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Generation and functional characterization of an in vitro binding assay of HNF4α

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Hepatocyte nuclear factor 4 α (HNF4α), a highly conserved member of the nuclear receptor family, was first described in the liver and later in kidney and the proximal tubule where it controls the expression of many enzymes and transporters closely related to drug metabolism as well as lipid and carbohydrate metabolism. This close relation to drug metabolizing enzymes such as cytochrome P450 as well as drug transporters (e.g. OATP2) rend HNF4α a prime suspect in drug-drug interaction as well as drug related adverse effects. However unlike other nuclear receptors such as the structurally similar RXR, HNF4α is still considered an orphan nuclear receptor rendering structure associated predictions of drug interactions and adverse effect impossible. Therefore we generated a one hybrid reporter gene assay, consisting of different HNF4α-isoforms, designed to identify transcriptional activity modulating ligands of HNF4α. Using the one hybrid system in transfected HeLa cells, we were able to confirm the activity inhibiting character of the HNF4α F-domain, as well as the reduced activity of the newly discovered HNF4α isoform missing exon 5 and 6. Additionally we were interested whether the AMP-kinase mediated HNF4α activity reducing effect of metformin can be replicated in the one hybrid system, as well as whether the highly discussed potential ligands myristic acid and its respective thioester are activity modulating ligands of HNF4α. In both cases we did not detect any activity altering properties of the exogenously added substances. This study establishes a general method to identify exogenously added ligands for nuclear receptor HNF4α and provides a possible screening tool for drug-drug interactions and adverse effects.

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