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STUDIES ON SOLANUM ALKALOIDS: I. THE ANTI-ACCELERATOR CARDIAC ACTION OF β-DIHYDROSOLASODINE AND TETRAHYDROSOLASODINE

BY

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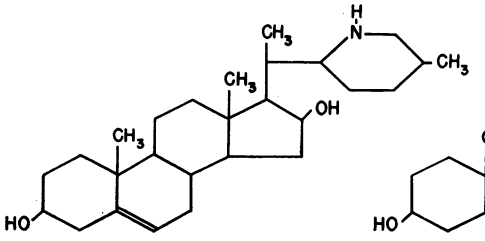
The veratrum alkamines, veratramine and jervine, and their glycosides, veratrosine and pseudojervine, have a selective antagonistic action to the cardio-accelerator effect of sympathomimetic amines and of accelerans stimulation (Krayer, 1949a ; Krayer, 1949b ; Krayer and Van Maanen, 1949 ; Krayer and Reiter, 1950). This appears to be a pharmacological property exclusively of the secondary amine bases amongst the veratrum alkaloids. The chemical studies on the structure of the solanum alkaloids were essential for the establishment of the steroid nature of the veratrum alkaloids (Rochelmeyer, 1937 ; Craig and Jacobs, 1941, 1943 ; Prelog and Szpilfogel, 1942 ; Uhle and Jacobs, 1945 ; Sato and Jacobs, 1949). Two secondary amine bases of the group of the solanum alkaloids, β-dihydrosolasodine and tetrahydrosolasodine, were studied and were found to have qualitatively the same anti-accelerator property as veratramine and jervine, thus giving further proof of the close relation between the two groups of alkaloids.

The two solanum alkamines used in this study were prepared in the Department of Chemistry, Auckland University College, by Briggs and Locker. The experimental work in support of the probable formulation of β-dihydrosolasodine (I),



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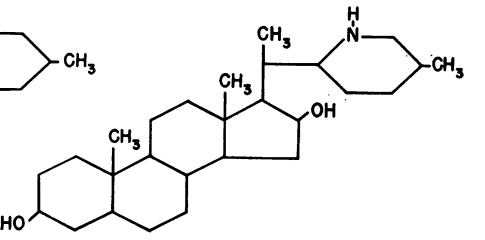

II

m.p. 260–264°, and of tetrahydrosolasodine (II), m.p. 285–287°, will be published elsewhere. The structural relationship to veratramine and jervine is evident from a comparison with the recent work of Sato and Jacobs (1949).

METHODS

The experiments were carried out in dogs under dial urethane anaesthesia and in spinal cats. In order to exclude vagal effects atropine was given and, in the dog, the vagi were severed in the neck. The heart-lung preparation of the dog (HLP) was used for studies on the isolated heart. The methods employed were identical with those previously described (Krayer, 1949a ; Krayer and Reiter, 1950). Establishment of constant levels of heart rate increase was achieved by continuous infusion of *l*-adrenaline. All doses of adrenaline and of the solanum alkaloids refer to the bases ; all doses of atropine refer to atropine sulphate.

The solanum alkamines were brought into solution with slightly more than the equivalent amount of hydrochloric acid, 0.3 c.c. 0.1 N-HCl for every 10 mg. As the hydrochlorides are not readily soluble, solutions of 1 : 500–1 : 1,000 of β-dihydrosolasodine and of 1 : 1,000–1 : 4,000 of tetrahydrosolasodine were used. The relatively low potency (compared to that of veratramine) necessitated the administration of large volumes of solvent when maximal effects were desired. To prepare isotonic solutions 5 per cent (w/v) dextrose solution was used, because in 0.9 per cent sodium chloride solution the solubility of the hydrochlorides was much less than in distilled water made acid to a *p*H of about six.

RESULTS

Experiments on heart rate and blood pressure of the dog and of the spinal cat

Action upon heart rate.—In the intact circulation of the dog with the vagi cut in the neck and atropine given in doses of approximately 3 mg. atropine sulphate per kg. the intravenous continuous infusion of adrenaline in a dose of 3 μg. per kg.

