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## Effect of histamine on acetylcholine-evoked contractile responses of chronically denervated cat skeletal muscle

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In a previous study (Block & Reit, 1973) we found that histamine injected i.a. toward innervated skeletal muscles potentiated their contractile responses to acetylcholine injected shortly afterward *via* the same route. Potentiation also occurred when the acetylcholine was injected i.a. shortly after i.a. bradykinin or during exercise or post-occlusion hyperaemia, but when injected shortly after angiotensin, inhibition occurred. Therefore, we concluded that histamine exerted its potentiating effect by causing vasodilatation within the muscles, thus allowing more of the acetylcholine to reach more of its skeletal muscle receptors in a shorter time. We have now extended our studies of this vasomodulatory relationship to chronically denervated skeletal muscle.

Cats were anaesthetized with pentobarbitone sodium (35 mg/kg i.p.) and 2 cm of one peroneal nerve were removed aseptically. Fourteen days later, the cats were again anaesthetized and then rendered spinal. The denervated anterior tibialis muscles were prepared as previously described for recording their contractile responses, and the sural arteries were cannulated centrally so that i.a. injections could be made close to the muscles (Block & Reit, 1973). Drugs were dissolved in 0.9% NaCl solution and injected in volumes of 0.1 ml or less.

In the normally-innervated muscles, histamine (0.1 μg/kg) injected 15 s before graded doses of acetylcholine (3-100 μg/kg) caused a shift to the left of the acetylcholine dose-response curve of 1.5 log units. In the chronically denervated muscles, the control acetylcholine dose-response curve had become shifted predictably 3 log units to the left. But neither histamine (0.001-0.1 μg/kg) nor bradykin (0.01-0.1 μg/kg) shifted it any further, even though angiotensin (0.001-0.1 μg/kg) was still able to inhibit the supersensitive contractile responses to acetylcholine. Since, as Hudlicka (1967) has reported, the vascular bed of chronically denervated skeletal muscle is widely dilated compared to that of innervated control muscles, the vasodilator substances probably did not potentiate the acetylcholine-evoked responses of chronically denervated muscle because they could not increase significantly the already large nutritive blood flow within those muscles. Therefore, our results raise the question whether denervation supersensitivity to acetylcholine *in vivo* may be due not only to an increased surface area of cholinoceptivity on the individual muscle fibers but also in part to increased nutritive blood flow within the muscle mass. (Supported in part by PHS Grant R01-08259-04).

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