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Research Article

HISTAMINE RELEASE AND ENDOTOXIN SHOCK IN THE PRIMATE *

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There is a growing interest in the pathogenesis and treatment of endotoxin shock as this type of shock becomes increasingly important in medical and surgical practices (1–4). Recent work has described the hemodynamic effect of endotoxin in the dog which is characterized by a sudden and severe hypotension following administration of a lethal dose of endotoxin (5, 6). Previous reports from this laboratory (7–10) have extended the earlier observations, and specific attempts have been made to gain an understanding of the basic mechanisms underlying the development of the irreversible phase of this type of shock (9–16). An extension of these studies has ascertained the degree of species variation in endotoxin shock (17, 18), and major differences have been noted between the hemodynamic responses of the dog and monkey.

Recent reports have suggested the prominent role of histamine in endotoxin shock in animals other than the primate (14, 19–23). The release of histamine in anaphylaxis has also been described (24, 25) with similarities noted between the vascular actions of histamine and endotoxin (8–10, 13, 26–31). A recent finding by Schayer (20, 21) has indicated an increase in histidine decarboxylase activity after endotoxin administration and in other forms of stress.

The purpose of the present investigation was to assess a variety of changes in the monkey, previously demonstrated in other species after endotoxin administration. Of primary interest are changes in blood histamine and histidine and the ultimate effects of their release in the primates. Results of this study confirm the view that histamine plays a crucial role in shock due to endotoxin and extend the suggestions of Schayer to include the basic mechanism of histamine release.

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METHODS

Eight adult male and female monkeys of the Cynopithecoid group, *Cercocebus torquatus Atys* (Sooty Mangabey) were used in the present investigation. Animals weighed between 5.7 and 11.0 kg and were first anesthetized with ether followed by a suitable intravenous injection of sodium pentobarbital (Nembutal). The amount of Nembutal required to sustain anesthesia varied so that animals were maintained between planes 1 and 2 of the surgical stage by appropriate administration of the anesthetic. Blood samples from 6 monkeys were obtained from a catheter inserted into the femoral vein and advanced to the inferior vena cava. Estimations for blood histamine [1] and histidine [2] were carried out and the procedures for the analyses have been described (14, 19). The following blood determinations were made in 4 animals before and after endotoxin administration: platelet and white blood cell counts (32, 33), blood-urea-nitrogen (BUN) (34, 35), and blood creatinine (36). Mean systemic arterial blood pressures were recorded by means of a Statham strain gage, and registered on a Sanborn direct-writing recorder. Determinations of hematocrits and blood pH were carried out on most animals coincident with electrocardiograph and heart rate recordings in several experiments. In 2 animals the following parameters were determined: mean systemic arterial pressure, portal venous pressure, heart rate, hematocrit and blood pH. Lethal doses of *Escherichia coli* endotoxin (Difco), 5.2 to 13.0 mg per kg (average, 8.9), were intravenously administered after sampling of blood for control determinations. All animals were dead within 30 hours (average, 6 hours) after endotoxin injection with the exception of Monkey 7 which was sacrificed at approximately 13 hours. Gross autopsies were made immediately after death and a variety of tissue samples was taken for histological analysis.

RESULTS

Figure 1 illustrates changes in mean systemic arterial blood pressure, hematocrit, blood pH, histidine and histamine following injections of lethal doses of endotoxin in six monkeys. There was a variable effect on blood pressure, with all animals

[1] 2-(4-Imidazolyl)-ethylamine.

[2] α-Amino-4 (or 5) -imidazolepropionic acid.

