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THE ACTION OF SUCCINYLCHOLINE ON THE TENSION OF EXTRAOCULAR MUSCLE

BY

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It is now well known that succinylcholine produces a contracture in the extraocular muscles of the mammalian eye (Hofmann & Lembeck, 1952; Lincoff, Breinin & DeVoe, 1957; Macri & Grimes, 1957). Hess & Pilar (1963) recently demonstrated that the extraocular muscles of the cat have two distinct types of muscle fibres similar to the twitch and slow fibres of the frog (Kuffler & Vaughan Williams, 1953a,b) and chicken (Ginsborg, 1960a,b) in the arrangement of their fibrils and in their innervation. Eakins & Katz (1965) observed that succinylcholine produces a slow, well maintained contracture of the medial rectus muscle of the cat eye, at a time when the twitch response of the muscle due to electrical stimulation of the third nerve was totally suppressed. It was concluded that succinylcholine affected both the twitch and slow contractile systems of this muscle.

In the experiments described in this paper, the succinylcholine-induced contracture of the cat extraocular muscles has been studied to determine the nature of the response.

METHODS

Cats, weighing 2 to 4 kg, were used. The animals were anaesthetized by the intraperitoneal injection of 36 mg/kg of sodium pentobarbitone. The trachea, femoral artery and femoral vein were cannulated.

The conjunctival sac of the eye was incised and a suture placed through the tendon of the superior rectus, medial rectus or lateral rectus muscle. The tendon of each muscle was then separated from the eyeball and severed. For tension recording, the animal's head was immobilized in a stereotaxic apparatus. Each muscle was then attached by means of its suture to a Grass force displacement transducer FT-03 (no spring attached). Slight tension was placed on the muscle so that both relaxation and contraction could be observed. In all of the experiments, the eyeball was collapsed by enucleation since, in preliminary studies, it was observed that this procedure allowed free movement of the muscles. All the animals were artificially ventilated with a Frumin-Lee respirator.

Femoral arterial blood pressure was measured with a Statham pressure transducer. All recordings were made on a Grass Polygraph (Model 5). Drugs were injected into a femoral vein, and the effect on one or more of the extraocular muscles of either eye was observed.

The following drugs were used in this study: succinylcholine chloride (Burroughs Wellcome), atropine sulphate, (+)-tubocurarine chloride (Burroughs Wellcome), hexamethonium chloride (Squibb), (−)-

adrenaline bitartrate, phenoxybenzamine hydrochloride (Smith Kline & French), and pronethalol (Ayerst). All doses refer to the salts.

RESULTS

Response of extraocular muscles to succinylcholine

Intravenous injections of succinylcholine produced a dose-dependent increase in tension in all the extraocular muscles studied. A typical result is shown in Fig. 1. Doses of succinylcholine from 1 to 16 μg/kg increased the magnitude and duration of the response. However, larger doses of succinylcholine, 32 to 128 μg/kg, produced a greater effect on the duration of the response than on the magnitude. In some animals an initial small transient decrease in tension preceded the contracture. This contracture frequently appeared to have two components, an initial fast phase and a later slower phase. In some experiments the late phase was observed after a decline in the initial phase and was seen as a second peak; in others, the slower phase followed immediately after the initial contraction and was seen as a slower increase in tension. Several possibilities exist to explain this. The phenomenon may be due to recirculation of the original succinylcholine, a secondary response to succinylcholine (possibly release of sympathetic amines), or the response of different motor units within the muscle to succinylcholine.

