Paradoxical Effects of Epinephrine on Excitation-Contraction Coupling in Cardiac Muscle

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That the catecholamine inotropy in cardiac muscle is characterized by two distinct alterations in the contractile process is by now well recognized. In isolated tissue preparations, as well as in the in situ heart, administration of these substances, or the equivalent procedure of sympathetic nerve stimulation, brings about not only an increase in systolic force or shortening, but also an appreciable reduction in the duration of contraction. While the possible relevance of these two facts to cardiac function has been commented upon, little has been said about them from the point of view of mechanism, and they have apparently been regarded as unrelated, or at least no more contradictory than many other facts in biology. In the light of a postulated site of action of these substances at the excitation-contraction coupling step, for which some support is presented below, the dual nature of the inotropic effect becomes rather more of a problem.

Considerable evidence, obtained following the original observations of Heilbrunn and Wiercynski, supports the current view that, upon membrane depolarization, an influx of calcium ion into the muscle fiber (or, at least, its appearance at some intracellular site critical for contraction) initiates the contractile process. Tracer studies have shown the applicability of this thesis to cardiac muscle where, in particular, alterations in contractile tension brought about by staircase were correlated with changes in an estimated calcium influx per beat. In addition, staircase and a number of allied inotropic effects related to rate and rhythm of contraction of a cat papillary muscle preparation were shown to be abolished in a medium sufficiently rich in calcium, indicating that these inotropic interventions are all mediated by the excitation-contraction coupling mechanism, which is presumably saturated in this calcium-rich (10.8 mmoles/liter), sodium-poor (112 mEq/liter) medium. The sodium deficit of 37 mEq/liter was replaced by choline chloride.

The inotropic action of epinephrine on cardiac muscle may arise similarly from an increase in net calcium transport to the myofilaments during contraction. This possibility is suggested by the roughly reciprocal relationship existing between extracellular calcium concentration and the increase in contraction brought about by addition of the drug to the medium. In the limiting condition of a sufficiently high calcium level, one would expect that epinephrine would confer on the muscle no further increase in contractile strength. In the experiments described below, this expectation is shown to be a fact.

In addition, the early relaxation caused by epinephrine takes place well in advance of membrane repolarization. In view of a consistently demonstrable correlation between electrical depolarization and development (or maintenance) of contractile force in ventricular preparations from several species, it seems reasonable to call the drug-induced relaxation an uncoupling effect. This substance thus exhibits a positive inotropic action, synergistic...
PARADOXICAL EFFECTS OF EPINEPHRINE

with that of calcium ion, followed, later in the contractile time course, by a relaxing effect, which in turn is antagonized by calcium ion. These paradoxical effects must place stringent requirements on any unifying hypothesis for the ionic mechanism of excitation-contraction coupling.

Methods

Cat papillary and trabecular muscles, ranging from 0.3 to 1.1 mm in diameter were used. Each of these was removed from the right ventricle of a cat anesthetized by intraperitoneal injection of 30 mg/kg of sodium pentobarbital. The muscle was placed in a circulating Tyrode bath within two minutes after opening the animal's chest. A gas mixture of 95% O₂: 5% CO₂ was bubbled through theTyrode reservoir, as well as through the fluid in the bath chamber. In one experimental sequence (fig. 7 below), 1-mm thick strips cut from frog ventricles were used. Those experiments involving only mechanical recording from papillary muscles were performed at 28 to 31°C because this low temperature minimized spontaneous changes of contractile tension. In the papillary muscle experiments involving combined electrical and mechanical recording, the bath temperature was maintained at 34°C. The frog ventricle strips were at the unmodified room temperature (20 to 24°C) of the Ringer's solution. In no experiment was the difference between any two bath temperature readings greater than 0.3°C. The experimental procedures were performed on those preparations which did not contract spontaneously (i.e., the vast majority) and while they were driven electrically at rates of either 13 or 24 beats per minute.

