PHARMACOLOGY

THE MECHANISM OF BRADYCARDIA INDUCED BY VERATRINE ALKALOIDS

V. V. Zakusov

Institute of Pharmacology and Chemotherapy (Director – Active Member AMN SSSR V. V. Zakusov), USSR Academy of Medical Sciences, Moscow

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According to modern concepts, bradycardia induced by veratrine alkaloids [5, 6] as well as by cardiac glucosides [4] is based on a Bezold-Jarisch type of reflex. One of the arguments in support of this point of view is the fact that no such bradycardia occurs upon section of the cervical vagi. Recently, however, we have obtained data indicating that bradycardia induced by veratrine alkaloids could also develop on the basis of a local reflex [1].

It is well known that veratrine alkaloids elicit bradycardia not only of the heart in situ but also of the isolated heart. In connection with this it could be expected that bradycardia arises by a local reflex in the latter case. The present work is concerned with verification of this hypothesis.

The morphologic substrate for local reflexes in the heart has long been established. As far back as the last century A. Dogiel [3] discovered the so-called cells of the second type in the cardiac ganglia, which are regarded by many modern histologists as afferent or sensory neurones of the autonomic nervous system [2]. The

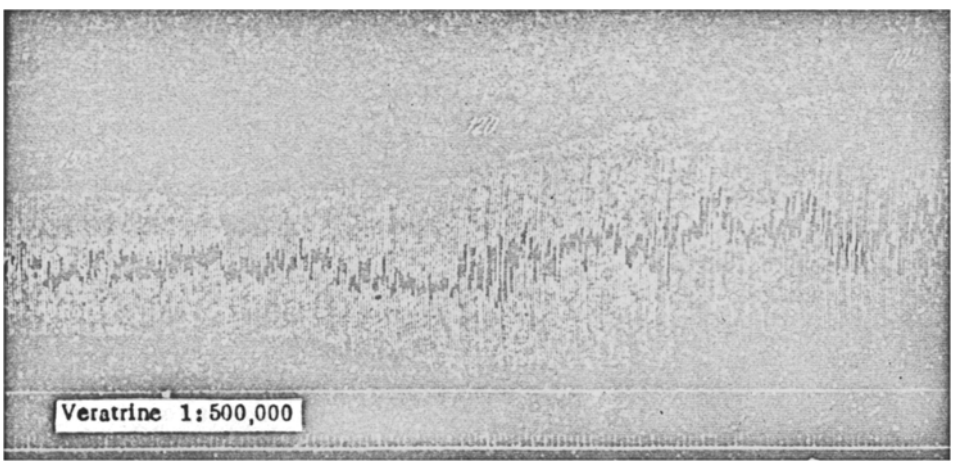

Fig. 1. The effect of veratrine alkaloids on the contractions of an isolated cat heart. Records from above down: cardiac contraction, mark indicating administration of the preparation, time marker (1 second).

efferent pathways of local reflexes in the heart are mediated by the postganglionic neurones of the vagi. Thus, upon stimulation of receptor formations in the heart the transmission of impulses from the afferent pathways to the efferent may be achieved in the cardiac ganglia.

METHODS AND RESULTS

Our experiments were for the most part performed on isolated hearts. The majority of experiments was carried out on cat hearts, the rest on white rat hearts. The hearts were isolated by the Langendorf method and were perfused with Kravkov's fluid, using the usual apparatus. The veratrine alkaloids were used in the form of a mixture – a Merck preparation called Veratrinum purissimum.

In the first series of experiments a check was made on the influence of veratrine alkaloids on the rhythm of contractions in the isolated cat heart. As should have been expected, these alkaloids produced definite bradycardia in relatively low concentrations ($1 \cdot 10^{-6}$) (Fig. 1) and arrhythmia and cardiac arrest in high concentrations ($1 \cdot 10^{-5}$ and higher).

In the next series of experiments the effect of veratrine alkaloids on the rhythm of cardiac contractions under the influence of ganglion-blocking substances was investigated, bearing in mind that if bradycardia so induced arose as the result of local reflexes it could be prevented by blocking transmission of impulses in the cardiac ganglia.

