Succinylcholine-Induced Contractures in Skeletal Muscles of Newborn Cat.* (25510)

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(Introduced by H. Grundfest)
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It has long been known that during the first postnatal weeks mammalian skeletal muscles (1,2), like those of denervated muscles(3) have an increased sensitivity to acetylcholine. This ACh-sensitivity has recently been demonstrated with more refined technics and the results so obtained indicate that the choline ester depolarizes immature(4) and denervated(5) muscle fibers over their whole surface. Since denervation is the only known factor clearly associated with ACh-sensitivity of mature mammalian muscles, the question arises as to whether this similar property of immature muscles is related to their incomplete functional innervation. Opportunity for testing this possibility was afforded during preparation of newborn kittens for neurophysiological studies, in which it was noted that intravenous succinylcholine produced generalized contractures. Since choline ester-induced contractures have been demonstrated in skeletal muscles of the mature mammal only after denervation(6,7), attempts were made to establish the relationship between succinylcholine-contractures and functional innervation in the newborn kitten.

Methods. Over 45 kittens, ranging in age from late fetal stage to 3 weeks, were initially anesthetized with ether to permit introduction of a tracheal and external jugular vein cannula, then allowed to recover after local anesthetization of exposed skin margins. Concentric needle electrodes were inserted into limb muscles for oscilloscopic registration of their electrical activity. The animals were tested for various types of reflex responses after which succinylcholine chloride (0.2-5 mg/kg in 0.5-1 ml Ringer's) was injected and artificial ventilation instituted.

Results. Skeletal muscles of unanesthetized, intact kittens, less than 2 days old, participated vigorously in a variety of excitatory and inhibitory reflex activities. Muscle action potentials from leg extensors elicited by minimal, but sustained stretch were rapidly eliminated during and for some time after pressure to the ipislateral foot pad (Fig. 1A). Contralateral foot pad pressure markedly augmented leg extensor activity, whereas superimposed ipislateral foot pad pressure abolished it (Fig. 1B). These findings do not support the conclusion that spinal inhibitory reflexes are poorly developed in 1-2 day old cats(8). On the contrary, they indicate existence of complex powerful spinal reflex pathways operating in the intact animal by the second postnatal day.

In the absence of spontaneous or evoked movements, skeletal muscles were electrically silent. Under such conditions, succinylcholine evoked a flurry of action potentials. Electrical silence (Fig. 1C) again ensued during development of generalized contractures of such severity as to rapidly induce a postural attitude which superficially resembled that seen in the decerebrate, mature cat (Fig. 2). This posture resulted from sustained contractures in both flexors and extensors; activity of the latter group predominating in neck, trunk and hindlimbs, the former, in the distal and to a lesser extent, proximal forelimb musculature.

Duration and intensity of the generalized contractures depended on age of animal and interval between successive injections of succinylcholine. Contractures, best demonstrated in late fetal and neonatal animals (less than 3 days), were less prominent in 3-7 day old kittens and absent after 10th-12th postnatal day. By the end of second week, succinylcholine produced effects entirely similar to those observed in mature animals, *i.e.*, gen-

* Financed by the NINDB and the Paul Moore Fund.

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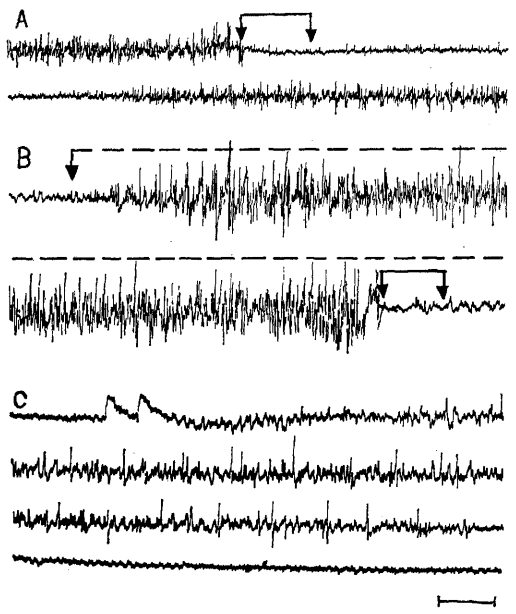

FIG. 1. A. Continuous EMG tracings from quadriceps under light stretch in 2-day-old intact kitten. Arrows indicate approximate duration of pressure to ipislateral footpad. Note persisting inhibition of quadriceps activity despite maintained stretch. B. Same preparation as in A, quadriceps relaxed. At arrow, pressure applied to contralateral foot pad evokes crossed extensor reflex activity (broken line) which is promptly abolished by ipislateral foot pad pressure (solid line). C. Continuous EMG tracing from relaxed quadriceps of another 2-day-old animal. Tracing commences a few seconds after intrav. succinylcholine (2 mg/kg). This induced an outburst of muscle action potentials which terminated in electrical silence. Time cal. 4 sec. in A; 2 sec. in B, and 1 sec. in C.

eralized twitchings and rapid flaccid paralysis. In the perinatal group, contractures, as judged by manipulation of limbs and head, were of extraordinary duration (3-10 min) and intensity. When these subsided, there generally supervened a prolonged period of flaccid paralysis (1-2 hours), after which spontaneous movements might return. Subsequent injections of succinylcholine then produced transient contractures or none at all prior to paralysis. Frequently, spontaneous movements were not observed for 3-4 hours after severe contractures induced by concentrations of succinylcholine 2-3 times higher than that routinely employed in this laboratory to paralyze adult cats (1-2 mg/kg).

