Cellular and Molecular Mechanism of Brainstem Cardiovascular Regulation

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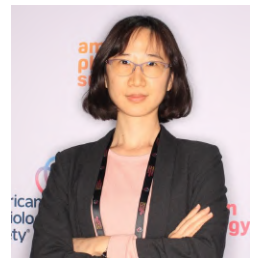

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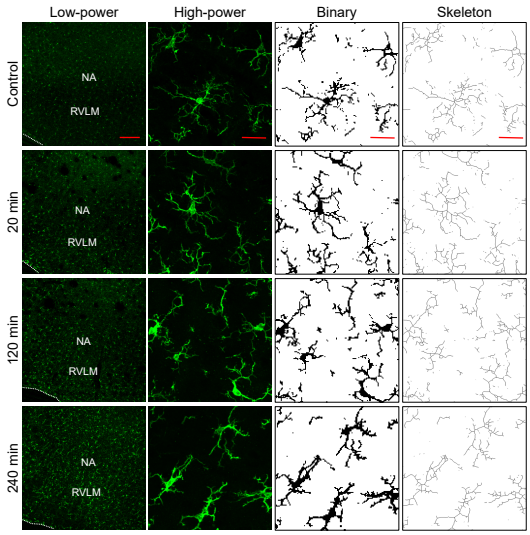
Our research interests are primarily on signaling cascades and neural circuits involved in brainstem cardiovascular regulation. Our approach is to integrate cellular and molecular biology into systemic physiology using radiotelemetric recording and spectral analysis of blood pressure and heart rate in clinically-relevant animal models, including neurogenic hypertension, hepatic encephalopathy, and cadmium-induced cardiovascular toxicity. We have further expanded our research horizons to image changes in functional connectivity between key brainstem nuclei involved in the baroreflex circuits, and showed that these changes bear physiological and pathological meaning. In recent years, we also extended research interest to the mechanism of neuron injury and astrocyte-and-neuron interaction during neurological complications.

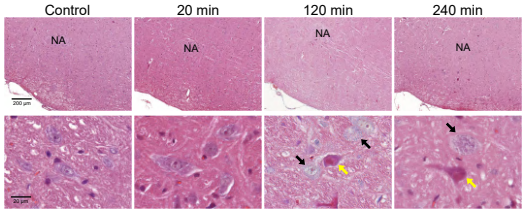
Neuroinflammation underpin cadmium-induced cardiovascular dysregulation

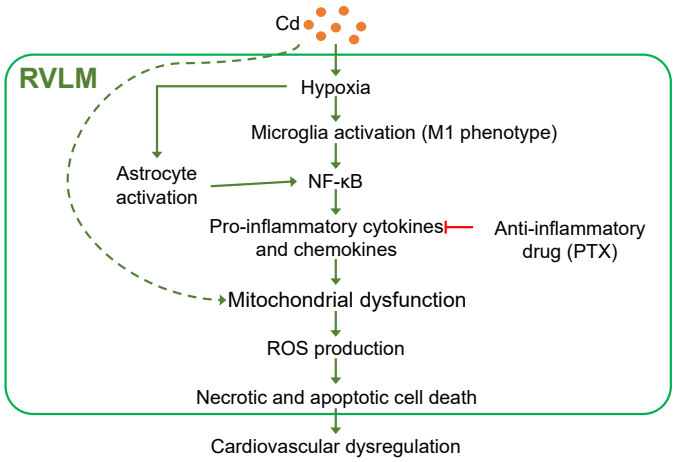
Cadmium is a heavy metal and environmental toxicant that has been shown to cause cardiovascular toxicity and mortality in mammals, few mechanistic studies address its acute circulatory actions. We found that cadmium elicits sub-lethal circulatory depression by causally inducing neuroinflammation and microglial/astrocyte activation in RVLM that leads to cardiovascular dysregulation.

