Activation of Muscle Spindles by Succinylcholine and Decamethonium: The Effects of Curare.

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Succinylcholine (Sch) is a synthetic quaternary ammonium base with a strong transient blocking effect on neuromuscular transmission (BOVET et al. 1949, 1951, BOVET 1951). The probable cause of this effect is depolarization of the motor end plate (BOVET et al. 1949, GINZEL et al. 1951, THESEFF 1952). This assumption is largely based on the work by PATON and his collaborators (PATON 1951, PATON and ZAIMIS 1951, BURNS and PATON 1951) on decamethonium, the effects of which resemble those of Sch. LUNDBERG and THESEFF (1952) have found that Sch depolarizes the muscle fibres themselves but it is not yet known to what an extent this may originate in end plate depolarization. Like other substances which paralyze by depolarization Sch first elicits fasciculation, then paralysis sets in (cf. decamethonium, BURNS and PATON 1951). The transitory nature of the effect (5—10 min.) is probably due to inactivation of the substances by cholinesterases (BOVET-NITTI 1949, but cf. also, LOW and TAMBLIN, 1951). THESEFF and several collaborators (v. DAREL and THESEFF 1951, HOLMBERG and THESEFF 1951) have introduced Sch into the clinic where it rapidly has become one of the most appreciated paralyzing agents.

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It will be shown below that Sch activates the muscle spindles without at the same time firing the Golgi tendon organs (B-endings of Matthews, 1933). Landgren, Lilliestrand and Zotterman (1952) report that Sch discharges the chemoreceptors of the glomus caroticum but not the baroreceptors of the sinus wall.

**Technique.**

Cats anaesthetized with Dial alone, Dinal-chloralose or Nembutal alone were used in all experiments. The spinal cord was exposed in the lumbar and sacral regions, transected at around L3—L4 and the lower part removed. The ventral and dorsal roots S1 and L7 were the only ones left for stimulation and recording. Dorsal root filaments were isolated for the recording of single fibre discharges from mm. gastrocnemius, soleus and tibialis anticus. All other nerve fibres to the leg were severed. When a single fibre had been isolated in the dorsal root, the muscles were pulled upon in turn to find out whether the spike belonged to any of the three muscles available. If so, this muscle was connected to the isometric steel tongue of the spring gauge (Karlén and Lindström, 1946) and initial tension adjusted to the desired value. With this particular tongue the measuring range of the apparatus, with different amplification, was from 0.5 to 2,000 g. The ventral roots were stimulated singly or together to produce a muscle twitch in order to determine the type of the response of the end organ. The leg was fixed at hip, knee and ankle.

Isolation of root filaments was carried out under the warm paraffin solution filling the cavity of the removed portion of the spinal cord. The spikes were recorded by means of amplifier and cathode ray oscillograph in the usual fashion, a sweep circuit serving to sample the discharge frequency at any desired interval. The second beam of the oscillograph recorded the myogram.

Intra-arterial injections of succinylcholine iodide (Colovirin, Vitrum) as well as of other substances tried were given through a cannula in the a. profunda femoris, alternatively from the aortic bifurcation by a cannula in the contralateral femoral artery. In the latter case the main aortic stem which continues between the two external branches as the internal iliac artery was tied. Curare was given as d-tubocurarine chloride (Abbott) and decamethonium as the iodide (Synacur, Kabi).

In all, some 80 muscle spindles and some 20 Golgi tendon organs were isolated. Of the spindles 35 belonged to the gastrocnemius muscle, 21 to soleus and 13 to tibialis anticus, the rest to the undivided gastrocnemius-soleus muscle.

**Results.**

**Description of general effect.** Fig. 1, which illustrates a typical experiment with the injection cannula in the deep femoral artery, begins with a sweep (T) illustrating that the recorded spike was from a muscle spindle. This is shown by the silent period during the rising phase of the contraction (Matthews 1933, Hunt and Kuffler 1951 a, b, Granit and Kaada 1952). Next follows the baseline discharge B of the control. The following records demonstrate the effect of an injection of 50 µg Sch, sampled by sweeps at the times marked on the left alongside the records. The frequencies in spikes/sec. are given on the right. The baseline frequency in this case was 31/sec. In the last records, taken after 5 min., there was still some effect left (48/sec.). Now 50 µg was a strong dose for this particular location of the cannula. Some 10 min. would have been required for complete disappearance of the effect. Sometimes the frequency did not return to the original level, generally it did. The relatively insignificant changes in the myogram should be noted.
**Thresholds.** These varied from animal to animal, apparently depending also upon the state of the circulation. A definite increase of frequency of the spindle discharge in the best preparations was found with 5 μg. (cannula in the a. prof. fem.), 10 μg. was still a small dose and 20 μg. a large one. If the tip of the cannula was at the aortic bifurcation the threshold was around 10 μg. and 20 μg. generally gave a regular increase of spike frequency. Large doses were between 50 and 100 μg. Some tension (see below) would be required to obtain high sensitivity to the drug. The small doses used for discharging muscle spindles had little if any effect on the muscle twitch.

