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Voltage-dependent anion channels: Potential therapeutic targets for metabolic disorders and cardiovascular diseases

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Abstract

Voltage-dependent anion channels (VDACs) in the mitochondrial outer membrane constitute the main permeability pathway across the outer membrane. VDACs may not only facilitate but potentially regulate the movement of ATP between the cytosol and the mitochondrial spaces. Therefore, VDACs are ideally suited to controlling ATP flux through the mitochondrial outer membrane, and consequently other mitochondrial functions such as apoptosis. Because VDACs interact with kinases and the adenine nucleotide translocase in important mitochondrial structures such as special contact sites and megachannels, a regulatory role in mitochondrial energy metabolism has been suggested. In the past, a number of *in vitro* studies have led to the hypothesis that VDACs may be involved in the regulation of a number of mitochondrial function. However, extrapolation from the *in vitro* data to the role that VDACs may play in cell function remained without convincing answer. The generation of VDACs deficient mice filled some of the gap that exist between the data obtained from reconstituted system and the *in vivo* VDACs function(s). The present review summarizes recent reports with VDACs deficient mice that shed light on the physiological function of mouse VDAC1 and VDAC3 in a cellular and organismal context.

Key words: Mitochondrial outer membrane, porin, VDAC, mice, ADP, hexokinase, glucose tolerance, exercise.

I. Introduction

Voltage-dependent anion channels (VDACs) are pore forming proteins found in the mitochondrial outer membrane of all eukaryotes (Colombini, 1979). VDACs have been commonly referred to as the "mitochondrial porins" by analogy to the porins of the outer membrane of gram-negative bacterial (Benz, 1985). VDACs are slightly anion-selective at low voltage and switch to sub-states characterized by lower conductance at a voltage above 20 mV (Colombini, 1979; Roos *et al.*, 1982 and Benz, 1985). The sub-states of VDACs are cation selective (Ludwig et al., 1988). VDACs are the main pathway for small metabolites across the mitochondrial outer membrane and play a key role in regulating mitochondrial function (reviewed in Colombini, 1994 and Colombini *et al.*, 1996).

VDACs have been cloned and sequenced from several species including human (Blachly-Dyson *et al.*, 1993 and Ha et *al.*, 1993), mouse (Sampson *et al.*, 1996 a and b), rat (Bureau *et al.*, 1992 and Anflous *et al.*, 1998), bovine (Dermietzel et al., 1994), *Drosophila melanogaster* (Ryerse *et al*., 1997), *Saccharomyces cerevisiae* (Mihara and Sato, 1985) and wheat (Elkeles *et al*., 1995). In mammals, three *VDAC* isoforms have been characterized: VDAC1, VDAC2 and VDAC3. The three VDAC isoforms belong to a single gene family that arose by gene duplication and

divergence (Sampson *et al*., 1997). The human and mouse VDAC sequences share ~25% similarity with the Saccharomyces and Neurospora VDAC sequences. The human genes of VDAC1 and VDAC2 have been assigned to chromosomes 5q31 and 10Q22, respectively (Decker *et al*., 1999). The mouse genes of VADC1, VDAC2 and VDAC3 map to the proximal regions of chromosomes 11, 14 and 8, respectively (Sampson *et al*., 1996 a and b) and share synteny with the human genes.

The first mammalian VDAC gene character-ized was isolated from human B lymphocytes and corresponds to HVDAC1 (Thinnes *et al*., 1989). The mature protein of HVDAC1 is 282 amino acids and does not contain the initiator methionine. Subsequently, a 36 KDa polypeptide was isolated from mamma-lian brain (Bureau *et al*., 1992). Comparison of partial protein sequences to cDNA clones isolated from a rat hippocampal brain showed that this protein corresponds to VDAC2. In addition, a type-1 porin has been purified from the plasma membrane of bovine astrocytes and has been designed BR1-VDAC (Dermietzel *et al*., 1994). BR1-VDAC shows identity with HVDAC1 and, by polyacrylamide gel electrophoresis, displays an apparent molecular weight of 34 KDa. There is over 90% identity between the human type-1 porin sequence and partial sequences of bovine heart and rat kidney mitochondrial porins (Kayser *et al*., 1989). All known VDAC sequences have a common pattern of secondary structure motifs (Blachly-Dyson *et al*., 1989).

II. Function

1) Studies in reconstituted system

VDAC is a voltage-gated protein and, *in vitro,* the membrane potential is the primary factor in determining the different conductance states. When VDAC proteins are inserted into planar phospholipid membranes, incremental increases in membrane conductance, clustered at about 4.5 nS, can be recorded. VDACs are typically open at low voltages (~10 mV) and close to a lower-conducting or closed state when either positive or negative potentials are applied. The open state of VDACs is slightly selective for anions over cations (Cl^- over K^+ by a factor of 5 at 0.1 M salt concentrations (Colombini, 1989). The closed state generally favors cations (Colombini, 1980 and Benz *et al*., 1990).

