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Modulation of microvascular blood flow and stroke outcome via GPR39

Abstract

Ischemic stroke is a leading cause of morbidity and mortality. Current therapies are now available to open occluded large vessels to reinstate blood flow, but patients with successful recanalization may not have good clinical outcomes. This discrepancy is due, in part, to continued microvascular obstruction, and improving downstream microvascular blood flow may improve stroke outcomes in our NeuroICU and interventional neuroradiology patients. P450 eicosanoids are lipid signaling molecules, derived from arachidonic acid, that are critical regulators of microvascular blood flow, and whose levels are known to be altered during stroke. Yet, the receptor mediating these effects was unknown. Recently, GPR39 was identified by our group to be a dual sensor of two P450 eicosanoids: the microvascular dilator 14,15-EET and constrictor 15-HETE. GPR39 is expressed in cells that have vasoactive implications such as arteriolar vascular smooth muscle cells and peri-capillary pericytes. Thus, GPR39 is in a unique position to sense the balance of vasoactive eicosanoids and modulate microvascular blood flow during stroke. In Aim 1, I will transiently occlude the middle cerebral artery (MCAO) of GPR39 transgenic knock-out (KO) mice and their wild type (WT) littermates to assess for infarct size differences. In Aim 2, I will assess functional recovery using behavior testing and use optical microangiography to assess differences in microvascular blood flow. Furthermore, since P450 eicosanoids have previously been shown to modulate stroke in a sex-specific manner, I will address each aim in both sexes. Results of our studies will elucidate the role of GPR39 in ischemic stroke, which may serve as a therapeutic target.