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ANALEPTICS AND SYMPATHOMIMETIC SUBSTANCES*

BY

J. H. BURN, M.D.

Professor of Pharmacology, University of Oxford

The substances that are used to restore a failing circulation can be divided into two classes, which, however, are not completely distinct, for some substances belong to both. The one class contains picrotoxin and strychnine among the non-proprietary substances, and cardiazol and coramine among the proprietary substances; these can all be used as medullary stimulants. The second class contains ephedrine and tyramine among the non-proprietary substances, and sympatol, veritol, and suprifren among the proprietary substances; these are used for their direct action on the heart and on the blood-vessels. Intermediate between these classes are substances like benzedrine which have both types of action.

On the whole medical practice in this country has confined itself to use of the first class. The custom of giving strychnine every four hours to persons dying of pneumonia is still prevalent, though not everyone who gives it has a good scientific argument ready to justify his action. There is one, however; for although strychnine has no action on the heart directly, it can stimulate the vasomotor centre in the medulla and cause a rise of blood pressure, which will in turn give a better coronary flow. It may be remarked how many there are who forget that the chief danger of a low blood pressure is in the diminution of the coronary flow, and that the higher the blood pressure the better the supply of oxygen to the heart becomes. Cardiazol, like strychnine and picrotoxin, has no direct action on the heart, and, this being so, we may ask how far it is justifiable to give it a name which suggests that it has. Coramine in very large doses does dilate the coronary vessels but without increasing the output, as Stoland and Ginsberg (1937) have shown; the main effect of coramine, however, is on the brain and medulla, and here again, in suggesting an important effect on the heart, the name is misleading. There are at least two reasons for reserving judgment on the efficacy of substances belonging to this first class: one is the difficulty of demonstrating their action on the blood pressure in animals; the second is the lack of evidence that low blood pressure is ever due to medullary failure. The vasomotor centre is not like the respiratory centre: when the medulla is destroyed respiration stops altogether; it does not continue at a slower rate, so that we have no difficulty in believing in the existence of a centre which controls the respiration. The blood pressure, however, does not fall abruptly; in the cat it is often maintained for several hours; there are undoubtedly centres in the spinal cord which play a part in maintaining the blood pressure as well as the vasomotor centre in the medulla.

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Carotid Sinus Reflex

Experimental evidence of the action of these substances has been obtained by my colleague Dr. M. Chakravarti, who has investigated the changes in the carotid sinus reflex. When both carotid arteries are clamped there is a fall of blood pressure in the carotid sinus beyond the clamp; impulses then pass from the carotid sinus to the vasomotor centre (or centres) and a reflex discharge of impulses from the centre causes vasoconstriction and a rise of blood pressure.

Chakravarti began by using decerebrate cats to exclude the influence of the anaesthetic, but he found that in these the carotid sinus reflex was almost unaffected; having learnt that Müller (1938) had obtained positive results in rabbits under urethane anaesthesia, he then made experiments on rabbits and also on decerebrate cats after giving nembuto to produce medullary depression and to diminish the size of the reflex. When picrotoxin, coramine, strychnine, or cardiazol was injected Chakravarti obtained an increase in the carotid sinus reflex, and in one or two experiments after injecting ephedrine also, though for the most part ephedrine had no effect. The following table shows the dosage of these substances which had equivalent effects and which increased the carotid sinus reflex by 15 to 20 mm. It also shows the maximum doses of these substances used in human therapy, as well as the ratio of this dose to the dose necessary to increase the carotid sinus reflex in the cat or rabbit.

Substance	Dose Increasing Carotid Sinus Reflex by 15 to 20 mm. (A)	Maximum Therapeutic Dose (B)	Ratio B/A
Picrotoxin ..	3 mg.	8 mg.	2.6
Coramine ..	0.2 gm.	0.5 gm.	2.5
Strychnine ..	1 mg.	2 mg.	2.0
Cardiazol ..	0.1 gm.	0.1 gm.	1.0

The figures in the table indicate the order of efficiency of the different substances, but the differences in the ratios given in the fourth column are small, and no great importance can be attached to them; it is impossible to make reliable comparisons of potency in animals of the size of cats and rabbits, because a sufficient number cannot be used.

