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Effect of Succinylcholine on Skeletal Muscle with Immobilization Atrophy

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The effects of succinylcholine (SCh) on both normal and immobilized canine gastrocnemius muscle were compared and contrasted with respect to potassium (K^+) flux, $\dot{V}_{O_2}$, and muscle tension. Muscle K^+ efflux and $\dot{V}_{O_2}$ increased more in immobilized atrophic than in normal muscle. Neither normal nor immobilized muscle showed increased tension with SCh. K^+ efflux from immobilized atrophic muscle was much less than that previously demonstrated from denervated muscle. The difference in response, however, cannot be attributed solely to the absence of supersensitivity in muscle with immobilization atrophy, for paraplegic muscle, which also does not manifest supersensitivity, responds to SCh with a large release of K^+. It may be that there is a trophic function from upper to lower motor neuron, as well as from lower motor neuron to muscle. (Key words: Neuromuscular relaxants: succinylcholine; Muscle, skeletal: atrophy: succinylcholine; Muscle, skeletal: potassium flux; Muscle, skeletal: oxygen consumption; Ions: potassium: skeletal muscle; Oxygen consumption: skeletal muscle.)

MUSCULAR ATROPHY due to an upper or lower motor neuron lesion is known to be associated with a hyperkalemic response to succinylcholine (SCh).[1] We[2] and others[3,4] have speculated that muscular atrophy resulting from disuse or immobilization may cause a similar response. The present study demonstrates that immobilization atrophy in the dog produces only a small increase in potassium (K^+) release by SCh.

Materials and Methods

Either hind limb of five mongrel dogs (weights, 13 to 21 kg) was immobilized in the neutral position in a plaster cast during anesthesia with pentobarbital sodium (25 mg/kg, intravenously). The animals were examined daily and the casts changed as needed; generally, this was done each week. Then, 29 to 44 days after the initial immobilization in each dog, venous flows from the gastrocnemius muscles of both immobilized and normal legs were isolated and collected during endotracheally administered halothane anesthesia, according to a method previously described.[2] Net flux of muscle K^+ and muscle $\dot{V}_{O_2}$ were determined, as before,[2] from measurements of muscle blood flow and arteriovenous (A-V) differences across the muscle.

After control observations had been made in triplicate for both normal and immobilized muscle, the response to a single intravenous injection of SCh (0.25 mg/kg) was determined. Significance of differences was tested using the t test for paired or unpaired data, $P < 0.05$ being considered significant.

Results

SCh produced a slight K^+ efflux from immobilized muscle; this was greater than that from normal muscle (fig. 1, table 1), and was primarily due to an increase in A-V difference (table 2) rather than blood flow (table 1). In figure 1, data relating to K^+ flux in denervated skeletal muscle are from a previous study[2] (see Discussion). $\dot{V}_{O_2}$ of immobilized atrophic and normal muscle increased after SCh (fig. 2, table 1); statistically the increases were not different. K^+ content of normal muscle was slightly greater than that of immobilized muscle (table 3). However, the muscle biopsies were taken immediately after the period of observation, and, during the period of observation, immobilized muscle lost more K^+ through efflux than did normal muscle (fig. 1, table 1). Normal muscle weight exceeded immobilized muscle weight (table 3) to the same extent that it had exceeded denervated muscle weight in a similar study.[2] No increase in tension was observed in immobilized muscle after administration of SCh (as had been demonstrated previously[2] in denervated muscle), and electromyography was therefore not performed. Changes in val-

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TABLE 1. K⁺ Flux, $\dot{V}_{O_2}$, and Blood Flow of Normal and Immobilized Skeletal Muscle after SCh (0.25 mg/kg, Five Dogs Each, Mean ±SE)

