form a single, integrated percept, and when the stimuli before one eye do not dominate completely, the left-eye view alternates over time with the right-eye view. This is generally granted even when the neuroanatomy of the hemidecussating human visual system is explicitly recognized and the assumption has to be made that in some unknown way each eye remains a separate functional unit as it contributes to the binocular result (*2*).

This concept of the binocular relation is not completely correct. The facts which it ignores were reported half a century ago, but, so far as we know, they appear in no modern treatment of the problem. H. Köllner, at Liepzig, was interested in nasal-temporal differences in vision. He recognized that the temporal fields are larger than the nasal fields in man, and asked whether they might be predominant even in the mutual visual field. His paper reported observations of binocular color rivalry (*3*). It is well known that when one eye is shown one color while the other eye is shown a spatially congruent different color, the two colors will either fuse into one, or one color will alternate with the other over time. However, Köllner noted that the initial sensation was of a bipartite field of color, whereby the color before the left eye appeared to the left of the color before the right eye. That is, at first, sensation corresponds to stimulation from the temporal visual field only; this suggested to Köllner predominance of the crossed fiber visual afferent system.

Köllner's method is very simple. A red glass is held before the left eye and a blue glass is held before the right eye. When the eyes are opened one fixates the center of a white surface. One sees red to the left of fixation and blue to the right of fixation.

Since rivalry or fusion quickly takes the place of the initial sensation of the bipartite color field, some practice may be necessary in observing the phenomenon. We have found it easier to observe if the eyes are open only a moment. We came across Köllner's paper after completing a tachistoscopic study of binocular color rivalry in which we found that the most common sensation at a duration of exposure of 100 msec is a bipartite color field where the stimuli in the nasal visual field are not seen. This can be taken as a replication of Köllner's effect (*4*).

We have also found that when a thin strip of black tape is placed vertically down that part of each glass corresponding to the fovea, and fixation is maintained so the strips are seen as one, the colors nasal to the strips are not seen at all for several minutes. By this simple method an apparent binasal hemianopia is established in the color fields, similar to that occurring initially, but allowing study for prolonged periods. Rotation of the strips changes the spatial characteristics of the color field, which now remains bipartite in nature, generally without fusion of the colors over the whole field or suppression of one eye. When the strips are placed horizontally, then rivalry or fusion does occur.

The immediate purpose of this communication is to call attention to Köllner's effect. It must play a role in an adequate description of the binocular relation. The usual question has been what the brain can do when discrepant stimuli are presented to corresponding areas of the two eyes. The observations reported here represent an unexpected answer. The puzzling questions are these: what is the mechanism which controls initial suppression of the nasal fields, and why is the sensation of a bipartite color field prolonged when the strips are presented? The further puzzling question of the means by which one whole eye later comes to be suppressed also remains unanswered (*5*).

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5. The possibility that eye movement is implicated in the shift from processing based upon the distinction between nasal and temporal fields to processing based on the distinction between the left and the right eye is attractive, and is discussed (*4*).

19 November 1962

Vascular Smooth Muscle: Dual Effect of Calcium

Abstract. *The first part of the contractile response of rabbit aorta to epinephrine is depressed by elevation of calcium concentration; the second is potentiated. These observations suggest that the rate-limiting factor for the former is membrane excitability (depressed by increased calcium), while that for the latter is the role that calcium plays in coupling membrane excitation with the development of tension by the contractile protein (a function that is augmented by increased calcium).*

Increases in calcium concentration may either depress (*1*, *2*) or augment (*3–5*) the contractile response of vascular smooth muscle. The unique finding of the current study is that within a single contraction of this muscle both effects may be evident: one component of the response is depressed while another is potentiated. From information available about specific subcellular actions of calcium, this observation permits an analysis of the rate-limiting factors of the two components of the total response of vascular smooth muscle.

