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THE ACTION OF BEE VENOM, COBRA VENOM AND LYSOLECITHIN ON THE ADRENAL MEDULLA

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A VARIETY of effects produced by different snake venoms and by bee venom may be explained by their enzymatic character as phosphatases. By splitting off oleic acid from lecithin a lytic substance, lysolecithin, is formed which has the property of penetrating and dispersing monolayers of lipo-proteins [Schulman & Rideal, 1937; Schulman & Stenhagen, 1938]. A similarly active substance appears to be formed from cephalin.

The protoplasmatic structure of the cells may be regarded as consisting of mixed films of lipo-proteins [Rideal & Schulman, 1939] in which pharmacologically active substances are anchored. By the action of lysolecithin this structure is destroyed and the active substances are released. It has been shown that lysolecithin releases histamine from perfused tissues, and it has been concluded that its liberation largely contributes to the symptomatology of venom and lysolecithin poisoning [Feldberg & Kellaway, 1938; Feldberg, Holden & Kellaway, 1938]. Recently Kellaway & Trethewie [1940] have shown that lysolecithin also releases adenylic compounds from perfused hearts and Feldberg, Kellaway & Trethewie, as well as Gautrelet & Corteggiani [1939], found that acetyl choline is released by lysolecithin from a suspension of cellular material of guinea-pig's brain.

In the protoplasm of the medullary cells of the adrenals there is kept in an inactive linkage another pharmacologically active substance, adrenaline. In the experiments described in this paper, we have tried to find out whether this substance is released and brought into circulation by the lytic action of lysolecithin on the medullary cells when it is either injected arterially into the adrenals or formed from their lipins following an arterial injection of venom.

The release of adrenaline might be the direct outcome of the lytic action of lysolecithin, in which case it would be demonstrable in *in vitro* experiments by the action of lysolecithin on a suspension of cells and cell debris from the adrenals. It might, however, be effected by the intermediate liberation of histamine, which would then in its turn act as a secretory stimulus. Since histamine is known to cause an output of adrenaline in cats and not in rabbits, lysolecithin, if acting in this way, would have no secretory action on the adrenal medulla of rabbits.

Methods

In cats we have examined the output of adrenaline by the adrenals *in situ* and by isolated perfused adrenals. A few experiments were made in rabbits. In cats the brain and spinal cord were pithed under ether-chloroform anaesthesia. The rabbits were anaesthetized by intravenous injection, through an ear vein, of chloralose. For the *in situ* experiments the abdominal viscera were removed and the drugs injected through a cannula tied into the central stump of the coelic artery, the abdominal aorta and inferior vena cava having been tied below the adrenals. The method has been described by Feldberg, Minz & Tsudzimura [1934].

Perfusion of the cat's left adrenal. Perfusion was carried out with oxygenated Locke solution from a Dale-Schuster pump through a cannula tied into the central stump of the coelic artery. In order to keep the temperature of the inflowing fluid constant, a glass T-piece was inserted into the rubber tubing near the cannula and attached to an overflow. The perfusion pressure was regulated by the height of the overflow, and the temperature by an increase or decrease of the stroke of the pump. The perfusion pressure was kept between 60 and 90 mm. Hg, and the rate of perfusion between $1\frac{1}{2}$ and $2\frac{1}{2}$ c.c. per min. The venous outflow was collected from a cannula tied into the adrenal vein. The experiment was performed on eviscerated spinal cats. From the origin of the coelic artery the side branches of the aorta were tied and cut for a length of about $1\frac{1}{2}$ in., leaving the tissue between the adrenal and the aorta undisturbed. A corresponding piece of the inferior vena cava was similarly cleaned. The left renal vessels were tied and cut near the hilum in order to leave a small arterial branch open which often originates from the renal artery and supplies the adrenal. The tissue at the lateral side and at the back of the gland was cut between numerous double ligatures, so that at the end of the preparation the adrenal was attached to the prepared piece of aorta and vena cava only, all other connexions with the body having been severed. When the splanchnic nerve was

