Intercellular Communication in Cardiac Muscle

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THE heart muscle was conceptualized as an anatomical syncytium for many years (Heidenhain, 1901; Godlewsky, 1902). With the development of electron microscopy, it was proved that cardiac fibers are composed of isolated cells separated by specialized zones—the so-called intercalated discs (Sjöstrand and Andersson, 1954). The discs comprise three junctional specializations: (1) the macula adhaerens (desmosome), (2) the fascia adhaerens, and (3) the gap junction or nexus (van Breeman, 1953; Moore and Ruska, 1957; Sjöstrand et al., 1958).

At the level of desmosomes, the apposing plasma membranes are separated by a gap of 250–300 Å and a fibrillar material is seen inside the adjacent cells (Muir, 1965; Fawcett, 1966). At the nexus, the cell membranes are in intimate contact (Dewey and Barr, 1964; Goodenough and Revel, 1970), and in its central area, several structures are seen bridging the gap with a periodicity of 100 Å (Fig. 1). Freeze-cleaving studies indicate that the nexus is characterized by particles closely packed in a hexagonal array (Kreutziger, 1968; Bullivant, 1969; Goodenough and Revel, 1970; McNutt and Weinstein, 1970; Peracchia, 1973, 1980). These particles are usually 70–80 Å in diameter showing dots (20–25 Å) in the central region (Gilula, 1978). Hydrophilic channels connecting the cytoplasm of adjacent cells seem to pass through the center of the nexus subunits (Loewenstein, 1966; Furshpan and Potter, 1968; Bennett and Dunham, 1970; De Mello, 1980a—see Fig. 2).

Intercellular Junction and the Electrical Coupling of Heart Cells

As cardiac muscle consists of cells with surface membrane of high electrical resistance, it became difficult to understand how the depolarization of a myocyte could initiate activity in its neighbors.

The possibility of a chemical mechanism was considered (Spereelakis et al., 1960), and the localization of acetylcholinesterase near intercalated discs (Jöö and Cziliik, 1962) represented an apparent support for this theory. However, the complex chemical machinery required for the synthesis of a chemical transmitter, as well as synaptic vesicles, is absent in cardiac cells.

The concept that the heart cells are electrically coupled has emerged from different types of observations. When a subthreshold pulse is injected into a cardiac cell, electrotonic potentials can be recorded in cells located nearby (Weidmann, 1952; Woodbury and Crill, 1961; van der Kloot and Dane, 1964; De Mello, 1975). In Purkinje fibers, the core resistivity is quite low (105 Ω cm) and the space constant is higher (1.9 mm) in comparison with the length of the cells (125 μm) (Weidmann, 1952), which indicates that the intercellular junctions have a low electrical resistance (Weidmann, 1969). In myocardial fibers, the values of space constants are smaller [1300 μm (Kamiyama and Matsuda, 1966); 880 μm (Weidmann, 1970)], and the intracellular longitudinal resistance (470 Ω cm) higher than in Purkinje fibers (Weidmann, 1970). This higher value of $R_j$ can be ascribed to the density of myofibrils and mitochondria, or to a smaller junctional conductance (Weidmann, 1970).

Barr et al. (1965), utilizing a method similar to that described by Osterhout and Hill (1930), showed that the impulse conduction along a thin bundle of frog atrium was blocked by immersing the central portion in isotonic sucrose solution while keeping the two ends in Ringer’s solution. By enhancing the extracellular resistance with sucrose solution, the longitudinal flow of current through myoplasm and external solution was suppressed and the propagation abolished. The conduction was, however, reestablished if an electrical shunt was created between the two pools of Ringer’s solution. The spread of conduction, in spite of the sucrose gap, is only feasible if both intracellular and the extracellular resistance is relatively low.

In rat atrium, the depolarization of one cell causes appreciable variations in the membrane potential of adjacent cells (Woodbury and Crill, 1961). In these studies, a steep decrement of the electrotonic potential was found (λ = 130 μm) when the cell was polarized through an intracellular microelectrode. The three-dimensional characteristics of rat trabecula certainly

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explains the enormous decrement of the electrotonic potentials. Considering, however, the small size of these cells, a \( \lambda \) of 130 \( \mu \)m is still compatible with the idea of cell-to-cell coupling (Woodbury and Crill, 1961).