From the results it can be concluded that these substances certainly do have an action on the vasomotor centre, or at least on some part of the central mechanism which controls the blood pressure. On the other hand, the amounts which must be given to a rabbit or a cat to

demonstrate this action are very large, being from 40 to 50 per cent. of the human therapeutic dose, so that in man this action can scarcely be exerted.

The Awakening Action

While it is not easy to make a quantitative comparison of the action of substances like picrotoxin, cardiazol, coramine, and strychnine on the medullary centres controlling the blood pressure, it is easy to compare their potency in other directions. Mice which are narcotized by the administration of a barbiturate such as nembutal can be aroused by the injection of these substances, and the awakening power can be estimated. Chakravarti injected groups of mice intravenously with nembutal, using a dose which kept 100 per cent. narcotized for two hours. He injected the awakening agent twenty minutes later, for he found that the respiratory rate was lowest in the largest percentage at this time. His doses were stated in terms of the average lethal dose; that is to say, he determined the awakening effect of one-half, one-quarter, and one-eighth of the average lethal dose of each substance, and by plotting the results graphically was able to estimate the dose of each substance which would awaken 50 per cent. of the mice within one hour. This he called the awakening dose, and was able to compare it with the lethal dose, and so to get a value for the relative awakening power for each substance. The values for cardiazol, picrotoxin, strychnine, and coramine were 5.6, 5.0, 4.2, and 2.9, respectively; that is to say, the dose of cardiazol killing 50 per cent. of mice was 5.6 times as great as the dose required to awaken within one hour 50 per cent. of mice narcotized with nembutal. For benzedrine the ratio was as high as 12.9, and for ephedrine as low as 2.2.

A comparison made in this way suggests that there are important differences between the various compounds in their power to arouse from mild narcosis produced by barbiturates. A different picture is, however, obtained when the awakening dose, determined in mice as described, and expressed in mg. per kg., is compared with the maximum human therapeutic dose in mg. The ratio of the human dose to the awakening dose is then approximately the same for picrotoxin, cardiazol, strychnine, and coramine, being 8.0, 6.9, 6.6, and 6.7, respectively; for benzedrine it is lower, being 2.5, and for ephedrine it is 0.2. These results indicate that there is little difference between the four medullary stimulants, but that all four are better than either benzedrine or ephedrine.

Barbiturate Poisoning

Of more practical importance were Chakravarti's observations on the effect of giving to groups of mice a dose of the barbiturate nembutal, which by itself would kill 80 per cent., and combining with this a dose of the stimulant substance. Tested by this method, picrotoxin and cardiazol stood out as far superior to all the others, and the antagonism between these substances and the barbiturate was clearly revealed. When one average lethal dose of picrotoxin was injected the mortality was reduced to 38 per cent., and when twice this amount was given the mortality was reduced to 6 per cent. Similarly with cardiazol; the administration of one average lethal dose reduced the mortality to 13 per cent., and of twice this amount to 7 per cent. With the other substances no such antagonism was observed; the mortality due to the nembutal was unchanged by one or two average lethal doses of strychnine; after giving benzedrine, coramine, or ephedrine the mortality increased to 100 per cent.,

whether one or two average lethal doses were given. Here we have an indication that, in barbiturate poisoning, picrotoxin and cardiazol are the substances with much the greatest effect, and should be used exclusively.

Convulsive Action

Recently cardiazol has been much used in the treatment of schizophrenia. Convulsions are, however, produced by all these substances, even by ephedrine, and a simple method of demonstrating this is by intravenous injection into pigeons; some substances cause vomiting in addition. Picrotoxin, cardiazol, and ephedrine cause both vomiting and convulsions, while strychnine, coramine, and benzedrine cause convulsions only. There appears, therefore, to be a closer similarity in the central actions of picrotoxin, cardiazol, and ephedrine than in that of the others. Since ephedrine exerts its central action in large doses only—for example, 30 to 40 mg. for a pigeon—its use as a convulsant in human therapy is excluded. Between picrotoxin and cardiazol there seems to be no important difference; picrotoxin is approximately thirty times stronger, and could very well be used instead of cardiazol.