Cadmium induces microglia activation in rostral ventrolateral medulla (RVLM)



Cadmium induces necrotic and apoptotic cell death in RVLM

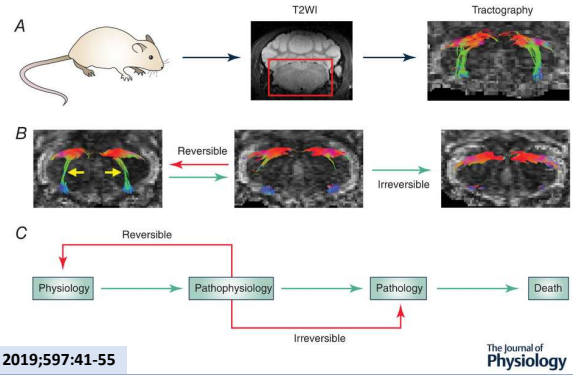




Front Physiol. 2019;10:772; *J Inflamm Res.* 2021;14:3863-77

Diffusion tensor imaging in the baroreflex circuit

We also combined molecular imaging with our physiological evaluation of brainstem cardiovascular regulation using diffusion tensor imaging (DTI) to detect functional connectivity between key brainstem nuclei involved in the baroreflex circuit. Under pathophysiological conditions when the disruption of the functional connectivity is reversible, the associated disease condition (e.g. neurogenic hypertension) is amenable to remedial measurements. However, fatality ensues when pathophysiological conditions evolve to pathological conditions (e.g. hepatic encephalopathy) when the functional connectivity is irreversibly severed.

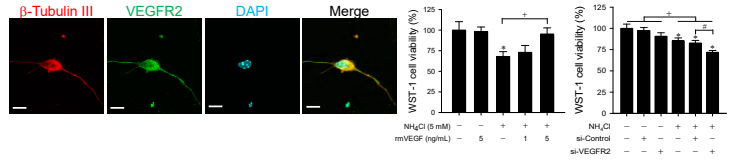


J Physiol. 2019;597:41-55 The Journal of Physiology

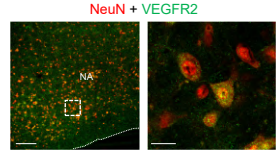
Protective role of VEGF/VEGFR2 during hepatic encephalopathy

Acute hepatic failure is a devastating consequence of hepatotoxic liver injury that can lead to the development of neurological complication called hepatic encephalopathy (HE). In this study, we found that VEGFR2 heterozygous mice and loss-of-function of VEGF by immunoneutralization in C57BL/6 mice showed a reduction of survival rate during HE. Loss-of-function of VEGF also significantly reduced ATP production or exacerbated apoptotic cell death. We therefore suggest that endogenous VEGF/VEGFR2 plays a protective role against the impairment of baroreflex and fatality may via blunting mitochondrial dysfunction-induced bioenergetics failure and apoptotic cell death in RVLM during HE.

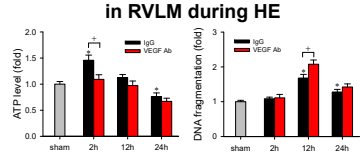
VEGF/VEGFR2 maintains cell viability in *in vitro* model of HE



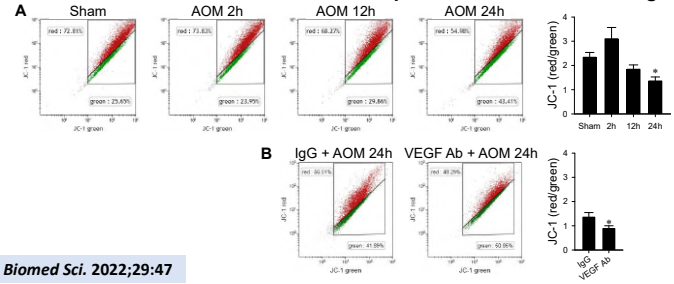
VEGFR2 is present in RVLM neuron



VEGF protects ATP production and diminishes apoptotic cell death in RVLM during HE



VEGF maintains mitochondrial membrane potential in the RVLM during HE



J Biomed Sci. 2022;29:47