PHARMACOLOGY

THE EFFECT OF RESERPINE ON THE VEGETATIVE REFLEXES

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Numerous investigations have shown that reflexes from the interoceptors are of fundamental importance in the regulation of the activity of the cardiovascular system. It is also well known that reflex influences from certain receptor fields may take part in the development of different pathological processes, including hypertensive diseases.

In studying drugs used in the treatment of hypertension it is, therefore, important to take into consideration their influence on the interoceptive reflexes.

Hypotensive drugs which have recently become widely used are various preparations obtained from the root of rauwolfia (reserpine, rescinnamine, alseroxylon, rauwiloid and also total rauwolfia alkaloids). Reserpine is particularly widely used in the treatment of hypertension and of several other pathological conditions.

Investigations carried out previously on the effect of total alkaloids of Rauwolfia serpentina on the vegetative serpentina on the vegetative reflexes [2] showed that this preparation depresses the reflexes from the mechano- and chemoreceptors in various receptor fields (the mechanoreceptors of the carotid sinus, the large intestine and the urinary bladder, the chemoreceptors of the pericardium) and also from the central ends of the divided vagus and tibial nerves.

The total alkaloid preparations of rauwolfia is known to contain alkaloids with different, and sometimes directly opposite, types of action. In this connection it was interesting to determine whether the changes which we observed in the interoceptive reflexes were associated with the effect of one of the principal alkaloids contained in rauwolfia — reserpine.

The majority of information in the literature concerns the effect of reserpine on the reflexes from the mechanoreceptors of the carotid sinus and from the central ends of the vagus nerve trunk, divided in the neck, and the sciatic nerve [4, 7, 8].

This research is not of a systematic character and does not permit a full enough idea to be gained of the influence of reserpine on vegetative reflexes, the reflex pathways of which are connected at different levels of the central nervous system. In addition there is an almost complete absence of information on the effect of reserpine on reflexes arising in response to stimulation of chemoreceptors.

The aim of the present work was to study the influence of reserpine on the reflex reactions of the circulation of the blood and respiration arising from the mechano- and chemoreceptors of different receptor fields, namely: the mechanoreceptors of the carotid sinus, the large intestine and the urinary bladder; the central ends of the divided vagus, brachial and tibial nerves, and also from the chemoreceptors of the pericardium and the small intestine.

EXPERIMENTAL METHOD

Experiments were carried out on anesthetized and decerebrate cats. Reflexes affecting the arterial blood pressure and respiration from the mechanoreceptors of the urinary bladder and large intestine were elicited by distension of the organs, reflexes from the mechanoreceptors of the carotid sinus by clamping the common carotid artery. In order to stimulate the vagus, brachial and tibial nerves, rectangular impulses were used from an electronic stimulator (frequency 30-50 cps, duration of impulse 2-2.5 millisec, voltage 0.5-6 v).

In order to elicit reflexes from the chemoreceptors of the pericardium and small intestine we used the method of perfusion of these organs, with their nerve connections with the body maintained. To stimulate the chemoreceptors we used acetylcholine in a concentration of $1:10^{-5}$, $1;10^{-4}$ and in a volume of 0.3-0.5 ml.

The reflexes obtained from the chemoreceptors of the small intestine were pressor in character; the reflexes from the chemoreceptors of the pericardium were either pressor or depressor in different experiments.

The arterial pressure was recorded in the carotid artery by means of a mercury manometer and the respiration by a Marey's capsule, via a tracheal cannula.

In the experiments we used pure reserpine obtained from the All-Union Research Chemopharmaceutical Institute, and also reserpine marketed in tablet form by the firm "SANABO". In view of the very low solubility of reserpine in water, we used the latter in the form of a 0.1% solution in glacial acetic acid.

In order to exclude the possibility of any influence of acetic acid on the reflexes, control experiments were carried out, which showed that acetic acid, when administered in the concentration used for dissolving the preparation, had no essential effect either on the level of the arterial pressure or on the reflexes.