Action on the Respiration

Chakravarti has also compared these substances for their effect in stimulating respiration. He attempted to do this first in decerebrate cats in which the respiratory rate was reduced by repeated injections of nembutal. These substances produced a rise in respiratory rate, but he found again that a quantitative comparison could not be made in these animals. In mice narcotized with nembutal, however, he was more successful. He determined the mean respiratory rate in groups of twenty-five to thirty mice, and obtained results which show that cardiazol is much more potent than strychnine, coramine, and picrotoxin. These three do not greatly differ from one another, but all are less than half as active as cardiazol when doses of equal toxicity are given. On the other hand, ephedrine and benzedrine are both much more active than cardiazol. When these three substances are compared in terms of the average lethal dose, then the stimulant action on the respiration of one-half the average lethal dose of cardiazol is similar to that of 1/64 of the average lethal dose of benzedrine and to that of 1/256 of the average lethal dose of ephedrine.

In summarizing the experimental observations on the four medullary stimulants it is difficult to avoid disappointment. None of them can be shown to have any valuable action on the vasomotor system. Cardiazol appears to be the best respiratory stimulant, but otherwise it is not better than picrotoxin. For use in schizophrenia, when a convulsant action is desired, or for recovering those who are dying from barbiturate poisoning, picrotoxin is at least as good as cardiazol, and certainly cheaper.

Restoration of the Blood Pressure

That medullary stimulants have little value in circulatory failure is not very surprising, since there is little evidence that the low blood pressure is due to failure of medullary control. The low blood pressure is more likely to be due either to the liberation from damaged tissue into the blood stream of substances which increase the permeability of the capillaries, or perhaps to the failure of the vasoconstrictor impulses to exert their usual effect when the supply of cortical hormone is exhausted.

Most other forms of circulatory failure are due essentially to failure of the heart muscle, and it is probably

more rational to use therapeutic agents which directly stimulate the heart, such as ephedrine and the other sympathomimetic substances, than to employ medullary stimulants. In this country the use of these sympathomimetic substances has been small, apparently because it is little known. If a sudden fall of blood pressure occurs during spinal anaesthesia as shown by disappearance of the pulse in the temporal arteries, ephedrine is injected intramuscularly in a dose of 30 to 60 mg. But apart from its employment by anaesthetists, ephedrine is not much used to restore a failing circulation. In Germany, as a result of the efforts of the late Paul Trendelenburg, sympatol was introduced. This is the same as synephrine; it differs from adrenaline in having only one -OH group in the ring; the side-chain is the same. Its effect is qualitatively like that of adrenaline, but its vascular action is much less intense, though more prolonged. It is stated to have the advantage over ephedrine of producing no toxic effects. Gremels (1936) points out that it has the great advantage over adrenaline that it causes a much smaller increase in the oxygen consumption of the heart. He has shown that if the pressure in the left auricle is recorded, and large doses of adrenaline are given repeatedly, the rise of auricular pressure produced by adrenaline becomes steadily bigger, indicating an increasing degree of failure of the left ventricle. He considers that this failure is due to a partial asphyxiation of the heart muscle owing to the enormous increase in the oxygen consumption which adrenaline causes. If now sympatol is injected in doses which cause the same pressor response as the adrenaline, then after two or three doses the rise in left auricular pressure becomes much less, and the signs of heart failure disappear. Thus Gremels finds that sympatol actually repairs the damage done to the heart by adrenaline.

Sympatol has been much used in the treatment of incipient heart failure in pneumonia. It can be given by subcutaneous injection every half-hour, and appears to be a far more satisfactory and logical treatment than is the repeated injection of strychnine. In action sympatol has much less vasoconstrictor effect than adrenaline in relation to its power to improve the force of the heart-beat.

Other substances having a similar action are suprifren and veritol, and perhaps tyramine. The relative advantages of all these substances, including ephedrine and sympatol, are not easy to assess, and whatever differences are found experimentally the substances are, I think, all worth careful clinical trial in circulatory failure where the heart is becoming exhausted. They do not seem to have had such a trial in this country yet, in spite of the great probability that they are more effective than substances acting on the medulla.

Action of Sympathomimetic Agents

In a lecture delivered here not long ago Gaddum (1938) put forward a hypothesis concerning the action of ephedrine which I believe can also be used to explain the action of other sympathomimetic substances. Gaddum and Kwiatkowski (1938) observed that low concentrations of ephedrine augment the constrictor action of adrenaline on the blood-vessels of the rabbit's ear, the cat's nictitating membrane, and the frog's heart; further, they observed that ephedrine augments the action of sympathetic nerves on these organs. They attributed these observations to the inhibition by ephedrine of the amine oxidase which destroys adrenaline; Blaschko, Richter, and Schlossmann (1937) have shown that *in vitro* such an inhibition occurs. Thus the augmentation of the action of adrenaline was due to a slower rate of destruction of adrenaline or of the

humoral transmitter liberated by the sympathetic nerves; Gaddum compared this augmentor action of ephedrine to that of eserine on the response to acetylcholine.

