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Lack of voltage-dependent anion channel in human mitochondrial myopathies

SIR—In several hundreds of patients with a mitochondrial myopathy an enzyme defect in mitochondrial energy metabolism is identified. However, in a substantial number of subjects no enzyme defect can be detected, although diminished substrate oxidation and ATP production rates are found in their muscle *in vitro*. The hypothesis, that in this group of patients proteins for transport of various ions and substrates across mitochondrial membranes might be affected, led us to study these transport proteins more systematically. Among 40 investigated patients, 1 was found with a diminished content of the voltage-dependent anion channel (VDAC or human porin).

Figure: Immunoblots with VDAC and ANT antisera

Samples of muscle 600 g supernatants from patient (lanes 4) and 3 controls (lanes 3, 5, 6) were dissolved in sodium dodecylsulphate and loaded on polyacrylamide gels (10–15% gradient), together with biotinylated molecular weight markers (lanes 1: 39.8, 29.0, 20.1 kDa) and purified ANT (lanes 2: 29 kDa). All lanes of controls and patient contained 100 mU cytochrome c oxidase (the patient's muscle had normal cytochrome c oxidase activity). After electrophoresis (Phast System, Pharmacia-LKB, Woerden, Netherlands) proteins were electroblotted to nitrocellulose. Immunolabelling of the proteins was done with 4 different antibodies: human B-lymphocyte VDAC monoclonal antibodies from 2 different cell lines (mAb-No 4 in panel I and mAb-No 6 in panel II),¹ anti-bovine heart VDAC² (panel III), and anti-C-terminal bovine heart ANT³ (panel IV). Immunodetection was done applying the Biotin-ECL method (Amersham International, UK).

The patient was born at term from non-consanguineous parents. He had dysmorphism, hypotonia, respiration and feeding problems, and seizures. He was treated for hypothyroidism. Because of lactic acidosis a quadriceps muscle biopsy specimen was taken at the age of 2 years. Decreased rates of pyruvate and malate oxidation and of ATP production were found. The content of the membrane transport proteins VDAC and ATP/ADP translocator (ANT) were estimated immunochemically. The amount of VDAC protein (35 kDa, marked by -v- in figure) appeared to be clearly decreased, with use of monoclonal anti-N-terminal human VDAC (figure; panels I, II), and polyclonal anti-bovine-heart VDAC (panel III) antibodies. The ANT content (29 kDa, marked by -A-) appeared to be slightly reduced. The polyclonal antiserum also reacted with other supernatant proteins (panel III). In this panel the VDAC deficiency of the patient was additionally confirmed: apart from the VDAC protein the amounts of all proteins, including ANT, were similar to those in controls.

To our knowledge, this case is the first in which a lack of VDAC protein has been shown in human pathology. The detailed function of VDAC is still under investigation. VDAC is a pore-forming protein in the outer mitochondrial membrane, which at low transmembrane voltage is open for anions such as phosphate, chloride, and adenine nucleotides. At higher transmembrane voltage or in the presence of VDAC-modulating proteins VDAC can function as a selective channel for cations and uncharged molecules.⁴ These features make VDAC likely to play a regulatory role in mitochondrial energy metabolism.⁵ The lack of VDAC might cause a bottleneck in the outer membrane

of the patient's muscle mitochondria with respect to ADP and/or inorganic phosphate transport inwards, or ATP transport outwards, thereby disturbing energy metabolism.

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No aspirin in red wine

SIR—Muller and Fugelsang (June 4, p 1428) suggest that wine is a good source of salicylic acid and that this may explain a preventive effect in cardiovascular diseases. We measured salicylic and acetylsalicylic acid in red Bordeaux wines (Rineau 1993, Lavergne 1993, and Mondetour, 1992) with high-performance liquid chromatography and a highly specific fluorescence detection method. The method was validated by varying extraction conditions, mainly extraction solvents and extraction time. In red wine we found 0.7 mg salicylic acid per litre and no acetylsalicylic acid (detection limit 0.025 mg/L). Thus, by contrast with Muller and Fugelsang we found negligible amounts of (acetyl)salicylic acid in wine. Even if wine did contain larger amounts of salicylic acid this would not be expected to affect cardiovascular risk. Salicylic acid and dihydroxybenzoic acids do not affect thromboxane B₂ formation and platelet aggregation; this specifically requires acetylsalicylate (aspirin), which inactivates cyclo-oxygenase by irreversible acetylation.¹

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CORRECTION

Effect of simvastatin on coronary atheroma—In figure 1 of the article by MAAS investigators (3 Sept, p 633), the indicators for placebo and simvastatin were incorrect. Placebo is represented by open circles connected by solid lines and simvastatin by filled circles connected by interrupted lines.