Interaction of tryptophan metabolites with the human aryl hydrocarbon receptor in silico: tryptophan as antagonist and failure of kynurenine to dock

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Abstract

It is almost universally thought that modulation of immune function by tryptophan (Trp) metabolites involves activation of the aryl hydrocarbon receptor (AhR) mainly by kynurenine (Kyn), based on enhanced expression of cytochrome P-450 enzymes and their increased activities in cell systems and in vivo. However, DiNatale et al. (Toxicol. Sci. 2010; 115: 89-97) reported the failure of Kyn at 10 M to activate the AhR, whereas a similar concentration of kynurenic acid (KA) was effective. The recent study by Solvay et al (J Immunother Cancer 2023; 11: e006728) called into question the direct link between Kyn and the AhR and demonstrated down regulation of the AhR by Trp. In the present study, we have performed for the first time molecular docking in silico to the human AhR of the above and a range of other Trp metabolites produced in the various degradative pathways and by gut microbiota. We demonstrate that, of 29 Trp metabolites, only Kyn and 3-hydroxykynurenine fail to dock to the AhR and propose that AhR activation by Kyn is an indirect effect mediated by KA. The strongest docking is observed with FICZ (6-Formylindolo[3,2-b]carbazole), cinnabarinic acid, 5-hydroxytryptophan, N-acetyl serotonin and indol-3-yllactic acid. We propose that Trp, which docks strongly to the AhR is an AhR antagonist. Differences in AhR activation by Trp metabolites in cell systems and in vivo may be determined by the prevailing physiological conditions. The strong docking of 5-hydroxyindoles to the AhR may underpin the effects of serotonin pathway metabolites on biological processes.

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