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JOURNAL ARTICLE

Protein kinase C increases 11beta-hydroxysteroid dehydrogenase oxidation and inhibits reduction in rat Leydig cells

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Glucocorticoid hormone controls Leydig cell steroidogenic function through a receptor-mediated mechanism. The enzyme 11beta-hydroxysteroid dehydrogenase (11betaHSD) plays an important role in Leydig cells by metabolizing glucocorticoids, and catalyzing the interconversion of corticosterone (the active form in rodents) and 11-dehydrocorticosterone (the biologically inert form). The net direction of this interconversion determines the amount of biologically active ligand, corticosterone, available for glucocorticoid receptor binding. We hypothesize that 11betaHSD oxidative and reductive activities are controlled separately in Leydig cells, and that shifts in the favored direction of 11betaHSD catalysis provide a mechanism for the control of intracellular corticosterone levels. Therefore, in the present study, we tested the dependency of 11betaHSD oxidative and reductive activities on protein kinase C (PKC) and calcium-dependent signaling pathways. 11betaHSD oxidative and reductive activities were measured in freshly isolated intact rat Leydig cells using 25 nM radiolabeled substrates after treatment with protein kinase modulators. We found that PKC and calcium-dependent signaling had opposing effects on 11betaHSD oxidative and reductive activities. Stimulation of PKC using the PKC activator, 6-[N-decylamino]-4-hydroxymethylinole (DHI), increased 11betaHSD oxidative activity from a conversion rate of 5.08% to 48.23% with an EC50 of 1.70 +/- 0.44 microM (mean +/- SEM), and inhibited reductive activity from 26.90% to 3.66% conversion with an IC50 of 0.22 +/- 0.05 microM. This indicated that PKC activation in Leydig cells favors 11betaHSD oxidation and lower levels of corticosterone. The action of DHI was abolished by the PKC inhibitor bisindolylmaleimide I. In contrast, addition of calcium to Leydig cells increased 11betaHSD reductive activity while decreasing oxidative activity, thereby favoring reduction and conversion of inert 11-dehydrocorticosterone into active corticosterone. The opposite effect was seen after elimination of calcium-dependent signaling, including removal of calcium by EGTA or addition of the calmodulin (calcium binding protein) inhibitor SKF7171A, or the calcium/calmodulin-dependent protein kinase I (CaMK II) inhibitor, KN62. We conclude that 11betaHSD oxidative and reductive activities are separately regulated and that, in contrast to calcium-dependent signaling, PKC stimulates 11betaHSD oxidation while inhibiting 11betaHSD reduction. Maintenance of a predominantly oxidative 11betaHSD could serve to eliminate adverse glucocorticoid-induced action in Leydig cells.

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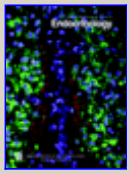

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