meant to be stimulated a piece of nerve long enough to be put into a Collison fluid electrode was prepared, and left attached to the gland. The perfusion cannula was tied into the clamped coelic artery, the aorta was tied proximally and perfusion started by opening the clamp. After a minute or two, to allow the blood to be washed out, the aorta was tied below the adrenal, and a fine glass cannula was inserted into the adrenal vein through an opening in the vena cava inferior and tied in position. The gland with the attached vessels was then removed from the body. For this purpose the perfused piece of aorta was tied *in situ* to a large match to prevent kinking or shrinking of the vessel. The match was further used for fixing the perfused tissue. For the injections the rubber tube near the cannula was momentarily clamped and the injections were made through the rubber tube into the cannula in the same way as ordinary intravenous injections. The injection volume was 0·4 c.c. The venous outflow was collected and assayed for adrenaline on the arterial blood pressure of a cat, the brain and spinal cord of which had been destroyed. In those experiments in which the effect of acetylcholine on the perfused adrenal was examined, the assay of adrenaline was carried out on cats which had been given atropine in order to abolish the depressor action of any acetylcholine present in the perfusate. In some experiments the perfusate was also assayed for histamine. In that case a sample was made alkaline by the addition of NaOH and kept at 60–70° C. until all adrenaline had been destroyed. The fluid was then neutralized with HCl and tested for histamine on a piece of guinea-pig's jejunum suspended in Tyrode solution.

The venom used was that of the Indian cobra (*Naia naia*) and of the bee. The potency of the latter was such that a concentration of 1 in 10^{10} often caused contraction of the isolated guinea-pig's jejunum. The lysolecithin was kindly prepared for me by Dr Winterstein (Basle) by the action of bee venom on lecithin. The haemolytic power of the preparation was such that concentrations up to 1 in 6000 caused complete haemolysis of a 2·5 % suspension of washed red cells of the rabbit within 60 sec.

Results

Experiments on the adrenal medulla of cats

Experiments in situ.

Bee venom. Its injection into the central stump of the coelic artery of an eviscerated cat caused a long lasting rise in arterial blood pressure with acceleration of the heart beat. These effects resulted from an output

of adrenaline from the suprarenals and were absent after their removal. Doses of 1 μg. of venom or less were ineffective. The effect of 5–10 μg. was sometimes pronounced; usually, however, larger doses were required. The rise in pressure started after a latent period of 40–60 sec., and was sometimes preceded by a fall due to the depressor action of the venom. In the experiment of Fig. 1 the injection of 4 μg. of venom (at *B*) after a latency of about 1 min. caused a small rise of pressure lasting a few minutes. The subsequent injection of 150 μg. (at *C*) produced an initial strong output of adrenaline raising the blood pressure to about 150 mg. Hg, followed by a prolonged period of a more moderate and slowly decreasing output. The blood pressure had not returned to its original level 50 min. after the injection, indicating that the output

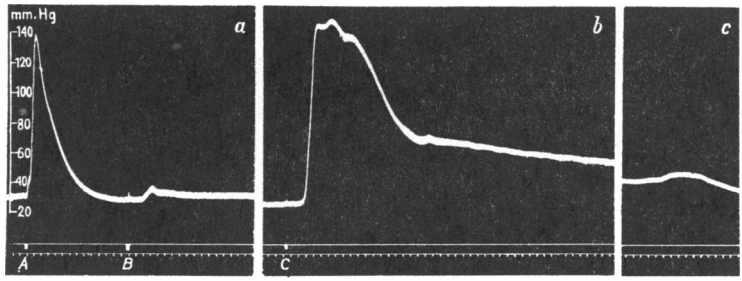

Fig. 1. Arterial blood pressure of 3·2 kg. pithed cat; eviscerated; renal vessels tied at hilum; abdominal aorta and vena cava inferior tied below the adrenals. At *A* intravenous injection of 5 μg. adrenaline; at *B* and *C* arterial injection of 4 and 150 μg. bee venom respectively. Between *b* and *c* interval of 25 min. Time in half minutes.

of adrenaline had not come to an end within this period. Sometimes the return of the blood pressure to its pre-injection level did not proceed steadily, but was interrupted by irregular rises of pressure. When the injections of bee venom were repeated the effects became progressively smaller.

