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Correlation of Plasma Catecholamine Levels with Hemodynamic Changes in Canine Endotoxin Shock *

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In the following experiments we attempt to quantitate the range of plasma catecholamine levels during canine endotoxin shock and to clarify some of the mechanisms involved in the changes. Basic to these investigations was a sensitive and reliable method for recovering the amines in plasma, a need that had been reflected in other studies (1–4).

The availability of such an assay permitted a series of comparative studies on normal anesthetized animals, on those given varying doses of endotoxin at different rates of administration, on dogs subjected to adrenalectomy and high cervical cord section and then given endotoxin, and on the effects of endotoxin on catecholamine levels in endotoxin-resistant dogs.

It was observed that the plasma concentrations of epinephrine were related to the level of the systemic arterial blood pressure although other factors also appeared to affect the amounts. Changes in blood pressure were not correlated with variations in the plasma content of norepinephrine. Repeated challenge with large doses of endotoxin conferred resistance to its lethal action, but this effect was not associated with an alteration in the pattern of the plasma catecholamine response. After cervical cord section shock could be induced in the absence of detectable plasma catecholamine, and under these conditions shock was significantly accelerated.

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Methods

Plasma catecholamine assay. For each assay 35 ml of blood was drawn from the femoral artery into a tube containing 1.0 ml heparin sodium (1,000 U per ml) and 20 mg sodium metabisulfite. Centrifugation was immediately carried out at 5° C for 10 minutes at 3,000 rpm; the plasma was drawn off and stored in the frozen state, and the assays were performed 1 to 14 days later by the method of Anton and Sayre (5).[1] Catecholamine recoveries were performed simultaneously with known samples of crystalline standards and the unknown plasma samples.

With this technique plasma catecholamines are adsorbed onto aluminum oxide, eluted with perchloric acid, and oxidized to a fluorescent trihydroxyindole derivative. Fluorescent norepinephrine and epinephrine derivatives are distinguished by differences in wave length. Because recovery of 75% or more of either epinephrine or norepinephrine could be made with concentrations as low as 0.5 mμg per ml or as high as 50 mμg per ml, the values expressed were not corrected for recovery.

Endotoxin. Escherichia coli endotoxin of the Boivin type was used in all experiments and was prepared as previously described (6).

Experimental model. Adult mongrel dogs of both sexes ranging in weight from 5 to 12 kg were used. The animals were lightly anesthetized with pentobarbital, the femoral artery and vein were cannulated, and indwelling plastic catheters were fixed in place. The femoral arterial pressure was monitored continuously with a Statham pressure transducer coupled to a Sanborn Twin-Viso recorder. There were five experimental groups. With the exception of one group (II), catecholamine samples were measured at the nadir of hypotension after endotoxin and at postendotoxin intervals of 30, 60, and 240 minutes. A brief description of each group follows.

Group I. Effect of varying endotoxin doses on plasma catecholamine levels. Endotoxin doses of 0.01, 0.05, 0.25, 0.5, and 2.0 mg per kg were used. Fluctuating mortality rates occurred in groups of dogs from season to season, although the same lot of endotoxin was used. Therefore, only the absolute doses of endotoxin are

[1] We are grateful for the valuable assistance given to us by Dr. A. H. Anton in establishing the method in our laboratory. Dr. C. A. Chidsey of the National Institutes of Health, Bethesda, Md., was also most helpful.

presented without attempting to correlate the dose with the mortality rate. Each of the above doses of endotoxin was given to 6 to 29 dogs, and 32 control dogs received no endotoxin. The endotoxin was rapidly injected as a single bolus through the femoral vein catheter. Samples of blood for catecholamine determinations were taken as described.

Group II. Effect of the rate of endotoxin administration on plasma catecholamine levels. Ten dogs were given 0.75 mg per kg of endotoxin as a rapid intravenous injection, and 10 received the same dose by slow intravenous drip over a period of 30 minutes. In the control group, samples were taken as described. Since no rapid fall in blood pressure occurred with slow infusion, sampling was slightly modified. Blood was withdrawn 20, 40, 60, and 240 minutes after beginning the slow infusion.