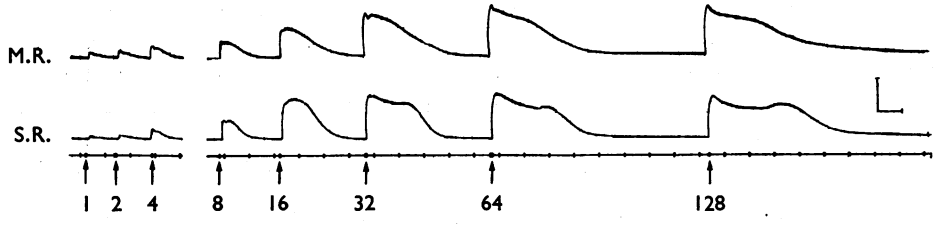

Fig. 1. Cat, 3.7 kg, pentobarbitone anaesthesia. Effect of increasing intravenous doses (in μg/kg) of succinylcholine on the tension of the medial rectus muscle (M.R.) and superior rectus muscle (S.R.). Calibrations, 10 g tension and 1 min.

All of the extraocular muscles studied responded to succinylcholine in a qualitatively similar manner. In an attempt to determine whether or not tachyphylaxis occurred, submaximal doses of succinylcholine were repeated every 10 min for up to 5 hr. No reduction in the magnitude and duration of the response was observed.

Effect of drugs on the action of succinylcholine

After establishing at least three consistent submaximal responses to succinylcholine, atropine, 1 to 4 mg/kg, was injected intravenously. Atropine was without effect on the resting tension of the muscle and did not inhibit the response of the muscle to succinylcholine.

The intravenous injection of 25 to 500 μg/kg of tubocurarine markedly reduced the response of the muscle to intravenous succinylcholine. In Fig. 2 it can be seen that 50 μg/kg of tubocurarine produced a 60% inhibition of the response to 7.5 μg/kg of succinyl-

choline; 90% or greater inhibition was produced by a total dose of 250 μg/kg of tubocurarine. The duration of the inhibition was 30 to 120 min, depending on the dose of tubocurarine.

The intravenous injection of 5 to 10 mg/kg of hexamethonium during the succinylcholine-induced contracture initially decreased the muscle tension towards the control level, but

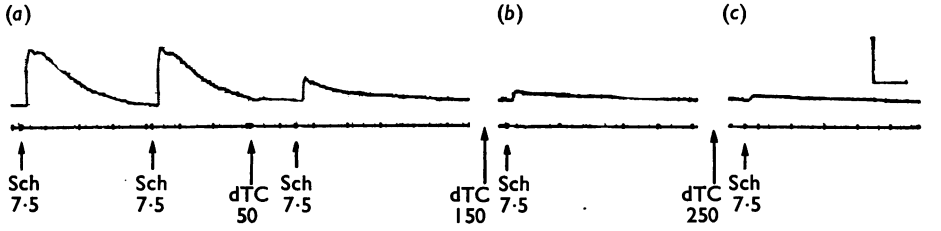

Fig. 2. Cat, 4.0 kg, pentobarbitone anaesthesia. Effect of tubocurarine on the response of the medial rectus muscle to succinylcholine. (*a*) Effect of 50 μg/kg of tubocurarine (dTC) on the response to succinylcholine (Sch); (*b*) response of the extraocular muscle to succinylcholine after a total dose of 150 μg/kg of tubocurarine; (*c*) response of the muscle to succinylcholine after a cumulative dose of 250 μg/kg of tubocurarine. All drugs were given intravenously. All doses in μg/kg. Calibrations, 5 g tension and 1 min.

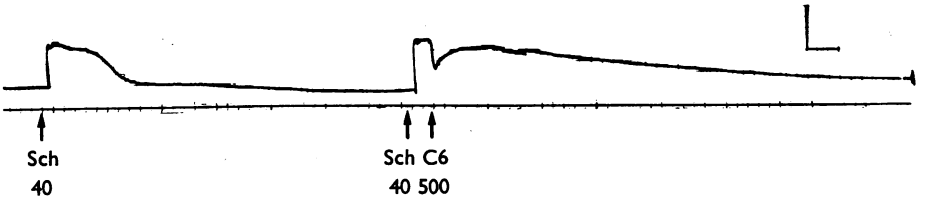

Fig. 3. Cat, 4.0 kg, pentobarbitone anaesthesia. Effect of hexamethonium (Cb) injected during the response of the medial rectus muscle to succinylcholine (Sch). All drugs were given intravenously. Doses in μg/kg. Calibrations 10 g tension and 1 min.

