EFFECT OF TROPANE ON ACETYLCHOLINE RECEPTORS OF THE CEREBRAL CORTEX

Academician V. V. Zakusov*
and S. N. Kozhechkin

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KEY WORDS: sensomotor cortex; microiontophoresis; tropane; acetylcholine; atropine.

Tropane is the basic structural unit of biologically active compounds such as cocaine, ecgonine, atropine, etc. Tropane is known to have a stimulating action on the CNS [1, 2]. On microiontophoretic investigation of neurons of the ventrolateral thalamus, tropane potentiated the stimulating effect of noradrenalin. It is suggested that activation of adrenoreceptors of deep brain structures (the thalamus, and so on) lies at the basis of excitation of cerebral cortical neurons in response to systemic administration of tropane [1]. However, it is difficult to explain excitation of cortical neurons observed following microiontophoretic application of tropane to them by activation of adrenoreceptors. We know that the basic effect of noradrenalin, applied microiontophoretically to cerebral cortical neurons is not excitation, but inhibition of electrical activity [3, 4].

The aim of this investigation was a microiontophoretic study of possible interaction between tropane and membrane acetylcholine receptors of cortical neurons. Acetylcholine (ACh) is the principal claimant for the role of excitatory mediator in the cerebral cortex.

EXPERIMENTAL METHOD

Experiments were carried out on 17 adult rabbits weighing 3-3.5 kg, immobilized with diplacin† (5 mg/kg) and artificially ventilated. Action potentials (AP) of sensomotor cortical neurons were derived extracellularly by one barrel of a five-barreled micropipet, filled with 3 M NaCl. The remaining barrels were used for microiontophoretic application and were filled with aqueous solutions of the following substances: tropane hydrochloride (0.3 M, pH 4.5), ACh chloride (0.3 M, pH 4.0), atropine sulfate (0.3 M, pH 4.5). One barrel, filled with 3 M NaCl, was used to monitor and compensate current artefacts.

EXPERIMENTAL RESULTS

The predominant effect of tropane, like ACh, when applied microiontophoretically to the cortical neurons, was excitation, reflected in an increase in spontaneous AP frequency. Tropane excited 27 and ACh 31 of the 67 neurons tested (Table 1). Electrical activity of a considerable proportion of neurons was inhibited by tropane (29 of 67 neurons) and ACh (23 of 67). Characteristically, the direction of response of the neurons to tropane and ACh was the same. The overwhelming majority of neurons excited by ACh (31) were excited by tropane (27), of those inhibited by ACh (23) 20 were inhibited by tropane, and of those not responding to ACh (13) 12 did not respond to tropane.

The pattern of excitatory neuronal responses to tropane was very similar to the pattern of typical responses to ACh. The response usually had two phases: short inhibition followed by powerful excitation, often with a long aftereffect.

The excitatory responses to tropane were smaller in magnitude than those of ACh despite the use of equimolar solutions of the substances and equality of the microiontophoretic currents. Typical curves of excitatory effect as a function of dose of ACh and tropane applied to the same neuron are given in Fig. 1. A considerable

*Academy of Medical Sciences of the USSR.
†1,3-di(β-platyneciniumethoxy)benzene hydrochloride.

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TABLE 1. Correlation between Different Types of Responses of Sensomotor Cortical Neurons to Microiontophoretic Application of ACh and Tropane

ACh	Tropane			Total
	+	–	no effect	
+	27	1	3	31
–	0	20	3	23
No effect	0	1	12	13
Total	27	22	18	67

Legend. Numbers indicate number of neurons; +) increase in frequency, –) decrease in frequency of AP.

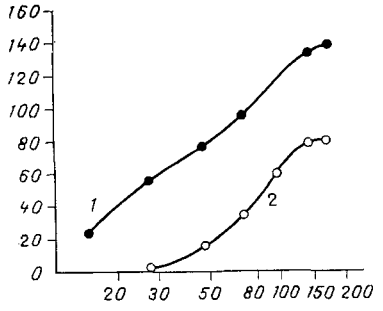

Fig. 1

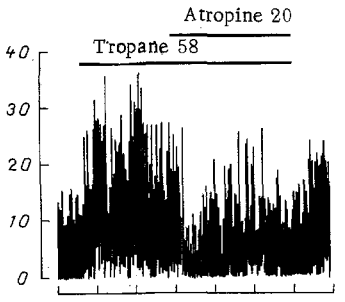

Fig. 2

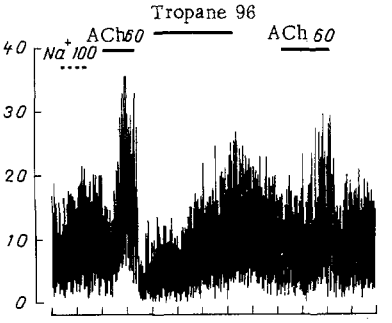

Fig. 3

Fig. 1. Dependence of excitatory effect of tropane and ACh on sensomotor cortical neurons on dose of microiontophoretically applied substances. Abscissa, microiontophoretic current, in nA ($1 \cdot 10^{-9}$ A). Quantity (dose) of substances applied to neuron is proportional to strength of current; ordinate, increase in spontaneous discharge frequency of neuron (in % of initial frequency of AP before application of agents taken as zero. 1) ACh; 2) tropane.

