THE INFLUENCE OF NOCICEPTIVE STIMULI ON THE CONVULSANT ACTION OF CAMPHOR

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The investigations of L. A. Orbeli [4] and many other authors convincingly showed that nociceptive stimuli, even when of short duration, cause obvious changes in the reactivity, creating a new "background" for the staging of events in the body along different lines from normal, in response to external influences.

In view of this discovery, we decided to examine the changes in the character of action of drugs when administered to animals after brief nociceptive stimulation. A series of papers from one of us [2, 3] has been devoted to the explanation of this problem; in particular, the influence of nociceptive stimuli on the convulsant action of certain analeptics has been studied.

It has previously [2] been shown that after the intraperitoneal injection of strychnine nitrate to guinea pigs in a dose of 3.0 -3.2 mg/kg, marked convulsions were observed in all the animals in control experiments. After injection of the same doses of strychnine into animals previously subjected to strong nociceptive stimulation for five minutes (stimulation of the paw with current from the mains, stepped down to 85-90 v), convulsions were either not present at all or they were very mild (only movements of the jaws or scratching were observed).

It was shown later [3] that after the subcutaneous injection of cardiazol to white rats in a dose of 70 mg/kg, clonic convulsions, sometimes becoming tetanic, were observed in control animals. When rats were injected with the same dose of cardiazol 1-10 minutes after the application of a nociceptive stimulus for ten minutes (stimulation of the paw with the current from the mains, stepped down to 30 v), although convulsions were observed in nearly all the animals, they always developed later. The number of cases of clonic convulsions turning into tetanic decreased after nociceptive stimulation.

Nociceptive stimuli thus had an undoubted effect on the intensity of the convulsant action of the analeptics studied, which had different points of main application: Strychnine acts mainly on the spinal cord and cardiazol on the midbrain.

In order to obtain certain general conclusions it was important to ascertain the effect of nociceptive stimuli on the convulsant action of camphor, the point of application of which is the cerebral cortex. The present work is devoted to the investigation of this problem.

EXPERIMENTAL METHOD

Our experiments were carried out on 200 male white mice and 4 male guinea pigs. All the mice received subcutaneous injections of camphor in a dose of 1 mg/g body weight as a 20% solution, and observations on the general condition of the animals were conducted for 2 hours and more. The time of appearance of the first signs of a convulsive state, the intensity of the fits (on a five point system: 0 - no fits, 5 - death) and their duration were recorded visually.

The experimental animals were divided into two groups: 100 mice acted as controls and 100 mice were subjected to nociceptive stimulation (compression of the root of the tail by means of an apparatus, specially constructed by V. V. Levoshin, permitting accurate dosage of the stimulus) for three minutes before the injection of the camphor. The injection of camphor was given to the mice two minutes after the end of stimulation. Each mouse was used only once in the experiment.

We carried out 8 additional experiments on 4 guinea pigs, at first conducting on each animal a control experiment, in which a 20% solution of camphor (0.2-0.24 mg/g body weight) was injected intraperitoneally, and then 10 days later, an experiment on each animal with nociceptive stimulation (the hind paw was stimulated by current from the mains, stepped down by means of a rheostat to 80 v). Stimulation was continued for ten minutes and the same dose of camphor as in the preceding experiment was given three minutes afterwards. During the experiment the animal was kept in a box specially adapted for actographic recording; tracings were made on a slowly revolving kymograph drum.

EXPERIMENTAL RESULTS

In the overwhelming majority of the mice (92 of 100), clonic convulsions, sometimes turning into tetanic, were observed in the control experiments after receiving injections of camphor in this dose. The convulsions began at different times after the injections of camphor, on the average 23 minutes. In only 29.3% of the animals (in 27 of the 92) was the latent period of the convulsions more than 30 minutes.

The mortality among the mice in the control experiments was high: more than half the total number of

animals which developed convulsions died (57 of 92). The time of death varied considerably. In the surviving animals (9 of 35) the convulsions were strong or of moderate intensity (3-4 points).

A different picture was observed in the animals subjected to nociceptive stimulation before the injection of camphor. In this group, convulsions were observed in only 68 of the 100 mice. They began only a little later than in the control animals, on the average 30 minutes after the injection of camphor. The latent period of the convulsions exceeded 30 minutes in 45.5% of the experimental animals (30 of 68).

