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Cardiac Muscle Cells Communicate in Life, but Fail to Give a Message of their Decay (Engelmann, 1875)

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The title of the present paper is a free translation of the conclusions drawn 105 years ago by Engelmann (7). His original text reads "Der Process des Absterbens breitet sich nirgends von Zelle zu Zelle aus, sondern beschränkt sich auf die direkt angegriffenen Zellen, nachweislich auch in den Fällen, wo die Zellen während des Lebens ihren Erregungszustand einander durch Kontakt mittheilen". I shall refer to "direct contact" first, then to "demarcation".

CELL-TO-CELL CONTACT

Authors of textbooks, until the late 1960's, described heart muscle as a morphological syncytium (e.g. Selkurt, 13; Schneider, 12). The propagation of the cardiac impulse was explained in the same way as the propagation of excitation in nerve. In 1954, with the advent of high resolution electron microscopy, Sjöstrand and Andersson (14) described cardiac muscle as being composed of well defined individual cells, their regions of contact (intercalated disks) being specially organized cell boundaries.

There was much dispute before the view now generally accepted was first mentioned 1970 in a students' textbook by Davson (3): a "functional syncytium" with low electrical cell-to-cell resistance but a high resistance between the extracellular fluid and the inside of every single cell.

This view rests on the following lines of evidence.

1) Measuring the spatial decay of a subthreshold potential difference set up by membrane current results in a so-called space constant (λ) of the order of 1 mm, i.e. of several times the length of a single cell, 0.1 mm (e.g. 15, 17). This result is possible only if cells are coupled by low-resistance junctions.

2) A propagating impulse in a bundle of frog atrial muscle can "jump" a region of membrane made inexcitable, provided the extracellular longitudinal conductance is given a minimal value (2). This is in principle the "salt bridge experiment" first performed in 1930 with the alga Nitella by Osterhout and Hill (10), who showed that propagation along an excitable cable requires moderately low extra- and intracellular longitudinal resistances.

3) The ion most important as a carrier of electrical charge within the intracellular compartment (K^+) has been shown to diffuse from cell-to-cell (18). A bundle of fibres, less than 1 mm in diameter and 7-10 mm in length, was placed in a double chamber (Fig. 1). One part was superfused with ^{42}K-Tyrode solution (charging compartment), the other part continuously washed by non-radioactive Tyrode. At the end of several hours, when steady-state diffusion was reached, the bundle was rinsed with non-radioactive solution and frozen in liquid N_2. Slices of equal length were counted for radioactivity. The spatial distribution of ^{42}K, together with a knowledge of the influx and efflux rate constants, lead to the following results: (i) K^+-permeability of the

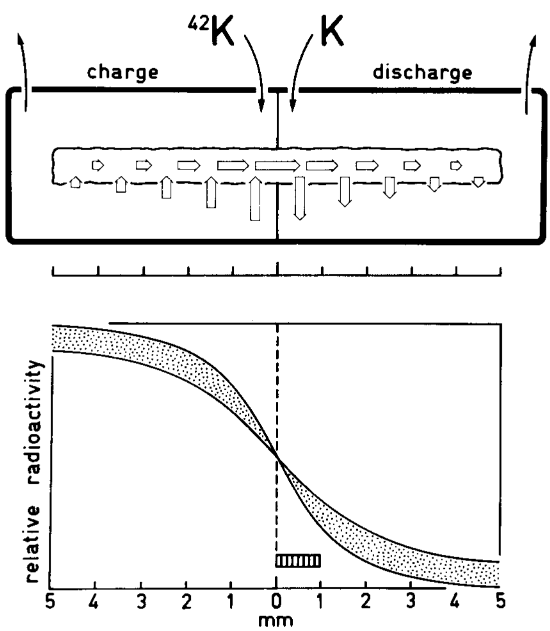

Fig. 1. Upper panel: Muscle bundle in a double chamber. Arrows indicate net movement of tracer. Lower panel: Theoretical curves illustrating steady-state ^{42}K distribution. The steeper curve is drawn for a space constant of 1.3 mm, the flatter one for λ = 2.2 mm. These two space constants correspond to the extreme values found experimentally with 20 bundles. From ref. 18. Inset of lower panel indicates cell length of Purkinje fibres drawn to scale.

intercalated disks separating adjoining cells is less than 1/5000 of K^+-permeability of the surface membrane, and (ii) the electrical resistance to the flow of K^+-current is 3 Ohm or less for one cm^2 of disk membrane.

