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ACTIONS OF SUCCINYLCHOLINE CHLORIDE ON THE CIRCULATION

BY

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The neuromuscular blocking properties of succinylcholine are well known, but reports on the action on the heart rate and blood pressure are more contradictory. Thesleff (1952) states that Bovet, Bovet-Nitti, Guarino, Longo and Fusco (1951) reported that succinylcholine iodide had both a muscarinic and a nicotinic effect on the blood pressure, but could not himself observe a fall in blood pressure of a muscarinic type in his own experiments. Somers (1953) also states that succinylcholine has only a nicotinic action. However, Hunt and Taveau (1911) reported that the injection of succinylcholine in a majority of intact animals caused a slowing of the heart rate which was not seen in atropinized or vagotomized animals ; in the latter, succinylcholine caused a prolonged hypertension. Exceptionally, they observed a hypotension like that caused by muscarine. They also found that succinylcholine could oppose the hypotensive effects of other muscarinic substances. It therefore seemed desirable to reinvestigate the effects of succinylcholine upon the circulation in view of these discrepancies in the literature.

Thesleff (1952) concluded that the increase in blood pressure seen with relatively high doses was not due to stimulation of the carotid sinus or carotid body, and that it was much diminished after blocking the ganglia with hexamethonium or tetraethylammonium. The latter observation has been corroborated by Vidal Beretervide (unpublished observations). Thesleff explained the rise in blood pressure after giving succinylcholine by stimulation of autonomic ganglia and mobilization of adrenaline.

However, in his experiments ganglion blocking substances did not entirely prevent a rise in blood pressure. After dibenamine there was an inversion of the blood pressure response followed by a slight rise in pressure ; a direct vasoconstrictor action of succinylcholine could not therefore be excluded. Experiments have therefore been performed to analyse the mechanism of action of succinylcholine in causing a rise of blood pressure. Most authors (Bovet *et al.*, 1951 ; Glick, 1941 ; Ginzel, Klupp, and Werner, 1951c ; Evans, Gray, Lehmann, and Silk, 1952) have found that succinylcholine is decomposed by pseudo cholinesterase and by true cholinesterase, whereas Bovet *et al.* state that succinylcholine inhibits pseudo cholinesterase but not true cholinesterase. Evans *et al.* found that succinylcholine was not destroyed by true cholinesterase but was metabolized by the pseudo cholinesterase of serum, though at a slower rate than ACh ; succinylcholine was found to be a competitive inhibitor of ACh hydrolysis by both esterases, the true esterase being the one more strongly inhibited. Finally Evans *et al.* (1952) say: "It is reasonable to assume that succinylcholine acts by inhibiting the true acetylcholine esterase at the neuromuscular junction, and that the removal of the drug by the pseudo cholinesterase of the serum normally curtails its effect." As support for this interpretation they recall that the longest response seen so far is that reported by Harper (1952) when neostigmine was given. If the hypothesis of Evans *et al.* is true, then the accumulation of ACh is the cause of the neuromuscular block when succinylcholine is administered. It therefore seemed desirable to determine whether succinylcholine potentiates ACh *in vivo* by inhibiting cholinesterase.

METHODS

Forty dogs and forty-five rabbits were used, either unanaesthetized or anaesthetized with pentobarbitone sodium (25–30 mg./kg.) or chloralose (0.1 g./kg.) intravenously. Drugs were injected intravenously. In conscious animals sufficient succinylcholine chloride was used to paralyse the respiratory muscles completely (0.12 mg./kg. for dogs ; 0.3–0.4 mg./kg. for rabbits). In anaesthetized animals the doses used were about 50 to 100 times the paralysing doses. Artificial respiration was always used. Blood pressure was recorded from the femoral artery with a mercury manometer.

Electrocardiograms, using classical or precordial leads, with hypodermic needles as electrodes, were recorded with a direct writing apparatus. Atropine sulphate was used in a dose of 2 mg./kg.; ACh was given in doses of 0.1–0.5 mg./kg.

The succinylcholine chloride used was synthesized in Laboratorios Galien. "Pendiomid" (azamethonium, A.N.) and "Regitine" (phentolamine, A.N.) were obtained from the Ciba Laboratories.