**The effect of tension.** Initial tension proved to be very important if small doses were used because in such cases the amount of tension determined whether the effect was absent or present. However, if large doses were used they overcompensated for low initial tension. Fig. 2 serves to illustrate this fact. At zero initial tension the frequency rose from 2 to 40/sec. in one min. The tension was next augmented to 80 g. and the frequency for the same dose of 100 μg. rose in half a minute from 8 to 128/sec. The last curve in Fig. 2 was a repetition of the experiment at 80 g. initial tension but, as soon as the frequency had risen to 76/sec., the string joining muscle and myograph was suddenly cut across by a pair of scissors. The frequency of discharge first fell a little, as it would have done in a similar experiment without Sch (Matthews 1933), but it still remained a great deal above that of the same spindle at zero initial tension just as if stretch merely had facilitated the onset of a process that then remained active. In every experiment, when zero tension was used with a sensitive spindle, it was always found possible to activate the receptor by a sufficient dose of Sch. In accordance with these results it was also found possible to increase the rate of firing after Sch by giving the muscle a pull and, as long as it still responded to nerve stimulation, also by setting up one or several contractions. These facilitations by contraction or stretch generally outlasted the stimulus for several seconds.

**Silent spindles.** Cumulative effects. With silent spindles the visible effect of Sch proved to be of shorter duration than with spontaneously active ones. A concealed remainder could then be uncovered by a second dose immediately after cessation of firing. A case in point is illustrated by Fig. 3. There is a silent baseline at 140 g.

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**Fig. 2.** Solas spine. Effect of Sch at different initial tensions (i. t.). Lowermost curve at zero i. t. The other two at 80 g. i. t. but, at arrow, sudden change to zero i. t. in the case thus marked. Each curve illustrates effect of injection of 100 μg. Sch into aortic bifurcation.

**Fig. 3.** Gastroc. spindle, silent. Initial tension 140 g. T, twitch; B, baseline discharge. Marked as Fig. 1. Two successive injections (see text) of Sch into a. prof. fem. Calibration, 21 g. Time, 100 cy./sec. Note, spike gradually diminishing.
initial tension. After injection of 10 µg. Sch into the deep femoral artery a brief discharge followed which disappeared within half a minute. Immediately afterwards the muscle was removed from the myograph (i.e., given zero initial tension) and 10 µg. again injected. The next set of records (0.2—1.0) shows a very much greater effect than before despite removal of the favourable influence of initial tension.

**Effect of lasting change of tension.** As stated above, there were sometimes fasciculations immediately after the injection of a small or moderate dose of Sch. These led to irregular silent periods and frequency variations. With larger doses these effects quickly disappeared. Sometimes they were superseded by a slow 'tonic' contracture before full paralysis set in. This will be called 'lasting change of tension' merely because it lasted over a number of sweeps. Fig. 4 illustrates an analysis of ten muscle spindles from the point of view of the myographically observed lasting changes of tension. Tension after Sch varied between —10 and +10 grams whilst the initial tensions of the muscles studied varied from 75 to 480 g. For each spindle the initial tension is placed at zero abscissa. The rise in the frequency of the discharge is plotted on the ordinate in multiples of baseline frequency, each value at the point corresponding to the positive or negative deviation from the initial tension on the abscissa. It is seen that there is no relation whatever between lasting change of tension and firing frequency of the ten spindles under Sch. Clearly, therefore, the effect of Sch cannot be due to changes of tension caused by long lasting contractions or slackening of the muscle fibres themselves.

It is possible to approach the same problem in another way. This is by using excessive doses of Sch which quickly immobilize the muscle. Fig. 5 illustrates effects on the same spindle of doses of 500, 1,000 and 4,000 µg. Sch under artificial respiration. They were given in the order enumerated. Clearly the muscle spindle was capable of firing to each of these doses despite complete paralysis of the muscle already by the first one. Some spindles did not stand doses of that order but stopped after a brief high-frequency discharge.