The mortality among the animals subjected to stimulation in relation to their total number was lower (44 of 100) than in the control group, although in relation to the number of animals in which convulsions were observed, it was the same (62 and 64%). The times of death among the experimental animals varied considerably; we could detect no regularity about these variations nor in those in the control group. The intensity of the convulsions in the animals which survived after the fits was slightly less than in the control group. For instance, strong convulsions and those of moderate intensity (3-4 points) were observed in only four animals.

The experiments on mice thus showed that nociceptive stimuli decrease the frequency of development of convulsions after injection of camphor, and lengthen their latent period.

In the experiments on guinea pigs the findings were as follows: in the control experiment in guinea pig No. 1, after the injection of 0.2 mg/g of camphor convulsions began after eight minutes and lasted for 26 minutes. In the same guinea pig, after nociceptive stimulation, the beginning of convulsions was observed after 13 minutes, and they lasted 17 minutes. The intensity of the convulsive attack was the same in both experiments. In guinea pig No. 2, after injection of 0.2 mg/g of camphor, convulsions began after seven minutes and lasted ten minutes; in the same guinea pig the injection of camphor after preliminary nociceptive stimulation had no appreciable effect on either the time of onset of the convulsions (after nine minutes) or their duration (12 minutes), but the intensity of the fit was perceptibly weakened. In guinea pig No. 3, after injection of 0.24 mg/g of camphor, convulsions started after 23 minutes and lasted for 41 minutes; the injection of camphor into the same guinea pig after nociceptive stimulation produced absolutely no fit at all. Guinea pig No. 4 received an injection of 0.24 mg/g of camphor, and in the control experiment fits developed after 23 minutes and lasted for 42 minutes. In the same guinea pig the injection of camphor after preliminary nociceptive stimulation gave rise to a fit only after 91 minutes, which lasted, moreover, for 16 minutes, and was greatly weakened by comparison with that observed in the control experiment.

The experiments on guinea pigs, admittedly few in number, thus showed that nociceptive stimulation lengthened the latent period of the fit developing after injection of camphor, as a rule shortened its duration and weakened its intensity.

As the experimental results show, nociceptive stimulation after the injection of camphor has a retarding influence on the development of the convulsive state in both mice and guinea pigs. By comparing these results with those of previous experiments with strychnine and cardiazol, we can see that the nociceptive stimuli affect the action of all these analeptics in the same fashion.

Since our experiments were performed on different animals we are debarred from making a quantitative comparison of the effects obtained, although in every case, irrespective of the points of main application of the action of the drugs that were studied, nociceptive stimulation delayed the development of the convulsive attack. We are inclined to explain the similarity that we observed in the effects by the fact that, in all the investigations, under the influence of the nociceptive stimulation the development of inhibition took place in the central nervous system, and this prevented the manifestation of the convulsant action of strychnine, cardiazol and camphor. The inhibition developing in the central nervous system under the influence of nociceptive stimulation is evidently parabiotic in nature, as we have previously shown [1, 2].

In a paper recently published by V. S. Sheveleva [5], convincing results are described showing the development of inhibition in different divisions of the central nervous system under the influence of nociceptive stimulation, and proving its parabiotic nature.

SUMMARY

The effect of nociceptive (pain) stimulation on the convulsant effect of camphor was studied on white mice and guinea pigs. Camphor was injected subcutaneously in a dose of 1 mg/g to mice and intraperitoneally in a dose of 0.20-0.24 mg/g to guinea pigs. Convulsions in mice were recorded visually and evaluated according to the 5-point system (0 - absence of convulsions, 5 - death); in guinea pigs convulsions were registered actographically and recorded on a kymograph. Camphor was injected 2 minutes following discontinuance of the stimulation, which lasted 3 minutes in mice and ten minutes in guinea pigs. Experiments proved that following nociceptive stimulation, the times of onset of convulsions, as compared with controls, are postponed, the convulsions occur in a smaller number of animals, while the intensity of the already developed convulsions becomes lower. The authors hold that these effects of nociceptive stimulations on the convulsant effect of camphor are evidently caused by the development of inhibition in the central nervous system, preventing the convulsive attack.

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