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Who Knew? Dopamine Transporter Activity Is Critical in Innate and Adaptive Immune Responses

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The dopamine transporter (DAT) regulates the dimension and duration of dopamine transmission. DAT expression, its trafficking, protein–protein interactions, and its activity are conventionally studied in the CNS and within the context of neurological diseases such as Parkinson's Diseases and neuropsychiatric diseases such as drug addiction, attention deficit hyperactivity and autism. However, DAT is also expressed at the plasma membrane of peripheral immune cells such as monocytes, macrophages, T-cells, and B-cells. DAT activity via an autocrine/paracrine signaling loop regulates macrophage responses to immune stimulation. In a recent study, we identified an immunosuppressive function for DAT, where blockade of DAT activity enhanced LPS-mediated production of IL-6, TNF-α, and mitochondrial superoxide levels, demonstrating that DAT activity regulates macrophage immune responses. In the current study, we tested the hypothesis that in the DAT knockout mice, innate and adaptive immunity are perturbed. We found that genetic deletion of DAT (DAT−/−) results in an exaggerated baseline inflammatory phenotype in peripheral circulating myeloid cells. In peritoneal macrophages obtained from DAT−/− mice, we identified increased MHCII expression and exaggerated phagocytic response to LPS-induced immune stimulation, suppressed T-cell populations at baseline and following systemic endotoxemia and exaggerated memory B cell expansion. In DAT−/− mice, norepinephrine and dopamine levels are increased in spleen and thymus, but not in circulating serum. These findings in conjunction with spleen hypoplasia, increased splenic myeloid cells, and elevated MHC-II expression, in DAT−/− mice further support a critical role for DAT activity in peripheral immunity. While the current study is only focused on identifying the role of DAT in peripheral immunity, our data point to a much broader implication of DAT activity than previously thought. This study is dedicated to the memory of Dr. Marc Caron who has left an indelible mark in the dopamine transporter field.