Influence of the immune system on reward circuitry: Implications for addiction and depression.

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Depression is a debilitating condition associated with high rates of addiction comorbidity. We have found that the pro-inflammatory cytokine interleukin-6 (IL-6) is highly upregulated in serum from patients with treatment-resistant major depression, as well as in mice after chronic social stress, which induces a mixed phenotype of addiction- and depression-like behavioral responses. The source of IL-6 is from bone marrow derived leukocytes, which is released in response to stress and can penetrate the brain and act directly on neural circuits controlling mood, emotion, and reward. To study peripheral IL-6, we have generated bone marrow chimeric mice that lack IL-6 only in bone marrow derived leukocytes and found that these mice were resilient to social stress. We also administered systemic monoclonal antibodies to sequester IL-6 and promote resilience. Our current investigation suggests that stress causes a breakdown of the neurovasculature, which leads to impairments in the blood brain barrier and greater influx of inflammatory signals into the brain. We are now testing the functional relevance of stress-induced neurovascular damage in a battery of depression- and addiction-like behaviors. Our initial results suggest that peripheral immune signals interface directly with brain reward centers to control depression- and addiction-like behaviors.