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Anti-inflammatory effects of a PPAR-γ agonistic phthalimide analogue

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Previously, we isolated a new compound paecilocin A as a PPAR-γ binding molecule from the jellyfish-derived fungus *Paecilomyces variotii*. Based on the molecular framework of paecilocin A, a series of phthalimide analogues were synthesized and evaluated for PPAR-γ binding activity. In a subsequent screening for competitive binding activity, 4-hydroxy-2-(4-hydroxyphenethyl) isoindoline-1,3-dione (PD1) showed good PPAR-γ agonistic activity. Since one of the functions of PPAR-γ is suppression of inflammatory responses, the present study aimed to investigate anti-inflammatory activity of PD1. Transcriptions of mRNA were determined by reverse transcriptase-PCR. Inflammatory protein expressions were determined by ELISA and Western blot method. In Lipopolysaccharide (LPS)-stimulated murine macrophage RAW264.7 cells, PD1 suppressed the induction of pro-inflammatory factors including inducible Nitric Oxide Synthase (iNOS), Nitric Oxide (NO), Cyclooxygenase 2 (COX-2), Tumor Necrosis Factor α (TNF-α), interleukine 1β (IL-1β), and interleukine 6 (IL-6) in both mRNA level and protein level. In parallel, PD1 enhanced expression of anti-inflammatory factors such as arginase-1 and interleukine 10 (IL-10). PD1 simultaneously suppressed LPS-evoked Nuclear Factor kappa B (NF-κB) p65 subunit phosphorylation in macrophages. The anti-inflammatory mechanism of PD1 is proposed to be via inhibition of NF-κB pathway. In subsequent *in vivo* animal experiment employing carrageenan-induced acute inflammatory paw edema model, PD1 showed significant reduction in paw swelling. Histological analysis of tissue sections revealed reduction of cellular infiltration of immune cells in PD1-treated groups. These findings suggest that PD1 may serve as an anti-inflammatory lead.

Biography

Jee H Jung has his expertise in isolation, structure elucidation, and biological evaluation of new compounds from marine organisms. In recent years, his research was focused on the study of bioactive compounds from marine invertebrate-derived microorganisms. Further studies on optimization of lead compounds by docking simulation-based analogue synthesis and enhancement of bioavailability by nanoparticle formulation are also his major research interests.

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