The output of adrenaline was associated with a loss of adrenaline from the adrenals. For instance, when the right adrenal was removed before, and the left after two or three injections of 100–200 μg. of venom, the yield of adrenaline obtained on saline extraction from the left gland was 20–30 % less than that obtained from the right gland.

Bee venom, even in doses which caused a moderate output of adrenaline, decreased the response of the adrenals to a subsequent stimulation of the splanchnic nerves. The onset of the rise of pressure resulting from the secreted adrenaline was delayed, the rise proceeded more gradually

and was less pronounced. In some experiments splanchnic stimulation became ineffective.

Post morten the adrenals removed after the injections of venom had a spotted appearance resulting from numerous haemorrhages. Histologically there was local and diffuse polymorphonuclear leucocytic infiltration, capillary congestion, haemorrhages, lysis of the red blood cells and some destruction of cortical cells. There were no visible changes or abnormalities in the medullary cells.

Cobra venom. The effect on the suprarenal medulla resembled that of bee venom. In Fig. 2 (at *A* and *D*) are seen the responses to two

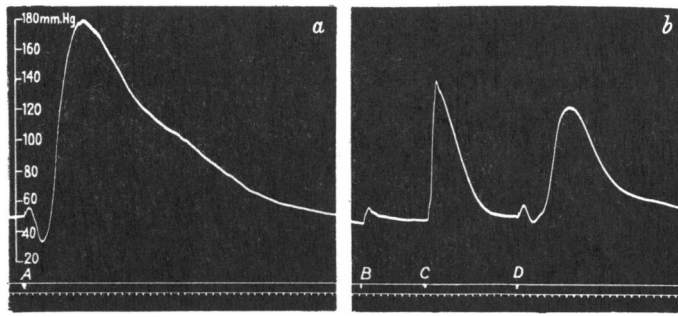

Fig. 2. Arterial blood pressure of 2·7 kg. pithed cat; eviscerated; vessels tied as in experiment of Fig. 1. At *A* and *D* arterial injection of 140 μg. cobra venom; at *C* intravenous injection of 5 μg. adrenaline; at *B* arterial injection of 0·5 c.c. saline solution. Time in half minutes.

arterial injections of 140 μg. of venom (in 0·4 c.c. volume). After removal of the adrenals the arterial injections were purely depressor in action.

The *post mortem* appearance of the adrenals resembled that described for bee venom. There was also a diminution of the adrenaline content of the medulla.

Lysolecithin. Its injection into the central stump of the coelic artery in a concentration of 1 in 1000 or stronger caused, after a latency of 30–60 sec., a rise in arterial blood pressure lasting from a few minutes to 2 hr. and being associated with acceleration of the heart beat. These effects resulted from an output of adrenaline from the adrenals and were absent when these had been removed or when the injections were made intravenously. In these cases lysolecithin produced only its depressor action. The effects of two arterial injections of 8 mg. of lysolecithin are

shown in Fig. 3, at *A* before, and at *B* after removal of the left adrenal, the right one having been removed before the beginning of the experiment.

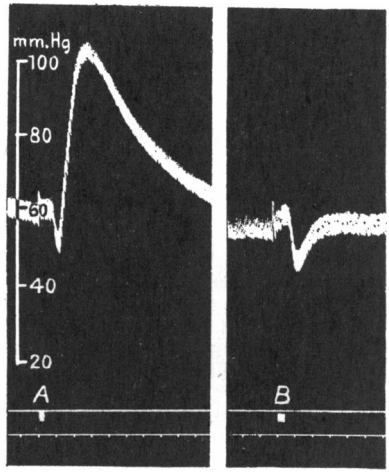

Fig. 3. Arterial blood pressure of 2·8 kg. pithed cat; eviscerated; vessels tied as in experiment of Fig. 1; right adrenal removed. At *A* and *B* arterial injection of 8 μg. lysolecithin in 0·4 c.c. saline solution. Between *A* and *B* removal of left adrenal. Time in half minutes.

