

HISTOPATHOLOGY OF THE NERVOUS ELEMENTS IN THE HEART AND THE AORTA OF DOGS AFTER INTRAVENOUS INJECTION OF ADRENALIN AND CAFFEINE

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It is not our intention to discuss in detail in the present paper the extensive literature concerning the influence of adrenalin and caffeine upon various animals. This question has been studied by numerous Russian and foreign authors from various aspects and to various purposes. [1,2,3,6,7,9,12,13,14]. Adrenalin, as a drug, is known to exert a favorable therapeutic effect upon man and animals, when injected subcutaneously in the accepted doses of the commonly used solution (1:1000). The same dose of the usual adrenalin solution, injected intravenously, however, has quite a different effect. Repeated intravenous injections, even of very small doses of adrenalin, lead to permanent changes in the blood vessels, changes, which affect above all the blood vessel wall. Initially, the vascular lesions consist in the infiltration of the tissues by an exudate; later, this is followed by sclerosis and petrification of the blood vessel wall.

Besides, it has been reported that intravenous injection of adrenalin produces acute myocarditis. [1,2,6,7,8,12]. O. P. Vishnevskaya showed on white rats that this condition develops extremely rapidly, towards the end of the first day after the injection. [1,2]. Szekeres, Mehes and Kovacsics [12] found that intravenous injection of caffeine into guinea pigs was followed by connective tissue proliferation and perivascular infiltrates in the myocardium, pericardium and at the base of the cardiac valves. A similar effect was observed in the heart of guinea pigs after prolonged (65-150 days) intraperitoneal injection of caffeine. Numerous authors reported that simultaneous injections of caffeine increased the incidence of myocarditis, produced by intravenous injections of adrenalin [6, 12].

The above question attracted our attention for two reasons: in the Laboratory of General Physiology, directed by V. N. Chernigovskii, intravenous injections of adrenalin and caffeine had been used to produce a neurotic state in the heart of dogs: administration of the above substances was to be combined with exposure to various conditioned and unconditioned stimuli. The necessity arose to study the morphology of the nervous elements in the heart of the experimental animals at various stages of the physiological experiment. This aspect of the investigation coincided with our own interests as our laboratory had been studying for a long time the morphological response of nervous formations in the peripheral nervous system in various organs and tissues under normal and pathological conditions. In the light of these investigations we set ourselves the task to study the histopathology of the nervous elements in the heart and aorta, after exposure to the pharmacological substances mentioned above. Simultaneously we studied the state of the myocardium in the same animals.

METHODS AND RESULTS

The main group of experimental animals consisted of 9 dogs which had been given daily intravenous injections of caffeine (1% solution in a dose of 1 ml) and adrenalin (1:1000 solution in a dose of 1 ml) and another dog which had been given the same doses every second day.

The control group consisted of 4 dogs: two of them were given the same doses of the substances mentioned above every second day by subcutaneous injection, and the two others received daily subcutaneous injections.

Only two of the 9 dogs in the main experimental group were killed: "Luna", after 3 injections, and "Pestryak",

after 17 daily injections. The remaining 6 animals perished after 1,2,3,8 and 9 daily injections respectively. The only dog which received adrenalin and caffeine injections every second day lived much longer and perished after 80 injections.



Fig. 1. Signs suggestive of neuron stimulation: formation of protoplasmic processes. Edema of the pericellular space. The dog "Vernyi" (2 injections on 2 consecutive days). Campos. Magnification 40×7 .

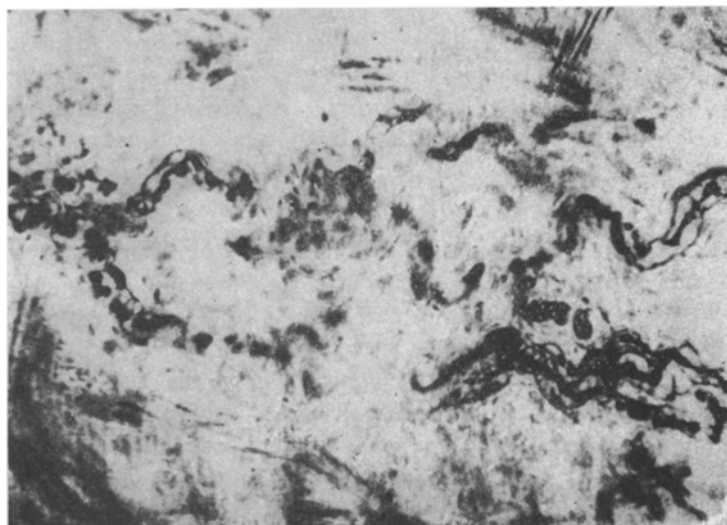


Fig. 2. Disintegration of thick sensory nerve fibers in the receptor zone of the aortic arch. The dog "Kashtanka". (80 injections, given every second day). Campos. Magnification 40×15 .

