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Propagation in Vertebrate Visceral Smooth Muscle†

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Smooth muscle cells behave electrically as if their interiors were directly connected without an intervening extracellular space. Although both light and electron microscope studies indicate that they do not comprise a true syncytium, regions of contact between the membranes of two cells have been described. This special kind of contact could account for all the present data and it is suggested the term "nexus" be applied to this structure because of its functional significance.

1. Introduction

The purpose of this paper is to define and evaluate four alternative intercellular relationships in smooth muscle. Discussions in the literature relating to intercellular morphology and function in smooth muscles are usually vague. The functional characteristics of three intercellular relationships, syncytial, ephaptic and discrete, will be made more explicit. In addition, a fourth alternative, the nexus, will be proposed and reasons given for believing the nexus to be the one most compatible with both the morphological and electrical data.

2. The Mode of Propagation

Many believe that propagation of action potentials in vertebrate gut, uterine and various other smooth muscles occurs because active muscle cells directly cause the excitation of neighboring resting muscle cells without intervention of nerve elements (Davson, 1959; Woodbury, 1960). Evidence that propagation can occur in naturally nerve-free structures has been obtained from chicken embryonic muscle (Prosser & Rafferty, 1956). Furthermore, extensive experimentation on vertebrate intestinal smooth muscle using:

(*a*) denervation techniques (Gunn & Underhill, 1914; Gasser, 1926; Klinge, 1951; Prosser & Sperelakis, 1956;

(*b*) pharmacological methods (Prosser & Sperelakis, 1956; Alvarez & Mahoney, 1922), and

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(*c*) electrophysiological techniques (Prosser & Sperelakis, 1956; Bozler, 1938; Ichihawa & Bozler, 1955; Bülbring, Burnstock & Holman, 1958; Goto, Torigoe & Togo, 1959; Goto, Kuriyama & Yoshiharu, 1960), indicate that propagation is not mediated by nerve elements.

The possibility that mechanical stretching of resting cells by active ones is sufficient to account for propagation is rendered unlikely by the long latency (0·2 to 1·5 sec.) for responses to stretch and the necessity for very large (5–12%) and very quick (1–2 msec.) stretches to elicit responses (Burnstock & Prosser, 1960a). That mechanical cell-to-cell pulls are necessary is negated by the following observations:

(*a*) that action potentials can propagate past a region of mechanical immobilization (Burnstock & Prosser, 1960a; Sperelakis & Prosser, 1959) and thereafter cause a contraction (Burnstock & Prosser, 1960a); and

(*b*) action potentials can propagate between separate but closely apposed intestinal rings where there is no mechanical link (Sperelakis & Prosser, 1959).

Other possible mechanisms of propagation may be roughly classified as electrical or chemical.

In the following discussion, the term propagation will refer to the spread of action potentials without regard to mechanism. Conduction will refer to propagation by means of electrotonic spread as along a continuous membrane and transmission will refer to propagation across a gap between functionally separated membrane structures, electrically (ephapses) as across the crayfish giant motor synapses (Furshpan & Potter, 1959), or chemically, as is the case of most synapses and myoneural junctions.

INTERCELLULAR MORPHOLOGY

Consideration of any one of these modes of propagation requires an assumption concerning the morphological relationships between smooth muscle cells. The possibility of conduction occurring depends at least on the presence of a continuous membrane; in the case of smooth muscle the cells would have to comprise a protoplasmic syncytium. However, there are several cases which have long been considered as conduction, vertebrate heart and crayfish (Watanabe & Grundfest, 1962) and earthworm (Kao & Grundfest, 1957), giant axons, where propagation apparently occurs across a gap between the plasma membranes of two discrete cells. The electron microscopic study of Hama (1959) demonstrates the osmophilic components of the two plasma membranes of the septa of earthworm giant axons are separated by as little as 40 Å. There is neither delay, unidirectional propagation, nor a post-junctional potential at these septal

junctions. On the other hand, Hama's micrographs show rows of vesicles, similar to synaptic vesicles, aligned along the inner side of each plasma membrane. The electrophysiological situation of the lobster giant axon as reported by Watanabe & Grundfest (1962) is only slightly different. The regions of close (100 Å) apposition of the plasma membranes of adjacent cells are only patches of the total septal area. Small delays (40 to 410 microsec.) which were dependent on direction of propagation and the post-junctional potentials were observed. There have been no high resolution electron micrographs published. Watanabe & Grundfest (1962) conclude from measurements of electrotonic current spread and electrical properties of the septal membranes that septal transmission is electrical and hence ephaptic.

