THE SENSITIVITY TO HYPERTENSIN, ADRENALIN AND RENIN OF UNANESTHETIZED NORMAL, ADRENALECTOMIZED, HYPOPHYSECTOMIZED AND NEPHRECTOMIZED DOGS *

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In 1898 Tigerstedt and Bergmann [1] discovered a pressor substance in normal kidneys to which they gave the name renin. This substance had a prolonged pressor effect when injected intravenously into animals, successive injections had a diminishing pressor action (tachyphylaxis), and it was not found in organs other than the kidneys. Their findings have been widely confirmed by subsequent investigators. With the development of a method of inducing hypertension experimentally in animals by Goldblatt, Lynch, Hanzal, and Summerville [2] and with the resultant evidence that this renal hypertension was apparently due to a humoral mechanism,[3, 4] the rôle played by renin in experimental hypertension has recently been the subject of extensive study by many. Kohlstaedt, Helmer, and Page [5] found that purified preparations of renin had no constrictor action when perfused in Ringer's solution through the vessels of an isolated rabbit's ear, but that when perfused with blood proteins ("reninactivator") a strong constrictor action was obtained. This has been confirmed by others.[6, 7] Following a series of experiments by Houssay and his collaborators on the pressor and constrictor properties of venous blood of ischemic kidneys (recently reviewed by Houssay [8]), Braun-Menendez, Fasciolo, Leloir, and Muñoz [9, 10, 11, 6] of the same laboratory in 1939 discovered a pressor substance, hypertensin, in the venous blood of ischemic kidneys. In its chemical, physical, and pharmacological properties it was identical with the pressor substance produced by the in vitro incubation of renin with blood globulins (hypertensin precursor; hypertensinogen). It differed in its properties from adrenalin, pitressin, tyramin, and urohypertensin. Hypertensin is rapidly destroyed by hypertensinase which is widely distributed throughout the body and which has no action on renin or on precursor.[6, 12] Page and Helmer [13] independently described the production of the same pressor substance which they called angiotonin, by the interaction of renin and blood colloids. The term "renin-activator" applied to the blood colloids seems inappropriate, however, since from the studies of Braun-Menendez et al.[9, 10, 14] it is apparent that renin is an enzyme and that the globulin fraction of the blood is the substrate on which it acts. Kohlstaedt and Page [15] and Leloir, Muñoz, Fasciolo, and Braun-Menendez [16] subsequently demonstrated the liberation of renin from the venous blood of

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perfused kidneys. The relationship between renin and experimental renal hypertension, therefore, seems established.

There is a considerable body of evidence indicating that there is a close relationship between the pituitary and adrenal glands and hypertension and that the normal kidney exerts a protective action against the development of experimental renal hypertension. One of us (B. A. H.[8]) has recently summarized the present knowledge of these relationships. The purpose of this communication is to report a study made of the sensitivity to hypertensin, adrenalin, and renin of normal, adrenalectomized, hypophysectomized, and nephrectomized dogs in an attempt to clarify further the relationship which exists between these organs and renal hypertension.

Methods

Unanesthetized normal, adrenalectomized, hypophysectomized, and nephrectomized dogs weighing between 7 and 12 kilos were injected intravenously with 2 units of hypertensin, 10 gamma of adrenalin (Parke Davis) and 2 c.c. of a solution of hog renin in the order stated. The blood pressure was recorded by a cannula in the femoral artery (novocaine being used as a local anesthetic) connected to a mercury manometer. The animals were usually quiet during the experiment.

Hypertensin was prepared according to the method of Muñoz, Braun-Menendez, Fasciolo, and Leloir [11]; 0.18 c.c. contained 1 unit which is the amount as defined by Braun-Menendez, Fasciolo, Leloir, and Muñoz,[17] which gives rise to an elevation of blood pressure of 25 to 30 mm. Hg in a 10 kilogram chloralosed dog. Renin was prepared from the cortex of hogs' kidneys according to the method of Braun-Menendez, Fasciolo, Leloir, and Muñoz [6] and contained 1 unit in 0.025 c.c. The unit of renin as defined by Leloir, Muñoz, Braun-Menendez, and Fasciolo [18] is the amount which when incubated at 37° C. for two hours with an excess of precursor (6 to 8 c.c. of hypertensinase-free bovine plasma) is capable of forming 0.5 unit of hypertensin.

