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INJECTIONS OF ADRENALINE AND NORADRENALINE, AND FURTHER STUDIES ON LIVER SYMPATHIN

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It is fairly generally conceded that adrenaline injected into the portal vein of mammals causes a smaller rise of blood pressure than when injected into the saphenous, femoral, or jugular veins. This difference between the two modes of administration is less when a large amount of adrenaline is used and it has been shown many times (for references see Dawes, 1946) that it persists when the injection is made very slowly so that it cannot be attributed to retardation of the release of adrenaline into the general circulation. One explanation is that the liver destroys adrenaline, and that the rise of blood pressure after intraportal injection depends on the amount of adrenaline escaping into the general circulation.

The theory that the substance liberated on stimulation of the hepatic nerves in the cat is noradrenaline or some similar substance was put forward by Bacq (1934) and by Stehle and Ellsworth (1937). Greer, Pinkston, Baxter, and Brannon (1937, 1938) have also considered noradrenaline as a possible sympathetic mediator, and have compared the effects of hepatic nerve stimulation (liberating presumably pure sympathin E) with those of injections of adrenaline and noradrenaline in the same animal. In a similar series of experiments, Gaddum and Goodwin (1947) found no evidence against the theory that liver sympathin is noradrenaline. It was of interest, therefore, to observe the effects resulting from intraportal, intrajugular, and intra-arterial injections of *l*-adrenaline and *dl*-noradrenaline in the same animal. In the experiments described below, the activities of the two amines were compared quantitatively with one another by these routes with the object of ascertaining their site of action and fate. It was hoped, also, to obtain further evidence of the similarity of action between injections of noradrenaline and hepatic nerve stimulation.

Dawes (1946) showed that the pressor action of adrenaline injected into the portal vein of a spinal cat was both increased and prolonged by the simultaneous injection of aromatic diamidines and monoamidines, of aliphatic diguanidines, diamidines and monoamidines, and of guanidine itself. This work has been repeated for guanidine, and extended to include the effect of guanidine upon the injection of noradrenaline and hepatic nerve stimulation. Similar experiments with cocaine and ephedrine have also been included.

METHODS

In different experiments, spinal cats, cats anaesthetized with chloralose or urethane, and rabbits under urethane or pentobarbitone were used. Blood pressure records were taken from the carotid artery and injections of the drugs made into the femoral, jugular, or splenic veins, or into the external iliac artery so that the injected solution passed into the vessels of the opposite leg. In some experiments, injections were made into one of the two main splenic arteries. Contractions of the nictitating membrane were recorded isotonically, 7–10 days after denervation by removal of the superior cervical ganglion.

The uterus was fixed at its lower end and its movements recorded directly. Movements of the duodenum were recorded by tying off a segment which was filled with warm saline and connected by a cannula and rubber tubing to a bottle, the upper part of which contained air and was connected to a piston recorder. Solutions of *l*-adrenaline and *dl*-noradrenaline were prepared from the pure bases with $N/100$ HCl.

The hepatic nerves were separated from the hepatic artery and divided centrally. They were stimulated by means of platinum electrodes and an ordinary coil. In most of the experiments with liver sympathin, cocaine hydrochloride (8 mg./kg.) was given intramuscularly.

RESULTS

In confirmation of Dawes (1946), it was found that the relation between doses of adrenaline producing equal rises of blood pressure by the jugular and by the portal routes differed according to the amount injected. The results shown in Table I are

TABLE I

COMPARISON OF EQUI-PRESSOR DOSES OF *l*-ADRENALINE AND *dl*-NORADRENALINE BY THE INTRAPORTAL AND INTRAJUGULAR ROUTES IN CATS

Drug	Intra-portal injection (A) μg.	Intra-jugular injection (B) μg.	Portal (A) / Jugular (B)	Blood pressure rise mm. Hg
l-adrenaline	10	2	5.0	19
	20	5	4.0	40
	40	12.5	3.2	83
	80	27.5	2.9	124
dl-nor-adrenaline	10	5	2.0	41
	20	8	2.5	56
	40	17.5	2.3	95
	80	40	2.0	120

the mean values for 10 cats; it will be seen that when the dose of adrenaline injected into the portal vein is large, proportionately more reaches the general circulation through the hepatic veins and the ratio of portal to equi-pressor jugular dose decreases. On the other hand, the corresponding ratio with noradrenaline remains fairly constant. Why is this difference present? It is well known that both amines, being derivatives of phenyl-ethylamine, are readily destroyed by the liver amine oxidase *in vitro*.