In 1966, Weidmann using a different approach, studied the permeability of the intercellular channels to \( { }^{42}\mathrm{K} \). He found that when one half of a bundle of ventricular fibers is exposed to radioactive K and the other half is continuously washed with nonradioactive solution, a steady state with respect to tissue \( { }^{42}\mathrm{K} \) is achieved in about 6 hours. At the end of this time, an appreciable amount of \( { }^{42}\mathrm{K} \) can be detected in the half of the bundle not exposed to radioactivity. Under these conditions, the longitudinal spread of \( { }^{42}\mathrm{K} \) represents a measurement of the relative hindrance of the myoplasm (including the intercellular junctions) to K movement, as compared to that of the nonjuncional membrane. Due to the establishment of ionic barriers at the end of the bundle (healing-over), the amount of \( { }^{42}\mathrm{K} \) was finite near the cut end. This finding supports the view that \( { }^{42}\mathrm{K} \) moved from cell-to-cell through the intercellular junctions (Weidmann, 1966).

The quantitative analysis of these results indicates that the permeability of the intercellular junctions is about 5,000 times greater than the permeability of the nonjunctonal membrane to outward movement of \( { }^{42}\mathrm{K} \) (Weidmann, 1966).

Further indication that the heart cells are connected through high conductance gates was obtained by measuring the membrane potential near the cut area, immediately after injury. In Purkinje fibers, the depolarizing current, elicited by lesion, flows over an area of about 2,000 \( \mu\)m away from the damage site (De Mello, 1972). The spread of depolarization is fortunately quickly suppressed by the establishment of ionic barriers (healing-over) (Engelmann, 1877).

Having dealt with some of the most relevant information supporting the view that heart cells are electrically coupled, we can now turn our attention to the anatomical site of coupling.

The evidence gathered thus far supports the view that the nexus is involved in the electrical coupling of heart cells. In this type of junction, the leak of current through intercellular space, for instance, is negligible. On the other hand, correlation studies between the morphological features of the intercellular junctions and the electrical coupling are indicative that the nexus is the site of coupling. The exposure of cardiac muscle to hypertonc solution produced not only separation of the membrane at the nexus, but also cell decoupling (Barr et al., 1965; Dreifuss et al., 1966; De Mello et al., 1969). Morphological as well as electrical uncoupling induced by hypertonic solutions was reversible (Barr et al., 1965).

The involvement of gap junctions in the electrical coupling was also supported by studies of synchronization of beating in cultured embryonic heart cells. It became clear that synchrony develops only upon contact between isolated myocytes (see Cavanaugh, 1955; De Haan and Hirakow, 1972), and that, when two independently beating myocytes grow together, the cell beating faster paces the other. Goshima (1969) and Hyde et al., (1969) found, for instance, that mouse myocardial cells beating synchronously were electrically coupled and gap junctions have been described in thin sections of pairs of cells of chick embryo (De Haan and Hirakow, 1972).

A tissue culture model consisting of spheroidal ventricular cell clusters (50–250 \( \mu\)m in diameter), dissociated from embryonic chick hearts, has been used to study the electrical interactions between cells (Sachs and De Haan, 1973; De Haan and Fozzard, 1975; Ypey et al., 1979). According to these observations, the cells of the aggregate were isopotential, which means that the cluster behaves like one large cell. However, discrepant results with respect to the isopotentiality of these clusters have been reported by McLean and Sperelakis (see Sperelakis, 1979).

After being brought together, the cells require some time to establish communication. This time varies...
from a few minutes to 1 hour (Mark and Strasser, 1966; De Haan and Hirakow, 1972). Although it is known that Ca and Mg were essential for the formation of cell contacts and development of electrical coupling (Loewenstein, 1967), the dynamic mechanism by which membrane particles are assembled, making possible the fusion of hemichannels at the area of cell contact, is not known. Cycloheximide, an inhibitor of protein synthesis, abolishes the synchronization of heart cell clusters (Griep and Bernfield, 1978), suggesting the participation of cellular mechanisms in the synthesis and aggregation of gap junction particles.