RESULTS

Conscious Animals

The intravenous injection of succinylcholine causes an immediate and profound bradycardia at the onset of paralysis. The heart rate falls from 250 to 50/min. (rabbit) or from 100 to 30/min. (dog) with slight variations of frequency superimposed (Fig. 1). Artificial respiration causes the heart rate to return to normal in 10–15 sec., and it falls to the previous value 15–20 sec. after ceasing artificial respiration. In rabbits, inflation of the lungs with nitrogen gives precisely the same results. This bradycardia is not seen if the animal is anaesthetized. Fig. 2 shows the effect of injecting pentobarbitone in conscious animals which had previously been injected with succinylcholine, but had not been treated by artificial respiration; the bradycardia ceased and the heart resumed its normal rhythm. A similar result was obtained by injecting 1.5–2 ml. of 10% procaine intracisternally in rabbits. Severing or anaesthetizing the vagi, or giving atropine, also prevents the bradycardia. In anaesthetized animals it was confirmed that vagal excitability was not modified even after administration of very large doses of succinylcholine. When such large doses were given, a profuse salivation and augmented tear secretion were observed both in dogs and rabbits, as Bovet *et al.* (1951) and Ginzel *et al.* (1951) have reported.

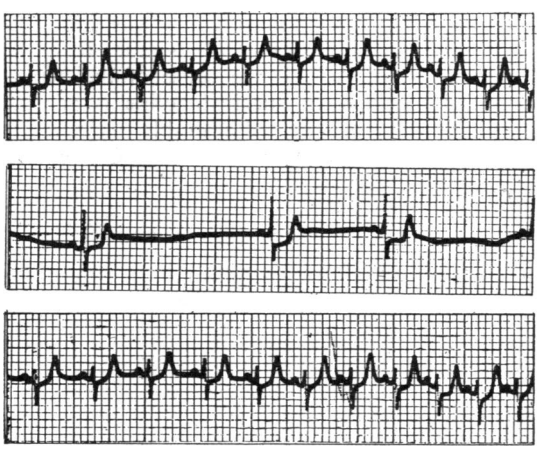

FIG. 1.—Electrocardiogram, conscious rabbit. Top record, normal rhythm, 250 beats/min. Middle record, after intravenous injection of 1 mg. succinylcholine chloride without artificial respiration, 60 beats/min. with sinus arrhythmia. Bottom record, 10 sec. after artificial respiration was begun; 250 beats/min.

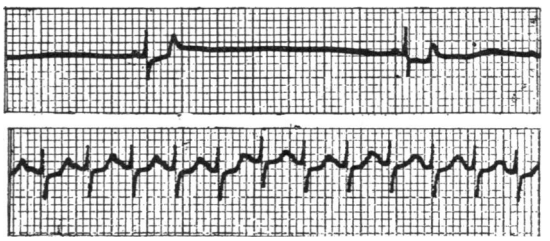

FIG. 2.—Electrocardiogram, conscious rabbit. Upper record, after the injection of succinylcholine without artificial respiration, 40 beats min. Lower record, a few seconds after intravenous injection of pentobarbitone; the rate has returned to 215 beats/min.

The femoral arterial blood pressure was recorded in rabbits under local anaesthesia (1–2% procaine). After an injection of succinylcholine the blood pressure was not altered for 60–90 sec. after the beginning of the bradycardia. It then began to fall, apparently by diminution of the minute-volume, but 10–15 sec. after artificial respiration was renewed the blood pressure rose rapidly to its previous level.

Provided that artificial respiration was maintained, large doses of succinylcholine caused big rises in blood pressure in conscious rabbits (Fig. 3).

Anaesthetized Animals

Large doses of succinylcholine chloride always caused a rise of blood pressure in dogs, rabbits, and cats as Thesleff (1952), Bovet *et al.* (1951, 1952), and Bourne (1952) have found. Exceptionally, an initial slight and very transient fall of blood pressure preceded the rise in dogs. Bilateral adrenalectomy or ligature of the suprarenal vessels in dogs diminished the rise of blood pressure caused by succinylcholine chloride but did not abolish it (Figs. 4 and 5). Hexamethonium chloride or "Pendiomid" in doses of 5–10 mg./kg. completely abolished the hypertensive response; there was no residual hypertension such as that seen by Thesleff (1952). In the same way yohimbine and phentolamine abolished the rise of blood pressure but did not reverse it.

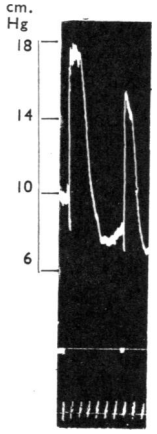

FIG. 3.—Conscious rabbit. Record of blood pressure from femoral artery. Pressor responses to 75 and to 50 mg. of succinylcholine i.v. Time, min.