The normal Tyrode's solution used had the following composition in millimoles/liter: NaCl, 137; KCl, 2.7; NaHCO₃, 11.9; Na₂HPO₄, 0.4; MgCl₂, 0.5; CaCl₂, 1.8; glucose, approximately 7.0. The components of the Ringer's solution, in millimoles/liter were: NaCl, 110; KCl, 2.5; NaHCO₃, 2.4; CaCl₂, 1.0; glucose, approximately 7.0. Alterations made in the compositions of these media are indicated below. Epinephrine was used in all of the experiments reported here. In two experiments, results with norepinephrine (1 μg/ml) were comparable to those shown in figure 3. As a precaution against oxidation of the epinephrine¹² disodium ethylenediamine tetracetic acid (10⁻⁵ M) was added to all perfusing solutions. In a few experiments (figs. 5 and 6 below) time courses of both contraction and of transmembrane potential were recorded. This was accomplished with an arrangement previously described.¹¹ Briefly, contraction was recorded only from a 0.25-mm length of the cylindrical trabecular by means of suction, delivered through two glass capillary tubes (60 μ I.D. at their tips), placed in contact with the muscle at its side, at right angles to its long axis. One of these was fixed to the edge of the containing lucite bath chamber, the other was cemented to the anode pin of a mechano-electric transducer (RCA 5734). Thus contraction was registered only from that length of muscle lying between the two glass capillaries, a length that amounted to 0.15 mm unstretched, or about 0.25 to 0.30 mm when optimally stretched. Transmembrane potentials were recorded, push-pull, from this portion of the muscle with a conventional micro-electrode and cathode follower assembly.

While, as has been shown,¹¹ this arrangement allows for a micro-electrode measurement from one point, which is quite reasonably representative of the electrical events throughout the 0.25-mm segment of the muscle, the requirements for recording of mechanical activity are not met as completely. Although that portion of the muscle close to the glass capillary tips is satisfactorily isometric (shortening by less than one to one-half percent of muscle length), the axial segments of the muscle distributed farther and farther away (in a radial direction) from the suction attachments, must shorten to a considerably greater extent, thus contributing, in the process, an unknown component to the measured force. Although the utilization of very thin trabeculae (0.3 mm) should tend to minimize this non-uniformity of isometric condition, no ready means has been thought of to determine to what degree this has been accomplished. Thus, this technique would supply values for "isometric tension" of unknown validity if these data were to be used in quantitative comparisons.

In those experiments, therefore, where much emphasis is subsequently placed on the values obtained for developed tension, a different arrangement was employed for recording the isometric tension time course, and electrical events were not monitored (fig. 1). The muscle was held in such a way as to enable the recording of tension from all elements throughout its radial extent. A lucite plate, containing six cylindrical holes (only one of which is shown in the diagram) in its underside was lowered onto the muscle bundle by turning a screw. The holes, extending into the plate for 1 mm beyond its forward vertical edge, were of different diameters and the one whose diameter was closest to that of the muscle was chosen. The under edge of each cylindrical hole had been milled away horizontally to the extent of one-third of its volume. As the upper plate was brought down flush with a smooth horizontal lucite surface below, the muscle's volume could not be loosely contained.
in the hole and a small amount was crushed between the two apposed horizontal surfaces, thus firmly anchoring the muscle at this end.

Silver stimulating wires (Teflon-coated to their tips) were embedded in the upper plate, one in contact with the muscle at its farthest extent in the cylindrical hole, the other extending just beyond the forward vertical boundary of the plate a short distance away. The fiber membranes would thus be depolarized where the muscle bundle left the hole when a pulse, positive at the muscle electrode, was applied.

At the end projecting out into the Tyrode bath, the muscle was snared by a nylon strand 25 μ in diameter. The ends of the nylon had been drawn through a glass capillary tube, from which they emerged higher up, to be anchored to the outer surface of the tube under a thin rubber or polyethylene band. The glass capillary was firmly attached at its other end to the transducer (anode pin). The ends of the strand were then gently pulled, one at a time, until the muscle was drawn firmly against the end of the glass capillary, and the loop, seen in a dissecting microscope, made a more or less neat circle in a plane at right angles to the muscle's axis. The snare was pulled somewhat tighter than was necessary to limit observable muscle shortening during contraction to under 1.5%. This usually involved the formation of a noticeable girdling groove in the muscle.

Crushing the muscle to a further extent, comparable to that in the usual knot-tying procedure, did not result in an increase of recorded tension or, if done carefully, much decrease. With muscles of larger diameter (0.8 mm and up) the portion of the loop farthest from the glass tube was seen, in occasional preparations, to move with contraction. Critical results were, therefore, verified in thin muscles (0.3 to 0.4 mm), where the entire loop, as well as the glass rod, remained stationary within the limits noted, regardless of developed force. The muscle lengths from which tension was thus recorded ranged between 1 and 3 mm when unstretched.