Induction of gap junction formation has been described with estrogen, in ovarian follicle (Merk et al., 1972) and in uterine muscle (Bergman, 1968). In tracheal smooth muscle, Kannan and Daniel (1978) found that the number of gap junctions was increased by chemical agents, such as tetraethylammonium (TEA) or 4-aminopyridine.

In cardiac muscle, it is known that the impulse conduction is more rapid in preparations perfused with blood as compared to Tyrode’s solution (Rosen et al., 1972). More recently, evidence has been presented that the electrical coupling of cardiac cells is enhanced by angiotensin II (Hermsmeyer, 1980).

**Junctional Permeability**

An approach that is both different and useful, which demonstrates the presence of high permeability channels between cells, consists of injecting fluorescent compounds into the cytoplasm and following their movement to neighboring cells (Loewenstein and Kanno, 1964).

The selection of appropriate compounds is based on their toxicity and low binding to cytoplasmic components, as well as their high fluorescent yield. Fluorescein (mol. wt. 332), a negatively charged molecule, when injected iontophoretically into a normal cardiac Purkinje cell diffuses longitudinally along the fiber (Pollack, 1976; De Mello, 1978).

The longitudinal diffusion of molecules in cardiac fibers also can be followed by the cut-end method which consists of mounting a trabecula in a chamber divided by a rubber membrane. After one half of the preparation is exposed to Ca-free solution for a few minutes to avoid healing-over (Delèze, 1965; De Mello et al., 1969), the muscle is cut at about 1 mm from the rubber partition and immediately exposed to the compound that penetrates into the cells. After 10–15 minutes, Ca is readmitted to the bath, healing is established, and the molecule is trapped inside. Its diffusion to the other half of the muscle, which is continuously perfused in normal Tyrode solution, can be measured.

This method was initially used by Imanaga (1974) to study the diffusion of Procion Yellow (mol. wt. 697) along sheep Purkinje fibers. He found that the compound moved from cell-to-cell and after 4 hours, it could be detected 2.4 mm away from the rubber partition. As the permeability of the surface cell membrane to Procion Yellow is low (Imanaga, 1974), the possibility that the dye leaves the cell, accumulates in the extracellular space and diffuses back into the neighboring cells, seems unlikely.

Weingart (1974), Tsien and Weingart (1976), using the same method, showed that the intercellular channels in heart are permeable to TEA (mol. wt. 130) and to 3H-cAMP (mol. wt. 328), respectively.

The permeability of the nexus falls with increasing molecular weight of the compounds. So, for K it is 7.7 × 10⁻³ cm/sec (Weidmann, 1966); for TEA 1.27 × 10⁻³ cm/sec (Weingart, 1974), for cAMP, 1.33 × 10⁻⁶ cm/sec (Tsien and Weingart, 1976), and for Procion Yellow, 1.4 × 10⁻⁸ cm/sec (Imanaga, 1974). The molecular size of the solvated molecule is, certainly, a more correct criterion for determining the permeability limit of the hydrophilic channels.

The cut-end method was recently used to study the cell-to-cell movement of fluorescein in canine Purkinje fibers (De Mello, 1979a). This dye, however, crosses the surface cell membrane in these fibers (De Mello, 1979a), as well as in other tissues (see Bennett, 1977). This means that, in the absence of separately conducted washout studies, the data obtained with fluorescein cannot be quantified. In Purkinje fibers, the dye is quickly removed from the extracellular medium, ruling out the possibility that the compound returns to the next cell through the surface cell membrane. It seems then possible to conclude that the longitudinal movement of the compound found in these fibers occurred through the gap junctions (De Mello, 1979a).

A major advance in the study of cell-to-cell communication was the introduction of Lucifer Yellow CH (mol. wt. 476) (Stewart, 1978). As the permeability of the surface cell membrane to this compound is very small, the movement of the dye through the gap junctions can be trustily measured. The dye was found to move from cell-to-cell in embryonic tissues (Bennett et al., 1978) in crayfish giant axons (Stewart, 1978) and in heart fibers (De Mello, 1980a).

