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EFFECT OF VINCAMIN ON THE NORADRENALINE CONTENT OF RAT TISSUE

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Abstract—The alkaloid Vincamin considerably reduces the noradrenalin content of the brain, intestines and suprarenal glands of rats. This reduction is lasting, and can be counteracted by iproniazid pre-treatment.

VINCAMIN (Devincan®Richter) is a crystalline alkaloid isolated from *Vinca minor* L. Its chemical structure is as yet unknown; it is probably a heterocyclic compound containing an indole ring.

The pharmacological effects of the alkaloid have thus far not been completely clarified. Szporny and Szász[1] have established a two-phase blood pressure reduction on cats and rabbits as an effect of Vincamin. Immediately after intravenous administration, the blood pressure drops for a few minutes, is then re-established, and subsequently begins to drop slowly, reaching 60 per cent of its initial value in 2 hr. The same authors have also demonstrated the absence of any ganglion-blocking or adrenolytic effect.

Sedation similar to the effect of reserpine can be induced on mice and rats by the administration of considerably larger dosages of Vincamin. According to investigations carried out by Nagy and Szabó,[2] this compound has no influence on the cardiac output. Its effect on blood pressure is a result of the decrease in peripheral resistance.

Extensive clinical studies have shown that this compound is a hypotensive drug which the patients tolerate easily.

Contrary to reserpine, however, it cannot be used for the treatment of psychoses.

On the basis of the above pharmacological and clinical data, it seemed advisable to investigate the effect of Vincamin on the noradrenaline content of tissues in order to clarify its exact mechanism.

METHODS

The Vincamin used in our experiments had been prepared in the Research Laboratories of our factory and its grade of purity was checked by the paper chromatographic method of Szász *et al.*[3]

The Vincamin was dissolved in 10% ascorbic acid.

Noradrenaline isolation was carried out according to Euler.[4] Noradrenaline was isolated from tissue homogenate by hydrochloric acid–ethanol extraction. The crude extract was separated from the other substances which may affect the biological assay by phenol–hydrochloric acid chromatographic method.[5]

The noradrenaline content of the isolated material was measured according to Crawford and Outschoorn[5] by its hypertensive effect on rats. The noradrenaline sensitivity of rats anaesthetized with urethane was raised with a 1 mg/kg dose of Mecamylamine administered intravenously. In our observation Mecamylamine is better suited than the generally used Hexamethon due to the more prolonged effect of the first. The blood pressure of the rats was registered by mercury manometer with transmission.

With cerebral tissue, the determination according to the above method was carried out on the whole brain but the cerebellum. Two rats were used for each determination. The duodenum and the upper jejunum were used from the intestines (1 g). With suprarenal gland tissue, the amine concentration raising the total blood pressure of the unilateral suprarenal gland was determined.

RESULTS

In the first part of our investigation, we examined in a number of experiments the effect of 50 mg/kg Vincamin, administered intraperitoneally, on the noradrenaline content of the brain. Results obtained 2 hr after the administration of the injection are shown in Table 1. The blood pressure curves in Fig. 1 obtained from the brain extract of animals treated with Vincamin and of controls demonstrate the nature of our investigations.

TABLE 1. EFFECT OF VINCAMIN (50 MG/KG INTRAPERITONEALLY) ON THE NORADRENALINE CONTENT OF THE BRAIN*

Drug	Time (hr)	Noradrenaline	Mean
Control	–	218, 207, 227, 234, 189, 214, 190	211
Vincamin	1	70, 56, 64, 63	63
Vincamin	2	0, 0, 0, 17, 0	0(3)

* The values represent mμg/g wet tissue. 0 denotation means that the concentration has dropped below the lower value that could be measured.

It may be seen from Fig. 1 and Table 1 that the above quantity of Vincamin reduces the noradrenaline level of the brain below the measurable value (5 mμg/g). The control noradrenaline values of our experiments are in good agreement with the data published in the literature.

After having demonstrated the reducing effect of Vincamin on the cerebral noradrenaline level, we proceeded to examine this reduction as a function of time. As shown by Fig. 2, the noradrenaline level decreases considerably in the first hour, reaches a minimum value after 2 hr, and then begins to rise slowly reaching the level of the control after 48 hr. As time progresses, the noradrenaline level rises above that of the controls and reaches the level of the latter again only after 192 hr.