**Effects of curare and Sch on gamma fibres.** These effects were studied on the combined gastrocnemius-solens muscle. The small gamma fibres in the ventral roots were shown by Lexell (1945)
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to activate the muscle spindles. His results have since been confirmed and further developed by KUFFLER, HUNT and QUILLIAM (1951) as well as by HUNT and KUFFLER (1951 a, b) and GRANIT and KAADA (1952). HUNT (1952) has recently reported in a preliminary note that the gamma end plates are paralyzed by d-tubocurarine "in doses which also blocked transmission in ordinary muscle fibres". Acetylcholine was found to fire the muscle spindles, but not when given after a blocking dose of d-tubocurarine, suggesting that Sch fired the muscle spindles over the gamma motor end plates setting up contractions of the intrafusal fibres. Sch might act in the same way or/and also by direct excitation of the sensory end organ. Since, as will be shown below, Sch does not activate the Golgi tendon organs which possess afferent fibres of much the same size and conduction rates as the muscle spindles (MATTHEWS, 1953; BARKER, 1948; HAGEBARTH & WOHLFART, 1952; HUNT and KUFFLER, 1951 b) it is less probable that Sch would act by direct peripheral excitation of afferent nerve fibres.

Fig. 6 illustrates a practically silent spindle the muscle of which in record Te has been stimulated by a series of 10 nearly maximal shocks. In the third record shock strength has been increased to five times maximum and the shocks now produced an initial spindle discharge owing to co-stimulation of the high-threshold gamma efferents. This stimulus strength and the same number of shocks were maintained throughout the rest of the experiment. A dose of 100 µg. Sch was injected into the contralateral femoral artery at the bifurcation. The fourth record (B) shows the effect on the firing rate of the spindle. It is clear that stimulation in record 0.5 to begin with, elicits at least as many impulses as before Sch, despite a considerable effect of the drug, on the motor end plates to judge by the diminution of the muscle contraction. After a while, however, the direct effect of gamma excitation is blocked (record 0). In the following records (10—20) excitability gradually returns in both gamma and alpha fibres.

Record 5 is particularly interesting. There was actually some contraction left, though not well visible at the low amplification used on the strain gauge. Despite the removal of the discharge set up by gamma fibre stimulation, the spindle itself apparently has been sensitized by Sch because the slight stretch to which it is subjected on the falling phase of a contraction greatly accelerates its rate of firing. It should be recalled that in the normal state this spindle was silent and that spindles sensitized by Sch in this way respond

![Fig. 6. Gastroc. spindle. Initial tension 350 g. Baseline (B) silent because an occasional spike seen was not intercepted in sampling with sweep circuit. Te, tetanus, slightly submaximal shock artefacts, marked by dots. This stimulus frequency at 5 X maximum value for contraction used from next record onwards. Note that, as long as muscles are non-paralyzed, the shock artefacts are emphasized by effect of co-contractions in muscles around the spine. Time after injections into aortic bifurcation on the left. Calibration, 480 g. Below, time in 50 cy/sec. Full explanation in text.](image-url)
the increased firing of the resting spindle after curare, favours the suggestion that this drug in suitable doses also may have a transient facilitatory effect directly on the sense organ (iii) or on the gamma end plate (ii). The mechanical effect (i) should facilitate its appearance in contraction alone. Then a dose of 0.4 mg. d-tubocurarine was added and the following records (0.5—1.5) illustrate the complete paralysis ultimately obtained. The low resting discharge characteristic of the state is found in record B after removal of stimulation. Despite heavy doses of curare complete paralysis of alpha fibre end plates is not always obtained.

It was decided to complete the experiment by an injection of 100 mg. of Sch but when this was given the spindle died (in the sense that stretch could not stimulate it). Another stretch-sensitive end organ was located but, in the absence of a muscle contraction, could not be tested in the customary way by a shock to the muscle nerve in order to find out whether or not it gave a silent period during twitch. Its baseline rate of firing is found under spindle 2 B. Then 100 μg. Sch was injected and, despite complete paralysis of both alpha and gamma fibres, the typical increase in the spontaneous rate of firing was obtained. According to Hunt (1952) acetylcholine which also fires the muscle spindles should be ineffectual after paralysis of the gamma end plates by d-tubocurarine.

In most experiments, including that of Fig. 7, every spindle was first tested by Sch before curare was given. The general result of all these experiments was that most spindles could be excited by Sch after paralysis of the gamma end plates by curare but that generally very much larger doses were required for this to occur. In this respect, however, there were considerable variations from spindle to spindle.

