THE NEUROMUSCULAR BLOCKING ACTION OF SUXAMETHONIUM ON THE RAT DIAPHRAGM

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Experiments are described using the rat isolated phrenic nerve diaphragm preparation, in which suxamethonium produced a neuromuscular block consisting of an initial phase of fairly sharp onset followed by a prolonged phase, which first remained at a steady level and then slowly decreased in intensity over several hours. Suxamethonium block is antagonised by potassium and intensified by tubocurarine in both phases. It would therefore appear that the depolarising action of suxamethonium is complicated by some measure of competitive inhibition in the isolated nerve-muscle preparation as in the intact animal.

The nature of the neuromuscular block produced by suxamethonium showed a marked species variation. Zaimis (1953) reported some competitive features of the block in monkeys, dogs, rabbits and hares. However, on isolated rat and kitten phrenic nerve diaphragm preparations, Stovner (1958) showed that the neuromuscular block produced by succinylmonocholine was more competitive in nature than that produced by suxamethonium.

There is much clinical evidence for the existence of a mixed neuromuscular block produced by suxamethonium. Grant (1952), Ruddell (1952), Hodges (1953), Guerrier and Williams (1954), and Brennan (1956) have reported reversal of prolonged suxamethonium paralysis by neostigmine in man and in other intact animals.

Experimental

Method

The details of the dissection and assembly of the apparatus were those described by Bülbring (1946) and modified by Chou (1947). The fan-shaped muscle strip was stimulated indirectly through the phrenic nerve at 6/min. with supramaximal rectangular pulses of 0·1 to 0·3 m-sec. duration. Muscle contractions were recorded by a spring-loaded lever. The muscle was immersed in a bath containing Tyrode solution modified by halving the concentration of calcium chloride (bringing the concentration nearer to the ionised concentration in the blood) (McDowall, Miechowski and Shafei, 1949), and reducing the concentration of magnesium chloride from 0·01 to 0·0025 per cent (Taugner and Fleckenstein, 1950). The fluid was aerated with 95 per cent oxygen and 5 per cent carbon dioxide. The capacity of the bath was 75 ml. and the temperature was maintained constant in all experiments at 37° ± 0·25°. Doses referred to are in terms of suxamethonium bromide, potassium chloride and tubocurarine chloride.

RESULTS

Different preparations showed a wide variation in sensitivity to suxamethonium. In comparison with tubocurarine the preparations were relatively insensitive to suxamethonium.

The effect of potassium chloride on the neuromuscular block produced by suxamethonium. The two phases of the neuromuscular block produced by the addition of 600 μg. of suxamethonium to the bath fluid are shown in Fig. 1a. There was an initial sharp onset of block during the first 8 to 10 min., followed by a fairly steady prolonged phase and then the block slowly diminished in intensity over several hours.

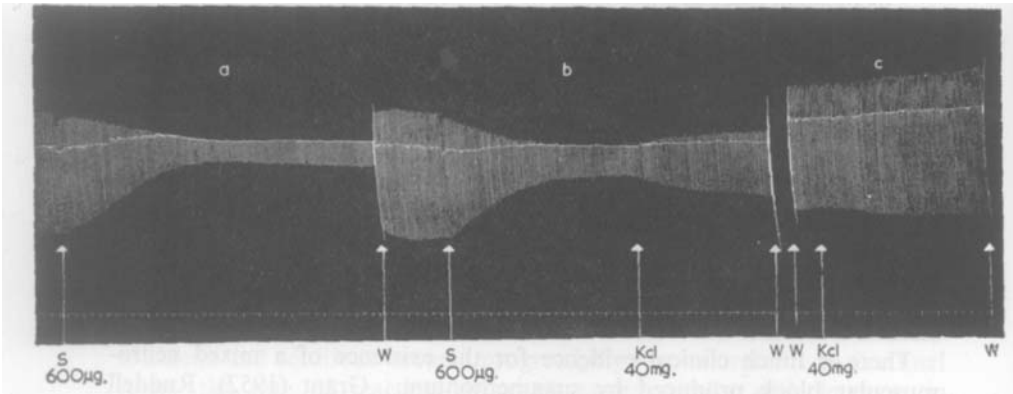

FIG. 1. The antagonism by potassium chloride of the neuromuscular block produced by suxamethonium. Rat isolated diaphragm preparation stimulated through phrenic nerve, 6/min. At S, suxamethonium added to bath fluid for 20 min. At W, preparation washed with Tyrode solution. In (b) potassium chloride added to bath fluid 11 min. after the addition of suxamethonium. Time 30 sec.

Potassium chloride added to the bath fluid during the prolonged phase reduced the block (Fig. 1b). The suxamethonium was left in the bath for 20 min. and in Fig. 1b the potassium was added to the bath fluid 11 min. after the addition of suxamethonium.

The antagonism by potassium, added to the bath fluid during the prolonged phase of suxamethonium block is shown again in Fig. 2c and the antagonism when potassium was added during the initial phase of the block in Fig. 2b. The addition of potassium chloride alone to the bath fluid resulted in increased response of the diaphragm strip to indirect stimulation (Figs. 1c and 2d).

The effect of tubocurarine on the neuromuscular block produced by suxamethonium. When tubocurarine was added to the bath fluid either during the initial or prolonged phases of neuromuscular block produced by suxamethonium, the block was intensified (Figs. 3d and 3b). The suxamethonium was in the bath for 15 min. In Fig. 3d the tubocurarine was added 1 min. after the addition of the suxamethonium to the bath fluid, and in Fig. 3b the tubocurarine was added 9 min. after the addition

of the suxamethonium. Control results with suxamethonium and tubocurarine alone are shown in Figs. 3a and 3c.