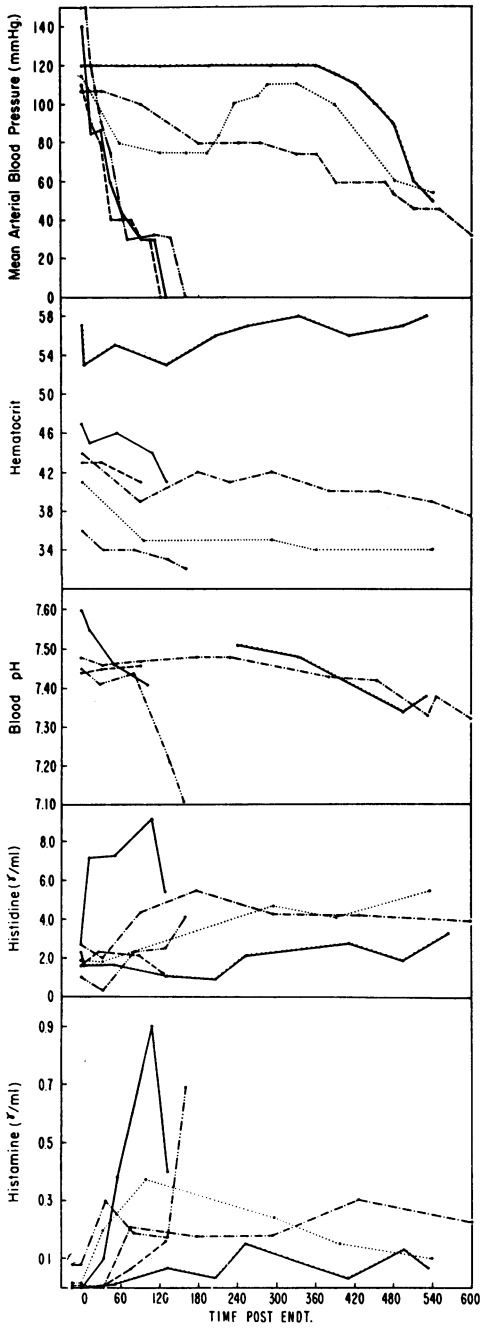

FIG. 1. CHANGES IN MEAN SYSTEMIC ARTERIAL BLOOD PRESSURE, HEMATOCRIT, BLOOD pH, HISTIDINE AND HISTAMINE AFTER INJECTIONS OF LETHAL DOSES OF ENDOTOXIN IN SIX MONKEYS. Abscissa: time in minutes post endotoxin. Ordinate: *animal* 1 LLL; 2 . . . . .; 3 .—.—; 4 ----; 5 —..—; 6 ————.

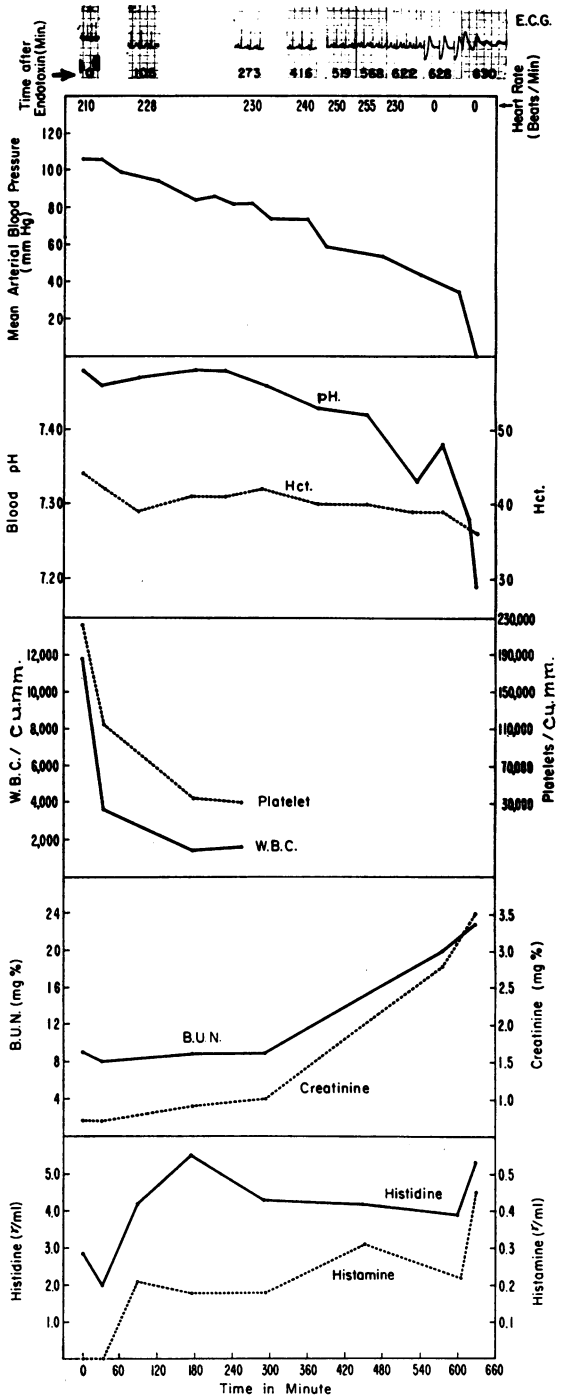

FIG. 2. RESULTS FROM A TYPICAL EXPERIMENT (MONKEY 3). Abscissa: time in minutes post endotoxin. Ordinate: note ECG tracing in upper frame. Pre-endotoxin paper speed, 10 mm/sec; postendotoxin paper speed, 25 mm/sec (time in minutes after endotoxin appears on each ECG section).

