EFFECT OF CENTRAL CHOLINOLYTICS ON ELECTRICAL CONVULSIONS IN MICE AND RABBITS

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The anticonvulsant activity of the central cholinolytics [1,2,3] during specific excitation of the central cholinergic systems has been studied in considerable detail [4,5,8], although few investigations have been made of the anticonvulsant properties of the substances of this group against convulsions of different origin. Nevertheless the close study of the anticonvulsant properties of different substances and of the points of application of their action may facilitate the more rational synthesis of new compounds and may contribute towards the more efficient utilization of existing substances for therapeutic purposes.

In the present research a comparative study was made of the anticonvulsant action of a number of central cholinolytics of different structure, whose activity against electric convulsions has not hitherto been investigated.

METHOD

Experiments were conducted on mice and rabbits. Clip electrodes (gauze soaked in a 4% solution of sodium chloride) were fixed to the ears of a mouse, and a sinusoidal current with a strength of 5 mA was passed through for a period of 0.5 sec. An additional resistor of 30,000 Ω was included in the circuit. The mice were placed in the basket of an actograph, by means of which the animals' movements could be recorded on the paper of a kymograph rotating at uniform velocity.

The drugs (metamysil, aprophene, methyldiphacil, and pentaphene) were injected intraperitoneally in a dose of 20 mg/kg, 10 min before application of the stimulus. Each substance was tested on 10 animals.

Since under these conditions the whole of the brain, and above all the cortex, was stimulated by the electric current, experiments were carried out on rabbits to determine the effect of the muscarine-like cholinolytic metamysil and the nicotine-like cholinolytic methyldiphacil on the convulsions caused by stimulation of the motor area of the cortex and the subcortical regions. These compounds were injected intravenously in doses of 5 and 20 mg/kg 10 min before application of the stimulus.

RESULTS

Transient stimulation of the brain of the mice with an electric current causes a severe convulsion, in which three phases may be distinguished: an initial clonus, a tonic phase, and a period of clonic spasms [7,10,11]. The duration of the convulsion in our experiments varied around a mean of 30 sec (2,20, and 8 sec for each phase).

It will be seen from Figs. 1 and 2 that the cholinolytics produced a definite anticonvulsant effect and considerably depressed or, in some cases, totally abolished the tonic phase of the convulsion. In this respect a more marked depressant action was observed from the use of those drugs possessing stronger central muscarine-like cholinolytic properties.

Because of what is known about the role of the cortex and the subcortical formations in the development of clonic and tonic convulsions, and also of the differences, previously reported by us [2,3], in the strength of the blocking effect of the central muscarine-like and nicotine-like cholinolytics on the cholinergic synaptic systems of

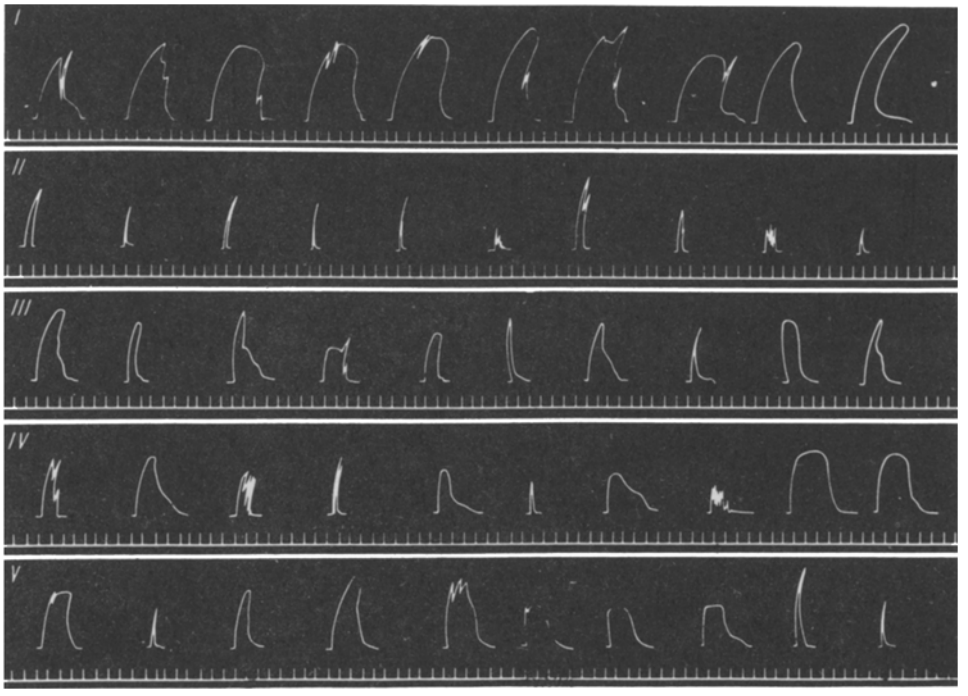

Fig. 1. Effect of central cholinolytics on convulsions in mice caused by electrical stimulation of the brain. Top curve in each kymogram—tracing of convulsive movements of mouse, bottom—time marker (5 sec). All substances used in a dose of 20 mg/kg. I) control; II) metamysil; III) aprophene; IV) methyldiphacil; V) pentaphene.