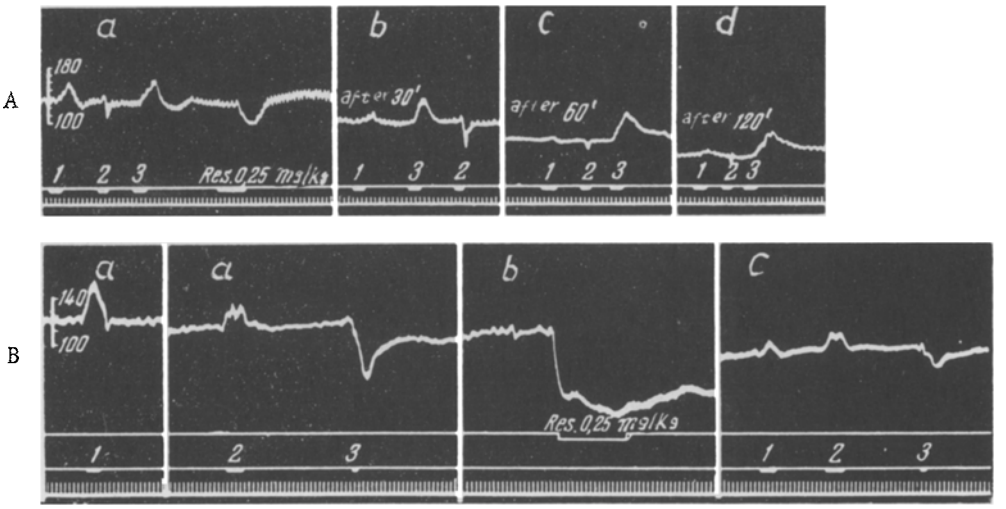

Fig. 1. The effect of reserpine on reflexes from the mechanoreceptors of the carotid sinus, the chemoreceptors of the pericardium and the central ends of the divided vagus and tibial nerves. Legend (from above down): arterial pressure; marker of injection of the drug and stimulation marker; time marker (5 seconds). A: 1) Reflex from the carotid sinus; 2) reflex from the vagus nerve; 3) reflex from the tibial nerve. a) Before injection, and injection of 0.25 mg/kg of reserpine; b) 30 minutes after injection of reserpine; c) 60 minutes after; d) 120 minutes after. B: 1) Reflex from the carotid sinus; 2) reflex from the tibial nerve; 3) reflex from the chemoreceptors of the pericardium. a) Before injection; b) in response to injection of 0.25 mg/kg; c) 60 minutes after injection of reserpine.

In all the experiments the reserpine was injected intravenously.

When the experimental results were being worked out, the change in the magnitude of the reflexes was calculated as a percentage in relation to the initial level of the arterial pressure.

EXPERIMENTAL RESULTS

As the experiments showed, reserpine, when injected in a dose of 0.25 mg/kg, caused a fall in the arterial pressure of 50-60 mm Hg. After 5-10 minutes the pressure was restored to its initial value.

It must be pointed out that the action of reserpine developed gradually, and the arterial pressure, when restored to its initial level, fell again after 30-60 minutes to 30-40 mm below the initial level. The maximum fall in the arterial pressure was observed at the end of the 2nd-3rd hour, and reached 50-70 mm. The fall in the arterial pressure in response to injection of reserpine was also accompanied by marked bradycardia.

From 30 to 60 minutes after injection of reserpine in a dose of 0.25 mg/kg, a clear depression of the reflexes was observed. It must be pointed out that the reflexes from the mechanoreceptors of the carotid sinus were diminished by 50-60%, and those from the mechanoreceptors of the urinary bladder and large intestine by 30-40%.

The reflex on the arterial pressure from the central end of the divided vagus and branchial nerves, like the reflex from the carotid sinus, showed little resistance to the action of reserpine. In a dose of 0.25 mg/kg, reserpine reduced these reflexes by 40-50%. The reflex from the central end of the divided tibial nerve in some experiments not only was not depressed, but was obviously increased (Fig. 1, A).