A similar result was found in rabbits under urethane (Table II) although the ratios of portal dose to equi-pressor jugular dose for adrenaline have always been higher than in the cat. For the jugular route in rabbits, adrenaline was found to be a much more active pressor agent than nor-adrenaline, a fact clearly shown when all the results are plotted graphically (Fig. 1). Great similarity exists between equi-pressor doses of adrenaline and noradrenaline by jugular or splenic vein in the cat

TABLE II

COMPARISON OF EQUI-PRESSOR DOSES OF *l*-ADRENALINE AND *dl*-NORADRENALINE BY THE INTRAPORTAL AND INTRAJUGULAR ROUTES IN RABBITS

Drug	Intra-portal injection (A) μg.	Intra-jugular injection (B) μg.	Portal (A) / Jugular (B)	Blood pressure rise mm. Hg
l-adrenaline	25	2	12.5	24
	50	4	12.5	35
	100	10	10.0	54
	200	25	8.0	80
dl-nor-adrenaline	25	10	2.5	17
	50	20	2.5	24
	100	33	3.0	35
	200	75	2.7	48
	300	100	3.0	60

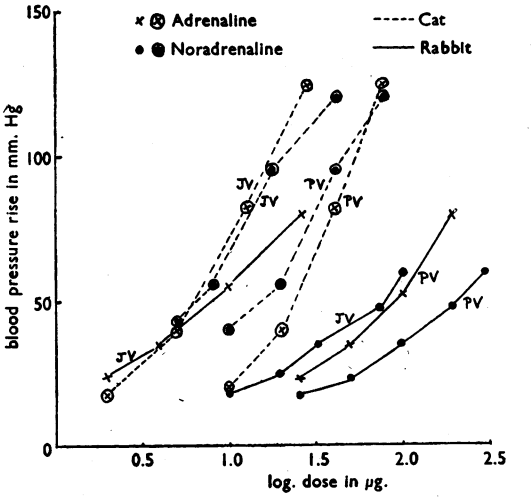

FIG. 1.—The effect of intrajugular (J.V.) and intraportal (P.V.) injections of *l*-adrenaline and *dl*-noradrenaline on the blood pressure rise in cats and rabbits. Note the great similarity between corresponding doses in the cat, and a wide margin between intrajugular doses of the two amines in the rabbit.

(the dotted lines), but a wide margin is indicated between equi-pressor doses by jugular vein in the rabbit. Barger and Dale in 1910 pointed out that adrenaline and other similar methylamino-bases had the property of exaggerating inhibitor as compared with motor effects, whereas the amino- and ethylamino- bases, including noradrenaline, possessed excitor with little or no inhibitory actions. They also noted that a dose of ergotoxine sufficient to reverse the pressor effect of adrenaline in the spinal cat did not reverse that of noradrenaline. The observations reported here may be linked with the fact that in the rabbit, in contrast to the cat, there appears to be no sympathetic depressor component capable of being unmasked by blocking agents such as ergotoxine (Cannon and

TABLE III

RATIO OF DOSE OF *dl*-NORADRENALINE PRODUCING A RISE OF BLOOD PRESSURE OF 48 MM. HG TO EQUI-ACTIVE DOSE OF *l*-ADRENALINE BY THE TWO ROUTES

Animal	No.	Preparation	Mean initial blood pressure mm. Hg	Dose ratio: *dl*-noradrenaline / *l*-adrenaline	
				intra-portal	intra-jugular
Cat	5	Chloralose	118	0.8	0.5
	2	Urethane	65	1.5	1.3
	3	Spinal	62	1.8	1.5
Rabbit	2	Urethane	55	2.0	8.0

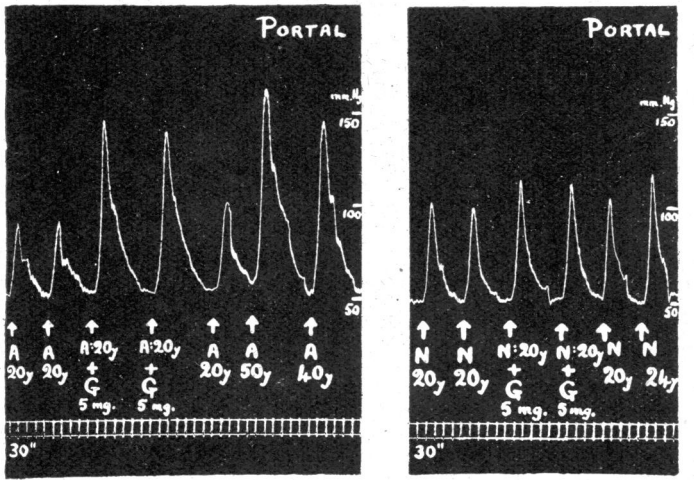

FIG. 2.—Spinal cat. 2.5 kg. Blood pressure record. All injections into the portal circulation; 5 mg. guanidine carbonate (G) greatly increases the pressor action of 20 μg. adrenaline (A) but scarcely affects the pressor action of 20 μg. noradrenaline (N).