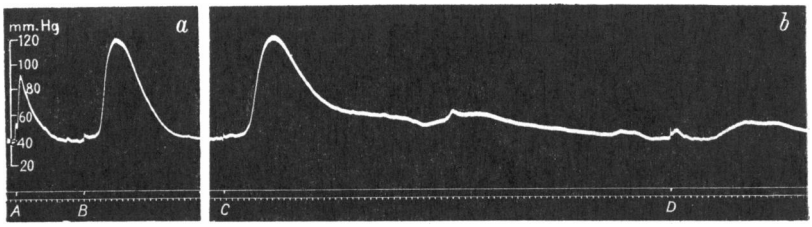

Fig. 4. Arterial blood pressure of 2·8 kg. pithed cat; eviscerated; vessels tied as in experiment of Fig. 1. At *A* intravenous injection of 5 μg. adrenaline; at *B*, *C* and *D* arterial injection of 8 μg. lysolecithin in 0·4 c.c. saline solution. Time in half minutes.

The effect of a first large dose of lysolecithin was usually weaker and more evanescent than that of a second similar one. The difference was sometimes pronounced. In the experiment of Fig. 4 it consisted mainly in the duration of the output of adrenaline. After the first injection (at *B*) the blood pressure had returned to about its original level within 10 min., whereas after the second injection (at *C*) it took over 30 min. Subthreshold doses of lysolecithin injected repeatedly usually remained ineffective, but rendered the medulla more sensitive to a subsequent

larger dose. In the experiment of Fig. 5 five ineffective injections of 2·5 μg. of lysolecithin, in 0·5 c.c. fluid, were given; the effect of the last one is seen at *A*. The medulla of the right adrenal—the left one having been removed before the beginning of the injections—responded now to an arterial injection of 8 μg., in 0·4 c.c. (at *B*) with a strong and long lasting output of adrenaline. The output had not come to an end about 2 hr. after the injection when the adrenal vein was tied (at *C*) and the gland removed (at *D*). In some experiments the prolonged output of adrenaline proceeded less regularly. The blood pressure tracing showed irregular rises of 30–80 mm. Hg, lasting for several minutes and following one another over a period of 2 hr. or longer.

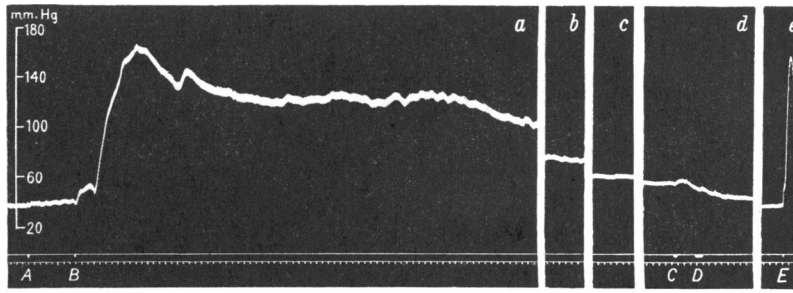

Fig. 5. Arterial blood pressure of 3·9 kg. pithed cat; eviscerated; vessels tied as in experiment of Fig. 1; right adrenal removed. At *A* and *B* arterial injection of 2·5 and 8 μg. lysolecithin respectively. At *E* intravenous injection of 5 μg. adrenaline. At *C* vein of left adrenal tied near vena cava; at *D* left adrenal removed. Between *a* and *b* and *b* and *c* interval of 30 min., between *c* and *d* of 15 and between *d* and *e* of 5 min. Time in half minutes.

When large doses of lysolecithin were injected more than twice the output of adrenaline became delayed and smaller. It could even become negligible, as shown in the experiment of Fig. 4 at *D*. The effect of splanchnic stimulation on the adrenal medulla was similarly altered. In some experiments splanchnic stimulation became ineffective. A weakening effect on the splanchnic response was already observed after a single injection of lysolecithin.

The decrease in the response to lysolecithin did not result from a depletion of adrenaline in the medulla. Although repeated large injections lowered the adrenaline content, the loss did not amount to more than 30 %. In the experiment of Fig. 5, for instance, the right adrenal which was removed at the beginning of the experiment yielded 193 μg. of adrenaline on saline extraction. The left gland removed after

the lysolecithin injections yielded 143 μg. The corresponding figures for the adrenaline content of the adrenals in experiment Fig. 4 were 150 and 112 μg. respectively.