Some authors reported that even the first intravenous injection of adrenalin caused the animals' death due to adrenalin shock. [7,11]. The same authors emphasized that animals which had been suffering adrenalin shock and had survived the first injection became much more tolerant to subsequent injections of that substance. Repeated injections increase the animal's resistance to adrenalin. 6 out of 8 dogs survived repeated daily intravenous injections of adrenalin and caffeine.

Quite a different picture could be observed after subcutaneous injection of the substances mentioned above. None of the animals in this group perished although they were given a great number of doses daily (10,20) or every second day (10,41).

The physiological findings obtained in studies on the Higher Nervous Activity of the dogs used for the histological investigation, will not be discussed in the present paper.

The findings will be discussed only with regard to the effect exerted by the drugs in question upon the nervous system in the heart and the aorta after intravenous and subcutaneous injection respectively.

The hearts of 13 dogs were fixed in 12% neutral formalin solution. The condition of the myocardium in the right and left ventricle and of the papillary muscles was studied in sections stained with hematoxylin-eosin and the presence of fatty degeneration was established by the method of Daddy. The intramural nervous system in the heart and the aortic arch were impregnated with silver by the method of Campos and Gross-Bielschowsky.

In the case of 12 dogs autopsy was performed and the material was fixed in the first hour after death, and only 1 dog ("Kashtanka") was dissected 8 hours after its death.

Intravenous injection of adrenalin and caffeine frequently causes, as we said above, the animals' death after the first injection. We were unable to find pathological changes in the myocardium and in the intramural nervous system in the heart of animals succumbing after a single intravenous injection of adrenalin and caffeine. In dogs succumbing after the second and third injection a more or less marked picture of acute focal interstitial myocarditis could be found, consisting in the proliferation of the connective tissue elements in the interstitial tissue, and in the appearance of small round cell infiltrates. In one case (the dog "Luna", killed after the third injection) we found, in addition to the accumulation of round cell elements, focal fatty degeneration in the myocardium of the left ventricle. The picture of focal interstitial myocarditis was even more marked in the heart of dogs succumbing after 8,9 and 17 injections respectively. In these animals a proliferative reaction of the connective tissue surrounding the arterioles and the small myocardial arteries could be seen; the wall of these blood vessels was considerably thickened due to edema and connective tissue proliferation. The round cell infiltrates in the myocardium had increased in size. Proliferation of the connective tissue elements in the wall of the aortic arch could be observed.

Those authors who studied experimental myocarditis [1,2,6,8] reported that in rabbits and white rats a single injection of caffeine and adrenalin was followed by myocardium degeneration, leading to partial necrosis of the muscle fibers and their replacement with connective tissue. We were unable to observe, with the aid of Daddy's method, marked myocardium degeneration in the dogs. As we said above, we found only in one case small foci of fatty degeneration in the myocardium, after 3 injections of adrenalin and caffeine.

The picture found in the heart and the aorta of the dog "Kashtanka" is of particular interest. This dog was distinguished from the other animals in the same group by the fact that it received intravenous injections not daily, but every second day; the number of injections, however, was much higher than in the other dogs of the group in question.

In the dog "Kashtanka" we found only a slight proliferation of the connective tissue elements in the myocardial stroma. It can be assumed that in this dog the signs of acute interstitial myocarditis caused by the first intravenous injection of adrenaline and caffeine, in the course of time underwent regression.

We were unable to detect any pathological changes in the myocardium and the aorta of 4 dogs in the control group which were given subcutaneous injections of adrenalin and caffeine partly daily and partly every second day. In those animals which had been given 2-3 injections of adrenalin and caffeine on consecutive days, irregular varicose thickenings could be seen in the nerve fibers of large and medium caliber, passing through the auricular or ventricular myocardium; in addition, the formation of small vacuoles in the axis cylinders and, in some places, fraying of the neurofibrils in the axis cylinders could be observed. In various parts of the nerve fiber these changes were of different degree. The continuity of the nerve fibers was preserved. In the nerve cells of the intramural cardiac ganglia, marginal location of the nuclei, and the formation of pseudopodium-like processes containing small vacuoles could be observed.

Fig. 1 shows a nerve cell with its protoplasmatic processes and edema of the pericapsular space.

In those animals which perished after 8,9,17 and 80 injections respectively severe irreversible changes in the nerve fibers and nerve cells could be seen. The degree of the changes found in the nervous elements in the heart and the aorta as well as the number of nervous elements affected by the process was proportional to the number of inject-

ions received by the animal. In 4 dogs a great number of thin and thick nerve fibers in a state of Wallerian degeneration could be seen in the auricles in the vicinity of the intracardial nervous plexus and ganglia.

