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THE DEPRESSOR ACTION OF THE VERATRUM ALKALOIDS

BY

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In two recent papers Stutzman and his colleagues have raised some new points about the mode of action of the veratrum alkaloids upon the cardiovascular system. Using "Veriloid" ("a purified reproducible extract of *Veratrum viride* prepared by the Riker Laboratories of Los Angeles") they observed that cutting both cervical vagi eliminated the bradycardia, but did not alter quantitatively the fall of blood pressure when this extract was injected intravenously into dogs (Stutzman, Simon, and Maison, 1951). Yet there is ample evidence that cutting the vagi abolishes or very greatly reduces the fall of blood pressure and heart rate which follows the rapid intravenous injection of a single dose of crude extracts of *Veratrum album* or *Veratrum viride*, or of the pure substances veratridine, protoveratrine, or cevadine. Now, veriloid, according to Stutzman, Maison, and Kusserow (1949), is a mixture of alkaloids from which none of the previously described potent alkaloids of *Veratrum viride* has been obtained. It therefore seemed possible that veriloid contained alkaloids which acted in a different manner from those previously investigated. In the first part of this paper, by applying the methods of investigation previously used on other veratrum alkaloids, we have shown that veriloid possesses qualitatively similar properties.

Stutzman, Simon, and Maison (1951) also observed that *infusions* of germitrine, protoveratrine, germidine, germerine, and veratridine into dogs anaesthetized with pentobarbitone (nembutal) caused a fall of blood pressure which was not altered quantitatively by cutting the vagi. They therefore concluded that under these circumstances the Bezold reflex, the afferent fibres of which run in the vagi, is not responsible for the depressor action. In this respect also their results differed from those of previous workers in this field, who had used rapid single injections to test the reaction of the animal. The question is relevant to clinical practice, since a slow intravenous infusion might be expected to mimic the conditions in the circulation after a dose had been taken by mouth. Experience with the use of the veratrum alkaloids for studying the Bezold reflex over a number of years by no means agrees with the conclusions of Stutzman and his colleagues. In the first place it is not suggested that the Bezold reflex is alone responsible for the fall of blood pressure and heart rate on intravenous injection of *veratridine* in the dog, since in 1943 Krayer, Wood, and Montes showed that there was a central action, which caused a fall of heart rate. Yet the dose required to produce this central action was somewhat larger than that required to produce the Bezold reflex on injection into the

thoracic visceral circulation. In cats (Dawes, 1947) there is an even greater difference between the minimal effective dose for the Bezold reflex and that needed for a central action; thus a large fall of blood pressure and heart rate was obtained on rapid intravenous injection of a dose, which was ineffective on injection into the ascending aorta. Some of the records published by Jarisch and Richter (1939), in which multiple small doses of veratrine had been used in the cat to produce a prolonged fall of blood pressure, which was abolished by cooling the vagi, also led the authors to conclude that the Bezold reflex was the principal agent in producing the hypotension.

These considerations have led to a brief investigation of the mode of action of *infusions* of veratridine, described in the second part of this paper.

Methods

Cats and dogs were anaesthetized with chloralose (50–70 mg./kg.). Blood pressure was recorded with a mercury manometer from the carotid artery, and injections or infusions were made into the external jugular vein. The vagi were cooled by laying them on hollow thermodes, 1 cm. long, through which cold alcohol was circulated from an ice-salt mixture reservoir; the temperature of the thermodes was recorded by thermocouples. Heart rate was recorded by the method described by Dawes (1951). Coronary perfusions in the dog were carried out by the method described by Dawes (1947). Respiration was recorded by measuring the changes in volume of the body below the neck (Dawes, Mott, and Widdicombe, 1951). Action potentials were recorded from slips dissected from the cervical vagi, a conventional capacitance-coupled amplifier being used.