Lyman, 1913), and in consequence the ratio of dose of noradrenaline to equi-pressor dose of adrenaline in rabbits is higher than that found in cats. On the other hand, the difference may be related to the initial blood pressure level. For example, as Table III shows, in cats under urethane with low blood pressures, noradrenaline is less active than adrenaline, whereas in cats under chloralose with high blood pressures, it is more active by both routes.

The potentiation of adrenaline injected into the portal circulation

Dawes showed that intraportal injection of amidines and guanidines into spinal cats increased the pressor action not only of intraportal adrenaline but also (and equally well) of the more active sympathomimetic amines, such as corbasil, epinine, and noradrenaline. I have used guanidine only as the potentiating agent, and have compared its effect on adrenaline injections with that on noradrenaline injections. Fig. 2 shows the potentiation of 20 μg. adrenaline, injected into the portal vein of a spinal cat, by 5 mg. guanidine mixed in the same syringe. On intrajugular injection, 5 mg. guanidine itself had no significant effect on blood pressure and showed little or no potentiation of 5 μg. of adrenaline. There is therefore a striking difference between the action of guanidine on adrenaline injected by the portal vein and by the jugular vein. Dawes suggested that the reduction of the inactivation of adrenaline in the liver by guanidine and amidine derivatives was not due to inhibition of mono-amine oxidase, but might be due to some interference with the uptake of adrenaline by the liver cells which prevented it reaching the enzyme.

When these experiments were repeated with noradrenaline, no such potentiation was noted with intraportal doses of guanidine (Fig. 2) or with intrajugular doses of guanidine. The inactivation of intraportal doses of noradrenaline therefore is unaffected by the simultaneous injection of intraportal doses of guanidine. Similar results were recorded in cats under chloralose or urethane and in rabbits under urethane, so that this fact is independent of anaesthetic and is not confined to one species. Dawes showed that if a short interval of time was left between the injection of the guanidine and that of adrenaline the potentiation was less and that it disappeared altogether if the interval was ten minutes. It is possible that the slower-acting noradrenaline may reach the enzyme when the guanidine is partially inactivated. Alternatively, the liver cells may inactivate noradrenaline slowly, especially as it may be that the substance liberated on stimulating the hepatic nerve in the cat is noradrenaline and not adrenaline (Bacq, 1934).

The action of guanidine on intra-arterial injection

It is well known that the injection of adrenaline into the femoral artery causes a much smaller rise of blood pressure than intrajugular or intrafemoral injection. Thus in spinal cats with a cannula in the external iliac artery (so that the injected solution passed into the vessels of the opposite leg), 12 μg. adrenaline were required on intra-arterial injection to cause the same rise of blood pressure as 2 μg. adrenaline by the jugular vein. As with

TABLE IV

COMPARISON OF EQUI-PRESSOR DOSES OF *l*-ADRENALINE AND *dl*-NORADRENALINE BY THE INTRA-ARTERIAL AND INTRAJUGULAR ROUTES IN SPINAL CATS

Cannulae in the external iliac artery and jugular vein

Drug	Intra-arterial injection (A) μg.	Intra-jugular injection (B) μg.	Arterial (A) / Jugular (B)	Blood pressure rise mm. Hg
l-adrenaline	12	2	6.0	28
	25	5	5.0	49
	40	16	2.5	76
dl-nor-adrenaline	10	2	5.0	29
	15	5	3.0	43
	40	16	2.5	62

the splenic vein injections, however, the ratio of equi-pressor doses by the two routes slowly decreased as the blood pressure rise increased (Table IV). When noradrenaline was injected similarly, ratio values slowly decreased, in contrast to fairly constant values after splenic vein injections. It follows that the inactivation processes of adrenaline and noradrenaline are very similar in the limb muscle vessels. Guanidine did not reduce the inactivation of either adrenaline or noradrenaline when injected simultaneously into the femoral artery. In several animals even a depressed action was noted. If vasodilatation caused by guanidine was the principal cause of potentiation in the liver, then one would expect a potentiation on arterial injection. This does not occur and hence small doses of guanidine do not exert an effect on limb muscle vessels.

