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Inflammation-induced aversion is elicited by prostaglandin-dependent modulation of dopaminergic neurotransmission

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Systemic inflammation causes malaise and general feelings of discomfort. This fundamental aspect of the sickness response reduces the quality of life for people suffering from chronic inflammatory diseases and is a nuisance during mild infections like the common cold or the flu. To investigate how inflammation is perceived as unpleasant and causes negative affect, we used a behavioral test based on Pavlovian conditioning (conditioned place aversion) where mice avoid an environment which they have learned to associate with inflammation-induced discomfort. By using a combination of cell-type-specific gene deletions, pharmacology and chemogenetics, we examined the role of specific signaling molecules and neural circuits. We demonstrate that systemic inflammation induced by lipopolysaccharide (derived from E. coli) or interleukin-1β triggers aversion through MyD88-dependent activation in brain endothelial cells followed by cerebral prostaglandin E2 synthesis mediated by cyclooxygenase 1. Furthermore, we found that inflammation-induced prostaglandin E2 targets EP1 receptors on striatal dopamine D1 receptor-expressing neurons and that this signaling sequence induces aversion through GABA-mediated inhibition of dopaminergic cells. DREADD Gq-mediated activation of dopaminergic cells in the midbrain prior to the LPS challenge abolished the inflammation-induced aversion, suggesting that a decrease in dopaminergic firing is the direct cause of LPS-triggered aversion. Collectively, these findings demonstrate that prostaglandin E2-mediated modulation of the dopaminergic motivational circuitry is a key mechanism behind the negative affect induced by inflammation.

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