Results

Mode of action of veriloid

A more detailed study of the mode of action of veratridine (Dawes, Mott, and Widdicombe, 1951) has shown that the Bezold reflex in the cat is blocked by cooling the vagi to 9–11° C., at which temperature most vagal cardiac efferents are still active. Single injections of veriloid were therefore made in cats, and the cervical vagi were cooled during some of these injections. Cooling to 8° C. always abolished the fall of blood pressure and heart rate (Fig. 1). Cutting the vagi also abolished it, except in one cat, in which the response was greatly reduced. These observations are quite consistent with an action on the receptors for the Bezold reflex in the coronary circulation, and the one instance in which a small response remained after cutting the vagi can be attributed to a much smaller action on the central nervous system or perhaps the carotid body.

In two dogs veriloid was injected into the left circumflex coronary artery, perfused from the left internal mammary artery (cf. Dawes, 1947). As little as 0.4 μg. veriloid caused a fall of 20 mm. Hg of blood pressure, and 1 μg. caused a large hypotension and bradycardia on injection into the coronary artery; this response was abolished on cutting the vagi (Fig. 2). Injections of the same doses of veriloid intravenously or into the right ventricle were without effect. These observations substantiate the view that veriloid does not differ from the other active veratrum alkaloids in its ability to elicit the Bezold reflex.

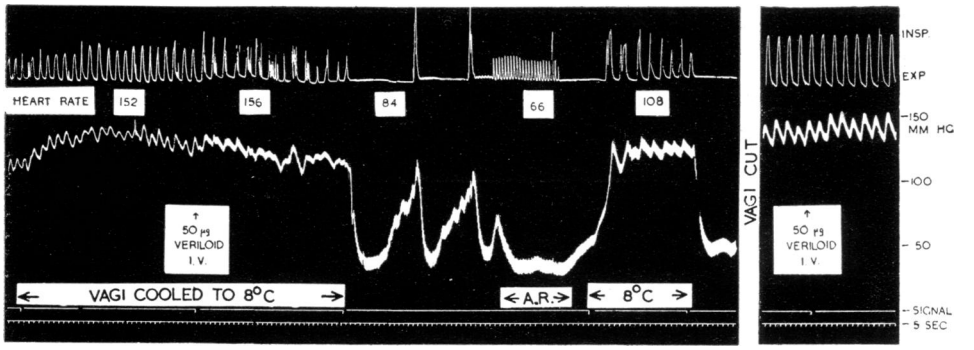

FIG. 1.—Cat, 2.8 kg., chloralose. Records of respiratory movements (above) and blood pressure (below). Both vagi were cooled to 8° C., and at 12.15 p.m. 50 µg. veriloid were injected intravenously. Two and a half minutes later the vagi were warmed, the blood pressure and heart rate fell precipitously, and breathing ceased. Artificial respiration (A.R.) was applied for a short time, and then the vagi were cooled again; the blood pressure and heart rate rose and respiration began again. After cutting the vagi the injection of the same dose of veriloid at 2 p.m. was without effect.