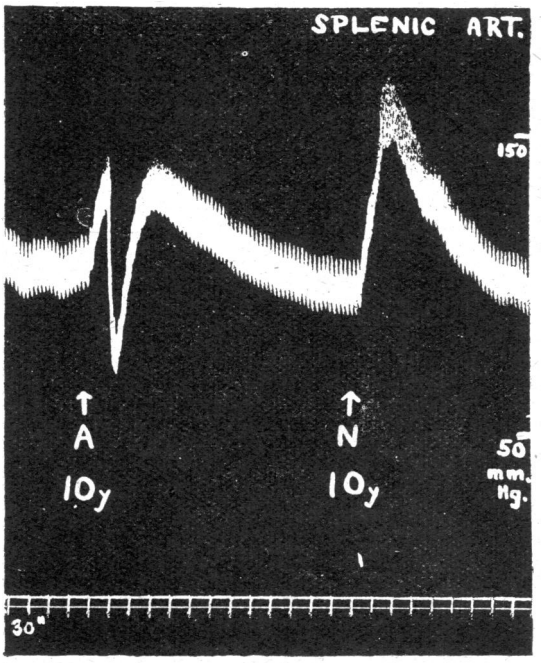

FIG. 3.—The effect on the blood pressure of 10 μg. adrenaline (A) and 10 μg. noradrenaline (N) injected into the splenic artery of a chloralose cat.

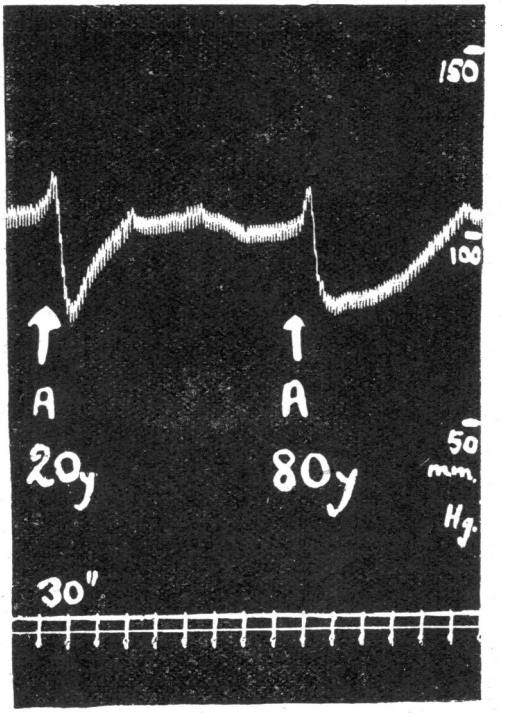

FIG. 4.—Cat. Chloralose. 3.0 kg. Blood pressure record. The effect of adrenaline injected into the splenic artery. Note that the vasodepressor component of 20 μg. is similar to that of 80 μg., but that the latter effect is more prolonged.

When injected into the artery supplying the caudal end of the spleen, adrenaline in small doses caused a small rise followed by a large fall in blood pressure, quite similar to the effect of injecting crude cattle spleen extracts into the jugular vein of cats under chloralose (Euler, 1946a). This depressor component was not completely abolished by intra-arterial doses of atropine, nor was it augmented by eserine. Benadryl in a dose of 0.5 mg. eliminated the depressor action of adrenaline at a time when the normal histamine response (10 μg.) was neutralized. It suggests, therefore, that the injection of adrenaline caused a liberation of histamine in the spleen, but more work must be completed before a definite conclusion can be reached.

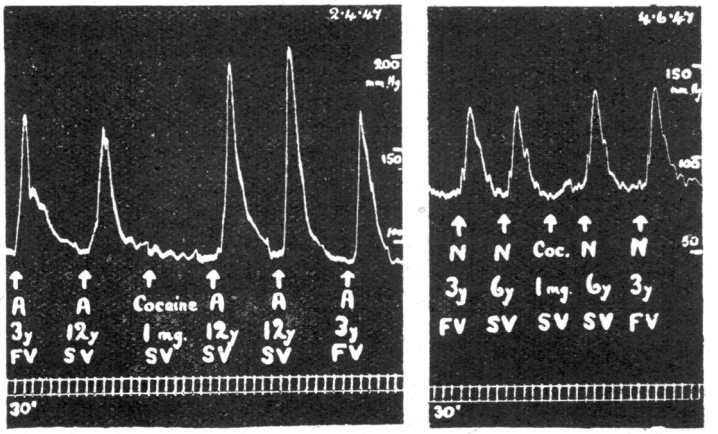

FIG. 5.—Chloralose cats. Blood pressure records. After 1 mg. cocaine hydrochloride injected into the splenic vein (S.V.) 12 μg. adrenaline intraportally is augmented, but not 3 μg. adrenaline and 3 μg. noradrenaline intrafemorally (F.V.) or 6 μg. noradrenaline intraportally.

