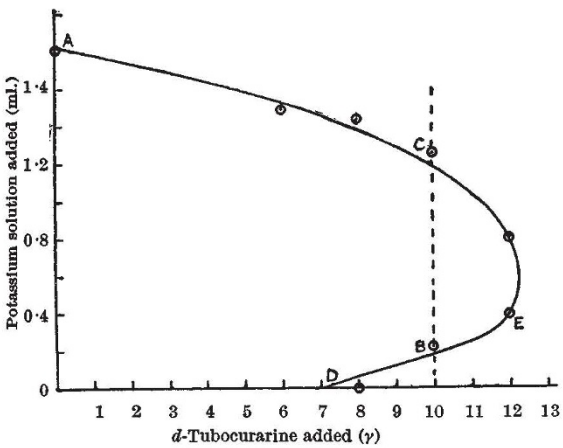
Interaction between Curare and the Potassium Ion at the Motor End Plate

In a previous paper[1] evidence was presented that there is a relation between the curariform activity of an onium ion and the charge density on its quaternary central atom. A consideration of this theory and of the fact that the paralysing action of curare can be reversed by a fall of temperature[2] led to an investigation of the antagonism between curare and the potassium ion[3].

By working below 30° C., it has been possible to study the actions on the rat diaphragm[4] of potassium ion concentrations which reduced neuromuscular transmission while leaving the muscle fibres fully responsive to direct electrical stimulation. Under these conditions, it was possible to demonstrate a neuromuscular block by high concentrations of the potassium ion alone (point *A* on graph). This block may be similar to that produced in ganglia by high doses of potassium chloride[5]. The graph also shows that by bringing the muscle into equilibrium with increasing concentrations of curare it has been possible to demonstrate that the addition of curare reduces the concentration of potassium required to cause a 50 per cent block. When the dose of curare which causes a 50 per cent block at normal concentrations of potassium ions is exceeded, the addition of potassium ion has two opposite actions (dotted line). First it antagonizes and decreases the block, the point *B* giving the potassium ion concentration which produces a 50 per cent block, and then after reducing the block still further a point is reached when more potassium sums with the curare and causes the block to increase again. The point *C* represents the 50 per cent block produced by adding excess potassium ions. The line *D*—*E* corresponds to the potassium ion – curare antagonism observed earlier[3].



Relationship between *d*-tubocurarine chloride added to a 40 ml. bath and the amount of Tyrode solution containing 100 times the normal amount of potassium chloride required to maintain the neuro-muscular conduction of the preparation in a state of 50 per cent block

It appears to us that the interaction between curare and the potassium ion is an ion exchange reaction (cf. ref. 6 in this connexion), and that the region of the motor end-plate contains an ion exchanger. Moreover, we would like to suggest that in normal neuromuscular transmission the onium ion group of acetylcholine liberated by the nerve impulse reacts with the exchanger, to which potassium ions are normally bound, and that the potassium ions so displaced stimulate the muscle fibre, possibly by depolarizing it. The liberation of acetylcholine ions and their displacement of potassium ions from the ion exchanger would give rise to potentials of the liquid junction type. Moreover, the depolarization of the muscle fibre by the potassium ions would set up electrotonic and action potentials. The complexity of end-plate potentials[7,8] is therefore not unexpected. The marked similarity between the actions of potassium and acetylcholine[9] becomes easy to understand; and the continued occupation of the receptors of the ion exchanger by curare, stable choline esters and acetylcholine after eserine[10], by preventing the reoccupation of those receptors by potassium ions in preparation for the next impulse, explains the blocking action of these substances. We can represent the reaction between the receptors of the exchanger and the potassium ion briefly as follows:

$$R^- + K^+ \rightleftharpoons RK.$$

Normally, the acetylcholine liberated by a nerve impulse, by combining with free receptors and blocking the left to right part of the equilibrium, would leave the dissociation of potassium ions unopposed, with a consequent local rise in potassium concentration at the muscle fibre. If we decrease the free receptors by raising the potassium ion concentration, then acetylcholine cannot combine; hence the blocking action of excess potassium and its summation with curare when the number of free receptors is the limiting factor. Curare acting on normal muscle would decrease that potassium bound to the receptor which is available for exchange with acetylcholine. In this case, potassium ions would antagonize curare by increasing the available bound potassium.

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Effect of Drugs on Actin

In previous work from this laboratory it has been established that the polymerization of actin is influenced by various ions in different ways. In view of the possibility that the change of globular actin into fibrous actin plays an important part in the mechanism of muscle contraction, it is especially interesting that calcium and potassium (or sodium) ions show antagonistic action at some concentrations[1].

When globular actin polymerizes, the reaction-rate can be followed by the rising viscosity of the solution. The reaction is usually of an autocatalytic type; therefore the rate is best measured by the reciprocal value of the time needed to reach 50 per cent polymerization. Such a study, using 0·001 *M* calcium chloride and varying concentration of potassium