Fig. 2. Reduction of excitatory effect of tropane by atropine. Abscissa, time (in min); ordinate, firing rate of neuron (spikes/sec). Horizontal lines indicate duration of microiontophoretic application of substances; numbers above them show strength of microiontophoretic currents (in nA).

Fig. 3. Reduction in magnitude of excitatory response of neuron to ACh by tropane. Legend as to Fig. 2.

shift to the right of the dose–effect curve for tropane will be apparent, evidence that it is less effective than ACh.

On the basis of the foregoing facts it can be postulated that tropane interacts with the same receptors of the nerve cell membrane as ACh. The specificity of activation of muscarinic ACh receptors by tropane is confirmed by reduction of the excitatory effect of tropane by the muscarinic cholinolytic atropine (Fig. 2). Antagonism between atropine and tropane was observed in all of the four neurons tested.

A fact which deserves special attention is the reduction of the excitatory response of the neuron to ACh after preliminary microiontophoretic application of tropane. One typical example of such antagonism between tropane and ACh is illustrated in Fig. 3. It will be clear from Fig. 3 that both tropane and ACh have an excitatory action on the neuron, although in the case of tropane this effect was much weaker and developed more slowly. ACh, applied against the background of residual excitation of the neuron after application of tropane had ended, did not induce such powerful excitation as that which characterized it before tropane. The acetylcholine

response developed slowly, did not reach its initial value, and was often interrupted by periods of marked inhibition of unit activity. Antagonistic interaction between tropane and ACh of this kind was observed in five of seven neurons tested.

It can be concluded from these results that tropane specifically activates muscarinic ACh receptors in the cerebral cortex. While it has low intrinsic activity (effectiveness), by occupying ACh receptors it can enter into competitive relationships with the natural ACh of nerve tissue and reduce the excitatory effect of the latter. The muscarinic cholinolytic effect of atropine is perhaps based on this same property of tropane, which accounts for the greater part of its molecule. Inhibition of activity of some of the cells studied by microiontophoretically applied tropane may be due to its competition with excitatory cholinergic background influences, acting on single neurons from neighboring cortical structures, and also deep brain formations and the periphery.

Excitation of the cortex discovered by the writers previously in response to systemic injection of tropane in doses not exceeding 10 mg/kg was evidently due mainly to activation of adrenoreceptors of subcortico-cortical excitatory pathways [1]. After systemic injection of tropane in larger doses, more than 20 mg/kg, we observed inhibition of electrical activity of cerebral cortical neurons. The cause of this inhibition may be the cholinolytic action of tropane described above. This same property of tropane may be responsible for the inhibition of central nervous processes which develop in the case of overdosage with its derivatives, such as cocaine, atropine, and so on.

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EFFECT OF ATYPICAL NEUROLEPTICS CARBIDINE AND SULPIRIDE ON STRIATAL SYNAPTOSOMAL TYROSINE HYDROXYLASE ACTIVITY IN THE RAT BRAIN

A. A. Meos, V. S. Kudrin, and K. S. Raevskii

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KEY WORDS: corpus striatum; tyrosine hydroxylase; dopamine; carbidine; sulpiride.

Neuroleptics, both typical and atypical, have the property of accelerating dopamine (DA) turnover in the brain, the limiting factor in its biosynthesis being tyrosine hydroxylase (TH) [4]. It is suggested that the point of application of atypical neuroleptics may be presynaptic dopamine receptors (autoreceptors), located on terminals of dopaminergic neurons and participating in regulation of the biosynthesis and release of the neurotransmitter [13].

The aim of this investigation was to study the effect of the original Soviet neuroleptic carbidine* and to compare it with that of sulpiride on regulation of TH activity in synaptosomes of the rat corpus striatum. Sulpiride (a benzamide derivative) is one of the best known atypical neuroleptics [7]. Carbidine is a derivative of γ-carboline and has a unique spectrum of action, combining features of a neuroleptic and an antidepressant [1]. The neurochemical mechanisms lying at the basis of the psychotropic action of carbidine have received little study. Only indirect evidence has been obtained that the drug can modify DA biosynthesis [2, 3].

*3,6-dimethyl-1,2,3,4,4a,9a-hexahydro-γ-carboline di-HCl.

Laboratory of Neurochemical Pharmacology, Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.)

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