NOVEL LIGANDS OF CONSTITUTIVE ANDROSTANE RECEPTOR IN STUDY OF HEPATIC METABOLISM.

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Constitutive Androstane Receptor (CAR) is the primary regulator of drug metabolism and detoxification. CAR activation is connected with mitogenic effects leading to liver hypertrophy and tumorigenesis in rodents. Therefore currently known mouse CAR activators, including phenobarbital (PB) and potent agonist TCPOBOP (1,4-bis[2–(3,5-dichloropyridyloxy)]benzene), are both referred as to rodent non-genotoxic carcinogens and liver tumor promoters. Recently, stilbenoids resveratrol and *trans*-3,4,5,4´-tetramethoxystilbene (TMS) have been show to abrogate or alleviate *N*-nitrosodiethylamine/PB-induced liver carcinogenesis or associated aberration in Nrf2, NF-κB, STAT3 or oxidative stress signaling.
Thus in the present work, we examined if TMS may be an inverse agonist of mouse CAR. Unexpectedly, we have identified TMS as a novel moderate murine Car agonist in cellular reporter gene experiments, in *in silico* docking experiments as well as in induction experiments in mouse hepatocytes, in AML-12 hepatic cells, or in mice. TMS significantly up-regulates *Cyp2b10, Cyp2c29* and *Cyp2c59* mRNAs, but down-regulates expression of genes involved in gluconeogenesis and lipogenesis such as *Pck1*, *G6pc*, *Scd1, Acaca* and *Fasn* in similar degree as TCPOBOP. Importantly, TMS does not induce genes involved in liver proliferation or apoptosis such as *Mki67*, *Foxm1*, *Myc, Mcl1, Pcna, Bcl2, Bax* or *Mdm2* in C57BL/6 mice, does not promote liver hypertrophy or EdU incorporation in AML-12 cells and has no statistically significant effects on Ki67 and Pcna labeling indexes in mice, but slightly up-regulates *Gadd45β* mRNA expression.
We can thus conclude that TMS is a novel mouse Car ligand with limited effects on hepatocyte proliferation, but controlling Car-target genes involved both in xenobiotic and endobiotic metabolism.