

Reduced Central Serotonin Up-Regulates Prostaglandin E₂ Production in the Anteroventral Preoptic Region during Systemic Inflammation

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Serotonin (5-HT) is a neuromodulator involved in several central-mediated mechanisms, such as endocrine processes, behavior and sleep. Dysfunction of the serotonergic system is mainly linked to psychiatric disorders, but emerging evidence suggests that immune system activation may also alter brain 5-HT signaling. However, whether central 5-HT modulates systemic inflammation (SI) remains unknown. Thus, we measured 5-HT and its metabolite 5-hydroxyindole-3-acetic acid (5-HIAA) in the anteroventral preoptic region [AVPO - the hierarchically most important region for body temperature (Tb) control] during lipopolysaccharide (LPS)-induced SI. We also combined LPS treatment with intracerebroventricular (icv) injection of 5-HT and measured Tb ("hallmark" of SI), AVPO PGE₂ (an essential mediator of fever) and PGD₂ (a cryogenic mediator), plasma corticosterone (CORT - a stress marker with an endogenous anti-inflammatory effect) and IL-6 (an immune mediator) levels. We also assessed tail skin temperature [used to calculate heat loss index (HLI)] to assess a key thermo effector mechanism.

As expected we observed LPS-induced increases in Tb, AVPO PGE₂ (whereas PGD₂ remained unchanged), plasma CORT and IL-6 levels, as well as a decrease in HLI. These changes were accompanied by reduced levels of AVPO 5-HT and 5-HIAA. Besides we also observed negative correlations between 5-HT and 5-HIAA with plasma CORT levels and Tb, respectively. Moreover, icv 5-HT microinjection caused a U-shaped dose-response curve in LPS fever, in which the intermediate dose reduced the febrile response. Icv 5-HT microinjection prevented the LPS-induced increases in AVPO PGE₂ (whereas did not alter PGD₂), plasma CORT and IL-6 levels; besides preventing the reduced HLI. Our data are consistent with the notion that the AVPO 5-HT synthesis is down-regulated during SI favoring AVPO PGE₂ synthesis and consequently potentiating the immune response.

These results reveal a novel effect of central 5-HT as an anti-inflammatory neuromodulator that may take place during psychiatric disorders treatment with 5-HT reuptake inhibitors besides suggesting that 5-HT modulation *per se* is a potential therapeutic approach for inflammatory diseases.