The experiment of Fig. 8 was set up in order to begin with injection of 0.5 mg. of d-tubocurarine without previous injection of Sch. Record Te was taken at a little above half maximum strength for a muscle contraction elicited by a series of 5 shocks (shock artefacts separately photographed in last record). The small spikes during contraction, as will be seen by following out the experiment, apparently belong to tendon organs. They gradually disappeared when curare prevented the tension from reaching sufficiently high values. The big spike is the one seen in record B. Records 0 and 0.1 show the characteristic diminution of the muscle contraction which is accompanied by the initial facilitation of the spindle discharge immediately after curare. Half a minute after...
curare (0.5) there is complete disappearance of the small spikes in addition to great diminution of the initial effect of stimulation.

Another 0.5 mg of d-tubocurarine was given before record 6 while, at the same time, myograph sensitivity was increased and stimulus strength augmented until the initial effect on the spindle showed up again. Apparently, therefore, this effect was due to gamma fibre excitation. We often found gamma fibre sensitivity lingering on for a while, despite a very small remnant muscle contraction difficult to remove although large doses were used. To judge by this particular experiment, this may happen also in an animal which has not previously received Sch.

Another 0.5 mg of d-tubocurarine was added. Records at 0.4 and 1.5 sec. afterwards have been reproduced. There is now nearly complete block of the alpha and gamma endings. At this moment stimulation was removed and 200 μg. Sch injected. This is a strong dose, but the effect, also, was quite in keeping with expectation, as seen from records 0.25 and 0.45, and it quickly disappeared (records 0.75 and 1.0). In the last but one record stimulation again was added. The just noticeable initial acceleration seen in this record was regularly present in a number of successive similar sweeps with stimulation.

**Decamethonium.** This substance in doses of 20—100 μg. was tried on two animals the injection being given at the aortic bifurcation. The muscle was completely paralyzed with the large dose. In both cases the spontaneous rate of firing of the spindle was accelerated but very much less so than after Sch. The effect developed slowly and was semi-permanent (observed for 1 hour). It differed also from the effect of Sch in being either highly irregular or coming in fairly regular grouped discharges of 2—4 spikes at a time. In one case d-tubocurarine was successfully used to counteract decamethonium (cf. Burns and Paton (1951) for similar antagonism on alpha end plates) and re-establish the spindle's normal regular rate of slow firing. There is an obvious parallel between these effects and those on alpha end plates (cf. Paton 1951).

**B- or tendon organs.** Fig. 9 illustrates the lack of effect of Sch on a Golgi tendon organ. By definition this organ discharges during a twitch or contraction according to the total amount of tension developed. Soleus was used at an initial tension of 110 g. In the same experiment one muscle spindle in soleus had responded to 10 μg. Sch and given a good response to 20 μg. (a rise of 20 spikes/
es of respectively 28 and 48/sec whilst two tendon organs failed to respond to respectively 50 and 90 μg.

These figures also indicate that the gastrocnemius and tibialis anterior spindles set up higher rates of discharge in response to Sch than those in the soleus. This, in fact, was a general experience.

Discussion.

According to the results of Katz (1950) the rate of steady discharge of the muscle spindle is proportional to the amount of depolarization at the afferent terminals. His work was carried out on frogs but there is little reason to doubt its general validity. The depolarization may be set up by stretch of the intrafusal fibres together with the ordinary muscle fibres or else by selective stimulation of the spindle organ alone owing to contraction caused by gamma fibre excitation though, strictly speaking, it has never been possible to demonstrate this contraction (Leekell 1945, Kuffler, Hunt and Quilliam 1951, Hunt and Kuffler 1951a, b). There is as yet no evidence to prevent us from assuming that depolarization set up at the gamma end plates can spread to accessible afferent endings on the intrafusal fibre (particularly to the so called secondary ending, Barker 1948). It seems, however, reasonable not to evoke new principles before it becomes necessary to do so.

In order to explain the effect of Sch which, as stated, cannot be shown to extend to the Golgi tendon organs, there are thus two main alternatives: direct effect on the spindle end organ, or indirect, mechanical, owing to an effect on the gamma fibre end plates. It seems possible to exclude the alpha fibres because there is no obvious relation between contraction-tension after Sch and rate of spindle firing and because large doses paralysing both alpha and gamma end plates still excite the spindle organs.