On several occasions, the muscles were stretched from equilibrium length to a length optimal for contraction and the length values, as estimated with an ocular micrometer and dissecting microscope, agreed to within 0.1 mm, with those obtained from the vernier of the micromanipulator on which the transducer housing was mounted. In addition, contractile tensions recorded at each length, in the course of several successive stretchings and unstretchings of the preparation, were reproducible (fig. 3, below, graph at right). This indicates that the muscles did not slip at either attachment. On the few occasions when routinely obtained length-tension curves could not be well reproduced, the slippage that was responsible could usually be seen.

**Results**

1. **Effect of Epinephrine in Normal Tyrode's Solution**

The two well-recognized effects of epinephrine on the contraction of a cat papillary muscle are shown in figure 2. The super-

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**Figure 1**

Arrangement for recording isometric contractile tension. Stimulating electrodes are the spiralling wires. T and O show the Tyrode and gas inlets, respectively, to the bath chamber. The large water bath, which controls the temperature of the Tyrode inflow, as well as five alternative holes (of graded diameters) for mounting the muscle, are not shown. See text for detailed description.

**Figure 2**

Isometric tension time courses of a cat papillary muscle at 28°C. Lowest and broadest trace is a control record. Traces with successively increasing peaks were obtained two minutes, two and one-half minutes, three minutes and three and one-half minutes after adding 1 μg/ml of epinephrine to the Tyrode medium. The muscle was stimulated at a rate of 15/min.
imposed traces, obtained from a representative experiment, show sequential changes in the contractile time course at varying times after addition of 1.0 μg/ml of epinephrine to the Tyrode reservoir. The characteristic increase in the rate of rise of tension and in peak tension are evident, as well as the earlier onset of the relaxation phase. The magnitude of the increment in peak tension shown here, 60% of the control, is typical of results obtained in such an experiment. After attainment of the steady state in epinephrine, tension was double that in the control. The degree of shortening of time from onset of contraction to peak of tension is known to be variable. At the low bath temperature employed here, however, this effect is dramatic and is consistently obtained.

II. EFFECT OF EPINEPHRINE IN A CALCIUM-RICH MEDIUM

Both a decrease in extracellular sodium (frog ventricle) as well as an increase in extracellular calcium (guinea pig atrium) have been shown to augment radiocalcium uptake by contracting cardiac muscle. Since the buffer systems in conventional Tyrode's solution and, probably, other effects limit the maximal attainable chemical activity of calcium ion, both sodium and calcium concentrations were altered, to 75 mEq/liter and 8.1 mmoles/liter respectively, to reach the limiting condition of an optimal calcium influx per beat. The deficit in sodium chloride concentration was replaced by an equal concentration, 74 mEq/liter, of choline chloride. No attempt was made to correct the small alteration in osmolarity resulting from the greater calcium chloride content of this solution.

In a total of 20 experiments, isometric contractile tension in this calcium-rich, sodium-poor medium was determined at each of several muscle lengths, before and after the addition of epinephrine, in amounts of 1 to 2 μg/ml. The greatest increase of developed tension produced by epinephrine amounted to 10% of the contractile tension in the high-calcium medium alone. In half of the experiments, either the increase was less than 5%, or a small decrease (4 experiments) was noted. These findings indicate that conditions promoting uptake of calcium by the muscle during activity can result in a contractile ceiling, in the presence of which epinephrine exerts no further inotropic effect.

Three representative experiments of the type in which epinephrine caused no increase of developed tension are shown in figure 3. In the graph at the left, length-tension curves are shown for the calcium-rich medium with
and without added epinephrine. Although this 1-mm thick muscle exhibited relatively large spontaneous contractile variations, the two curves are roughly superimposable. Another finding, consistent in all experiments, is shown in figure 3; alterations in contractile tension with variations in muscle length are not at all diminished in the calcium-rich medium. It is clear then, that, although epinephrine cannot increase the contraction of a short muscle (e.g., the 1.9-mm points), a further increase in contraction is clearly achievable by a lengthening of the muscle, the effect of which is, apparently, not directly linked with calcium transport.