Post mortem the adrenals removed after the lysolecithin injections showed the same changes as those described for bee and cobra venom.

Perfusion of the left adrenal.

The venous perfusate contained detectable amounts of adrenaline. During the first 10–15 min. after the beginning of the perfusion, the output of adrenaline per minute amounted to 0·8–1·5 μg. per min. It then decreased quickly and fell within 40–60 min. to between 0·1 and 0·15 μg. per min. (see Figs. 7, 8). Usually the output remained practically constant at this level for the next hour, or it showed a further gradual decline so that the adrenaline concentration in the venous perfusate eventually became too low to be detected by the blood-pressure method. The drugs were injected when a low constant output had been reached.

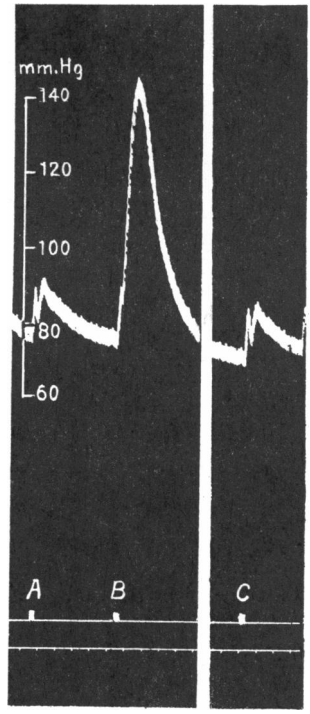

Fig. 6. Arterial blood pressure of pithed cat; injections of 0·5 c.c. perfusate from perfused cat's adrenal collected before (*A*) and after (*B* and *C*) 1 μg. acetylcholine chloride. Time in half minutes. For details see text.

Some fluid always leaked from the tissues, and this was collected and assayed separately. It contained no detectable amounts of adrenaline. This leakage fluid increased somewhat as perfusion was continued. During the first half hour of perfusion less than 2 c.c. and sometimes less than 1 c.c. were collected. After 1½ hr. perfusion the leakage fluid sometimes amounted to 2 c.c. in 15 min., and further increased slowly as perfusion was continued.

Stimulation of the splanchnic nerve caused a large increase in the output of adrenaline. At the end of the stimulation the output returned quickly to its original low level. In a few experiments the amount of adrenaline secreted by a single maximal impulse was determined from the total amount secreted during a given number

of maximal stimuli applied at a rate of 1–2 per sec. It amounted to 0·05–0·1 μg.

Acetylcholine injection caused an evanescent output of adrenaline (Figs. 6, 7, 8). Fig. 6 shows on the arterial blood pressure of a cat the effects of perfusate collected before (*A*), during the first (*B*) and the second (*C*) 1½ min. after an injection of 1 μg. of acetylcholine chloride into a perfused suprarenal. The output of adrenaline from this injection is plotted in tracing of Fig. 7 at *A*. Sometimes the increased output of

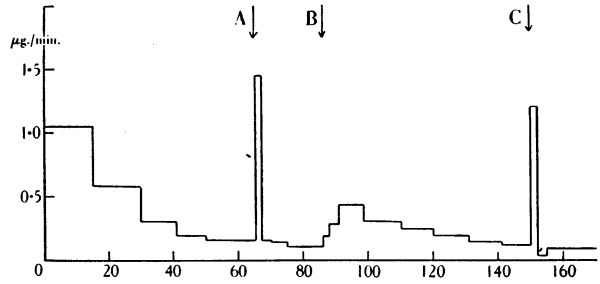

Fig. 7. Output of adrenaline from perfused left adrenal of a 2·8 kg. cat. At *A* and *C* injection of 1 μg. acetylcholine chloride; at *B* injection of 0·5 μg. lysolecithin. Ordinates: output of adrenaline in μg. per min.; abscissae: time of perfusion in minutes.

adrenaline was followed by a short period in which the output fell below the original "resting level" (see Fig. 7 at *C*). With prolonged perfusion the sensitivity of the gland to acetylcholine diminished. The values given in Table I are therefore taken from experiments during early stages of perfusion. It will be seen that the output increased with the dose injected.

