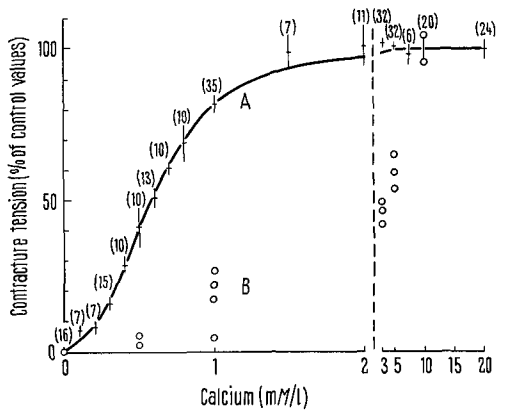

Fig. 2. The influence of the concentration of calcium in the superfusion medium on contracture tensions, the latter being expressed as percentages of a control value. Curve A: Magnesium, 4 mM. Results (from 12 ventricles) expressed as means $\pm$ standard errors of means; number of data averaged to give each point given in brackets. Curve B: Magnesium, 20 mM. Individual data from one ventricle.

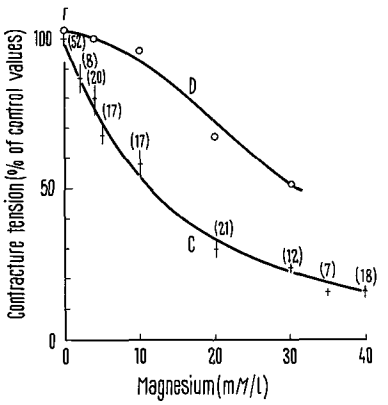

Fig. 3. The influence of the concentration of magnesium in the superfusion medium on contracture tension. Curve C: Calcium, 1 mM. Results (from 6 ventricles) expressed as means $\pm$ S.E. of means; numbers of data for each point given in brackets. Curve D: Calcium, 5 mM. Individual data from one ventricle.

Responses to changes in concentration of calcium or magnesium were immediate when these occurred actually during a contracture, and complete in about 5 sec. This rapidity is more suggestive of changes near the cell surface than of gross alterations in the amounts of calcium or magnesium inside and the results can be interpreted in terms of a competition of the two cations for superficial binding sites, with the tension depending on the proportion of sites occupied by calcium: On this view, the failure of tension to rise indefinitely with extracellular calcium concentration would be due to saturation of the sites. A comparable competition between calcium and magnesium is seen in uterine muscle of the rat[5], but, in frog ventricle, the action of calcium is antagonized by sodium[6,7].

The concentration of calcium in the blood of *H. aspersa* is usually 4–16 mM and, in hydrated snails, magnesium averages about 3.6 $\pm$ S.D. 1.2 mM[1]. Though some of the calcium is not ionized[8], there is enough present that even large variations can have only negligible influence on excitation-contraction coupling. Normal fluctuations in magnesium should have a greater effect, but, here too, the data suggest it would be unimportant.

Zusammenfassung. Die isometrische Kontraktionsspannung in der isoliertenHerzkammer – mit Wechselstrom gereizt – nimmt mit der Kalziumkonzentration im Medium bis zu einem «Plateau» zu. Dem Kalziumeffekt wird durch Magnesium entgegengewirkt während Veränderungen der Natriumkonzentration keinen entscheidenden Einfluss haben.

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On the Mechanism of Compensatory Hypertrophy in Skeletal Muscles

It has recently been shown that in the rat, following tenotomy of the gastrocnemius muscle, a rapid and striking hypertrophy of the synergistic soleus and plantaris muscles occurs[1,2]. In a preliminary attempt to identify the physiological mechanisms operating during compensatory hypertrophy, it seemed important to test the role of the neural influence or at least the necessity for intact neural circuits in inducing compensatory hypertrophy. Two alternative working hypotheses may in fact be considered to explain how the overload imposed on skeletal muscles following tenotomy of synergists might determine compensatory hypertrophy. On the one hand, the increased strain, signalized by the stretch receptors, may induce through reflex pathways an increased functional activity. In this case the compensatory hypertrophy that follows would be essentially similar to that due to physical exercise, in both cases the causal agent inducing hypertrophy being increased 'active' muscle work dependent on increased neural stimulation. Alternatively one can envisage a direct effect of mechanical tension on skeletal muscle, not dependent on nerves: the hypertrophy, in this case, would be produced by the increased 'passive' stretching of the loaded muscles. A similar mechanism has been suggested to explain the transitory hypertrophy of the denervated hemidiaphragm

