ISSN: 2694-1724
DOI: 10.33552/ARAR.2022.02.000540
Archives of Rheumatology & Arthritis Research
Iris Publishers

Mini Review

Selective Androgen Receptor Modulators (SARMs)

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Received Date: November 12, 2022

Published Date: November 30, 2022

Abstract

Selective androgen receptor modulators (SARMs) bind to androgen receptors differently depending on their chemical structure. As a result, SARMs promote anabolic cellular activity while avoiding many of the negative side effects associated with currently available anabolic steroids. SARMs have been studied for the treatment of breast cancer and cachexia, as well as for performance enhancement. The androgen receptor (AR) belongs to the nuclear receptor superfamily of steroid hormones, and binding of its endogenous ligands modulates its function as a transcription factor. The effects of the AR-androgen interaction are complex and vary depending on sex, age, tissue type, and hormonal status.

Introduction

SARMs are a family of medications that have the same anabolic qualities as traditional anabolic steroids (testosterone, stanozolol, nandrolone, etc.) but with far lower androgenic effects. These drugs first appeared in the doping field in the early 2000s. The most common agents in this class are ligandrol, ostarine, RAD-140, and andarine. According to the World Anti-Doping Agency (WADA) prohibited list, SARMs are illegal at all times (in and out of competition) and are included under section S1.2 (other anabolic agents), which also includes clenbuterol. The compilation of WADA testing numbers reports from 2015 to 2019 revealed a consistent increase in adverse analytical results (AAF) related to SARMs, notably ostarine and ligandrol.

Basic laboratory tests were conducted in order to evaluate and optimize the pharmacodynamic and pharmacokinetic features of SARMs based on their target site of action. SARMs have been chemically designed to target AR function more specifically in certain tissues while limiting off-target effects. There is little variety in AR structure, but the regulatory environment of each tissue permits SARMs to be tissue specific. SARMs' impact on skeletal muscle in both eugonadal and hypogonadal rats has been studied using animal models. Animal models of muscular dystrophy have been utilized to study the efficacy of SARMs in muscle pathology, with promising results. SARMs have also been tested in rats as reversible hormonal contraceptives. While preliminary study, researchers have looked into the usage of SARMs in Alzheimer's disease, Prostate cancer, BPH, and osteoporosis. SARMs are being researched in the pre-clinical and clinical stages as potential treatments for cancer-related cachexia, breast cancer, benign prostatic hyperplasia, and hypogonadism. Several Phase 1 or Phase 2 clinical trials are now underway to investigate the usage of SARMs.

Osteoporosis is a prevalent illness in which bone mass decreases and qualitative skeletal alterations increase the risk of fracture. Selective androgen receptor modulators (SARMs) are tissue-specific agonists that function as partial or weak AR agonists in androgenic tissues but primarily as full AR agonists in synthetic metabolic tissues. Many scaffolds of SARMs have been discovered

in the last 20 years, with numerous compounds showing promise and undergoing clinical trial review. However, finding SARMs with high activity and low side effects remains difficult. Watanabe et al. studied BA321, a new SARM that binds to both AR and estrogen receptors (ER) without causing androgenic effects and can totally repair bone loss in orchiectomized mice.

Prostate Cancer

SARMs may potentially be useful in treating prostate cancer. Pekka et al. recently published mouse data demonstrating that FL442, a new SARM, reached high tissue concentrations in the prostate and acted as an AR antagonist in prostate cancer (PCa) cell models with efficacy comparable to enzalutamide, an antiandrogen used in the treatment of castration resistant PCa [1-8].

Alzheimer's

Men who are hypogonadal show lower levels of episodic memory, working memory, processing speed, visual spatial processing, and executive function. These activities are partially governed by brain areas affected by the AR. Moffat et al. conducted a sub-analysis of the Baltimore Longitudinal Study of Aging with 407 men without dementia who were followed for an average of 9.7 years.

SARMs have the potential to play a role in the treatment of cognitive diseases such as Alzheimer's disease. Androgen deficiency is regarded as a substantial risk factor for Alzheimer's disease and circulating testosterone levels are negatively associated to Amyloid β(Aβ) levels in the brains of elderly men. Androgens inhibit Aβ buildup via increasing the expression of neprilysin, which destroys amyloid. Akita et al. have revealed that NEP28, a new SARM, boosts neprilysin activity while also having systemic anabolic effects with lower androgenic effects.

NEP28 is a novel SARM with strong androgen receptor selectivity. Researchers evaluated the effects of NEP28 on muscle, prostate, and brain in mice that had been androgen depleted by orchidectomy and then administered with placebo, NEP28, dihydrotestosterone, or methyltestosterone. They revealed that NEP28 had tissue-selective effects comparable to or greater than current SARMs. Furthermore, NEP28 treatment boosted the activity of neprilysin, a recognized A-degrading enzyme. These findings suggest that SARM is effective in treating not just osteoporosis and sarcopenia, but also Alzheimer's disease [9-11].

In 2015, Hikichi et al. investigated an experimental SARM, TSAA-291, to assist clarify the mechanics of tissue specificity. The researchers examined dihydrotestosterone (DHT) and TSAA-291 using reporter assays, a method for determining the extent to which a transcription factor activates target genes.

While essentially comparable gene responses were seen in skeletal muscle cells utilizing reporter assays, TSAA-19 agonist activity in prostate cells was about half that of DHT. Thus, despite binding to ARs in the same tissues, TSAA-291 elicited a distinct cellular response in the prostate than DHT. This phenomenon was explained in part by the discovery that TSAA-291 caused varied cofactor recruitment in the prostate and consequently different downstream effects.

This finding implies that conformational changes in ligand-AR complexes are at least partially responsible for the distinct cellular responses. This is corroborated by the findings of Unwalla et al., who revealed that modest changes in SARM conformation can have a significant influence on activity.

Conclusion

The AR is a sophisticated signaling mechanism that influences tissue formation, growth, and maintenance. While steroid hormones have important therapeutic applications, the broad activation of AR receptors causes treatment-limiting adverse effects. SARMs, like SERMs before them, have the potential to change the treatment of many debilitating illnesses due to their tissue selectivity.

SARMs offer a wide range of potential therapeutic uses, including the treatment of cachexia, BPH, hypogonadism, breast cancer, and prostate cancer, but given their new modes of action and potential to treat and complement illnesses with a lack of effective medications or therapies with intolerable side effects, more research and development of these drugs is required [4,7,8].

Acknowledgement

None.

Conflict of Interests

None.

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