Helical strips of rabbit aorta (*6*) were mounted in phosphate-buffered Krebs solution, aerated with 100 percent oxygen, and maintained at 38°C. Isometric contractions in response to epinephrine were recorded for 5 minutes. The epinephrine was then rinsed from the bath and the muscle was allowed to relax to its rest tension before it was stimulated again.

The total contraction of vascular smooth muscle in response to epinephrine is differentiable into a fast (F-) component and a slow (S-) component (*7*). The former is completed within 45 to 60 seconds after the initial stimulation; the latter may progress throughout the remainder of a 20-minute observation period. In the current study variations in calcium concentration in the medium influenced differentially the two parts of the response to epinephrine.

Figure 1 presents the results of a typical experiment (one of 20) in which the characteristics of the epinephrine response during calcium depletion of the strip in a calcium-free Krebs solution were studied. In the 16 instances in which epinephrine was administered within 10 minutes after the shift to a calcium-free medium, the F-component showed an average increase of 15 percent. In each of these instances the S-component was diminished. Subsequently the F-component also decreased. A brief exposure to calcium after calcium depletion brings about recovery, primarily of the slow component.

The relationship between calcium concentration and the magnitude of each of the components of the response was studied more quantitatively in experiments in which the calcium was first thoroughly depleted from the tissue, as was evident from its almost complete loss of responsiveness, and then added back in specific concentrations. The response was allowed to become stabilized at each calcium concentration. This stabilization required at least 1 hour after the change in calcium concentration was made. The tracings in the upper part of Fig. 2 are such stabilized responses of a single aortic strip. These responses are representative of those of 12 strips studied in this manner. The F-component is greatest in responses in low concentrations of calcium and is depressed as the calcium concentration increases. In other experiments it has been demonstrated that the F-component may be completely eliminated by concentrations of calcium of 6 m*M* or more. In contrast, the S-component is usually absent at calcium concentrations below 0.3 m*M* and reaches its maximum in calcium concentrations of about 1 m*M*. In a normal concentration of calcium (1.6 m*M*) the responsiveness of the F- and S-components does not vary significantly over an 8-hour period.

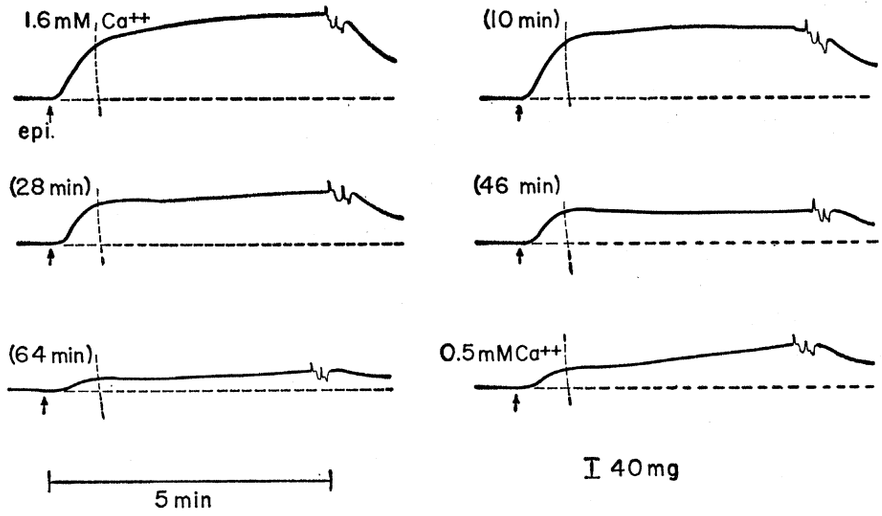

Fig. 1. Effect of Ca depletion on the response to epinephrine. (Top left) Response of strip in normal Krebs. The next four curves show the responses after the bath had been replaced and strip had been in Ca-free Krebs solution for times indicated in parentheses. After 10 minutes in Ca-free solution the F-component (preceding the dashed arc) is slightly greater and the S-component (tension developed after dashed arc) is depressed. With longer time in the Ca-free solution the S-component is virtually eliminated and there is a secondary depression of the F-component. (Bottom right) Response 3 minutes after a change to 0.5 m*M* Ca in the bath. There is recovery of the S-component. Irregularities in the response curves at the end of 5 minutes are rinse artifacts.