The maneuvers shown in the center graph of figure 3 were done within a period of 35 minutes and in the sequence shown by the arrows and numerals. Length-tension data were obtained in normal Tyrode solution (x). The medium was changed to calcium-rich Tyrode (1); muscle length in the calcium-rich solution was at a value which gave approximately two-thirds of maximal tension. Epinephrine, 2 µg/ml, was then added without changing muscle length (2). The epinephrine was washed out (3); and the muscle was stretched to the length optimal for contractile tension (4). Finally epinephrine was added without changing length (5). It is thus unlikely that the apparent failure of epinephrine to augment contractile tension is referable to errors inherent in the measurement of muscle length. Similarly, a spontaneous decline in contractility of the preparation, with time, would not provide a reasonable explanation for these results. Several experiments of this type were done with similar findings.

In the graph at the right of figure 3, the results of several determinations of the length-tension relationship in one preparation are plotted. The data obtained from this thin muscle show minimal scatter. The arrows arising from the points indicate whether the data were obtained during a shortening or lengthening sequence. It is clear that chance variations in measured lengths (and/or tensions) are small and do not account for the consistently though slightly larger tensions obtained in the absence of epinephrine. The twitches recorded at optimal length shown in figure 4 illustrate this point. Although this systematic difference could be due to a small decline in contractility with time (the epinephrine points were obtained 10 to 20 minutes later), it is to be expected due to the premature termination of contraction by the drug.

### III. EARLY RELAXATION INDUCED BY EPINEPHRINE

A characteristic effect of epinephrine on the time course of contraction is shown in figure 5. The solid traces show records of
transmembrane potential (above) and tension (below) in normal Tyrode medium containing 1 μg/ml of epinephrine. An early relaxation, occurring long in advance of membrane repolarization, is evident. Prior to the addition of epinephrine, relaxation occurred (not shown here), as always with this tissue, at the time of repolarization. The control electrical event was essentially as shown in the solid trace. The dashed lines (again, action potential above, contraction below) were obtained after changing to the calcium-rich medium, in the continued presence of epinephrine. Although the low sodium content of this medium (50% of control) has appreciably shortened the action potential plateau, the mechanical time-to-peak is, in fact, lengthened in such a way that relaxation again coincides roughly with membrane repolarization. It is unlikely that the calcium-rich medium completely reverses the uncoupling effect of epinephrine. Addition of epinephrine to the calcium-rich medium almost always shortens somewhat the contractile time-to-peak (see fig. 4 and Discussion).

A related and curious phenomenon is shown in figure 6, where, at the left, the epinephrine-induced (10 μg/ml) early relaxation is again seen in Tyrode's solution which was normal except for a moderately increased calcium of 4.0 mM. Here, in addition, two distinct mechanical responses accompany the first action potential. The second, small contraction could be seen under the dissecting microscope, even when the glass transducer lever was disconnected from the muscle, so it was not an undamped oscillation. Also, a second action potential triggered a potentiated beat, suggesting still more strongly that this beat was indeed the third, and not the second, contractile event in the sequence. The traces on the right, recorded immediately after those on the left, show a cyclic waxing and waning of tension that accompanies sustained membrane depolarization (see reference 11 for details of technique). It appears that the small additional contraction shown in the traces on the left represents the beginning of a second cycle, cut short by membrane repolarization.

IV. EPINEPHRINE EFFECTS ON CONTRACTION AND CONTRACTURE

Attempts to visualize some common mechanism underlying the paradoxical actions of this drug described above (see Discussion) suggested the possibility that epinephrine might modify a contraction and a potassium chloride contracture in quite different ways. The experiment was done on a strip of frog ventricle and figure 7 shows that epinephrine, in an amount (1 μg/ml) which greatly augments contractile tension, considerably depresses the development of contracture by the same preparation. Although recorded tension in a contracture can vary spontaneously in magnitude, this maneuver, on washing out the drug, could be repeated as often as de-
Potassium chloride contracture in a strip of frog ventricle. Maneuvers shown in the four horizontal tension tracings are consecutive ones. Complete sequence of changes in the composition of the bathing medium is shown in the shaded bars. Composition of the medium at the end of each trace is the same as that at the beginning of the next lower trace, as is indicated by the shaded bars. KCl Ring refers to a Ringer medium in which potassium concentration has been raised to 100 mEq/liter, through replacement of sodium. Epi. Ring is normal Ringer containing 1 μg/ml of epinephrine. Epi. KCl Ring is the 100 mEq/liter potassium Ringer referred to above, to which has been added 1 μg/ml of epinephrine. Contracture tensions (KCl Ring) in the first and third horizontal traces are about equal, although different amplifier gains make them appear not to be so. At the right-hand side (KCl Ring) of the lowest trace, washing out epinephrine from the contracture medium appears to bring about a restoration of contracture tension.

sired, and three preparations all gave the same result. This phenomenon has occurred also in cat papillary muscle.

