Estrogen and HRT promote a proanabolic skeletal muscle environment in older women

Peter M. Tiidus
Department of Kinesiology and Physical Education and Faculty of Science, Wilfrid Laurier University, Waterloo, Ontario, Canada

The paper by Dieli-Conwright et al., entitled “Influence of hormone replacement therapy on eccentric exercise induced myogenic gene expression in postmenopausal women” (1), in this issue of the Journal of Applied Physiology adds to a growing list of recent studies and reviews that have found positive effects of estrogen and hormone replacement therapy on skeletal muscle. The primary significance of this paper is that it begins to elucidate some of the mechanisms by which estrogen is able to exert an anabolic influence of skeletal muscle of older women.

The ability of estrogen and hormone replacement therapy (HRT) to maintain or augment muscle mass and strength in aging females has been controversial, with previous studies both supporting and opposing findings of positive effects. Recently, a number of well-controlled studies have added their support to the findings for estrogen and HRT to limit muscle mass loss and sarcopenia and to augment muscle power and functional abilities, particularly in early post-menopausal women (10, 12). Because of the robust nature of the design and findings of Ronkainen et al. (10), it has been suggested that their findings now tip the balance of evidence in favor of a positive influence of HRT on skeletal muscle mass and strength retention in older women (9). In addition, a recent meta-analysis of 23 studies concluded that HRT alone without any addition of exercise could result in ~5% greater strength in postmenopausal females relative to age-matched controls not on HRT (6). If age-related lean body mass loss can be prevented or delayed in aging female populations and strength and muscle function maintained, this can have significant potential benefits in delaying functional decline, in preserving independent living and quality of life in this population, and in reducing their dependence on health care-related interventions.

Despite the growing evidence for positive benefits of HRT, the mechanisms by which it can influence skeletal muscle mass and strength remain elusive. Numerous studies, including Dieli-Cortwright et al. (1), have suggested that estrogen is the hormone primarily responsible for positive effects on skeletal muscle with little evidence for significant progesterone influence (5, 7). With the use of animal models, some studies have suggested that estrogen might influence muscle force by modification and direct influence on the myosin molecule (8). Others have provided evidence that estrogen can augment satellite cell activation (4) and limit exercise-induced muscle damage, leukocyte infiltration, and inflammation in animal and human models (2, 7).

The Dieli-Conwright study is the first to demonstrate that HRT can create a positive anabolic signaling environment in skeletal muscle and more importantly to demonstrate this in a human population (1). They do this by reporting positive effects of HRT on expression of mRNA from genes that control myogenic growth and differentiation, such as MyoD, MRF4, Myf5, and myogenin and suppression of expression of mRNA from proteolytic genes such as MuRF-1 and FOXO3. In addition, they demonstrate a robust negative effect of HRT on myostatin (a negative regulator of myogenesis) and the opposite effect on mRNA expression for follistatin, a primary negative regulator of myostatin activity. It is of particular interest that these effects appear to be chronically present when muscle from sedentary postmenopausal women with HRT are compared with muscle from those without HRT. Furthermore, the anabolic mRNA profiles are much more robustly evident at 4 h after a bout of eccentric exercise in the HRT groups relative to controls (1). These findings strongly suggest that an important means by which HRT will induce a positive effect on muscle recovery after damaging exercise is by exerting control over myogenic and proteolytic regulatory gene expression. By demonstrating the presence of a potentially more anabolically favorable environment in muscles of even sedentary women taking HRT, this study supports and provides a physiological mechanism for previous studies that have reported benefits of HRT on lean body mass and maintenance of skeletal muscle size in older female populations (1). In addition, by demonstrating a very robust response in upregulation of mRNA expression of myogenic regulators and a corresponding down-regulation of proteolytic gene mRNAs, the Dieli-Conwright et al. (1) study suggests that estrogen may enhance postdamage repair in skeletal muscle. These results, although intriguing, do not yet identify a specific signaling pathway or pathways for the expression of these and possibly other estrogen effects on anabolically related events in skeletal muscle after damaging exercise.

Because both estrogen receptors α and β have recently been found in male and female skeletal muscle (14) and because the estrogen receptor coregulator gene expression is also influenced by estrogen in human muscle cells (3), it seems likely that at least some of the effects of HRT may be receptor mediated. Indeed, estrogen receptors have been demonstrated to mediate the enhanced protective and regenerative effects of estrogen on postischemic brain cells (11) as well as enhanced muscle satellite cell activation and proliferation after eccentric exercise (4). What remain to be determined are the downstream signaling factors and cascades that are involved in connecting estrogen receptor binding and activation with the altered gene expression demonstrated in skeletal muscle. Estrogen receptor signaling is complex and can involve a number of cascades and second messengers with receptors interacting with each other, acting from both the membrane and cytosolic locations and...
possibly being activated by factors other than estrogen in various target tissues (13).

A further potentially intriguing question arising from the Dieli-Cortwright study (1) stems from the relatively wide age span (55–65 years) of the participants and inclusion criteria that required only 3 months of continuous HRT before the start of the study. Although the authors do not comment on this, it seems possible that some of the subjects were several years postmenopausal, prior to their initiation of HRT. Brain studies in rodents have indicated a loss of the neuroprotective and anti-inflammatory effects of HRT if it is not initiated soon after menopause (11). Similarly, it is possible that HRT may no longer be as effective in humans if it is initiated several years postmenopause (11). However, all subjects involved in this study, despite age and possible delays in initiation of HRT, appeared to exhibit similarly robust responses in myogenic gene expression following eccentric exercise. More controlled studies will be needed to determine whether indeed the potential of HRT to influence postexercise myogenic gene expression, inflammation, damage, or regenerative potential in skeletal muscle would be hampered by a delay in postmenopausal initiation of HRT in human females.

The Dieli-Cortwright et al. study (1) provides significant new insights into the potential for HRT to greatly enhance anabolic myogenic signaling gene expression in skeletal muscle and thus enhances our understanding of possible mechanisms for HRT effects in augmenting skeletal muscle repair and retention of muscle mass in older women. Nevertheless, many more questions remain to be answered before we can begin to more completely understand the complex mechanisms of HRT influence on skeletal muscle strength and muscle mass preservation in postmenopausal females.

REFERENCES


