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JOURNAL ARTICLE

Mullerian inhibiting substance inhibits testosterone synthesis in adult rats

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Mullerian inhibiting substance (MIS) is a gonadal hormone that causes regression of the Mullerian ducts during male sexual differentiation. Postnatally, MIS inhibits the proliferation and differentiation of immature Leydig cells, and transgenic mice that overexpress MIS have decreased serum testosterone concentrations. To elucidate the effects of MIS on androgen regulation in the postnatal testis, we examined testosterone synthesis in adult Sprague-Dawley rats following intratesticular and intraperitoneal injections of MIS. Intratesticular MIS injection achieved high local concentrations of MIS (574.0 +/- 60.0 ng/mL) at 4 hours, with a corresponding decline in serum testosterone concentrations to 0.7 +/- 0.1 ng/mL, compared to 1.1 +/- 0.2 ng/mL with intraperitoneal MIS and 1.6 +/- 0.1 ng/mL with intratesticular vehicle (IT-Veh) ($P < .001$). Intratesticular administration of MIS (IT-MIS) resulted in much higher serum and testicular interstitial fluid MIS concentrations than the intraperitoneal route. To directly examine the testosterone production rate in MIS-treated animals, we isolated Leydig cells from MIS and vehicle-injected testes. Primary Leydig cells exposed to MIS had a lower testosterone production rate and decreased expression of p450c17 (hydroxylase/lyase) and luteinizing hormone (LH) receptor mRNAs than that of vehicle-injected controls or the noninjected contralateral testis. In conclusion, intratesticular administration of MIS caused a decline in serum testosterone concentrations by decreasing the rate of testosterone biosynthesis, confirming that MIS can regulate adult Leydig cell androgen production. The ability of MIS to down-regulate mRNA expression of the p450c17 and LH receptor genes suggests that this effect is mediated transcriptionally. These data indicate that, in addition to its role in embryonic differentiation of the male reproductive tract, MIS has a regulatory function in the postnatal testis. We conclude that one such function is for MIS to directly inhibit adult Leydig cell steroidogenesis.

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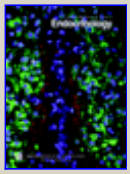

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