Discussion

I. THE EXCITATION-CONTRACTION COUPLING PROCESS AS A SITE FOR THE INOTROPIC ACTION OF EPINEPHRINE

It has been shown that, by the combined maneuvers of raising extracellular calcium and of lowering the presumably competing extracellular sodium, epinephrine can be deprived of its positive inotropic action. This finding is compatible with, though admittedly not proof of, the thesis that the drug causes an increased calcium transport to some unspecified contraction-critical site during activity of the muscle. It might be argued that the calcium-rich medium brings contractile tension to a maximal value, determined by some relatively fixed limiting factor, e.g., available energetics. The failure of epinephrine to drive developed tension beyond this value would then indicate only that the unknown mechanism through which the drug operates is also limited by this factor, and not necessarily connected with calcium transport. Our experiments also show (fig. 3, Circulation Research, Vol. XVIII, May 1966)
middle graph), however, that, at a less than optimal length, when the muscle’s contractile tension is not augmented by epinephrine (manipulation 2), tension can be increased readily by further stretch.

A more direct experimental approach to this question has been employed by others. Their radiocalcium results indicate that nor-epinephrine causes an increase in calcium turnover, and this only with activity. Contradictory results from another group may be due to differences of technique. Current attempts, using a technique for perfusion of a papillary muscle artery, to characterize the various calcium pools in this tissue may provide the experimental basis for a more rigorous test of this thesis.

II. THE EARLY RELAXATION

If epinephrine does, in fact, augment calcium transport, then the observation of epinephrine-induced early relaxation, which can occur long in advance of membrane repolarization, poses a problem. The first effect can be alternatively accomplished, and the second antagonized, by increases in extracellular calcium level. Either epinephrine has two unrelated actions, or a single mechanism results, at first in an enhancement of the transient calcium level at some unspecified site, and then in a depression of this level. A single effect of epinephrine on the handling of calcium ion by the transport mechanism would not appear to reconcile these two findings. Similarly, an effect on the postulated competition, by extracellular sodium ion, for the calcium carrier does not clarify the paradox.

A possible explanation involves the assumption that the proposed carrier molecule, which mediates the presumably passive transport of calcium and sodium ions, has also an appreciable affinity for potassium ion. This assumption is compatible with the well-known negative inotropic effect of increased extracellular potassium concentration. The calcium influx occurring with membrane depolarization could be seen as being brought about by potassium efflux, coupled to calcium movements through the sharing of a common carrier. The driving force for the potassium movement during a twitch of the ventricular muscle would be supplied by the membrane depolarization. Such a system might have properties similar to the one postulated by Rosenberg and Wilbrandt to explain "passive uphill transport of glucose" as resulting from downhill mannose transport, sharing a common carrier in the erythrocyte membrane. The mechanism, in the papillary muscle, would presumably be located, not in the outer membrane, but in one or more of the barriers bounding the endoplasmic reticular space. The postulated potassium "efflux" might not result in a net loss from the muscle cell. This would depend on subsequent diastolic interchanges between the reticular space and the sarcoplasm proper.

In terms of this picture of an interaction of the three ions through a common carrier, the contradictory epinephrine results might be harmonized through an assigned action of the drug solely on the handling of potassium ion by the carrier, e.g., a decrease in dissociation constant of a hypothetical potassium-carrier complex. The sequence of events would then be: (1) greater potassium "efflux" into the reticular space, with consequently greater calcium movement in the reverse direction, into the sarcoplasm proper; (2) an augmented rise in potassium level in the reticular space, occurring later in time, now competing more effectively (because of the drug action) with calcium and thus depressing calcium movement into the sarcoplasm proper. A simpler explanation for the epinephrine-induced relaxation might be considered; that the increased calcium influx due to the drug depletes the calcium level in the vicinity of the transport barrier, whereas, in the calcium-rich medium, this does not occur. However, addition of the drug to the calcium-rich medium (fig. 4) almost always shortens the duration of contraction somewhat. This argues against this possibility.