Noradrenaline, on the other hand, produced a pure rise of pressure at all dose levels (Fig. 3).

This effect of adrenaline on the blood pressure is very striking. It is possible, by using small doses intravenously, to obtain part of the effect (see Gaddum and Goodwin), but the dilatation following injection of 80 μg. into the splenic artery is increased in length but not in depth, when compared with that after 20 μg. adrenaline (Fig. 4), whereas large doses intravenously produce pure vasoconstriction. In addition, these effects are independent of the anaesthetic, since comparable results have been obtained in cats under ether or chloralose. It is worthy of note that the latent period of noradrenaline injections is more than three times that of adrenaline by splenic artery, and this may indicate that the active adrenergic material in the spleen is not noradrenaline, which may have to be methylated or altered before it is effective. A similar longer latent period with noradrenaline than with adrenaline has already been noted (West, 1947a).

Intra-arterial doses of guanidine almost completely removed the depressor component of adrenaline, leaving the vasoconstrictor action, but had no effect on the noradrenaline response. When compared in the same cat under chloralose, equipressor responses were produced by 80 μg. of noradrenaline by splenic artery and 20 μg. by splenic vein (a ratio of 4 : 1), and by 300 μg. of adrenaline by splenic artery and 40 μg. by splenic vein (a ratio of 7.5 : 1). Thus noradrenaline is a much more potent pressor agent by splenic artery than adrenaline, and in addition relatively more adrenaline than noradrenaline is inactivated in the spleen.

The action of cocaine and ephedrine

Experiments similar to those reported for guanidine were completed with 1 mg. doses of cocaine hydrochloride and 100 to 150 μg. doses of ephedrine hydrochloride. Fig. 5 shows the potentiation by intraportal doses of cocaine of intraportal but not intrafemoral adrenaline, and an absence of potentiation of intraportal noradrenaline. This supports the theory that the inactivation of noradrenaline in the liver is a slow process and is not affected by the simultaneous administration of substances such as guanidine and cocaine in small doses. As is well known, cocaine was found to enhance both adrenaline and noradrenaline responses when given by the same routes intrajugularly and intra-arterially (Table V). When used in larger doses, all adrenaline and noradrenaline responses (including intraportal noradrenaline) were enhanced. Ephedrine was an effective enhancing agent by all routes. Thus, there are three types of potentiating agent used in this work: (*a*)

TABLE V

THE EFFECT OF INTRAVENOUS AND INTRA-ARTERIAL GUANIDINE AND COCAINE ON THE PRESSOR ACTIONS OF *l*-ADRENALINE AND *dl*-NORADRENALINE INJECTED BY SIMILAR ROUTES INTO CATS

A = adrenaline. norA = noradrenaline.
+ = potentiation. 0 = no potentiation.
Dose of guanidine was 5 mg. and that of cocaine was 1 mg.

Route of injection	Potentiating agent	Jugular vein		Splenic vein		Iliac artery	
		A	norA	A	norA	A	norA
Jugular vein	Guanidine	0	0	0	0	0	0
	Cocaine	+	+	0	0	0	0
Splenic vein	Guanidine	0	0	+	0	0	0
	Cocaine	0	0	+	0	0	0
Iliac artery	Guanidine	0	0	0	0	Trace	0
	Cocaine	0	0	0	0	+	+

TABLE VI

THE ACTIONS OF *dl*-NORADRENALINE AND *l*-ADRENALINE, INJECTED INTO THE PORTAL AND JUGULAR VEINS, ON THE BLOOD PRESSURE, DENERVATED NICTITATING MEMBRANE, GUT AND PREGNANT UTERUS OF TWO CHLORALOSE CATS, COCAINE HYDROCHLORIDE (8 MG./KG.) WAS GIVEN INTRAMUSCULARLY

++ = large effect. + = moderate effect. 0 = no effect

Route of injection	Drug	Dose μg.	Mean blood pressure rise mm. Hg	Nictitating membrane rise mm.	Relaxation of gut	Contraction of uterus
Splenic vein ..	Adrenaline	20	70	15	++	++
	Noradrenaline	10	68	13	+	++
Jugular vein ..	Adrenaline	5	70	12	++	++
	Noradrenaline	4	69	5	0	0

ephedrine, acting generally in the body and probably impeding or preventing enzyme inactivation processes when used in certain concentrations; (*b*) cocaine, acting in a manner similar to that of ephedrine but not enhancing intraportal doses of noradrenaline when itself given intraportally in small doses; and (*c*) guanidine, possibly acting directly on the liver cells preventing penetration of adrenaline to the amine oxidase, at the same time producing no potentiation of intraportal noradrenaline.