TABLE I. Output of adrenaline from perfused cat's adrenal.

Amount of acetylcholine chloride injected in μg.	Output of adrenaline chloride in μg.
0·05	—
0·1	0·1; 0·5
0·25	0·1
0·5	0·3; 1·0
0·8	1·0
1·0	2·7
2·0	2·6; 5·2
5·0	4·3; 5·5
10·0	8·3

Histamine. Compared with acetylcholine the perfused adrenals are rather insensitive to histamine. A small but definite output of adrenaline could be obtained by the injection of 5 μg. of histaminedichloride.

Lysolecithin injection was followed by intense vaso-constriction which made it necessary to raise the perfusion pressure. The leakage fluid increased considerably and assumed a reddish colour due to the presence of haemolysed red corpuscles. It increased further as perfusion continued and 1 hr. after the injection it often reached 0·5–0·6 c.c. per min.

Unlike acetylcholine, lysolecithin caused a prolonged output of adrenaline. The difference in the response of the two drugs is illustrated in Figs. 7, 8. With doses of lysolecithin, such as 0·5 μg. or less, there was only a slight increase in the output of adrenaline, which reached its maximum within a few minutes and returned to normal after 40–70 min. (Fig. 7). With larger doses of lysolecithin the output reached an

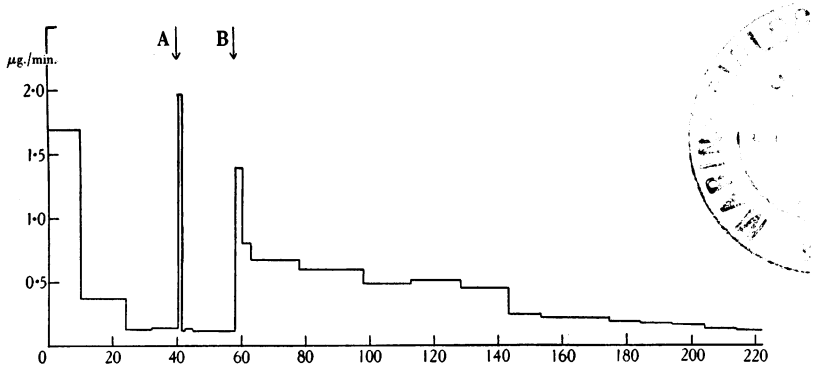

Fig. 8. Output of adrenaline from perfused left adrenal of a 3·3 kg. cat. At *A* injection of 1 μg. acetylcholine chloride; at *B* injection of 2 μg. lysolecithin. Ordinates and abscissae as in Fig. 7.

extremely high maximum within the first 2 min. and then decreased again, first quickly and later slowly. In the experiment of Fig. 8 the output of adrenaline per min. was 0·13–0·14 μg. before, and rose to 1·4 μg. in the first 2 min. after the injection of 2 μg. of lysolecithin, but fell again in the next few minutes to less than half this value; the output then decreased slowly and did not return to its original level until 2½ hr. after the injection. The total output during this period was 61 μg. In another experiment after the injection of 8 μg. of lysolecithin 17·5 μg. of adrenaline was secreted in the first 1½ min., the output then decreased at once and the total output in the following 8½ min. amounted only to 21 μg. The output returned to normal after 155 min., a total of 114 μg. of adrenaline having been secreted during this period.

The perfusate collected after the injection of lysolecithin contained no detectable amounts of histamine. The presence of 1 in 20 million of

histamine in the perfusate would have been detected by our assay on the isolated guinea-pig's jejunum.

That the adrenaline appearing in the perfusate after injection of lysolecithin was liberated from the adrenals was shown by the diminution of their adrenaline content. For instance, in one experiment the right adrenal which was not perfused yielded 250 μg. of adrenaline on saline extraction. The left adrenal was perfused; during 200 min. following the injection of 8 μg. of lysolecithin, 161 μg. of adrenaline were collected in the venous perfusate. The adrenal then yielded only 80 μg. of adrenaline on extraction.

Extracts of the suprarenals.

