rats; again, only the responsiveness to vasopressin, but not that to phenylephrine or angiotensin-II, was decreased after hemorrhage in fasted adrenalectomized rats (Fig. 6).

A 2×2 factorial analysis of initial values from this experiment revealed that adrenalectomized rats had gained less weight than sham-operated rats, their MABP was lower and HR was higher, their plasma volume was not different, and their plasma norepinephrine and renin concentrations were elevated (not shown). These results are similar to those reported in another study (6).

Discussion

All fed and fasted control rats and all fed adrenalectomized rats survived the stress of hemorrhage and associated blood sampling. In marked contrast, all fasted adrenalectomized rats died. These results coupled with our previous findings (6) show that the adrenal glands

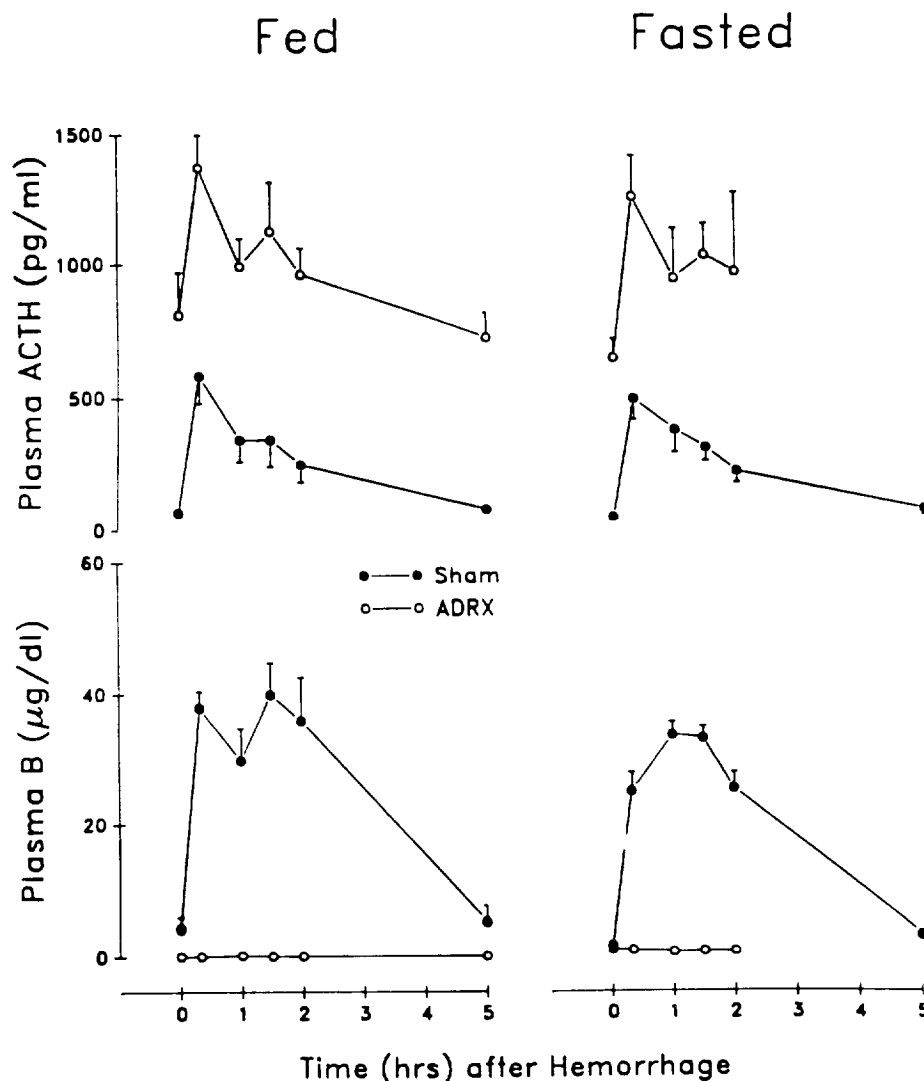


FIG. 3. The responses of plasma ACTH and corticosterone after 15 ml/kg·5 min hemorrhage in conscious fed and 20- to 24-h fasted sham-adrenalectomized (Sham) and adrenalectomized (ADRX) rats. There was a significant difference (by two-way ANOVA) between the Sham and ADRX groups for the responses of ACTH and corticosterone (for both fed and fasted treatments). Values represent the mean \pm SE.

and their hormonal products *per se* are not required for survival after a stress to the cardiovascular system of moderate intensity. It is likely that the potentiated responses of other hormones involved in the maintenance of vascular pressure to this degree of hemorrhage that occur in adrenalectomized rats (6) adequately compensated for the loss of the adrenal hormones. In accord with the conclusion of Selye (4), however, there is a marked interaction between fasting and adrenalectomy on the capacity of rats to withstand hemorrhage stress.