The effect of adrenaline and noradrenaline on other organs in vivo

Records were taken of the actions of the two amines on the blood pressure, gut, uterus, and denervated nictitating membrane of two pregnant cats. The results of equi-pressor doses by the splenic and jugular veins are shown in Table VI. It is of interest to note that noradrenaline by splenic vein exerted its effects on the membrane, gut, and uterus, i.e., it showed excitor and inhibitor actions, yet an equi-pressor dose by jugular vein gave very feeble actions. It is possible that part of the exogenous noradrenaline may be converted to adrenaline in the liver by N-methylation. Similar results were shown in two spinal non-pregnant cats, intraportal doses of noradrenaline being rather more active on the gut than on the uterus. (Table VII). The fact that noradrenaline in moderate doses may inhibit the non-pregnant uterus and intestine *in vivo* confirms the results of previous workers (Gaddum and Goodwin).

TABLE VII

THE ACTIONS OF *dl*-NORADRENALINE AND *l*-ADRENALINE BY THE INTRAPORTAL AND INTRAJUGULAR ROUTES ON THE BLOOD PRESSURE, GUT, AND NON-PREGNANT UTERUS OF TWO SPINAL CATS

Cocaine hydrochloride (8 mg./kg.) was administered intramuscularly

++ = large relaxation. + = definite but smaller relaxation. 0 = no effect

Route of injection	Drug	Dose μg.	Mean blood pressure rise mm. Hg	Relaxation of gut	Relaxation of uterus
Intraportal	Adrenaline	10	62	++	++
	Noradrenaline	18	60	++	+
Intrajugular	Adrenaline	4	66	+	++
	Noradrenaline	6	66	slight	0

Experiments with liver sympathin

Stimulation of the hepatic nerves in the cat almost invariably caused a rise of blood pressure, part of which was due to constriction of the hepatic artery. The rise occurred even when a clamp on the artery itself raised the blood pressure a few mm. Hg, so that the second effect was due to the liberation of sympathin (Gaddum and Goodwin). Fig. 6 shows the effect of hepatic nerve stimulation before and immediately after the intraportal injection of 5 mg. guanidine carbonate. It will be seen that no potentiation of liver sympathin occurred. In the same animal, adrenaline by the splenic vein was potentiated by guanidine but noradrenaline was not. To overcome any damaging effect of guanidine on the liver cells, the adrenaline responses were completed after liver sympathin and noradrenaline effects had been shown, but the same result was obtained.

In an animal which had not received cocaine, the effect of hepatic nerve stimulation was not potentiated by the simultaneous intraportal injection of cocaine hydrochloride (1 mg.). Gaddum and Goodwin made it clear that cocaine was not essential for work with liver sympathin, since stimulation of the hepatic nerves caused a rise of

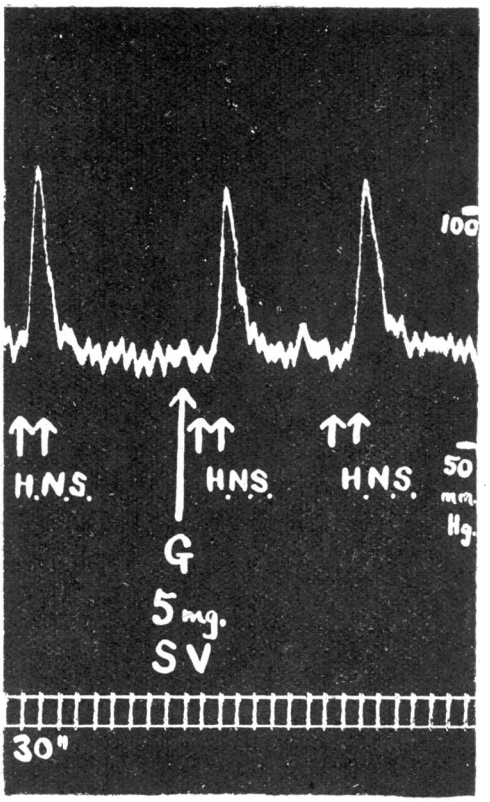

FIG. 6.—Cat 3.6 kg. Chloralose. Cocaine. Blood pressure. Stimulation of hepatic nerves for 30 sec. (H.N.S.). 5 mg. guanidine carbonate injected into the splenic vein (S.V.) 15 sec. before stimulation do not potentiate the pressor action.

blood pressure, contraction of the denervated nictitating membrane, and inhibition of the intestine before cocaine had been given. They stated that whereas cocaine caused a definite increase of the effect on the nictitating membrane, it did not always affect the blood pressure rise. The observations with guanidine and cocaine emphasize the great similarity in action between liver sympathin and noradrenaline (Figs. 2 and 6). Ephedrine potentiated the pressor effect of hepatic nerve stimulation in a feeble way. The actions of liver sympathin on the nictitating membrane and pregnant uterus (excitor responses) and on the gut and non-pregnant uterus (inhibitor responses) agreed very well with those produced by equi-pressor doses of intraportal noradrenaline.