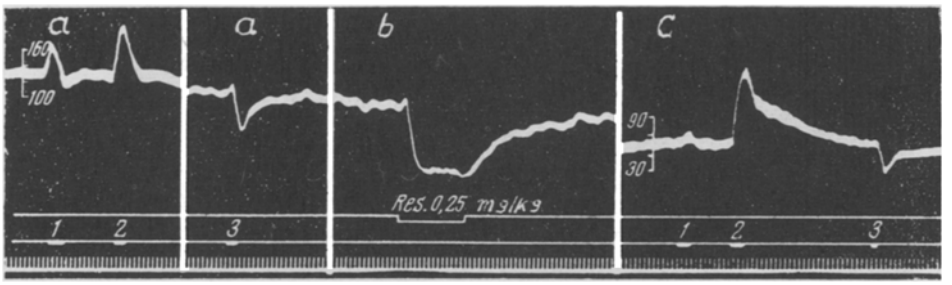

Fig. 2. The effect of reserpine on reflexes from the mechanoreceptors of the carotid sinus, the chemoreceptors of the pericardium and the central end of the divided vagus nerve. Ditilin (a curare-like drug). Legend (from above down): arterial pressure; marker of injection of drug; stimulation marker; time marker (5 seconds). 1) Reflex from the carotid sinus; 2) reflex from the tibial nerve; 3) reflex from the chemoreceptors of the pericardium. a) Before injection; b) injection of 0.25 mg/kg; c) 60 minutes after injection of reserpine.

The reflexes from the mechanoreceptors thus did not possess the same resistance to the action of reserpine. The lowest resistance to reserpine was shown by the reflexes from the central end of the divided vagus nerve and from the mechanoreceptors of the carotid sinus.

When injected in a dose of 0.25 mg/kg, reserpine caused considerable depression of the reflexes on the arterial pressure from the chemoreceptors of the pericardium were diminished by 35-40% and those from the chemoreceptors of the small intestine by 50-55% by comparison with the initial level (see Fig. 1, B).

In a dose of 0.5 mg/kg, reserpine caused a fall in the arterial pressure which lasted more than two hours. At the same time, when reserpine was given in this dose a more marked depression of the reflexes took place, as far as their complete disappearance.

It must be pointed out that the reflexes on respiration arising in response to stimulation of the receptor fields which we studied were more resistant to the action of reserpine than were the reflexes on the arterial pressure. For instance, the reflex on respiration in response to stimulation of the vagus nerve was not at all

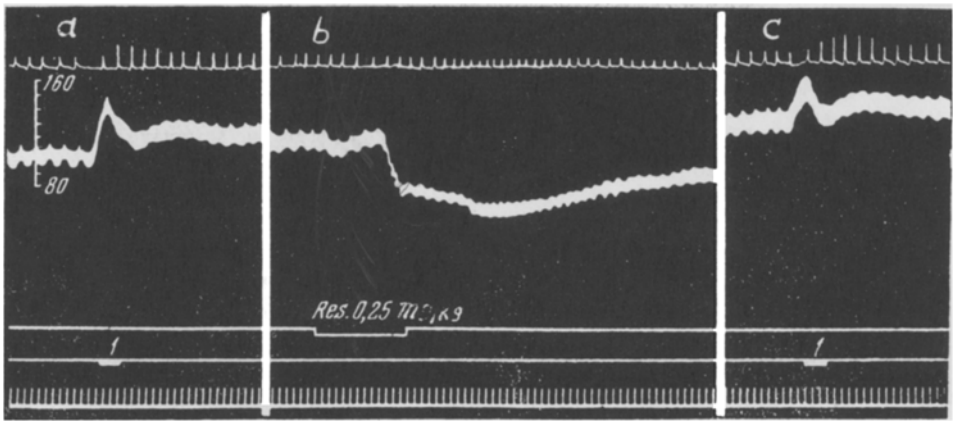

Fig. 3. The effect of reserpine on the reaction of the arterial pressure to stimulation of the peripheral end of the divided splanchnic nerve. Legend (from above down): respiration; arterial pressure; marker of injection of the drug; stimulation marker. a) Background; b) reaction of the arterial pressure and respiration to the injection of 0.25 mg/kg of the drug; c) 60 minutes after the injection.

depressed under the influence of reserpine even when the drug was given in doses which caused complete depression of the reflexes on the arterial pressure.

