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Mechanism of Tracheal Constriction by Succinylcholine

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The purpose of this study was to identify the mechanism by which succinylcholine produced large increases in endotracheal tube cuff pressure in barbiturate-anesthetized dogs (n = 7). Cuff pressure was measured *in vivo* by a transducer connected to a fluid-filled, high-volume, low-pressure cuff. Intravenous succinylcholine, 0.5 and 1 mg/kg, produced mean increases in cuff pressure of 12 ± 2 (±SE) and 27 ± 5 cm H_2O, respectively, which reached peak effect in 1 to 3 min and declined slowly over the next 10 min. Bilateral vagotomy, intravenous administration of atropine (0.2 mg/kg) and hexamethonium (5 mg/kg) prevented or terminated succinylcholine-induced increases in cuff pressure. Isolated preparations from an additional three dogs were employed to study the direct actions of succinylcholine on trachealis muscle *in vitro*. In organ baths, succinylcholine (10^{-6} to 10^{-3} M) did not contract canine trachealis muscle, and concentrations of 10^{-5} M and above significantly relaxed carbamylcholine-induced contractions. The authors conclude that succinylcholine elicits contraction of trachealis muscle by a stimulant action on parasympathetic pathways rather than by a direct action on airway smooth muscle. Since vagotomy prevented the succinylcholine response, the site of stimulant action is not at autonomic ganglia. (Key words: Airway: trachea. Equipment: tubes, endotracheal. Intubation: endotracheal. Neuromuscular relaxants: succinylcholine. Parasympathetic nervous system: atropine; ganglionic blocking agents; vagus.)

TRANSIENT HYPERTENSION and disturbances of cardiac rhythm frequently occur following injection of succinylcholine. Since both are prevented by ganglionic blockade,[1,2] they have been attributed to stimulation of the autonomic nervous system rather than to direct actions on heart and blood vessels. During studies with endotracheal tube cuff-pressure as a monitor of bronchomotor tone in dogs, we noted consistent, large increases in cuff-pressure following injection of succinylcholine. To identify possible mechanisms, the effects of atropine, hexamethonium, and vagotomy were tested on the *in vivo* response, and isolated preparations were employed to study the direct actions of succinylcholine on trachealis muscle *in vitro*.

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Methods

After induction of anesthesia with iv thiamylal (12 mg/kg) and paralysis with an initial bolus of iv succinylcholine (1 mg/kg), dogs (n = 7) weighing 17–26 kg were intubated with a 7.5- or 8-mm cuffed endotracheal tube. Respiration was controlled by a Harvard® ventilator set to deliver a tidal volume of 400 ml at a frequency of 15/min. Dogs were studied in both prone and supine positions; since similar results were obtained in both circumstances, the data were pooled without regard to position. Most experiments were performed in five dogs that were part of a colony used for chronic studies of drug effects on pulmonary resistance (R_L). These animals were not subjected to surgical procedures other than venipuncture, and light anesthesia was maintained with 2 mg/kg increments of thiamylal administered at roughly 20-min intervals, as in previous studies.[3] Two additional dogs used to study the effects of vagotomy, were anesthetized with 1–2 per cent halothane while the vagal trunks were exposed bilaterally just distal to the cricoid cartilage. Halothane was discontinued 30 min before challenge with succinylcholine, and anesthesia was maintained with increments of thiamylal. These animals were then challenged with succinylcholine before and after bilateral vagotomy.

High-volume, low-pressure cuffs (hi-lo®, National Catheter Co.) tracheal tubes were used in all studies and were flushed with water prior to intubation to remove air bubbles. After insertion of the endotracheal tube with cuff collapsed, the cuff was connected to a pressure transducer (Harvard 375® or Statham P23AC®) and distended with water to a pressure of about 40 cm H_2O. A needle was inserted into the endotracheal tube and connected to a second pressure transducer for the concomitant measurement of airway pressure. Care was taken to position the cuff in the lower cervical trachea. It should be noted that the 7.5- to 8-mm endotracheal tubes were of relatively small diameter for the size of the dogs employed. Tracheal lumens were adequate to accept 8.5- to 9.5-mm tubes, but smaller tubes permitted a greater cuff volume and a better recording of changes in cuff pressure.

To elicit increases in cuff pressure, succinycholine was administered as a bolus intravenous injection of 0.5 or 1.0 mg/kg. Atropine (0.2 mg/kg) and hexamethonium (5 mg/kg) were administered by intravenous injection at the peak of the succinylcholine-induced increase in cuff pressure.

