THE MECHANISM OF AMINOPYRINE CONVULSIONS

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Aminopyrine is widely used nowadays in medical practice. Overdosage of this drug may cause many complications such as, for example, dizziness, weakness, convulsions and collapse.

Henkel [3] concluded from his experiments on frogs, in which the central nervous system was transected at different levels, that the convulsive attack which develops after administration of large doses of aminopyrine is depressed by some divisions of the central nervous system and enhanced by others. This author did not, however, discover the mechanism of development of aminopyrine convulsions. It remained uncertain whether these convulsions were the result of a nervous reflex process or whether they developed by automatic stimulation of the central nervous system.

Yu. I. Detsik and I. I. Fedorov [1], when studying the mechanism of aminopyrine convulsions, showed that after intravenous injection of aminopyrine into a subcutaneous leg vein of dogs, without anesthesia, in a dose of 50-60 mg/kg body weight, convulsions quickly developed (at the prick of a needle) with tonic and clonic phases, lasting up to one minute.

When aminopyrine was injected into the suboccipital space, convulsions arose in response to a much smaller dose (8 mg/kg) than after intravenous injection.

On the basis of these findings it may be suggested that the dominant factor in the development of the convulsive attack is the direct action of aminopyrine on the brain substance, but in their later experiments these authors showed that when aminopyrine was injected into the common carotid artery the convulsive attack developed quickly in response to even smaller doses (2.5-3.0 mg/kg body weight) than when it was given into the suboccipital space. They came to the conclusion that the mechanism of the convulsive attack was dependent on the action of aminopyrine on the receptors of the blood vessels, and mainly on the receptors of the carotid sinus.

During perfusion of the isolated carotid sinus of dogs, under morphine anesthesia, with a 4% solution of aminopyrine, I. I. Fedorov and V. I. Zapadnyuk [2] observed slight motor excitation, a quickening of the respiration rate and sometimes whining at the moment of injection, but no convulsions were produced even when the aminopyrine was perfused through both isolated carotid sinuses.

These authors nevertheless assert that the aminopyrine convulsion is reflex in origin. They suggest that for a convulsion to develop it is necessary to have the combined action of aminopyrine not only on the carotid sinus but also on the receptor apparatus of other vascular zones, on the receptors of the internal organs and, possibly, directly on the central nervous system.

The problem of the dominant factor in the mechanism of development of aminopyrine convulsions thus remained unsolved.

It is difficult to agree with these authors' conclusions. In the first place, aminopyrine causes convulsions

when injected into the common carotid artery in much less doses than when injected by other routes. Secondly, during the action of aminopyrine on the isolated carotid sinus no convulsions developed, which is evidence of the direct action of aminopyrine on the brain, which it reached via the internal carotid artery.

In order to elucidate the mechanism of action of aminopyrine we undertook the present investigations.

EXPERIMENTAL METHOD

In all, 29 experiments were performed on 12 dogs.

In the first place we showed that a convulsive attack developed in response to injection of aminopyrine into dogs not only under morphine anesthesia, but also in a state of profound morphine – hexobarbital anesthesia, which we found very suitable for our experiments.

It was also found that under these conditions, the convulsions caused by aminopyrine did not developed in all the dogs (only in 8 of the 12 dogs). Finally, the repeated production of a convulsive attack was, as a rule, impossible within the first two hours of the last attack.

In our experiments the convulsive doses of aminopyrine, injected into the femoral vein or artery, were roughly the same, and amounted to about 30 mg/kg body weight. When aminopyrine was injected into the common carotid artery, convulsions developed with much smaller doses, namely 2.5 mg/kg body weight, which is in agreement with the findings in the literature. Only after the establishement of the convulsive dose by injection of aminopyrine into the common carotid artery were the principal variants of the experiments carried out.

EXPERIMENTAL RESULTS

In the first series of experiments we studied the effect of aminopyrine when injected into the common carotid artery after preliminary ligation of the internal carotid artery. As has already been pointed out, on injection of aminopyrine into the common carotid artery without preliminary ligation of the internal carotid artery, convulsions developed in response to a dose of 2.5 mg/kg body weight.

After preliminary ligation of the internal carotid artery, no convulsions developed in these same dogs even after injection of much larger doses of aminopyrine into the common carotid artery (5 mg/kg and 12.5 mg/kg and over), in spite of the possibility of the drug acting on the receptor apparatus of the carotid artery. In these conditions a convulsive attack could be produced, however, if aminopyrine was injected in doses exceeding the intravenous doses, i.e., 30 mg/kg. In the dog Polkan, for instance, convulsions developed only when the dose of aminopyrine was increased to 50 mg/kg body weight.

On the basis of these experiments it may be postulated that the essential link in the mechanism of production of convulsions is the automatic action of aminopyrine directly on the brain substance. This view is also supported by the results obtained in the next series of experiments, in which the external carotid artery was ligated and the aminopyrine was injected into the common carotid artery. In these experiments the aminopyrine passed through the internal carotid artery directly to the vascular system of the brain and convulsions developed rapidly (to the prick of a needle) with a dose of 2.4-2.0 mg/kg body weight.

In this particular case the possibility of reflex action from the carotid sinus reflexogenic zone is not excluded. In this connection it might be thought that important factors in the mechanism of the convulsive attack are both the direct action of aminopyrine on the brain and its reflex action via the carotid sinus reflexogenic zone.

For this reason, in some experiments, after ligation of the internal carotid artery the aminopyrine was injected into that vessel peripherally to the point of ligation, thereby avoiding the carotid sinus reflexogenic zone. It was found that to obtain a convulsive attack under these conditions required a much smaller dose (1.0-0.6 mg/kg body weight), a dose which when injected, failed to produce a convulsive attack in any other experiment which we carried out.

On the basis of the results obtained, we conclude that the main link in the mechanism of production of aminopyrine convulsions is the direct action of the drug on the brain, and not its reflex effect from the various vascular reflexogenic zones.

SUMMARY

When injected into the common carotid artery the convulsive dose of aminopyrine in dogs was 2.5 mg/kg, while into the femoral artery or vein it was about 30 mg/kg. After unilateral ligation of the internal carotid artery the convulsive dose of aminopyrine injected into the ipsilateral common carotid artery increased greatly and even exceeded the intravenous dose. Following unilateral ligation of the external carotid artery a dose of less than 2 mg/kg of aminopyrine induced convulsions, when injected into the common carotid artery of the same side. The convulsive dose of aminopyrine was even lower (0.6 mg/kg) when injected directly into the internal carotid artery (following ligation of this vessel below the site of injection).

Hence, the direct effect of this drug on the brain is to be regarded as the principal link in the mechanism of convulsions induced with aminopyrine.

LITERATURE CITED

[1] Yu. I. Detsik and I. I. Fedorov, The Mechanisms of Disease and Recovery. 31-34 (L'vov, 1951) [In Russian].

[2] I. I. Fedorov and V. I. Zapadnyuk, Fiziol. Zhur. [Ukrain.] 3, 5, 119-123 (1957).

[3] E. Henkel, Ueber die Kraftwirkung des Pyramidons. Diss. Halls (Saale, 1937).