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Regulation of Skeletal Muscle Acetylcholine Receptors

To the Editor:—In a recent review it is stated that if an upper motor neuron (UMN) dysfunction is bilateral and the patient is tetraparetic, "The upper limb muscles relative to the lower appear more sensitive to nondepolarizing muscle relaxants (NDMR)."[1]

To my knowledge, the only report that might confirm this statement refers to patients with syringomyelia in whom the motor deficit of the upper limbs is caused by a *lower* motor neuron (LMN) dysfunction.[2]

I wish to stress this point because, according to the authors of the review, any evidence of muscle denervation should be accompanied by hyposensitivity to NDMR, and any hypersensitivity exhibited by denervated or injured muscles should be regarded as a "contradictory finding."

I think that any evidence of axonal sprouting (even that occurring after muscle injury[3]) should be regarded as a predisposing factor to the subsequent development of hypersensitivity to NDMR.

As mentioned by the authors,[1] a definite hyposensitivity to the action of d-tubocurarine has been observed in the gastrocnemius muscle of the rat 14 days after a 75–80% transection of the sciatic nerve.[4] It also should be remembered, however, that a definite hypersensitivity to the action of the same drug has been demonstrated in the anterior tibial muscle of the rabbit 42 days after the peroneal nerve has been crushed and then allowed to regenerate.[5]

A distinction, therefore, should be made between the early effects produced by denervation and the late effects produced by reinnervation:[6] by the reduced amounts of acetylcholine (ACh) released by intact terminals,[7] and by the low synaptic efficacy of neuromuscular junctions in multiply innervated muscle fibers.[8]

So far as hyperkalemic accidents are concerned, I think that the distinction to be made in patients with UMN dysfunction is not between congenital and acquired lesions, but between lesions that cause muscle *decentralization*[9] and lesions that cause decentralized muscles to be transiently *denervated*.[10]

Diaschisis phenomena, which are a frequent complication of acute UMN lesions, may result in transient states of functional denervation that may cause an extrajunctional proliferation of ACh receptors (AChRs)[11] similar to that induced by sepsis or by chronic treatment with NDMR.

Such an *LMN* dysfunction, which may be unrecognized in comatose patients,[12] should be considered an important factor to which ascribe hyperkalemic accidents caused by succinylcholine in patients recovering from acute UMN lesions.

If it is considered, on the other hand, how frequently decentralized muscles of hemiparetic or tetraparetic patients have been challenged with an intubating dose of succinylcholine in the past three decades, the likelihood of any correlation between UMN dysfunction and hyperkalemia appears to be very poor[9,13] (in the absence of other predisposing factors such as diaschisis, sepsis, and chronic treatment with NDMR).

These observations indicate that extrajunctional proliferation of AChRs is not a normal consequence of UMN dysfunction. They also suggest that the altered sensitivity that decentralized muscles exhibit toward the action of cholinergic agonists,[14–16] to the action of anti-AChR-antibodies,[17,18] and to that of NDMR should be ascribed to junctional or prejunctional factors.

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In Reply:—We thank Fiacchino for pointing out an ambiguous statement in our review article[1] that, following an upper motor neuron (UMN) lesion, "The upper limb muscles, relative to lower muscles, are more sensitive to the effects of nondepolarizing muscle relaxants (NDMR)." The message that was conveyed was that "the proximal muscles compared to distal appear more sensitive to the effects of NDMR." This conclusion was based on the reports that central or UMN denervation causes resistance to NDMR[2–4] and on the electromyographic evidence that central denervation, more frequently, affects the distal rather than proximal muscles.[5,6] The reports of Fiacchino *et al.* substantiate this claim whereby following UMN denervation, the trapezius muscle was more sensitive than the abductor digiti minimi[7] and that the adductor pollicis brevis was more sensitive than the flexor hallucis brevis.[8] Unfortunately, because of the lack of controls in these latter studies,[7,8] it was not possible to determine whether the sensitivity of these muscles was increased or decreased compared to normal muscles. We, however, disagree that syringomyelia is a disease of the lower motor neuron. The syringomyelic cavity dissects into and progressively replaces the gray matter of the posterior and anterior horns of the spinal cord.[9] Depending on the stage and severity of the disease, symptoms and signs of upper and/or lower motor neuron lesion may be present.

The claim that axonal sprouting should be regarded as a predisposing factor for subsequent development of *increased* sensitivity to NDMR is not consistent with other reports. Changes occurring with immobilization of a limb for example include, among others, terminal nerve sprouting,[10] yet resistance to NDMR has been observed.[11] Following reinnervation recovery from injury or remobilization, the response to depolarizing or NDMR will be quite variable,[12,13] and this variability may be related to prejunctional and postjunctional factors, including total receptor number and proportion of mature to immature receptors.[1]

We concur with Fiacchino's views that upper or lower motor denervation is not always accompanied with resistance to NDMR or hyperkalemia to succinylcholine. In our review,[1] we have enumerated reports in which exceptions have occurred (*vide* page 829 of review[1] and references 133–140). We also have listed a number of reports confirming hyperkalemia with succinylcholine following UMN denervation in which sepsis, concomitant chronic treatment of NDMR, or other predisposing factors were not present. We disagree with the notion that extrajunctional proliferation of acetylcholine receptors is not a normal consequence of UMN dysfunction. Increased sensitivity to acetylcholine or succinylcholine due to receptor spread[14,15] and proliferation of extrajunctional acetylcholine receptors, quantified by ^{125}I-α-bungarotoxin, has been observed following cordotomy[16] or other UMN disease of the spinal cord.[17] Electromyograph studies following stroke in humans have confirmed the denervation state by the presence of fibrillation potentials and positive sharp waves.[5] The magnitude and the duration of these changes, however, may not be as prominent as that seen following lower motor neuron denervation.

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