

Piperine, a Primary Component of Black Pepper, inhibits Prostaglandins Generation by Suppression of COX Activity on Arachidonic Acid Metabolism in LPS-Stimulated RAW264.7 Cells

Son DongJu^o, Park ByeoungSoo, Lee SungEun*, Kazuyuki Kitatani**, and Park YoungHyun

College of Natural Sciences, Soonchunhyang University, Asan, Korea * College of Agriculture and Life Sciences, Seoul National University, Suwon, Korea ** Department of Pathological Biochemistry, Kyoto Pharmaceutical University, Kyoto, Japan

Piperine (piperinoyl-piperidine) is a nitrogenous pungent substance contained in black pepper, the well know spice obtained from *Piper nigrum* L. (*Piperaceae*). Pharmacological studies have shown that piperine reduces inflammation and pain, possesses anticonvulsant and antiulcer activity, protects the liver and has deleterious effects on testis function. Prostaglandins(PGs) are a family of intercellular and intracellular messengers derived from arachidonic acid(AA) by phospholipase(PL) and cyclooxygenase(COX). These mediators exert a wide range of effects on processes such as smooth muscle tone, vascular permeability, cellular proliferation, and inflammatory/immune function. In this study, Piperine, a primary component of black pepper, potently reduced the generations of PGE₂ and PGD₂ in RAW264.7 cells stimulated by lipopolysaccharide(LPS) in a dose-dependent manner when added to the culture media at the time of stimulation. In order to elucidate the mechanism involved in the anti-inflammatory activity of Piperine, we investigated its effects on the AA metabolism and enzyme activity such as cPLA₂⁻, sPLA₂⁻ and COX-activity, and protein expression such as cPLA₂⁻ and COX₂-expression. In the results, LPS stimulated the generations of PGE₂ and PGD₂ in RAW264.7 cells in a dose- and time-dependent manner. Piperine inhibited the COX activity, but did not suppress the cPLA₂⁻, or sPLA₂⁻ activity in LPS-stimulated RAW264.7 cells. Furthermore, Piperine did not affect the cPLA₂⁻, or COX₂ expression. These results suggest that Piperine may inhibit the generations of PGE₂ and PGD₂ in LPS-stimulated RAW264.7 cells probably through the suppression of the COX activity in LPS-stimulated RAW264.7 cells.

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Mechanism of immunostimulating action of polysaccharide isolated from Platycodon grandiflorum in RAW 264.7 macrophages

Yoon YeoDae^o, Han SangBae, Hong DongHo, Kang JongSeong*, Lee HyunSun, Kim HwanMook

Kor Res Inst Biosci Biotech (KRIBB):*College of Pharmacy, Chungnam Natl. Uni.

In our previous study, we reported that PG, a polysaccharide isolated from Platycodon grandiflorum, activated macrophages and B cells, but not T cells. Here, we investigated in more detail the mechanism of action of PG in macrophage activation. Since PG cannot penetrate cells due to the large molecular mass, it should bind to membrane receptors of macrophages. We showed that some antibodies to cell surface molecules (CD14, CD11b, TLR2, and TLR4) inhibited RAW264.7 macrophage activation, suggesting the possible binding sites of PG. The role of TLR4 as the PG receptor was also confirmed by the results that PG activity in macrophages from C3H/HeJ, known to have a defective TLR4, was completely inhibited. Ligation of TLR2/4 by PG also resulted in the activation of JNK, p38 and ERK1/2 MAPKs, which was examined by immunoblotting and kinase assays. It also resulted in the phosphorylation of IκBs, the translocation NF-κB into the nucleus and the initiation of gene transcriptions of IL-1b, IL-6, TNF-α and iNOS. In spite of the similarity in their mode of action, PG and LPS were differentiated by using polymyxin B, which only inhibited macrophage activation by LPS, but not PG. Taken together, our results indicated that PG, as a plant-derived polysaccharide, activated macrophages by mediating TLR signaling cascades and might accelerate the innate immunity against to infectious pathogens and cancers.