Is Aging Modulated By Angiotensin1-7?
Systemic Administration of Angiotensin1-7 Induces Metabolic, Endocrine and Musculoskeletal "Rejuvenation" In Old Female Mice: Interaction with long-term Endurance Exercise

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Background: As aging progresses, loss of skeletal muscle, bone mass and the appearance of decelerated metabolism predominate, resulting in declining health and gradual incapacitation. We have previously reported that angiotensin1-7 (Ang1-7) favorably affects the metabolic profile in the fructose-induced dysglycemic/dyslipidemic/obesity model in the rat, owing, in part, to antioxidant effects such as down regulation of NOX-4. Exercise seems as a reasonable additional intervention as it exerts positive effects on most aspects of aging. Here we tested the separate effects of chronic (3 months) endurance training via treadmill exercise (6 days/week, 20 minutes/day) alone, continuous Ang1-7 infusion alone (0.576mcg/k/d) or their combined effect in aged female mice (age~17 months). First, **exercise** *per se* exerted beneficial effects on all studied parameters, including enhanced total bone density & content (determined by Dual energy X-ray absorptiometry-DEXA), increased locomotor distance and speed and restoration of serum glucose and triglycerides to the range seen in younger mice. Second, the **combination of exercise and Ang1-7** resulted in significant elevation in estradiol levels as well as further increase in bone mineral density and content as compared to exercise alone. Third, not only were these beneficial effects of **Ang1-7 alone** not evident when supplemented to sedentary mice, but Ang1-7 rather induced a significant reduction in the distance and speed of locomotion, increased behavioral signs of anxiety, reduced glucose sensitivity and induced the accumulation of fat inside the gastrocnemius muscle. The present results support our previous studies about the beneficial effects of endurance exercise in old age and point to an additive effect of Ang1-7 in exercising–but not sedentary mice. In elderly female mice, the key additive effect of Ang1-7 appears to reside in the induction of increased estradiol secretion despite old age, which, in turn, enhances bone quality. Central and or peripheral effects of Ang1-7 and /or estradiol likely also potentiate locomotor activity. In contrast, Ang1-7 treatment to sedentary mice is potentially harmful through deleterious effects on skeletal muscle resulting in enhanced intramuscular fat accumulation, reduced locomotor distance and speed. By alternate regulation of the renin-angiotension system, formerly unknown metabolic and endocrine effects may be set to motion to affect not only cardiovascular disease and basic components of the metabolic syndrome such as reduced locomotor activity, but also key elements of the aging process itself.