# SOME FACTORS WHICH MODIFY THE EPINEPHRINE REACTION

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Oliver and Schafer (1) found that extracts of the suprarenal glands when injected intravenously produced a marked rise in blood pressure. Elliott (2) studied the vascular response to epinephrine in great detail and found that the rise in blood pressure following the injection of epinephrine into an animal with the central nervous system destroyed was, within certain limits, directly proportional to the amount injected. Investigations carried out by numerous workers demonstrated that the seat of action of epinephrine was chiefly, at any rate, the nerve endings of the sympathetic system, and that the effect of epinephrine was synonymous with stimulation of the sympathetic nerve supply. The point of action of epinephine was therefore considered to be entirely peripheral. The effect of stimulation of the sympathetic nerve supply to any structure being known, the effect of epinephrine on any organ could be correctly predicted.

That epinephine, in addition to its well defined peripheral action, has a central action as well was suggested by the experiments of S. J. Meltzer and C. Meltzer (3). They found that the intravenous injection of epinephrine caused definite vasoconstriction in the vessels of a rabbit's ear, but this constriction was followed immediately by dilation exceeding that which existed before the injection. Langley (4) obtained similar results in the case of the submaxillary gland while Lewandowsky (5) found that the rise in systemic blood pressure in cats following the administration of epinephrine was frequently followed by a fall below the original level.

Moore and Purinton (6) first demonstrated that the vascular response to very minute amounts of epinephrine was a definite fall in blood pressure, and this observation has been frequently confirmed by various workers in recent years.

Dale found that the pressor response to a moderately strong dose of epinephrine was converted into a pure depressor effect if ergotoxin were administered between the epinephrine injections. He concluded that there are two sets of vasomotor fibres in the sympathetic—constrictors and dilators—the effect of ergotoxin being paralysis of the vaso-constrictor nerve ending. Epinephrine administration after ergotoxin caused a pure fall due to peripheral action on the vaso-dilator nerve endings.

Hoskins and McClure (8), working with pure "adrenalin" confirmed the earlier results of Moore and Purinton. They concluded that, as the effect of small doses of adrenalin was to cause a fall in blood pressure, the suprarenals do not ordinarily produce sufficient secretion to maintain any pressor influence.

Cannon and Lyman (9) found, after ligation of the coeliac axis, the superior and inferior mesenteric and the renal arteries that stimulation of the splanchnic caused a sheer fall in blood pressure. This they attributed to liberation of a small amount of epinephrine into the circulation.

These observers showed also that considerable modification of the vascular response to epinephrine could be produced by varying the rate of injection. A certain dose given very slowly might cause a pure fall in blood pressure, while the same dose injected quickly might be followed by a rise in blood pressure succeeded by a slight fall with return to normal shortly thereafter, or else by a pure rise with no successive fall. These authors also found that the blood pressure level previous to the administration of epinephrine was an important factor in determining the type of response to the drug. Thus they found that a dose of epinephrine which at first caused a pure fall in blood pressure, caused a rise only after the blood pressure had been lowered by pithing. They concluded that the depressor effect of epinephrine was not due either to central action or to stimulation of supposed vaso-dilator endings of the sympathetic but to the condition of the muscle of the vessel wall.

They held that vaso-dilatation resulted from epinephrine action when the muscle was tonically shortened, vaso-constriction when relaxed. Hartman (10) later found that effect of small doses of epinephrine given by intravenous injection was dilatation of the limb vessels and constriction of those in the

splanchnic area. Hoskin, Gunning and Berry (11) showed that small doses of epinephrine produced constriction in the vessels of the cutaneous area and dilatation of the vessels of the limb muscles. Hartman and Fraser (12) obtained dilatation in vessels of the splanchnic area and of the limb muscles by central action of epinephrine. They attributed this result to direct stimulation of vaso-dilator cells, but they admit that dilatation may result by peripheral action as well. Gruber (13) failed to obtain vaso-dilatation in limb vessels the nerves to which had been severed. He attributed this result to loss of tonicity of the vessel walls, and is of the opinion that small doses of epinephrine cause dilatation by direct peripheral action.

Hartman and Fraser (12) also demonstrated that the dilator response of the limb vessels to adrenalin was effected by temperature. Thus they found that in a limb which had ceased dilating from artificial heat, the usual dose of adrenalin injected into the general circulation caused an increase in volume of the organ where previously the same dose of adrenalin produced either no effect or else constriction of the same.

It is quite evident in the light of the experiments above referred to that the response to the administration of epinephrine as judged by the change observed to take place in systemic blood pressure is no indication of the exact nature of what is occurring. It is rather the sum total of vascular changes in various parts. Either constriction or dilatation of vessels may be the predominating effect, depending very largely upon the dosage employed. Also constriction may result in one area and pure dilatation in another, while constriction followed by dilatation in any area is also a possibility.