The ultrastructure of the intercalated disc has been intensively studied by Sjöstrand, Andersson-cedergen & Dewey (1958). As with the invertebrate axons, individual cell membranes are apparently separated by a gap of the order of 100 Å. Neither delay, post-junctional potentials nor preferred direction of transmission occurs at these junctions. Sjöstrand *et al.* (1958) suggest that the space between the osmophilic membrane component (the only component seen in the electron micrographs) represents the lipid component of the membrane. The implications of this alternative to the assumption that all gaps seen in an electron microscope represent space filled by extracellular electrolyte will be discussed later.

The question of the discreteness of the smooth muscle cells also has been revived with the advent of electron microscopy. There are many examples of the regions of close apposition of smooth muscle cells, but there is no consensus as to the structure and dimensions of the regions of contact. It is apparently agreed upon that myofilaments at least do not run between cells. Thaemert (1959) has concluded from electron micrographs of rat stomach that there are in fact protoplasmic anastomoses between smooth muscle cells. He has suggested that the term "anastomotic intercellular bridges" be applied to such connections. Thaemert claims such "bridges" are very labile and are easily destroyed by preparative procedures. In an earlier study Mark (1956) considered there were two kinds of bridges between uterine smooth muscle cells: first, ones with protoplasmic continuity; and second, those which have transverse membrane structures separating the myoplasms of the cells in contact. The latter type bridge has been described by both Bergman (1958) and Prosser, Burnstock & Kahn (1960) as occurring in a wide variety of smooth muscles, including those from cat intestine and pig esophagus and ureter. Bergman has estimated there are six bridges per ureteral cell.

On the other hand, Caesar, Edwards & Ruska (1957) have reported negatively, stating that the membrane of each cell of the mouse urinary

bladder is distinct and surrounds only one cell. Thus the complete range of possible relations from protoplasmic continuity to completely discrete cells has been represented by electron microscope findings. Since the situation, then, is muddled at best, a few comments may be allowed. First, electron microscopic sections represent a very small proportionate volume of a given tissue. Second, the observation of a bridge must be a very rare event in terms of any reasonable number of bridges per cell. Third, an oblique angle of section may cause the transverse membrane structure to be obscured, especially in thick sections (Sjöstrand, 1956). Finally, the structure of the reported regions of contact may be so labile that the "bridges" are easily "washed out". None of the published micrographs of smooth muscle are of sufficiently high resolution to discern whether the transverse membrane structure comprises a fusion of two-cell membranes or not. Bergman (1958), however, considers that they are double membranes and this would be consistent with the regions of contact observed between several other kinds of cells.

ELECTROPHYSIOLOGY OF SMOOTH MUSCLES

There are two subquestions implicit in the question of how smooth muscle cells are electrically related. The first subquestion has been already broached. It concerns the mechanism of propagation. In one form it asks: does electrical activity in a group of cells cause enough outward current to flow across resting cell membranes to cause excitation and, if so, what is the equivalent circuit? The second subquestion is not concerned directly with the mechanism of propagation, but rather with the extracellular voltage fields set up around groups of active and resting cells. It asks what must the geometrical arrangement of cell membranes be to allow large numbers of active cells to be current sinks and large numbers of resting cells to be current sources at the same time. That this is the case can be deduced from extracellular recorded injury and action potentials and the fact that the sucrose gap technique can be used on smooth muscles. These two questions are discussed below in terms of simple alternative arrangements of cells.

Injury potentials and high potassium depolarizations have been recorded from various smooth muscles (Prosser & Sperelakis, 1956; Bozler, 1938; Ichihawa & Bozler, 1955; Bozler, 1948). To an even greater extent than for skeletal muscle and nerve these extracellularly recorded potentials are smaller than transmembrane resting potentials measured using microelectrodes. These differences are due to IR loss when current flows between areas. Since the smooth muscle cells are so small, the area of membrane involved in extracellular measurements is rather larger than for striated muscle. Thus, in the absence of membrane resistances proportionately larger for smooth muscle, it must be concluded that current

flowing in the internal circuit (i.e. through the myoplasm) must encounter regions of high resistance. In other words, there must be a large internal IR drop. The high resistance elements must be the bridges between the cells. When current flow between normal cells and cells depolarized by high external potassium concentration is minimized by interposing a region of high extracellular resistance using a sucrose gap (Burnstock & Straub, 1958; Marshall & Csapo, 1961), values from the extracellular measurements approach the microelectrode measured values of the resting potential.