I have previously made observations not only on ephedrine but also on tyramine, and since there were many points of resemblance in the action of the two substances and in the relation of each to the action of adrenaline, it occurred to me that probably many of the effects of tyramine could also be explained in the way Gaddum has explained the action of ephedrine. Tainter and I (Burn and Tainter, 1931) observed that after removal of the superior cervical ganglion and degeneration of the post-ganglionic fibres, the pupil of the cat's eye no longer dilates when large doses of tyramine are injected, and is only very slightly affected by large doses of ephedrine, although of course the denervated pupil responds to much smaller doses of adrenaline than the normal. Gaddum supposed that the action of ephedrine on the normally innervated pupil must depend on the slowing down of the rate of destruction of the humoral transmitter released from the nerve endings; when the nerves degenerated and no more humoral transmitter was liberated ephedrine ceased to act. I thought that the same explanation would apply to tyramine, though with this difference. Tyramine does not inhibit the action of amine oxidase as ephedrine does; but since tyramine is destroyed by the oxidase it is clear that when tyramine and adrenaline are both present the rate at which the enzyme can destroy adrenaline is diminished because some of the molecules of enzyme are engaged in destroying tyramine. This interference with the destruction of one substance by another is called substrate competition, because the two substrates are supposed to compete for the enzyme.

My colleague Dr. Edith Bülbring has made some observations which support this view. She has demonstrated that the constrictor effect of adrenaline becomes greater after the addition to the blood of a certain amount of tyramine. Working also on the cat in which the brain has been destroyed, after exclusion of the suprarenal glands she has found that the contractions of the nictitating membrane caused by doses of 5 μ g. and 10 μ g. adrenaline were increased by infusing a 1 in 10,000 solution of tyramine. Similar observations were made when the cervical sympathetic chain was stimulated.

A third observation was made on the spleen volume of the cat, which was recorded under urethane-chloralose anaesthesia. Investigations were made into the effect of adrenaline in causing a diminution in the volume when the doses were injected intravenously. Tyramine was then injected in a dose of 0.8 mg., and the injections of adrenaline were repeated. The effect of 0.6 μ g. after the tyramine was greater than that of 1 μ g. before. Dr. Bülbring's work is still in progress, but it indicates from the results obtained already that tyramine augments the action of adrenaline, though not so powerfully as does ephedrine. Tyramine is destroyed by the amine oxidase which destroys adrenaline. When tyramine and adrenaline are both present the oxidase must therefore be partly occupied in destroying tyramine and cannot inactivate the adrenaline as quickly as the absence of tyramine; the effect of adrenaline is therefore augmented.

Action of Cocaine

There has been divergence of view about the peripheral action of cocaine since last century. Limbourg (1892) showed that when dropped into the eye after removal of the superior cervical ganglion it did not cause dilatation of the pupil, whereas if dropped into the normally innervated eye it did. From this observation sprang the

suggestion that cocaine was a sympathomimetic substance. In 1910 Fröhlich and Loewi showed that cocaine augmented the action of adrenaline on the blood pressure and on the pupil, and in 1926 Tainter and Chang showed that it abolished the action of tyramine on the blood pressure. All these observations seemed to connect cocaine somehow or other with the sympathetic system, but it was certainly not clear how. Tainter and I in 1931 stated that we did not think cocaine could be regarded as sympathomimetic, since it had no stimulant action on the isolated heart or on the isolated auricles; further, in doses which inhibited the action of adrenaline it acted as a stimulant of the muscle of the isolated intestine or of the cat's uterus; again, when injected into the arterial cannula taking blood from a pump to the hind leg of a dog cocaine caused vasodilatation.