Dogs were bilaterally nephrectomized under ether anesthesia by the lumbar or abdominal route. The adrenals were removed in two stages at least two weeks apart using the lumbar approach. After the removal of the second adrenal, 20 grams of sodium chloride alone or complemented in part with sodium citrate were administered daily by stomach tube. The experiment was performed on the adrenalectomized and nephrectomized dogs 40 to 48 hours after operation. All animals used showed definite symptomatic evidence of adrenal or renal insufficiency. Hypophysectomy was performed by the temporal approach, the animals being used one month to three years after the operation.

Venous blood was withdrawn before adrenalectomy and again about 40 hours after adrenalectomy, some three to four hours before the dogs were injected with the pressor substances. The indirect method of Leloir, Muñoz,

Braun-Menendez, and Fasciolo [18] was used to determine the concentration of renin in the blood, and the method of Muñoz, Braun-Menendez, Fasciolo, and Leloir [11] was used to determine the concentration of precursor in the plasma.

Results

The effect of the intravenous injection of 2 units of hypertensin, 10 gamma of adrenalin, and 2 c.c. of a solution of hog renin on the blood pressure of nine normal unanesthetized dogs, 12 dogs 40 to 48 hours after adrenalectomy, six hypophysectomized dogs, and nine dogs 40 to 48 hours after nephrectomy is summarized in table 1. The number of animals used was too small for statistical analysis.

1. Normal Dogs. Following the intravenous injection of 2 units of hypertensin, the blood pressure rose on an average 35 ± 13 mm. Hg with a range of 18 to 48; after 10 gamma of adrenalin, 30 ± 9 mm. Hg with a range between 13 and 45; and after 2 c.c. of renin, 51 ± 15 mm. Hg ranging between 30 and 78 mm. The upper limit of the normal response, therefore, was considered to be 48 mm. Hg to hypertensin, 39 mm. to adrenalin, and 66 mm. to renin. In general, there was a parallelism in the blood pressure response to hypertensin and adrenalin. In only one dog (No. 5) was the response to renin less than that to hypertensin. The duration of the pressor action of renin noted in four cases lasted on the average 37 minutes and in no instance exceeded one hour.

2. Adrenalectomized Dogs. The initial blood pressure of the adrenalectomized dogs was considerably lower than in the normal controls, and all dogs were moderately weak and apathetic. Despite this, there was a normal or even increased sensitivity to hypertensin in all but one case (No. 5) and to adrenalin a variable response with possibly a tendency to a slight decrease in sensitivity. The response to renin was variable. In dogs 2, 3, 4, 6, 9, and 10, the response to renin was normal and to hypertensin normal or above normal. In dogs 1, 7, 8, and 12, there was a normal or increased sensitivity to hypertensin, indicating a normal reactivity of the vessels, but a definitely diminished pressor response to renin in comparison with the pressor effect of hypertensin. Since the pressor action of renin is due to the hypertensin formed from its interaction with precursor,[5, 9] it seemed of importance to ascertain the concentration of precursor in the blood. It will be noted (table 2) that precursor was markedly reduced in the arterial blood approximately 40 hours after adrenalectomy as compared with values obtained before ablation of the second adrenal in dogs 7, 8, 11, and 12 in which the response to renin was decreased, and normal in dogs 9 and 10 in which the response to renin was normal. Dogs 5 and 11 were in frank insufficiency and shock and sensitivity to all three drugs was decreased. The duration of action of renin in these adrenalectomized dogs was usually shorter than in the controls. There was only a rough correlation between

TABLE I

The sensitivity of *unanesthetized* normal, adrenalectomized, hypophysectomized, and nephrectomized dogs to the intravenous injection of 2 units of hypertensin, 10 gamma of adrenalin, and 2 c.c. (80 units) of a solution of hog renin in the order stated.