The electrical stimulation of smooth muscle is qualitatively similar to that of other excitable tissues. Excitation occurs at the cathode. From this it has been inferred that the exciting current outward across the membrane must flow along an intracellular path. A minimum number of cells must be excited before non-decrementing propagation occurs (Bülbring *et al*, 1958; Barr, 1958), and naturally there must be a minimum number of cells in parallel for the propagation to continue (Burnstock & Prosser, 1960b).

The velocity of propagation in smooth muscles is slow. Atropine and eserine at (10^{-4} W/V) concentrations have no effect on the velocity of propagation in isolated cat intestinal muscle (Prosser & Sperelakis, 1956). Increases of external potassium and prolonged exposure to acetylcholine cause comparable decreases of propagation velocity in guinea-pig *Taenia coli* in concentrations which have quantitatively similar affects on the diastolic membrane potential (Burnstock, 1958). The actions of blocking drugs, D-tubocurarine, 933-F and procaine type, do not occur at low enough concentrations to suggest chemical transmission (Prosser & Sperelakis, 1956). Concentrations of blocking drugs such as hexamethonium (10^{-4} W/V), (Feldberg, 1951) and atropine (10^{-4} W/V), (Bozler, 1949), which abolish the peristaltic reflex, presumably by blocking the ganglion cells in the intrinsic plexuses, do not abolish pendular movements or tone which are dependent only on muscle cell to muscle propagation.

The propagation velocity parallel to the long axes of the cells ranges from 1·5 to 15 cm/sec. for various visceral smooth muscles. Muscles with slower velocities tend to have longer action potentials, so that in all cases many cells are depolarized at the same time. The propagation velocity orthogonal to the long axes is about an order of magnitude less than parallel in cat intestinal circular muscle. This is the velocity usually observed in *in vivo* experiments on intestine (Prosser & Sperelakis, 1956; Sperelakis & Prosser, 1959; Brune & Kotowski, 1956), since it corresponds to the velocity along the axis of the intestine as a whole. Smooth muscle preparations free of nerve plexuses and other contaminating tissues may be obtained by dissecting mucosa and longitudinal muscle coat away from the circular muscle layer of mammalian small intestines (Gunn & Underhill,

1914; Gasser, 1926; Klinge, 1951; Prosser & Sperelakis, 1956). In sheets of ganglion-free intestinal circular muscle electrical activity spreads everywhere from a stimulated corner (Fig. 1). Propagation in the transverse direction demonstates activity spreading from one fiber bundle to another and is approximately equal to the velocity of activity down the intact intestine. Thus the spread of activity down the intact intestine may not be due to spiraling, but rather to bundle to bundle propagation.

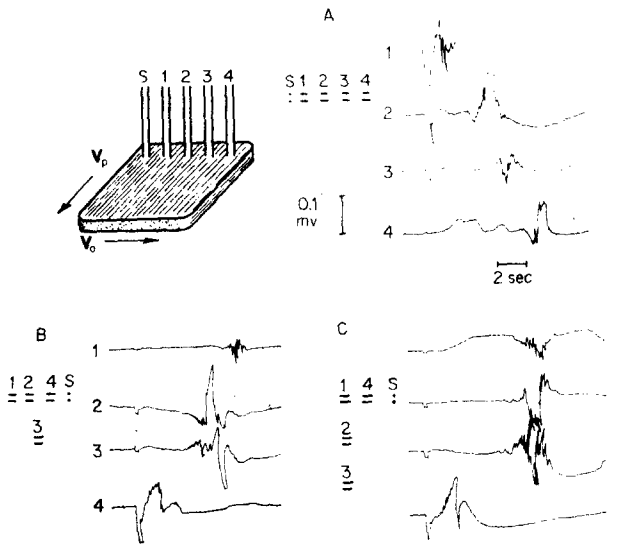

FIG. 1. Propagation Velocities in Different Directions. Inset at upper left illustrates the placement of external electrode pairs for record A on a sheet of ganglion-free circular muscle from cat intestine. The distance between electrode pairs is always 1 cm. Number to the left of tracings indicates from which electrode pair the tracings were taken. Action potentials propagate to all parts of the sheet of muscle.