Discussion

The original observation by Wilson and Wright (1936), that potassium antagonised the action of curare has since been used to distinguish between drugs which produced neuromuscular block by competition with

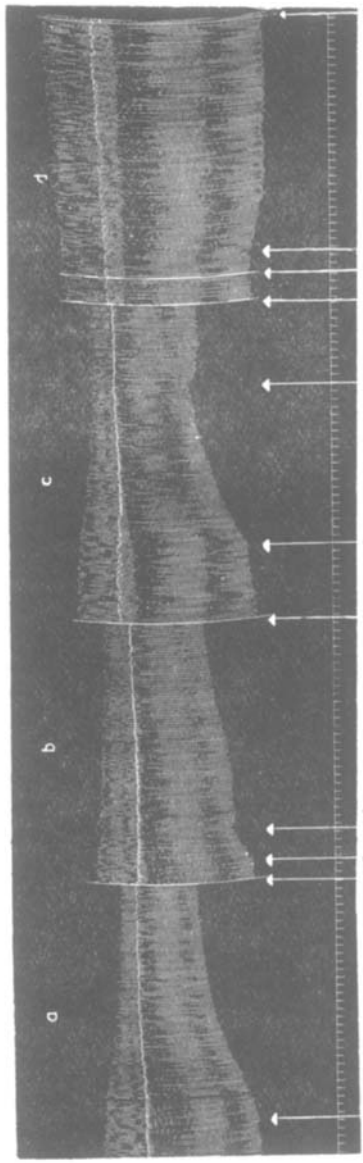

Fig. 2. The antagonism by potassium of the neuromuscular block produced by suxamethonium, when potassium added during the initial phase (b) or during the prolonged phase of block (c). Rat isolated diaphragm preparation stimulated through phrenic nerve, 6/min. At S, suxamethonium added to bath fluid for 15 min. In (b) potassium added to bath fluid 2 min. after suxamethonium. In (c) potassium added to bath fluid 10 min. after suxamethonium. At W preparation washed with Tyrode solution. Time, 30 sec.

acetylcholine, like tubocurarine, and drugs which produced block of the neuromuscular junction by depolarisation (Paton and Zaimis, 1949; Jenden, Kamijo and Taylor, 1951; Bowman, 1958). The antagonism by potassium of both the initial phase (Fig. 2b) and the prolonged phase (Figs. 1b and 2c) of the suxamethonium block indicates therefore the presence of a competitive feature in this block.

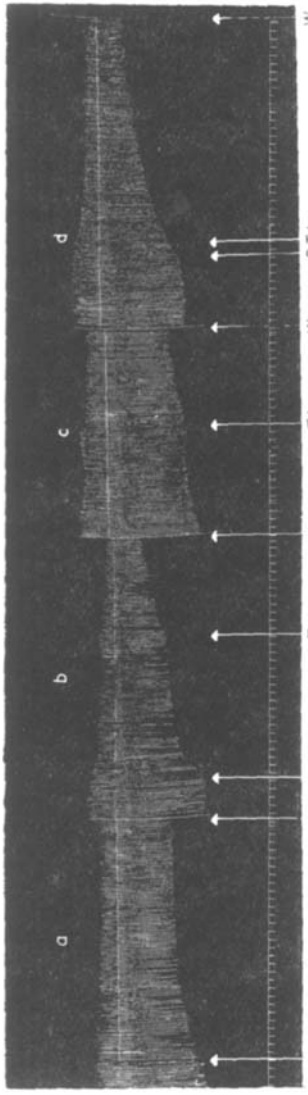

FIG. 3. The intensification by tubocurarine of the neuromuscular block produced by suxamethonium; tubocurarine added during the initial phase (d) and during the prolonged phase of block (b). Rat isolated diaphragm preparation stimulated through phrenic nerve, 6/min. At S, suxamethonium added to the bath fluid for 15 min. In (b) at Tubo., 40 μg. tubocurarine chloride added 9 min. after suxamethonium. In (d) 40 μg. tubocurarine added 1 min. after suxamethonium. At W preparation washed with Tyrode solution. Time, 30 sec.

There are several reports of antagonism existing between depolarising and competitive drugs. The administration of tubocurarine after depolarising drugs like decamethonium and suxamethonium inhibited the

effect of these drugs (Castillo, Phillips and de Beer, 1949; Paton and Zaimis, 1949; Vogel and Steinke, 1956; Dillon, Sabawala, Taylor and Gunter, 1957). The effect of other competitive blocking agents on a block produced by tubocurarine was additive (Winter and Lehman, 1950; Wescoe and Riker Jr., 1951). When tubocurarine was added to the bath fluid either during the initial or prolonged phase of neuromuscular block produced by suxamethonium, the block was intensified (Figs. 3d and 3b). Again this indicates a competitive element.

The observations reported here may be related to the hydrolysis of suxamethonium. Whittaker and Wijesundera (1952) showed that horse serum cholinesterase hydrolysed suxamethonium in two stages: (i) fairly rapidly to succinylmonocholine and choline and (ii) much more slowly to succinic acid and choline. Human plasma cholinesterase acted similarly (Tsuji, Foldes and Rhodes Jr., 1955). Low and Tammelin (1951) reported the breakdown of suxamethonium *in vitro* by both true and pseudocholinesterases.

The competitive features reported here may be connected therefore with the formation of succinylmonocholine, which produces a neuromuscular block showing several competitive features (Stovner, 1958).

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