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Smooth muscle physiology, past and future

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The history of smooth muscle physiology from the work of Engelmann on the ureter (1869) to the introduction of intracellular electrodes by Bülbring (1954) is outlined. Attempts at classifying smooth muscles are discussed. The observation that passive shortening has an inhibitory effect during twitches and contractures of the turtle aorta indicates the presence of a feedback mechanism like that demonstrated in other muscles, including the heart. This mechanism, which does not involve changes in membrane potential, may play a role in the control of tonus in blood vessels and other organs which are subject to rhythmic mechanical changes.

History

The history of smooth muscle physiology begins with two important papers by Engelmann, published 1869 and 1870. He found that in the ureter electric current has the same polar effects as in nerve and concluded that the origin and conduction of peristaltic waves is myogenic. He summarized his results in the following words: 'Under all conditions the ureter responds to stimulation exactly as if it were a collossal hollow muscle fibre'. This sentence is particularly remarkable because it was made several years before similar findings were made for the heart, also by Engelmann, and only 2 years before the all or none law was described for cardiac muscle. Engelmann also noted that after an effective stimulus the muscle was inexcitable for a few seconds. His investigations aroused much interest at the time (Biedermann 1895), chiefly because in the ureter the polar effects of electric current could be studied visually. However, no attempts seem to have been made to apply the results to other smooth muscles with more complex movements, although the question of the myogenic or neurogenic nature of their activity was discussed.

Systematic attempts to understand the function of vertebrate smooth muscle were made much later, chiefly by electrophysiological methods. Cannon & Rosenblueth (1937) and Eccles and his collaborators (Eccles & Magladery 1937), using mainly the nictitating membrane of the cat, studied chiefly the mechanism of the control of smooth muscle by motor nerve fibres and furnished important information on the action of transmitters on smooth muscle fibres (Rosenblueth 1950). Cannon & Rosenblueth (1937) also found that the nictitating membrane did not respond to direct electric stimulation. This result and the finding that the cat uterus is inexcitable led to the conclusion that generally the activity of smooth muscles was neurogenic.

However, I observed that excitability and conduction of uterine muscle depends on the action of oestrogens and demonstrated the unitary character of this type of muscle and of other visceral muscles, chiefly by electrophysiological studies. It was particularly significant that in all these muscles monophasic and diphasic potentials could be recorded during conducted responses, a result which could be explained only by assuming physiological continuity between the fibres. Plataeu-type potentials like those of cardiac muscle were observed in some of these muscles. That in spite of their unitary character the movements of these muscles are complex, was explained as the result of changes in excitability, chiefly caused by nervous and chemical influences, and by variation in the activity and location of pacemakers.

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In this way the activity of a large group of smooth muscles could be explained by invoking only simple, generally accepted principles. These smooth muscles were called visceral smooth muscles and they were contrasted with the remaining types of smooth muscles, such as vascular smooth muscle and the nictitating membrane, which are activated by motor nerves, much like skeletal muscles. Their fibres were assumed to be separate units and were therefore called multiunit smooth muscles (Bozler 1941, 1948).

Thus smooth muscles were classified into two groups, one of which closely resembles cardiac muscle, while the other corresponds to skeletal muscle. Subsequent studies have shown, however, that some of the muscles included into the group of multiunit smooth muscles, particularly vascular smooth muscle, have most of the characteristics of visceral muscles. The original classification may still be practically useful, because it divides smooth muscles into those which are chiefly controlled by motor nerve fibres and another group in which myogenic activity predominates, a distinction which reflects large differences in the gross behaviour of the muscle. However, a classification recently proposed by Burnstock (1970) takes into consideration also other, more subtle, differences in the organization of smooth muscle and promises to serve as an excellent guideline in the description of the function of smooth muscle.

By the introduction of modern methods smooth muscle physiology has recently made great progress. This phase has been initiated by Bülbring and her collaborators (Bülbring 1954) and began with the application of intracellular electrodes in the taenia coli. In the past there has often been the danger for smooth muscle physiology to develop as a separate discipline, because most of the research was carried out by those who were only interested in the function of particular organs. Smooth muscle physiology can develop successfully only in conjunction with the study of other excitable tissues and can in turn contribute to the basic knowledge of the whole field.