Group III. Studies of plasma catecholamines in endotoxin-resistant dogs. Twelve dogs surviving an initial dose of 0.5 to 0.75 mg per kg of endotoxin 3 weeks previously were given a second rapid injection of 0.75 mg per kg of endotoxin. Catecholamine samples were obtained as described.

Group IV. Studies of plasma catecholamines in adrenalectomized dogs and in dogs with complete cervical spinal cord section. Bilateral adrenalectomy through a transperitoneal approach was performed in four dogs 2 to 6 days before endotoxin was administered. During this period the dogs were maintained with daily injections of desoxycorticosterone acetate (2.5 mg) and cortisol (1.3 mg per kg in two divided doses).

Another group of four dogs underwent laminectomy and complete cervical cord section between C-7 and T-1 1 to 2 days before receiving endotoxin. This procedure resulted in complete paralysis of the hind legs and marked paresis of the front legs.

Both groups of dogs were given a rapid intravenous injection of 0.25 mg per kg of endotoxin. Catecholamine sampling was carried out as described.

Results

Group I. Effect of varying endotoxin doses on plasma catecholamine levels. The results are demonstrated in Figure 1. Control dogs not given endotoxin had no changes in blood pressure and plasma catecholamine concentrations during the course of the 4-hour experiment. Changes in blood pressure after each of the doses of endotoxin are detailed in Table I. Dogs given 0.01 mg