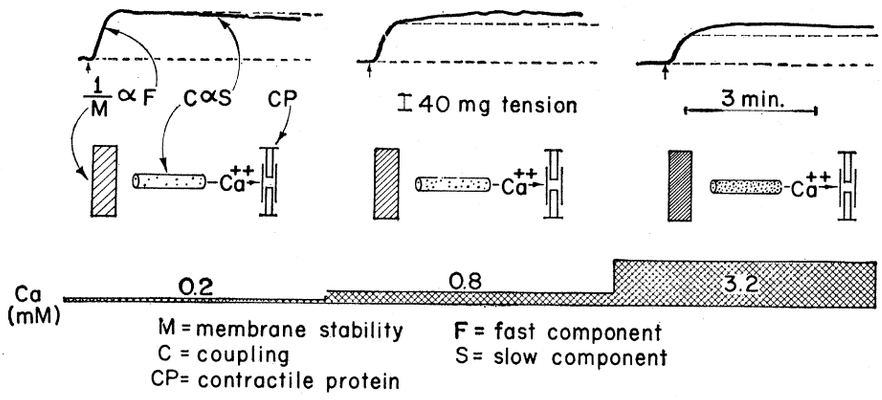

Fig. 2. Effect of Ca on F- and S-components of response to epinephrine (small arrow, 1 μg/liter in bath). (Top) Three tracings recorded from a single artery strip in baths containing Ca in the concentrations designated at the bottom. The lower dashed line at the base of each response represents rest tension, and the upper dashed line represents the magnitude of tension developed by the F-component. Note that the F-component decreases with increasing concentrations of Ca. The progressive increase in tension shown above the dashed line is the S-component. No S-component is seen in responses in 0.2 m*M* Ca, but there is a gradual increase in tension developed in the higher concentrations of Ca. The three-stage diagram under each tracing illustrates a mechanism proposed to account for the observed changes. As the concentration of Ca increases, the membrane stability is increased, thus depressing the F-component which reflects membrane excitability. In contrast, when the coupling system contains more Ca the S-component becomes greater.

Since previous investigations into the relationship of vascular smooth muscle to calcium concentration have dealt only with total response, and not with the relation between calcium and the individual components of the response, it is not surprising that conflicting evidence has been obtained. Cow, using an isolated vessel preparation, found that an increase in calcium concentration in the bath depressed the response to epinephrine (*1*). Yasargil noted that an elevation in calcium concentration of the perfusate caused a marked constriction of the isolated perfused umbilical artery (*4*). Feinberg, Boyd, and Katz recently reported that calcium has a vasodilator effect on the coronary vessels in the intact animal (*2*). Studying the same vascular bed, Scott *et al.* reported that small increments of calcium in the perfusate cause vasoconstriction, whereas in high concentrations calcium causes vasodilatation. (*5*).

Studies with smooth muscle from other sources have shown a similar ambivalence in response to added calcium. However, in these other tissues there have been more detailed analyses than there have been with vascular smooth muscle, and these analyses indi-

cate a basis for the dual effect of calcium. For example, Holman has demonstrated that calcium has a stabilizing effect on membrane of smooth muscle (*8*). Reduction of calcium chloride concentration to 5 percent of normal caused an initial increase in excitation in a taenia coli preparation, with action potential frequencies remaining at a high rate. When the same preparation was exposed to high concentrations of calcium there was a transient cessation of action potentials.

On the other hand, Axelsson and Bulbring have demonstrated that calcium is essential for the coupling of membrane excitation with tension development by the contractile protein (*9*). In the taenia coli, when calcium chloride was removed from the bath, the action potentials persisted but there was a failure of tension development. The importance of calcium in the coupling reaction is emphasized when the permeability of the membrane to this cation is increased by depolarization with potassium sulfate (*3*). In this case the magnitude of the response is related directly to the calcium concentration in the environment.