In three dogs, R_L was recorded by the method of Van Neergaard and Wirz,[4] using an esophageal balloon and simultaneous measurements of flow and transpulmonary pressure; our procedure has been described in detail elsewhere.[3] The electrocardiogram was monitored by oscilloscope in all experiments and, in the two dogs undergoing vagotomy, systemic blood pressure was recorded by cannulation of a femoral artery. To test the effect of vagal stimulation on cuff pressure, the cut distal stumps of the vagi were stimulated (Grass S-88 stimulator) for 5 to 10 s with a train of square wave pulses (1- to 5-ms duration) at a frequency of 50 Hz and sufficient voltage (30–50 V) to produce a transient asystole.

Trachealis muscle for use as isolated preparations was obtained from three dogs killed by exsanguination under barbiturate anesthesia. Tracheas were removed within 30 min of death, cut into individual rings, and placed in an oxygenated Krebs-type[5] solution. The cartilagenous portions of individual tracheal rings were removed save for small nubbins bearing the attachments of the trachealis muscle. After stripping away the tunica fibrosa on the ventral surface of the trachealis muscle,[6] the muscles were mounted in 50-ml organ baths containing a Krebs-type solution,[5] maintained at 37.5° C and aerated with 5 per cent carbon dioxide and 95 per cent oxygen. Contractions were recorded isotonically with Harvard 356® transducers against 1-g counterweights. The preparations were allowed to equilibrate for at least one hour prior to testing drug effects, and during this time were washed repeatedly with fresh Krebs solution. The effects of succinylcholine were tested on trachealis muscle in its resting state and also on muscle that was partially contracted with carbamylcholine, 5×10^{-8}, 3×10^{-7}, and 10^{-6} M. The lowest carbamylcholine concentration was just suprathreshold for initiation of contraction. Succinylcholine was added to the baths in cumulative concentrations from 10^{-6} to 10^{-3} or 6×10^{-3} M in increments of half log units, and sufficient time was allowed to obtain the maximal effect of each concentration.

Mean cuff pressure or *in vitro* muscle contraction, before and at the peak of succinylcholine effect, were compared by *t* test at the $P < 0.05$ level of significance.