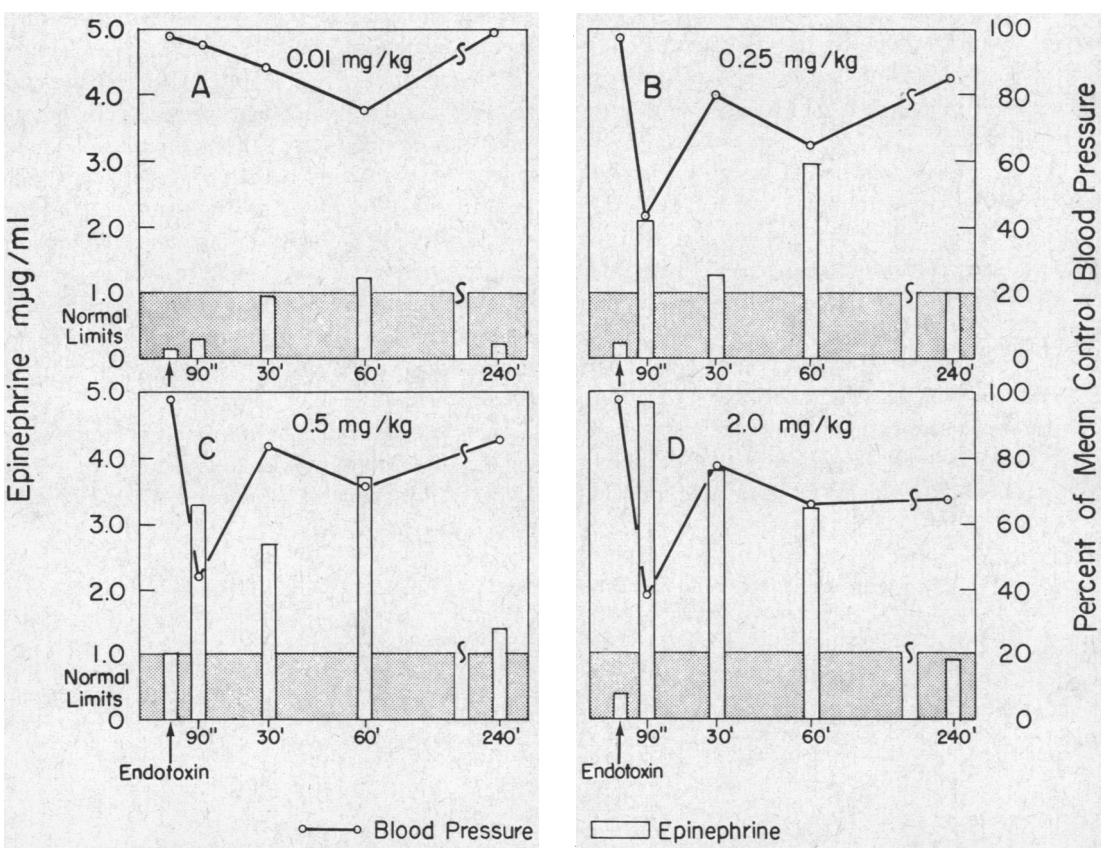

FIG. 1. COMPARISON OF BLOOD PRESSURE AND PLASMA EPINEPHRINE RESPONSES WITH REPRESENTATIVE DOSES OF ENDOTOXIN. Dosage amounts are indicated at the tops of sections A, B, C, and D.

TABLE I

The death rate and the per cent of the mean control blood pressure at time intervals after different doses of endotoxin

Endotoxin dose	No. of dogs	Death rate	Per cent of the mean control blood pressure after endotoxin				
			Control period	Nadir (90 sec)	30 min	60 min	240 min
mg/kg		%			%		
	32		100	99	101	101	100
0.01	6		100	95	89	76	107
0.05	6	33	100	65	83	78	94
0.25	6	16	100	42	81	66	86
0.5	10	50	100	44	84	71	86
2.0	29	65	100	39	77	64	66

per kg of endotoxin showed a small and gradual fall in blood pressure. The nadir of hypotension was reached 1 hour after endotoxin injection. The mean blood pressure at that point was 76% of the control pressure, rising gradually thereafter to control levels. All of these dogs survived. Doses of 0.05, 0.25, 0.5, and 2.0 mg per kg produced a sudden and marked hypotension. The nadir of this decline appeared at approximately 90 seconds postendotoxin. Thereafter the pressure rose rapidly but failed to reach control level during the 4 hours of subsequent observation. The mortality rates were 33%, 16%, 50%, and 65%, respectively.

The mean plasma norepinephrine levels (Table II) remained within normal limits in all groups except those receiving 2.0 mg per kg of endotoxin. This group showed a slight elevation 1 hour after endotoxin injection. In occasional individual dogs a sporadic norepinephrine elevation took place. The failure to detect consistent rises in plasma norepinephrine will be discussed later.

The mean plasma epinephrine levels are shown in Table III. With 0.01 mg per kg of endotoxin a slight epinephrine elevation (1.2 mμg per ml) was observed only at 1 hour postendotoxin. With larger doses of endotoxin epinephrine levels rose above normal at 90 seconds postendotoxin and remained elevated at intervals of 30 minutes and 1 hour. By 4 hours, normal or near normal concentrations were found. Whereas doses of 0.05, 0.25, 0.5, and 2.0 mg per kg resulted in similar blood pressure changes, the early epinephrine elevation tended to increase as the dose increment of endotoxin was increased. The respective 90-second postendotoxin levels were 2.3, 2.1, 3.4, and 5.0 mμg per ml. In Table IV the magnitude of relative changes in blood pressure is compared with simultaneous alterations in plasma epinephrine. With 0.05 mg per kg of endotoxin the blood pressure fell to 60% of the control 90 seconds after endotoxin, and the plasma epinephrine concentration rose fivefold. With 2.0 mg per kg the blood pressure fell to 40% of the control, and the plasma epinephrine concentration rose elevenfold. Somewhat similar ratios were observed at other time intervals.

