USE OF ACETYLCHOLINESTERASE REACTIVATORS AND OF CENTRAL CHOLINOLYTICS IN THE TREATMENT OF EXPERIMENTAL TETANUS

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The therapeutic efficacy of acetylcholinesterase reactivators dipyroxime and isonitrozin, and also of the central cholinolytics benactyzine and adiphenine, was studied in experiments on rabbits with tetanus produced by intravenous injection of one lethal dose of tetanus toxin. Dipyroxime in a dose of 25 mg/kg had no therapeutic action, and in doses of up to 30-40 mg/kg caused death of the animals. Benactyzine and adiphenine, in a dose of 3-4 mg/kg, abolished tonic convulsions for 1.5-2 h, and isonitrozin in a dose of 25 mg/kg did so for 4-5 h. After combined administration of reactivators and cholinolytics, convulsions were abolished for 4-5 h.

KEY WORDS: experimental tetanus; acetylcholinesterase; muscarinic cholinolytics; acetylcholinesterase reactivators.

Disturbance of inhibitory mechanisms by tetanus toxin [7, 9, 17, 19, 20] involves the formation of generators of pathologically enhanced excitation in the CNS [10, 18], and this lies at the basis of the varied neuropathological syndromes of tetanus and, in particular, of the convulsive syndrome [8, 10, 11, 21]. Under these conditions secondary inhibition of acetylcholinesterase (AChE) activity is also evidently a possibility, with the consequent excess of acetylcholine in the corresponding CNS structures, which could potentiate paroxysmal activity. The writer found inhibition of AChE activity in the motor components of the CNS of animals with experimental tetanus [1]. Other workers obtained similar results [3, 4]. There is evidence in the literature of the favorable effect of AChE reactivators in experimental tetanus and also clinically in man [22-25], as well as in poisoning by anticholinesterase compounds [2, 14]. In the last case positive results have been described after the use of central cholinolytics [5, 16].

It was accordingly decided to test both AChE reactivators and central cholinolytics in the treatment of experimental tetanus.

In the investigation described below the efficacy of the cholinesterase reactivators dipyroxime (TMB-4) and isonitrozin, and also of the central cholinolytics benactyzine and adiphenine, was tested.

EXPERIMENTAL METHOD

Experimental tetanus was produced in rabbits of both sexes weighing 2-3 kg by intravenous injection of one lethal dose of tetanus toxin per animal equivalent to 30 μg/kg. All the animals died in the course of 3-5 days. On the appearance of signs of the disease (trismus, rigidity of the muscles), which usually developed 40-50 h after injection of the toxin, and in the later stages of tetanus the animals were given the test drugs, dissolved in 4 ml physiological saline, by intravenous injection. The doses of the drugs were: for TMB-4 and isonitrozin 25 mg/kg, benactyzine 3 mg/kg, and adiphenine 4 mg/kg.

Since in rabbits with experimental tetanus the head is nearly always thrust backward or upward (opisthotonus) on account of rigidity of the neck muscles, lowering of the head after injection of the test drugs was taken to be as a result of their action. In the later stages of the disease, in the presence of clonic convulsions, the absence of convulsions in the animals in response to tapping on the cage in which they were kept was taken to be due to the action of the drugs tested.

AChE activity was determined by Hestrin's method in Panyukov's modification [15] in the motor cortex and anterior horns of the sacral portion of the spinal cord of animals killed by air embolism 0.15-2 h after injection of the toxin.