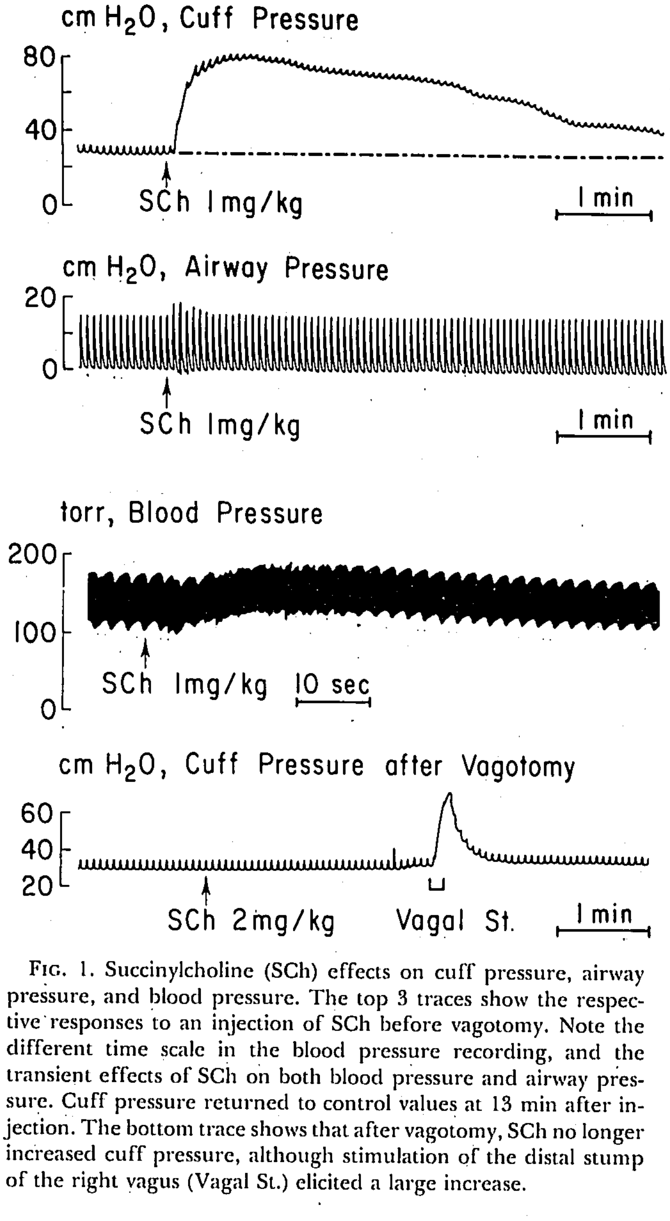

FIG. 1. Succinylcholine (SCh) effects on cuff pressure, airway pressure, and blood pressure. The top 3 traces show the respective responses to an injection of SCh before vagotomy. Note the different time scale in the blood pressure recording, and the transient effects of SCh on both blood pressure and airway pressure. Cuff pressure returned to control values at 13 min after injection. The bottom trace shows that after vagotomy, SCh no longer increased cuff pressure, although stimulation of the distal stump of the right vagus (Vagal St.) elicited a large increase.

TABLE 1. Succinylcholine-induced Increases in Cuff Pressure

Dose (mg/kg)	Tracheal Cuff Pressure (cm H_2O)		Number of Trials
	Control	Δ Pressure*	
0.5	36 ± 5	12 ± 2	11 (5 dogs)
1.0	35 ± 1	27 ± 5	7 (5 dogs)

* Increase in cuff pressure above control value, mean ± SE.

Results

Intravenous administration of succinylcholine, 0.5 or 1 mg/kg, caused a significant increase in cuff pressure (table 1), which reached peak effect in 1–3 min after injection (figs. 1 and 2), and declined slowly over the next 10 min. Fasciculations were sometimes evident during the first minute after injection, and

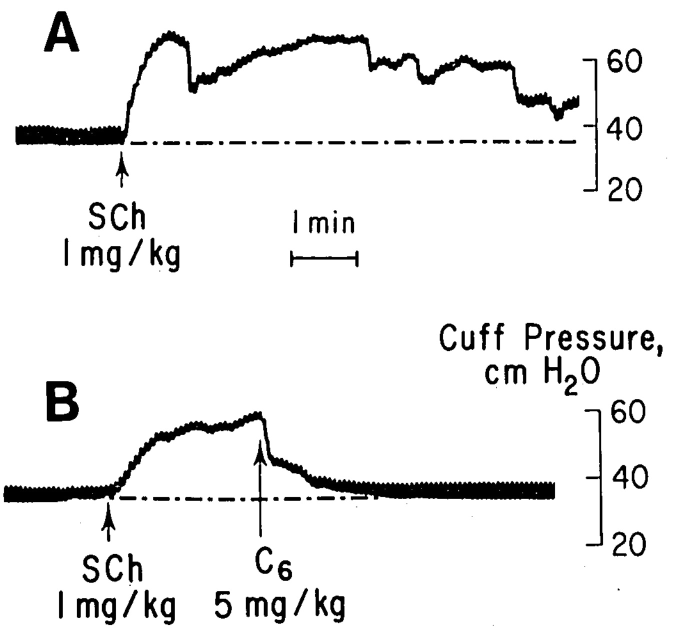

FIG. 2. Increases in cuff pressure elicited by succinylcholine (SCh). The response in trace A persisted for 14 min before returning to control values. Trace B shows a second response to succinylcholine, in the same animal, which was promptly terminated by hexamethonium (C_6).

were accompanied by a transient increase in airway pressure (fig. 1) for 2–6 breaths. Thereafter, airway pressure returned to preinjection values (10–20 cm H_2O) whereas cuff pressure remained elevated. These doses of succinylcholine produced transient arrhythmias and usually increased heart rate by 10 to 100 beats/min. Prior to succinylcholine administration, heart rates ranged from 80–140 beats/min. A slight increase in blood pressure (fig. 1) immediately after injection of succinylcholine was noted in the two animals with femoral cannulae. Mean R_L as determined 1–3 min after injection of succinylcholine (0.5 or 1 mg/kg), was not significantly increased, although minor and inconsistent fluctuations were observed in some experiments. Thus, in 11 trials, R_L averaged 1.9 ± 0.4 cm $H_2O \cdot l^{-1} \cdot s$ before injection of succinylcholine, and 2.0 ± 0.3 after succinylcholine.