In two dogs catecholamines were sampled near death. The blood pressure had fallen to less than 15% of the control pressure. The epinephrine

TABLE II

The plasma norepinephrine level at time intervals after different doses of endotoxin

Endotoxin dose	No. of dogs	Plasma norepinephrine level after endotoxin*				
		Control period	Nadir (90 sec)	30 min	60 min	240 min
mg/kg				*mμg/ml*		
	32	0.2 ± 0.05	0.3 ± 0.11	0.1 ± 0.08	0.3 ± 0.11	0.3 ± 0.16
0.01	6	0.1 ± 0.09	0.2 ± 0.14	0.6 ± 0.2	0.7 ± 0.36	0.5 ± 0.78
0.05	6	0.5 ± 0.86	0.3 ± 0.27		0.3 ± 0.5	0.9 ± 1.38
0.25	6	0.04 ± 0.03	0.5 ± 0.58	0.3 ± 0.15	0.7 ± 0.5	0.3 ± 0.26
0.5	10	1.6 ± 1.0	0.5 ± 0.3	0.4 ± 0.2	0.6 ± 0.4	0.3 ± 0.1
2.0	29	0.2 ± 0.05	0.4 ± 0.52	0.3 ± 0.26	1.1 ± 1.06	0.3 ± 0.24

* Mean ± 2 SE.

TABLE III

The plasma epinephrine level at time intervals after different doses of endotoxin

Endotoxin dose	No. of dogs	Plasma epinephrine level after endotoxin*				
		Control period	Nadir (90 sec)	30 min	60 min	240 min
mg/kg				*mμg/ml*		
	32	0.4 ± 0.1	0.4 ± 0.15	0.8 ± 0.32	0.5 ± 0.3	0.2 ± 0.04
0.01	6	0.1 ± 0.42	0.4 ± 0.4	0.9 ± 0.49	1.2 ± 1.0	0.8 ± 1.3
0.05	6	0.4 ± 0.12	2.3 ± 0.61		3.8 ± 3.1	0.8 ± 0.36
0.25	6	0.2 ± 0.1	2.1 ± 1.1	1.3 ± 0.62	3.0 ± 0.36	1.0 ± 0.42
0.5	10	1.0 ± 0.3	3.4 ± 1.0	2.7 ± 0.8	3.6 ± 0.6	1.4 ± 0.2
2.0	29	0.5 ± 0.16	5.0 ± 2.4	4.0 ± 1.86	3.2 ± 1.56	0.9 ± 0.52

* Mean ± 2 SE.

levels were 17.5 and 19.1 mμg per ml, but norepinephrine was not detected in the plasma of either dog.

In summary, a small dose of endotoxin failed to produce sudden hypotension and elicited only a slight delayed elevation of epinephrine. Doses of endotoxin that resulted in immediate hypotension provoked epinephrine elevations but little or no rise in norepinephrine. The magnitude of the initial epinephrine elevation varied with the dose of endotoxin. At 4 hours there was little difference in epinephrine levels, and the concentrations approached normal values except in samples obtained during the agonal period.

Group II. Effect of the rate of endotoxin administration on plasma catecholamine levels. The results are shown graphically in Figure 2. As pointed out above, rapid injection of 0.75 mg per kg of endotoxin produced sudden hypotension, but a slow injection of the same dose resulted in a gradual decline in blood pressure. At 20 to 40 minutes postendotoxin the blood pressures of both groups were similar. The mean blood pressure in the slowly infused dogs was 87%, and that of the rapidly infused dogs was 70%, of the control pressure. Both groups showed a gradual fall in pressure from this point to a similar low at 1 hour postendotoxin, i.e., 50% of the control pressure. Despite the lack of a profound early hypotensive episode in the dogs given a slow endotoxin infusion the plasma epinephrine level at 20 minutes was 2.42 mμg per ml, the same as that in the rapidly infused dogs. At 1 hour postendotoxin, however, the epinephrine level in the rapidly infused dogs was twice that of the slowly infused dogs. The levels were 7.79 and 3.21 mμg per ml, respectively. At 4 hours both groups showed lesser elevations, 2.77 and 3.82 mμg per ml, respectively. No significant elevations of norepinephrine were found in either group. The mortality rate of the rapidly infused dogs was 80% and that of the slowly infused dogs was 40% ($p < 0.2$).