Considering these established effects of calcium on two different processes involved in the overall contractile response (that is, membrane excitation and coupling), a hypothesis can be developed to describe the mechanisms by which an increase in calcium produces the depression of the F-component and the potentiation of the S-component observed in the current study. One must postulate that the excitability of the membrane governs the F-component (see Fig. 2). When the membrane is stabilized by an increase in concentration of calcium, its threshold for excitability is raised, and the magnitude of the F-component is decreased. Conversely, when calcium concentration is reduced below physiological levels the membrane is labilized, its excitability is increased, and a larger F-component results. Of the series of events that occurs between the initiating stimulus and ultimate tension development by the contractile protein, the rate-limiting process for the F-component seems to be membrane excitability. On the other hand, the rate-limiting factor for the S-component appears to be a process that varies directly with the calcium concentration. This factor could well be the availability of calcium for the coupling process. It would follow, then, that below a given concentration (about 0.3 m*M*) there is insufficient calcium available for this process to effect a S-component of an epinephrine response. Above this concentration, for a limited range (up to 1.0 m*M*), the magnitude of the S-component is a direct function of the amount of calcium available for coupling. These relationships between membrane excitability and the F-component on the one hand, and calcium coupling and the S-component on the other, are shown diagramatically in Fig. 2.

Relationships between extremes of calcium concentration and the two parts of this contractile response follow from the assumption that membrane excitation and excitation-contraction coupling constitute two consecutive processes in a single sequence of events leading to tension development by the contractile protein. If the available calcium for the coupling becomes extremely low, coupling will then become the rate-limiting factor of the F-component as well as of the S-component. This is illustrated in Fig. 1, where, after the aortic strip has been in a calcium-free environment for 28 minutes, the F-component, as well as the S-component, is decreased in magnitude. Conversely, extremely high concentrations of calcium depress the S-component as well as the F-component.

The unique feature of the response of the isolated aortic strip to epinephrine is that, in a given total response, opposing effects of an increased concentration of calcium on two separate processes, membrane excitation and coupling, can be identified. It is evident, therefore, that when only the total response is recorded, its magnitude will be depressed in situations where the F-component (membrane excitation) is the limiting factor, while it will be potentiated when the S-component (coupling) is the limiting factor. This situation forms an obvious basis for the conflicting results that have been described as effects of various calcium concentrations on vascular responsiveness (*10*).

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Beading Phenomena of Mammalian Myelinated Nerve Fibers

Abstract. *Fresh mammalian nerve, when subjected to a small stretch, shows a beading phenomenon. The larger fibers appear as a series of dilations and constrictions at intervals of 40 to 75 μ. Upon relaxation this beading is gone within a minute. The beading is not produced by the special technique of freeze-substitution used to show the phenomenon.*

Our previous studies of axoplasmic flow (*1*) raised the possibility that peristalsis, which was recently observed cinematographically in fibers of dorsal root explants (*2*), might be found in mature, living, and relatively intact mammalian nerve fibers. However, the usual techniques of histological preparation are inadequate for investigations where rapid changes in shape might be expected to occur during the slow penetration of fixatives (*3*). In order to "catch" and hold the shape of nerve fibers in their living form, the technique of quenching (quick-freezing) nerves at very low temperatures followed by freeze-substitution was used (*4*).

Sciatic nerves of anesthetized and just-killed rabbits and rats were gently freed from their surrounding limb muscles. They were kept straight (but not overly stretched) while they were quick-frozen with Freon-12. The temperature of the Freon was reduced toward −160°C with liquid nitrogen. The stick-like frozen piece of nerve was then kept in a 1 percent solution of osmium in acetone at −20°C for 7 days so that freeze-substitution could take place. During this time ice goes into solution from the tissue and acetone and osmium enter; the process starts at the surface and occurs successively at such fine increments that