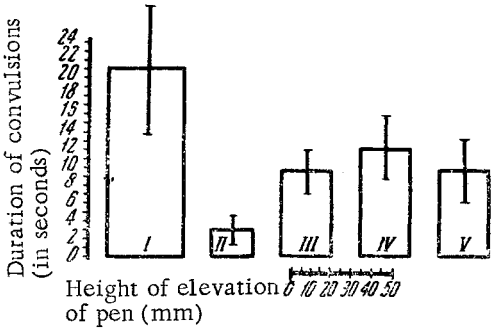

Fig. 2. Graphic illustration of mean data of experiments on mice. Legend as in Fig. 1.

the cortex and subcortex, 36 experiments were carried out on rabbits in which electrical stimulation was applied to the cortex and subcortex.

These experiments showed that the central cholinolytics metamysil and methyldiphacil in most cases did not prevent the onset of convulsions, but considerably reduced their severity. The difference in the strength of the blocking action of these substances in convulsions caused by stimulation of the cortex and subcortex was very appreciable (see table).

The data obtained by many investigators, including ourselves, show that nicotine and arecoline hyperkineses are specific. The ability of cholinolytic drugs to prevent these hyperkineses demonstrates that these substances possess specific anticonvulsant properties, which cannot in any circumstances be regarded as universal.

As our experiments showed, the difference between the cholinolytic activity and the ability of compounds to prevent leptazol or electrical convulsions is a feature not only of previously known drugs (pentaphene, arpenal, spasmolytin), but also of new compounds closely related to them in structure and pharmacological action (metamysil, methyldiphacil, etc.).

The difference between the blocking effects of the substances in convulsions of different origin can be explained on the assumption that specific zones exist in the central nervous system which are selectively sensitive to nicotine, arecoline, leptazol, and other agents: excitation of these zones leads to the development of a convulsion. At the same time, it must also be assumed that the points at which the impulses relay along the effector path from these formations are located in different levels, and that probably they do not all contain cholinergic synapses. These