Table 2 shows the effect of 50 mg/kg Vincamin, administered intraperitoneally, on the noradrenaline level of the intestines and on the total amine content of the suprarenal glands. In the intestines, the noradrenaline level drops below the measurable value

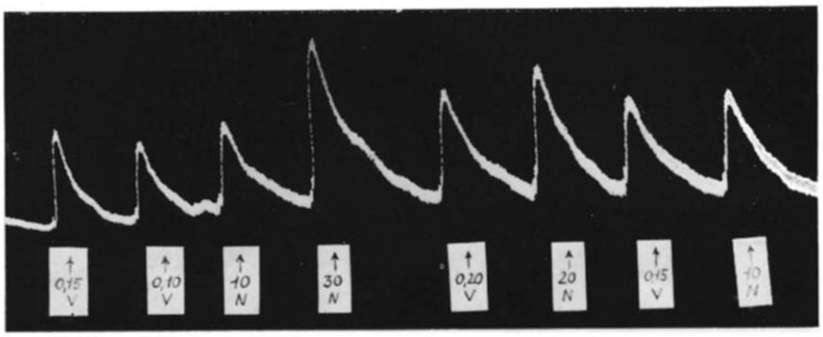

FIG. 1. (a)

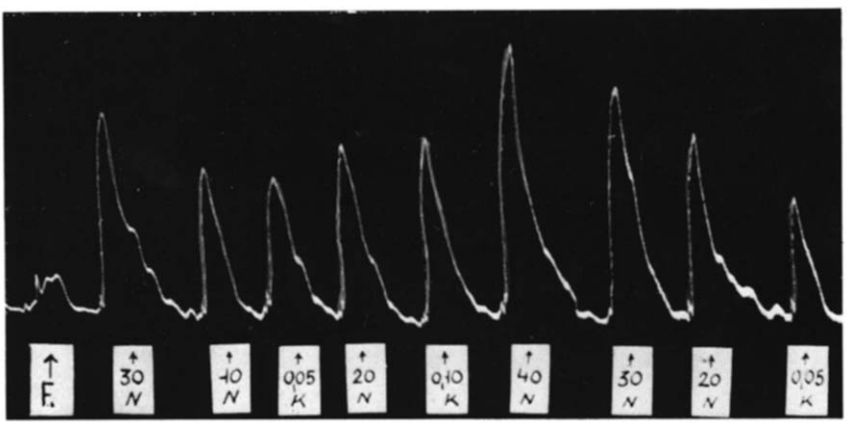

FIG. 1. (b)

FIG. 1. (a) The noradrenaline content of the brain extract of animals pretreated with Vincamin. N = noradrenaline standard/mμg. The cerebral extract of animals pretreated with Vincamin (50 mg/kg, intraperitoneally) ml/0·5 ml extract = 200 mg cerebral tissue. It can be seen that 0·15 ml V = 10 mμg noradrenaline, V = 17 mμg/g.(b) Noradrenaline content of the cerebral extract of control animals. N = Noradrenaline standard/mμg; K = cerebral extract of control animal/ml; F = physiological NaCl solution. 1 ml extract = 1050 mg cerebral tissue. It can be seen that 0·1 ml K = 20 mμg noradrenaline = 190 mμg/g.

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similar effects in the suprarenal glands, a more prolonged dosage is required. Though we unquestionably observed a secondary rise of the cerebral adrenaline level in the course of our experiments, we are unable at present to explain this phenomenon.

Results obtained with iproniazid pretreatment, which acts as a monoamine oxidase inhibitor, show that Vincamin protects the cerebral noradrenaline against the action of the degrading enzyme. As Vincamin causes no further increase in the noradrenaline level as compared to the value after iproniazid pretreatment, Vincamin resembles reserpine in this respect, too.

TABLE 3. THE EFFECT OF 50 MG/KG VINCAMIN ADMINISTERED 16 HR AFTER A 100 MG/KG IPRONIAZID PRETREATMENT*

Drug	Noradrenaline	Mean
Control	192, 234, 189, 190, 204	202
Iproniazid	285, 210, 382, 245, 290	282
Iproniazid + Vincamin	197, 242, 270, 390, 253, 224	263

* Values in mμg/g wet tissue.

Summing up the results of our experiments, we may state that the effect of Vincamin on noradrenaline metabolism resembles that of reserpine. As the pharmacological and clinical effects of the two substances are only partly in agreement, these results may only partly explain the mechanism of the Vincamin effect. Clarification of the exact mechanism of the Vincamin effect and the essential investigation of the characteristics by which it differs from reserpine form the subject of further study.

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