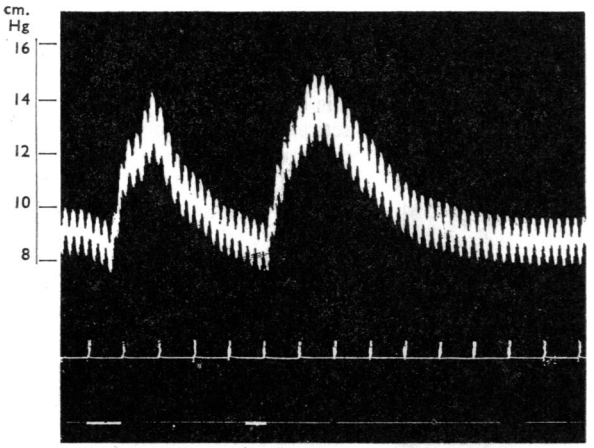

FIG. 4.—Adrenalectomized dog under pentobarbitone anaesthesia. Succinylcholine 50 mg. (at 1st signal) and 60 mg. (at 2nd signal) i.v. causes a rise in blood pressure. Time, 15 sec.

In dogs given 2 mg./kg. atropine sulphate the rise of blood pressure caused by the injection of ACh was considerably potentiated by administration of succinylcholine (Figs. 6 and 7). Not only was the hypertension caused by ACh much greater but it was of longer duration. In some such experiments subsequent injections of succinylcholine after administration of ACh caused smaller hypertensive responses, but the effect of ACh was always clearly increased. Succinylcholine also potentiated, though to a much smaller degree, the hypertensive effects of benzoylcholine in some experiments but did not potentiate the rise of blood pressure caused by nicotine or carbaminoylcholine. Nicotine actually blocked the effect of succinylcholine on the ganglia (Fig. 8). In anaesthetized dogs, which had not received atropine, succinylcholine did not reduce or abolish the fall in blood pressure caused by administration of ACh as Hunt and Taveau (1911) found, but on the contrary increased the fall of blood pressure. This was best demonstrated by injecting ACh during a constant intravenous infusion of succinylcholine, 0.1% w/v in normal saline, at a rate of 3–4 mg./min. (Fig. 9) or by injecting ACh at the peak of the hypertension caused by previous injections of succinylcholine. In this last instance, not only was the fall of pressure greater, but it lasted 8 to 10 min. instead of a few seconds.

DISCUSSION

In conscious animals succinylcholine chloride seems to act as a stimulant to the vagus centre, for bradycardia is only observed when the nervous centres are neither anaesthetized nor destroyed. Cutting the vagi or injecting atropine also abolishes the bradycardia. The bradycardia does not appear to be due to anoxia although artificial respiration abolishes it. Thus anoxia usually first causes tachycardia, and the modifications in the electrocardiogram due to anoxia—as, for instance, the depression of the S–T segment—did not appear in the tracings when bradycardia occurred. Moreover, the rapid disappearance of bradycardia with artificial respiration, and its disappearance on inflation of the lungs with nitrogen, also demonstrate that anoxia is not the determining factor. Bradycardia also does not occur in the anaesthetized animal, or in an animal whose bulbar centres have been paralysed by procaine and which is without artificial ventilation. These observations suggest that it is distension of the lungs, and not modification of the oxygen content of the blood, which causes the abolition of bradycardia by artificial ventilation. Though reports of the action of