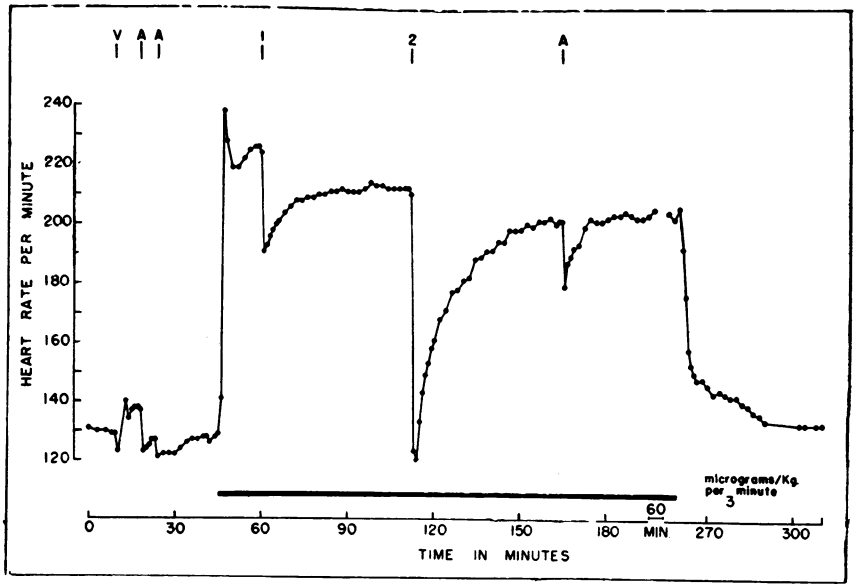

FIG. 1.—The action of β-dihydrosolasodine on cardio-acceleration caused by adrenaline. Dog female, 7.5 kg. Dial urethane. At V, the vagi were cut in the neck. At A, 10 mg. of atropine sulphate were injected intravenously. At 1 and 2, 0.77 mg. and 3 mg. β-dihydrosolasodine per kg. respectively were injected intravenously. Black bar, continuous infusion of 3 μg. *l*-adrenaline base per kg. per min. infused intravenously.

per min. increased the heart rate very rapidly to the maximal value for this dose. After a period of ten to fifteen minutes, in some cases, a steady state was established at somewhat lower than the maximal rate obtained initially, in others a slow decline in rate continued over a period of about an hour, as was shown earlier (Krayer, 1949a).

The intravenous injection of the solanum alkaloids caused an abrupt decrease in rate proportional in intensity to the dose (Fig. 1). The maximum drop in heart rate was completed within 1–2 minutes. After this the heart rate increased again, at first steeply, then more gradually, and, with the doses of 0.3 to 3 mg. per kg. used in these experiments, a new equilibrium was established at a level somewhat below the pre-injection level. Upon discontinuation of adrenaline infusion the heart rate promptly fell to or near the initial level (see Fig. 1).

In the spinal cat the effects were similar (Fig. 2). Fig. 2 shows that there were apparently no marked differences in the quality and intensity of action between β-dihydrosolasodine and tetrahydrosolasodine. No irregularities of rate and rhythm occurred and the hearts continued beating at a regular sinus rhythm throughout.

Action upon blood pressure.—The increase in blood pressure caused by the adrenaline infusion in the dog and in the spinal cat was not antagonized by the solanum alkaloids even in doses which annulled temporarily the cardio-accelerator action. With the smallest doses there was no effect; with larger doses there was an increase in blood pressure (Fig. 3). The latter may in part have been due to the volume of solvent administered on account of the relatively low solubility of the compounds. In Fig. 3 the dose of 10 mg. of β-dihydrosolasodine was contained in 5 c.c. of 5 per cent glucose solution and the injection was made in 50 seconds.