The ganglion-blocking substances used included pentamin** ($1 \cdot 10^{-5}$), hexonium ($1 \cdot 10^{-4}$), novocaine ($1 \cdot 10^{-5}$) and barbamyl** ($4 \cdot 10^{-5}$). It was found that these substances, with the exception of hexonium were not entirely suitable for this purpose since simultaneously with blocking ganglionic transmission in the heart they depressed cardiac activity; in other words they themselves caused slowing of cardiac contractions. Hexonium, however, proved a most convenient preparation for this investigation since it blocked transmission of impulses in the ganglia without causing appreciable depression of cardiac contractions. Following preliminary perfusion of the cardiac vessels with a solution of hexonium bradycardia was elicited by veratrine alkaloids to a smaller extent and in some cases no bradycardia at all was observed (Fig. 2).

Cardiac arrest under the influence of veratrine alkaloids occurs much later following treatment with ganglion blocking substances. For example, when under ordinary conditions veratrine alkaloids led to

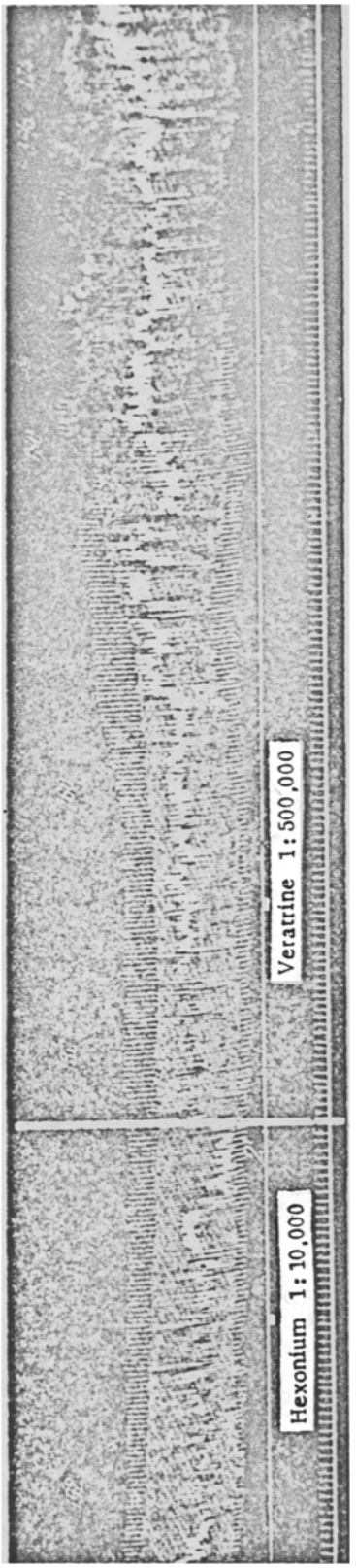

Fig. 2. The effect of veratrine alkaloids on contractions of the isolated cat heart following its treatment with hexonium.* Records the same as in Fig. 1.

* Transliterated. Probably hexamethonium – Publisher.

** Russian trade name.

arrest of the isolated rat heart in concentration of $1 \cdot 10^{-6}$ 3-6 minutes after its administration, following treatment of the heart with hexonium such effect was only achieved after 6-12 minutes.

It was important to establish the effect of veratrine alkaloids on cardiac contractions under conditions of experimental myocarditis since it has been shown that in the latter condition, produced by adrenalin and theophylline, transmission of impulses in the cardiac ganglia of the vagi is either hindered or completely blocked.

Myocarditis was induced in cats by successive intravenous injection of adrenalin (0.3-0.35 ml/kg), 0.1% solution of the hydrochloride, and theophylline (75 mg/kg). The onset and development of myocarditis was monitored by electrocardiograms and by the state of excitation transmission from the vagi to the heart. When the presence of myocarditis was established objectively, the heart was excised and placed in the usual apparatus for perfusion of isolated organs.