Tracer studies performed in other tissues (see Simpson et al., 1977), lead to the conclusion that the hydrophilic channels are permeable to neutral or negatively charged molecules of a molecular weight not greater than 1,200. Based on tracer and electron-microscopic observations, it seems reasonable to assume that the channel diameter in heart fibers is about 10 Å (McNutt and Weinstein, 1973; Weingart, 1974).

The specific electrical resistance of gap junctions varies with the preparation. In heart, the values reported (Woodbury and Crill, 1961; Weidmann, 1966; Kriebel, 1968; Spira, 1971) are around 1 Ω/cm².

It is important to emphasize, however, that the geometry of the system, as well as the junctional area, must be considered in estimating the gap junction resistance (Sheridan et al., 1978). As measurements of junctional area are not completely reliable, estimations of junctional resistivity are rather imprecise.

For a single channel (1–2 nm in diameter and 20 nm long), the resistance was calculated to be 10¹⁰ Ω (Loewenstein, 1975).
The capacity of gap junctions should theoretically be quite low. Assuming a membrane capacity of 1 μF/cm², the junctional capacity is probably half of this value considering that the two apposing membranes are in series (see Bennett, 1977). However, Freygang and Trautwein (1970) suggested that the coupling of heart cells is not purely resistive, but partly realized through a capacity. They found a capacity of 3.6 μF/cm² oriented longitudinally with a time constant of 60–70 μsec which they ascribe to connections between Purkinje cells. The precise meaning of these findings to heart physiology is not yet clear, and certainly requires further investigation.

**On the Control of Junctional Permeability**

It is known that the injury potentials of cardiac muscle are quickly reversed (healing-over) (see Fig. 3A), but can be reestablished by applying a new lesion near the previous one (Engelmann, 1877). These findings indicate that the rapid disappearance of the ion through the surface cell membrane does not result in death of adjacent cells ("der Tod schreitet nicht von Zelle auf Zelle fort").

Pre-established transversal barriers between heart cells were proposed by Rothschuh (1951) to explain the healing-over, but this idea was rejected because the core resistance of cardiac fibers is low (Weidmann, 1952). The healing-over seems, then, to depend on a sealing process localized near the injured area which halts the spread of depolarizing current from damaged to non-damaged cells (see Weidmann, 1967; De Mello, 1972). As Ca ions are essential for the healing-over (Deléze, 1965; De Mello et al., 1969; De Mello, 1972), it seems conceivable that the increment in free [Ca++] , elicited by lesion might reduce drastically the junctional conductance (see De Mello et al., 1969 and Fig. 3B). This hypothesis is supported by the fact that the intracellular injection of Ca causes electrical uncoupling in normal cardiac cells (De Mello, 1972, 1974a, 1975). This uncoupling, which is accompanied by an increase in input resistance of the injected cell, is completely reversible. The reestablishment of cell-to-cell coupling seems to depend on homeostatic mechanisms involved in the maintenance of a low free [Ca++] , such as the uptake of Ca by the sarcoplasmic reticulum, mitochondria, or the extrusion of the ion through the surface cell membrane (De Mello, 1975).

A photoprotein, aequorin, has been used as a Ca indicator to study the influence of the ion on junctional conductance in Chironomus salivary gland (Rose and Loewenstein, 1975). These studies indicate that when Ca was injected into the cell, the electrical coupling was abolished only when the light emission was seen to spread all the way to the intercellular junctions.

As the synthesis of high energy phosphate bonds is required for active Ca uptake by sarcoplasmic reticulum or mitochondria, it is expected that metabolic inhibitors interfere with cell communication. No indications of such effects were reported from experiments of this kind.

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the cytosol (De Mello, 1975, 1979b). However, Mg\(^{++}\) was unable to change the electrical coupling of cardiac cells (De Mello, 1975). This finding suggests that the site controlling the junctional conductance is not specific for Ca ions.

Correlation studies between the packing arrangement of particles in invertebrate gap junctions and the physiological state at the time of fixation (Peracchia, 1974; Peracchia and Dulhunty, 1974, 1976) indicate that only gap junctions with disorderly packed particle arrays seem to present normal permeability. Conditions which lead to a rise in free [Ca\(^{++}\)] and cell decoupling cause a tight and hexagonal packed particle array (Peracchia and Dulhunty, 1976). This finding means that Ca ion trigger crystallinity in isolated gap junctions (see Peracchia, 1980).