Cannon and Rosenblueth (1937) found that, after the administration of large doses of both ergotoxine (5 mg./kg.) and cocaine to the same cat, the injection of adrenaline caused a pure fall of blood pressure but that stimulation of the hepatic nerves caused a rise. We have observed similar results with ergotamine (3 mg./kg.). By a chance observation, a large dose of dihydroergotamine (2 mg./kg.) was given intraportally in a cat under chloralose. This is about 10 times the normal adrenaline reversal dose, and the effect of subsequent hepatic nerve stimulation surprisingly produced a pure fall of blood pressure (Fig. 7). Likewise, small intraportal doses of noradrenaline produced a fall while corresponding doses of adrenaline had little or no effect. It was not always possible to repeat this result in later experiments. For example, if the dihydroergotamine was given in small increments the normal adrenaline reversal was observed, but after hepatic nerve stimulation or noradrenaline administration a pure rise of blood pressure was produced. Variable results were also produced if the dihydroergotamine was given by the intrajugular route. In addition, intra-arterial noradrenaline gave a rise and intra-arterial adrenaline a fall of blood pressure, whereas intrajugular noradrenaline gave a very small depressor effect. These results only refer to cats under chloralose, and it is hoped to extend this work in order to see if the phenomenon occurs with other anaesthetics. It is of interest to note that dihydroergotamine does not always reverse the adrenaline response in dogs (Orth and Ritchie, 1947).

In two cats, the effects of stimulating the splenic nerve (dissected out in a manner similar to that used for the hepatic nerve) have been recorded. So far, stimulation has produced a pure rise of blood pressure, no depressor component being observed; the rise although usually small was not potentiated by intra-arterial cocaine or guanidine.

DISCUSSION

For small blood pressure rises in cats, noradrenaline was more active than adrenaline by both the jugular and the splenic routes. As the pressure rise increased, so the sensitivity of the animal increased for adrenaline but decreased for noradrenaline. Ratios of equi-pressor doses of the two amines were thus variable, and this observation may help to explain why such ratios have not been consistent in the past. For example, Crimson and Tainter (1938, 1939) quoted many values for intrafemoral injection ranging from 0.5 to 1.2. For rabbits, noradrenaline was much less active than adrenaline by all routes studied. Two explanations of these phenomena have been recorded: (1) the rabbit appears to have no sympathetic depressor component comparable with that found in the cat, so that the response to adrenaline is pressor only in the rabbit; (2) the

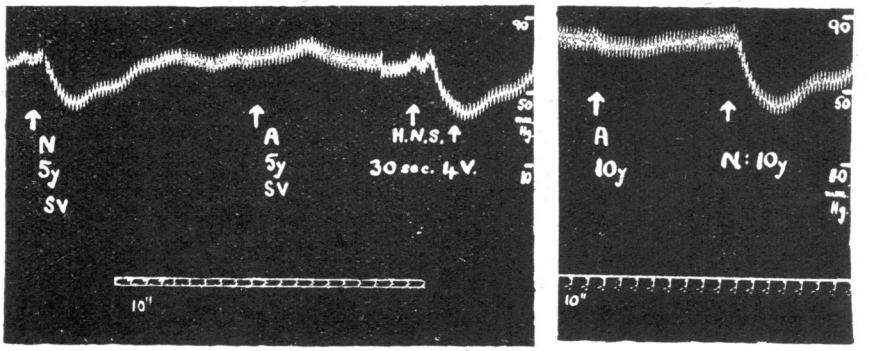

FIG. 7.—Cat. Chloralose. Cocanie. Dihydroergotamine (2 mg./kg.) intraportally. Note that hepatic nerve stimulation (H.N.S. 30 sec.) and intraportal noradrenaline produce depressor effects, whilst intraportal adrenaline scarcely affects the blood pressure.

initial blood pressure levels partially regulate the ratio of equi-pressor doses of the two amines, for in low pressure animals (rabbits under urethane, spinal cats, and cats under urethane) the ratio is higher than 1.0, i.e., the pressor action of noradrenaline is less than that of adrenaline, whereas in high-pressure animals (cats under chloralose) it can be lower. In addition, it has been shown (West, 1947b) that adrenaline and not noradrenaline is a normal constituent of rabbit's blood. It is possible that adrenaline is the normal mediator liberated by adrenergic nerves in the rabbit, but that the mechanism is a little more complex in the cat.

