EFFECT OF NEOSTIGMINE ON EXPERIMENTAL ATROPINE PSYCHOSIS IN ANIMALS

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The ability of neostigmine to diminish or to completely prevent disturbances of conditioned reflexes in animals and of mental activity in man caused by atropine has been described by M. Ya. Mikhel'son and co-workers [5, 8]. Neostigmine is used as an antidote in atropine poisoning.

Meanwhile, results have been obtained showing that neostigmine does not always abolish the effects of atropine. N. V. Savateev [9], for instance, reported that disturbances of conditioned reflexes in cats caused by large doses of atropine are not abolished by neostigmine. V. B. Prozorovskii [7] found that in albino mice the development of paralysis of the central nervous system caused by lethal doses of atropine is not prevented by neostigmine. It has also been found that neostigmine does not abolish the depression of the respiratory center in atropine poisoning [13] and does not remove the block of the reticular formation caused by atropine [10].

Such conflicting results suggest that the methods used to study the effect of neostigmine must be supplemented by the method of investigating the action of neostigmine on experimental atropine "psychosis" in animals, produced by N. A. Gol'denberg's method [2]. The present investigation was carried out for this purpose.

EXPERIMENTAL METHOD

Experiments were carried out on 80 adult dogs weighing 4-10 kg. To reproduce the characteristic signs of a behavioral disturbance classed as components of "delirium" in these animals, a 2% aqueous solution of atropine sulfate was used in a dose of 4 mg/kg.

Thirty minutes after administration of atropine, when the animals had developed severe symptons of atropine psychosis, a 0.1% aqueous solution of neostigmine was injected subcutaneously in one of the following doses: 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, and 0.6 mg/kg. Each of these doses of neostigmine was investigated on 10 dogs.

To compare the severity and duration of the symptoms of the psychosis in all the dogs, control experiments were carried out in which atropine alone was given. After 7-20 days, these dogs received the same dose (4 mg/kg) of atropine, followed by an injection of neostigmine. The duration and severity of the behavioral disturbances and the autonomic disorders in the dog followed a stereotyped pattern in repeated experiments, as M. A. Gol'denberg [2] emphasized.

For the investigation of the effect of neostigmine on the course of the atropine psychosis, the method of observation was used. In clinical psychiatry, this is the most important method of recording psychopathological disorders.

EXPERIMENTAL RESULTS

Following injection of neostigmine in doses of 0.1 and 0.2 mg/kg into animals with atropine psychosis, the peripheral effects of its toxic action were observed (vomiting, tremor, paresis of the limbs), and these were intensified when the dose of neostigmine was increased to 0.3 mg/kg or more. At the same time, large doses of neostigmine diminished the autonomic disorders caused by atropine poisoning (the pupils were constricted and salivation was caused).

However, both in doses of 0.01 and 0.05 mg/kg, when no visible peripheral symptoms of its action in general were present, and in doses of 0.1 and 0.2 mg/kg, neostigmine had no effect on the severity of the characteristic signs of the behavioral disturbance of the animals during the period of excitation and asthenia. The dogs continued to move about the laboratory without stopping, to bark angrily into space, to collide with obstacles, and to "climb up the wall."

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During the action of neostigmine in doses of 0.3 and 0.4 mg/kg, the animals' movements became slower and jerky because of the marked tremor and weakness of the limbs. The dogs fell periodically and lay on their side, but they continued to bark and howl from time to time, and they constantly tried to stand up. The signs of asthenia were more marked than in the control experiments (in which atropine alone was injected).

After administration of neostigmine in doses of 0.5 and 0.6 mg/kg to the animals with atropine psychosis, the marked toxic action of the drug was the most prominent feature. The dogs lay on their side and developed clinical convulsions and gross weakness of the limbs (sometimes they could not stand up).

It may be considered that in experiments described by some authors [5, 8], the disturbances of the conditioned reflexes caused by small doses of atropine (0.17 and 0.5 mg/kg) in dogs were abolished by neostigmine because one of the main factors in the disturbance of the conditioned reflexes by atropine was the peripheral disorders preventing the response reaction after application of the conditioned stimulus. Neostigmine restored the conditioned-reflex reaction in the animals probably because it removed the peripheral component of the atropine poisoning. After administration of atropine in a "psychological" dose (2-9 mg/kg), on the other hand, it has been found [3] that the central action is most important, and despite the removal of certain peripheral phenomena of atropine poisoning, in this case neostigmine had no effect on the disturbances of the animals' general behavior.

This investigation confirms the view that anticholinesterase substances containing quaternary nitrogen, the class to which neostigmine belongs, possess a weak central action or produce no central effects whatever [1, 6, 11, 12]. Interesting experiments in this direction were carried out by M. D. Mashkovskii and R. Yu. Il'yuchenok [4], who observed no changes in the general behavior of dogs when given neostigmine in doses not producing severe peripheral effects.

The results now obtained are in agreement with those described by other authors [7, 9, 10, 13], according to whom administration of neostigmine is ineffective for disturbances of the activity of the central nervous system in animals caused by atropine. A critical examination must be made of claims that neostigmine can be used for removing the phenomena of the atropine psychosis.

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