Fig. 2 shows various stages of Wallerian degeneration in thick medullated fibers in the aorta. The disintegration affects not only those nerve fibers which run in bundles and form plexuses; isolated thick medullated fibers which form the receptors can be seen to disintegrate completely into fragments. The receptors are also destroyed and the terminal branches of the sensory nerve fibers are replaced by granules and lumps as shown in Fig. 3. The nerve cells in the intramural ganglia lose their usual round shape, become pyknomorphic and are not filling out their capsular space, a fact which creates the impression of pericellular edema.

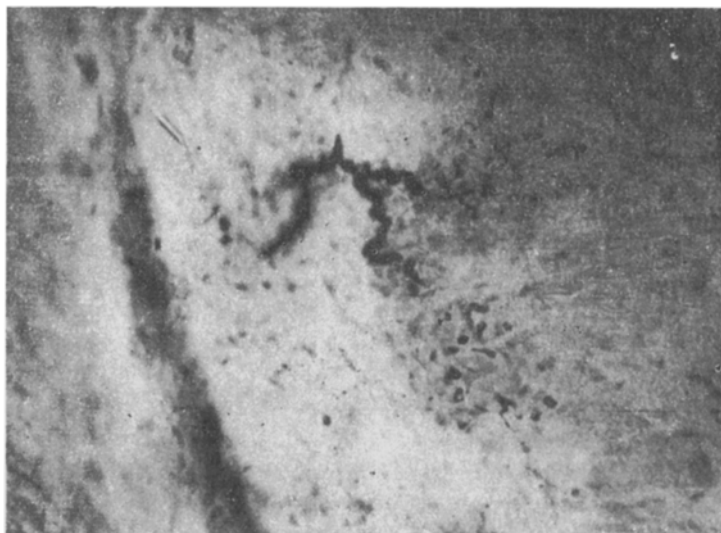


Fig. 3. Disintegration of a sensory nerve ending in the endocardium. The dog "Atka" (8 injections, given daily). Campos. Magnification 40×15 .

On the basis of our observations we are able to state that intravenous injections of adrenalin in the officinal solution and of 1% caffeine solution in a dose of 1 ml - administered daily or every second day - cause, in addition to myocardial lesions, changes in the intramural nervous elements of the heart: the nerve cells, nerve fibers of all calibers and in the sensory endings.

The gradual development of the histopathological process in the animals' heart and aorta can be observed. It is a basic feature of this process that the changes in the myocardial interstitium begin early and increase in intensity parallel to the number of injections; the death of the animals, however, can not be explained with these changes, inasmuch as we were unable to detect severe myocardial lesions in some dogs which succumbed after numerous repeated intravenous injections. (4 dogs.)

In the animals studied by us the development of the histopathological process in the nervous elements of the heart took quite a different course. Here too, a gradual development of the pathological structural changes in the intramural nervous apparatus can be observed. Initially, the lesions were of reversible character and became manifest in the so-called signs of stimulation. Characteristic signs of stimulation of the intramural neurons could be seen in dogs, which had received 2-3 intravenous injections. These changes consisted in the formation of processes, covered by outflowing neuroplasm, and resembling pseudopodia. Reactive neuron changes of the type described above were found in the intramural cardiac ganglia of persons who had died under symptoms of coronary insufficiency and also in other parts of the nervous system: e.g. in the intestinal nervous plexuses of cats after resection of the spinal ganglia and the solar plexus and after transection of the celiac nerves [4,5].

The investigations mentioned above have shown that reactive changes of the described type can reach a considerable degree. In the group of dogs studied by us, however, dogs which had been given 2-3 injections of adrenalin with caffeine, the above reactive changes were of relatively low intensity; in those animals which had been given a greater number of injections on the other hand, the changes were replaced by degenerative changes of the

neurons and the nerve fibers. Once the histopathological changes in the nervous elements of the heart and the aorta have developed, they soon take on a destructive, irreversible character. In those dogs which had been given more than 3 injections, we found a great number of nerve fibers in a state of far reaching disintegration. Physiologists and pharmacologists as well as clinicians who resort to intravenous injections of adrenalin and caffeine to study the response of the damaged heart to various stimuli will have to take into account the fact that the substances in question cause irreversible lesions in the nervous system of the heart: a heart, the nervous system of which has been damaged, may respond with distorted and quite unexpected reactions, reactions which could lead the investigator to erroneous conclusions.

SUMMARY

Repeated intravenous injections to dogs adrenalin (1: 1000 solution) with caffeine (1% solution) in a dose of 1 ml provoke severe injuries of the intramural nervous system of the heart. These derangements are manifested in progressive destruction of the nerve fibers of all calibers as well as of the sensory nerve endings. Irritation phenomena appearing in some of the nerve cells of the intracardiac ganglia after 2-3 injections, are later replaced by pyknosis if these injections are continued. There was focal interstitial myocarditis, and proliferative connective tissue reaction in the aortic wall. No histopathological changes in the myocardium, nervous elements of the heart or aorta were detected in control animals to which these substances were injected subcutaneously.

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