Synthesis and Physiological Activity of Novel Sphingolipid Analogues

- Development of potent antagonists for natural sphingosine-1-phosphate -

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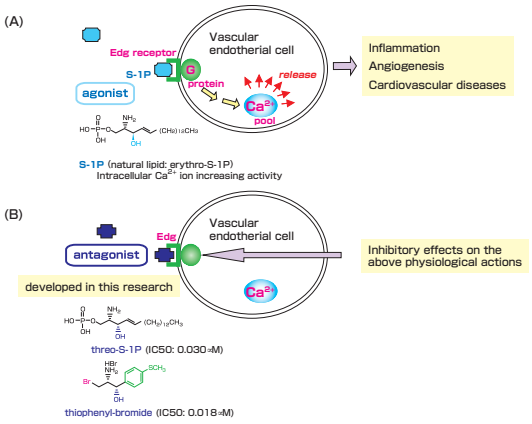
Recently sphingosine-1-phosphate (S-1P), one of the sphingolipids metabolites, has attracted considerable attention as an extracellular mediator. It has been shown that S-1P binds to cell surface Edg receptors to cause Ca^{2+} ion release from intracellular stores. The search for agonists and antagonists toward Edg would provide the basis for development of novel therapeutic agents. We have synthesized novel S-1P analogues such as *threo*-S-1P, which is C-3 stereoisomer of natural *erythro*-S-1P. Bioassays of the S-1P analogues using HL60 cells have indicated that the *threo*-aminoalcohol derivatives (3 kinds) inhibit the Ca^{2+} ion increasing activity of natural S-1P at low concentrations (IC_{50} = 0.02-0.18 μM) by competitive binding to Edg receptors.



Cellular Responses to Agonist (A) and Antagonist (B) for Edg Receptor

Numerical Computation of Enzyme Function

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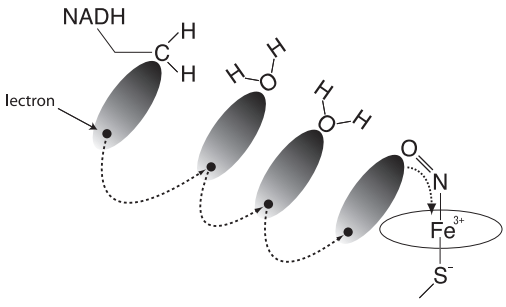
Nitric Oxide reductase (NOR) isolated from the denitrifying fungus *Fusarium oxysporum* is a cytochrome P450-type heme enzyme [1-3]. NOR catalyzes a nitric oxide (NO) reduction reaction in which two NO molecules are converted into a nitrous oxide molecule using two electrons directly transferred from NADH [4].

The reaction path for NO reduction in NOR was obtained using the semiempirical method SAM1 [5].

We analyzed the two electron transfer system that supported the function of NOR using the docking simulation and the quantum chemical calculation. Then, we propose the system that the two electrons transmit as a charged soliton (Figure 1).



Schematic representation of the two electron transfer system, the charged soliton as illustrated by the dashed line