TABLE I

Platelet and white blood cell counts, blood-urea-nitrogen and blood creatinine determinations in four monkeys given lethal doses of endotoxin

Determination	Monkey no.	Control	Time post endotoxin in minutes 0–60	60–120	120–180	180–270	270–420	420–560
Platelets/mm³	3	224,000	114,000		36,000	32,000		
	4	196,000	56,000	96,000	*			
	5	88,000		34,000	17,000*			
	6	234,000	108,000	118,000	*			
White blood cells/mm³	3	11,800	3,550		1,400	1,600		
	4	14,600	1,800	2,300	*			
	5	27,500		10,000	4,350*			
	6	17,750	4,700	4,050	*			
BUN (mg%)	3	9	8		9	9	20	23
	4	11	13	16	17*			
	5	8		10	11–12*			
	6	14	15	17	*			
Blood creatinine (mg%)	3	0.7	0.7		0.9	1.0	2.8	3.5
	4	1.6	1.8	2.7	2.8*			
	5	0.9		1.3	1.5*			
	6	1.2	1.5	2.4	*			

* Death occurred during this time interval.

eventually becoming hypotensive within 8 hours after endotoxin. Hematocrits showed a steady decline except in Experiment 1 in which an early fall was followed by a return to the control value. The progressive development of acidosis was evident in most animals after endotoxin. Changes in blood histidine were variable, in most instances showing a significant rise above control values. All experiments demonstrated large increases of blood histamine, which became evident within the first hour after endotoxin injection.

Table I gives the values for platelet and white blood cell counts, BUN and creatinine for four of the six animals reported in Figure 1. There are marked decreases in platelet and white cell counts in all monkeys, although the time after endotoxin injection during which the lowest values were observed was variable. Significant increases in BUN and creatinine were observed in all animals within 1 to 2 hours after endotoxin administration.

Figure 2 designates the changes in a variety of parameters in Monkey 3. Steady decreases in

TABLE II

Blood pressures, heart rates, hematocrits and pH determinations in two monkeys given lethal doses of endotoxin

Measurement	Monkey no.	Control	Time post endotoxin in minutes 0–15	15–30	30–120	120–240	250–480	480–780
Mean systemic arterial blood pressure (mm Hg)	7	115	100	105	75	87	124	117
	8	110	100	90	37	30	18*	
Portal venous pressure† (mm Hg)	7	7.0	7.5	7.2	7.6	8.3	9.1	9.8
	8	7.0	8.0	7.0	7.0	6.5	7.7*	
Heart rate (beats/min)	7	185	190	190	207	202	204	220
	8	200	195	200	188	187	158*	
Hematocrit	7	47.5	48.0		47.0	48.0	52.5	54
	8	38.5	35.5		37.0	37.0	37.0*	
Blood pH	7		7.41		7.40	7.44	7.40	7.35
	8	7.43	7.43		7.42	7.36	7.14*	

* Death occurred during this time interval.
† Portal venous pressures indicate maximal readings for the time indicated.

TABLE III

Histological findings in five monkeys given lethal doses of endotoxin

Organ	Monkey no. and sex				
	1 ♂	2 ♀	3 ♀	4 ♀	5 ♀
Adrenal	Marked congestion	N	N	N	
G.I. tract	N*	N	N	N	N
Heart	Small vessels engorged; one small area of hemorrhage	N	N	N	N
Kidney	Marked capillary and glomerular engorgement; in some tubules cells swollen, cytoplasm fluffy	N	N	Early tubular epithelial degeneration predominantly in cortical region	
Liver	Congested; no cellular alterations	N	N	N	Multiple foci round cell infiltrate, old
Lung	Patchy cellular infiltrate	N	N	N	N
Pancreas		N	N	N	N
Spleen	Congested	N	N	N	N
Time of death post endotoxin (min)	840	1,600 (est.)	630	120	160
Dose of endotoxin (mg/kg)	13.0	5.2	10.4	10.1	10.0

* Normal.

mean arterial pressure, blood pH and hematocrit are observed after injection of endotoxin. Sudden decreases in platelet and white cell counts are noted, while the blood levels of creatinine, BUN, histamine and histidine show marked increases during the 10 hour postendotoxin period. The electrocardiograph was normal until 622 minutes after endotoxin, just prior to death.

