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A selective excitatory effect of lithium on cholinoceptive neurones in the spinal cord and brain of cats and rats: a possible significance in manic-depression

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The administration of lithium salts to manic-depressives causes a marked reduction in the transport of choline into erythrocytes (Lee, Lingsch, Lyle & Martin, 1974). If this action of lithium has any significance for its effectiveness in manic-depression then lithium may have an action similar to that of hemicholinium at central cholinergic synapses. This possibility has been examined at a number of sites in brain and spinal cord, but the results were opposite to those anticipated and revealed what appeared to be a selective excitatory action of lithium on cholinoceptive neurones. This selectivity leads to the tentative suggestion that the effects may be presynaptic and restricted to cholinergic nerve terminals: lithium may have a similar action at the neuromuscular junction (Kelly, 1968; Carmody & Gage, 1973).

The experiments were carried out in cats and rats anaesthetized with pentobarbitone or urethane-pentobarbitone respectively. Lithium was administered microelectrophoretically from 5-barrelled micropipettes containing LiCl. Other barrels contained acetylcholine bromide (ACh), NaCl, hemicholinium and, in a few experiments, sodium glutamate.

The first experiments were carried out upon feline Renshaw cells in the spinal cord because they have an identifiable cholinergic input from motor axon collaterals. Lithium was administered for periods of up to 50 min whilst observing either the background firing rate or the magnitude of the discharge to a submaximal antidromic ventral root volley. On most cells there was a gradual increase in the firing rate or synaptic discharge, with little or no effect in the first 5-10 minutes. The excitation was slowly reversible. Appropriate controls demonstrated that the excitation was not due to the passage of current.

Other spinal interneurones, for which evidence of a cholinergic input is lacking, were not excited by Li or ACh. Hemicholinium depressed the synaptic discharge of Renshaw cells and also caused excitation, as reported previously (Quastel & Curtis, 1965). However, unlike Li, hemicholinium produced a similar excitation of non-cholinoceptive spinal interneurones.

In tests on supraspinal neurones in cats and rats, lithium excited most (about 80%) of all cells excited by ACh in cerebral cortex, thalamus, caudate nucleus, hypothalamus and brain stem but usually failed to excite non-cholinoceptive neurones in the same regions of the CNS. In the hypothalamus, where cells may also be excited by histamine, there was no correlation between histamine-evoked and Li-evoked excitation. There appeared to be a difference between presumed relay neurones and non-relay neurones in the thalamus in that non-relay cells were usually insensitive to Li, although equally sensitive to ACh.

The unique action of Li upon cholinoceptive neurones poses a problem in defining its mode of action but adds a further dimension to the spectrum of central actions of this ion of possible relevance to its use in the treatment of manic-depressives.

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The effects of phenytoin on adenosine triphosphatase activities of synaptosomes and their components

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The mechanism of the anticonvulsant action of phenytoin is often assumed to involve the sites of active translocation of sodium ions out of the cells and nerve terminals of the central nervous system. These sites are closely associated with adenosine triphosphate (ATP)-hydrolysing enzymes which are activated by various cations. The recent observations in our laboratory that the anticonvulsant ethosuximide inhibits a synaptosome sodium, potassium-activated, magnesium-dependent adenosine triphosphatase (Na,K-ATPase), that the enzyme involved may be located in the external membrane of the synaptosome, and that a magnesium-activated ATPase (Mg-ATPase) located in the vesicle-containing fraction prepared from synaptosomes is also inhibited by ethosuximide, led us to investigate the effects of phenytoin on these enzymes.

Synaptosomes were prepared by homogenizing rat cerebral cortex in 0.32 M sucrose solution containing 1 mM EDTA and subjecting the mitochondrial fraction, obtained by differential centrifugation, to further centrifugation on a sucrose density gradient (Balfour & Gilbert, 1971). The sodium-activated, magnesium-dependent ATPase (Na-ATPase), Mg-ATPase and Na,K-ATPase activities were determined by measuring the release of inorganic phosphate from Tris-ATP as described previously (Gilbert, Scott & Wyllie, 1974).

Phenytoin (2×10^{-7}-2×10^{-4} M) did not significantly alter the Mg-ATPase activity of the synaptosomes, however the drug inhibited the Na,K-ATPase activity by approximately 80%. The synaptosomes exhibited Na-ATPase activity, in the absence of exogenous potassium ions, and this activity corresponded in magnitude to the Na,K-ATPase activity which was insensitive to phenytoin. The Na-ATPase activity was not itself altered by phenytoin.

Festoff & Appel (1968) have suggested that the effect of phenytoin on the Na,K-ATPase activity of synaptosomes depends upon the ratio of sodium : potassium in the assay medium. In their studies phenytoin inhibited the enzyme when the ratio was less than 5 : 1 but it stimulated the enzyme when the ratio exceeded 25 : 1. In the present work phenytoin inhibited the activity at all ratios tested (150 : 10, 100 : 30 and 100 : 2).

Fractions enriched in vesicles, membranes or mitochondria were prepared from disrupted synaptosomes by a method similar to that of Whittaker (1966). As in the case of the anticonvulsant ethosuximide, phenytoin inhibited only that Na,K-ATPase activity which was associated with the fractions containing the external membranes of the synaptosomes. Like ethosuximide, phenytoin also inhibited a Mg-ATPase which was present in the fractions containing vesicles.

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