Muscle damage during exercise: possible role of free radicals and protective effect of vitamin E

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Damage to skeletal muscle during or following extensive or unaccustomed exercise is a well-recognized phenomenon. It is known to occur in healthy normal subjects and manifests itself as both morphological and biochemical changes indicative of damage. The manner in which the muscle is used appears to be particularly important in determining the extent of damage which may occur for a given work-load. Eccentric exercise appears to be particularly deleterious in this respect (Newham *et al.* 1983).

One of the means by which damage to tissues, including muscle, can be assessed is by monitoring the efflux of intracellular cytoplasmic enzymes. This feature has been widely utilized in examination of the mechanisms of breakdown in tissues such as the heart, but has only been sparsely utilized in the study of skeletal muscle damage. We have used this technique in the study of damage to skeletal muscle both in vitro (Jones *et al.* 1983) and in vivo (Jackson *et al.* 1983) and these investigations have provided considerable information on mechanisms by which muscle breakdown can occur in a variety of situations.

Interest in the possibility that oxygen-centred free radicals could be involved in the damage which occurs following exercise was prompted by the suggestion that the myopathy of vitamin E deficiency in animals was precipitated by unaccustomed exercise (Allen *et al.* 1975). Vitamin E is thought to exert its major effect in the body by detoxification of lipid-soluble free radicals (Tappel, 1962) and the inference was therefore drawn that free radical production may be increased by exercise (Brady *et al.* 1979). There is a large increase in O_2 utilization by mitochondria during exercise and Packer and co-workers have hypothesized that this may increase the oxidative stress to the tissues in exercising subjects (Davies *et al.* 1982; Quintanilha & Packer, 1983). Work examining this area has primarily concentrated in two areas: (1) to demonstrate an increased free radical activity in the muscle during exercise in animals and (2) to determine the effect of variations in body vitamin E status on the response to exercise.

Examination of free radical-reaction products in tissues during exercise

Demonstration of increased free radical activity in biological tissues is a relatively-difficult process since no single test is currently accepted as ideal for this purpose. Products of free radical-mediated lipid peroxidation are the most commonly assessed indices. In particular the malonaldehyde production and the release of volatile hydrocarbons have been extensively utilized for this purpose.

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Malonaldehyde is a product of free radical-mediated peroxidation of polyunsaturated fatty acids and Brady *et al.* (1979) have reported increased levels of this substance in muscles and the liver of exhaustively exercised rats. Other workers have studied the release of hydrocarbons (such as pentane) as an index of lipid peroxidation during exercise and have found this to be increased in both animals (Gee & Tappel, 1981) and man (Dillard *et al.* 1978); however, neither of these groups appears to have considered the effect of increased blood flow to tissues on hydrocarbon excretion. Tissues such as muscle are relatively poorly perfused at rest and it may be that increased efflux of hydrocarbons occurs, not because of increased lipid peroxidation, but because of a wash-out effect from tissues with the increasing blood flow (Snider *et al.* 1986).

Our studies of damage to skeletal muscle in vitro induced by excess contractile activity and other stresses have revealed a transient rise in muscle malonaldehyde content following damage to muscle induced by excessive contractile activity (Jackson & Edwards, 1987), but similar changes were not seen in vivo (Jackson *et al.* 1983).

An alternative way to directly detect free radicals in muscle tissue is by the use of physical techniques. Electron-spin-resonance spectrometry (ESR) is such a technique and is widely used to examine free radical species in chemical systems, but has been relatively sparsely used in biological material. Davies *et al.* (1982) have studied the effect of exercise on ESR signals from skeletal muscle and have claimed that an increase in an ESR signal of g value 2·004 occurs following exercise to exhaustion. We have used similar techniques to examine the effect of excess contractile activity on the ESR signal from muscle in vivo (Jackson *et al.* 1985*a*) and have found that the stimulation protocol used resulted in a 70±20% increase in the amplitude of the major ESR signal, and also induced significant damage to muscle as demonstrated by an increase in the plasma creatine kinase (*EC* 2.7.3.2) activity.

The major problem surrounding this work is whether the reported increases in free radical activity are primary or secondary to the damage. Halliwell & Gutteridge (1984) have suggested that in many circumstances lipid peroxidation may be a consequence of the tissue damage rather than its cause and this is obviously an area which requires further work.

Effect of vitamin E on exercise-induced damage

In animals it appears that vitamin E deficiency myopathy may be precipitated by exercise (Allen *et al.* 1975) and other workers have demonstrated that vitamin-E-deficient animals have substantially reduced exercise endurance (Quintanilha & Packer, 1983). In addition we have studied the effect of subclinical vitamin E deficiency on the response of animal muscle to damaging contractile activity (Jackson *et al.* 1983). Studies both in vitro and in vivo have demonstrated that a low muscle vitamin E content potentiates the damage to skeletal muscle which occurs for a given stress. Addition of excess vitamin E to the medium surrounding isolated normal muscle did not modify the response to a damaging stimulation.

It therefore seems likely that vitamin E is an essential component in the mechanisms which muscle has to prevent exercise-induced damage and that vitamin E deficiency predisposes the muscle to this form of degeneration. However, there is no evidence at the present time that supplementation of animals or humans with normal vitamin E status, has any further protective effect.

Conclusions

It seems clear that vitamin E deficiency exacerbates exercise-induced damage to skeletal muscle, but although there is some evidence for an association between exercise-induced damage and increased free radical activity the actual role of these substances in the pathogenic mechanism remains unclear. Alternative hypotheses implicating calcium-dependent degenerative processes in the mechanism of damage have also been proposed (Jones *et al.* 1984; Jackson *et al.* 1984) and it may be that these have some relation to the free radical-mediated processes described here (Jackson *et al.* 1985*b*).

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