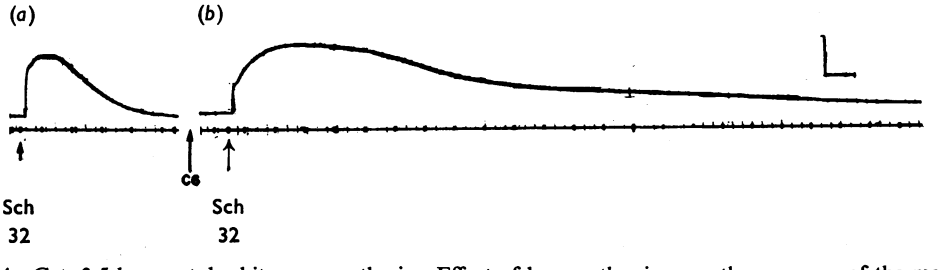

Fig. 4. Cat, 3.5 kg, pentobarbitone anaesthesia. Effect of hexamethonium on the response of the medial rectus muscle to succinylcholine (Sch, in μg/kg). Between (*a*) and (*b*), 10 mg/kg of hexamethonium (C6) was injected. Note the depression of the initial phase of contraction followed by a marked increase in the second slower phase. All drugs given intravenously. Calibrations, 10 g tension and 1 min.

was followed by a secondary rise in tension which persisted longer than the control response to succinylcholine (Fig. 3). When hexamethonium was injected after recovery of the response to succinylcholine, no effect was observed on the resting tension. However, the response to subsequent injections of succinylcholine was significantly modified. The initial contraction was reduced but the slower secondary phase was greatly increased (Fig. 4).

Because some of the effects of succinylcholine are known to be modified by adrenergic-blocking agents (Katz, 1965), it was decided to examine the effects of phenoxybenzamine, a sympathetic α-receptor blocking agent and pronethalol, a sympathetic β-receptor blocking agent, on the response of the extraocular muscle to succinylcholine. Phenoxybenzamine, 5 mg/kg intravenously, did not reduce the response of the muscle to succinylcholine, but sometimes potentiated the response. On the other hand, the intravenous injection of 2.5 to 10 mg/kg of pronethalol in divided doses greatly reduced the response to succinylcholine (Fig. 5). The duration of inhibition varied from 40 to 120 min depending upon the dose of pronethalol. The larger doses of pronethalol, if given rapidly, sometimes increased the

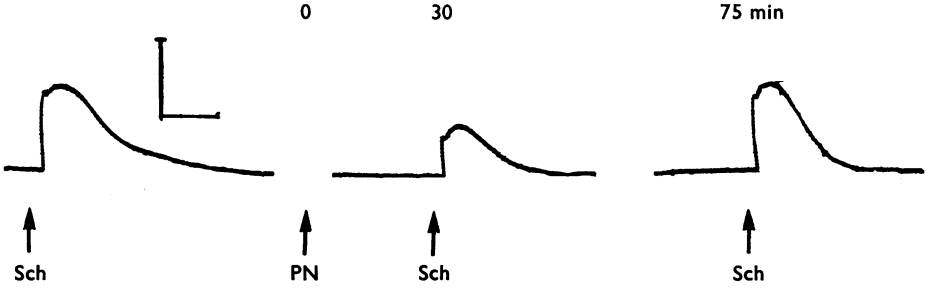

Fig. 5. Cat, 3.5 kg, pentobarbitone anaesthesia. Inhibition of response of the superior rectus muscle to succinylcholine (Sch, 10 μg/kg) by pronethalol (PN, 2.5 mg/kg). Control response, then maximum inhibition of this response 30 min after pronethalol, and recovery after 70 min. Calibrations, 5 g tension and 1 min.