If we consider the vascular action, we have recently observed that in the perfused vessels of the dog's hind leg, when no adrenaline is present in the blood, the injection of doses such as 1 to 2 mg. cocaine causes a slight vasoconstriction. When larger doses of cocaine are used, and when the tone is maintained by adrenaline, the injection causes vasodilatation, as Tainter and I found. This action, constrictor in small doses and dilator in larger doses, especially when adrenaline is present, is reminiscent of the action of ephedrine. In many experiments ephedrine causes vasodilatation in the same circumstances, and we can explain the action of cocaine as Gaddum has explained that of ephedrine, by supposing that the cocaine has attached itself temporarily to the sympathetic receptors so that the adrenaline molecules are denied access. On the isolated intestine my colleague Macgregor (1939) has confirmed earlier workers that the stimulant action of cocaine in ordinary dosage is replaced by an inhibitory action in larger doses; sometimes this inhibitory effect is seen with ordinary doses. Macgregor found that the same was true for the virgin cat uterus. Hence so far as the blood vessels and smooth muscle are concerned cocaine can be regarded as sympathomimetic; even the stimulant action on the intestine and uterus has a parallel in the stimulant action of tyramine which has been described, and which once led Tainter to describe tyramine as musculotropic. On the pupil, Macgregor has made the interesting discovery that the effect of denervation depends on the mode of administration. After removal of the superior cervical ganglion, and degeneration of the post-ganglionic fibres, instillation of cocaine into the conjunctival sac is not followed by pupil dilatation; if, however, the cocaine is injected intravenously the denervated pupil dilates more than the normal. This result seems to indicate that the absorption of cocaine from the conjunctival sac after degeneration of the post-ganglionic fibres must be very slow. With the exception of the heart, then, other organs respond to cocaine in such a way as to indicate that it is a sympathomimetic substance. If it has any sympathomimetic effect on the heart, this is masked by a toxic action.

Action of Procaine

Macgregor has made the interesting discovery that procaine has a sympathomimetic action which is even less doubtful than that of cocaine, since he was able to observe a stimulant action on cardiac muscle. When the isolated auricles of a cat's heart were suspended in Locke-Ringer solution, the addition of procaine to make a concentration of 1 in 50,000 caused an increase in the amplitude of the contractions.

On the pupil, procaine was found to exert a dilator action when it was injected intravenously. There was no

dilatation when procaine was applied externally. When one pupil was denervated by removal of the superior cervical ganglion, procaine produced a slightly greater dilatation in it than in the normal pupil. In the isolated intestine procaine caused inhibition in those circumstances in which cocaine caused inhibition; in the isolated uterus of the virgin cat the inhibitor effect of procaine was, however, very slight. Procaine has previously been shown to augment the pressor action of adrenaline, and Macgregor has found that it augments the pressor action of tyramine also. In isolated tissues like the uterus procaine abolishes the inhibitor action of adrenaline.

Thus we have in procaine, too, a substance with a sympathomimetic action of its own, and able in some circumstances to augment the action of adrenaline and in others to depress it. To complete the evidence for this interpretation of the action of cocaine and procaine it must be shown that these two substances can inhibit the action of amine oxidase. Mrs. Philpot, working in the Biochemical Laboratory, has recently been able to do this. She has measured the increase in the oxygen uptake of liver extracts due to the addition of tyramine or adrenaline, using the Warburg manometric technique. When cocaine or procaine was added the extra oxygen uptake was inhibited. Thus we can extend the hypothesis put forward by Gaddum to explain the action of ephedrine, not only to the related substance tyramine, but also to two substances the only relation between which is that they are both local anaesthetics. Cocaine and procaine have no chemical similarity, and the similarity of their sympathomimetic action naturally gives rise to the question whether all local anaesthetics are sympathomimetic. Tripod, working in my laboratory, has made a beginning of this study, and has so far observed that stovaine, butyn, and percaine all inhibit intestinal rhythm in the same manner as adrenaline.

Summary

Cardiazol, coramine, picrotoxin, and strychnine are all able to increase the carotid sinus reflex in the rabbit or the cat when the reflex is first depressed by nembutal. Unfortunately the doses necessary are very high, being from 40 to 50 per cent. of the maximum human dose.

Picrotoxin and cardiazol are both of value as antidotes in barbiturate poisoning; the other substances are not.

Picrotoxin should be just as efficient as cardiazol for use in the treatment of schizophrenia.

As a respiratory stimulant in nembutal narcosis in mice benzedrine and ephedrine are most efficient, and then cardiazol. Coramine, strychnine, and picrotoxin are very feeble.

Reasons are given for regarding substances like ephedrine and sympatol as more likely to be of use in circulatory failure than medullary stimulants.

Further observations on the pharmacology of tyramine, cocaine, and procaine are described.

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