Group	Dog No.	Wt.	Initial Pressure	Elevation of Blood Pressure after:			Duration of Action of Renin
				2 Units Hypertensin	10 Gamma Adrenalin	2 c.c. Renin	
		Kg.	mm.Hg	mm.Hg	mm.Hg	mm.Hg	min.
Normal dogs	1	8.5	135	45	41	78	—
	2	8.5	125	30	25	48	—
	3	8.6	150	40	30	65	—
	4	10.5	170	27	22	50	—
	5	9.0	180	40	28	33	—
	6	12.5	160	30	36	40	53
	7	8.5	200	40	35	65	45
	8	10.0	120	18	13	30	30
	9	8.5	130	48	45	48	19
	Average			35	30	51	37
	Probable error			±13	±9	±15	±13
Adrenalectomized 48 hours previously	1	9.0	80	65	60	38	—
	2	8.0	98	52	40	65	—
	3	9.0	100	32	20	40	—
	4	11.0	130	35	12	45	45
	5	9.0	60	18	25	20	10
	6	9.0	70	50	25	40	10
	7	10.0	95	50	18	20	22
	8	10.0	75	37	20	28	23
	9	10.5	90	38	18	50	40
	10	10.0	25	40	16	40	25
	11	10.0	60	26	16	25	15
	12	8.5	60	50	36	40	9
	Average			41	26	38	22
	Probable error			±12	±13	±12	±12
Hypophysectomized 1 month to 3 years previously	1	8.0	128	42	40	45	—
	2	9.0	140	44	44	50	—
	3	12.0	140	48	35	55	—
	4	8.0	130	30	30	40	—
	5	9.0	135	24	−5	30	—
	6	9.0	130	35	30	40	14
	Average			37	29	43	—
	Probable error			±8	±16	±8	
Nephrectomized 48 hours previously	1	11.0	148	53	40	82	—
	2	11.0	135	52	25	80	—
	3	10.0	125	30	25	50	—
	4	10.5	180	30	25	60	180
	5	11.0	120	30	32	85	165
	6	9.0	130	65	55	120	60
	7	12.0	180	48	30	88	77
	8	12.5	160	22	10	38	38
	9	10.0	130	60	75	85	80
	Average			43	35	77	100
	Probable error			±15	±18	±23	±53

the initial level of the blood pressure and the sensitivity to the pressor substances.

3. Hypophysectomized Dogs. The sensitivity of six unanesthetized hypophysectomized dogs to the injection of hypertensin, adrenalin, and renin appeared to be entirely normal (table 1).

4. Uremic Dogs. Four out of nine of the dogs nephrectomized 40 to 48 hours previously (No. 1, 2, 6, and 9) showed an increase in sensitivity to hypertensin, and three of these four dogs (No. 1, 6, and 9) to adrenalin. The basic cause of the hyper-reactivity of the vessels to these drugs is not apparent. The same dogs (No. 1, 2, 6, and 9) showed a greater increase in pressure than normal following the injection of renin, due at least in part to the hypersensitivity of the vessels to the hypertensin formed by the action

TABLE II

The concentration of precursor and renin in the plasma of unanesthetized dogs before and 48 hours after adrenalectomy.

Dog No.	Units of Precursor per c.c.		Units of Renin per c.c.	
	Before	After	Before	After
7	0.26	0.09	None	None
8	0.18	0.03	"	"
9	0.19	0.25	"	"
10	0.21	0.22	"	"
11	0.22	0.12	"	"
12	0.40	0.09	"	"

of renin on the precursor of the blood. In addition, two other dogs (No. 5 and 7) showed an increase in sensitivity to renin. The pressor effect of renin was notably prolonged in four of five of the dogs in which it was determined.

5. Anesthetized Dogs Nephrectomized One to Three and One-Half Hours Previously. The sensitivity to hypertensin, adrenalin, and renin was determined in nine dogs nephrectomized one to three and one-half hours previously. It was necessary to use chloralose anesthesia (10 c.c. of a 0.8 per cent solution per kilo intravenously) because of the restlessness of the animals so soon after operation. A control series consisted of nine normal chloralosed dogs whose kidneys were explored but not manipulated. The results are seen in table 3. Chloralose anesthesia did not diminish the sensitivity to hypertensin, adrenalin, or renin, nor was the duration of the pressor action of renin altered. In the recently nephrectomized animals there was no increase in sensitivity to either hypertensin or adrenalin, nor in the majority of the animals to renin. In three (No. 3, 7, and 8), however, the pressor response to the injection of renin was decidedly greater than normal, and in two (No. 2 and 8) the pressor effect lasted two and two and a quarter hours respectively. In two dogs (No. 8 and 9), the amount of precursor in the blood before and three hours after operation was unchanged.

