Dopamine Regulates Cell Cycle Regulatory Proteins via cAMP, Ca^{2+}/PKC, MAPKs, and NF-κB in Mouse Embryonic Stem Cells

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This study examined the effect of dopamine on DNA synthesis and its related signal cascades in mouse embryonic stem (ES) cells. Dopamine inhibited DNA synthesis in both a dose- and time-dependent manner. Dopamine, SKF 38393 (D1 receptor agonist), and quinpirole (D2 receptor agonist) decreased the level of [^{3}H]-thymidine incorporation. The level of cyclic adenosine 3, 5-monophosphate (cAMP) was increased by SKF 38393 but not by quinpirole. The protein kinase C (PKC) protein was translocated from the cytosolic fraction to the membrane compartment by dopamine. Dopamine also increased $[Ca^{2+}]_i$, which was blocked by EGTA (an extracellular Ca^{2+} chelator), BAPTA-AM (an intracellular Ca^{2+} chelator), nifedipine (a L-type Ca^{2+} channel blocker), SQ 22536 [an adenylyl cyclase (AC) inhibitor] and neomycin [a phospholipase C (PLC) inhibitor]. Dopamine, SKF 38393, and quinpirole increased the level of p44/42 mitogen activated protein kinases (MAPKs), p38 MAPK, and stress activated protein kinase/Jun-N-terminal kinase (SAPK/JNK) phosphorylation. Dopamine also increased level of H_2O_2 formation and activated the transcription factor family NF-κB. Moreover, SKF 38393, quinpirole, and dopamine inhibited cell cycle regulatory proteins, which is consistent with the change in the level of [^{3}H]-thymidine incorporation observed. The dopamine-induced decrease in cyclin E, cyclin dependent protein kinase-2 (CDK-2), and cyclin D1, CDK-4 were blocked by pertussis toxin (G protein inhibitor), SQ 22536, neomycin, bisindolylmaleimide I (PKC inhibitor), SB 203580 (p38 MAPK inhibitor), PD 98059 (p44/42 inhibitor), and SP 600125 (SAPK/JNK inhibitor). In conclusion, dopamine inhibits DNA synthesis in mouse ES cells via the cAMP, Ca^{2+}/PKC, MAPKs, and NF-κB signaling pathways.