Fed and fasted control rats restored arterial blood pressure to near-normal values within 60 min of hemorrhage and sustained this over the 5-h period of study. Although plasma glucose levels were fairly constant in the fed control rats, glucose production appeared to have been increased in the fasted rats after 2 h. Similarly, although plasma β -hydroxybutyrate concentrations in the fed control rats remained fairly stable, there tended to be an increase in the concentrations of this energy

substrate during the first 2 h after hemorrhage in fasted rats. Thus, the fasted control animals appeared to mobilize substrate after hemorrhage, first in the form of fatty acids and subsequently in the form of glucose. The time course of such responses is compatible with the known actions of elevated levels of vasopressin, catecholamines, and glucocorticoids, which are secreted in response to the hemorrhage (6, 13-17). Hormonal responses to hemorrhage in fed sham-adrenalectomized rats are of lower magnitude than those in adrenalectomized rats (6), possibly accounting for the lack of response in plasma substrates after hemorrhage in these animals.

The major differences in responses between fed and fasted adrenalectomized rats that we measured were those that began to occur 60 min after hemorrhage. At about this time, both MABP and plasma glucose levels began to decline slowly in the fasted adrenalectomized rats. The decline in these variables was sustained for the

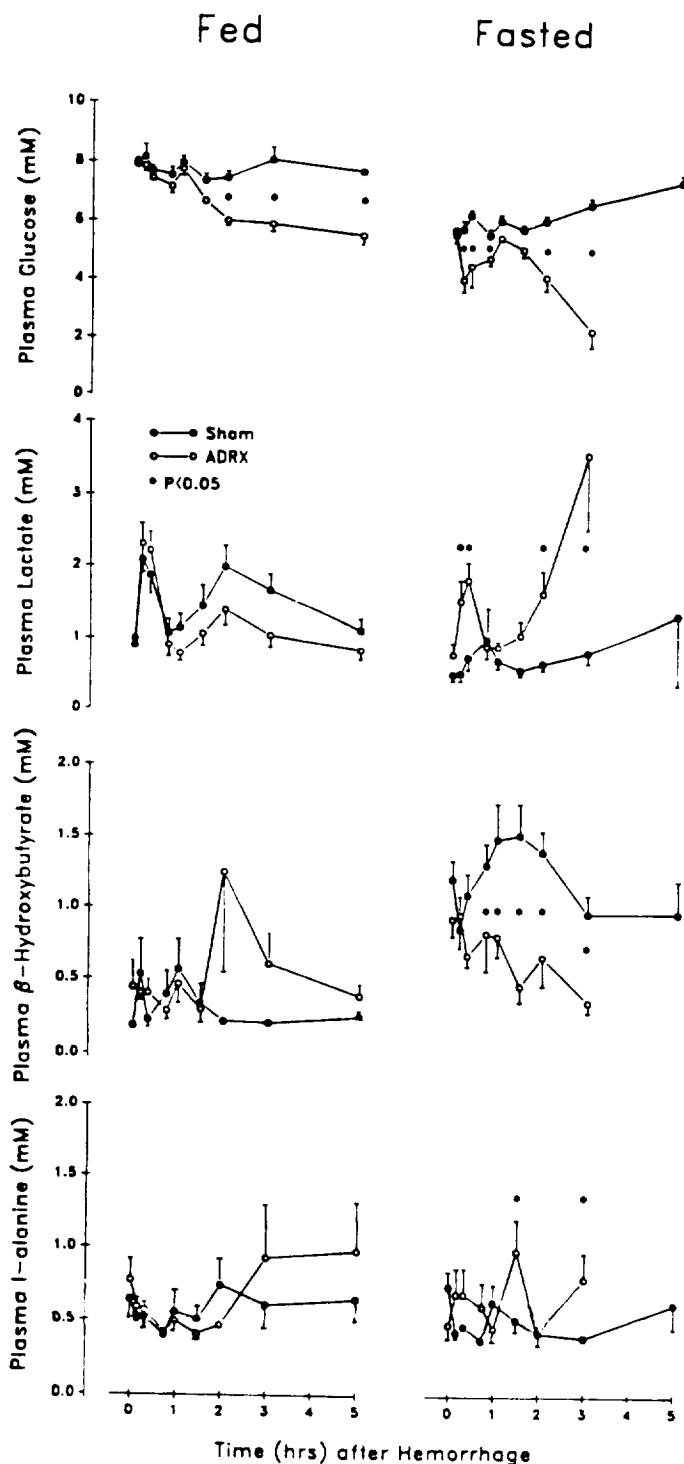


FIG. 4. The responses of plasma glucose, lactate, β -hydroxybutyrate, and l-alanine to 15 ml/kg, 5 min hemorrhage in conscious fed and 20- to 24-h fasted sham-adrenalectomized (Sham) and adrenalectomized (ADRX) rats. There was a significant difference (by two-way ANOVA) between the fasted Sham and ADRX groups for the responses of all plasma substrates and between the fed Sham and ADRX groups for the responses of glucose. ●, Significant difference at that time point by Newman-Keuls test. Values represent the mean \pm SE.

