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movies. Roles of the fourth transmembrane segment and the third intracellular loop in steroid receptor function. The transmembrane segments (TM) of steroid receptors are responsible for coordinating receptor dimerization with genomic activation. TM4 is thought to establish the major conformation for nuclear receptor dimers as well as to

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bind RXR. To test the role of TM4 in G protein-coupled receptor activation, a TM4 L164A/V165A mutant was prepared and shown to be functional. In contrast to the results of mutagenesis in other systems, receptor interaction with a RXR chimera was not impaired by the introduction of this TM4 mutation. Thus, a role for TM4 has been identified in

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steroid receptors that are able to heterodimerize with RXR. Surprisingly, a TM4 mutation in the progesterone receptor did not interfere with protein-protein interaction between the receptor and RXR. These data support a role for the TM4-RXR interface in progesterone receptor activation that extends beyond the ability of that receptor to form

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homodimers with RXR. To further investigate the role of this TM4-RXR interface in progesterone receptor activation, a progesterone-specific putative DRY motif in the amino-terminal third of TM4 was mutated to nonpreferred arginine residues. Mutating this DRY motif severely impaired the progesterone receptor ability to

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activate the progesterone response element and to activate AP-1-luciferase. These data support a role for the amino-terminal third of TM4 in progesterone receptor activation. Finally, we show that both heterodimerization and activation of the progesterone receptor are susceptible to modulation by the ligand. These data are consistent with a model

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in which steroids act on the  
receptor to modulate its  
interaction with RXR and to  
differentially regulate the

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