RESERPINE AND VASCULAR TONE*

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THE DISTRIBUTION OF NORADRENALINE

The task which I have set before me in preparing this lecture is an ambitious one, for it is no less than to suggest that there is a factor playing a part in the control of vascular tone which has hitherto been neglected. The view I shall put forward is based on work which has been done jointly with my colleague Dr. Michael J. Rand (Burn and Rand, 1958, a, b). I may begin by pointing out that in 1946 an important discovery was made, when v. Euler described the presence in sympathetic nerves of a chemical substance related in structure to adrenaline, but differing from it in not having a -CH, group attached to the nitrogen atom, so that it was called noradrenaline. v. Euler suggested that this was the humoral transmitter of the impulses passing down the sympathetic nerves, the impulse becoming effective by the liberation of some noradrenaline.

However, in 1948, Schmiterlöw first showed that noradrenaline had a wider distribution. He found that noradrenaline was present in the walls of arteries and veins also, being particularly abundant in the outer part of the wall where the nerves entered. In 1951 v. Euler and Purkhold estimated the amounts present in other organs, such as the spleen, the kidney, the liver and the salivary glands of the sheep, and in the same year Goodall estimated the amount in the heart. Noradrenaline was present in all these organs. Both v. Euler and Purkhold on the one hand and Goodall on the other studied the effect of removing the sympathetic fibres, and they observed that after a week or two the amount of noradrenaline in the organs was very much less.

However, from that time until now there has been no indication of the function of noradrenaline present in these organs, and most workers appear to have regarded it as an inert store.

ACTION OF NICOTINE ON THE HEART

Our own approach to this problem has been largely accidental, depending chiefly on our interest in the action of nicotine. We are pharmacologists studying the effect of drugs, and it is proper that we should always be interested in a substance which is probably the most widely used drug of all. I will describe first some observations on the heart.

We have made many studies in the Oxford laboratory, not on the heart itself, but on the auricles or atria, which are easily dissected from the heart when this is removed from a rabbit. They can be suspended in a bath so that their contractions are recorded by a lever writing on a drum. In 1953 I asked my colleague Kottegoda to study the action of nicotine in this preparation. Now nicotine is known to be a substance which stimulates ganglia, so that the ganglion cells send impulses along their fibres. In the rabbit atria there are ganglion cells around which the fibres of the vagus nerves terminate, and the ganglion cells transmit the vagal impulses to the atrial tissue. We therefore expected that when nicotine was added to the bath in which the atria were suspended, the contractions would become slower or they would stop altogether. Adding nicotine would be like stimulating the vagus.

Actually, however, little inhibitory effect was seen, and we were surprised to find that it was overcome by a stimulant effect which became more evident when the nicotine had been in the bath for 1–2 minutes. By adding some atropine, and thus excluding inhibition, the stimulant phase of the nicotine action was seen quite clearly. There was no possibility in 1953 of analyzing this stimulant action further. It was obviously an

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action like that of adrenaline, and since we knew from Goodall’s work that some noradrenaline and adrenaline were present in the heart, we supposed that perhaps nicotine released these substances from whatever structures in which they were held. However, we could not test this idea.

**The Action of Reserpine**

Much interest has been taken in the last five years in an alkaloid reserpine which was isolated from *Rauwolfia*. It has a tranquillizing action in man, and in addition a hypotensive action. It is used chiefly in mental hospitals, but it has to be used with care because it may produce not only tranquillity but also depression, and even melancholy. When it was found to deplete certain regions of the brain of hydroxytryptamine, its tranquillizing action was ascribed to the loss of this substance. However, in 1956, it was found to deplete the adrenal glands of adrenaline and noradrenaline, and later it was shown to deplete the brain of these substances also, so that its tranquillizing action might as well be explained by this action.

In the same year, 1956, Bertler, Carlsson and Rosengren made the observation that when reserpine was given to rabbits it caused the noradrenaline and the adrenaline present in the heart to disappear. Whereas the hearts of normal rabbits contained a mean amount of 1.57 µg/g reckoned as noradrenaline, the hearts from rabbits treated with reserpine and killed 16 hours later contained only 0.03 µg/g. We therefore examined the atria from rabbits injected with reserpine, and found that the stimulant action of nicotine was completely absent. This observation confirmed the view that the stimulant action was due to the liberation of noradrenaline and adrenaline from the stores in the heart.

**Normal Action of the Noradrenaline Store**

In the course of our observations we found that the rate at which the atria contracted when suspended in the isolated organ bath at 30°C differed according to their origin. Atria from normal rabbits contracted more quickly, the mean rate for nine atria being 146 per minute, while atria from rabbits treated with reserpine and killed 16 hours later contained only 0.03 µg/g. We therefore examined the atria from rabbits injected with reserpine, and found that the stimulant action of nicotine was completely absent. This observation confirmed the view that the stimulant action was due to the liberation of noradrenaline and adrenaline from the stores in the heart.