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Combined effects of denervation and tenotomy of a synergist on weight change in the rat soleus and plantaris muscles

Group	Experimental procedure[a]		No. of animals	% difference of muscle dry weight (means ± S.E.) between right and left side[b]	
	Right side	Left side		Soleus m.	Plantaris m.
1	No operation	No operation	8	+0.4 ± 3.1	+2.8 ± 2.3
2	Denervation	Sham-operation	8	−27.6 ± 1.4	−21.1 ± 1.6
3	Tenotomy of synergist	Sham-operation	8	+25.5 ± 2.9	+17.1 ± 2.3
4	Denervation plus tenotomy of synergist	Sham-operation	8	−8.5 ± 3.2	−9.1 ± 1.8
5	Denervation plus tenotomy of synergist	Denervation	8	+17.7 ± 3.8	+15.3 ± 2.2

[a] Further explanation is given in the text. [b] At 5 days following operation.

subjected to the rhythmical pull due to the contraction of the innervated contralateral muscle[3–5]. Likewise the relative growth that occurs in rat muscles denervated at birth may be related also to the stretching caused by the growing skeleton[6]. To discriminate between these mutually exclusive possibilities, the interaction of compensatory hypertrophy and denervation atrophy of soleus and plantaris muscles of the rat was analyzed.

Materials and methods. Female Wistar rats, weighing between 130–150 g, were used in these experiments. Denervation was performed in one group of animals by removal of a segment of the tibialis nerve at the popliteal fossa; in another group of rats the gastrocnemius muscle was tenotomized as described by GOLDBERG[1]; in a third group both operations were accomplished in the same leg. In all cases a sham operation was carried out on the controlateral limb. In a further group of rats both denervation and tenotomy of the synergist were performed on one side and simple denervation on the other.

Results and discussion. Dry weight changes of the soleus and plantaris muscles are reported in the Table. It is apparent that, after combined denervation and tenotomy, the result is not significantly different from an algebraic summation of the opposite effects of the 2 factors not combined. Factorial analysis confirms that the interaction between denervation and tenotomy of synergist is not significant (the F values being 1.43 and 0.36 for soleus and plantaris muscle respectively, $p > 0.05$), that is their effects are essentially additive. The results from the experimental group 5 are in keeping with this conclusion. The relative hypertrophy which follows tenotomy of the gastrocnemius in these denervated animals is not significantly different from that seen in normally innervated (group 2) rats ($p > 0.1$ for soleus and > 0.5 for plantaris muscle in the t-test).

The results of the present experiments appear to indicate that the early response inducing hypertrophy of skeletal muscles following tenotomy of a synergist occurs practically independently of innervation, and suggest that non-neural factors are operating during compensatory hypertrophy. Changes in blood flow, brought about by increased tension or by other mechanisms, directly or through neural reflex pathways running along routes different from the main peripheral nerve trunks, may play a role in inducing compensatory hypertrophy. However, general considerations[7], and the fact that blood flow is increased in different types of muscle atrophy[8], make it unlikely that an increase in the blood flow could be the primary and immediate cause of compensatory hypertrophy. A more important factor appears to be the direct effect of increased tension on skeletal muscle. Mechanical tension is known to affect directly muscle energy metabolism: as shown by FENG[9], the resting metabolism of frog muscle increases during passive stretch of muscle. Recent incorporation studies on isolated rat muscles[10] indicate that the same factor affects protein metabolism as well. Several other lines of evidence from in vitro[11,12] and in vivo[3,4,6] experiments suggest that mechanical tension is one of the basic 'trophic' factors acting on skeletal muscles, which, together with the neural influences, exerts a fundamental regulatory function adapting the muscles to the variable physiological demands[13,14].

Riassunto. L'ipertrofia compensatoria dei muscoli soleo e plantare di ratto in seguito a tenotomia del sinergista gastrocnemio non appare mediata dall'innervazione, ma è verosimilmente legata a un effetto diretto della accresciuta tensione meccanica sui muscoli interessati.

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