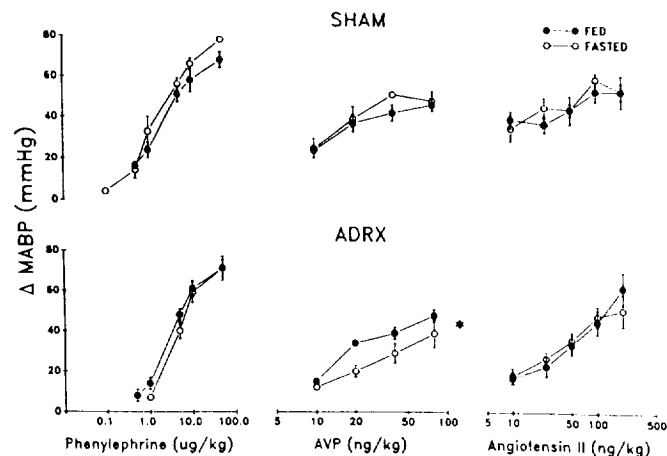


FIG. 5. Peak changes in MABP before hemorrhage in sham-adrenalectomized control (SHAM) and adrenalectomized (ADRX) rats, either fed (●) or fasted for 20–24 h (○) after injections of phenylephrine, arginine vasopressin, or angiotensin-II. *, Significant difference between responses of fed and fasted rats by ANOVA. Values represent the mean \pm SE (n = 4–7/group).

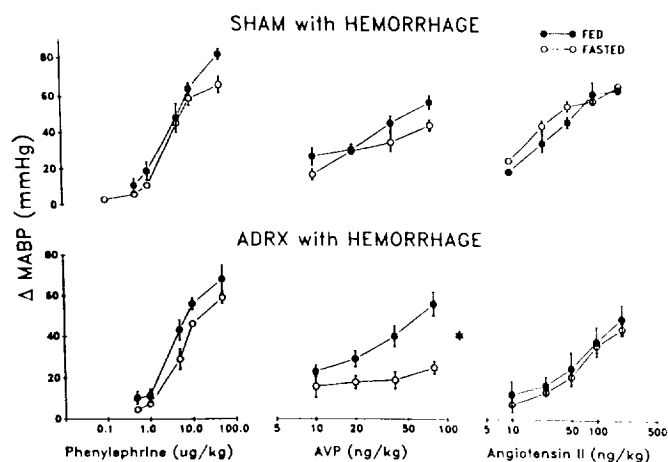


FIG. 6. Peak changes in MABP 2 h after hemorrhage in sham-adrenalectomized control (SHAM) and adrenalectomized (ADRX) rats, either fed (●) or fasted for 20–24 h (○) after injections of phenylephrine, arginine vasopressin (AVP), or angiotensin-II. *, Significant difference between responses of fed and fasted rats by ANOVA. Values represent the mean \pm SE (n = 4–7/group).

next few hours until death usually occurred. From our data, the cause of death could have been equally well hypoglycemia or circulatory failure. Plasma β -hydroxybutyrate levels did not rise in the fasted adrenalectomized rats as they did in the fasted controls, but, instead, declined slowly during the posthemorrhage period. The lowest level of this substrate observed in the fasted adrenalectomized rats was equivalent to concentrations in the fed animals. Since heart muscle preferentially uses fatty acids for energy under conditions of starvation, it may be that the slow fall in this substrate in fasted adrenalectomized rats was also a factor contributing to death.

It is somewhat surprising that the magnitudes of the ACTH responses to hemorrhage were the same in all four groups of rats despite the fact that initial ACTH concentrations were markedly elevated in the adrenalectomized animals. This result suggests that basal and stress-induced ACTH release are controlled by distinctly different mechanisms, in agreement with previous findings (18). Additionally, it is surprising that the fasted adrenalectomized rats did not exhibit a greater ACTH response, particularly at 90 and 120 min, than the fed adrenalectomized rats, given the fact that both arterial blood pressure and glucose levels were considerably lower at these times in the former group (19).

It is clear from our vascular responsivity studies that fasting does not alter vascular responsiveness to either catecholamines or angiotensin-II in control or adrenalectomized rats before or 2 h after hemorrhage. This result suggests strongly that death in fasted adrenalectomized rats after hemorrhage does not result from vascular insensitivity to catecholamines, although such an effect has been proposed by others (1, 2). There was a decrease in responsivity to vasopressin in fasted adrenalectomized rats both before, but more markedly after, hemorrhage; a similar effect was not found in control rats. It is possible that the marked vasopressin response observed after hemorrhage in fasted adrenalectomized rats (see following paper) resulted in either receptor loss and/or target tissue insensitivity.

The specific action of the corticosteroids that allows adequate responsiveness to stress is unknown and could, of course, be on any of the myriad processes affected by these hormones, such as cardiac contractility (20), or various aspects of substrate mobilization, such as gluconeogenesis (21-23). In an interesting parallel to these studies, Exton *et al.* (24) showed in elegant *in vitro* studies on hormone-stimulated hepatic gluconeogenesis and glucose production that it was necessary to fast adrenalectomized rats overnight to reveal the major glucocorticoid-mediated effects on these end points. We have studied further the interaction between fasting and adrenalectomy that results in hemorrhage-induced mortality in the following paper.

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