**Effect of Reserpine on the Vessels**

In view of the results on the atria of rabbits treated with reserpine, we therefore studied the action of nicotine on the perfused ears of rabbits treated with reserpine. We found that in these ears nicotine had no constrictor action. We therefore extracted the skin of rabbit ears to see if we could detect the presence of noradrenaline, and we found that in extracts of the skin of normal rabbits contained a mean amount of 1.57 µg/g reckoned as noradrenaline, the hearts from rabbits treated with reserpine and killed 16 hours later contained only 0.03 µg/g. We therefore examined the atria from rabbits injected with reserpine, and found that the stimulant action of nicotine was completely absent. This observation confirmed the view that the stimulant action was due to the liberation of noradrenaline and adrenaline from the stores in the heart.

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rabbits there was a substance behaving like noradrenaline. We detected its presence by injecting the extract intravenously into rats and observing the rise of blood pressure. However, in the skin of the ears of rabbits injected with reserpine no such substance was present, for the extracts had no pressor activity. The mean amount present in the skin of normal rabbit ears was 0.1 μg/g.

Now Adams-Ray and Nordenstam (1956) have found chromaffin cells in human skin, which are cells containing adrenaline in granules which take certain stains. We therefore wondered if chromaffin cells were present in the skin of rabbit ears. Mr. E. H. Leach, of the University Department of Physiology, very kindly examined the ears of two normal rabbits and of two rabbits treated with reserpine. He found chromaffin cells in the normal rabbit ears adjoining the blood vessels; but they were absent from the ears of rabbits treated with reserpine. It therefore seemed possible that the constrictor action of nicotine in normal ears was due to nicotine releasing adrenaline from chromaffin cells.

We remembered, however, that Schmiterlow (1948) had observed the presence of noradrenaline in artery walls, and we therefore extracted the aortae of a series of rabbits, some normal and some treated with reserpine. We found by testing the extracts on the rat blood pressure that the normal aortae contained a mean amount of 0.5 μg/g of material estimated as noradrenaline, while the aortae from reserpine-treated rabbits contained less than one-fifth of this.

ACTION OF NICOTINE ON THE VASCULAR SYSTEM

We have known for a long time that smoking accelerated the heart rate and that it caused peripheral vasoconstriction, but we have supposed that this was an effect of nicotine on sympathetic ganglia. We now see that it is probably also an effect of nicotine on the store of noradrenaline and adrenaline in the heart and in or near the blood vessels. This makes it easier to understand the drop in skin temperature which Roth, McDonald and Sheard (1944) have recorded during smoking, and the great fall in blood flow through the hand.

There appears to be general agreement that the relation of smoking to thromboangiitis obliterans is well established. Wright (1955) states that the disease will rarely become or remain quiescent, and that gangrene and ulcers will continue indolent or progress adversely, so long as the patient continues to smoke even occasionally. Furthermore, even after the lesions have healed and the disease has remained quiescent for months, or even years, while the patient has not smoked, the renewal of the use of tobacco will almost invariably be followed within a few weeks or months by reactivation of the disease. This situation can be understood more easily if nicotine causes excessive vasoconstriction by releasing adrenaline or noradrenaline either from the artery wall or from chromaffin cells adjoining it.

OTHER SUBSTANCES RELEASING NORADRENALINE

If I may be forgiven for saying something on what may seem a purely academic pharmacological topic, I will add that we have found other substances besides nicotine which release noradrenaline from the store in the artery walls. Carlsson and his colleagues (1957) observed that in cats treated with reserpine, the amine tyramine did not cause a rise of blood pressure. Tyramine is almost the simplest substance possessing the skeleton of adrenaline, and from the time it was first examined by Dale and Dixon (1909) it has been thought of as a substance acting like adrenaline but in a feeble fashion. Carlsson and his colleagues did not discuss their observation except that they said it is known that for the normal action of tyramine the adrenergic nervous system must be intact.

Since we had discovered that in the reserpine-treated cat the store of noradrenaline disappeared from the artery walls, we were at once led to suppose that the tyramine failed to cause its rise of blood pressure, because its normal method of causing a rise was by releasing noradrenaline from the store, and that tyramine was a substance which might be called an adrenaline liberator rather than a substance which acted like adrenaline.

Other differences between adrenaline and tyramine were recorded many years ago. Fröhlich and Loewi (1910) showed that cocaine increased the action of adrenaline, but Tainter and Chang (1927) showed that cocaine abolished the action of tyramine. Again when tissues were denervated by cutting the sympathetic supply, the effect of
adrenaline was increased, but the effect of tyramine and of ephedrine was abolished (Burn and Tainter, 1931; Burn, 1932). Hence previous work supplied some justification for the view that the difference between adrenaline and tyramine was not merely a quantitative difference, but that it was a difference in kind.