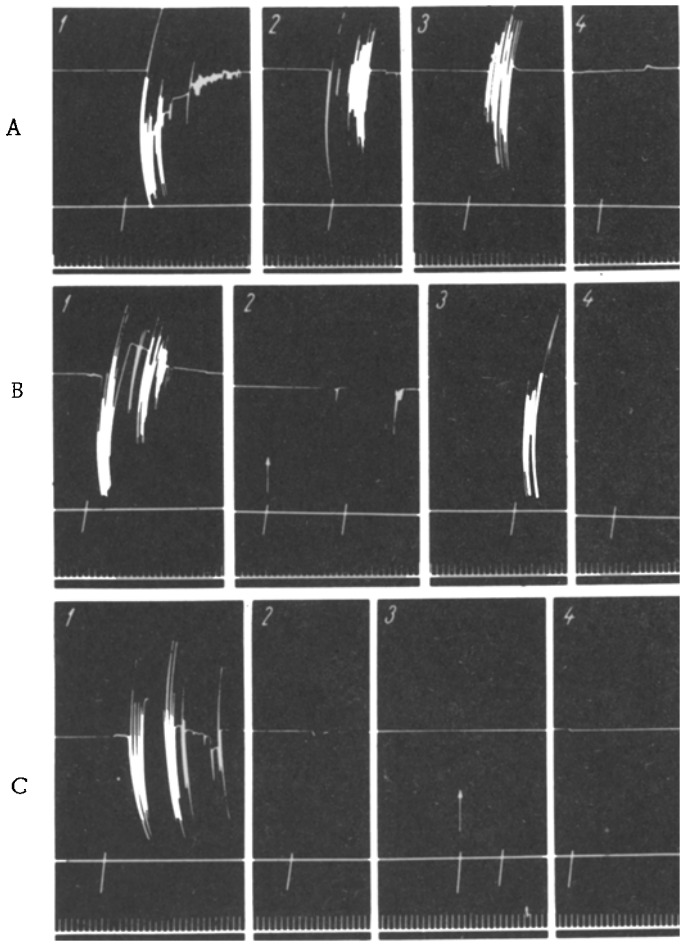

Fig. 3. Nicotine and arecoline convulsions in rabbits. Experiments on 3 animals with successive administration of substances. 1) arecoline, 2) nicotine, 3) arecoline repeated, 4) nicotine repeated in convulsive doses in all cases. A) experiment on intact rabbit; B) experiment on intact rabbit with prevention of nicotine convulsions by means of spasmolytin (2, upward arrow) and preservation of convulsant effect of arecoline (3); C) experiment on rabbit with brain divided at the level of the posterior colliculi. Absence of nicotine (2) and presence of arecoline (1) convulsions in normal conditions. Prevention of arecoline convulsions (3, upward arrow) by metamysil.

Effect of Metamysil and Methyldiphacil on Convulsions in Rabbits Caused by Electrical Stimulation of the Brain

Preparation	Dose (in mg/kg)	Stimulation of cortex		Stimulation of subcortex	
Control	–	$^{6}/_{6}$	(4)	$^{6}/_{6}$	(4)
Metamysil	3	–	0	$^{3}/_{5}$	(1)
	5	$^{5}/_{5}$	(3)	$^{2}/_{5}$	(1)
Methyldiphacil	5	$^{4}/_{5}$	(3)	$^{5}/_{5}$	(3)
	20	$^{2}/_{5}$	(2)	–	

Note. Numerator—number of cases of convulsions; denominator—number of animals in experiment. Mean number of points indicating severity of convulsion is given in parentheses: 0) absence of convulsions, 1) appreciable reaction to stimulation, 2) weak convulsions, 3) strong, 4) convulsions similar to those seen in controls.

suggestions are supported by the experimental findings obtained by ourselves and by other investigators.

Nicotine is known to cause convulsions when administered repeatedly, but only after a definite time interval, measured in days, whereas arecoline convulsions may develop approximately 1 h after the first administration of arecoline. Taking account of the ability of nicotine, in large doses, to block structures sensitive to it, and also the possibility of producing convulsions with arecoline after administration of nicotine in a convulsive dose (Fig. 3), it must be admitted that the great majority of nicotine-sensitive elements are situated at higher levels of the brain than the point of application of the action of arecoline or of the pathways leading from it. The correctness of this assumption is also confirmed by the fact that, after section of the brain at the level of the posterior colliculi, arecoline in minimal doses caused convulsions of the previous intensity, whereas administration of nicotine in minimal doses (0.45 mg/kg) in 7 of 10 cases was not accompanied by convulsions.

It has been shown [6] that after section of the brain at the level of the anterior colliculi the convulsant effect of arecoline is completely preserved, whereas the effect of nicotine is considerably depressed. Our findings, together with the data cited above, showed that the severity of leptazol convulsions after section of the brain at this level is practically unchanged. Since the central cholinolytics in optimal anticonvulsant (in relation to nicotine and arecoline) doses only partially prevented or lowered the severity of leptazol convulsions, it must be assumed that excitation from the brain centers due to leptazol spreads in a downward direction, mostly through noncholinergic synaptic systems. A similar conclusion may also be drawn in respect of electrical convulsions, although in this case the central cholinolytics are more effective than when leptazol is given.

The results of our experiments using electrical convulsions agree with those obtained by V. E. Smirnov [7]. Substances with mainly muscarine-like cholinolytic properties (metamysil, diphazin) had a more marked depressant (inhibitory) effect on electrical convulsions than the nicotine-like cholinolytics (arpenal, methyldiphacil, spasmolytin). This difference was more clearly seen during stimulation of the pyramidal and nonpyramidal regions of the brain.

Taking into consideration the different points of application of the action of the nicotine-like and muscarine-like cholinolytics, and also the existence of noncholinergic descending pathways of spread of nervous impulses during the convulsive paroxysm, the treatment of patients with hyperkineses of central origin must be by means of a combined method, using substances with different types of action.

The discovery of the stronger anticonvulsant effect of the muscarine-like cholinolytic metamysil during stimulation of the subcortical region, and also of the more marked depression of the "tonic phase" of the convulsion than with the nicotine-like cholinolytics during stimulation of the brain in mice, on the one hand, and the acceptance by the majority of neurologists that the subcortex plays a leading role in the development of tonic convulsions, on the other hand, enabled us to recommend metamysil (like the other central muscarine-like cholinolytics) for the treatment of hyperkineses of an extrapyramidal character. The first clinical trials of metamysil on more than 50 patients with extrapyramidal paralyses and hyperkineses gave very encouraging results [9]. A scientific documentary film has been made on the subject of the therapeutic action of metamysil.

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