In record A where the electrode pairs are on a line orthogonal to the long axes of the cells and fiber bundles, the action potentials propagate between electrode pairs at a uniform velocity, V_o, of about 5 mm/sec.

For record B the stimulating electrode pair was moved to the other end of the line of recording electrode pairs and recording electrode pair #3 was placed 1 cm away from pair #2 in the direction of the long axes of the cells. Record B shows propagation can occur in both directions and that the propagation velocity parallel to the cell axes, V_p, is much greater than V_o. V_p is here approximately 4 cm/sec.

For record C the stimulating electrode pair and the recording pairs #4 and #1 are on a line orthogonal to the cell axes, while the recording electrode pairs 1, 2, and 3 are on a line in the direction of the cell axes. The propagation velocity is much slower orthogonal to the cell axes than parallel to them and the electrical activity appears as a band sweeping across the muscle sheet at the slower velocity, V_p.

The intracellular recordings from a variety of smooth muscles (Bülbring *et al*, 1958; Goto *et al*, 1959; Goto *et al*, 1960; Sperelakis & Prosser, 1959; Barr, 1958) show small graded transient membrane depolarizations as well

as larger, faster depolarizations which correspond to action potential spikes of other tissues (Fig. 2). The action potentials often, but not always, arise from the slow transients (Goto *et al*, 1960; Sperelakis & Prosser, 1959; Holman, 1958). The question which the existence of the slow waves poses is, are they pacemaker potentials or are they junction potentials analogous to EPSP? The evidence is in favor of the latter, both for the uterine (Goto *et al*, 1960; Marshall, 1959) and guinea-pig intestinal muscle (Bülbring *et al*, 1958; Holman, 1958), since there is a high degree of synchrony of appearance of slow waves in one cell and action potential spikes in a neighbor. Moreover, it appears that slow waves can occur at any time relative to spikes in the same cell. If the slow waves were simply pacemakers, slow waves should always appear before spikes, or at least one might expect they would not appear for a period after a spike. However, slow waves do occasionally occur on the repolarizing limb of spikes.

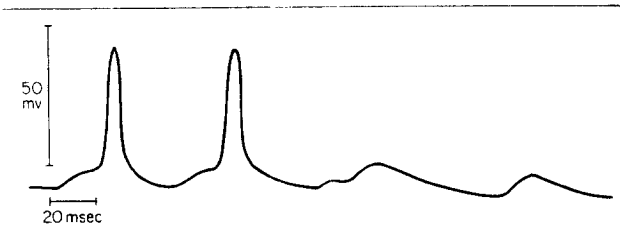

FIG. 2. Microelectrode recording of action potentials and slow waves from circular muscle layer of cat intestine. Slow waves seem to initiate the two spikes but are unable to do so for for the third and fourth times. Note the "third" slow wave is compound. Although this may have prevented the initiation of this spike, the next failure must be differently explained. The slow waves may be due to electrotonic spread from action potentials in neighboring cells.

Thus it would appear one could most easily explain the variety of wave forms observed in smooth muscle cells in terms of a spike and a junction potential which can occur with almost any temporal relationship according to time of firing of the impaled cell relative to its neighbors. On the other hand, in cells which are being regularly driven by neighbors, as in a preparation which is dominated by one region or is being electrically driven (Bülbring *et al*, 1958), one usually does not see a junction potential type slow wave preceding the spikes. In addition, most smooth muscle preparations are spontaneously active and so some pacemaker activity must be present. Thus the conclusion that the slow waves observed are only junction potentials is premature.

