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Inhibition of retinoic Acid Receptors as a novel approach to Male Contraception

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It has been known for many years that dietary vitamin A is essential for male reproduction and that most of its biological functions are mediated through its active metabolite, all-trans retinoic acid (ATRA). We and others are exploring how interfering with ATRA signaling pathways might be exploited as novel approaches to male contraception. We have focused on ATRA's function through its binding to the retinoic acid receptor alpha (RARα) transcription factor to regulate spermatogenesis, using a combination of genetic, molecular, and pharmacologic approaches. We initially extended reports of 'testicular toxicity' in rats resulting from the administration of the pan-RAR antagonist BMS189453 and showed that in the mouse model, spermatogenesis could be inhibited by this antagonist, importantly in a reversible manner and without overt side effects. Inhibition of fertility was assessed by testis weight, sperm counts, detailed analysis of testicular histology, and mating studies. These observations were then extended by assessing the lowest doses that could interfere with spermatogenesis and the length of time of treatment that can be tolerated and allow restoration of fertility. We were able to induce sterility followed by complete restoration of fertility at doses as low as 1.0 mg/kg for treatment periods as long as 16 weeks. In fact, mating studies and morphological analyses suggested a more rapid recovery in mice subjected to these extended dosing periods. We are now exploring the molecular targets of antagonist actions and the possibility of developing RARα-specific antagonists. Specifically, we are examining the molecular basis for this shortened recovery period, generating RARα-selective antagonists, and determining the downstream targets of RARα signaling. Our results suggest that spermatogenesis is exquisitely sensitive to disruption of retinoid signaling and that RAR-antagonists may represent new lead molecules in developing non-steroidal male contraceptives.

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