4) Tracer molecules of various molecular volumes, either radioactive or fluorescent, can be introduced into the internal compartment of a cardiac muscle strip by cutting in a Ca^{++}-free solution, letting the tracers enter and subsequently sealing with Ca^{++}-containing solution (see below). So far, quantitative diffusion studies have been made using tetraethylammonium$^+$, fluoresceinate$^-$, cyclic AMP, Procion Yellow^{3-} and digoxin. Permeability coefficients of these tracers fall rather steeply with increasing molecular weight (19), by more than two orders of magnitude from tetraethylammonium (M.W. = 130) to digoxin (M.W. = 800).

5) The structure of the intercalated disk is highly complex (see 9). The greater part of the narrow gap between the two cell membranes is easily penetrated by tracers of extracellular space, such as horse raddish peroxydase. One of the types of specialized intimate cell contacts is of interest in the present connexion: the nexus membrane. This structure occupies about 10 % of the total area of the disk membrane (11) and is composed of a hexagonal arrangement of subunits (9). There is evidence suggestive of the existence of (aequous?) pores spanning the nexal membrane, their diameter being estimated at 1-1.5 nm (9). The dimensions of one of the largest molecular species known to diffuse from cell-to-cell, Procion Yellow, are 0.5 x 1 x 2.7 nm (19). At present, therefore, the agreement between structural and functional findings is satisfactory.

EVIDENCE FOR DEMARCATION BETWEEN SURVIVING AND DECAYING CELLS

1) Engelmann (7) had observed that damaged cells undergo contracture, while neighbouring cells preserve their normal histological appearance as well as the ability to contract upon stimulation. Baldwin (1), in an electron microscopical study, described damaged cells as "opaque" and showed a membrane between damaged and undamaged cells; this membrane in all likelihood corresponds to the site of the former intercalated disk.

2) As judged by the recording of resting potentials and of input resistance close to a region freshly damaged, the process of healing over (demarcation) requires the presence of Ca^{++} ions in the bathing solution (4).

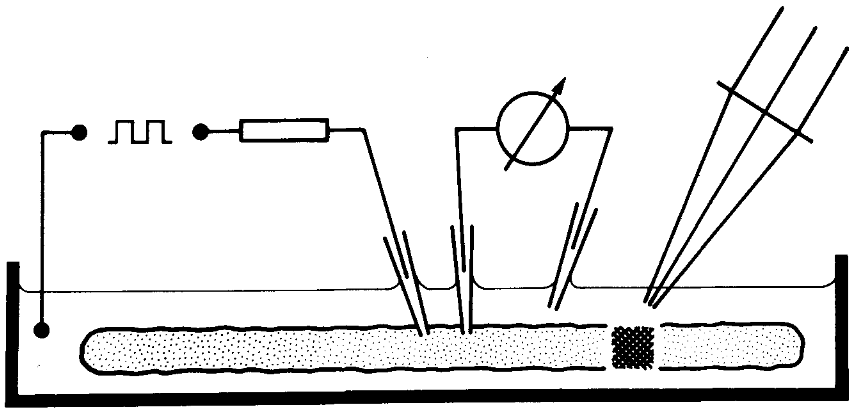

Fig. 2. Purkinje fibre of a sheep heart damaged by a laser pulse. Resting membrane potential and membrane resistance are monitored. There is full recovery (demarcation) within a minute if the bathing solution contains calcium. From ref. 4.

3) Iontophoreses of Ca^{++} and Sr^{++} into cells through intracellular microelectrodes de-couples cardiac cells from one another (5). The same gradual and partly reversible uncoupling can be shown to result from O_2-lack (20) or metabolic poisoning (6).

4) While the common denominator for demarcation, as well as for uncoupling, is generally believed to be a critical level of free calcium facing the nexal membrane, the situation at present is complex: Intracellular application of Na^+ and H^+ also induce uncoupling (6), an experimental fact that must be taken into consideration in any future attempts to analyze the phenomenon.

5) To know more about the sequence of events following coronary artery occlusion would obviously be desirable. It is evident from histochemical pictures that in a later stage of occlusion (1 hour) the boundary between surviving and decaying tissue is sharp and interdigitated (e.g. 8), as if a given cell in the border region would either be located too far from intact tissue and therefore perish, or else survive by metabolic contact with its surviving neighbours.

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