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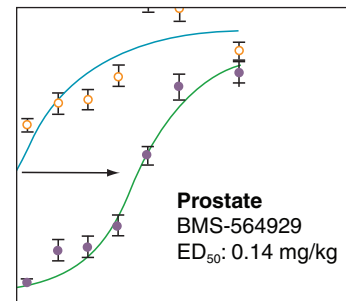
pharmacological perspectives from biology, chemistry and genomics

VIEWPOINTS

10 Androgen Receptors and Tissue-Selective Modulation: Putting 5 α -Reductase in SARMs Way, Or Is That The Other Way Around?

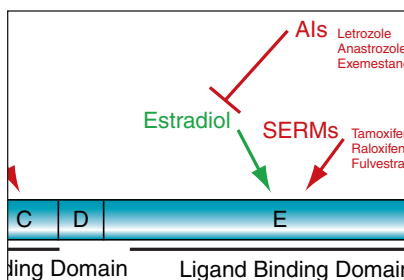
Selective Androgen Receptor Modulators (SARMs) are a novel class of AR ligands that possess tissue-selective pharmacological activities. SARMs of various chemical structures have been discovered and characterized, and lead compounds with much improved specificity for AR, in vivo pharmacokinetic profiles, and higher degree of tissue selectivity have entered clinical development, and are expected to dramatically expand the clinical applications of androgens. With the rapid progress in SARM discovery and increasing demand for mechanism-based drug design, more and more research efforts have been devoted to the mechanisms of action of the observed tissue selectivity of SARMs. There is increasing enthusiasm in adapting the molecular mechanisms of action from SERM research to the SARM field; however, is the SARM story really so complicated? The tissue-specific expression of 5 α -reductase might provide a simple explanation for this puzzle.

Wenqing Gao and James T. Dalton



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Is 5 α -reductase the key?

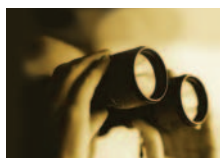
13 Breaking Tamoxifen Resistance In Breast Cancer: Zinc-Finger Targeting Or Aromatase Inhibition?



page 13
Aromatase therapy

Tamoxifen is one of the most successful and widely used chemopreventive agents ever, and is an effective therapeutic agent for inhibiting growth of hormone receptor positive breast cancers. Tamoxifen and some of its metabolites bind to estrogen receptors and allow subsequent DNA binding at estrogen responsive genes, blocking some estrogenic signals while maintaining others, depending on the tissue. When used therapeutically for up to five years, cases of tamoxifen resistance appear, requiring alternative therapies. One recent proposal uniquely targets a zinc finger of the DNA binding domain of estrogen receptors, rather than the ligand binding domain, to circumvent resistance. In light of the most recent clinical data, however, it is now clear that aromatase inhibitors are the preferred first line therapy for all stages of breast cancer in post-menopausal women, whether they have had previous tamoxifen exposure or resistance.

Mark Nichols



REVIEWS

17 GPCRs over Time: Mammoth Findings

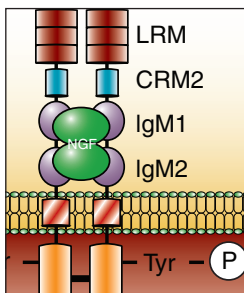
The common seven-transmembrane-domain (TMD) architecture of G protein-coupled receptors (GPCRs) has been preserved over a vast period of time, and highly conserved amino acid motifs and residues have evolved to establish ligand and signal transduction specificities. Because the structure of only a single GPCR has been successfully described at high resolution (i.e., bovine rhodopsin), sequence comparisons among species have been sought as an alternative source of structure-function information about GPCRs. The mining of evolutionary data from sequenced genomes and targeted retrieved orthologs has proven helpful for understanding the physiological relevance of individual GPCRs and for interpreting the clinical significance of GPCR mutations in structural terms. Sequence analysis of GPCR pseudogenes, which are considered as genomic traces of past functions, as well as recent success in sequence analysis of GPCR genes from extinct species, provide further information. This review discusses recent advances and approaches aimed at developing a better understanding of GPCR biology based on evolutionary data.

Holger Römpler, Claudia Stäubert, Doreen Thor, Angela Schulz, Michael Hofreiter, and Torsten Schöneberg

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GPCR genealogy

26 Nerve Growth Factor in Inflammation and Pain



page 26
Making sense
of sensitization

Nerve growth factor (NGF) is a well-studied neurotrophin, which by definition is necessary in development for the differentiation of neurons and the proper functioning of nervous tissues. In the adult, however, NGF appears to function primarily to mediate inflammatory and immune responses after tissue injury, especially to initiate and maintain hypersensitivity, a hallmark symptom of inflammation. As part of the inflammatory response, NGF directly or indirectly alters the sensitivity of small diameter sensory neurons that communicate noxious information. The receptors and intracellular signaling cascades that mediate this sensitizing action of NGF are not yet fully elaborated. Although the general consensus is that NGF produces peripheral sensitization by activating the neurotrophin receptor (NTR) TrkA, recent work suggests that the p75 NTR also contributes. The extent to which the two NTRs act independently or together remains to be determined. Furthermore, controversy exists as to the downstream signaling pathways involved in NGF-induced peripheral sensitization.

Grant D. Nicol and Michael R. Vasko