When adrenals are ground up in saline solution there remains in the debris only a fraction of its adrenaline. This is brought into solution when the debris are dissolved by the addition of lysolecithin. We proceeded as follows. The ground-up adrenals were centrifuged at 1000 r.p.m. for a few minutes to spin down the coarse material. The supernatant fluid was removed and spun down again at 3000 r.p.m. for 25 min., and a new residuum was formed. It was washed and taken up in a small amount of saline solution and divided into two equal parts. To one 1 c.c. of saline solution (the control sample), to the other 1 c.c. of a solution of lysolecithin of 1 in 50 was added. After a few minutes both parts were made up to 9 c.c. with saline solution and again centrifuged for 20 min. at 3000 r.p.m. The supernatant fluid was removed and 1 c.c. of lysolecithin 1 in 50 was added to the control and 1 c.c. of saline solution to the other sample. When both solutions were assayed on the arterial blood pressure of a cat, the sample in which the lysolecithin had been allowed to act on the cell debris produced a much stronger rise of pressure than the control solution.

Experiments on rabbits

The intravenous injection of several mg. of lysolecithin caused a steep fall in arterial blood pressure usually resulting in death. The depressor effect was associated with a rise of pressure in the pulmonary artery and was probably mainly due to pulmonary vaso-constriction. A similar injection into the central stump of the coelic artery of an eviscerated rabbit had a strong pressor effect which, when the blood-pressure level was high, was sometimes preceded by a depressor effect (Fig. 9*A*). With repeated arterial injections of the same dose of lysolecithin the pressor effect often varied in degree and usually became

weaker. Removal of the adrenals did not materially change the response. The effects seen in Fig. 9 were obtained after removal of the adrenals. In a few instances the pressor responses were definitely weakened and particularly shortened by the removal of the adrenals, in other experiments this procedure produced no visible change in the response. Lysolecithin, therefore, has either no or only a slight and inconstant secretory action on the adrenal medulla of rabbits, and the

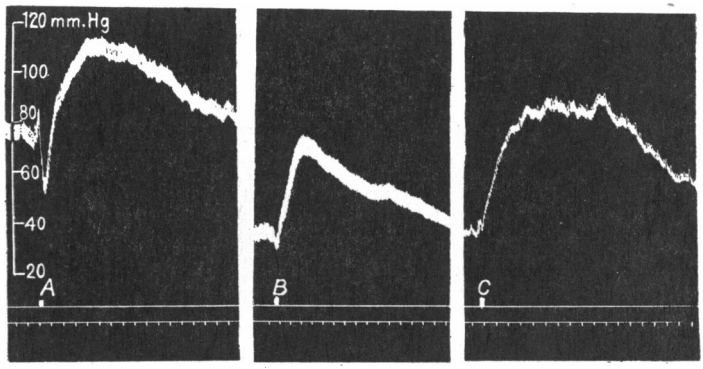

Fig. 9. Arterial blood pressure of a 3 kg. rabbit anaesthetized with chloralose and eviscerated; both adrenals removed; both vagi cut; arterial respiration. Injections into the central stump of the coelic artery (at *A*) of 8 μg., (at *C*) of 15 μg. lysolecithin and (at *B*) of 0·4 μg. histamine dichloride. Time in half minutes.

pressor effect on arterial injection must be attributed mainly to peripheral vaso-constriction. This conclusion was further substantiated by experiments in which injections were made into the iliac artery of one side, the resulting pressor response not being influenced by previous cutting of the femoral and sciatic nerves of the side of injection.

Discussion

We have attributed the long lasting output of adrenaline from the cat's adrenals following the arterial injection of bee venom or cobra venom to formation of lysolecithin in the gland, because these venoms are strong phosphatases and are known to form lysolecithin in the tissues [Feldberg & Kellaway, 1938], and because we could show that lysolecithin causes a long lasting output of adrenaline from the medullary cells. In addition to the formation of lysolecithin, the formation of lysocephalin may contribute to the effects of these venoms on the adrenals.