Discussion

The observations on adrenalectomized dogs indicate that the vessels reacted normally or almost normally in response to injections of hypertensin and adrenalin until the advent of terminal shock. The sensitivity to injections of renin was normal in six cases and reduced in six cases, which is in accord with the observations of Williams, Diaz, Burch, and Harrison [19] and of Friedman, Somkin, and Oppenheimer.[20] Remington, Collings, Hays, and Swingle [21] noted a normal response of adrenalectomized dogs to large

Table III

The sensitivity of *chloralosed* normal and recently nephrectomized dogs to the intravenous injection of 2 units of hypertensin, 10 gamma of adrenalin, and 2 c.c. (80 units) of a solution of hog renin in the order stated.

Group	Dog No.	Wt.	Initial Pressure	Elevation of Blood Pressure after:			Duration of Action of Renin
				2 Units Hypertensin	10 Gamma Adrenalin	2 c.c. Renin	
		Kg.	mm.Hg	mm.Hg	mm.Hg	mm.Hg	min.
Normal dogs 1 to 5 hours after exploration of kidneys	1	10.0	130	25	32	20	10
	2	9.0	150	40	66	60	27
	3	8.0	165	25	30	40	10
	4	9.0	170	36	10	60	10
	5	9.0	105	50	24	40	30
	6	7.0	160	48	40	40	30
	7	9.0	140	44	30	20	40
	8	9.0	120	62	66	40	20
	9	11.0	160	35	16	45	60
	Average			41	35	41	26
	Probable error			±11	±19	±13	±16
Nephrectomized 1 to 3½ hours previously	1	12.5	130	48	50	55	24
	2	13.0	130	30	45	60	120
	3	12.0	120	36	34	70	58
	4	11.0	130	50	36	44	33
	5	7.0	140	28	82	40	43
	6	10.5	170	27	40	40	26
	7	10.5	130	62	43	75	28
	8	8.5	110	64	57	78	135
	9	13.5	120	58	52	43	43
	Average			45	49	56	56
	Probable error			±14	±13	±14	±39

doses of renin but a diminished response to small doses beginning almost immediately after the withdrawal of cortical extract. The dose used by us may have been too large to detect the early appearance of diminished sensitivity. In four cases there was a normal response to hypertensin but a diminished response to renin. In these cases the reactivity of the vessels may be considered normal. In these same cases, but not in two others in which the sensitivity to hypertensin and renin was normal, the concentration of precursor in the plasma was found to be distinctly reduced, which probably is a factor not only in the diminished pressor response to renin, but also in

the short duration of its action, since Leloir, Muñoz, Braun-Menendez, and Fasciolo [18] have shown that the amount of hypertensin formed by the action of a given amount of renin depends upon the amount of precursor present. In two dogs in which the pressor response to renin was normal the concentration of precursor in the plasma was found to be normal. These studies give no clue as to the cause of the diminution in the concentration of precursor. No renin was found in the blood of any of the dogs 40 to 48 hours after adrenalectomy by the indirect method of Leloir, Muñoz, Braun-Menendez and Fasciolo,[18] which is capable of detecting 0.2 unit of renin or even less with accuracy. Although the possibility still exists despite this negative finding, it seems unlikely that the cause of the reduction of precursor was the liberation of renin by the kidney such as occurs in certain shock-like conditions.[22]

When the adrenalectomized animals were in profound shock, such as dogs 5 and 11 and several others not included in this series, the sensitivity to hypertensin and renin was uniformly depressed, and that to adrenalin variable. Elliot [23] reported a marked pressor response to large doses of adrenalin in cats in terminal adrenal insufficiency. Armstrong, Cleghorn, Fowler, and McVicar [24] likewise observed in cats in adrenal insufficiency a good pressor effect from the injection of adrenalin in doses similar to those used by us.