Table II lists a number of changes in two monkeys after administration of endotoxin. Animal 7 did not become hypotensive during the entire period of observation and was subsequently sacrificed. The second monkey exhibited a progressive decrease in arterial blood pressure with death occurring at approximately 7 hours. Portal venous pressures changed very little during the postendotoxin period. A progressive decrease in heart rate of Animal 8 was evident as hypotension developed. A slight degree of hemoconcentration was seen in Monkey 7, although changes in hematocrit in the second animal were negligible. A significant decrease in pH occurred in Monkey 8.

All of the electrocardiograms were normal until just prior to death when the systemic blood pressure was extremely low.

The results of the histological sections are shown in Table III. The differences seen in the sections of Monkey 1 may be associated with respiratory difficulty and cyanosis, noted after induction of anesthesia, which were corrected by intubation and aspiration of pulmonary secretions. No other consistent histologic changes were noted except those observed in the kidneys of two animals.

DISCUSSION

Role of histamine in endotoxin shock. The large increases of blood histamine reported in the present study may account for the progressive development of systemic hypotension observed in the monkey given a lethal dose of endotoxin. An increased blood level of histamine could act on the peripheral vasculature to effect a decrease in the total peripheral resistance. Vascular resistance is known to decrease in various vascular beds of the dog (9, 10) after the injection of endotoxin. The present findings give further support for the role of histamine as a "shock toxin" (20, 21).

The mechanism of histamine release in endotoxin shock. It has recently been proposed by

Schayer (20, 21) that the rate of histamine synthesis is accelerated in endotoxin shock because of the increased activity of histidine decarboxylase. The findings of the present study extend his view to account for the increase in histamine on the basis of a rise in histidine, which supports the concept that endotoxin induces new histamine synthesis. Previous work in dogs (19) has indicated that the progressive increase of the histamine: histidine ratio is related to the relative rates of formation, conversion and destruction of the two components in question. It is possible that a rise in plasma histamine has resulted because of the marked decrease in the numbers of circulating platelets and white blood cells (37, 38). Similar decreases have been reported in the dog administered endotoxin (22) and in various forms of shock in man and animals (39–41). Histamine may possibly be released from the bound form in whole blood to the circulating form in plasma (25, 42), and from tissue such as muscle (43) or lung (44), or from various other sources (37).

Species variations in endotoxin shock. Major differences have been noted between the hemodynamic responses (1, 17, 18) and histological findings (1) of the dog and monkey after injections of lethal doses of endotoxin. The gradual fall in systemic arterial pressure, the small increase in portal venous pressure and the postmortem tissue findings in the present series of monkeys were similar to those in monkeys of a different species (1, 18). These findings are in marked contrast to those observed in dogs (5, 6, 45). The relative phylogenetic proximity of monkey to man gives added interest to the observations of gross species differences. The common hemolysis and hemoconcentration in dogs given lethal doses of endotoxin (18, 26–28) were not apparent in the monkeys of the present study. No cardiac abnormality was observed in the monkeys' electrocardiographic tracings until just prior to death, this observation being similar to that of dogs (6).

Correlation with human bacteremic shock. Case studies of bacteremic shock in man have been reported (2–4). Similarities in the findings of the monkeys of the present study and those in man are evident. Kidney disturbances have been reported in man after infections due to gram-negative bacilli (2, 3). Renal dysfunctions have included anuria, oliguria, hematuria and uremia which are usually conceded to be precipitated by the effects of systemic hypotension and consequent renal ischemia (4). Findings suggestive of ischemic changes in the kidneys were noted in the present study, and this observation is consistent with changes seen in human bacteremic shock (1–4, 46–48). The finding of an elevated blood creatinine and BUN in man and monkey suggests that renal failure is common to both. Other similarities noted were changes in hematocrit and blood pH. Further basic and clinical investigations are needed to provide a more thorough understanding of the intimate mechanism of bacteremic shock.

SUMMARY

The increasing interest in the pathogenesis and treatment of endotoxin shock has prompted the present investigation. Eight monkeys were given lethal doses of endotoxin and a number of parameters studied. Results indicate the prominent role of histamine in endotoxin shock and extend the suggestions of Schayer to include the basic mechanism of histamine release. Species variations were noted which stress the importance of the close phylogenetic proximity of monkey to man. Relationships between human and experimental bacteremic shock have been indicated.

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CORRECTION

On page 1133 of the article entitled "Inhibition of L-Thyroxine Monodeiodination by Thyroxine Analogs" by Frank C. Larson and Edwin C. Albright (J. clin. Invest. 1961, **40**, 1132), three molar concentrations were omitted from Table I. The subheadings for columns 1, 2 and 3 of the table under the heading, "Per cent inhibition with increasing molar concentrations," should have been "10^{-7}, 3×10^{-7} and 10^{-6}," respectively.