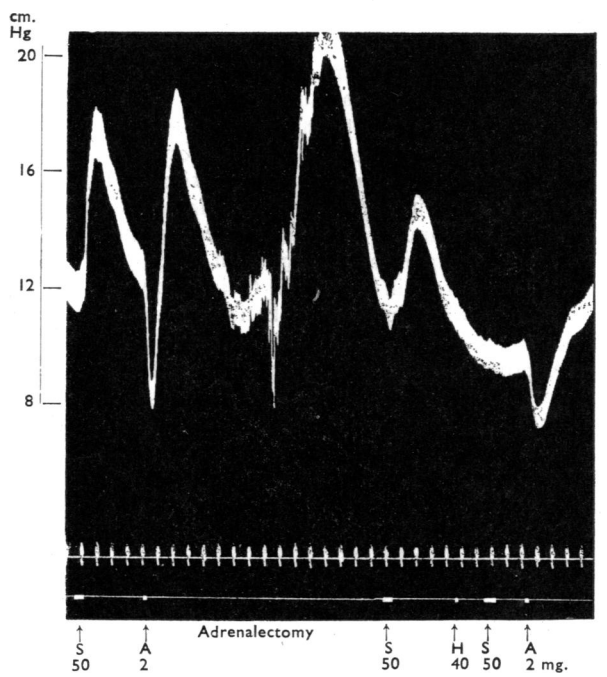

FIG. 5.—Dog, pentobarbitone anaesthesia, atropine sulphate, 1 mg./kg. Injections of succinylcholine chloride (S) 50 mg. and acetylcholine (A) 2 mg. cause a rise of blood pressure. Adrenalectomy (giving rise to a hypertension during manipulations of adrenals). After adrenalectomy, succinylcholine chloride 50 mg. still causes a rise in blood pressure. After hexamethonium (H) 5 mg./kg., succinylcholine 50 mg. no more provokes a hypertension, and acetylcholine 2 mg. causes only a hypotension. Time, min.

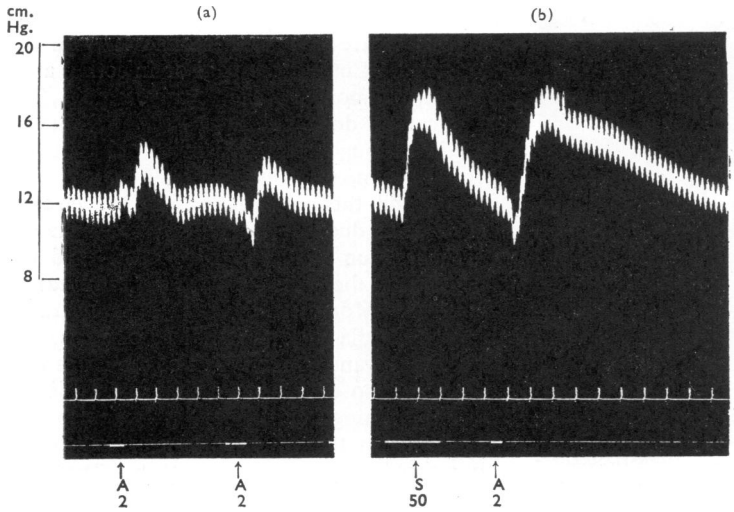

FIG. 6.—Dog, pentobarbitone anaesthesia, atropine sulphate 2 mg./kg. (a) Injections of acetylcholine chloride (A) 2 mg. (b) Injection of succinylcholine chloride (S) 50 mg. followed by acetylcholine chloride 2 mg. Succinylcholine potentiates the hypertension caused by acetylcholine. Time, 15 sec.

succinylcholine in conscious man (Thesleff, 1952; Mayrhoffer, 1952) do not mention cardiovascular changes, it seems advisable not to use succinylcholine in conscious man without previous administration of atropine, until it has been established that there is not a species difference.

Administration of large doses of succinylcholine to anaesthetized animals causes a rise of blood pressure by excitation of sympathetic ganglia and the adrenal glands. The part played by the adrenals is important in dogs; but a rise of blood pressure still occurs in their absence, and is probably due to direct stimulation of the ganglia.

Appropriate doses of ganglionic-blocking drugs abolish the rise of blood pressure. Administration of dibenamine and phentolamine also abolishes the hypertension, which excludes a direct vasoconstrictor action by succinylcholine. Succinylcholine also does not modify the pressor actions of adrenaline or noradrenaline.

The evidence suggests that succinylcholine does not act in competition with acetylcholine. In dogs it potentiates the muscarinic effects of ACh and it also increases its nicotinic action. Since succinylcholine itself has no vasodilator action, potentiation of the muscarinic action of ACh suggests that it may inhibit cholinesterase *in vivo*.

The small potentiation of the rise of blood pressure caused by benzoylcholine, and the absence of potentiation of the pressor effects of carbaminoylcholine and nicotine, suggest that this effect is due to the inhibitory action of succinylcholine on true cholinesterase, as demonstrated by Evans *et al.* (1952).

That succinylcholine does not potentiate the actions of carbaminoylcholine and nicotine is attributed to the fact that these substances are not split by cholinesterases. The feeble potentiation of benzoylcholine is explained by the weak inhibition by succinylcholine of pseudo cholinesterase, which hydrolyses benzoylcholine. Since succinylcholine does not affect the pressor action of adrenaline or noradrenaline, the potentiation of the response to acetylcholine by the enhancement of the activity of liberated adrenaline or noradrenaline can be excluded.