The favourable effect of initial tension might be interpreted either way but the fact that it was easy to elicit a very high frequency of spindle discharge by Sch in a completely slack muscle, provided that sufficiently large doses were used, is very much in favour of the view that Sch, whatever effects it may have on the gamma end plates, also stimulates the sense organs directly. Similarly the facilitating effect of stretch or contraction after a dose of Sch that has paralyzed the gamma end plates (Fig. 8) suggests that the end organ itself had been sensitized by the drug. Since Sch also acted on several muscle spindles after paralysis of alpha and
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gamma end plates by curare, although larger doses were required, (differing in this respect from acetylcholine studied by Hunt, 1952), it is likely that the substance has a direct effect on the sensory end organs. The amount required for this effect varied a great deal from case to case but it should be realized that the threshold of the Sch-effect also showed considerable variations both from end organ to end organ and from animal to animal. The blood supply must also be of importance because feeble animals had very high thresholds to Sch. One animal practically failed to respond.

Decamethonium, if it depolarizes the gamma end plates— as seems likely because it depolarizes the alpha end plates (Burns and Paton, 1951)—would be expected to stimulate the muscle spindles and give the same effect as Sch if the latter merely acted on the gamma end plates. This is not the case. Decamethonium causes considerably less spindle firing and the discharge, coming as it does in brief recurring outbursts, is more suggestive of 'fasciculation' of the intrafusal muscle fibres than of direct spindle excitation. Finally the stimulating effect of Sch on the chemoreceptors of the glomerus caroticum (Landgren, Liljestrand and Zotterman, 1962) proves that this substance actually can stimulate an end organ lacking the complicating muscular structure integrated into the muscle endings. A final decision between the two alternatives discussed above would seem to require direct measurements of spindle depolarizations or similar measurements at their afferent terminals (Katz, 1950).

In the early phase of the Sch-effect on the muscle spindles it was often possible to obtain the same or even stronger facilitation to gamma fibre stimulation than in the normal spindle. The same transient facilitation was noted with d-tubocurarine. It is impossible, at the moment, to know whether this effect was a faciliation at the gamma end plates or at the muscle spindles. An increase of the spontaneous rate of firing of some spindles to small doses of curare may perhaps be interpreted in favour of the latter alternative and exclude a wholly mechanical explanation, valid merely for the rising phase of a contraction (see p. 144). We have not attempted a complete analysis of this question.

Hunt (1952) mentions that the same doses of curare paralyze both alpha and gamma end plates. Whilst this may be true with reference to the moment at which full motor paralysis has set in, it nevertheless seems likely that, by carefully dosing curare, one may strike a state of balance in which actually the gamma effect is present despite considerable, perhaps even maximum, alpha blockage. In this respect there would probably be considerable variations from spindle to spindle.

Summary.

The effect of the neuromuscular blocking agent succinylcholineiodide (Sch) was studied, by intraarterial injection, on single muscle spindles in cats. Spindle afferents were isolated in the dorsal roots. The injection was made into the ipsilateral arteria profunda femoris or at the aortic bifurcation from a contralateral cannula introduced through the femoral artery. In all, some 30 muscle spindles were studied under myographic control (strain gauge). Of these 21 belonged to m. soleus, 10 to m. tibialis anticus, 3 to m. gastrocnemius, and the rest to the joint gastrocnemius-soleus muscle. In addition 20 Golgi tendon or B-organs were studied.

Sch in subparalytic doses caused a strong transient regular discharge of the muscle spindles, reaching lower maximum frequencies in soleus than in the other muscles. The same stimulating effect was obtained with larger doses after full paralysis of alpha motor end plates.

The Sch-discharge was analyzed with respect to threshold, time course, initial muscle tension and efferent (small fibre or) gamma excitation of the muscle spindles.

Though spindle excitation by Sch was favoured by an increase in initial tension or stretch, it could always be obtained in wholly slack muscle by slightly increasing the dose of Sch. After full paralysis by d-tubocurarine of the excitatory effect of both the ordinary alpha motor fibres as well as the gamma fibres sufficiently large doses of Sch still elicited in most spindles the typical transient increase of discharge rate.

Sch ultimately paralyzed the gamma end plates. Before d-tubocurarine or Sch paralyzed the gamma end plates there often appeared a transient phase of facilitation.

Decamethonium, tried in a few cases, also increased the discharge rate of the muscle spindles but the effect, apart from lasting for at least an hour (longer times not tried) as against some 3—10 minutes with Sch (depending upon dosage and preparation), consisted in irregular bursts of discharges which could be blocked by curare in large doses. It thus differed greatly from the highly regular and transient outburst of spikes obtained by Sch which rapidly reached its maximum and then slowly decayed.

Golgi tendon or B-organs were not fired by Sch.
In the discussion it is pointed out that several of the results are best understood on the basis of the assumption that Sch, whatever it may do to the gamma fibre end plates, also affects the sensory spindle organs directly.

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