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Perspective Article

Selective androgen receptor modulators – Prospects for emerging therapy in osteoporosis?

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Significant medical need exists for new therapy that will increase bone strength beyond what is achieved with anti-catabolic bone agents such as bisphosphonates. PTH has shown its ability to increase cancellous bone mass and has a positive impact in reducing the incidence of vertebral fractures. However, its high cost and mode of administration marginalize its widespread usage across the world. An orally delivered drug that would restore bone mass and strength of the skeleton to prevent vertebral and non-vertebral fractures would have significant benefit to large numbers of people at elevated risk of suffering a debilitating skeletal fracture.

Androgens have long been suggested to have anabolic effects on the skeleton. It is clear that androgens contribute to significant bone gain during adolescence in boys and in hypogonadal adult males. However, it has not been proven that androgens can increase bone mass in adults who are androgen replete or in elderly males with age-related reductions in androgens.

Significant progress has been achieved in our understanding how nuclear receptors act as transactivation factors in gene expression and of how these effects are translated at the tissue level. Selective estrogen receptor modulators including raloxifene have been approved for the prevention and treatment of osteoporosis. Other more efficacious SERMs are in development and should offer therapeutic advantages over current SERMs including tamoxifen and raloxifene. Knowledge and understanding of drug discovery efforts acquired in the discovery of SERMs could transfer to other nuclear receptors to identify selective receptor modulators including androgen, termed selective androgen receptor modulators (SARMs). We sought to identify selective androgen receptor modulators to test the hypothesis that a SARM could have beneficial effects on the skeleton and be devoid of the adverse side effects of testosterone administration including prostate hypertrophy and HDL reduction.

Highly selective androgen receptor modulators were identified. These agents selectively bound with high affinity to the androgen receptor comparable to testosterone. Further these SARMs acted as agonists in AR-dependent cell proliferation assays. *In vivo* assays suggest that SARMs were identified that showed the ability to significantly increase the weight of the levator ani muscle, while having minimal effects on the prostate weight. This suggested that the ability to obtain tissue selective action with androgen receptor agonists, a first step in identifying SARMs. Additionally, compounds showed the ability to prevent the loss of muscle mass in a model of casting immobilization. Finally, SARMs were tested in orchidectomized and aged male rats to evaluate their effects on bone parameters. SARMs were shown to increase periosteal apposition and decrease endocortical and trabecular bone turnover. These effects suggest that SARMs produce increased bone mass by improving cortical bone and preventing loss of cancellous bone. Together, these apparent opposite activities on different bone surfaces may have positive long-term consequences in the treatment of osteoporosis.

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