OPPOSITE EFFECTS ON CELL PROLIFERATION BY WNT1 AND WNT7A PROTEINS IN CULTURED PC12 CELLS

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The Wnt proteins constitute a large family of secreted glycoproteins that bind to 7-TM Frizzled (FZD) receptors and to type-5 or-6 low density lipoprotein receptor-related proteins (LRP5/6). Interaction of Wnts with different FZD receptors and LRP5/6 activates a "canonical" signalling pathway leading to a traslocation of ß-catenin into the nucleus where it activates gene transcription by interacting with T-cell factor (TCF) and lymphoid enhancer-binding protein (LEF) transcription factors. Wnt can also activate calcium-dependent-ß-catenin-independent pathways. Wnt abnormalities have been associated with neurodevelopmental disorders, neuronal degeneration, and several types of tumors. An unscheduled activation of cell cycle in differentiated neurons contributes to neurodegeneration in a variety of CNS disorders, including Alzheimer's disease. The molecular events that drive the abnormal cell cycle in neurons destined to die are unknown. Wnt signalling was considered as a potential candidate because Wnt stimulates proliferation of a variety of cells, including CNS neuroprogenitors. However, the role of Wnt may not be univocal because may favour proliferation or may act as tumor suppressor. We therefore decided to examine the effect of Wnt1 and Wnt7a on cell proliferation using undifferentiated PC12 cells, which originate from the neural crest and are widely employed as a neuronal cell model. Heterologous expression of Wnt1 enhanced, whereas expression of Wnt7a reduced [^{3}H]thymidine incorporation in PC12 cells. Searching for the underlying mechanisms, we examined the activation of the canonical Wnt/ß-catenin/TCF-LEF pathway and the "Wnt/calcium pathway" by co-transfecting the cells with a reporter gene controlled by either TCF-LEF or the calcium-activated transcription factor, NFAT. Wnt1 and Wnt7a activated both pathways, but to a different extent. While Wnt1 preferentially activated the calcium pathway, Wnt7a mainly activated the canonical pathway. Pharmacological inhibition of protein kinase C, which is a component of the calcium pathway, abrogated the increase in cell proliferation induced by Wnt1 without affecting the antiproliferative action of Wnt7a. The action of Wnt7a was instead occluded by lithium ions, which mimic the activation of the canonical pathway, and was largely reduced by Dickkopf-1, which acts as an inhibitor of the canonical pathway. These data suggest that Wnt-induced regulation of cell proliferation, at least in PC12 cells, depends on the balance between the calcium/PKC pathway and the canonical pathway.