is a potent synthetic antimineralocorticoid with progestogenic and antiandrogenic properties, which is widely used for contraception and hormone replacement therapy. We investigated its potential role on adipocyte differentiation. The effects of DRSP were studied in murine preadipocyte cell lines and primary cultures of human preadipocytes. Differentiation markers and mechanisms underlying phenotypic variations in response to DRSP were explored. Early exposure to DRSP during differentiation led to a marked dose-dependent inhibition of adipose differentiation and triglyceride accumulation in 3T3-L1 and 3T3-F442A cells. DRSP also markedly inhibited adipose conversion of human primary preadipocytes derived from visceral (mesenteric and epicardial) and subcutaneous fat. This effect was MR-dependent and did not involve the glucocorticoid, androgen, or progesterone receptors. DRSP inhibited clonal expansion of pre-adipocytes and decreased expression of PPARγ, a key transcriptional mediator of adipogenesis, but had no effect on lipolysis, glucose uptake, and PPARγ binding to its ligands. DRSP exerts a potent antidiapogenic effect that is related to an alteration of the transcriptional control of adipogenesis via an antagonistic effect on the MR. Selective MR blockade therefore has promise as a novel therapeutic option for the control of excessive adipose tissue deposition and its related metabolic complications.

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The Role of GH and IGF-I in Mediating Anabolic Effects of Testosterone on Androgen-Responsive Muscle

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Testosterone (T) supplementation increases skeletal muscle mass, circulating GH, IGF-I, and TGF-β expression, but the role of GH and IGF-I in mediating T’s effects on the skeletal muscle remains poorly understood. Here, we show that T administration increased body weight and the mass of the androgen-dependent levator ani muscle in hypophysectomized as well as castrated plus hypophysectomized adult male rats. T stimulated the proliferation of primary human skeletal muscle cells (hSKMCs) in vitro, an effect blocked by transfecting hSKMCs with small interference RNA targeting human IGF-I receptor (IGF-IR). In differentiation conditions, T promoted the fusion of hSKMCs into larger myotubes, an effect attenuated by small interference RNA targeting human IGF-IR. Notably, MKR mice, which express a dominant negative form of the IGF-IR in skeletal muscle fibers, treated with a GnRH antagonist (acyline) to suppress endogenous T, responded to T administration by an attenuated increase in the levator ani muscle mass. In conclusion, circulating GH and IGF-I are not essential for mediating T’s effects on an androgen-responsive skeletal muscle. IGF-I signaling plays an important role in mediating T’s effects on skeletal muscle progenitor cell growth and differentiation in vitro. However, IGF-IR signaling in skeletal muscle fibers does not appear to be obligatory for mediating the anabolic effects of T on the mass of androgen-responsive skeletal muscles in mice.

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Mechanisms of Progesterone Receptor Inhibition of Inflammatory Responses in Cellular Models of Breast Cancer


Both pro- and antimitogenic activities have been ascribed to progesterone receptor (PR) agonists and antagonists in breast cancer cells; however, the transcriptional responses that underlie these paradoxical functions are not apparent. Using nontransformed, normal human mammary epithelial cells engineered to express PR and standard microarray technology, we defined 2370 genes that were significantly regulated by the PR agonist R5020. Gene ontology (GO) analysis revealed that GO terms involved in inflammation and NF-κB signaling were among the most significantly regulated. Interestingly, on those NF-κB responsive genes that were inhibited by agonist-activated PR, antagonists either 1) mimicked the actions of agonists or 2) reversed the inhibitory actions of agonists. This difference in pharmacological response could be attributed to the fact that although agonist- and antagonist-activated PR is recruited to the promoters of NF-κB-responsive genes, the physical presence of PR tethered to the promoter of some genes is sufficient for transcriptional inhibition, whereas on others, an agonist-activated PR conformation is required for inhibition of NF-κB signaling. Importantly, the actions of PR on the latter class of genes were reversed by an AF-2-inhibiting, LXXLL-containing peptide. Consideration of the relative activities of these distinct antiinflammatory pathways in breast cancer may be instructive with respect to the likely therapeutic activity of PR agonists or antagonists in the treatment of breast cancer.

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Regulation of Thyrotropin-Releasing Hormone-Expressing Neurons in Paraventricular Nucleus of the Hypothalamus by Signals of Adiposity

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Fasting-induced suppression of thyroid hormone levels is an adaptive response to reduce energy expenditure in both humans and mice. This suppression is mediated by the hypothalamic-pituitary-thyroid axis through a reduction in TRH levels expressed in neurons of the paraventricular nucleus of the hypothalamus (PVN). TRH gene expression is positively regulated by leptin. Whereas decreased leptin levels during fasting lead to a reduction in TRH gene expression, the mechanisms underlying this process are still unclear. Indeed, evidence exists that TRH neurons in the PVN are targeted by leptin indirectly via the arcuate nucleus, whereas correlative evidence for a direct action exists as well. Here we provide both in vivo and in vitro evidence that the activity of hypothalamic-pituitary-thyroid axis is regulated by both direct and indirect leptin regulation. We show that both leptin and α-MSH induce significant neuronal activity mediated through a postsynaptic mechanism in TRH-expressing neurons of PVN. Furthermore, we provide in vivo evidence indicating the contribution of each pathway in maintaining serum levels of thyroid hormone.

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