HYPERKINESIS OF CENTRAL ORIGIN INDUCED BY TETRIDINE AND ITS INHIBITION BY ANTICHOLINESTERASE (CHOLINE-SENSITIZING) AGENTS

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Many researchers engaged in the study of effects induced by barbiturates have observed peculiar motor activity in both animals and people. This reaction is known as barbiturate, or stem, hyperkinesia and has been described in detail by I. V. Markova [4,6]; the same author has shown that stem hyperkinesia can be induced by other somnifacients (besides barbituric acid derivatives) and by anticonvulsants [5]. In experiments on white mice, I. V. Markova discovered that proserine [neostigmine]* (0.01-0.1 mg/kg) can be used to prevent and eliminate barbiturate hyperkinesis.

We discovered that tetridine (2,4-dioxy-3,3-diethyltetrahydropyridine), a pyridine derivative similar in structure and narcotic effect to barbiturates [1,7,8], induces stem hyperkinesia in different animals (frogs, mice, rats, rabbits and guinea pigs). We used medinal [barbital sodium], Nembutal and hexenal [hexobarbital] to demonstrate the similarity of barbiturate hyperkinesia to tetridine hyperkinesia.

The purpose of this work was to investigate the effect of anticholinesterase agents (proserine, eserine and phosphacol [diethyl p-nitrophenyl phosphate]) and cholinolytic agents (atropine, scopolamine, tropacine [ester of diphenylacetic acid hydrocloride], pentaphene [diethylaminoethyl ester of phenylcyclopentacarbonic acid], arpenal [acylated diethylpropylene diamine], methyldiphacyl [diphenylacetic acid β-diethylaminoisopropyl ester hydrochloride] and methyldiazyl [benzilic acid β-diethylaminopropyl ester hydrochloride]) on tetridine hyperkinesia in guinea pigs and white mice.

METHOD

All the compounds mentioned above were administered intraperitoneally to the guinea pigs and subcutaneously to the mice. Hyperkinesia was induced by tetridine, used in doses of 100-130 mg/kg for the guinea pigs and in doses of 150-200 mg/kg for the mice. The hyperkinesia induced by these doses lasted two hours or more.

Since hyperkinesia was particularly well defined in the guinea pigs, the majority of the experiments were performed on these animals; the anticholinesterase and cholinolytic agents were administered to them on a background of developed hyperkinesia, but to the mice before the administration of tetridine.

RESULTS

The administration of anticholinesterase agents (0.06-0.16 mg/kg proserine, 0.15-1.0 mg/kg eserine salicylate or 0.2 mg/kg phosphacol) to guinea pigs on a background of tetridine hyperkinesia completely inhibited the latter for 10-60 min (Fig. 1). This inhibition could be reproduced several times in the same animal (but was not attempted more than two to three times in our investigations because of the other effects induced by any additional injections – fasciculation, etc.).

The administration of cholinolytic agents (5 and 50 mg/kg atropine sulfate, 0.5 and 25 mg/kg scopolamine hydrobromide, 12.5 and 50 mg/kg tropacine, 10 and 15 mg/kg pentaphene, 40 mg/kg arpenal, 10 mg/kg methyldiphacyl or 10 and 20 mg/kg methyldiazyl) to mice 10-15 min before the tetridine injection did not prevent the development of hyperkinesia. This agrees with the data N. A. Kharauzov [9] obtained in his study of diphacyl's

*Here and hereafter the terms in brackets are the preferred or more commonly used English expressions for the immediately preceding Russian names [Publisher's note].

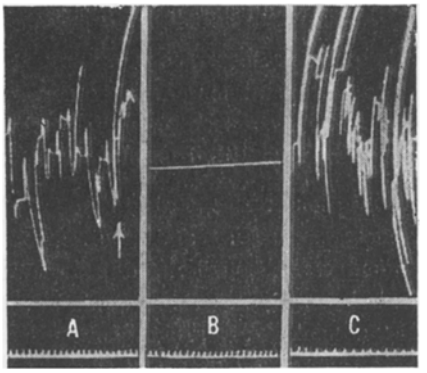

Fig. 1. Kymogram of hyperkinesia induced in a guinea pig by the intraperitoneal injection of 130 mg/kg tetridine. The animal is lying on its side, the recording apparatus connected to its hind leg. A) Before administration of eserine salicylate; B) 15 min after administration of 1 mg/kg eserine—total inhibition of hyperkinesia; C) 24 min after eserine injection – hyperkinesia restored.