**The Role of the Na Pump on Intercellular Communication**

In cardiac muscle, as in other excitable tissues, Ca is extruded from the cell interior against a concentration gradient, and the energy required for this transport is provided by the concentration gradient of Na across the surface cell membrane (Reuter and Seitz, 1968; Glitsch et al., 1970). It is known, for instance, that the increase of an intracellular Na concentration enhances Ca influx in squid axons (Baker et al., 1969) and in heart cells (Glitsch et al., 1970).

Recent observations showed that the iontophoretic injection of Na into cardiac cells causes hyperpolarization, increases the intracellular longitudinal resistance, and produces cell decoupling (De Mello, 1974b, 1976). The hyperpolarization probably is due to the activation of the sodium pump (Mullins and Fruento, 1963; Vassalle, 1970). The effect of high [Na\(^+\)], on the electrical coupling is dependent on the extracellular Ca concentration (De Mello, 1976). The iontophoretic injection of Na into heart cells had a negligible effect on cell-to-cell coupling in preparations immersed in low Ca solution (De Mello, 1976).

The rise in free [Na\(^+\)] activates a Na/Ca exchange (Mullins, 1981), with consequent increment of [Ca\(^{++}\)], and cell decoupling. The inhibition of the Na pump with ouabain also increases the intracellular longitudinal resistance, causes cell decoupling, and decreases the conduction velocity (De Mello, 1976; Weingart, 1977). The effect of ouabain on intracellular resistance was accelerated in high Ca solutions and slowed down in low Ca medium (De Mello, 1976). This means that, in the presence of the drug, an increment in [Ca\(^{++}\)] tends to elicit cell decoupling.

K-free solution, which is known to inhibit the Na pump in cardiac muscle (Page et al., 1964), also suppresses cell communication in canine Purkinje fibers (De Mello, unpublished observations). The extrusion of Na ions through the surface cell membrane is then essential for the preservation of cell-to-cell communication in heart since a high internal Na\(^+\) activity would drive Ca\(^{++}\) into the cells (see Glitsch, Reuter and Scholz, 1970; Mullins, 1981).

The intracellular free Ca concentration required to cause cell decoupling is difficult to estimate because of the active Ca uptake by the sarcoplasmic reticulum, by mitochondria, and also because of its binding by contractile proteins. By comparing the time-course of contractures elicited by ouabain and the increase in intracellular longitudinal resistance, Weingart (1977) reached the conclusion that the threshold concentration of free [Ca\(^{++}\)], required to produce cell decoupling in myocardial fibers is larger than that necessary for the activation of the mechanical process (Weingart, 1977). The possibility exists that in salivary glands, cell decoupling occurs gradually and that the junctional permeability is smoothly regulated by variations of free [Ca\(^{++}\)], between 10\(^{-7}\) and 5 X 10\(^{-6}\) M (Rose et al., 1977). Studies on the effect of intracellular Ca injection in cardiac cells (De Mello, 1975), as well as on the reestablishment of cell-to-cell communication elicited by intracellular injection of EDTA in preparations previously uncoupled by dinitrophenol (De Mello, 1979a), might indicate that—in heart muscle also—the junctional resistance is smoothly modulated. There is not enough evidence at the moment, however, to decide whether single channels are closed in an all-or-nothing way, or if all channels are smoothly closed.

As the free [Ca\(^{++}\)], is enhanced during the excitation process (Niedergerke, 1963; Bassingthwaighte and Reuter, 1972), it seems reasonable to think that the junctional conductance in heart might be reduced during the time of maximum increment in free [Ca\(^{++}\)].

Weidmann (1970), however, was unable to detect any change in intracellular longitudinal resistance during the action potential of myocardial cells. The low diffusion coefficient of Ca in the cytoplasm (Kushmerick and Podolsky, 1969) certainly reduces the possibility that the concentration of free [Ca\(^{++}\)], at the gap junctions increases markedly, but a reexamination of this problem is necessary.

