ACE INHIBITION AND ANGIOTENSIN RECEPTOR BLOCKER TREATMENT ON SKELETAL MUSCLE FAT CONTENT IN AGED RATS

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Introduction

Age-related changes in body composition (increased fat mass, decreased lean mass), muscle energy expenditure and physiology, may contribute to declining physical performance and ultimately disability. It is unclear whether these pathophysiological changes precede the development of or are a consequence of declining function and whether preventing these changes will also prevent the progression of disability. Therefore it is necessary to develop longitudinal methodologies for assessing "real time" in vivo determinations of the pathophysiological changes and the effect of potential interventions. We are currently funded (NIA 1 R01 AG024526-01A1) to assess the long-term effects of an angiotensin converting enzyme (ACE) inhibitor, enalapril, and antgiotensin receptor blocker (ARB), losartan, on physical performance, muscle quality and body composition in aged rats. Studies in hypertensives and obese rat models of these conditions show that both ACEi and ARB treatment results in weight loss and improvements in insulin sensitivity (1-3; for some examples). Our central hypothesis revolves around the idea that age-related "insulin resistance" contributes to the disregulation of metabolic functioning of skeletal muscle tissue and may contribute to declining performance. While the loss of muscle mass per se with aging does not seem to result in glucose intolerance, the increased fat content within skeletal muscle could play a role in the development of insulin resistance and have profound effects on muscle quality (4).

Experimental

In conjunction with the ARMIS, we propose to collect preliminary data on a group of aged rats who have received enalapril or losartan, or vehicle control for a period of 6 months (24 to 30 months of age). Our previous studies have demonstrated that rats of this age and within this timeframe show attenuation of age-related physical decline, which is accompanied by an overall loss in fat mass as measured using dual X-ray absorptiometry. Using MR technology (4.7T) we should be able to develop more refined measurements of determining longitudinal changes in quality of skeletal muscle, specifically changes in fat content of skeletal muscle and relate these changes to declining performance. We propose to measure three animals per group, for a total of 9 animals, at three time points (24 months—pre drug; 27 months—when performance begins to decline in older animals; and 30 months—where a majority of animals begin to decline). We will assess fat content in eld and soleus muscle using standard SE images w/without water suppression, followed by a localised voxel (STEAM).

Results and Discussion

This study is scheduled to begin in December 2005.

Conclusions

This application represents a first step in describing longitudinal changes in the age-related pathophysiolgy of skeletal muscle and the onset of declining physical performance, as well as the role of long-term ACEi and ARB treatment in reversing these changes. In the long- term, evaluating the therapeutic effects of long-term ACE inhibition and ARB treatment on changed metabolism in adipose tissue and skeletal muscle as well as changes in body composition and physical function in rodents will influence ongoing randomized clinical trials in humans and help elucidate the biological mechanisms by which the changes occur. The results from this study will be used as preliminary data for a larger NIH funded study to assess the effects of a variety of pharmacological and behavioral interventions on declining performance and muscle quality. We plan to include aims that are specifically focused on imaging and that will support and enhance studies that are currently conducted at the AMRIS.

References

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