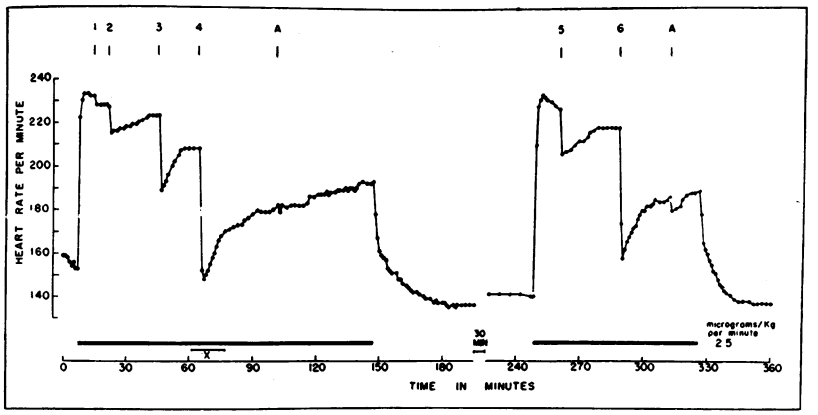

FIG. 2.—The action of β-dihydrosolasodine and tetrahydrosolasodine on cardio-acceleration caused by adrenaline. Cat, female, 3 kg. Spinal preparation. At 1, 2, 3, and 4: 0.1, 0.3, 1, and 3 mg. β-dihydrosolasodine per kg. respectively were injected intravenously. At 5 and 6: 0.25 and 3 mg. of tetrahydrosolasodine per kg. respectively were injected intravenously. At A, 10 mg. atropine sulphate were injected. Black bars, continuous infusion of 2.5 μg. *l*-adrenaline base per kg. per min. infused intravenously. X refers to Fig. 3.

The heart rate decreased from 208 to 148 within two minutes after the beginning of the injection, and adrenaline acceleration was completely abolished for four to five minutes. The blood pressure rose to its maximal value within two minutes; it was still slightly elevated ten minutes later when the heart rate had again risen to 170 per minute.

Effect of atropine.—As was shown in the earlier experiments with the veratrum alkaloids, atropine given during the continuous infusion of adrenaline in the dog or in the spinal cat, as a rule caused a transient decrease in blood pressure and drop in heart rate. It was without an apparent influence upon the effect of the solanum alkaloids.

Experiments on the heart-lung preparation (HLP) of the dog

As with the veratrum alkaloids the effect of the solanum alkaloids could be obtained in the isolated mammalian heart accelerated by the continuous infusion of adrenaline and under the influence of atropine. The heart rate decreased abruptly. The effect was maximal within a few minutes and was persistent (Fig. 4). If the adrenaline infusion was discontinued, the heart rate gradually fell as the adrenaline was being slowly destroyed, and a level of heart rate was again established usually within one hour and as a rule below the initial level. This process could be hastened by removing the blood of the HLP and substituting fresh blood not containing adrenaline or solanum alkaloid.