**Has Intracellular pH an Influence on the Electrical Coupling?**

In 1977, Turin and Warner found that when embryonic cells of Xenopus were exposed to 100% CO\(_2\), the intracellular pH dropped from 7.7 to 6.4, the resting potential was reduced, and the electrical coupling abolished. As the intracellular injection of Ca in nerve cells is known to reduce the intracellular pH (Meech and Thomas, 1977), it was suggested that the effect of high [Ca\(^{++}\)], on the electrical coupling might be ascribed to a fall in pH. In cardiac Purkinje fibers, cell decoupling can be produced by the intracellular injection of H\(^+\) (De Mello, 1979c, 1980b), an effective way to reduce the pH. The possibility exists, however, that the decoupling action of intracellular acidosis is related to the release of Ca from intracellular stores. Rose and Rick (1978) found in Chironomus salivary gland cells that, after exposure to 100% CO\(_2\), the free [Ca\(^{++}\)] increased. In these experiments, the changes in intracellular Ca were visualized with aequorin and no direct measurements of free [Ca\(^{++}\)] were made. In cardiac Purkinje fibers exposed to 100% CO\(_2\), Weingart and Reber (1979) reported an increase in intracellular Ca.
cellular longitudinal resistance. In embryonic cells of Fundulus, evidence was presented that acidification of the cytoplasm led to electrical uncoupling, an effect due to a direct action of protons on channel molecules (Spray et al., 1981).

In isolated junctions of eye lens, changes in particle packingsuggestive of low permeability can be produced by Ca or H independently (see Peracchia and Peracchia, 1978). Although in heart no conclusive evidence exists that H ion, by itself, changes the junctional conductance, the possibility that Ca and H ions have independent effects on the transference of information between cardiac cells cannot be ruled out. As the buffer capacity of cardiac cells is quite large (Ellis and Thomas, 1976), it is not clear if the intracellular pH regulates the junctional resistance under physiological conditions.

The possibility that other factors are involved in the control of junctional permeability must be considered. In salivary glands of Drosophila, for instance, cyclic-AMP induces an increase in cell-to-cell communication (Hax et al., 1974).

Cell-to-Cell Communication in the Sinoatrial and Atrioventricular Node

Morphological studies of the sinoatrial node showed that the natural pacemaker is composed of small cells (15–20 µm in length; 5–8 µm in diameter) organized as functional units (see Trautwein and Uchizono, 1963; Truex, 1961).

Early electrophysiological studies of the node (Dudel and Trautwein, 1958) showed that the functional units are electrically coupled. In more recent observations (Bonke, 1973), it was found that the space constant of the rabbit sinoatrial node was 465 µm, that is, 23 times larger than the length of a single node cell. These findings indicate that cells inside the natural pacemaker are connected by low resistance channels.

Small nexuses between these cells were described by James and Scherf (1968). Freeze-fracture studies (Masson-Pevet, 1979) not only confirm the presence of gap junctions in this tissue but also indicate that the mean area of the gap junctions is much smaller here than in atrial muscle.

In the atrioventricular (AV) node, fluorescein does not flow from cell-to-cell (Pollack, 1976). The same holds true for the sinoatrial (SA) node (De Mello, 1980a), whereas fluorescein was seen to diffuse longitudinally in the sinoatrial ring bundle (De Mello, unpublished observations). These results might indicate that the diameter or the number of hydrophilic channels is smaller in the SA and in the AV node than in the atrium or Purkinje fibers. Despite the lack of cell-to-cell diffusion of fluorescein in the AV node, the cells are electrically coupled (De Mello, 1977). The space constant in this tissue is quite small (430 µm) but still larger than the length of a single node cell (De Mello, 1977). On the other hand, the input resistance is high (880 ± 75 KΩ, De Mello, 1977; 1.4 MΩ, Ikeda et al., 1980) compared to that of atrial cells (320 ± 42 KΩ, De Mello, 1977). As a first approximation, the intracellular longitudinal resistance (rj) was determined and found to be 40.9 ± 3.6 MΩ/cm, a value much higher than that reported in atrial trabeculae of the rabbit (9.6 ± 2.2 MΩ/cm—De Mello, 1977). Although further study on the spread of electronic potentials in the AV node is certainly necessary, it appears likely that the delay of impulse conduction in this tissue is largely due to a high intracellular resistance along the pathway of conduction. The high intracellular resistance might be explained by the small diameter of node cells, but also by a small number of gap junctions in the tissue (Maekawa et al., 1967; James and Scherf, 1968; De Felice and Challice, 1969).