Intravenous administration of atropine (0.2 mg/kg) or hexamethonium (5 mg/kg) at 2–3 min after injection of succinylcholine produced a prompt fall in cuff pressure to or below baseline values (fig. 2*B*; table 2), and subsequent injections of succinylcholine failed to elicit increases in cuff pressure. In two dogs undergoing bilateral vagotomy, succinylcholine (1 mg/kg) increased cuff pressure by 26 and 24 cm H_2O before vagotomy, but failed to change cuff pressure after the vagi were sectioned (fig. 1). Stimulation of the cut distal vagal stumps (fig. 1, lower trace) elicited large increases in cuff pressure, demonstrating that cuff pressure was still capable of recording contraction of the trachealis muscle. Subsequent injection of hexamethonium (5 mg/kg) in both dogs abolished the increase in cuff pressure elicited by vagal stimulation, demonstrating that the ganglionic synapse was distal to the site of vagotomy.

In experiments with isolated preparations of trachealis muscle, succinylcholine did not elicit contraction in any preparation (n = 6) and significantly relaxed preparations that had been contracted with carbamylcholine (figs. 3 and 4).

Discussion

Fasciculations of skeletal muscle could have contributed to the initial rise in cuff pressure, but the increase in pressure was of much longer duration than fasciculations, or the transient increase in airway pressure (fig. 1). Furthermore, the increase in cuff pressure occurred with repeated doses of succinylcholine that did not cause fasciculations, and was promptly terminated by administration of atropine or hexamethonium. Therefore, the sustained rise in cuff pressure reflects contraction of visceral (trachealis) rather than skeletal muscle.

Because of its structural resemblance to acetylcholine, succinylcholine might contract tracheal smooth muscle by a muscarinic action, and in other experiments we have observed a slight contraction in guinea pig tracheal chains exposed to high concentrations (10^{-4} to 10^{-3} M) of succinylcholine. However, the increase in cuff pressure cannot be attributed to muscarinic effects of succinylcholine, since succinylcholine did not contract isolated preparations of canine trachealis muscle, and relaxed rather than potentiated contractions induced by carbamylcholine. The decreased responsiveness to cholinergic stimulation following administration of high concentrations of succinylcholine has been previously reported in *in vitro* preparations of intestine[1] and heart.[7]

TABLE 2. Reversal of Succinylcholine Effect by Atropine (0.2 mg/kg) or Hexamethonium (C_6; 5 mg/kg)

Tracheal Cuff Pressure (cm H_2O)			
Control	After SCh*	After SCh + Atropine	After SCh + C_6
32	60	20	—
38	50	38	—
22	34	20	—
36	63	—	1
37	56	—	34
35	59	—	34

* 0.5 mg/kg in experiments with atropine (3 dogs) and 1 mg/kg in experiments with C_6 (3 dogs).

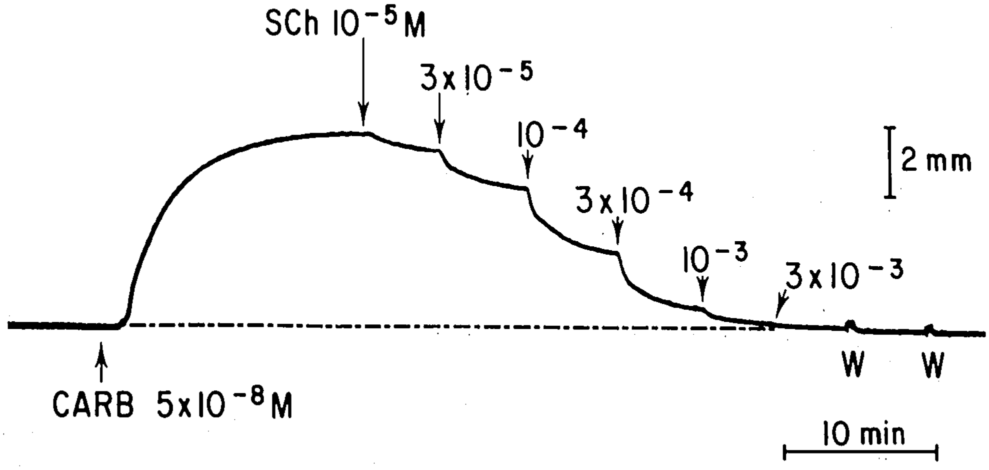

FIG. 3. Succinylcholine (SCh) relaxation of *in vitro* trachealis muscle, previously contracted with carbamylcholine (CARB). SCh concentrations (M) refer to the cumulative concentrations produced by addition (↑) of successive increments. Bath solution was changed at W (wash).