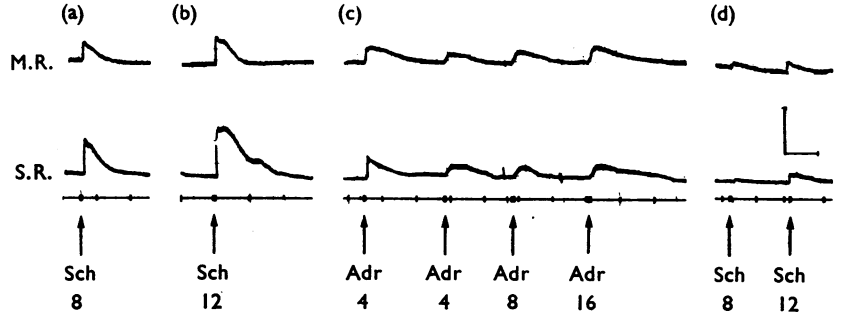

Fig. 6. Cat, 4.0 kg., pentobarbitone anaesthesia. Inhibition of the response to succinylcholine by adrenaline. (*a*) and (*b*) Control responses of the medial rectus muscle (M.R.) and superior rectus muscle (S.R.) to succinylcholine (Sch); (*c*) response of the extraocular muscles to adrenaline (Adr); (*d*) effect of the control succinylcholine doses 2 min after the last response to adrenaline. All drugs were given intravenously, and doses in μg/kg. Calibrations 5 g tension and 1 min.

tension of the extraocular muscles, an effect that may be due to an initial stimulation of sympathetic β-receptors. In addition, pronethalol occasionally increased the response of the muscles to succinylcholine before the onset of inhibition.

After the demonstration that inhibition of β-receptors by pronethalol reduced the response of the muscle to succinylcholine, the effect of adrenaline was examined. Intravenous injections of 2 to 15 μg/kg of adrenaline raised the tension of the extraocular muscles. These doses of adrenaline also antagonized the response of the muscle to subsequent doses of adrenaline and succinylcholine (Fig. 6).

DISCUSSION

It has now been established that there are two functionally distinct nerve-muscle systems in frogs (Kuffler & Vaughan Williams, 1953a,b) and in chickens (Ginsborg, 1960a,b), the small nerve slow-muscle fibre system and the large nerve twitch-fibre system. Morphological studies have also shown the presence of two distinct types of striated muscle fibres (Krüger, 1949; Günther, 1949; Krüger & Günther, 1958; Hess, 1960). One type of fibre has large irregular, poorly-defined fibrils (Felderstruktur) and multiple motor endings of the "*en grappe*" type; the other type of fibre has a fibrillar pattern with small well-delineated punctate fibrils (*Fibrillenstruktur*) and receives a single ending of the "*en plaque*" type, typical of normal motor endplates. Twitch type behaviour has been related to *Fibrillenstruktur* fibres and slow type behaviour to *Felderstruktur* (Hess, 1961; Peachy & Huxley, 1962). Both these types of striated muscle fibres have been demonstrated in the extraocular muscles of the cat (Hess & Pilar, 1963). It is well known that mammalian extraocular muscles can respond by a contracture to acetylcholine (Duke-Elder & Duke-Elder, 1930; Brown & Harvey, 1941; Hess & Pilar, 1963), a characteristic previously described for slow muscle fibres in the frog (Kuffler & Vaughan Williams, 1953b). Recently, it had been suggested (Eakins & Katz, 1965) that succinylcholine has two actions on the extraocular muscles of the cat, a depression of the fast or twitch system and a simultaneous stimulation of the slow muscle system, resulting in a sustained contracture similar to that observed after acetylcholine.