Guanidine on intraportal injection into cats and rabbits potentiated intraportal adrenaline. This potentiation was not shown by guanidine injected into the jugular or femoral veins or into the external iliac or splenic arteries. The effect is thus a local and transitory one on liver cells, presumably preventing the penetration of adrenaline (Dawes, 1946). Noradrenaline in equi-pressor intraportal doses was not potentiated, suggesting that the hepatic inactivation of this amine is not so rapid as with adrenaline. Similarly, suitable intraportal doses of cocaine were found to potentiate intraportal adrenaline but not intraportal noradrenaline, whereas by all other routes studied both were potentiated. Further, intraportal doses of noradrenaline produced effects on the pregnant cat uterus (excitor) and on the gut (inhibitor) when the equi-pressor dose by jugular vein was ineffective. In addition, it has been shown that the inactivation processes for the two amines in the muscle vessels of the limb are similar *in vivo*, since the ratios of equi-pressor doses by the arterial and femoral routes slowly decreased in both cases.

The effects of intraportal noradrenaline have nearly always been similar to those of hepatic nerve stimulation. The simultaneous administration of cocaine and guanidine has not potentiated the pressor effect of stimulation. After large doses of dihydroergotamine by splenic vein, both noradrenaline and hepatic nerve stimulation caused depressor actions when corresponding doses of adrenaline had no effect. In a biochemical study of this and other problems, Blaschko (1942) came to the conclusion on indirect evidence that adrenaline is produced by N-methylation of noradrenaline which may be first formed in the body from tyrosine. It is possible that noradrenaline may be produced in the liver and may act as the adrenergic mediator in that organ, in which case the inactivation process of noradrenaline naturally would be suppressed. A similar position occurs in the spleen, where injections of noradrenaline into the splenic artery and splenic nerve stimulation both produce vasoconstriction, whereas adrenaline injections result in the biphasic response with the marked depressor component. In addition, the ratio of equi-pressor doses of adrenaline by splenic artery and splenic vein is higher (7.5:1) than for corresponding doses of noradrenaline (4:1). Hence relatively more adrenaline is inactivated in the spleen than is noradrenaline, a result similar to that found for the liver. These observations with the liver and spleen may be linked up with the findings of Euler (1946a, b) that extracts of mammalian spleen, heart, liver, and sympathetic nerves contain a pressor substance with properties like those of noradrenaline or dihydroxy-norephedrine. In addition, he found large quantities of histamine in extracts of mammalian splenic nerves (Euler, 1947). This may account for the depressor component of the adrenaline response after injection into the splenic artery, since it is eliminated by benadryl. More recently, Bacq and Fischer (1947) have reported that extracts of mammalian spleen contain only noradrenaline, extracts of human coronary nerves and arteries only adrenaline, but extracts of mammalian splenic nerves and sympathetic chains a mixture of noradrenaline and adrenaline. Their interpretation of these facts is that in some tissues the synthesis of adrenaline

is stopped at the stage of noradrenaline, whilst in other tissues methylation occurs and adrenaline is formed. They support Euler's suggestion that the term " sympathin " be used for a mixture of varying proportions of adrenaline and noradrenaline.

Summary

1. The pressor effects of *dl*-noradrenaline and *l*-adrenaline, injected into the jugular, femoral, and splenic veins and the splenic and external iliac arteries of cats and rabbits, have been examined.

2. Adrenaline was less active by portal than by jugular vein, though the ratio value for equi-pressor doses by these routes decreased as the pressure rise increased. Noradrenaline was less active by portal than by jugular vein, but the ratio value remained constant.

3. When injected into the portal circulation, noradrenaline was not potentiated by the simultaneous administration of guanidine or cocaine whereas equi-pressor doses of adrenaline were enhanced. Noradrenaline therefore is not rapidly absorbed from the blood stream during its passage through the liver.

4. Intra-arterial and intrajugular injections of adrenaline and noradrenaline were not potentiated by the simultaneous administration of intra-arterial or intrajugular guanidine, but both were enhanced by cocaine.

5. Further similarity in the effects of hepatic nerve stimulation and intraportal injections of noradrenaline have been recorded. Guanidine or cocaine in suitable intraportal doses, for example, do not potentiate the action of liver sympathin. After large intraportal doses of dihydroergotamine, hepatic nerve stimulation and small intraportal doses of noradrenaline produced depressor responses, when corresponding doses of adrenaline were without effect.

6. When injected into the artery supplying the caudal end of the spleen, adrenaline produced a depressor response, possibly due to the liberation of histamine. Noradrenaline, on the other hand, produced a pure rise of blood pressure.

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