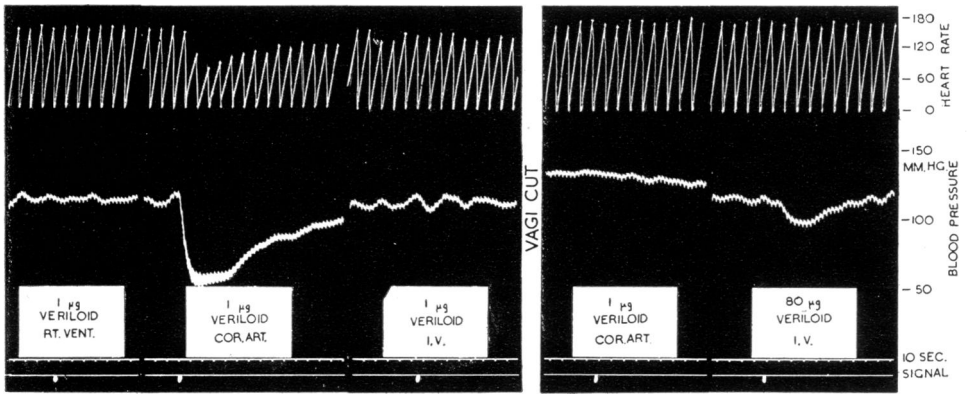

FIG. 2.—Dog, 8.0 kg., chloralose. Records of blood pressure (below) and mean heart rate (above, integrated over 10 secs.). Injection of 1 µg. veriloid into the left circumflex coronary artery (Cor. Art.) caused a fall of blood pressure and heart rate; the same dose injected into the right ventricular cavity (Rt. Vent.) or intravenously (I.V.) had no action. Cutting the vagi abolished the effect of a coronary injection, though 80 µg. injected intravenously then caused a very small fall of blood pressure.

Veriloid in both cats and dogs had, for a veratrum alkaloid, an unusually long duration of action on intravenous injection. This feature was particularly noticeable in its effect on breathing. Stutzman *et al.* (1949) observed that like other veratrum alkaloids it caused slowing or stoppage of respiration, an effect which was abolished by vagotomy, and was also abolished by cooling the vagi to 8° C. (Fig. 1). The action of veratridine in sensitizing or exciting pulmonary stretch receptors has already been described (Dawes, Mott, and Widdicombe, 1951), and it therefore seemed likely that veriloid would possess the same property, since the pulmonary stretch fibres are blocked by cooling the vagi to about 10° C. Action potentials

were recorded from single fibre preparations dissected from the cervical vagi, with a rhythm characteristic of the discharge from the pulmonary stretch receptors. Injections of veriloid greatly increased the discharge in response to normal or artificial respiratory movements, and the discharge continued at a considerable frequency even during expiration. As Fig. 3 shows, the sensitization was still present more than

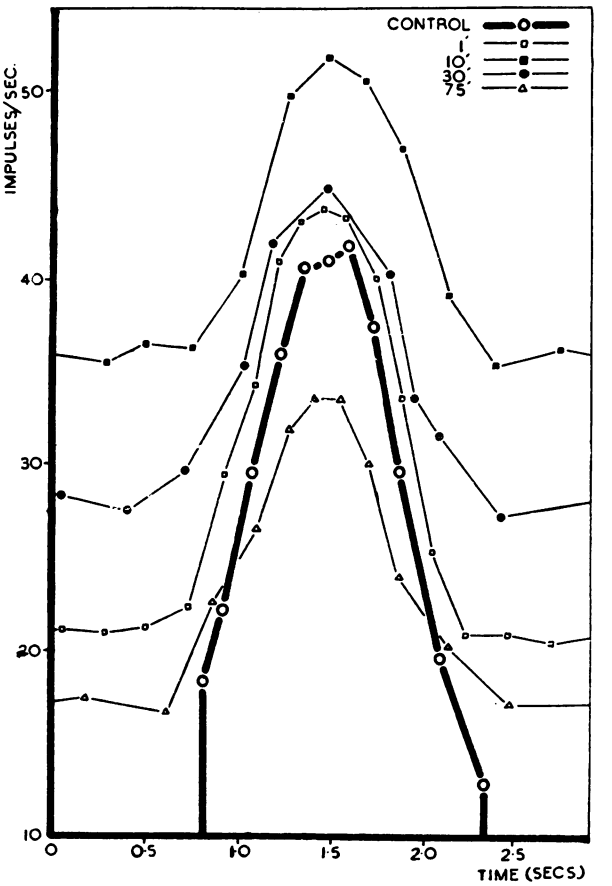

FIG. 3.—Cat, 2.8 kg., chloralose. Artificial respiration from a pump. The graphs show the discharge frequency of a single vagal pulmonary stretch fibre plotted against the artificial respiration cycle (each of which lasts 3 seconds), before and at various times after a single injection of 40 μg. veriloid. The discharge frequency is much increased after veriloid and the fibre fires continuously during expiration; the latter phenomenon lasts for more than an hour.

an hour after a single intravenous injection of 40 μg. veriloid into a cat. This is a forceful illustration of the ability of veriloid to cause repetitive discharges in afferent nerve structures, a property which seems fundamental to the characteristic activity of the veratrum alkaloids.