These characteristics make the impulse conduction in AV node extremely vulnerable to change in resistance of the non-junctional membrane. Acetylcholine, for instance, can easily suppress communication in the AV node and SA node by decreasing the surface cell membrane resistance (De Mello, 1977, 1980a) and consequently reducing the coupling coefficient. This seems to be an example of suppression of cell communication by a decrease in electrotonic spread between the node cells in which an increase in junctional resistance is not necessarily involved.

On the other hand, the effect of ouabain on AV transmission is probably more related to a rise in intracellular longitudinal resistance produced by the increment in free [Ca++] (Ikeda et al., 1980).

Physiological Implication of Cell-to-Cell Coupling

The presence of intercellular channels between cardiac cells and the modulation of their permeability by intracellular factors, such as Ca or H ions, have several physiological and pathological implications (see Fig. 4).

The velocity of impulse conduction, for instance, is known to depend on the rate at which the membrane capacity, ahead of the impulse, is discharged beyond threshold and also on intracellular longitudinal resistance (rj) and extracellular resistance (Hodgkin, 1954). Changes in rj can consequently alter the conduction velocity in heart fibers. It is well established that the electrical activity of heart fibers is intimately related to cell metabolism. Anoxia or metabolic inhibitors lead to changes in action potential or complete block of impulse conduction (Haas, 1972). Inhibition of the sodium pump seems to reduce the velocity, in part, through a rise in intracellular longitudinal resistance (De Mello, 1976; Weingart, 1977).

Hypoxia also enhances the intracellular resistance in myocardial fibers probably due to the rise in free [Ca++] (Wojtczak, 1979). Supporting this view is the fact that the resting tension and the Ca efflux are increased by the lack of oxygen (Vleugels and Carmeliet, 1976; Wojtczak, 1979). These and other findings (see De Mello, 1980a) indicate that the impulse conduction in heart fibers and electrical synchronization are also dependent on processes required for the maintenance of a low free [Ca++]i. It is important
to emphasize, however, that metabolic inhibition impairs the impulse conduction not only by enhancing \( r_u \) but also by a reduction in amplitude and in \((dV/dt)_{max}\) of the upstroke of the action potential (see Gettes, 1974).

As ischemia reduces the intracellular pH of cardiac cells (Neely, Whitmer and Rovetto, 1975), it is reasonable to think that the rise in \([H^+]\) might reduce the junctional conductance and abolish cell-to-cell communication, directly or through an increase in free \([Ca^{++}]\).

Conduction is impaired and reentry occurs in myocardial ischemia (Gettes, 1974), conditions which are known to elicit arrhythmias (Wit et al., 1972). These observations are indicative that arrhythmias by myocardial infarction might be, in part, explained by a rise in \([H^+]\), or \([Ca^{++}]\). The same rationale can be applied to cardiac arrhythmias produced by digitalis toxicity in which the increment of free \([Ca^{++}]\) is probably the major cause of cell decoupling (De Mello, 1976; Weingart, 1977).

The increment in \([Na^+]\), and the reduction of Na gradient across the surface cell membrane are important factors which, together with the rise in junctional resistance, might explain the changes in impulse conduction and cardiac rhythm produced by high doses of digitalis.

Lesion of myocardial cells leads to the creation of diffusion barriers between damaged and nondamaged cells (healing-over) suppressing the flow of injury current, and metabolites originated in lesioned cells (De Mello, 1972). Thanks to the healing-over process, large masses of normal heart cells are protected from the harmful effects of injury. This important homeostatic mechanism is possible only because heart cells are connected through channels that are immediately closed by cell damage. The role of intercellular junctions in other aspects of heart cell biology, such as metabolic cooperation and development, is unknown.

It is easy to visualize that further studies with regard to these areas will provide basic information which is necessary to understand the intimate mechanisms involved in heart cell communication.

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_Circ Res._ 1982;51:1-9
doi: 10.1161/01.RES.51.1.1

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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