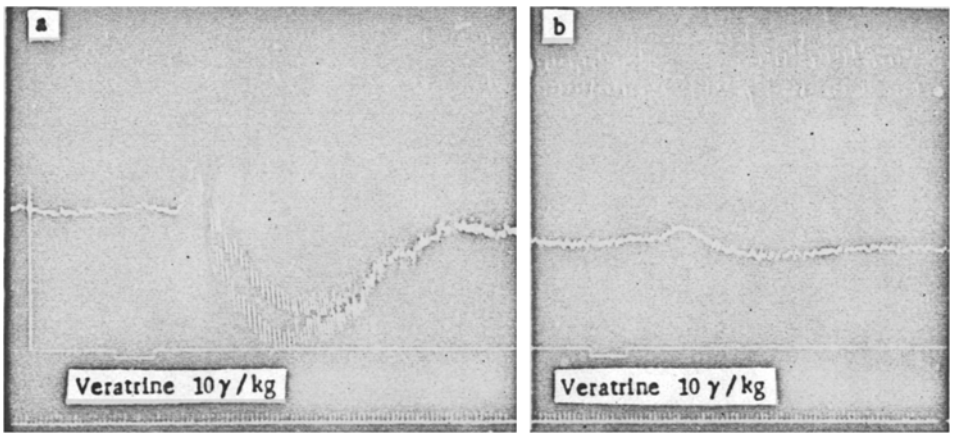

Fig. 3. The effect of veratrine alkaloids on blood pressure before (a) and after (b) introduction of hexonium into the blood.
Records from above down: blood pressure, administration of veratrine, time marker (1 second).

The results of these experiments corresponded to those of the preceding ones: veratrine alkaloids caused less marked bradycardia or no bradycardia at all when transmission of impulses in the cardiac ganglia was either prevented by ganglion blocking substances or hindered by conditions associated with experimentally produced myocarditis. In the latter case cardiac arrest by veratrine alkaloids occurred after longer delay.

The effect of veratrine alkaloids on the rhythm of cardiac contractions following the use of ganglion blocking substances was also studied in intact animals. In these cases, too, bradycardia was less pronounced (Fig. 3).

Finally, the effect of veratrine alkaloids on the rhythm of cardiac contractions in the presence of experimentally produced myocarditis was checked in experiments on intact animals.

The results of these experiments also coincided with the data obtained in experiments on the isolated heart, i.e., in the presence of experimental myocarditis bradycardia caused by veratrine alkaloids (10-20 mg/kg) was considerably less marked than in the normal heart.

Bradycardia of the isolated heart caused by veratrine alkaloids can thus be diminished by hexonium and other ganglion blocking substances. Moreover, these alkaloids give less pronounced slowing of cardiac contractions in the presence of experimentally produced myocarditis in the isolated heart, when transmission of impulses in the cardiac ganglia of the vagi is hindered. There are, therefore, grounds for considering that bradycardia of the isolated heart caused by veratrine alkaloids in relatively small doses develops along the line of local reflexes.

The suggestion that excitation of the vagal ganglia in the heart occurs under the influence of these alkaloids is refuted by the fact that the transmission of impulses from the vagi to the heart is not facilitated but inhibited in these cases.

In the intact organism, no veratrine alkaloid-induced bradycardia is observed after transection of the cervical vagi. Consequently, in the intact organism bradycardia arises reflexly by the Bezold-Jarisch type of effect. The question regarding the reason why local reflexes in the heart do not appear under the influence of veratrine alkaloids so far remains unanswered. It can only be supposed that only with complete denervation of the heart is it possible for local reflexes to arise in it.

Analogous effects may be observed under the influence of cardiac glucosides.

It follows that local reflexes can arise in the heart not only under the influence of veratrine alkaloids but also of cardiac glucosides. Consequently, this phenomenon is of a general character.

SUMMARY

Veratrine alkaloids in small doses cause bradycardia. This action depends mostly on the Bezold reflex. Under the effect of veratrine alkaloids bradycardia may appear in the isolated heart of the local reflex type. It is not yet clear why local reflexes of the heart in situ do not manifest themselves following section of the vagus nerves.

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