Investigation of human mitochondrial myopathies by phosphorus magnetic resonance spectroscopy

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The investigation of human muscle disease by phosphorus (31P) magnetic resonance spectroscopy began in Oxford in 1981 (Ross et al., 1981). Since then we have investigated over 300 patients, many of them several times, with a variety of primary muscle disorders or systemic disorders that are reflected in muscle metabolism (for summaries, see Radda et al., 1984; Radda & Taylor, 1985). We developed a relatively simple protocol in which the energetics of the flexor digitum superficialis muscle is examined by placing the forearm of the subject inside a 1.9 T superconducting magnet of a Fourier transform n.m.r. spectrometer. Signals from phosphocreatine (PCr), ATP, Pi and hexose monophosphates are recorded with the aid of a carefully positioned surface-coil and intracellular pH is derived from the chemical shift of the Pi resonance. A patient examination takes between 30 and 45 min during which approx. 30 n.m.r. spectra are accumulated at rest, during a 7 min two-stage exercise period and during a 10 to 15 min recovery phase (Taylor et al., 1983).

We measure a set of characteristic parameters in normal individuals and can use these to characterize and quantify different types of abnormalities, several of which are associated with mitochondrial myopathies. We use the following 'normal' indices:

(i) At rest, intracellular pH and the relative concentrations of PCr, Pi and ATP are essentially invariant from normal individual to individual. From these values we calculate the concentration of free ADP assuming that creatine kinase is at equilibrium and obtain a low and relatively constant value for ADP concentration (6 ± 3 μM). The (phosphorylation potential)-1 (i.e. [ATP]/([ADP] x [Pi])) at rest is 2.8 ± 1.3 x 10^6 M^-1 in normal subjects (Arnold et al., 1985).

(ii) During aerobic, dynamic exercise there is a characteristic relationship between the decrease in Pi and intracellular pH (Taylor et al., 1983).

(iii) During recovery, the rate of PCR resynthesis has a t/2 of 52 ± 16 s and represents the rate of oxidative phosphorylation. The PCR resynthesis rate also reflects the rate of pH recovery (Arnold et al., 1984), the latter being relatively slow, and is likely to be a measure of H+ export from the muscle cell.

(iv) The decrease of ADP concentration to its resting level (within 2 min) is also characteristic.

We have studied 12 patients with evidence of mitochondrial myopathies in whom the clinical manifestations ranged from mild external ophthalmoplegia without symptoms or signs of limb weakness to severe generalized weakness and exercise intolerance (Arnold et al., 1985). At rest, an n.m.r. abnormality could be demonstrated in 11 of the 12 patients, 10 having evidence of a reduced muscle energy state with at least one of the following abnormalities: low phosphorylation potential, low [PCr], high [ADP] or high [Pi]. Two patients had abnormal resting muscle intracellular pH.

Evidence of impaired rephosphorylation of ADP to ATP during recovery from exercise was found in approximately half the patients. In three patients the rephosphorylation was affected severely enough to alter PCR resynthesis significantly (c.f. Radda et al., 1982). In these subjects ADP recovery was also slow. Additionally ADP recovery was slow in three patients whose PCR recovery times were within normal limits. These observations show that at the early stages of ATP resynthesis (represented by the decrease in [ADP]), the increased demand for oxidative phosphorylation puts a greater stress on mitochondrial function and therefore abnormalities are more readily detected.

An interesting observation was that although severe lactic acidosis (i.e. increase in blood lactate) was produced by exercise in most of our patients, the intracellular pH changes were not very significant and the rate of pH recovery where it could be measured was shown to be more rapid than in normal subjects. This suggests some adaptation of the acid-extrusion mechanism in order to remove rapidly the damagingly large amounts of intracellular lactate produced.

We finally mention that one of the patients examined also showed cerebral involvement, and 31P n.m.r. measurements on the brain of this patient also showed an elevated [Pi] and decreased phosphorylation potential (D. J. Hayes, D. Hilton-Jones, D. L. Arnold, J. Duncan & G. K. Radda, unpublished work).

31P n.m.r. in vivo thus appears to provide reasonable sensitivity and specificity in the diagnosis of human mitochondrial myopathies. This non-invasive technique has a role in defining the pathophysiology of these conditions and may prove useful in evaluating therapeutic interventions.

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Abbreviation used: PCr, phosphocreatine.