Upon expression of mouse VDAC isoforms in yeast cells missing the major yeast VDAC gene (*por1*), isolated mitochondria exhibit large differences in their outer membrane permeability to NADH, depending on the mouse VDAC isoform expressed (Xu *et al*., 1999). Electro-physiological studies of purified proteins inserted into artificial bilayers also showed differences in channel properties. While VDAC1 displayed the prototypic version of VDAC activity that is conserved among other species, VDAC2 showed two conductance states, whereas VDAC3 was found not to gate well even at high membrane potential. These results indicate that the different mammalian isoforms may fulfill different cellular functions.

Under a variety of conditions, the mitochon-drial outer membrane has been shown to limit the rate of metabolite flux. In parallel, treatments that close VDACs greatly inhibit mitochondrial function by restricting the flux of adenines nucleotides into the mitochondrial intermembrane space (Colombini et al., 1987; Benz et al., 1988; Gellerich et al., 1989; Liu and Colombini, 1992 and Lee et al., 1994). It has been reported that pyridine dinucleotides regulate (decrease) the permeability of the mitochondrial outer membrane (Lee et al., 1994 and 1996). By using intact mitochondria from potato tubers, the authors demonstrated that β–NADH reduced the permea-bility of the outer membrane in a concentration dependent manner by a factor of 6. Although with less pronounced effect, NADPH exerts the same effect on the outer membrane. In a reconstituted system, both NADH and NADPH induce the closure of VDAC channels. The authors comment-ed that the results obtained in vitro may not reflect the situation in vivo. However, these observations suggest a new pathway for cross-talk between mitochondrial and

cytoplasmic energy production, and may explain an aspect of Crabtree effect (the respiratory inhibition after the addition of glucose or another hexose that is capable of being phosphorylated by hexokinase). In two separate reports, Rostovtseva and Colombini demonstrated that VDAC channels isolated from mitochondria of N. crassa and reconstituted into planar phosphor-lipid membranes mediate and gate the flow of ATP in their open state (1996 and 1997). Channel closure results in 50% reduction in ion conduct-ance and ATP flux is almost totally blocked. Hence, VDACs can regulate the movement of ATP between the cytosol and the mitochondrial spaces and therefore may participate in controlling ATP flux through the mitochondrial outer membrane.

2) Interaction with kinases

VDACs have been identified as the mitochondrial outer membrane binding sites for cytosolic kinases; e.g., glycerol kinase and hexokinase (Fiek et al., 1982 and Linden et al., 1982). The mitochondrial isoforms of creatine kinase (mi-CK) and adenylate kinase, located in the intermembrane space, have been also reported to interact with VDACs (Kottke et al., 1991 and Savabi, 1994). There is some evidence to suggest that this interaction occurs at the contact sites between the inner and outer mitochondrial membrane (Kottke et al., 1991 and Beutner et al., 1996). It is believed that this interaction facilitates access of kinases to ATP and overcomes the restriction that the mitochondrial outer membrane exerts on the permeability for the small metabo-lites (reviewed in Brdiczka and Wallimann, 1994). The functional coupling of mi-CK with VDACs to mitochondrial respiration has been extensively characterized by using the technique of selectively permeabilized skinned fibers prepared from the heart and the skeletal muscles (Veksler et al., 1987 and 1995; Saks et al., 1995 and Kay et al., 1997). This technique, unlike studies using isolated mitochondria, allows the study of the whole population of mitochondria within the muscle tissue and preserves their in vivo structure.

3) Apoptosis

Cell suicide is an everyday event in multi-cellular organisms and occurs by a process called apoptosis. It has been demonstrated that in rat brain the complex formed by hexokinase type 1, VDAC and ANT resemble the mitochondrial permeability transition pore (MPTP) (Beutner et al., 1996), a multi-component non-specific pore composed of VDAC, ANT and cyclophilin D likely involved in the processes of apoptosis and necrosis (reviewed in Bernardi 1999 and Halestrap et al., 2002). The MPTP opens in the inner mitochondrial membrane under conditions of elevated matrix Ca2+, especially when this is accompanied by oxidative stress and depleted adenine nucleotides. A connection between mitochondrial hexokinase localization and the anti-apoptotic action of the serine/threonine protein kinase B (Akt/PKB) has been found (Gottlob et al., 2001). It has been proposed that Akt/PKB exerts its anti-apoptotic action by preventing closure of a component of MPTP, VDAC. This further inhibits intracellular acidify-cation; mitochondrial hyperpolarization and the decline in oxidative phosphorylation that precedes cytochrome c release. By increasing the coupling of glucose metabolism to oxidative phosphory-lation via hexokinase:VDAC interaction, it has been speculated that this pathway may contribute to regulating MPTP opening.

