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

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ABSTRACT

Nonsteroidal Anti-Inflammaory 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 Receptorα (PPARα), which might be another pathway to relief 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 EC50 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.