Variable	Control	Time (Min) 0-10	10-20	20-30	30-40	40-50	50-60
K⁺ flux, μEq/min/100 g							
Normal	0.63 ±0.41	3.21*† ±0.21	2.76*† ±0.32	1.63 ±0.45	0.51 ±0.48	0.14 ±0.25	−0.04 ±0.32
Immobilized	0.75 ±0.26	10.66* ±2.72	4.19* ±0.10	−0.01 ±0.58	−0.91* ±0.75	−0.57* ±0.43	−0.52* ±0.38
$\dot{V}_{O_2}$, ml/min/100 g							
Normal	0.63 ±0.08	1.01* ±0.12	0.93* ±0.12	0.79* ±0.08	0.68 ±0.08	0.65 ±0.09	0.68 ±0.12
Immobilized	0.66 ±0.08	1.46* ±0.23	1.24* ±0.16	1.04* ±0.11	0.87* ±0.08	0.82* ±0.08	0.76* ±0.08
Muscle blood flow, ml/min/100 g							
Normal	7.9 ±0.8	11.4 ±1.1	9.8 ±0.9	8.5 ±0.9	7.7 ±1.0	7.0 ±1.0	6.4 ±1.2
Immobilized	12.1 ±4.8	17.0 ±2.3	13.5 ±1.9	11.6 ±1.8	9.9 ±1.5	9.0 ±1.4	7.6 ±1.0

* Different from control value, t test for paired data, $P < 0.05$.
† Normal < immobilized, t test for unpaired data, $P < 0.05$.

TABLE 2. Plasma and Whole-blood K⁺ Concentrations (mEq/l) in Arterial, Normal Muscle Venous, and Immobilized Muscle Venous Samples after SCh (0.25 mg/kg, Five Dogs Each, Mean ±SE)

K⁺ Source	Control	Time (Min) 1	4	7	13	19	29	39	49	59
Plasma										
Arterial	3.0 ±0.3	3.1 ±0.2	3.2 ±0.3	3.2 ±0.2	3.2 ±0.2	3.2 ±0.2	3.3 ±0.3	3.3 ±0.2	3.3 ±0.2	3.3 ±0.2
Normal	3.2 ±0.2	3.6* ±0.2	3.8* ±0.3	3.7* ±0.2	3.8* ±0.2	3.8* ±0.2	3.6* ±0.2	3.4 ±0.2	3.3 ±0.2	3.3 ±0.2
Immobilized	3.2 ±0.2	4.3* ±0.5	4.8* ±0.3	4.2* ±0.1	3.8* ±0.2	3.5 ±0.2	3.3 ±0.3	3.2 ±0.3	3.2 ±0.2	3.2 ±0.2
Whole blood										
Arterial	4.2 ±0.3	4.3 ±0.3	4.5 ±0.4	4.4 ±0.4	4.5 ±0.3	4.5 ±0.4	4.7* ±0.5	4.7* ±0.4	4.6 ±0.4	4.6 ±0.4
Normal	4.3 ±0.3	4.6 ±0.3	4.8* ±0.4	4.7 ±0.4	4.7 ±0.4	4.8* ±0.4	4.8* ±0.4	4.7 ±0.4	4.6 ±0.4	4.6 ±0.4
Immobilized	4.3 ±0.3	5.1 ±0.4	5.4* ±0.3	5.1* ±0.3	4.7* ±0.3	4.6 ±0.4	4.7 ±0.4	4.6 ±0.4	4.6 ±0.4	4.5 ±0.4

* Different from control value, t test for paired data, $P < 0.05$.

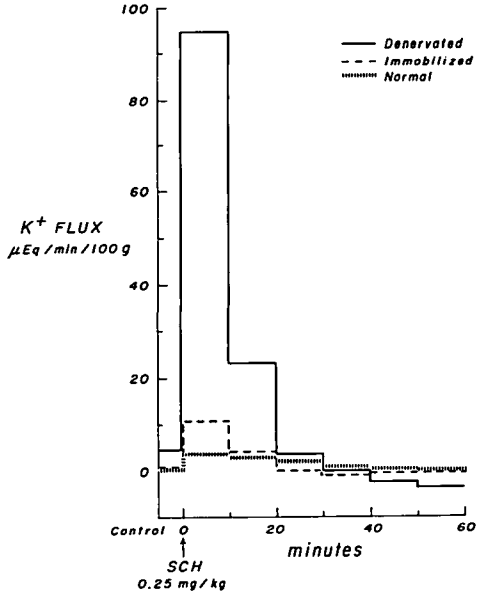

FIG. 1. K^+ fluxes of normal, immobilized, and denervated skeletal muscle after SCh injection. Efflux indicated by positive values, influx by negative values. Values for denervated muscle are from a previous study.[2]