In spite of the reports in the literature that anesthetics (urethane, nembutal) have a weak action on reflexes from the internal organs [1], we had to exclude the possibility that the effect of reserpine was enhanced by the anesthetics, for reserpine is known to potentiate the action of the latter [9].

For this purpose a special series of experiments was carried out on cats rendered immobile by means of the curare-like drug ditilin. Under these circumstances it was shown that reserpine, in a dose of 0.25 mg/kg, given to cats rendered immobile by ditilin, caused depression of the reflexes from the mechano- and chemoreceptors to a lesser degree than in animals under anesthesia (Fig. 2). Evidently the effect of the action of reserpine on the reflex reactions of the circulation of the blood during anesthesia was somewhat enhanced. However we obtained no essential difference in the action of reserpine in experiments under these particular conditions.

In a special series of experiments we investigated the mechanism of the action of reserpine on the interoceptive reflexes. The generally accepted view nowadays is that the reflexes from the carotid sinus and other receptor fields are effected mainly by the vasoconstrictor fibers of the thoracolumbar division of the sympathetic nervous system and have a common efferent part of the reflex arcs.

The experiments which we carried out showed that the reaction of the arterial pressure in response to stimulation of theperipheral end of the divided preganglionic trunk of the splanchnic nerve after removal of the adrenal gland was preserved when reserpine was injected in a dose of 0.5 mg/kg, i.e., in a dose at which the reflexes were almost completely depressed (Fig. 3).

The control experiments thus led to the conclusion that depression of the interoceptive reflexes by reserpine evidently does not depend on the influence of the drug on the efferent pathways of the vascular reflexes.

The effect of reserpine on the receptors was also studied. For this purpose reserpine, in a dose of 0.25 mg per kg, was injected into the nutrient fluid during perfusion of an isolated loop of small intestine with the nerve connections intact. The experiments showed that the reflex on the arterial pressure from the chemoreceptors of the small intestine was not altered by bringing the reserpine solution into direct contact with the receptors.

The effect of reserpine on the reflexes was thus, evidently, not connected with either its action on the receptor formations or with its action on the efferent pathways of the vascular reflexes.

The results of these investigations thus lead to the conclusion that the effect of reserpine on the interoceptive reflexes is central in character. This hypothesis was confirmed by two other facts.

In the first place, in decerebrate animals the influence of reserpine on these reflexes was much more weakly demonstrated than in the experiments on anesthetized animals. Even when large doses of reserpine (0.5 mg/kg) were given, the depression of the reflexes was much less than was observed in the anesthetized animals.

Further confirmation of the central action of reserpine was given by the selective nature of its influence on the reflexes arising in response to stimulation of different receptor fields.

The reflexes least resistant to the action of reserpine were those from the carotid sinus and the central end of the divided vagus nerve. Furthermore, the reflex from the tibial nerve in some experiments not only was not depressed but was clearly enhanced. This selective action may possibly be due to the fact that reserpine depresses to a lesser degree those reflexes whose afferent centripetal pathways pass through the spinal cord.

It may also be established from these experiments that depression of the vegetative reflexes does not depend on the effect of reserpine on the efferent paths of the interoceptive reflexes and the receptors themselves. It may be postulated that its action on the vegetative reflexes is due to its influence on the central circulatory control system. This point of view is confirmed by reports in the literature, according to which reserpine experts an influence on the hypothalamic region, which is to depress the vascular reactions in response to direct stimulation of the hypothalamus [3, 5, 6].

SUMMARY

Experimental investigations ascertained the selective nature of reserpine action on the interoceptive reflexes. The reflexes from the carotid sinus and the central section of the vagus were the least resistant to the effect of this preparation. In a series of experiments the reflex from the tibial nerve not only shows no inhibition, but becomes markedly intensified.

The experiments also proved that the negetative reflexes are inhibited irrespective of the reserpine effect on the efferent pathways of the interoceptive reflexes and receptor formations. Its effect on the vegetative reflexes is evidently caused by the action upon the central apparatuses of the blood circulation.

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