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TABLE 1. AChE Activity in CNS of Rabbits with Experimental Tetanus before and after Administration of Isonitrozin (M ± m)

Group of animals	Number of animals	AChE activity, mg acetylcholine/g tissue/min	
		spinal cord	motor cortex
Healthy (control)	11	8,45±1,35	3,17±0,96
Experimental tetanus, III degree	8	4,78±1,04	2,51±0,86
The same + administration of reactivator	13	4,97±0,34	3,72±0,93

EXPERIMENTAL RESULTS

Experiments on 14 rabbits showed that administration of sonitrozin abolished clonic convulsions for 4-5 h without significantly reducing tonic contraction. Dipyroxime, in a dose of 25 mg/kg, caused virtually no decrease in the convulsions, and an increase in the dose to 30-40 mg/kg led to death of the animals in the course of 5-10 min. According to data in the literature [2, 14], dipyroxime, unlike isonitrozin, does not pass through the blood-brain barrier and can reactivate only peripheral cholinesterase.

In 13 rabbits killed by air embolism 0.15-2 h after administration of isonitrozin, which abolished their clonic convulsions, the AChE level was determined in the motor zones of the CNS.

As Table 1 shows, isonitrozin reactivated AChE in the cerebral cortex but has no appreciable effect on AChE in the spinal cord.

Experiments on 15 rabbits showed that the cholinolytics abolished clonic and reduced tonic convulsions for 1.5-2 h; benactyzine was more effective in its action, evidently on account of the predominance of muscarinic cholinergic systems in the CNS [5]. Administration of central cholinolytics to animals (twice a day) with experimental tetanus of degree II-III did not significantly prolong their life. Similar administration of isonitrozin twice a day to 14 rabbits also had no significant effect on the course of the disease. Simultaneous administration of cholinolytics and isonitrozin gave a brief effect (4-5 h) in 15 animals.

It can thus be concluded from these experiments that the fall in AChE activity in the motor centers in tetanus is the result either of decompensation following the increased liberation of acetylcholine, ultimately leading to convulsions, or of depression of AChE activity by secondary toxic substances, since AChE reactivators are known to have a definite corrective action. Under these conditions administration of both cholinolytics and reactivators gives only a brief effect and can be regarded simply as a palliative measure, for it does not affect the action of tetanus toxin on nerve cells.

The increase in the concentration and potentiation of the activity of AChE in the motor centers of the CNS must lead to a reduction in their excessive content of acetylcholine, due to the formation of generators of pathologically enhanced excitation [10, 18], thereby weakening convulsive activity. In connection with these results close attention must be paid to clinical data on the beneficial therapeutic effect on AChE reactivators against tetanus in man [23-25].

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EFFECT OF CESIUM, LITHIUM, AND RUBIDIUM ON SOME ACTIONS OF MORPHINE

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The effect of cesium, lithium, and rubidium chlorides on the analgesic action of morphine (in the vocalization test) and on the course of dependence on it (by the "two bottle" test) was investigated. The chlorides were shown to reduce both the threshold of the pain response and the duration of analgesia produced by morphine. Cesium chloride was most active in this respect. All the compounds studied reduced the coefficient of morphine preference. The greatest effect was observed with cesium chloride, which reduced the preference coefficient to one-fortieth of the control level.

KEY WORDS: lithium; cesium; rubidium; dependence on morphine.

In the search for substances for the treatment of dependence on opiates compounds belonging to the alkali metal group could be interesting. The effects of some of them, such as lithium salts, have been investigated by several workers. Admittedly, data in the literature on the effect of lithium on the course of morphine dependence are contradictory. Saarnivara and Mannisto [10], for instance, state that lithium reduces the analgesic action of morphine, whereas Weischer and Opitz [11] found that the analgesic effect of codeine also is weakened by lithium. Meanwhile there are reports that lithium can potentiate the analgesic effect of morphine in experimental animals [6] and also its euphoric action in man [5].

The effect of rubidium on the actions of morphine has received less study. During prolonged administration of rubidium the analgesic effect of morphine is reduced [10], but, unlike lithium, rubidium stimulates motor activity induced by morphine [2].

The effect of cesium on the actions of morphine has not been studied. Considering that cesium possesses neurotropic properties [8], it was clearly desirable to undertake a comparative study of the effect of cesium, lithium, and rubidium on the actions of morphine under identical experimental conditions.

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