Group III. Catecholamine studies in endotoxin-tolerant dogs. The plasma catecholamine levels are shown in Table V in 12 dogs given an injection of 0.75 mg per kg of endotoxin 3 weeks after recovery from the same dose. The mortality rate in a group of dogs after the first injection was 80%. In a group of 12 survivors after this initial dose, seven dogs survived the second dose and five died, yielding a mortality rate of 42% ($p = 0.2$). The epinephrine levels in the seven surviving dogs were the same as those in the five dead dogs, and

TABLE IV

Ratio of initial mean blood pressure to pressure after two dose schedules of endotoxin correlated with ratio of initial mean epinephrine concentration and concentration after endotoxin

Endotoxin dose	BP 90 sec/ BP 0*	Epi 90 sec/ Epi 0	BP 60 min/ BP 0	Epi 60 min/ Epi 0	BP 240 min/ BP 0	Epi 240 min/ Epi 0
mg/kg						
	1.0	1.0	1.0	1.5	1.0	0.6
0.05	0.6	5.5	0.8	6.1	1.0	1.7
2.0	0.4	11.2	0.7	8.1	0.7	2.4

* Abbreviations: BP = blood pressure; epi = epinephrine.

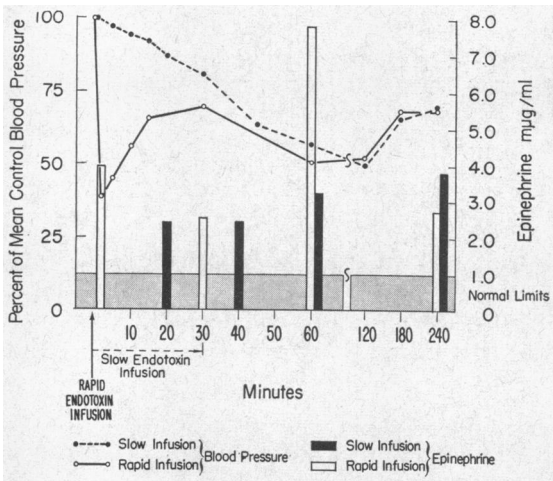

FIG. 2. COMPARISON OF BLOOD PRESSURE AND PLASMA EPINEPHRINE RESPONSES AFTER RAPID AND SLOW INFUSIONS OF 0.75 MG PER KG OF ENDOTOXIN.

these levels were the same as those in dogs after a primary injection.

Group IV. Catecholamine studies in adrenalectomized dogs and in dogs with complete cervical spinal cord section. The results of these experiments are shown in Table VI. Adrenalectomized dogs responded with a typical sudden decline in blood pressure 90 seconds after endotoxin. The pressure rose slightly 30 minutes later and then steadily declined. All were dead within 3 hours. Neither the epinephrine nor the norepinephrine levels rose above control values.

Control blood pressure in dogs with cervical cord section was 30% less than that of intact dogs. These dogs showed the usual sudden decrease in blood pressure 90 seconds after endotoxin. The pressure then rose gradually but never attained control levels. All of these dogs died within 8 hours. Neither epinephrine nor norepinephrine was detected in the plasma of these dogs.

Discussion

These studies confirm and extend the observations of others demonstrating that endotoxin-induced hypotension is a potent stimulus to epinephrine secretion. The decline in blood pressure occurring within 1 to 2 minutes after the injection of an appropriate dose of endotoxin is associated with a rise in plasma epinephrine. The duration of the elevated epinephrine concentrations is not prolonged, returning to normal levels within 4 hours. Whereas the lethal dose for 80% of the inoculated group (LD_{80}) in canine endotoxin shock requires around 0.75 mg per kg of endotoxin given quickly, initial hypotension with a rise in plasma epinephrine was noted with as little as 0.05 mg per kg of endotoxin.

There was no consistent elevation of plasma norepinephrine after any of the doses of endotoxin employed, a finding at variance with previous reports on canine endotoxin shock. This difference possibly arises because the method used in the present experiments appears to be more specific in distinguishing between norepinephrine and epinephrine (1, 7). Failure to demonstrate a consistent change in plasma norepinephrine during endotoxin shock does not preclude the possibility that significant release of norepinephrine occurred at the tissue level, as has been observed by Zetterstrom, Palmerio, and Fine (8).

