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The Aryl Hydrocarbon Receptor (AhR) Regulates P-glycoprotein at the Blood-Brain Barrier (BBB)

Xueqian (Shirley) Wang; Brian H. Hawkins, Destiny Sykes; Miller S. David
Laboratory of Pharmacology, NIH/NIEHS

At the blood-brain barrier (BBB), the ATP-driven efflux pump, P-glycoprotein (Pgp) is a major impediment to CNS pharmacotherapy. Signals that modulate Pgp transport function are complex and not fully mapped. Recent studies show that drugs and toxicants can upregulate expression of BBB transporters through a xenobiotic-activated nuclear receptor, e.g., pregnane X receptor. Here we show that ligands for the AhR induce Pgp transport in brain capillaries and therefore alter BBB function. AhR induces cytochrome P450 (CYP) 1A1 and 1B1 as well as phase II drug metabolizing enzymes, but its ability to modulate expression of transport proteins is largely unexplored. AhR is activated by widespread and persistent organic pollutants including polychlorinated biphenyls and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Upon ligand binding, AhR recruits chaperone proteins, translocates to the nucleus where it forms a heterodimer with AhR nuclear translocator (ARNT) and induces transcription. We used freshly isolated rat brain capillaries to investigate AhR-mediated modulation of P-gp mediated transport. Capillaries were incubated with a fluorescent P-gp substrate and imaged using confocal microscopy to measure luminal accumulation. Exposing rat brain capillaries to the AhR ligand, β -naphthoflavone (BNF, 0.5-5 μ M), for 4 hours increased specific P-gp transport in a concentration-dependent manner. Inhibiting transcription with actinomycin D or protein synthesis with cycloheximide abolished BNF-induced upregulation of transport. TCDD, at 0.05-0.5nM, also substantially increased P-gp transport activity and transporter expression. Resveratrol (5 μ M), a specific AhR antagonist, blocked the BNF- and TCDD-induced increases in transport. Finally, TCDD dosing of rats (1 μ g/kg or 5 μ g/kg) increased P-gp mediated transport and protein expression in brain capillaries assayed *ex vivo*. This is the first evidence that AhR ligands upregulate Pgp mediated transport in any tissue and that AhR ligands can affect drug transport at the BBB. These findings suggest that the BBB can be tightened selectively by environmental toxicants that are AhR ligands, providing increased protection, but at the expense of reduced penetration of certain therapeutic drugs.