P7. EVALUATION OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AS LIGAND FOR PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR.

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ABSTRACT

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) possess the antipyretic, analgesic and antiinflammatory 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 for mefenamic acid was ligands for PPARα. S(+)-ketoprofen and S(+)ibuprofen were almost the same efficacy. They produced the maximal response 528.4 and 531.9% of control, respectively. The \( EC_{50} \) of S(+)-ketoprofen and S(+)ibuprofen were 1.905X10⁻⁵ and 2.11 X 10⁻⁵ M in PPARα activation. Indomethacin produced small response. It produced the maximal response only 288.57% of control at 300 µM. The rank order for PPARα activation was S(+)ketoprofen ≥ S(+)ibuprofen > R(-)-ketoprofen ≥ R(-)-ibuprofen. Ibuprofen and ketoprofen isomers were tested for stereoselective activation to PPARα. The results showed that S-isomers of these drugs were more active than R-isomers. 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 of them.