Muscle damage revisited: does tamoxifen protect by membrane stabilisation or radical scavenging, rather than via the E2-receptor?

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Oestradiol (E2) protects skeletal muscle of male and female rats after exercise as evidenced by a lower release of a muscle enzyme, creatine kinase (CK) [1] and its isoenzymes MM and BB [2], and less morphological damage, assessed 48 h after exercise on cryosections [3]. This protective effect could be reproduced when muscles of animals, that had been treated with E2 before an experiment, were taken out and made to contract in an organ bath. The efflux of CK was measured every 30 min during 4 hours after the electrically-stimulated contractions to monitor muscle damage [4]. Tamoxifen, a partial E2 agonist, mimicked this protection when muscles of animals treated with tamoxifen were studied in the in vitro set up [5].

In explaining these phenomena a direct interaction of E2 or tamoxifen with membranes was considered, but dropped, due to lack of evidence and the obvious hormonal effects [1,5].

During exercise skeletal muscle may increase its O2 consumption 100-200 times. It is, thus, reasonable to assume that free radical mediated processes, such as lipid peroxidation, play an important role in the etiology of exercise-induced muscle damage. Indeed, the production of radicals is enhanced during exercise [6], and experiments rats have shown that rats, fed a vitamin-E-deficient diet for 6 weeks, showed more morphological signs of muscle damage than controls [3]. CK-efflux was also significantly higher than in controls. Interestingly, male rats showed much more tissue damage and a much higher CK-efflux than females, who only displayed minor signs of damage. Taken together, these experiments led us to conclude that female rats enjoy extra protection, also during vitamin-E-deficiency, from circulating E2. Others have also found that the vitamin E status in females, in contrast to that of males, does not affect training and exercise outcome [7].

E2 is a potent scavenger, and tamoxifen has been shown to have membrane-stabilising and anti-oxidant properties [8]. Our observations and those of others support the view that the protective effect of E2 and tamoxifen is not receptor-mediated, but due to an interaction with free radicals that are formed during exercise. We therefore now propose that musculoprotection is mediated by direct effects of oestrogen and tamoxifen on the membrane, leading to increased anti-oxidant defense.

The CK activity in serum before (bef) and after 2 hours treadmill exercise (aft), in units per liter (y-axis, UI). Total height of the bars represents total CK-activity, which consists of CK-MM (single hatched) and CK-BB (double hatched) activity. The results are given for male controls and vitamin-E-deficient animals, and for vitamin-E-deficient females (data from ref [3]). It can be seen that the increase in total CK-activity after exercise is caused mainly by an increase in the muscle enzyme CK-MM, indicating muscle damage.