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BUANUS WONGSUD : EVALUATION OF NON STEROIDAL ANTI-INFLAMMATORY DRUGS AS LIGAND OF PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR.THESIS ADVISORS: SRICHAN PHORNCHIRASILP, Ph.D., DENNIS R. FELLER, Ph.D. 100 P. ISBN 974-662-088-6

Nonsteroidal anti-inflammatory drugs (NSAIDs) possess antipyretic, analgesic and anti-inflammatory effects. The main mechanism is the inhibition of cyclooxygenase activity. To study whether NSAIDs were ligands for Peroxisome Proliferator Activated Receptor α (PPARα), which might be another pathway to relieve the inflammatory responses, H4IIEC3 cells could be used. In transactivation assay, H4IIEC3 cells were transfected by rat acyl CoA oxidase-luciferase plasmid. The result showed that ibuprofen, ketoprofen, naproxen, salicylic acid, indomethacin and diclofenac but not mefenamic acid were ligands for PPARα. Indomethacin produced small response. The maximal response produced was only 288.57 % of control at 300 μM. In addition, the stereoselective effect of ibuprofen and ketoprofen isomers was studied. S(+)-Ketoprofen and S(+)-ibuprofen had almost the same efficacy. The maximal responses were 528.4 and 531.9% of control, respectively. The EC_{50} of S(+)-ketoprofen and S(+)-ibuprofen were 1.905×10^{-5} M and 2.11×10^{-5} M, respectively. The rank order for PPARα activation was S(+)ketoprofen > S(+)-ibuprofen > R(-)-ketoprofen > R(-)-ibuprofen. Using the biochemical assay to measure the hepatic peroxisomal fatty acyl CoA oxidase activity, they exhibited the same rank order, S(+)-ketoprofen > S(+)-ibuprofen > R(-)-ibuprofen ≥ R(-)-ketoprofen. To study the stereoselective effect on PPARγ activation, CV-1 cells were co-transfected with the PPARγ and the response element of rat adipocyte differentiation-luciferase plasmid. Contrast to PPARα activation, indomethacin was the most active drug for PPARγ activation, then R(-)-ibuprofen and S(+)-ibuprofen, respectively. Thus our result proposed that NSAIDs were ligands for both isoforms of PPAR and this might be an additional mechanism that explain the anti-inflammatory property of the drugs.