Molecular mechanism of progesterone-induced antiproliferation in rat aortic smooth muscle cells

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Abstract

Previously we demonstrated that progesterone at physiologic levels dose dependently inhibited cell proliferation in cultured rat aortic smooth muscle cells (RASMCs). However, the molecular mechanism underlying of progesterone-induced antiproliferation was not clear. Here we demonstrated that progesterone induced a reduction of the [(3)H]thymidine incorporation into RASMCs during the S-phase of the cell cycle. Western blotting analysis revealed that the protein levels of cyclin A, cyclin E, and cyclin-dependent-kinase (CDK) 2 but not cyclin D1 and CDK4 decreased after progesterone treatment, but those of CDK-inhibitory proteins, p21 and p27, increased. Immunoprecipitation showed that the formations of the CDK2-p21 and CDK2-p27 complex were increased and the assayable CDK2 kinase activity was decreased in the progesterone-treated RASMCs. In contrast, the formations of the CDK4-p21 and CDK4-p27 complex and the assayable CDK4 kinase activity were not changed significantly by progesterone treatment. Pretreatment of RASMCs with a p21 or p27 antisense oligonucleotide reduced the progesterone-induced inhibition of [(3)H]thymidine incorporation into RASMCs. In conclusion, these data suggest that progesterone inhibits RASMCs proliferation by increasing the levels of p21 and p27 protein, which in turn inhibit CDK2 kinase activity, and finally interrupt the cell cycle.