In confirmation of Carlsson and his colleagues we observed that in the spinal preparation of a cat previously given reserpine, tyramine had only a slight pressor action and that it did not cause contraction of the nictitating membrane. At the same time the pressor action of noradrenaline was much greater than normal, as was shown by Bein, Gross, Meier and Tripod (1953). Evidence in favour of the view that the pressor action of tyramine was due to the lack of noradrenaline in the artery wall was that when an infusion of 1 mg noradrenaline was given during a period of about 15 minutes, and when the effect of this infusion on the blood pressure had subsided, the injection of tyramine was followed by a much greater pressor effect. It appeared as if the noradrenaline circulating in the blood had partly refilled the store in the artery wall. It was of interest to me that I had made the same observation in 1932 in experiments on the perfused hind leg of the dog. I then found that, in the perfused leg, tyramine had much less constrictor action compared with adrenaline than was to be expected from its pressor action in the spinal cat, but that when adrenaline was slowly infused into the blood, the constrictor action of tyramine increased. Not only was the effect of tyramine increased, but the effect of sympathetic stimulation was also increased, and this too we have recently confirmed.

Our results have then led us to the view that the sympathomimetic amines can be divided into two classes: those which act directly on the vessels, and those which liberate adrenaline, or more probably noradrenaline, from the vessel walls. The vessels of reserpine-treated animals are highly sensitive to the substances which act directly, which include noradrenaline, adrenaline and dopamine, and they exert a given pressor effect in much smaller doses than in normal animals. The vessels and the nictitating membranes of reserpine-treated animals are, however, insensitive to the action of substances like tyramine, phenylethylamine, amphetamine, ephedrine and the D form of phenylethanolamine. Their action in the reserpine-treated animal is restored by an intravenous infusion of noradrenaline, but not, I may point out, by an intravenous infusion of hydroxytryptamine. We therefore think that these substances exert their normal action on the vessels and the nictitating membrane by liberating noradrenaline.

**INTRAVENOUS DRIP OF NORADRENALINE**

Returning now to more practical considerations which are of interest to others than pharmacologists, I think that our results throw light on a phenomenon which has puzzled surgeons and particularly anaesthetists. Since the introduction of noradrenaline, the practice has increased of using an intravenous drip to maintain the blood pressure in circumstances in which it has fallen low. This is not an easy method of maintaining the blood pressure because fluctuations in the speed of the drip cause large variations in the blood pressure. The chief disadvantage, however, is that when the drip is finally stopped, the blood pressure very often falls abruptly, and the patient's condition is only restored when the drip is started again. There are a good many cases on record of the drip having to be continued for two or three days, and I have heard of it being continued for much longer periods. The fall of blood pressure on stopping the drip has also been observed in rabbits by Blacket, Pickering and Wilson (1950).

The problem is to know what has happened to the normal sympathetic tone, which seems to be strangely deficient as a result of the continued infusion of noradrenaline. One cause of the deficiency may be ganglionic block, for in 1939 Marazzi observed that adrenaline depressed the transmission of impulses through a sympathetic ganglion, and his observations were confirmed by Bülbbring and Burn in 1941. A second cause which seems perhaps more important is the effect of the noradrenaline infusion on the response of the vessel wall to sympathetic impulses. We have seen that in the cat or dog treated with reserpine, not only is the pressor effect of tyramine very feeble, but the pressor effect of noradrenaline is unusually great. These changes appear to depend on the disappearance of the store of noradrenaline in the vessel wall. When, however, an intravenous
infusion of noradrenaline is given during a period of 15 or 20 minutes, which results in a building up of the store in the vessel wall at the end of this time, then when the effect of the intravenous infusion on the blood pressure has passed off, the pressor effect of noradrenaline is very small. The same diminution in sensitivity to noradrenaline occurs in a normal animal when an intravenous infusion of noradrenaline is given. From these observations it appears to follow that the sensitivity of the vessel wall to the action of noradrenaline depends on the size of the store of noradrenaline present in the wall. Now since the sympathetic nerves act by liberating noradrenaline we may say that the sensitivity of the vessel wall to sympathetic impulses depends on the size of the store of noradrenaline present in the wall. Thus when the store is large, as after the intravenous infusion of noradrenaline, the sensitivity of the vessel wall to sympathetic impulses is very low, and it is for this reason that the abrupt fall of blood pressure occurs when the intravenous drip of noradrenaline is stopped.