MODEL INTERCELLULAR RELATIONSHIPS

For any given morphological relationship between smooth muscle cells one can imagine a pattern of current flow and an equivalent circuit for the

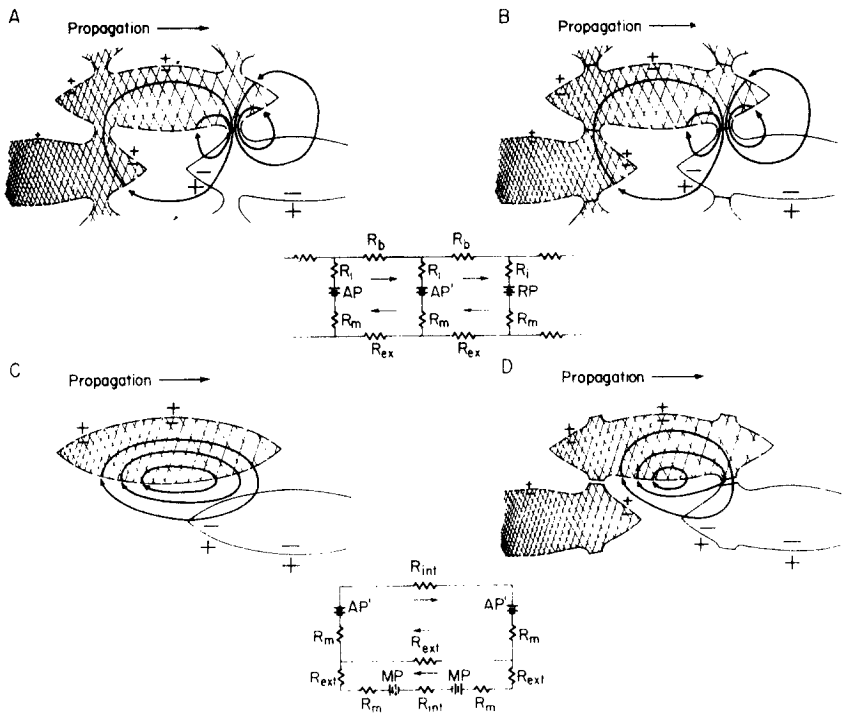

FIG. 3. Four Possible Intercellular Relationships Between Smooth Muscle Cells.

A. Syncytial. When cells are connected via true intercellular bridges with protoplasmic continuity, they constitute a three dimensional net of core conductors of non-uniform diameter. The current flow between active and resting membrane would be analogous to that occurring in unmyelinated nerve. The current flows inward at the active region. It continues from the active to resting membrane through the myoplasm, outward across the resting membrane and back to the active membrane by way of the extracellular fluid.

B. Nexal. Since a nexus differs from a true intercellular bridge only by the interposition of an unpolarized membrane structure, the pattern of current flow would be the same in both cases. Any model electrical networks for both would be equivalent and a simple one is drawn below them. The symbols used are: R_{ex}, resistance of extracellular fluid; R_m, resistance of cell membrane; AP, membrane potential of active region; R_i, resistance of myoplasm excluding intercellular bridges (or nexuses); R_b, resistance of intercellular bridges (or nexuses).

C. Discrete. When muscle cells are separate by an extracellular fluid gap, only the differences in membrane potential along individual active cells contribute to current flow in the extracellular fluid and hence across resting cell membrane. Therefore the current loop which includes an active and resting cell is always shunted by a low resistance loop which includes only the active cell and extracellular fluid.

D. Ephaptic. Since the ephapse is simply a region of small separation between two discrete cells, the pattern of current flow is qualitatively the same in both the ephaptic and discrete cases. Any model electrical networks for them would be equivalent and again a simple one is drawn below these two cases. The symbols used here are: R_{ext}, resistance of extracellular fluid; R_m, active region (not everywhere the same); R_{int}, resistance of myoplasm; MP, membrane potential of resting cell membrane.

advancing edge of an action potential. Four such patterns of current flow between smooth muscle cells are illustrated in Fig. 3. Only two equivalent circuits are shown, since the syncytium and the nexus on one hand and the ephapse and the discrete case on the other yield the same circuits. The cells in the figure are relatively foreshortened to allow better schematic visualization. The length to diameter ratio of vertebrate smooth muscle cells in nature may range from 10 to 500 as a function of stretch and cell type. The diagrammatic cells are cross-hatched and have dashed borders to represent relative depolarization. Since the rate of depolarization in the rising phase of the action potential is rather slow, relative to the propagation time per cell in smooth muscles (e.g. approximately 10 mV/ms and 2 ms for cat intestinal muscle), the cells at the leading edge of spreading activity will have a graded membrane potential along their length (perhaps 10–15 mV/cell). This is illustrated by the relative density of cross-hatching and length of dash representing the cell membrane. This gradient, however, would be diminished by the occurrence of significant delay in propagation between cells along the line of propagation.

