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Alkylcatechols Regulate NGF Gene Expression in Astroglial Cells via Both Protein Kinase C- and cAMP-Independent Mechanisms.

YOSHIKO FURUKAWA*, SHOEI FURUKAWA, FUMIO OMAE, HIROFUMI AWATSUJI, KYOZO HAYASHI

It has been previously demonstrated that, in mouse astroglial cells and fibroblast cells in culture, alkylcatechols cause a rapid increase in the amount of NGF released into the medium. To understand the mechanism of this alkylcatechol effect on NGF gene expression in astroglial cells, we examined the effects of protein kinases that influences intracellular signal transduction and of their inhibitors. The reagents to increase the intracellular content of cyclicAMP (cAMP) did not mimick alkylcatechol induction of NGF gene expression. Phorbol ester, a direct activator of protein kinase C (PKC), caused an increase in the NGF synthesis/secretion. The stimulatory effect of homocatechol (4-methylcatechol) on NGF synthesis was not completely inhibited by staurosporine, an inhibitor of PKC. The concomitant administration of homocatechol and PMA evoked a drastic and prolonged increase in NGF mRNA level. These results suggest that neither PKC-dependent pathway nor cAMP-dependent pathway is dominant in the stimulatory effect of alkylcatechols on NGF synthesis.

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Estrogen-Inducible pS2 Protein is not the Key Regulatory Component in the Proliferation of Human Breast Cancer Cells (MCF-7).

NORIYOSHI KIDA, TOMOAKI YOSHIMURA, HARUO TAKAHASHI,, SEIJI NAGAO, YOSHINORI NOZAWA, YOSHIKO FURUKAWA, KAZUTOSHI MORI, KYOZO HAYASHI*

Exposure of human breast cancer cells (MCF-7) to tumor promoters such as 12-O-tetradecanoyl phorbol 13-acetate (TPA) for 24 h at concentrations of 1-100 nM resulted in marked inhibition of DNA synthesis but a 3-5-fold increase in the amounts of pS2 protein in the medium. These results support our previous suggestion that pS2 protein is not involved in the mechanism controlling proliferation of MCF-7 cells. During the treatment with TPA, the intracellular content of pS2 protein was constant, suggesting that TPA did not induce secretion of pS2 protein but rather *de novo* synthesis of the protein. The increase in the pS2 protein content of the medium by TPA was inhibited by simultaneous addition of cycloheximide, but not by that of actinomycin D. Northern-blot hybridization analysis showed that the amount of pS2 mRNA was unchanged by treatment of the cells with TPA. These results indicate that TPA does not induce transcription of the pS2 gene, suggest that the main effect of TPA results from the induction of translation of pS2 mRNA.

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Effects of Oral Administration of a Stimulator for Nerve Growth Factor Synthesis in Basal Forebrain-Lesioned Rats.

ATSUMI NITTA, KATSUHITO MURASE, YOSHIKO FURUKAWA, KYOZO HAYASHI*, TAKAAKI HASEGAWA, TOSHITAKA NABESHIMA

Nerve growth factor (NGF) plays an important role in the survival and maintenance of cholinergic neurons in the central neuronal system. In senile dementia of the Alzheimer type, learning and memory are impaired by the loss of neurons in the magnocellular cholinergic neuronal system. We now found that 6-(4-hydroxybutyl)-2,3,5-trimethyl-1,4-benzoquinone (TMQ) stimulates NGF synthesis in mouse astroglial cells and that the compound has improving effects on memory and choline acetyltransferase (ChAT) activity in basal forebrain-lesioned rats, an amnesia animal model. TMQ ameliorated amnesia in the water maze and passive avoidance tasks. The compound not only restored the reduced ChAT activity in the parietal cerebral cortex, but also increased NGF content and ChAT activity in the hippocampus, although it did not change either of these parameters in any brain region in intact rats. These results suggest that the compound activates cholinergic neurons only in the damaged brain and, further, indicate that NGF stimulators could be used in clinical trials for the treatment of senile dementia of the Alzheimer type.