Experiments on smooth and cardiac muscle

This leads me to the second part of this talk, in which I have been given wide latitude. Let me first remark that I have proposed the title of this talk only jokingly, but I have been assured that the future of smooth muscle physiology is the keynote of this whole conference. In this spirit, in place of generalities, I would like to spend the rest of my time describing two experiments and their possible significance.

In the experiment illustrated in figure 1*a*, spontaneous contractions of a strip of the turtle aorta were recorded isotonically. If near the peak of a contraction the load was removed for about 1 s, the onset of relaxation was premature. An inhibitory effect was also demonstrated in another type of experiment (figure 1*b*). A moderate degree of contracture was produced by an excess of Ca or by an isosmotic KCl solution and was recorded isotonically. Again, allowing the muscle to shorten briefly, caused a temporary diminution in the level of the contracture. Note that the maximal extension was reached only after more than 10 s. This and other facts show that this is not a purely physical effect, but a diminution in activity. If the procedure was repeated, the effects summated. In this way the muscle may be extended by 15 to 20 %, diminishing the magnitude of the contracture to less than half its original magnitude. It has previously been observed that stretching induces a contraction under the same conditions (Bozler 1969). That these effects could be obtained in depolarized muscles suggests that changes in length can have direct effects on the contractile mechanism.

I would like to mention in this connexion some observations on cardiac muscle (Bozler 1972)

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because they suggest the experiments just described and because they make me feel more confident of the conclusions drawn from these experiments. A contracture was produced in ventricular strips of the frog ventricle by a high Ca or an isosmotic KCl solution. Quick stretch then induced, after the first passive rise in tension, a further very slow rise and subsequent fall in tension. If recorded isotonically, any passive change in length induced slow changes in the level of contracture. At low temperatures very regular sinusoidal oscillations of low frequency were produced. The effects were very similar to phenomena which have been discovered first in the flight muscles of insects (cf. Pringle 1967) and later also in skeletal muscle (Ruegg, Steiger & Schädler 1970). These properties can be demonstrated in glycerol extracted muscle fibres, showing that translocations of Ca are not involved in these contractile processes.

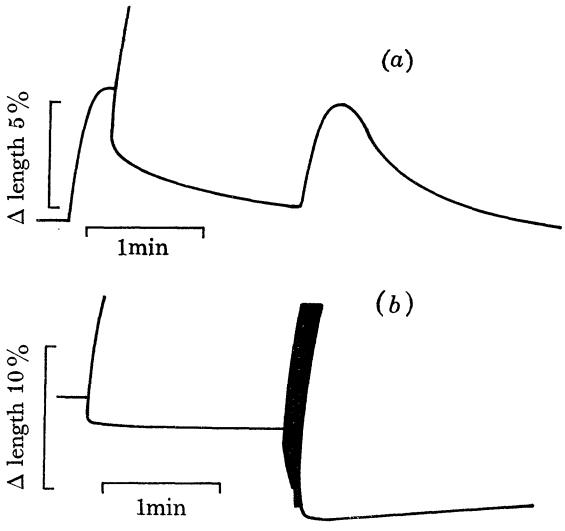

FIGURE 1. Inhibitory effect of brief shortening on spiral strips of turtle aorta. (*a*) Two spontaneous isotonic contractions, muscle in Ringer solution. At the peak of the first contraction the muscle was allowed to shorten briefly by 5% by removing and reapplying load, causing premature relaxation. (*b*) Aorta in a solution containing 118 mmol/l KCl. Contracture was recorded isotonically. On the left, muscle was allowed to shorten once by 5%, as above, causing transient relaxation. Later this procedure was repeated ten times in rapid succession. Upward movement indicates shortening; temperature = 21 °C.

What may be the physiological implications of these contractile phenomena? The effects described probably are most important in muscles which are subject to periodic extension. They may play a role in the control of vascular tone. In muscles which are subject to slow periodic changes in length, such as those of the respiratory passages, the processes described may actively regulate the width of the air passages. Such functions could be carried out without membrane changes and, if the analogy with insect flight muscles is correct, also without movements of Ca. Whether this is more than a flight of fantasy can be decided only by future research.

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