SUMMARY

1. Injection of succinylcholine to conscious animals causes profound bradycardia by central vagal stimulation. The bradycardia can be abolished by cutting the vagi, by administering atropine, by general anaesthesia, and by intracisternal injection of procaine.

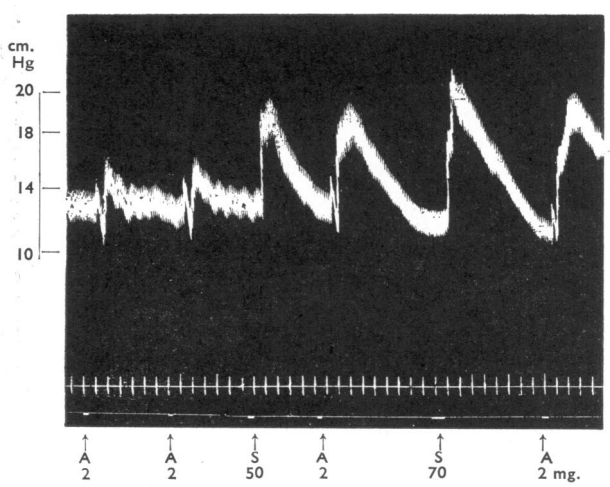

FIG. 7.—Dog, chloralose anaesthesia, atropine sulphate 2 mg./kg. Injections of acetylcholine chloride (A) 2 mg. before and after injections of succinylcholine chloride (S) 50 and 70 mg. Succinylcholine chloride potentiates the hypertension caused by injection of acetylcholine. Time, 30 sec.

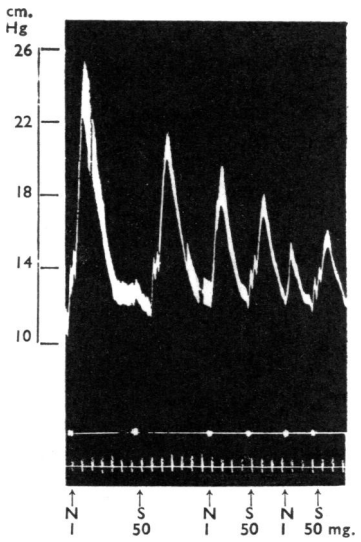

FIG. 8.—Dog, pentobarbitone anaesthesia. Blood pressure record. Nicotine sulphate (N) 1 mg. and succinylcholine chloride (S) 50 mg. are injected alternately. Hypertensions diminish progressively. Succinylcholine does not potentiate nicotine. Nicotine diminishes the pressor effect both of succinylcholine and of nicotine. Time, min.

2. This bradycardia can be abolished by artificial ventilation of the lungs with either air or nitrogen. It is suggested that this abolition is due to a reflex initiated by distension of the lungs.

3. Large doses of succinylcholine in anaesthetized or conscious animals under artificial ventilation cause a rise of blood pressure due to stimulation of sympathetic ganglia and the adrenal glands.

4. Succinylcholine potentiates the rise of blood pressure caused by injection of acetylcholine in atropinized animals, by inhibiting true cholinesterase. It does not act as a competitive substance for acetylcholine.

5. Succinylcholine has no direct actions on the blood vessels or on the heart.

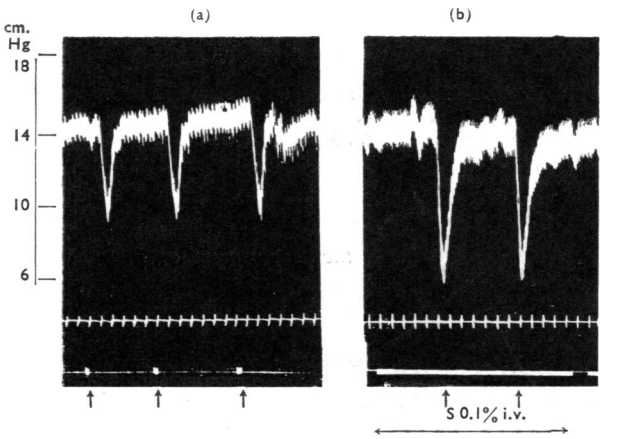

FIG. 9.—Dog, chloralose anaesthesia. At arrows, (a) 3 injections of acetylcholine chloride 50 μg. (b) 2 injections of acetylcholine chloride 50 μg., during a slow intravenous infusion of a solution of succinylcholine chloride (S) 0.1%. Succinylcholine potentiates the hypotension caused by injections of acetylcholine. Time, min.

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