Investigation of Radiotracer Metabolic Stability In Vitro with CYP-Overexpressing Hepatoma Cell Lines.

Info

PUBLISHED DATE
2022-08-07

JOURNAL
Cells

LINK
https://www.ncbi.nlm.nih.gov/pubmed/35954291

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Abstract

The characterization of novel radiotracers toward their metabolic stability is an essential part of their development. While in vitro methods such as liver microsome assays or ex vivo blood or tissue samples provide information on overall stability, little or no information is obtained on cytochrome P450 (CYP) enzyme and isoform-specific contribution to the metabolic fate of individual radiotracers. Herein, we investigated recently established CYP-overexpressing hepatoblastoma cell lines (HepG2) for their suitability to study the metabolic stability of radiotracers in general and to gain insight into CYP isoform specificity. Wildtype HepG2 and CYP1A2-, CYP2C19-, and CYP3A4-overexpressing HepG2 cells were incubated with radiotracers, and metabolic turnover was analyzed. The optimized protocol, covering cell seeding in 96-well plates and analysis of supernatant by radio thin-layer-chromatography for higher throughput, was transferred to the evaluation of three (18)F-labeled celecoxib-derived cyclooxygenase-2 inhibitors (coxibs). These investigations revealed time-dependent degradation of the intact radiotracers, as well as CYP isoform- and substrate-specific differences in their metabolic profiles. HepG2 CYP2C19 proved to be the cell line showing the highest metabolic turnover for each radiotracer studied here. Comparison with human and murine liver microsome assays showed good agreement with the human metabolite profile obtained by the HepG2 cell lines. Therefore, CYP-overexpressing HepG2 cells provide a good complement for assessing the metabolic stability of radiotracers and allow the analysis of the CYP isoform-specific contribution to the overall radiotracer metabolism.