The sensitivity of the epinephrine response to hypotension occurring early in endotoxin shock was best documented with a very small dose of endotoxin (0.01 mg per kg) and with the slow

TABLE V

The plasma catecholamine level and the per cent of the mean control blood pressure at time intervals after a single dose of 0.75 mg per kg of endotoxin and a second similar dose 3 weeks after the first

Group		Mean plasma catecholamine level and per cent of control BP after endotoxin											
		Nadir (90 sec)			30 min			60 min			240 min		
		BP	Epi	Nepi*	BP	Epi	Nepi	BP	Epi	Nepi	BP	Epi	Nepi
		%	mμg/ml		%	mμg/ml		%	mμg/ml		%	mμg/ml	
I. First endotoxin dose (10)†	A) Lived (2)	41	3.93	0.28	73	2.21	1.30	54	12.11	0.21	104	0.62	1.24
	B) Died (8)	23	4.20	1.59	65	3.16	2.24	55	6.34	1.95	62	3.19	0.34
	Composite means	38	3.98	0.50	71	2.45	1.03	51	7.79	1.51	69	2.77	0.45
II. Second endotoxin dose (12)	A) Lived (7)	40	2.61	0.89	72	2.89	0.83	57	4.71	1.45	75	1.41	1.64
	B) Died (5)	35	3.25	1.27	74	3.44	0.49	52	5.88	0.60	71	1.39	0.82
	Composite means	38	2.88	0.94	73	3.12	0.62	55	5.03	0.96	74	1.25	1.37

* Nepi = norepinephrine.
† The number of dogs in each group is shown in parentheses.

TABLE VI

The plasma catecholamine level and the mean blood pressure at time intervals after 0.25 mg per kg of endotoxin in intact dogs, adrenalectomized dogs, and dogs with cervical cord section

Group	No. of dogs	Mean plasma catecholamine level and mean blood pressure after endotoxin														
		Control period			Nadir (90 sec)			30 min			60 min			240 min		
		BP	Epi	Nepi	BP	Epi	Nepi	BP	Epi	Nepi	BP	Epi	Nepi	BP	Epi	Nepi
		mm Hg	*mμg/ml*		*mm Hg*	*mμg/ml*		*mm Hg*	*mμg/ml*		*mm Hg*	*mμg/ml*		*mm Hg*	*mμg/ml*	
Intact dog	4	142 (100)*	0.24	0.02	59 (42)	1.69	0.12	102 (72)	1.49	0.28	87 (61)	6.95	0.26	92 (64)	1.31	
Adrenalectomy	4	132 (100)	0.09	0.25	53 (40)	0.07	0.23	71 (54)	0.13	0.23	43 (33)	0.23	0.46	Dead		
Cord section	4	100 (100)			31 (31)			86 (86)			47 (47)			28 (28)		0.01

* The percentage of the mean control blood pressure is shown in parentheses.

infusion of a large dose (0.75 mg per kg). Both dose schedules produced a gradual decline in blood pressure. With 0.01 mg per kg the first and only detected elevation of epinephrine occurred when the blood pressure fell to 76% of the control pressure 1 hour postendotoxin. With the slow infusion of the much larger dose an epinephrine rise was first seen when the mean pressure declined to 87% of the control pressure 20 minutes postendotoxin. These observations are consistent with the suggestion of Nykeil and Glaviano (1) that epinephrine release is regulated by a baroreceptor reflex mechanism. The present finding that high cervical cord section prevented epinephrine release, as previously reported by Egdahl (2), also supports this concept.

Later in the course of endotoxin shock the relationship between the level of blood pressure and the plasma epinephrine concentration was not as clear-cut as in the earlier stages of shock. Epinephrine levels were nearly normal 4 hours after doses of 0.05 mg per kg and 2.0 mg per kg, although the mean blood pressure remained below control levels (66%) in the latter group. This would suggest that baroreceptor control of epinephrine release had been altered. In this regard Trank and Visscher (9) have made the interesting observation that the carotid sinus baroreceptor is modified during the course of endotoxin shock. The implications of their findings require further exploration.

