ジベンゾイルメタン系化合物の酸化的ストレスおよび小胞体ストレス評価によるドパミン神経系保護作用に関する研究

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A Dibenzoylmethane Derivative Protects Dopaminergic Neurons Against Both Oxidative Stress and Endoplasmic Reticulum Stress

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ABSTRACT: The enhancement of intracellular stresses such as oxidative stress and endoplasmic reticulum (ER) stress has been implicated in several neurodegenerative disorders including Parkinson's disease (PD). During a search for compounds that regulate ER stress, a dibenzoylmethane (DBM) derivative 2,2'-dimethoxydibenzoylmethane (14-26) was identified as a novel neuroprotective agent. Analysis in SH-SY5Y cells and in PC12 cells revealed that the regulation of ER stress by 14-26 was associated with its anti-oxidative property. 14-26 prevented the production of reactive oxygen species (ROS) when the cells were exposed to oxidants such as hydrogen peroxide and 6-hydroxydopamine (6-OHDA) or an ER stressor brefeldin A (BFA). 14-26 also prevented ROS-induced damage in both the ER and the mitochondria, including the protein carbonylation in the microsome and the reduction of the mitochondrial membrane potential. Further examination disclosed the presence of the iron-chelating activity in 14-26. In vivo, 14-26 suppressed both oxidative stress and ER stress and prevented neuronal death in the substantia nigra pars compacta (SNpc) after injection of 6-OHDA in mice. These results suggest that 14-26 is an antioxidant that protects dopaminergic neurons against both oxidative stress and ER stress and could be a therapeutic candidate for the treatment of PD.

抄録　F9 herp 欠損細胞にツニカマイシンを添加することで、小胞体ストレスによる細胞死の状態を作成し、合成したジベンゾイルメタン系化合物の細胞死抑制効果を評価したところ、2,2'-dimethoxydibenzoylmethane (14-26) に強い抑制作用が見られた。さらに、

その効果が、小胞体ストレスに作用しているか酸化的ストレスに作用しているかを検討したところ、両方に作用していることが分かった。また、パーキンソン病（PD）モデルでの評価を実施した結果、ジベンゾイルメタン系化合物の中で同様に 14-26 が強い細胞死抑制作用を示すことが判明し、ドパミン神経細胞を保護する抗酸化剤の候補化合物であることが分かった。

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