So far as these experiments go there is no reason to suppose that veriloid differs qualitatively in its mode of action from the pure veratrum alkaloids.

Infusion of veratridine

The second point raised by the work of Stutzman and his colleagues was the relative importance of the central and peripheral actions of the veratrum alkaloids on intravenous infusion. We infused veratridine at the rate of 2 μg./kg./min. into three cats, and during the infusion cooled the vagi to 8° C. Each infusion was continued for 10 minutes, with an hour's interval between infusions. In all three animals the results were striking and quite unequivocal. Cooling the vagi abolished the fall of blood pressure and heart rate (Fig. 4). In one cat we subsequently cut

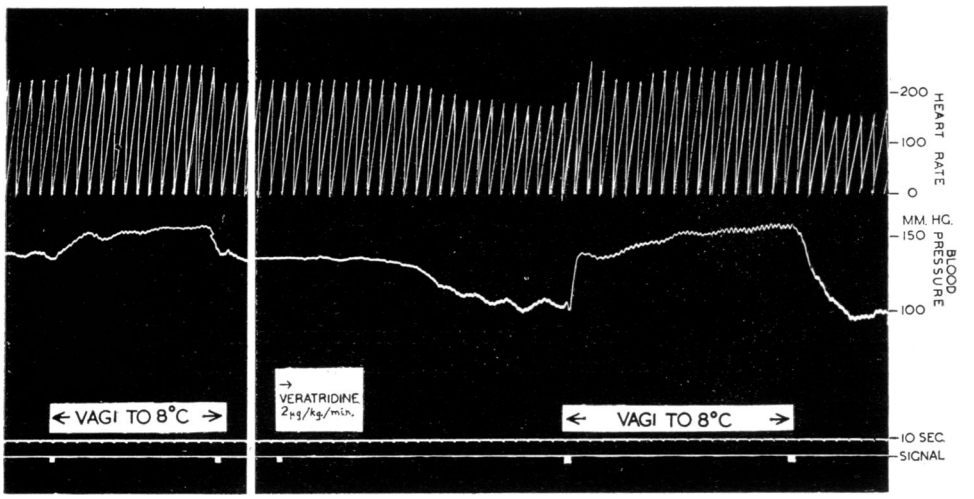

FIG. 4.—Cat, 2.9 kg., chloralose. Records of mean heart rate (above, integrated over 10 sec.) and blood pressure (below). Cooling the cervical vagi to 8° C. causes a small rise of blood pressure and heart rate. An infusion of veratridine at a rate of 2 μg./kg./min. causes a fall of blood pressure and heart rate which is abolished by cooling the vagi to 8° C.

the vagi and infused veratridine at a rate of up to 7 μg./kg./min. without any action whatsoever on blood pressure or heart rate.

In dogs our results were different and agreed more closely with those of Stutzman, Simon, and Maison (1951). In a total of 10 dogs infusions of veratridine at a rate of 1–4 μg./kg./min. gave very variable results. There was a great difference in sensitivity, but in all experiments where there was a fall of blood pressure this was accompanied by a fall of heart rate of proportionate magnitude. In two of these animals cooling the vagi to 8° C. abolished or much reduced the fall of blood pressure and heart rate. In three other dogs cooling the vagi did not significantly affect the response. In the remainder the findings were equivocal. It should be mentioned at this point that the rise of blood pressure and heart rate on cooling the vagi during an infusion of veratridine was always compared with the rise on cooling seen before and some considerable time after an infusion. The variation in these control responses explains the presence of findings which we regard as equivocal.

During these experiments both with veriloid and veratridine we encountered the phenomenon of tachyphylaxis on a number of occasions.

