5 - フェニルピリミジン誘導体の神経細胞保護作用における BDNF 遺伝子発現誘導の可能性に関する研究

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Possible involvement of induction of brain-drived neurotrophic factor in the neuroprotective effect of a 5-phenylpyrimidine derivative

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ABSTRACT : We used primary cortical neurons prepared from the brains of rat embryos (E18) to discover compounds which support neuronal survival, and found that a new 5-phenylpyrimidine derivative named FU248 [2-amino-5-(2,4-dichlorophenyl)pyrimidine] inhibited the neuronal cell death in a dose dependent manner up to 1 μg/mL. Semiquantitative RT-PCR analysis revealed that an exposure of the primary cortical neurons to 1 μg/mL of FU248 transiently and significantly enhanced the expression of genes including brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and neurotrophin-3 (NT-3). The enhancement of the gene expression was maximal 6 hr after the addition of FU248, and the expression returned to the basal level after 24 hr. Expression of neurotrophin-4 was not detectable throughout the experimental period. The amount of the transcript for BDNF was approximately nine times and sixteen times more abundant than those for NT-3 and NGF, respectively (t =6hr). Moreover, an anti-BDNF antibody suppressed the effect of FU248, whereas the control antibody did not show any effects on the neuronal survival. These findings strongly suggest that FU248 exerts its neuroprotective effect, at least in part, through induction of BDNF.

抄録　ラット胎児の脳から調製した初代培養神経の細胞死を抑制する化合物の探索を行い、新規5 - フェニルピリミジン誘導体、FU248 [2-amino-5-(2,4-dichlorophenyl)pyrimidine] を見いだした。半定量的RT-PCR解析の結果、初代培養神経細胞に1 mg/mLのFU248を添加するとBDNF、NGF、NT-3等の遺伝子の発現が一過的かつ有意に増加した。これらの遺伝子の発現はFU248添加後6時間目で最高に達し、その時点でBDNFのmRNA量はNT-3の約9倍、NGFの約16倍であった。また、抗BDNF抗体はFU248の作用を中和した。これら

の知見は、FU248の神経細胞保護作用の一部がBDNFの発現を介していることを示唆した。

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