Comment. The effects of intravenous succinylcholine on skeletal muscles in the newborn cat resemble that produced by close-arterial injections of relatively high concentrations of ACh in chronically denervated muscles of the mature animal(6,7). A large ACh-induced contracture in denervated muscle leaves in its wake a profound depression of excitability to electrical or subsequent chemical stimulation(6,9). In the newborn cat, succinylcholine-contractures appear to induce a similar depression as indicated by absence of spontaneous movements for long periods and failure of successive injections of succinylcholine to evoke contractures despite the fact that the choline ester may block neuromuscular transmission when some recovery does occur. Our study provides no direct information on the mechanism by which succinylcholine produces contracture in newborn cats. During ontogenesis(4), muscle fibers, like those in chronically denervated muscle (5), are sensitive to the depolarizing action of

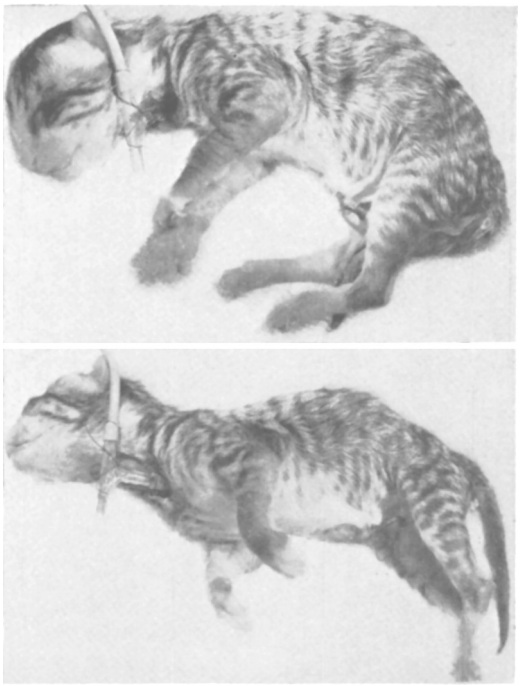

FIG. 2. Overt effects of succinylcholine in 1½-day-old kitten. *Above*, kitten, relaxed, lying on right side during recovery from ether anesthesia. *Below*, postural attitude 1 min. after intrav. succinylcholine (4 mg/kg). Note opisthotonus, extension of hindlimbs and flexion of distal forelimbs. Generalized rigidity persisted for 5 min. before flaccid paralysis supervened. Spontaneous limb movements were not observed even after 3 hr.

ACh over their whole surface and this sensitivity is associated with a high myosin-ChE and low myosin-ATP'ase activity(10,11). Global chemosensitivity of muscle fibers in the newborn animal could satisfactorily account for contracture-inducing effects of succinylcholine reported here. There is, however, no satisfactory explanation as to why succinylcholine fails to evoke contractures in the cat after 10th-12th postnatal day. If this is related to the finding that at this time the chemosensitivity of muscle fibers is restricted to the end-plate region(4), then it must be allowed that the changing responsiveness of skeletal muscles in newborn cats to succinylcholine is not *immediately* related to establishment of motor innervation, but to some factors which are brought into operation during the latter phases of ontogenesis.

Summary. Intravenous succinylcholine produces generalized, prolonged contractures in newborn cats prior to 10th-12th postnatal day. This sensitivity of immature muscles to succinylcholine is not related to detectable deficits in their functional innervation.

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Received November 13, 1959. P.S.E.B.M., 1960, v103.

Polymyxin B and Colistin: Activity, Resistance and Crossresistance *in vitro*.* (25511)

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Polymyxin B, a polypeptide antibiotic available for over a decade, has been used successfully in treatment of serious Gram-negative bacillary infections resistant to other antibacterial agents. It has been particularly effective against infections due to *Pseudomonas aeruginosa* but totally ineffective against Proteus infections; its use, however, has been limited by its neuro- and nephrotoxicity(1). Colistin, a new antibiotic recently introduced in Japan as Colimycin, is also a polypeptide and is produced by *Bacillus colistinus,* which is related to *B. polymyxa,* the source of polymyxin; it has similar antibacterial action but apparently lacks much of the toxic properties of polymyxin B. Both antibiotics have similar chemical constituents; each contains (+)-6-methyl-octanoic acid, d-leucine, l-leucine, l-threonine and 1-α,γ-diaminobutyric acid but polymyxin B contains d-phenylalanine which colistin lacks and the numbers of some of the other constituents differ(2-6). This paper deals with comparisons of *in vitro* activity of these 2 antibiotics against pathogenic organisms, most of them Gram-negative bacteria recently isolated from patients, and also reports observations on development of resistance and crossresistance to these 2 antibiotics *in vitro*.

Materials and methods. Polymyxin B sul-

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