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January 27th, 2021

Dear Dr. Stern,

Enclosed please find a manuscript entitled "**A paracrine mode of microglia in modulating basal sympathetic tonicity**" for publication in **Science** as a **Report**. None of the material has been published or is under consideration elsewhere, including the Internet.

Hypothalamic paraventricular nucleus (PVN) is a key nucleus in the regulation of autonomic function. Hyperactivation of PVN pre-sympathetic neurons is associated with numerous diseases, including cardiovascular diseases, metabolic disorders and even some neurodegenerative diseases. However, there is limited information on how the intrinsic activity of PVN neurons is maintained in normal condition. In this study, we focus on local cellular and molecular mechanisms for regulating the activation of PVN pre-sympathetic neurons.

As many researches including ours (*Science* 2020; PMID: 32029629) suggest, microglia are involved in regulating neural activities, and this action is mainly mediated through synaptic pruning and phagocytosis of neuronal components by microglia. In this study, we unexpectedly found that resident microglia regulate the basal activities of PVN pre-sympathetic neurons through a paracrine mode. Microglia constitutively released platelet derived growth factor (PDGF) B which sustained the expression of a few potassium I_A channels and maintained the basal K^+ currents in PVN pre-sympathetic neurons, providing a "brake" system by which neuron over-activation was prevented. As such, depletion of microglia, as well as microglia-specific abrogation of PDGFB expression, enhanced the activities PVN pre-sympathetic neurons, leading to a profound autonomic dysfunction. Interestingly, although microglia also regulated K^+ channel expression on PVN endocrinal arginine vasopressin (AVP) neurons, loss of microglia had limited effects on the activities of AVP neurons in a basal condition. These findings suggest that microglial modulation of neuronal K^+ channels and K^+ currents is a common feature in PVN, but its impact on firing property is neuron type-dependent.

The significance of our study is summarized as:

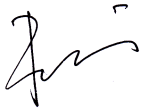
(1) For the first time to our knowledge, resident microglia are shown to regulate the intrinsic neuronal activity through a paracrine fashion in steady state.

(2) Microglia-derived PDGFB is critical in maintaining neuronal potassium channel expression through PDGFRα, which is a novel mechanism for preventing from neuron overactivity.

(3) We also demonstrate that microglia play a crucial role in regulating sympathetic outflow, highlighting a non-immune function employed by microglia in maintaining homeostasis for not only the central nervous system, but the whole body as well.

We thus believe that our study will be of interest to general readers and be of importance regarding scientific advance. Thanks for your time and effort in handling our manuscript.

Sincerely,



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