It might also be postulated that, in the absence of epinephrine, membrane repolarization results, similarly, in a rapid reverse movement of calcium from the region of the myo-
fibrils back into the reticular space, because of the high potassium concentration which exists at this instant in the reticular space. Whether the movement of calcium away from the myofibrils would be expected to be rapid enough, either during the action potential plateau in the presence of epinephrine or following membrane repolarization in its absence, to account for the observed time courses of relaxation is difficult to say. Calcium uptake by sarcoplasmic reticulum preparations from skeletal muscle appears to be an active process. This would not exclude the possibility that the principle of counterflow exerts a major influence on calcium movements.

III. EFFECTS OF EPINEPHRINE ON CONTRACTION AND CONTRACTURE

The contracture experiments were undertaken because they constitute a preliminary test of this hypothesis. If the calcium influx, during a contraction, results from a coupled potassium efflux, arising in turn from a suddenly-provided driving force (depolarization), one would expect that calcium movements accompanying a potassium chloride contracture must have some other basis, since no net potassium driving force is created in this condition. Thus, the postulated drug action on potassium should not result in an increase in developed tension. The experimental result is that epinephrine depresses potassium chloride contracture tension. This might well be explained by the proposed mechanism in which epinephrine causes the large amounts of potassium on both sides of the transport barrier to occupy a larger fraction of the total carrier population, leaving less available for the other ionic interactions presumably responsible for contracture tension.

It is possible that the muscle is altered in the contracture medium in such a way that epinephrine acquires an additional action on the contractile process which it does not normally possess, and that the mechanism of this action is not related to that of its normal inotropic effect. The arguments presented above would, of course, not apply in this case. In the absence of any information on the subcellular site of action of epinephrine, it can only be said that the surprising result obtained was predicted on the basis of the arguments presented.

IV. GENERAL COMMENTS

The proposal outlined, namely, an interaction of sodium, potassium and calcium through a common carrier, may offer some explanations for experimental results outside the area of epinephrine action. The outward driving force on potassium ion, in a potassium-free medium may be sufficiently increased to result in greater contractile activity and, ultimately, in contracture. The latter effect, in frog ventricle, has been shown to be associated with an increased radiocalcium uptake by the tissue.

The results on contracture might represent a further instance of a lack of correlation between the documented biochemical effects of epinephrine (on phosphorylase-a activity and on 3'5' cyclic adenosine monophosphate level) and its positive inotropic action. These substances were not assayed here, although it would be difficult to imagine that the appearance of a high extracellular potassium concentration would, of itself, inhibit the reactions involved, since these occur intracellularly, where the potassium level is normally higher than that used in the contracture medium. The authors, at present, offer no assessment of the validity of their proposed mechanism, other than to say that, in their opinion, it has contributed to an exposition of the problem posed by their experimental results.

Summary

The possibility that the inotropic action of epinephrine might be mediated through an effect on the excitation-contraction coupling process was explored, using techniques for measurement of isometric tension, together, in some experiments, with recording of the transmembrane potential time course from short lengths of cat papillary muscle. Four observations relevant to this question, have been made: (1) Extracellular calcium concentration can be raised and extracellular
sodium concentration lowered to a point at which contraction cannot be further augmented by the addition of epinephrine. (2) The early relaxation induced by epinephrine occurs well in advance of membrane repolarization. This effect is antagonized by increasing calcium concentration, although the action of epinephrine in augmenting developed tension appears to be synergistic with that of calcium ion. (3) The length-tension relationship is undiminished in the calcium-rich (8.1 mmoles/liter), sodium-poor (75 mEq/liter) medium.

Epinephrine, in a dose (1 to 2 μg/ml) which markedly augments twitch tension, profoundly decreases tension developed by muscle. A preliminary concept of the ionic mechanism of excitation-contraction coupling, which markedly augments twitch tension, the frog ventricle strip and the cat papillary muscle. A preliminary concept of the ionic mechanism of excitation-contraction coupling, compatible with these facts and with some others, is described.

References

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