

GABA_A Receptor Ligands Activate Liver Nuclear Receptors

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Background and Objective: The constitutive androstane receptor (CAR) exists in an inactive state in the cytoplasm of hepatocytes and is activated by chemicals with which it does not directly interact. An indirect (non-ligand) activator of CAR is the sedative phenobarbital (PB), which causes CAR to translocate to the cell nucleus. PB and other transcriptional activators of CAR-target gene CYP2B6 are also ligands of gamma amino butyric acid A receptors (GABA_AR), and there are at least sixteen different GABA_AR genes. We hypothesize that GABA_AR are involved in the upstream activation of CAR. The objective of this study was to demonstrate that specific subunits of GABA_A receptor are present in the liver and necessary for CAR activation.

Methods: Reverse transcription-polymerase chain reaction (RT-PCR) assays and western blot analyses of GABA_A receptor mRNA and protein levels were utilized to measure the expression of receptor subunits. GABA_AR ligands were screened for activation of CAR target gene CYP2B6, and HuH7 cell line was transiently transfected with CAR expression plasmid in order to measure CAR-driven luciferase reporter activity in response to treatments from a GABAergic chemical library.

Results: GABA_A receptors are differentially expressed in HuH7 cells versus primary human hepatocytes. Multiple ligands of GABA_A receptors are direct (ligand) and indirect (non-ligand) activators of CAR.

Discussion and Conclusions: Indirect activation of CAR by neuroactive pharmacological agents may involve upstream perturbation of hepatocyte GABA_A receptors.

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