This account may perhaps seem like special pleading which may have some relation to the true state of affairs or not. But it is more than that, for a practical suggestion emerges from it. The suggestion is that when the blood pressure of a patient has been maintained for some time by an intravenous drip of noradrenaline, and when there has been an alarming fall of blood pressure on stopping the drip, the correct procedure then is not to restart the drip, but to give an injection of ephedrine which causes a discharge of noradrenaline from the store in the vessel walls.

Ephedrine as we have seen acts like tyramine and phenylethylamine as an adrenaline liberator, and its effect is greatest when the store in the vessels is greatest. But ephedrine is more suited for injection in these circumstances than tyramine or phenylethylamine for these two substances are soon destroyed by amine oxidase. Ephedrine, however, having a methyl group on the \( x \)-carbon atom, cannot be destroyed by amine oxidase, and therefore goes on acting for a much longer time. It is, of course, always risky to assume that what happens in the cat or the dog will also happen in man, but the assumption in this case seems to me justifiable.

**Peripheral Vascular Diseases**

I may now turn to a different subject, that of peripheral vascular disease, for it will be clear that the store of noradrenaline in the vessel wall may be a contributory or even a causal factor here. We have found that there is a steady leak from the store in the heart, since the rate of isolated atria is much slower when the store is no longer there, and it is therefore likely that there is a leak from the store in the vessels. Hitherto no one has determined what happens to the store in the vessels when the nerve supply degenerates, but v. Euler and Purkhold made observations in the spleen, the liver, the kidneys and the salivary glands, and in all these tissues the store of noradrenaline declined to a small fraction of its original value.

We can readily suppose that the cold blue fingers of those with Raynaud’s disease, and the symptoms of Buerger’s disease, are due to a leak of noradrenaline from the store in the artery wall which is greater than the leak in ordinary individuals. If this is so, some relief of the symptoms should be obtained by the use of reserpine which will disperse the store in the walls. Scalfi, Jacono and Juliani (1956) have indeed given reserpine to thirteen cases of arterial disease, recording vasodilatation in the fingers by photoplethysmography. They found that when 1 mg reserpine was injected intramuscularly there was prolonged vasodilatation in eight of the cases. Three were cases of Raynaud’s disease and dilatation occurred in two; in the other case of this disease lesions of scleroderma were present. These authors did not explain why they had tried reserpine, and they did not use reserpine for treatment.

Patients with Raynaud’s disease are usually benefited by sympathectomy for a period of several months, but often at the end of a year they are no longer improved. The early benefit from sympathectomy is probably due to a fall in the store of noradrenaline in the artery wall, though this has not yet been directly observed. It may, however, be inferred, provisionally at least, since, as already described, a fall has been shown to occur in other organs, like the spleen, after sympathetic denervation. The later deterioration and return of the symptoms may perhaps be explained by the vessels picking up noradrenaline from the amount circulating in the blood, secreted...
into the blood from the adrenal glands. Thus the store may be replenished although the vessel is denervated.

From these considerations it is clear that reserpine may prove a satisfactory treatment for peripheral vascular disease in some patients at least. But reserpine has central effects producing depression. The usefulness of reserpine for any given patient will probably depend on whether the peripheral effect on the vessels can be obtained without producing central effects which are too severe.

RESERPINE IN THE TREATMENT OF HYPERTENSION

Apart from peripheral vascular disease there is the question of its action in hypertension, and here I will refer to the interesting observation made by Harington (1956) that some three or four hours after an intravenous injection of 3 mg reserpine the effect of an injection of hexamethonium was greatly increased. He observed this in six patients.

The effect of reserpine on vascular tone is not simple. As Bein (1955) has shown, it diminishes the stream of impulses from the sympathetic centres. In addition it removes the store of noradrenaline from the artery walls and in doing so makes them more responsive to such impulses as still arrive. Thus the fall of blood pressure due to the diminution in the central outflow is less than it would be. In other words, under the influence of reserpine the blood pressure falls, but not greatly, because the fewer impulses act on a more sensitive vascular bed containing less noradrenaline. The blood pressure may, however, be more dependent on sympathetic impulses and less on the noradrenaline leaking from the store in the artery wall. When hexamethonium is given, the fall of blood pressure is greater because of the removal of the central impulses which after giving reserpine are the only controlling factor.

In conclusion it may be said that reserpine is proving a most valuable tool for analyzing the factors which control vascular tone. We have learnt that the store controls the sensitivity of the organ to noradrenaline reaching it via the sympathetic nerves or via the blood stream. We have learnt that the store can be replenished from the blood stream. Finally we have some pointers to the better treatment of peripheral vascular disease and perhaps of hypertension itself.

Our own connexion with these developments has come from what might be called idle interest in an obscure and apparently academic pharmacological problem. Sometimes such an interest seems to justify itself.

REFERENCES


