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Roles and mechanisms of social defeat stress-induced prostaglandin E_2 synthesis in the mouse brain

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Prolonged or excessive stress caused by social environment induces psychological and physiological alterations, and increases a risk for psychiatric disorders. In repeated social defeat stress (SDS), a rodent model to study psychiatric disorders, we previously reported that prostaglandin (PG) E_2, an inflammation-related lipid mediator, and toll-like receptor (TLR) 2/4, innate immune receptors, are crucial for repeated SDS-induced social avoidance. However, the mechanism of SDS-induced PGE_2 synthesis in the brain and the involvement of TLR2/4 remain unknown. Here we show that SDS increased the PGE_2 contents in subcortical brain regions of wild-type mice, and that this increase was abolished by perturbations of TLR2/4, COX1 and COX2. It has been reported that free arachidonic acid for PGE_2 synthesis in the brain is supplied from monoacylglycerol lipase (MAGL)-mediated metabolism of endocannabinoid 2-arachidonoylglycerol. Consistently, systemic administration of JZL184, a MAGL inhibitor, inhibited SDS-induced PGE_2 synthesis in subcortical regions and social avoidance. These results suggest that SDS induces PGE_2 synthesis derived from 2-arachidonoylglycerol via the MAGL-COX pathway in subcortical regions to induce social avoidance, and that this PGE_2 synthesis is maintained by TLR2/4 activity.