Since succinylcholine-induced increases in cuff pressure are blocked by hexamethonium and vagotomy, as well as by atropine, the response is reflexly mediated and involves parasympathetic pathways. However, the precise site of action is yet to be determined. Ganglionic stimulation has been a traditional explanation for changes in autonomic function following administration of succinylcholine, but a direct action on autonomic ganglia was not apparent in our experiments. Thus in both experiments in which the vagi were sectioned, succinylcholine increased cuff pressure before vagotomy, but not afterwards; in these experiments, the parasympathetic ganglia were distal to the site of section in functional contact with trachealis muscle, and electrical stimulation of the preganglionic nerve (fig. 1) continued to elicit large increases in cuff pressure despite the lack of response to succinylcholine.

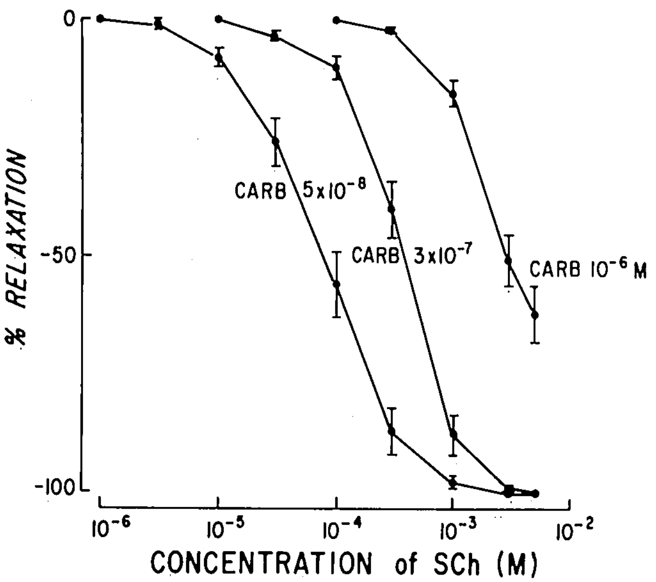

FIG. 4. Cumulative dose-response relationships for succinylcholine (SCh)-induced relaxation of trachealis muscle, previously contracted with carbamylcholine (CARB) 5×10^{-8}, 3×10^{-7}, or 10^{-6} M. Each point represents the mean of 4 to 6 experiments and brackets show the SE. Succinylcholine significantly reduced the CARB 5×10^{-8} M contraction beginning at SCh 10^{-5} M, significantly reduced the CARB 3×10^{-7} M contraction beginning at SCh 10^{-4} M, and significantly reduced the CARB 10^{-6} M contraction beginning at SCh 10^{-3} M.

Mathias *et al.*[8] investigated succinylcholine-induced bradycardia and proposed an action on peripheral sensory receptors, such as carotid sinus baroreceptors, rather than direct stimulation of ganglia. Although succinylcholine elicited tachycardia rather than bradycardia in our experiments, nicotinic agonists have been shown to stimulate many different types of sensory receptor.[9–11] Bolus injection of succinylcholine would present relatively high drug concentrations to pulmonary and vascular afferent receptors, and a nicotinic action at some of these sites is a feasible explanation for reflexly mediated tracheal constriction.

Our study has several practical implications. First, although measurement of tracheal cuff pressure is an appealingly simple technique for studying drug effects on airway smooth muscle during anesthesia,[12] changes in cuff pressure do not necessarily imply changes in R_L. This suggests that drugs can elicit airway reflexes which selectively affect trachealis muscle. Second, relaxation of the trachealis muscle following succinylcholine-induced constriction could result in an inadequate seal between cuff and trachea, if the cuff had been inflated at the peak effect of succinylcholine with a volume of air that was just adequate to accomplish a seal. This could be clinically important from the standpoint of protection of the airway. Finally, the relatively long duration of the succinylcholine-induced tracheal constriction indicates a sustained activation of autonomic reflex pathways following a single injection of succinylcholine.

In summary, our studies show that succinylcholine can elicit a marked contraction of trachealis muscle, and that this results from stimulation of parasympathetic reflexes rather than a direct action on tracheal smooth muscle.

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