In the present study, the contraction of the extraocular muscles seen after succinylcholine was unaffected by the prior injection of atropine. However, intravenous injections of hexamethonium were found to modify the succinylcholine response. Injection of hexamethonium during the response to succinylcholine resulted in an initial depression followed by a period of prolonged potentiation, suggesting that the muscle response was made up of two components, one depressed and the other potentiated by hexamethonium. The observation that curare inhibited the response of the muscle to succinylcholine, coupled with the fact that succinylcholine will contract the extraocular muscles *in vitro* (Hofmann & Lembeck, 1956), suggest that the site of action may be at the multiple nerve endings on the slow muscle fibre.

The observation (Katz, 1965) that some of the effects of succinylcholine are modified by sympathetic α- and β-receptor blocking agents has been extended in this study. The response of the extraocular muscles to succinylcholine was inhibited by the sympathetic β-receptor blocking agent pronethalol, but was not antagonized by the sympathetic α-receptor blocking agent, phenoxybenzamine. It should be pointed out, however, that the inhibition of the response to succinylcholine differed in several respects from the

classical vascular and cardiac sympathetic β-receptor blocking effects of pronethalol. These differences include the stimulating effect of pronethalol *per se*, the initial potentiation of the response to succinylcholine and the slow onset of the succinylcholine inhibition. These differences may be attributed to the different nature of the neuro-effector sites studied or the nature of the test drug (succinylcholine) which may exert only part of its effect via sympathetic receptors. It is also possible that the effect of pronethalol on the extraocular muscles may be unrelated to sympathetic receptors. This would appear unlikely since adrenaline was found to produce a sustained increase in tension in extraocular muscles. Furthermore, adrenaline was found to block the response of the muscle both to succinylcholine and to subsequent doses of itself, an observation resembling the previously reported blockade of sympathetic β-receptors by isoprenaline (Coret & van Dyke, 1949; Hermann, Chatonnet & Vial, 1954; Walz, Koppanyi & Maengwyn-Davies, 1960; Butterworth, 1963).

The results reported in this paper suggest that an adrenergic mechanism may be involved in at least part of the response of the extraocular muscles to succinylcholine. The ability of the sympathetic amines to shorten the extraocular muscles of the cat may be due to the presence of smooth muscle elements; however, it has long been known that, in many denervated mammalian skeletal muscles, adrenaline will produce a contracture (Euler & Gaddum, 1931; Bülbring & Burn, 1936), the effect being absent in normal skeletal muscle. Recently, Bowman & Raper (1965) have demonstrated that this response of denervated skeletal muscle to sympathomimetic amines is inhibited by sympathetic β-receptor blocking agents but was either unaffected or potentiated by sympathetic α-receptor blocking agents. These observations may be related to the increase in tension of the extraocular muscle seen after adrenaline in this study, since it has been noted before (Duke-Elder & Duke-Elder, 1930; Brown & Harvey, 1941) that extraocular muscle behaves in many respects like denervated mammalian skeletal muscle.

SUMMARY

1. The response to succinylcholine of the extraocular muscles has been studied in cats anaesthetized with pentobarbitone sodium.

2. Intravenous injection of 1 to 128 μg/kg of succinylcholine produced a dose-dependent increase in tension in all the extraocular muscles studied. The response frequently appeared to have two components, an initial fast phase and a later slower phase.

3. Atropine did not inhibit the response of the extraocular muscles to succinylcholine.

4. The intravenous injection of tubocurarine greatly reduced the response of the extraocular muscles to succinylcholine.

5. Hexamethonium appeared to depress the initial phase of the response to succinylcholine but greatly increased the second slower phase.

6. The effect of succinylcholine on the extraocular muscles was antagonized by the sympathetic β-receptor blocking agent pronethalol, but was not inhibited by the sympathetic α-receptor blocking agent phenoxybenzamine.

7. Intravenous injections of adrenaline increased the tension of all the extraocular muscles studied. These doses of adrenaline also inhibited subsequent doses of adrenaline and succinylcholine.

8. It is suggested that an adrenergic mechanism may be involved in the response of the extraocular muscles to succinylcholine.

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