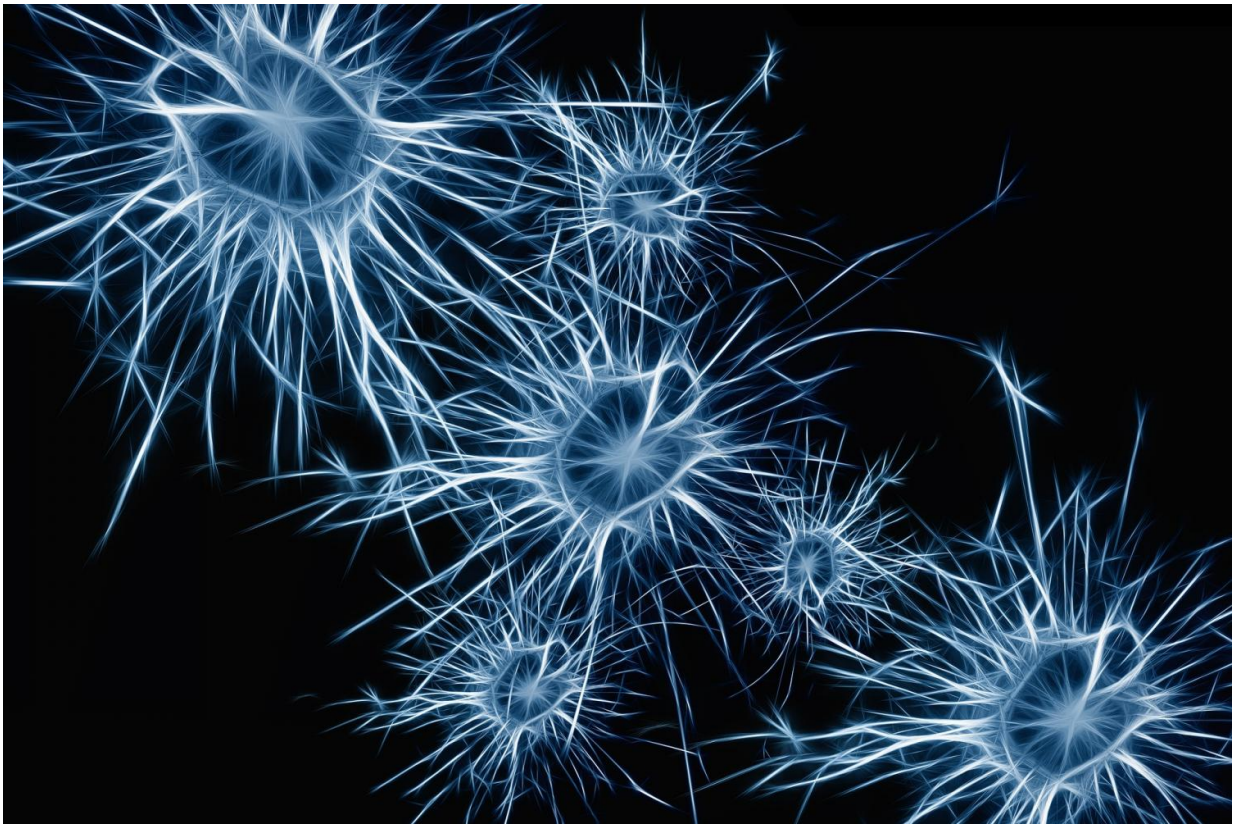


Unraveling key role of astrocytic dopamine receptor D2 in autoimmune disease MS

July 28 2022, by LIU Jia



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In a study published in the *Journal of Experimental Medicine*, research groups led by Prof. Zhou Jiawei from the Institute of Neuroscience, Center for Excellence in Brain Science and Intelligence Technology of

the Chinese Academy of Sciences (CAS) and Prof. Liang Xinmiao from the Dalian Institute of Chemical Physics of CAS, demonstrated that astrocytic dopamine receptor D2 (DRD2) plays a key role in the pathogenesis of multiple sclerosis (MS).

MS is an immune-mediated disease in the central nervous system (CNS), which is characterized by chronic and progressive inflammation, demyelination and neurodegeneration. Many patients are at first diagnosed with relapsing–remitting form of the disease which likely progresses into a second phase, secondary progressive multiple sclerosis (SPMS). Although there is more than a dozen of disease-modifying drugs available for MS treatment, the efficacy of these treatments remains limited.

Emerging evidence has suggested that the deregulated CNS innate immunity plays crucial roles on the onset and progression of the disease. Understanding on this highly complex process remains very limited. Therefore, it is critical to identify and characterize the cellular and [molecular basis](#) of disrupted CNS innate immunity in MS that provides a new avenue for the intervention of the disease progression.

Despite the increasing appreciation of the importance of CNS [glial cells](#) under pathological conditions, including experimental autoimmune encephalomyelitis (EAE), an animal model of MS, and MS, the molecular and [cellular mechanisms](#) underlying the regulation of astrocyte-associated CNS innate immunity and the functional contribution of these mechanisms to the EAE/MS pathogenesis remain elusive.

In this study, researchers identified DRD2 in astrocytes (aDRD2), but not in neurons, as a determinant of white matter astrocyte activation leading to the sustained inflammation primarily within the CNS during EAE. They found that selective ablation of aDrd2 remarkably abrogated

EAE progression. Moreover, they found that aDrd2 tightly controlled the expression of PTS which robustly regulates NF- κ B pathway-dependent inflammatory response via PKC-delta. Treatment of either dopamine or DRD2 agonist cabergoline activated NF- κ B pathway. Blockade of aDRD2 signaling using dehydrocorybulbine (DHCB), a DRD2 inhibitor derived from herb *Corydalis*, remarkably attenuated EAE phenotype.

These data suggested that DRD2/PTS/PKC δ signaling in astrocytes plays a key role in the propagation of [inflammatory response](#) that is a critical machinery driving neurodegeneration in EAE.

This study reveals previously uncharted mechanisms of [disease](#) pathogenesis, and raises the possibility that blockade of DRD2/PTS signaling in astrocytes could provide therapeutic benefit in autoimmunity diseases such as MS.

More information: Shen-zhao Lu et al, Inhibition of astrocytic DRD2 suppresses CNS inflammation in an animal model of multiple sclerosis, *Journal of Experimental Medicine* (2022). [DOI: 10.1084/jem.20210998](https://doi.org/10.1084/jem.20210998)

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