It seems plausible to assume that following adrenalectomy two factors are involved in the diminished sensitivity to injections of renin. First, at a late stage of adrenal insufficiency, the vessels lose their normal reactivity not only to renin but to hypertensin and at a later stage to adrenalin as well. Second, in certain animals but not in all (four of six of the dogs tested in this series) there is a clear reduction in the concentration of precursor in the blood so that the amount of hypertensin capable of being formed by the renin injected is reduced. Whether this factor plays a rôle in the fall of blood pressure of hypertensive animals after adrenalectomy can only be surmised at this time.

In the hypophysectomized animals no alteration from normal was noted in the sensitivity to hypertensin, adrenalin, or renin. Williams, Diaz, Burch, and Harrison [19] observed an increased sensitivity to renin in hypophysectomized rats. We are unable to explain the difference in our results. It is probable, however, that such factors as species variations and anesthesia account for the differences, or, as the authors suggest, the lower initial pressure of the rats after hypophysectomy. The initial pressure of our dogs was normal. Our results throw no light on the dampening effect of hypophysectomy on hypertension from renal ischemia.

Recently nephrectomized (one to three and one-half hours) dogs reacted normally to injections of hypertensin, adrenalin, and, in the majority of instances, to injections of renin. In three instances, however, the pressor action of renin was greater and in two it lasted much longer than in normal dogs. Forty-eight hours after nephrectomy distinct differences were ob-

served in that several dogs showed a clear increase in sensitivity to hypertensin and to adrenalin. There was likewise an increase above normal in the pressor response to renin in the majority of the dogs, which is in accord with the observations of other investigators.[1, 25, 26, 27, 28, 29] The duration of the pressor action of renin was more than twice as long as in the normal control dogs. At least three factors appear to account for the hypersensitivity to and the prolonged action of renin in the uremic dogs: (*a*) The vessels of the dogs 48 hours after nephrectomy are more sensitive than normal to the injection of the pressor substances used. (*b*) Given enough time, the amount of hypertensin formed by a given amount of renin depends upon the concentration of precursor present. Muñoz, Braun-Menendez, Fasciolo, and Leloir [11] demonstrated that 48 hours after nephrectomy the concentration of precursor is increased. Therefore, in these dogs the increase in the concentration of precursor undoubtedly plays a rôle in the heightened and prolonged pressor effect of renin. (*c*) It has been shown by Houssay, Braun-Menendez, and Dexter [22] that in dogs nephrectomized 48 hours previously renin after its injection intravenously persists in detectable amounts in the blood for two to three hours or more, whereas in normal dogs it disappears usually within an hour. The velocity of the reaction between renin and precursor to form hypertensin depends on the concentration of renin present.[18] Since renin persists for a longer time in the blood of these animals, the rate at which hypertensin forms is increased, thereby playing a part in the increased height to which the blood pressure rises as well as to the prolongation of the pressor action.

Summary

1. The sensitivity of unanesthetized normal, adrenalectomized, and nephrectomized (uremic) dogs to 2 units of hypertensin, 10 gamma of adrenalin, and 2 c.c. of a solution of hog renin has been determined.

2. Forty-eight hours after bilateral adrenalectomy, the sensitivity to hypertensin and adrenalin was usually normal unless terminal shock appeared. The sensitivity to renin was sometimes normal and sometimes reduced. The decrease in the sensitivity to renin at a time when the vessels were reacting normally to hypertensin was associated in four instances with a fall in the concentration of hypertensin precursor (hypertensinogen) in the plasma.

3. Dogs hypophysectomized one month to three years previously reacted normally to the injection of hypertensin, adrenalin, and renin.

4. Chloralosed dogs recently nephrectomized reacted normally to hypertensin and adrenalin and usually to renin. In three of nine dogs the pressor effect of renin was greater, and in two of nine it lasted distinctly longer than in the normal controls.

5. Unanesthetized dogs nephrectomized 48 hours previously frequently were hypersensitive to hypertensin, adrenalin, and renin. The duration of action of renin was usually markedly prolonged. The causes of the hypersensitivity to renin in these dogs are discussed.

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