III. VDACs deficient mice: A tool to study VDACs function(s)

Mice lacking the expression of VDAC1 and VDAC3 have been generated by gene targeting in embryonic stem cells (Sampson et al., 2001, Anflous et al., 2001 and Weeber et al., 2002). Double mutant mice (VDAC1/VDAC3) have been obtained by intercrossing VDAC1 and VDAC3 heterozygous mice. Although the VDAC1 and double mutant mice exhibit a partial in utero lethality and are growth retarded, the mice are viable and therefore offer the possibility to study the role of VDACs in cellular metabolism in intact organisms.

The functional coupling of mi-CK to

mitochon-drial respiration can be determined in the presence of creatine by measuring the mitochondrial sensitivity for MgADP-; i.e. the apparent Km for MgADP- (Km[ADP]). The Km[ADP] is high in skinned fibers in comparison to isolated mitochon-dria, reflecting the low permeability of the mitochondrial outer membrane for this metabolite in vivo. In the presence of creatine, the Km[ADP] shifts toward lower values. It is believed that in the presence of creatine, the mi-CK generates phos-phocreatine and ADP from newly synthesized ATP generated in the matrix. In this scenario, creatine enters mitochondria through VDAC, phospho-creatine is the high energy compound that leaves mitochondria through VDACs, while ADP is recycled back to the matrix via ANT to generate more ATP. Hence, this functional coupling increases the apparent concentration of ADP in the close proximity of ANT, which compensates for the low in vivo permeability of the mitochondrial outer membrane for ADP (Gellerich et al., 1989). By using VDACs deficient mice, it has been demonstrated that VDAC1 is involved in the exchange of ADP (the classical regulator of mitochondrial oxygen uptake) across the mitochon-drial outer membrane in the cardiac muscle and a glycolytic skeletal muscle, the gastrocnemius; however, VDAC3 controls ADP exchange in the cardiac muscle but not the gastrocnemius muscle (Anflous et al., 2001). It has also been demonstrated a partial respiratory chain defect in different muscle types from VDACs deficient mice.

Skeletal muscle is the principal site for glucose utilization during physiological condi-tions of energy demand such as during exercise, where glucose is metabolized by anaerobic glycolysis and aerobic oxidation to generate ATP. Skeletal muscle and fat are the primary target tissues for glucose utilization post-prandially, a regulatory mechanism controlled principally by insulin. By converting glucose to glucose 6-phosphate, hexokinase helps maintain the glucose concentration gradient that results in the movement of glucose into cells through the facilitative glucose transporters. During resting conditions, the transport step exerts the most control in regulating muscle glucose uptake, as GLUT1 or GLUT4 over-expression augments basal muscle glucose uptake (Hansen et al., 1995 and 2000; Marshall et al., 1993; Gulve et al., 1994; Ren et al., 1993 and Treadway et al., 1994). Hyperinsulinemia and exercise shift the control of muscle glucose uptake so that phosphorylation is a more important determinant of the rate of this process (Halseth et al., 1999 and Fueger et al., 2003 and 2004a and b). While the absence of VDAC1 leads to impaired glucose and insulin tolerance in mice, the additional absence of VDAC3 adds to the severity of the impairment and furthermore leads to exercise intolerance. It has been demonstrated that in vitro, hexokinase and VDAC form complexes (Brdiczka et al., 1994). By measuring mitochondria-bound hexokinase activity in different muscle types, we reported a significant decrease in VDACs deficient mice. Therefore, whereas muscle glucose uptake can be separated into three sequential steps: delivery of glucose from the blood to the muscle, transport across the sarcolemma and irreversible phosphorylation to glucose-6-phosphate; VDACs deficient mice point to the existence of an additional control step under conditions of high glucose flux; i.e., mitochondria-bound hexokinase activity.

VDAC1 deficient mice are insulin resistant yet there is reduced fatty acids oxidation in the heart despite a normal cardiac output (Anflous et al., 2003, Abstract). Therefore this mouse model constitutes a paradox in that the heart of diabetic patients uses preferentially fatty acids. So, this mouse model offers an original tool to dissect the mechanism(s) underlying this paradox, which will have benefit in designing strategies to bypass insulin resistance in Type-2 diabetes.

IV. Conclusion

VDACs represent a highly conserved multigene family mainly found in the outer membrane of mitochondria. The generation of mice lacking the expression of different VDAC isoforms has opened the door to new approaches

aimed at determining the physiological role of VDACs in cell function in their intact environment. Indeed, a growing body of evidence indicates that the mitochondrial outer membrane, rather than fulfilling only a structural role, plays a dynamic regulatory role in cell function. VDACs are at the interface between the cytosol and the intermembrane space and serve as a binding site for key metabolic enzymes. Using VDACs deficient mice will be very useful as a model for new strategies to screen for mitochondrial diseases and for the design of new therapeutic targets to bypass insulin resistance in Type-2 diabetes and dilated cardiomyopathies.

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