EFFECT OF VERATRINE ON NAD AND NAD · H_2 CONTENT OF THE MYOCARDIUM

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Experiments on anesthetized cats showed that veratrine, in a dose of 25 μg/kg, causes an increase in the content of NAD and a corresponding decrease in the content of NAD·H_2 in the tissues of the ventricle 3 and 10 sec after its injection into the chamber of the left ventricle. The features of similarity and difference between the effects of veratrine and serotonin, its agonist in a number of pharmacological effects, on the content of NAD and NAD·H_2 in the heart are discussed.

Veratrine induces several effects which are externally similar to those of serotonin. For instance, both veratrine and serotonin give rise to reflex responses (bradycardia, hypotension, and apnea) from the receptors of the heart and lungs [10]. Like serotonin, veratrine stimulates the chemoreceptors of the carotid sinus [1, 12, 16]. Both veratrine and serotonin have a cardiotonic action [9, 11, 13]. The primary mechanism of onset of the responses to serotonin and veratrine has been inadequately studied. However, pharmacological analysis has shown that the primary responses lying at the basis of the bradycardia, hypotension, and apnea induced by serotonin and veratrine are different.[3, 5-8, 10].

In order to determine the causes of this external similarity and also of the significant differences in the mechanism of the responses to serotonin and veratrine, it is evidently important to compare the biochemical changes induced by veratrine and serotonin. The writers have shown previously [2] that serotonin (7-35 μg/kg), if injected into the left ventricle of cats, increases the NAD content in the muscle of the left ventricle without altering the NAD·H_2 content. An increase in the NAD content is observed as early as 3 sec after intracardial injection of serotonin, i.e., before reflexes to serotonin appear. Against the background of reflex bradycardia the content of NAD and NAD·H_2 remains the same as in the latent period of the reflex.

The object of the present investigation was to determine the effect of veratrine on the content of NAD and NAD·H_2 in the myocardium.

EXPERIMENTAL METHOD

Just as in the earlier experiments with serotonin, cats weighing 2.5-3.5 kg were anesthetized with a mixture of urethane (600 mg/kg) and chloralose (40 mg/kg). The arterial pressure was recorded by a mercury manometer in the carotid artery. The heart rate was determined before the arterial pressure was recorded. To prevent the veratrine from entering the pulmonary vessels the drug was injected directly into the left ventricle. For this purpose a wide thoracotomy was performed under artificial respiration. A polyethylene catheter was introduced through the subclavian artery and ascending aorta into the left ventricle. Veratrine was injected in dose of 25 μg/kg in 0.5 ml physiological saline. When injected into the left ventricle in this dose veratrine induces reflex bradycardia from the cardiac receptors (threshold dose 10-20 μg/kg). The latent period of the reflex is 3.5-4 sec and its maximum occurs after 8-12 sec [4, 10]. The heart was quickly frozen in situ by means of Wollenberger's forceps cooled in liquid nitrogen 3 or 10

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sec after the injection of veratrine, i.e., at the same time intervals after injection of the drug and in the same phases of the reflex response as in the experiments with serotonin [2]. The left ventricle was minced in a mortar. The content of NAD and NAD·H_2 was determined enzymically: the first by Racker's method [14] and the second by a modified Stollar's method [15]. Experiments in which 0.5 ml physiological saline was injected into the animals' left ventricle acted as the control. The experimental results were subjected to statistical analysis. The arithmetic mean values and confidence limits at $P=0.05$ were calculated; the differences were considered significant if $P \leq 0.05$. At least five animals were used in each series of experiments.

EXPERIMENTAL RESULTS AND DISCUSSION

The mean NAD content in the myocardium of the control cats was 395.8 (415.86-375.74) μg/g weight of moist tissue. The NAD content in the myocardium 3 sec after injection of veratrine into the left ventricle was increased on the average by 46 μg/g to 441.7 (470.85-412.55) μg/g. When reflex bradycardia was present 10 sec after the injection, veratrine caused the same increase in the NAD content as during the first 3 sec. Its mean content at this period was 441.6 (490.0-393.2) μg/g. Consequently, when injected into the left ventricle of the cat's heart in a dose of 25 μg/kg, veratrine, like serotonin, gives rise to a statistically significant increase in the NAD content during the latent period and during reflex bradycardia.

The NAD·H_2 content in the myocardium of the left ventricle in the control animals was 168.1 (194.7-141.5) μg/g. Veratrine, when injected into the left ventricle of the cat's heart, caused the NAD·H_2 level to fall to 121.8 (142.65-100.95) μg/g. The combined total of NAD and NAD·H_2 after injection of veratrine was the same as in the control: 564.2 (594.9-533.9) μg/g in the first case and 565.0 (618.4-511.6) μg/g in the second.

Unlike serotonin, veratrine thus causes an increase in the NAD content through a redistribution of the oxidized and reduced forms of NAD.

The results of these investigations agree with those obtained by pharmacological methods and they show that the effects of serotonin and veratrine, despite their external similarity, differ in their primary mechanism of origin. With respect to the change in the NAD content, veratrine is not a true agonist of serotonin.

The increase in the NAD content under the influence of veratrine and serotonin could be a biochemical manifestation of their action which is or is not connected with one of the known pharmacological effects of these drugs. If such a connection exists, it is probably that the change in NAD content is the result of a certain pharmacological effect which is similar for both veratrine and serotonin. Otherwise the differences discovered in this investigation in the mechanism of the increase in NAD under the influence of veratrine and serotonin could not have existed. The fact that the redistribution of the oxidized and reduced forms of NAD is not the result of a reflex is also confirmed by the fact that this redistribution had already occurred 3 sec after injection of the drug, before any appreciable pharmacological responses to veratrine could be detected. The degree of the redistribution does not increase in the course of the hypodynamic changes.

However, the possibility cannot be ruled out that the increase in the content of the oxidized form of NAD, which is produced in different ways be veratrine and serotonin, is the initial common link in the chain of processes leading ultimately to one of the pharmacological effects which is characteristic of both veratrine and serotonin.

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