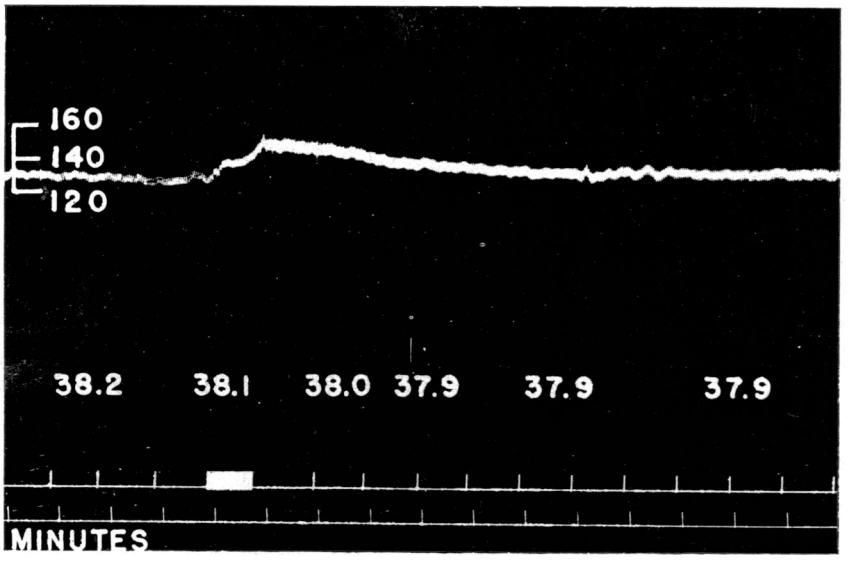

FIG. 3.—The action of β-dihydrosolasodine upon the blood pressure increase caused by continuous infusion of adrenaline. Cat, female, 3 kg. Spinal preparation. Corresponds to period X of Fig. 2 between time 61 and 77. From top to bottom: blood pressure taken by Hg-manometer from left carotid artery. Calibration on left in mm. Hg ; temp. in degree centigrade; single line; time in minutes. At the large signal: intravenous injection of 3 mg. β-dihydrosolasodine per kg. The other signals refer to the heart rates taken every minute. See Fig. 2.

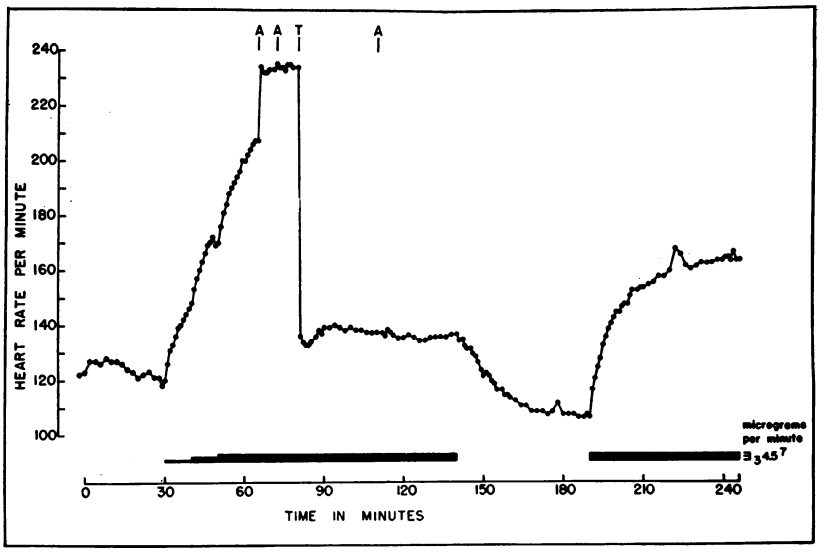

FIG. 4.—The anti-accelerator effect of tetrahydrosolasodine in the isolated mammalian heart in the presence of atropine. Hound-dog, male, 9.7 kg. Heart-lung preparation. Ventilated with 95 per cent O_2 and 5 per cent CO_2. Blood volume 800 c.c. at beginning. Temperature varied from 38 to 39° C. Mean arterial pressure 90 mm. Hg. Systemic output (= total output of left ventricle minus coronary flow 500 c.c./min.). At T, 5 mg. tetrahydrosolasodine were injected (1 : 4,000 in 5 per cent glucose). At A, 10 mg. atropine sulphate were injected. Black bars: continuous infusion of *l*-adrenaline (1 : 5,000); calibration at right in μg. base per min.