Recently Rocha e Silva [1939, 1940] has examined the pharmacological effects of crystalline trypsin, and found that they resemble in many details those of cobra venom. He concludes that the effects of this venom may be attributed to its proteolytic character. It is certain that the symptoms of some venoms like that of *Crotalus atrox* may be predominantly the result of a trypsin-like action. In the case of cobra and bee venom, however, the splitting of the lipins appears to be the decisive factor and the proteolytic action of a more secondary nature for the symptomatology. For instance, the action on the perfused guinea-pig's lung of trypsin and of the venom of *Crotalus atrox* are indistinguishable [Rocha e Silva, 1939], whereas the venom of the cobra and the bee lack the trypsin-like effects of digestion of lung tissue. Nevertheless the possibility remains that a proteolytic action may contribute to the adrenaline output produced by cobra venom.

The action of cobra venom, bee venom and lysolecithin on the output of adrenaline differs from that of other active substances such as acetylcholine or histamine in that it may be of extremely long duration. That is accounted for by the fact that lysolecithin damages the cells. The prolonged output may be regarded as the response of the medullary cells to injury, in this instance to a lytic form of injury. At the later stages of this injury the cells cease to secrete and become irresponsive to renewed stimulation either by its nerve or by lysolecithin. The injury, however, is not such as to produce changes in the medullary cells visible on histological examination.

Our results further suggest that the adrenaline is directly freed by the lytic action without an intermediate stage of liberation of histamine as the secretory stimulus. This conclusion is based upon the results obtained by the action of lysolecithin on suspended cellular material of the adrenals, upon the relative insensitivity of the cat's adrenals to histamine, and upon the absence of histamine in the venous perfusate obtained from the perfused adrenal of the cat after lysolecithin. The experiments on the adrenals of the rabbit, on the other hand, were not conclusive. The indication of an output of adrenaline by lysolecithin in this species, the adrenals of which are insensitive to histamine also, is contrary to the assumption of histamine as an intermediary. The output of adrenaline, however, is not certain, and if present at all it is weak and irregular.

In comparing the release of adrenaline from the adrenals with the release of histamine from other tissues, we have to take into account the fact that the adrenaline is released into the circulation, the histamine

into the tissue spaces. Evidence for the release of adrenaline by lysolecithin under physiological conditions, therefore, is more readily obtained than the release of histamine.

The circulatory effects of lysolecithin have hitherto only been described for cats and dogs. Our experiments on rabbits suggest that the depressor effect in this animal is mainly the result of vaso-constriction in the lungs. Lysolecithin, however, has some vaso-dilator action in the systemic circulation as shown by the depressor effect preceding the strong pressor response on its injection into the abdominal aorta. The fact that lysolecithin has a weak vaso-dilator and a strong vaso-constrictor action in the systemic circulation of the rabbit agrees with what is known about the vascular effects of cobra venom in this species.

Summary

1. *In cats* bee venom and cobra venom cause a long lasting output of adrenaline from the adrenals if injected into the central stump of the coelic artery after evisceration. The effect has been attributed to formation of lysolecithin in the adrenals since the venoms are strong phosphatases forming lysolecithin in the tissues, and since lysolecithin was found to cause an output of adrenaline similar to that produced by the venoms. The output of adrenaline was associated with a diminution of adrenaline in the adrenals. After repeated large doses of venom or of lysolecithin, the medullary cells became irresponsive to these or to other secretory stimuli.

2. The effect of lysolecithin has been studied on the isolated cat's adrenal perfused with Locke solution. Lysolecithin caused an output of adrenaline which lasted sometimes for more than 2 hr. and amounted to more than 0·1 mg. The long lasting output is regarded as a response of the medullary cells to injury, and has been contrasted with the strong but evanescent output produced by acetylcholine or by nerve stimulation.

3. Lysolecithin causes a release of adrenaline in *in vitro* experiments from a suspension of ground-up cellular material of the cat's adrenal.

4. *In rabbits* lysolecithin has either no or only a slight and inconstant secretory action on the adrenal medulla. Its intravenous injection causes a fall of arterial blood pressure associated with a rise of pressure in the pulmonary artery. Its injection into the abdominal aorta causes, even after removal of both adrenals, a rise in arterial blood pressure (peripheral vaso-constriction), sometimes preceded by a depressor effect (peripheral vaso-dilatation).

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