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MINI-REVIEW

Importance of the Mitochondrial Outer Membrane Channel as a Model Biological Channel

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Abstract

The channels of the mitochondrial outer membrane represent a useful model for studies into the mechanisms underlying phenomena of voltage-dependent gating and ion selectivity.

Key Words: Mitochondrial outer membrane channels; permeability; voltage gating; ion selectivity.

The first report on the reconstitution of voltage-dependent anion-selective channels, VDAC, from mitochondrial extracts was published ten years ago (Schein *et al.*, 1976). In the intervening decade, research reports coming out of several laboratories have increased our understanding of the structure and function of these channels and, to a lesser extent, the role they play in the normal function of the mitochondrion.

The channels are formed by a 30–35,000-dalton polypeptide located in the mitochondrial outer membrane and would seem to be responsible for the known permeability of this membrane to low-molecular-weight solutes (Colombini, 1979, 1985; Benz, 1985). The bore of the passive diffusion channel formed by the outer mitochondrial membrane protein is large, with estimates varying from 2 to 4 nm depending on the technique applied.

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Despite its apparently large inner diameter, VDAC displays differential permeabilities to anions and cations. Small metal ions (K^+, Na^+) diffuse more slowly than Cl^- through the channel, hence the use of the term anion-selective. The lower permeability of VDAC toward cations may have a physiological role. Most of the substrates and cofactors of oxidative phosphorylation are anions or carry no net charge under physiological conditions, while large organic cations, like polyamines, tend to be inhibitors of oxidative phosphorylation. Thus the outer mitochondrial membrane may act as a selective barrier against polar cationic respiratory inhibitors, by virtue of the anion selectivity of VDAC. This possibility has, in fact, been suggested by recent experiments on mitochondrial susceptibility to and uptake of polyamines and cationic drugs (Mannella *et al.*, 1986; Diwan *et al.*, 1987).

Another interesting characteristic of the mitochondrial channel is that it switches to a lower conductance state upon application of a small (20–30 mV) transmembrane potential. The occurrence of multiple permeability states of VDAC suggests that mitochondrial outer membrane permeability may be regulated *in vivo*. Schemes whereby such regulation might occur via interaction between outer and inner mitochondrial membranes have been proposed. Such interactions may involve direct contacts between the two membranes (Roos *et al.*, 1982) or interaction of VDAC with the inner membrane surface potential (Mannella, 1985). Others have suggested that the channels may close in response to Donnan potentials established across the mitochondrial outer membranes by fixed charges at the membrane's surfaces (Colombini, 1979). Alternatively, channel permeability may be directly regulated by endogenous effectors, a possibility raised by the inhibitory action exerted on VDAC permeability by a synthetic polyanion (Yeung *et al.*, 1986). Finally, the recent finding that VDAC tends to close at high osmotic potentials (Zimmerberg and Parsegian, 1987) raises the possibility of channel regulation in response to changes in oncotic pressure of the cytoplasm or intermembrane space.

The fact that VDAC displays both anion selectivity and voltage regulation makes it an attractive model system for studying the molecular mechanisms of voltage-gated channels. Its value as a model system is enhanced by its relative ease of isolation and functional reconstitution; by the fact that the gene from yeast has been sequenced and cloned (Mihara and Sato, 1985; Forte *et al.*, 1987), making it amenable to genetic manipulation; and by the apparent structural simplicity of the channel (Fig. 1). VDAC does not have a large extrinsic superstructure like those of the more massive gap junction connexons or acetylcholine receptors. It is formed by one or two 30-kDa polypeptides which (at least in the case of the fungal channel) are entirely intrinsic to the membrane (Freitag *et al.*, 1982; Linden and Gellerfors, 1983; Mannella, 1987). Thus VDAC is a kind of minimal protein channel, whose

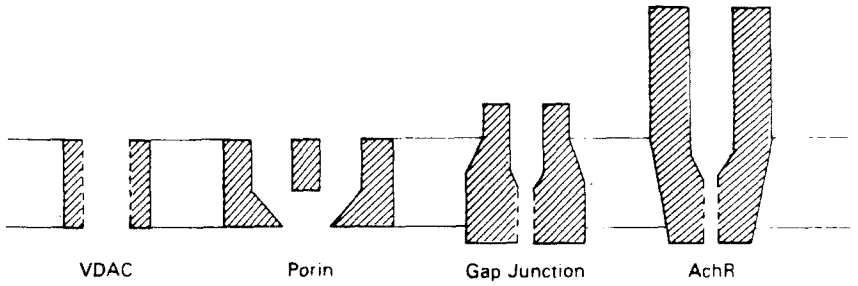

Fig. 1. Comparison of the shapes and sizes of four biological channels. VDAC, the mitochondrial outer membrane channel, is formed by one or two identical polypeptides, 30–35 kDa each. The bacterial porin triplet channel consists of three identical 36-kDa polypeptides. The gap junctional connexon is composed of six copies of a 28-kDa polypeptide. The acetylcholine receptor consists of five polypeptides in the range 50–58 kDa. Scale in this drawing is indicated by the separation of the horizonal lines representing the membrane bilayer, 5 nm.

structure is not complicated by ancillary functions such as establishing intercellular contacts or binding agonists. However, this is something of an oversimplification, since VDAC has been identified as the receptor for the enzyme hexokinase in mammalian cells (Fiek *et al.*, 1982; Linden *et al.*, 1982). As a model system, VDAC also appears to offer advantages over the bacterial porins, which are large passive diffusion channels that occur in outer envelopes of gram negative bacteria. While there are numerous types of porins (Nikaido *et al.*, 1980; Benz, 1985), they are generally less voltage-sensitive than VDAC. Also, porins may have a more complicated internal structure than VDAC (Fig. 1). Like VDAC, porins tend to form multiple channel complexes which in turn organize into periodic arrays on their respective membranes (Mannella *et al.*, 1983; Steven *et al.*, 1977). The channels in the bacterial arrays are triplets which curve toward each other in the membrane interior, appearing to fuse on the periplasmic side (Engel *et al.*, 1985). The channels in the mitochondrial arrays have individual lumens (Mannella *et al.*, 1984). VDAC is often referred to as mitochondrial porin, suggesting a possible evolutionary link with the bacterial proteins. However, in addition to the above-noted structural differences, there is no obvious homology between the sequence of yeast mitochondrial VDAC and available bacterial porin sequences (Mannella and Auger, 1986).

The following five papers summarize reports presented at a recent symposium[5] intended to review the status of our understanding of the functional

[5] The symposium, entitled "Biological Channels: Focus on the Outer Mitochondrial Membrane," was held November 14, 1986 and was sponsored by the Center for Biochemistry and Biophysics and the Department of Biological Sciences, State University of New York at Albany, by the Wadsworth Center for Laboratories and Research, New York State Department of Health, and by the General Electric Corporation.

and structural parameters of the mitochondrial channel, VDAC. These papers focus on the *in vitro* characteristics of VDAC, either in the mitochondrial outer member or after reconstitution into phospholipid bilayers. This research is setting the stage for experimentation to elucidate the molecular mechanisms of both the ion selectivity and voltage dependence of this biological channel. These reviews deal only cursorily with the issue of the physiological roles of VDAC, appreciation of which should increase as more is learned about the molecular basis for the functional properties of these channels.

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