

## ACTION OF SUCCINYLSCHOLINE ON MOTILITY OF ANEURAL SMOOTH MUSCLE AND ITS RELATIONSHIP TO ACETYLCHOLINE

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SUCCINYLSCHOLINE chloride is a voluntary muscle relaxant. Its principal clinical use is to increase muscle relaxation for 2 to 4 minutes (1). The brevity of its action has been attributed to its rapid breakdown by cholinesterase into succinic acid and choline (2), both of which are normal products of metabolism. It has been suggested that succinylcholine acts by persistent depolarization of the muscle fiber (3), but the recent work of Thesleff (4) denotes that the neuromuscular transmission is blocked by a lessened sensitivity of the endplate to the transmitter substance. Foldes *et al.* (5) failed to find evidence of histamine release in the use of succinylcholine, while Bourne, Collier, and Somers (6) concluded that it was a weak histamine liberator.

The action of succinylcholine on motility of smooth muscle has practical as well as theoretical interest. Castillo and de Beer (7) reported that succinylcholine had no effect on the circulation of cats and dogs *in vivo* when used in therapeutic doses, and Bourne, Collier, and Somers (6) found that the drug caused a rise in blood pressure in cats and dogs only when used in large doses, but hypotensive effects were not observed. Thesleff (8) noted a transient rise in blood pressure in cats when large doses were used. The careful work of Bourne, Collier, and Somers (6) and of Bovet *et al.* (9) indicated that succinylcholine increased motility in the exsected intestine of the rabbit. Bovet *et al.* (9), however, failed to find an effect of succinylcholine on the augmented tonus and peristalsis induced by acetylcholine or histamine. Also, they observed no effect on peristalsis in the undisturbed intestine of the dog. Thesleff (8), working with the isolated intestine of the rabbit and of the cat, concluded that the drug was ineffective when used in concentration up to 50 mg. per liter in the bath. Higher concentrations caused irregular contractions and decreased the sensitivity of the intestine to acetylcholine. Very large doses, he observed, resulted in transient inhibition of spontaneous peristalsis and a brief increase in tonus in the intact duodenum of the cat.

Foldes *et al.* (5), and Bourne, Collier, and Somers (6) reported that succinylcholine did not appear to block the ganglions of the autonomic

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nervous system, while Thesleff (8) found that very large doses resulted in a complete, but short, block of autonomic ganglions.

It appeared to be of interest to determine the influence of succinylcholine on motility of aneural smooth muscle. For this purpose preparations were made from the amnion of the developing chick. These strips contain muscle tissue and manifest rhythmicity and changes in tonus, but they are thought to be devoid of nervous elements of any description (10, 11). Motility is augmented by acetylcholine and depressed by adrenaline (10). This work was undertaken to ascertain the direct effect of succinylcholine on spontaneous motility of smooth muscle and to make observations on its relationship to acetylcholine.

#### PROCEDURE

Preparations from the amnion of the developing chick (twelfth to seventeenth day of incubation) were made, usually one from a specimen, and each was suspended as a strip in 100 ml. of well aerated Sollmann-Rademaekers' solution at 41 C., which is approximately the temperature of a bird's blood. A light lever made of paper was attached to one end of the preparation and a record of its motility made on a smoked drum in the usual manner. After a record of normal activity had been completed the drug was added to the bath.

About 80 per cent of the strips exhibited spontaneous rhythmicity; some manifested changes in tonus. Rhythmicity in a preparation usually persisted in a fairly uniform manner for about thirty minutes; it rarely continued constant for longer than one hour. Anhydrous succinylcholine chloride and acetylcholine chloride were used in these experiments.

#### SUCCINYLSCHOLINE CHLORIDE AND ANEURAL MUSCLE

For the purpose of determining the effect of succinylcholine on the spontaneous motility of nerve-free smooth muscle, 11 fresh, untreated preparations were used. Concentrations of the drug ranging from 1:1,000,000 to 1:5,000 were employed (0.1 mg. to 20 mg. in 100 ml. of solution). No clearly marked effects were observed at a concentration lower than 1:10,000 except in one determination when a slight increase in rate of contraction appeared to ensue from the addition of 1:100,000 of succinylcholine. But at a concentration of 1:10,000 or greater, an increased activity of the muscle was observed. However, the effects of succinylcholine, in any concentration used, when added to the bath were not striking. Generally, an increased rate resulted from a concentration of 1:10,000; an augmented rate and amplitude of contraction from 1:8,000; and an irregular contraction with increased rate, amplitude of contraction and tonus followed when a concentration of 1:5,000 had been added. This appeared to be the usual course but not the invariable one (fig. 1, tracings 1 and 3). Succinylcholine failed to

induce motility in quiescent amniotic muscle. At no concentration was succinylcholine observed to exercise an inhibitory influence on the spontaneous rhythmicity of aneural smooth muscle.

### THE RELATIONSHIP BETWEEN ACETYLCHOLINE CHLORIDE AND SUCCINYLCHOLINE CHLORIDE

Different preparations of nerve-free smooth muscle varied considerably in their response to acetylcholine. Moreover, after a muscle had been exposed to a drug there is danger that the initial application may influence subsequent doses of the same drug. Accordingly, 10



FIG. 1. No. 1 at S.C. shows the response of a muscle to 20 mg. of succinylcholine chloride (a concentration of 1:5,000). At A.C. 0.1 mg. of acetylcholine chloride was added (a concentration of 1:1,000,000). No. 2 at A.C. illustrates the type of response obtained from 0.1 mg. of acetylcholine chloride (a concentration of 1:1,000,000). No. 3 shows the stimulating effect of 10 mg. of succinylcholine chloride (1:10,000) at S.C.; at A.C. 0.2 mg. of acetylcholine chloride (1:500,000), and at S.C. 10 mg. of succinylcholine chloride (1:10,000) were added. Time is 0.5 minute intervals.

fresh muscles were used to determine the response to acetylcholine in concentrations ranging from 1:2,000,000 to 1:333,000, and a record made in each case. Some preparations were rather refractory to acetylcholine but reacted readily to another drug when it was added to the bath. In some instances the response was manifested by an increased tonus; while, in others augmented rate or amplitude of contraction was the prominent feature. In these experiments a 1:1,000,000 concentration of acetylcholine always evoked a response of some degree (fig. 1, tracing 2).