Measurement of changes in systemic blood pressure does not reflect subtle changes in tissue perfusion. Such changes might significantly alter the catecholamine response. Endotoxin doses of 0.05 mg per kg and 2.0 mg per kg produced a similar degree of initial hypotension, but the associated early plasma epinephrine concentration was two times greater with the large dose. It is tempting to postulate that large amounts of endotoxin evoke direct central nervous system stimulation causing an augmented release of epinephrine. Whereas Penner and Bernheim (10) observed direct stimulation of the central nervous system with Shiga exotoxin, Braude, Carey, and Zalesky (11), using radioactive *E. coli* endotoxin, failed to demonstrate endotoxin uptake in rabbit brain, a finding we have confirmed in dogs (12).

The composite effect of several factors responsible for epinephrine release is reflected in the marked elevations of plasma epinephrine noted in the agonal state. The very low systemic blood pressure was almost certainly accompanied by poor tissue perfusion, anoxia, and acidosis (13, 14). Lammerant and DeHerdt (15) found a striking elevation of plasma catecholamines in anoxic dogs and even higher levels when the anoxia was accompanied by circulatory failure.

If repeated injections of epinephrine are given to dogs, resistance to pharmacologic doses of the amine results, simulating endotoxin resistance (16). On this basis it has been proposed that the toxic effects of endotoxin are caused primarily by the action of increased amounts of endogenous epinephrine, and that endotoxin resistance is a result of epinephrine depletion or resistance to epinephrine. The present studies do not support this concept. Resistant dogs surviving a second lethal dose of endotoxin had essentially the same plasma catecholamine concentrations that followed the initial injection of endotoxin. Neither the magnitude nor the duration of the epinephrine

concentrations approached that necessary for epinephrine intoxication (17, 18). Whereas some investigators (19, 20) have reported that endotoxin accentuates the vascular action of small amounts of epinephrine, this additive effect has not been observed in endotoxemic dogs (21–23).

The production of endotoxin shock after cervical cord section and bilateral adrenalectomy, procedures that abolished or reduced the plasma catecholamine level, clearly demonstrates that the sympathoadrenal system is not essential for the mediation of the initial events in endotoxin shock. These findings confirm and extend the observations of others (22, 24, 25). The factors that sustain the hemodynamic and metabolic alterations in endotoxin shock remain largely undefined. Whereas the lethal course of canine endotoxin shock was accelerated under conditions in which plasma levels of catecholamine were not elevated, the precise role of endogenously released epinephrine in the pathogenesis of endotoxin shock must await further investigations, including quantitative studies on the microcirculation in relation to blood flow in individual organs and tissues.

Summary

Plasma catecholamine concentrations in canine endotoxin shock were measured with the more discriminating trihydroxyindole assay method of Anton and Sayre (5). A typical pattern of hemodynamic changes was obtained with doses of endotoxin ranging from 0.05 to 2.0 mg per kg. Plasma epinephrine rose simultaneously with the onset of hypotension and then gradually returned to normal. Contrary to the results of others using less sensitive assay methods little or no elevations of norepinephrine were observed. A slow infusion of a large dose of endotoxin produced a delayed and gradual onset of hypotension, resulting in a close correlation between the fall in blood pressure and the rise in plasma epinephrine.

Resistance to endotoxin in the dog was found to be unrelated to the time of appearance and concentration of plasma epinephrine. Resistant and nonresistant animals exhibited the same pattern of response. The plasma epinephrine response was abolished by cervical cord section or adrenalectomy. Under these two conditions small doses of endotoxin produced profound shock resulting in rapid death. These data indicate that circulating catecholamine is not necessary to initiate endotoxin shock. Whereas the lethal action of endotoxin was accelerated in the absence of circulating catecholamine, the definition of the precise role of these amines in the late stages of endotoxin shock requires further quantitative study.

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