Discussion

The experiments with veriloid show that this mixture of alkaloids has the same general properties in its action upon the cardiovascular and respiratory mechanisms as the other potent extracts and alkaloids of veratrum.

Stutzman and his colleagues have introduced in their two papers a number of hypotheses about the mode of action of these substances. The most important of these from the clinical standpoint is their view that the Bezold reflex is in no way responsible for the fall of blood pressure during the slow infusion of a veratrum alkaloid; yet it may cause bradycardia if the injection is rapid, since they also suppose that the *central* action of a veratrum infusion does not include bradycardia. On this basis it is not clear how they account, to take one example, for the fall of heart rate demonstrated by Kauntze and Trounce (1951) on intravenous infusion of veriloid in man. It has in fact been shown without doubt that the Bezold reflex causes both peripheral vasodilatation and bradycardia (Krayer and Acheson, 1946). The final proof of this concept is contained in the observation that the vasodilatation in the splanchnic area and the leg, which ensues on single intravenous injections of veratridine in the cat, is abolished by cooling the vagi to 8° C., thus blocking the *afferent* path of the reflex (Dawes, Mott, and Widdicombe, 1951). From general physiological principles it would indeed be surprising if a reflex mechanism which caused a profound bradycardia did not simultaneously cause vasodilatation; the co-ordination of cardiac and vasomotor centres might be supposed to lead to such a response.

This argument can be used another way round. A drug which causes peripheral vasodilatation by a direct action on the central nervous system might be expected also to cause bradycardia. And this would appear to be true of veratridine, since Krayer, Wood, and Montes (1943) showed that injection of veratridine into the separately perfused central nervous system of the dog caused a considerable fall of heart rate. We may conclude therefore that there is *prima facie* evidence (though naturally this is not established for every veratrum alkaloid) that these substances may cause both a fall of blood pressure and of heart rate both through the Bezold reflex and by a central nervous action.

The experiments recorded above with cats show that under light chloralose anaesthesia the fall of blood pressure during an infusion of veratridine is almost entirely due to the Bezold reflex. Presumably the peripheral receptors are in this instance more sensitive to the alkaloid than the cells of the central nervous system. In dogs under chloralose anaesthesia the results were somewhat different, but even in this species there were two experiments which clearly led to the same conclusion. It may be observed that our experiments differed from those of Stutzman in two important respects. He used pentobarbitone (nembutal) anaesthesia, and it is well known both that the Bezold reflex is particularly sensitive to changes in the depth of anaesthesia and that it is much less easy to obtain clear evidence of reflex peripheral vasodilatation under barbiturates. Another possible reason for the difference in our results may be that we did not cut the vagi, but only cooled them. In this way we were able to provide a control observation when they were warmed again, a feature of the experiments which is important when using a drug which can only be injected or infused at relatively long intervals of time.

We cannot tell either from our own experiments or those of Stutzman *et al.* which of the two mechanisms, Bezold reflex or central action, is the more important in man. It may, however, be timely to recall that the reflex cardiovascular reaction first described by von Bezold and Hirt (1867) in rabbits on injection of crude extracts of veratrum alkaloids, has only within the last five years been localized with certainty to an action on receptors in the coronary circulation, that these hypothetical receptors have not yet been identified, that direct evidence for their existence has only been obtained as yet in the cat and the dog, and that there are some indications of a difference even between these two species.

Summary

Veriloid, a mixture of veratrum alkaloids in clinical use for producing a fall of blood pressure, does not materially differ in its mode of action from that of the pure veratrum alkaloids. It elicits the Bezold reflex and sensitizes or excites the pulmonary stretch receptors.

The fall of blood pressure and heart rate caused by a slow infusion of veratridine in cats is abolished by cooling the vagi. In some, but not all, dogs a similar result is obtained under chloralose anaesthesia. In view of this apparent species difference it would be unwise to draw any conclusions about the precise mode of action of these drugs in man. There is the possibility both of a peripheral Bezold reflex and of a central nervous action.

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