LETTER TO THE EDITOR

Reply to ‘Mitochondrial changes in skeletal muscle in amyotrophic lateral sclerosis and other neurogenic atrophies—a comment’

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Based on new biochemical data, Vielhaber et al. (2005) made some comments on our recent findings on mitochondrial changes in skeletal muscle of patients with sporadic amyotrophic lateral sclerosis (ALS) (Krasnianski et al., 2005). However, the interpretation of the new data by Vielhaber et al. needs some critical discussion. There are three separate issues that have clearly to be differentiated: (i) mitochondrial dysfunction in the CNS in ALS, (ii) mitochondrial dysfunction in skeletal muscle in ALS and (iii) mitochondrial dysfunction in atrophic skeletal muscle due to other neurogenic diseases.

There is accumulating evidence for mitochondrial dysfunction in the CNS in ALS (Bowling et al., 1993; Fujita et al., 1996; Borthwick et al., 1999; Wiedemann et al., 2002). This issue, however, was neither the objective of our study nor of the studies by Vielhaber et al. (2000, 2003, 2005). In contrast to mitochondrial involvement in the CNS, the data on dysfunction of skeletal muscle mitochondria in ALS are controversial. For a long time it has been clearly established that chronic denervation can be associated with histological abnormalities such as core and target formations suggesting non-specific mitochondrial changes in denervated muscle (Dubowitz and Brooke, 1973). This implies that any investigation of mitochondrial dysfunction in the muscle of ALS patients has to be compared with appropriate diseased controls from denervation atrophies other than ALS. The muscle biopsies from two children with spinal muscular atrophy are most likely not ideal age-matched diseased controls for 40–66 year old ALS patients (Vielhaber et al., 2000). In contrast, our study including 23 similarly aged patients with other neurogenic atrophies clearly showed that the mitochondrial changes in skeletal muscle of patients with ALS are rather non-specific phenomena of denervation.

While Vielhaber et al. examined mainly vastus lateralis and rarely deltoid muscle, in our study biopsies were obtained from biceps brachii, deltoid, tibialis anterior and vastus lateralis muscles. Vielhaber et al. (2003) speculated that different muscles biopsied in their, and our, studies and ours might be a possible cause of discrepancies (Krasnianski et al., 2005). ALS is, however, a generalized motor neuron disease and not a ‘local ALS’ restricted to the vastus lateralis muscle. Since all muscle specimens investigated in our study revealed classical myopathological signs of neurogenic atrophy it is unlikely that severe mitochondrial changes might have been masked by the inclusion of unaffected normal muscle specimen.

Regarding the biochemical changes in ALS muscle Vielhaber et al. (2005) postulated contradictions between our study and their new findings. However, the discrepancies are quantitative rather than qualitative. The only contradiction is the interpretation of their data due to the lack of adequate controls (Vielhaber et al., 2000, 2003, 2005). It has to be emphasized that the so-called ‘mitochondrial dysfunction’ in ALS muscle postulated by Vielhaber et al. (2005) is based only on the finding of diminished activity of citrate synthase (CS) scaled complexes I and IV. Consistent with our study, no significant changes of complexes I and IV per gram wet weight could be detected in the ALS patients. Consistent with our data Vielhaber et al. found non-significantly increased CS activity per wet weight. However, if only CS activity rises in ALS muscle, then normalization of other enzyme activities for CS activity might produce statistically significant changes of undetermined implication. As a possible explanation for the discrepancies in mitochondrial enzyme activities Vielhaber et al. (2003, 2005) assume different disease durations in our patients in comparison to their
studies. Indeed, the recent data of Vielhaber et al. on early-stage ALS showed significantly decreased activities of complexes I and IV only when these were normalized for CS. Only CS-scaled activity of complex IV improved significantly in advanced ALS. CS-scaled complex I activity in advanced ALS was almost identical to that in the early-stage disease but was apparently no longer significantly different from normal. The authors provide no plausible explanation for this phenomenon. A respirometric study of skinned muscle fibres of ALS patients with disease duration similar to that in the patients of Vielhaber et al. (2003, 2005) showed the absence of large mitochondrial damage in ALS muscle suggesting that mitochondrial dysfunction in early-stage ALS is not systemic (Echaniz-Laguna et al., 2002). A possible explanation for the transiently reduced CS-scaled complex IV activity might be rather a compensatory adaptation during the time course of progressive denervation than a real ‘improvement’ of a primary, disease causing dysfunction. The hypothesis of Vielhaber et al. would have also required appropriate diseased controls with other neurogenic atrophies of different duration.

In contrast to our study showing only moderately diminished respiratory chain enzyme activities in ALS muscle in comparison to 21 patients with primary mitochondrial diseases, enzyme defects in ALS patients were more pronounced than in two diseased control patients harbouring the A3243G mutation of mtDNA (Vielhaber et al., 2005). It would be interesting to have further information on the serum lactate levels in these two patients, because this mutation is typically associated with the MELAS syndrome. It would be also interesting to know whether the postulated biochemical defects in ALS muscle lead to abnormal lactate as well.

Regarding the molecular data, Vielhaber et al. (2000, 2003) argue that the molecular analysis by the $^{32}$P-based system used in their studies is superior to the chemiluminescent system used in our study (Vielhaber et al., 2005). It is well known that the sensitivity of mtDNA quantification is strongly dependent on the sensitivity of the detection system. The sensitivity is much more influenced by background, than by the length of the fragments. We used the enhanced chemiluminescence system from Amersham that has very low background and high sensitivity. The sensitivity of the $^{32}$P-based system used by Vielhaber et al. is not superior to the chemiluminescent system used in our study (Kricka, 2001).

In summary, the new data presented by Vielhaber et al. do not significantly differ from our study but are only differently interpreted. The mild histochemical and biochemical mitochondrial changes in ALS muscle cannot be denied. However, comparison of the data with adequate diseased controls of sufficient numbers shows that the detected mitochondrial changes in ALS muscle are unspecific neurogenic phenomena, which are only mild in comparison with those found in primary mitochondrial diseases.

References


