Neuroimmune Circuitry: Linking the Dopamine Neuronal Activity and Peripheral Immunity in Parkinson

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Emerging evidence suggests that dopamine transmission within the CNS extends its influence beyond the brain, modulating peripheral immune function. Our recent findings in both Parkinson's disease (PD) patients and animal models of PD demonstrate that the degeneration of midbrain dopamine neurons is associated with marked alterations in peripheral immunity. We uncover a previously uncharacterized multisynaptic neural circuit linking midbrain dopamine neurons to the spleen, a major peripheral immune organ. Using a combination of viral tracing, in vivo chemogenetics, and molecular analyses, we show that dopamine neurons in the midbrain project to and modulate dorsal vagal complex (DVC) neurons that express D1-like and D2-like dopamine receptors. These DVC neurons, in turn, connect to the celiac ganglion, forming a functional relay to the spleen. In vivo activation of midbrain dopamine neurons led to dopamine release in the DVC and upregulation of immediate early gene expression in both the DVC and celiac ganglion, indicative of increased neuronal activity along our identified brain-body circuit. Functionally, stimulating this midbrain-to-spleen circuit resulted in reduced spleen weight and a selective reduction in naïve $CD4^+$ T-cell populations, without altering total T-cell counts, suggesting a targeted immune modulation effect rather than generalized immunosuppression. These findings define a novel midbrain-spleen axis through which central dopaminergic activity can influence peripheral immune homeostasis. This brain-body circuit opens new avenues for understanding the neural control of immunity and provides mechanistic insight into the immune dysregulation observed in conditions such as Parkinson's disease. Moreover, this work identifies new potential targets for therapeutic intervention aimed at restoring immune balance in disorders involving disrupted dopamine signaling.