In Fig. 3A the classical protoplasmic syncytium is represented. Lines of current can be drawn between active and resting cells which cut across only two membranes. The driving voltage would be the algebraic sum of the membrane potentials. Active cells would tend to be current sinks for a particular resting cell as a function of their stage of activity (membrane potential) and their electrical distance away (the intervening non-membrane IR drop). The situation would correspond to a three-dimensional core conducting lattice. The bridges between cells would be current attenuating regions of low safety factor and current from many cells would contribute to the excitation of any particular cell. Extracellular lines of current (voltage gradients) would always be from the inactive regions toward the active one. As opposed to discrete cell models, there is no extracellular current shunt. This model could certainly explain the experimental findings, but unambiguous histological demonstration of protoplasmic continuity is lacking (but see above).

In Fig. 3B another alternative is illustrated. The membranes of neighboring cells may be in contact in the sense that they coalesce to exclude intervening extracellular fluid and thereby become a unitary structure. This kind of close apposition of membranes has been called an "intercellular bridge" by Bergman, and a "non-anastomosing intercellular bridge" by Thaemert. A shorter, less general term which would be more comparable to the terms "synapse" and "ephapse" and which would also emphasize the special functional nature of the structure is desirable. It is suggested the term "nexus" could suffice for this. Since such a composite membrane structure, a nexus, would separate similar solutions (the

myoplasms), no diffusion potential could be caused by differential permeability to ions. Such a structure would undoubtedly offer a high resistance to current flow between cells, however. The external layers of the two apposing membranes are probably protein. If two such layers were to stick together, then any water trapped between them would be highly oriented. The only difference between the nexal model and the syncytial one would be a somewhat larger series resistance to internal intercellular current flow. In both cases, current would flow between two cell membranes whenever they are not in the same state of polarization, even though the transmembrane potentials at any two points in one particular cell are nearly the same. The nexal model could be used almost interchangeably with the syncytial one to explain the electrophysiological data. It also conforms to most electron microscope studies (but see above). The biggest difficulty with the nexal model is that the area of the nexal membrane would seem to be small relative to the membrane area of the rest of the cell. From this it is tempting to surmise that most of the IR drop during intercellular current flow would be at the nexal membrane and not be excitatory (i.e. too little current would flow across the excitable membrane). However, since nexal membranes may have a lower specific resistance (it is bathed on both sides by high potassium) and the displacement of membrane potential necessary to excite even for step voltages is not known, such a conclusion is not soundly based. In addition, the number of nexuses per cell is not known.

The simplest relationship between smooth muscle cells would occur when the cells are electrically discrete with no structurally special regions connecting them. This possibility is illustrated in Fig. 3c. Only a cell which has non-uniform membrane potential can contribute to current flow in the extracellular space. The driving voltage for current would be the difference in transmembrane potential at different points along an active cell. Any current pathway into an adjacent resting cell would be shunted by the extracellular space. The rate of rise of the intracellular recorded action potential and the recorded propagation velocities from cat circular intestinal muscle or guinea-pig *Taenia coli* would give a calculated driving potential of 10–15 mV/cell length. Considering the attenuation of current through the resting cell by the extracellular shunting effects, it does not seem a large excitatory displacement of the membrane potential of resting cells could occur if this model were correct. In addition, the current invading a resting cell would cause one region of membrane to be hyperpolarized. No hyperpolarizing junction potentials have been observed (Bülbring *et al*, 1958; Goto *et al*, 1959; Goto *et al*, 1960; Burnstock & Prosser, 1960b). Furthermore, any explanation of the sucrose gap experiments using this model is lacking.

A modification of the completely discrete cell organization of smooth muscle tissue is illustrated in Fig. 3D. Over certain regions membranes of two cells are close enough for the current flowing in the intervening extracellular space to be greatly attenuated, but are still far enough apart so that this region of extracellular fluid is always chemically homogeneous with the rest of the extracellular fluid. The minimum intercellular distance of cellular approach for this situation to obtain is perhaps 200 Å (even at this distance the loss of 8 pMK/cm^2 impulse would add 4 mM/l to the local potassium concentration if diffusion away was unimportant). The amount of current flowing through resting cells would be greater in this case than in the previously treated discrete one. The region of close cellular approach could reasonably be called an ephapse. However, most objections to the discrete case are not removed (the maximum possible driving voltage for current flow through resting cells would be again only 10–15 mV/cell length, etc.). Therefore, this model (Fig. 3D) is not much more attractive than the completely discrete one (Fig. 3C).