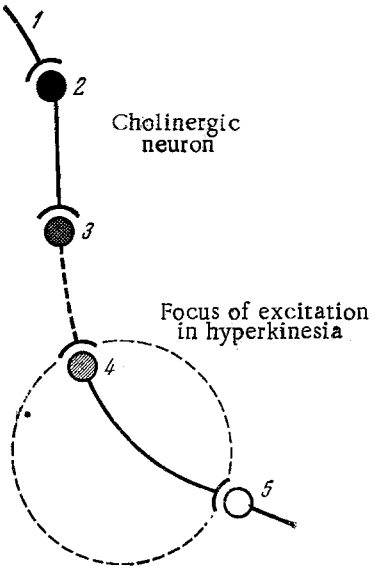

Fig. 2. Diagram showing relationship between cholinergic neuron and neuron whose stimulation leads to development of stem hyperkinesia.

[diphenylacetic acid diethylaminoethyl ester] effect on barbiturate hyperkinesia in rabbits. Scopolamine and methyldiazyl, however, intensified the narcotic effect and shortened the hyperkinetic period. Atropine (0.5, 5 and 100 mg/kg) and methyldiazyl (0.5 mg/kg) were administered to guinea pigs after the development of hyperkinesia. Neither of these drugs eliminated the hyperkinesia.

If atropine was administered first, the subsequent administration of the anticholinesterase agents (0.1-0.2 mg/kg proserine, 1 mg/kg eserine or 0.2 mg/kg phosphacol) failed to inhibit tetridine hyperkinesia even when repeated. A 0.5 mg/kg dose of atropine prevented the effects of anticholinesterase agents in 80-90% of the cases; doses of 5 and 100 mg/kg, in 100% of the cases.

The data presented demonstrate the ability of anticholinesterase agents to inhibit tetridine hyperkinesia. This effect is prevented by the administration of the cholinolytic agent atropine. The diagram in Fig. 2 illustrates the hypothetical relationship between the cholinergic neuron and the neuron which is stimulated in the development of stem (barbiturate and tetridine) hyperkinesia.

Since cholinolytic agents do not prevent or inhibit the hyperkinesia, neuron 4 cannot be cholinergic. Neuron 5 cannot be cholinergic for the same reasons. It is unlikely that the cholinergic neuron immediately precedes the neuron responsible for the hyperkinesia (neuron 3). If neuron 3 were cholinergic, the anticholinesterase agents would intensify hyperkinesia. Therefore, the cholinergic neuron must be located in front of the neuron which, when stimulated, causes hyperkinesia (this is neuron 2 in our drawing, situated one or several neurons above neuron 4), and so neuron 3 is the cholinergic neuron.*

The short duration of the inhibitory effect exerted by proserine, eserine and phosphacol cannot be attributed to their inactivation, since their repeated administration (and consequently, increase of their total dose) gives rise to peripheral effects (fasciculation, salivation, lacrimation, et al.) attending the central effect. It is, however, possible to assume the fixation of these agents by non-specific receptors, as Bovet [2] proposed in the case of succinocholine.

* This paragraph conforms to the Russian original, although it is clearly inconsistent and self-contradictory. It has been suggested that the last sentence should read: "...neuron 3 is not the cholinergic neuron," but we have no way of verifying this [Publisher's note].

The fact that phosphacol, which induces an irreversible or hardly reversible inhibition of cholinesterase, behaves in the same way as the reversible inhibitors eserine and proserine deserves special attention. Its interpretation requires investigation of the opinions of several authors [3,10] to the effect that the anticholinesterase and cholinesensitizing effects of this group of compounds should be differentiated. The latter effect is temporary and seems to be paramount in our experiments.

SUMMARY

Experiments were performed on guinea pigs and albino mice. An inquiry was made into the effect of cholinesensitizing and cholinolytic substances on the tetridine hyperkinesis in guinea pigs. Tetridine, as is the case with many barbiturates, apart from the anesthetic effect causes stem hyperkinesis in many animals. Cholinolytics (atropine, scopolamine, tropacine, pentaphene, arpenal, ethyldiazyl and methyldiphacyl) do not prevent tetridine hyperkinesis in mice. Atropine and methyldiazyl do not depress hyperkinesis in guinea pigs. Choline-sensitizing (anticholinesterasic) agents depress tetridine hyperkinesis temporarily. This effect may be repeatedly reproduced in the same animal. Inhibition of tetridine hyperkinesis by a choline-sensitizing agent may be prevented by a cholinolytic substance, such as atropine.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
