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JOURNAL ARTICLE

Leydig cell aging: steroidogenic acute regulatory protein (StAR) and cholesterol side-chain cleavage enzyme

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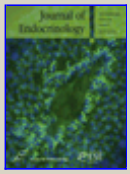
Primary points of control in steroidogenesis are the transport of cholesterol from intracellular stores to the inner mitochondrial membrane, and the subsequent conversion of cholesterol to pregnenolone by the cholesterol side-chain cleavage enzyme (P450scc). Testosterone production has been shown to decline in Brown Norway rat Leydig cells as the rats age. To better understand the mechanism by which aging Leydig cells lose steroidogenic function, we examined the effect of aging on steroidogenic acute regulatory protein (StAR), an important Leydig cell cholesterol transfer protein, and on P450scc. Leydig cells isolated from middle-aged (14 months) and old (24 months) rats produced significantly less testosterone than cells from young (4 months) rats. StAR mRNA (1.7 kilobase [kb]) was significantly reduced in Leydig cells from middle-aged and old rats, by 26% and 52%, respectively. Significant reductions also were seen in the steady-state levels of mRNA for P450scc, of 29% and 50%, respectively. Western blots revealed significant reductions in StAR protein, by 47% and 74%, respectively, and in P450scc protein, by 38% and 54%, respectively. In response to LH stimulation in vitro, testosterone production by Leydig cells in young, middle-aged, and old rats increased by 30-, 40-, and 33-fold, respectively, although the amounts of testosterone produced by the young cells significantly exceeded that produced by the middle-aged and old cells. StAR protein also increased in response to LH by 1.4- , 3-, and 11-fold, respectively, whereas P450scc protein remained unchanged. These results are consistent with the conclusion that compromise of StAR-mediated cholesterol transport may play a key role in age-related reductions in Leydig cell steroidogenesis. However, because P450scc is reduced in old Leydig cells, the reaction catalyzed by this enzyme would be rate-limiting under circumstances in which saturating amounts of cholesterol entered the mitochondria.



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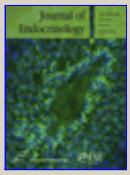

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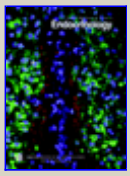

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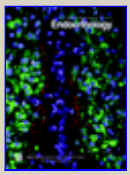

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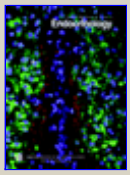

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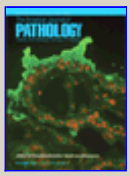

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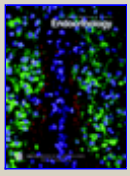

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