ELECTRICAL PARAMETERS OF SMOOTH MUSCLE CELLS

If propagation in smooth muscle is an electrical phenomenon, the characteristic length (λ) of the tissue is a functionally important parameter. A short characteristic length relative to the cell length would favor ephaptic transmission while a longer one would be suggestive of a bridge mechanism (syncytial or nexal). Using the simple uniform diameter core conductor formulation $\lambda = \sqrt{R_m/(R_i + R_o)}$, where R_m, R_i and R_o are the resistances per unit length of the membrane, myoplasm and extracellular fluid. From measurements of the transmembrane resistance, λ has been estimated to be 98μ for cat intestinal muscle (Barr, 1961). In this case the values of parameters used were $R_m = 1000$ ohm cm^2, $R_i = 250$ ohm cm, $R_o = 50$ ohm cm, cell diameter = 5μ and a shell of extracellular fluid = 0·06μ thick. This gives a conservatively short estimate of λ and the average extracellular space would be thereby only about 5%. If the extracellular space is taken as 20%, λ would be about 160μ.

The membrane resistance can be estimated from other considerations where direct measurements are lacking. From $i_m = C\frac{dv}{dt}$ at maximum rate of rise of the action potential, the chronaxie $\sigma \simeq T\ln 2$ and (membrane time constant) $T = R_mC_m$; we have $R_m = (\sigma \times dV/dt_{max})/(i_m \times \ln 2)$. For guinea-pig *Taenia coli* taking $dv/dt_{max} = 18$ v/sec, (Holman, 1958), $\sigma = 40$ msec, and $i_m = 1$ ma/cm^2; $R_m = 1050$ ohm cm. Using this value if the effective cell diameter is 5–10μ and the effective extracellular space is 5–20%, λ ranges from 100μ to 300μ. For circular cat intestinal muscle, taking $dv/dt = 10$ v/sec and $\sigma = 60$ msec, the equivalent range of λ is 94μ to 280μ.

Another method of estimating λ is available using the theoretical assumption that electrotonic spread before and after an action potential should be an exponential function of the characteristic length in a core conductor (Cole & Curtis, 1938). The leading edges of propagating action potentials recorded from smooth muscles are not exponential and thus not useful in this regard, perhaps because of pre-potentials and cell-to-cell interference. However, the trailing edges (last phase of repolarization) of action potentials from guinea-pig *Taenia coli* (Holman, 1958) and cat intestinal muscle (Barr, 1958) have an exponential time course. If characteristic lengths are calculated from these and the propagation velocities one obtains 125μ and 110μ respectively. While all these λ values are similar, there are difficulties with them. For instance, when $vT > \sqrt{R_m/(R_i + R_o)}$, the λ (after an action potential) should be larger than the λ (at rest) and should approach vT. In the case of smooth muscles this obviously does not occur; vT from the above figures would be 45 mm for guinea-pig *Taenia coli* and 43 mm for cat intestinal muscle. That R_m probably remains small throughout recovery might account for this. Another peculiarity of smooth muscle is the apparently large specific membrane capacitance. The spread of subthreshold currents from external electrodes in frog stomach muscle was found to fall off too slowly with distance to fit a single exponential. The voltage measurements closest to the current electrodes give a minimum characteristic length of 625μ and 700μ for "catelectrotonus" and "anelectrotonus," respectively (Shuba, 1961). By all estimates the characteristic length of smooth muscle is long relative to the cell length, and the distance over which the spread of voltage is significant covers several cell lengths. It would seem, therefore, from these considerations also, that a bridge model is more consistent with the data than one assuming discrete cells.

Since this paper was submitted, an electron microscopic description of the nexus has been published by M. M. Dewey & L. Barr (1962). *Science* **137**, 670.

The published electron micrographs show no intervening extracellular space between cell membranes. In fact, the outer lamallae of the two plasma membranes fuse to form a unitary structure.

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