Acetylcholine was added to each of 12 preparations after succinylcholine. The succinylcholine ranged from 1:1,000,000 to 1:5,000 in concentration. From 1 to 5.5 minutes after the addition of succinyl-

choline to the bath, acetylcholine was added (6 in concentration of 1:1,000,000, 4 in 1:500,000, and 2 in higher concentration). In each case an increased activity occurred in the muscle after the addition of the acetylcholine. The response with different preparations showed considerable variation both in type and degree of response. The variability complicated quantitative determinations regarding the influence of succinylcholine on the sensitivity of the muscle to acetylcholine. When the response to 1:1,000,000 acetylcholine was considered in the untreated and succinylcholine-treated muscle, no difference could be detected in respect to tonus, but computations respecting rate and amplitude of contraction suggested a slightly inhibitory influence of succinylcholine when used in concentration of 1:10,000 or higher on the effectiveness of acetylcholine, but a definite conclusion was unwarranted.

When the motility of a muscle in the bath had been enhanced by acetylcholine, the application of 10 mg. (1:10,000) or more of succinylcholine induced a slight and transient lessening of activity in about 50 per cent of the cases (fig. 1, tracing 3).

#### INFLUENCE OF ENVIRONMENTAL FACTORS

The Magnus or strip method was the only procedure applicable for obtaining graphic records of motility in these experiments. In order that results could be evaluated more accurately, the solution in the bath was modified in a number of respects to determine the effect of slight environmental changes on spontaneous motility in this muscle. Each of the following was added to fresh Sollmann-Rademaekers' solution in which a muscle was contracting rhythmically. As a rule, a fresh preparation was used for each trial. Data given are per 100 ml. of solution. When 1 ml. of Sollmann-Rademaekers' solution at room temperature (about 23 C.); or 0.02 ml. of 10 per cent hydrochloric acid; or 100 mg. of glucose; or 100 mg. of sodium chloride was added, no significant change was discernible. When 300 mg. of glucose was added, a slight drop in amplitude of contraction occurred; and when an additional 200 mg. of sodium chloride was added a decreased rate and amplitude were apparent from the tracing. In another instance, 100 mg. of sodium chloride and 100 mg. of glucose when added to the bath resulted in a lessened rate and amplitude. When 0.5 ml. of propylene glycol was added, an increased rate that was followed after a time by a depressed motility usually ensued. The muscle was stimulated slightly by 0.17 ml. of propylene glycol. Acid in effective concentration depressed motility in this muscle. Gaskell (12) observed a similar phenomenon when experimenting with innervated smooth muscle. A moderate increase in temperature augmented rate of contraction, with concurrent decrease in amplitude. Slight environmental changes did not seem to modify motility in this muscle to such a degree as to lead to misinterpretation of results when using drugs.

### DISCUSSION

Several agents capable of producing relaxation of skeletal muscle by blocking neuromuscular transmission of impulses have been introduced into anesthesiology during the past decade. Recently, reports have appeared in the literature on succinylcholine, an ultrashort relaxant, which has been found to meet clinical requirements. It is rapidly broken down by esterase into succinic acid and choline (2). When used in therapeutic doses it is stated to manifest marked specificity of action.

It is reported to have an inconsiderable effect on motility in innervated smooth muscle. Bourne, Collier and Somers (6) noted a rise in blood pressure in anesthetized animals only after large doses, but no hypotensive effects. Thesleff (8) found that moderate doses had no appreciable effect on blood pressure, nor on motility in intestinal or bronchial muscle. Qualitatively, succinylcholine has the same effect on motility in noninnervated smooth muscle as it has on innervated smooth muscle. Thesleff (8), using excised rabbit intestine, found no change in spontaneous contractions with concentrations of succinylcholine up to 50 mg. per liter of solution. Higher concentrations caused irregular contractions in the isolated intestine of the guinea pig. In spontaneously rhythmic aneural muscle an increased activity generally followed the addition of 100 mg. per liter of succinylcholine to the bath. After the addition of 200 mg. per liter, an irregular type of motility ensued (fig. 1).

Preparations of nerve-free smooth muscle responded readily to acetylcholine by increased motility. Succinylcholine, even in high concentration, when added to the bath before or after threshold doses of acetylcholine, did not significantly modify the response. Thesleff (8) found that high concentration of succinylcholine was required to lessen sensitivity of the excised intestine of the guinea pig to acetylcholine. Also, the work of Bovet *et al.* (9) indicates that succinylcholine in concentration of 2 to 20 mg. per liter of solution does not modify the enhanced activity of the intestine of the rabbit induced by acetylcholine.

### SUMMARY

The effects of succinylcholine and its relationship to acetylcholine on motility in strips of aneural smooth muscle prepared from chick amnion were studied.

Succinylcholine, in high concentration, augmented slightly motility in spontaneously rhythmic preparations; at no concentration, did it inhibit spontaneous activity. It failed to excite quiescent strips.

Acetylcholine enhanced motility in this muscle. High concentration of succinylcholine before or after acetylcholine had inconclusive or insignificant effects on the response to acetylcholine.

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