Collip (14) has recently demonstrated new methods of producing reversal of the effect of small doses of epinephrine. Thus he found that a dose of epinephrine which causes a fall in systemic blood pressure can be converted into a pure rise, or into a slight rise followed by a slight fall, or else the fall will be greatly decreased by the injection of a variety of tissue extracts such as those prepared from heart, spleen, thyroid gland, suprarenal and pituitary bodies. This reversal or antagonism of the depressor action of small doses of adrenalin by tissue extract is of short duration only, the depressor response returning within a few minutes after the administration

of the tissue extract. It was found that similar reversal of the depressor action could be brought about by increasing the depth of anaesthesia. Also on occasion the response of the systemic blood pressure to a definite dose of epinephrine can be altered by previous administration of sodium carbonate or acid phosphate; sodium carbonate tends to increase the pressor effect of epinephrine while acid phosphate tends to decrease it.

Snyder and Andrus (15) obtained reversal of the effect of epinephrine on the isolated heart of the terrapin due to alteration of the hydrogen ion concentration of the perfusate. Snyder and Campbell (16) have observed reversal of the constrictor effect of epinephrine on the perfused vessels of a frog following increase in the hydrogen ion concentration of the perfusate while the constrictor effect was increased by a decrease in the hydrogen ion concentration.

The isolated uterus of certain animals is always inhibited by adrenalin when applied in very small amounts. Collip (17) has shown that this inhibition reaction to epinephrine is antagonized by small amounts of tissue extract. As the antagonism of the epinephrine reaction on certain isolated uteri by certain tissue extracts is very definitely a peripheral effect, it is quite possible that the antagonism or reversal of the depressor action of small doses of epinephrine on the systemic blood pressure by tissue extracts or by increasing degrees of anaesthesia is due to changes brought about in the periphery. The writer inclines to the view of Dale (7) that vaso-dilator as well as vaso-constrictor nerve endings are stimulated by epinephrine. The dilator endings are probably depressed by some constituent or constituents of tissue extracts with the result that the systemic blood pressure response to a small dose of epinephrine is definitely altered as above indicated. The fact that a dose of epinephrine which will produce a pure fall in blood pressure in an animal under very light anaesthesia will product a rise or a rise and slight fall when the anaesthetic is increased may be explained on the assumption that the vaso-dilator endings are more readily depressed by the anaesthetic than are the constrictors. However, sufficient data have not as yet been obtained to enable one to explain in any definite manner just how these reversals of vascular reactions to epinephrine are produced.

The cardiac response alone, for example, may be so altered under varied conditions as to play a large part in bringing about the observed results.

That vaso-dilatation may be associated with central action of epinephrine is suggested by the demonstration by McGuigan (18) that the response of the systemic blood pressure to a definite dose of epinephrine is increased following the administration of just sufficient nicotine to block central impulses along sympathetic pathways.

While the depressor action of a small dose of epinephrine may be completely reversed by increasing the depth of anaesthesia, it is also true that the pressor response to a large dose of epinephrine is decreased by anaesthesia.* This is due as McGuigan (18) points out to decreased irritability of the vaso-constrictor nerve endings, due to the increasing concentration of the anaesthetic in the blood stream.

McGuigan (18) has shown that haemorrhage causes an augmentation of the pressor response to adrenalin. He has interpreted this effect as indicating an increased irritability of the sympathetic vaso-constrictor nerve endings in the vessel walls as a result of haemorrhage.

The synergistic action of cocaine and epinephrine is still another example of the modification of the epinephrine reaction. This was first demonstrated by Frölich and Loewi (19). Recent experiments by Heinekamp (20) demonstrate a synergistic action between morphine and epinephrine as regards their central action on medullary centres.

It is now recognized as a result of the experiments of Levy (21) that the administration of epinephrine during chloroform anaesthesia is not without danger. He found that, if the animal were under light chloroform anaesthesia at the time of administration of the epinephrine, but had previously been deeply anaesthesised, the heart tended to go into fibrilation.

The vascular response of an intact animal to epinephrine administration may be considerably modified by varying the mode of injection. Thus a dose of epinephrine which calls forth a decided pressor response when injected intravenously if given subcutaneously, may have little or no effect on the blood pressure. Becht (22) has shown that installation of epinephrine

* Unpublished results of Groot and Albrecht kindly furnished by Professor Hugh McGuigan.

into the spinal canal produces a slight fall in blood pressure or else no effect. If, however, blood stained fluid exudes from the puncture needle prior to the injection a rise in blood pressure is frequently obtained. Variations in the response to epinephrine such as the above are probably related to the rate at which the active principle is introduced into the general circulation.

SUMMARY

A number of factors, which have been shown by various writers to produce a modification of the epinephrine reaction have been outlined.

The fact that very small doses of epinephrine cause a fall in blood pressure and not a rise has been emphasized.

Epinephrine may cause vaso-dilation in one area and vaso-constriction in another at the same time (Hartman and Fraser; Hoskins, Gunning and Berry).

A reversal of the depressor action of epinephrine may be accomplished by lowering the blood pressure level (Cannon and Lyman).

The pressor response of epinephrine is reversed by ergotoxin (Dale).

The reversal of the depressor action of epinephrine may be brought about by injection of tissue extract or by increasing the depth of anaesthesia (Collip).

Changes in hydrogen ion concentration may affect epinephrine response (Snyder, Campbell and Andrus; Collip).

The pressor response to epinephrine is decreased by anaesthesia (McGuigan).

The pressor response to epinephrine is increased following haemorrhage (McGuigan).

The mode of administration effects greatly the response to epinephrine.

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