Chemistry and Biology of Neurotrophic Natural Products

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Neurotrophic factors, such as NGF and BDNF, are ever thought for useful agents for ameliorating neurodegeneration underlying Alzheimer's and Parkinson diseases. However, their peptidyl properties have brought about some serious issues to overcome before successful clinical application, e.g., unable to cross the blood-brain barrier and easily being metabolized. Low-molecular-weight compounds, which can mimic functions of neurotrophic factors, might be the promising alternative for treatment of neurodegenerative diseases. Thus we have continued searching for neurotrophic small molecules in natural products by using the primary cultured rat cortical neurons, resulting in the discovery of several active compounds. In this symposium, we focus on neurotrophic properties and synthetic studies of two particular natural products, talaumidin and merrilactone A, which we isolated from Brazilian *Aristolochia arcuata* and Chinese *Illicium merrillianum*, respectively. Talaumidin, a tetrahydrofuran-type lignan, was found to have neurotrophic property in the primary cultured rat cortical and hippocampal neurons as well as to show neuroprotective effects on cell death of PC12 caused by the deprivation of serum, H_2O_2 oxidative stress, and β-amyloid insult. On the other hand, merrilactone A, a cage-like pentacyclic sesquiterpene, could promote significantly neurite outgrowth in the primary cultured rat cortical neurons. Further, we have attempted total synthesis of both the compounds aiming at giving a general outline of their structure-activity relationships. Our studies on neurotrophic natural products demonstrate that low-molecular-weight natural products may be able to make a valuable contribution to develop new drug for treatment of neurodegenerative diseases.