Evidence implicating mitochondria as playing a crucial role in both necrotic and apoptotic cell death is rapidly accumulating. Mitochondria are essential in controlling specific apoptosis pathways (Green and Reed, 1998). Mitochondrial calcium uptake is required for glutamate excitotoxicity and there is a correlation between increases in mitochondrial calcium and increases in free radical generation, which are linked with cell death (Stout et al., 1998). The mitochondrial permeability transition pore may be crucial in both necrotic and apoptotic cell death. Activation of the permeability transition pore increases the mitochondrial membrane permeability to solids with a molecular mass of up to 1.5 kDa (Bernardi, 1999). It is activated by increases in calcium, and free radicals and cyclosporin A inhibits its activation. Cyclosporin A blocks neuronal damage produced by hypoglycaemia and ischaemia in vivo (Friberg et al., 1998).

A potential role of mitochondria in amyotrophic lateral sclerosis (ALS) is gaining increasing support. In this issue of *Brain*, Vielhaber and colleagues report further evidence implicating mitochondrial dysfunction in ALS (Vielhaber et al., 2000). The authors examined muscle biopsies of patients with ALS, compared with normal controls and as compared with patients with spinal muscular atrophy. Using saponin permeable muscle fibres, they detected abnormalities in NADPH autofluorescence imaging. The authors’ prior studies also showed abnormalities in complex I activity in the muscle biopsies of individuals with sporadic ALS compared with age-matched controls (Wiedemann et al., 1998). They also found that there were respiratory chain defects in individual fibres of 11 out of 17 patients with sporadic ALS. This correlated with the presence of cytochrome c oxidase negative muscle fibres on muscle histology. The authors quantified mitochondrial DNA by Southern blot and found diminished levels in 13 out of 17 patients and multiple deletions in one of the patients. Lastly, the authors found that there are decreased levels of membrane-associated mitochondrial manganese superoxide dismutase (SOD) in the ALS patients. Eight of the sporadic ALS patients had levels of the enzyme lower than the lowest value observed in the control group. It was suggested that the reduced levels of manganese SOD may contribute to mitochondrial damage and some of the observed mitochondrial abnormalities.

These findings are of considerable interest. They suggest that some sporadic ALS patients may have mitochondrial DNA damage that may contribute to disease pathogenesis. Nevertheless, the concern about the possibility that some of the alterations are related to denervation persists, despite the control group of spinal muscular atrophy patients. Further studies will therefore be needed to determine whether these results are in fact definitive.

There is substantial other evidence implicating mitochondrial dysfunction in sporadic ALS. There are mitochondrial abnormalities in liver biopsies from individuals with sporadic ALS (Masui et al., 1985; Nakano et al., 1987). Muscle biopsies of individuals with sporadic ALS also show increased mitochondrial volume and calcium levels within the mitochondria (Siklos et al., 1996). Peripheral blood lymphocytes from individuals with sporadic ALS show increased cytosolic calcium and impaired responses to inhibitors of oxidative phosphorylation (Curti et al., 1996). A recent study showed that there was reduced cytochrome oxidase activity in anterior horn motor neurons of patients with sporadic ALS, while succinate dehydrogenase activity, which is encoded by the nuclear genome, showed normal activity (Borthwick et al., 1999).

There is also evidence for mitochondrial DNA abnormalities, which may contribute to observed changes in electron transport activities. An out-of-frame mutation of mitochondrial DNA encoded subunit I of cytochrome c oxidase was reported in an individual with otherwise typical motor neuron disease (Comi et al., 1998). An interesting technique for attempting to determine whether mitochondrial DNA plays a role in producing electron transport activity defects is to utilize hybrid cell lines. These are produced by fusing a patient’s platelets into cell lines that are depleted of mitochondria. This then results in the mitochondria being present in a different nuclear context. If an electron transport defect is found, it implies that it is encoded on the mitochondrial genome. A study of ALS cybrids showed a significant decrease in complex I activity as well as trends toward reduced complex III and IV activities, and an increase in free radical scavenging enzyme activities (Swerdlov et al., 1998).

Another set of observations, suggesting that mitochondrial dysfunction may play a role in the pathogenesis of ALS are findings in transgenic mice which have point mutations in the enzyme copper–zinc SOD. These point mutations have been associated with autosomal dominant inherited familial ALS (Rosen et al., 1993). Neuropathological studies of transgenic mice with copper–zinc SOD mutations showed that mitochondrial vacuolization is an early pathological feature with at least two of the mutations (Dal Canto and Gurney, 1994; Wong et al., 1995). Mitochondrial
vacuolization precedes a rapid phase of motor weakness and loss of motor neurones in mice with the G93A copper–zinc SOD1 mutation (Kong and Xu, 1998). Furthermore, treatment of these mice with creatine, which may compensate for a bioenergetic defect, significantly improves survival, motor performance and delays loss of anterior horn motor neurones (Klivenyi et al., 1999).

The present study provides further evidence implicating mitochondrial dysfunction in the pathogenesis of ALS. Either inherited or acquired mitochondrial DNA mutations could play a role. Definitive evidence for this will have to wait further genetic studies which will be difficult due to the sporadic inheritance of most cases of ALS. Nevertheless, if mitochondrial defects were found to play a role in disease pathogenesis, this would have broad ranging implications for therapy. Further studies will therefore be of considerable interest in attempting to understand the pathogenesis of cell death in ALS.

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References