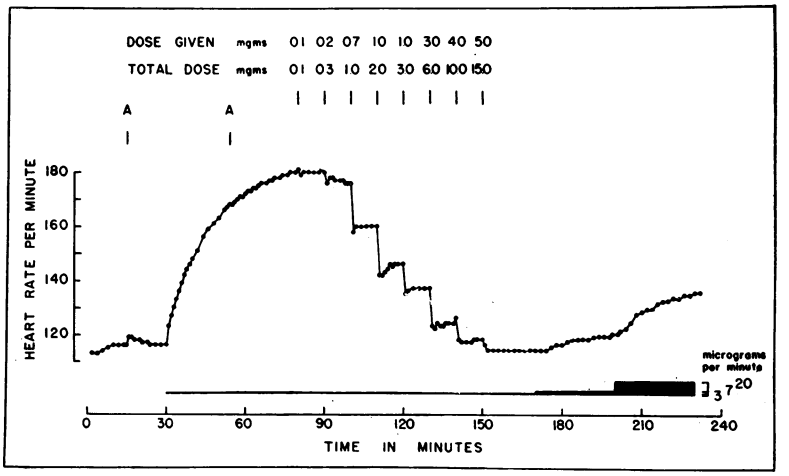

FIG. 5.—The graded inhibition by tetrahydrosolasodine of the cardio-accelerator action of adrenaline in the isolated mammalian heart. Dog, male, 9.2 kg. Heart-lung preparation. Ventilated with 95 per cent O_2 and 5 per cent CO_2. Blood volume 900 c.c. at the beginning. Temperature varied between 39.6 and 39.9° C. Mean arterial pressure 110 mm. Hg. Systemic output 500 c.c. per minute. Tetrahydrosolasodine solution 1 : 2,000 in 5 per cent glucose was administered in increasing doses. At A, 10 mg. of atropine sulphate were injected. Black bar: continuous infusion of *l*-adrenaline (1 : 5,000); calibration at right in μg. of base per minute.

Upon readministration of adrenaline, the heart rate again rose, but did not reach the level corresponding to the same infusion rate as before the administration of the alkaloids. This further suggests the persistence of their effect, although other factors may be involved in this decrease in response to intermittent continuous infusions of adrenaline (Krayer, 1949a).

Even if complete inhibition of acceleration was achieved, an increased rate of adrenaline administration still caused a positive chronotropic effect, but the increase in rate was slight (see Fig. 5).

The persistence of the effect of the secondary veratrum alkamines in the HLP was recently shown to make possible a quantitative comparison of their effect (Krayer, 1950). The method permits the determination of the dose of a secondary veratrum or solanum alkamine, causing 50 per cent inhibition of the cardio-accelerator action of *l*-adrenaline under standard conditions of blood volume, temperature, and rate of adrenaline infusion. This dose is referred to below as I_{50}. Fig. 5 is the record of a representative experiment.

After the establishment of a steady state of increased heart rate suitable doses of anti-accelerator compound were given in succession. Each single dose was slowly injected within one minute (or longer with the larger doses) in order to effect uniform distribution quickly. Thus steady states of rate corresponding to the total dose present in the HLP could be established within about ten minutes. With such fast-acting substances, a complete dose-response curve could be obtained in a single experiment, relating successive total doses to the corresponding inhibition of acceleration.

In Fig. 5 the I_{50} of tetrahydrosolasodine was very close to 2 mg. A second experiment with this compound and two with β-dihydrosolasodine gave I_{50} values of the same order, slightly higher or lower than 2 mg. A more exact determination requiring five to ten experiments could not be made for lack of substance. The results suffice, however, to establish the fact that the two solanum alkaloids are intermediate in potency to veratramine, with an I_{50} of 0.16 mg., and jervine, with an I_{50} of 7.6 mg., when examined under the same conditions (Krayer, 1950).

Throughout, the heart rhythm of the isolated heart of the dog remained a regular sinus rhythm. No irregularities were observed even with doses causing complete inhibition of acceleration. Atropine neither prevented nor abolished the effect. From the pressure and output records, it was evident that the solanum alkaloids did not antagonize the positive inotropic action of adrenaline.

Summary and Conclusions

In the anaesthetized dog, in the spinal cat, and in the heart-lung preparation of the dog, the solanum alkaloids, β-dihydrosolasodine and tetrahydrosolasodine, antagonize the positive chronotropic action of adrenaline. Large doses of atropine do not modify the anti-accelerator effect. The vasopressor activity of adrenaline is not diminished by doses which temporarily annul the cardio-accelerator action.

Qualitatively the anti-accelerator action of the two solanum alkaloids is like that of the chemically related veratrum alkaloids, veratramine and jervine. In potency they are weaker than veratramine but stronger than jervine.

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