

## 論 文 内 容 要 旨

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学位論文題目	Oral administration of natural occurring phosphatidic acid and lysophosphatidic acid protect against nonsteroidal anti-inflammatory drug-induced gastric ulcer (天然ホスファチジン酸およびリゾホスファチジン酸の経口投与は非ステロイド性抗炎症薬誘導性胃潰瘍を予防する)		
<p>内容要旨</p> <p>Lysophosphatidic acid (LPA) is a bioactive phospholipid that mediates diverse cellular responses such as cell proliferation, migration, anti-apoptosis and cytoskeletal rearrangement through its specific G-protein-coupled receptors (LPA<sub>1-6</sub>). Our previous study revealed that orally administrated synthetic LPA and its diacyl derivative phosphatidic acid (PA) ameliorate aspirin-induced gastric ulcer in mice. These results indicated a possibility that LPA or PA-rich foods or herbs protect against nonsteroidal anti-inflammatory drug (NSAID)-induced gastric ulcer. In this study, we analyzed the PA in various cereals because of its daily demand. Among examined, buckwheat (<i>Fagopyrum esculentum</i>) bran contained the highest level of PA (1.8 mg/g). We found that the PA-rich buckwheat bran lipid ameliorates indomethacin-induced gastric ulcer in mice via formation of LPA in the stomach. We also quantified LPA in 21 medicinal herbs used for the treatment of gastrointestinal (GI) disorders. We found that half of them contained LPA at relatively high levels (0.04-0.24 mg/g) compared to soybean seed powder (0.004 mg/g), which we previously identified as an LPA-rich food. Among LPA-rich herbs, peony (<i>Paeonia lactiflora</i>) root powder contained the highest level of LPA (0.24 mg/g). The LPA in peony root powder is highly concentrated in the lipid fraction that ameliorates indomethacin-induced gastric ulcer in mice. The peony root lipid enhanced prostaglandin E<sub>2</sub> production in a gastric cancer cell line, MKN74 cells that express LPA<sub>2</sub> abundantly. LPA in peony root prevented indomethacin-induced cell death and stimulated the proliferation of MKN74 cells via LPA<sub>2</sub> dependent manner. We also found that biologically significant level of LPA (2.4 μM) was present in stomach fluid, indicating that LPA/LPA<sub>2</sub> signal operates at the basic condition. Our results suggested that PA or LPA-rich diets become good remedies for the prevention of NSAID-induced gastric ulcer by strengthening LPA/LPA<sub>2</sub> signal in the human stomach.</p>			