Activation of Pregnane X Receptor for Xenobiotic Detoxification: A Novel Approach to Targeting Pollution-Related Diseases

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Air pollution (AP) contains many toxins that collectively harm nearly every organ in the body, and is a key risk factor for many chronic diseases. Aside from its toxic actions, AP may alter expression of the drug- and steroid-binding pregnane X receptor (PXR), which when activated upregulates expression of cytochrome P450 (CYP) enzymes, glutathione transferases (GSTs), and multidrug resistance protein 1 (MDR1), an adaptive metabolic array that mediates clearance of CS component toxins. We sought to identify new PXR agonists that may be useful for restoring PXR activity in conditions wherein it is suppressed, and their mechanisms of PXR binding and activation. We tested certain calcium channel blockers (CCBs) as a pharmacological subset of potential PXR ligands, analyzing by molecular docking methods, and identified a putative active site in the PXR LBD, along with the relevant bonds and bonding energies. We analyzed felodipine binding and agonist activity in detail, as it showed the lowest binding energy among CCBs tested. We found felodipine was a potent PXR agonist as measured by luciferase reporter assay, whereas CCBs with higher binding energies were less potent (amlodipine) or nearly inactive (manidipine), and it induced CYP3A4 expression in HepG2 cells, a known target of PXR agonism. Felodipine also both induced PXR mRNA in HepG2 hepatocytes and reduced AP (modeled by cigarette smoke extract)-induced diminution of PXR levels, indicating it modulates PXR expression. These findings significantly advance understanding of CCB-PXR interactions, by identifying both novel PXR agonists and mechanisms involved. Further research may yield translationally useful agents for protection against PXR-dysregulating agents.

Awards Won:
Third Award of $1,000