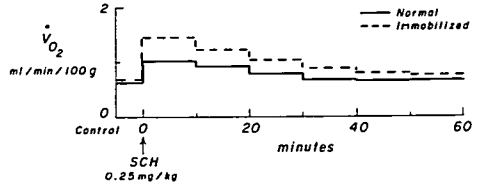

FIG. 2. $\dot{V}_{O_2}$'s of immobilized and normal muscle after SCh injection.

ues of blood gases and acid–base balance were insignificant and are not reported.

Discussion

Atrophy following immobilization of hind limbs in plaster was similar in extent to that observed following denervation for a comparable period.[2] The release of K^+ by SCh, however, was strikingly different (fig. 1). This was most noticeable during the first 10 minutes after SCh administration, during which time K^+ efflux from denervated muscle reached a mean value exceeding 90 μEq/min/100 g (wet weight), while K^+ efflux from immobilized muscle was about 10 μEq/min/100 g. Changes in $\dot{V}_{O_2}$ paralleled these changes in K^+ efflux and were probably related to graded activation of the Na^+–K^+ pump, an added increment in $\dot{V}_{O_2}$ of denervated muscle being related to the SCh-induced contracture.[2]

The explanation for the release of large amounts of K^+ by denervated muscle exposed to SCh is based on the greatly increased sensitivity of the muscle membrane to chemical depolarization.[5] Following denervation, the entire muscle membrane surface develops the sensitivity to chemical depolarization that is peculiar to end-plates[5] and that is accompanied by increased ionic fluxes of K^+[6] and Na^+.[7] With disuse atrophy secondary to

TABLE 3. K^+ Contents of Normal and Immobilized Muscle One Hour after SCh (0.25 mg/kg, Five Dogs Each, Mean ±SE)

Muscle	K^+ Content (mEq/100 g)	Muscle Weight (g)
Normal	9.06* ±0.18	64* ±3
Immobilized	8.40 ±0.26	39 ±3

* Normal > immobilized, $P < 0.05$, t test for paired data.

immobilization[8,9] or tenotomy,[10] the sensitivity of the muscle membrane is at most only slightly increased, and this may appear to explain the associated minimal shift of K^+ after SCh. But a similar slight increase in membrane sensitivity is also observed in cases of upper motor neuron lesions (paraplegia),[11,12] in which the release of K^+ after SCh is probably at least as great as that observed following denervation.[1] Clinical studies verify this observation.[13,14]

There is no obvious explanation for this disparity between supersensitivity and K^+ efflux in disuse atrophy, in denervation atrophy, and in cases of upper motor neuron lesion. Studies of K^+ flux sooner after immobilization might have shown greater K^+ efflux. Although in the rat, for example, the increase in sensitivity is greatest 10 days after immobilization[8,9] or cord section,[11,12] in the dog the peak hyperkalemic response following denervation or paraplegia occurs about 4 weeks after injury.[1] We studied one additional dog 3 weeks after immobilization and found a comparable K^+ flux. It is likely that factors other than, or in addition to, changes in membrane sensitivity are involved in the hyperkalemic response to SCh.

These factors may include the trophic function of the nerve.[15] Just as the lower motor neuron contributes some as yet undefined factor to the muscle to prevent disorders such as atrophy, fibrillations, development of supersensitivity, marked K^+ efflux with SCh, and loss of cholinesterase, so the upper motor neuron may likewise contribute some factor to the lower motor neuron to prevent some of these changes. This conceivably could involve hyperactive cord reflexes, some muscles being spastic and others flaccid.

We are puzzled as to the explanation for the hyperkalemic response in the patient with burns who has no associated neuromuscular trauma.[16] We[2] have reasoned that the hyperkalemic response to SCh in such patients may be due to the disuse atrophy and wasting that occur with prolonged confinement to bed. Wylie and Churchill-Davidson[3] and Siker *et al.*[4] have stated similar views, and have included prolonged bed rest following orthopedic procedures in their considerations. This argument is not supported by the findings of the present study.

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