3-15-2020

The role of insulin-like growth factor 1 in specific brain cells following ischemia

Cellas Hayes
University of Mississippi

Summary:

Overview:

My name is Cellas Ari'ka Hayes, and I am a first-year graduate student in the School of Pharmacy Department of BioMolecular Sciences. I am pursuing a Ph.D. in Pharmaceutical Sciences with an emphasis in Pharmacology. My project will assess the effects of insulin-like growth factor-1 (IGF-1), an anabolic polypeptide on the damage caused by ischemic stroke including glial cell death, neuronal tress, infarct size, neurological deficits, and behavioral changes.

Intellectual Merit:

Ischemia is one of the largest causes of neurological deficits that in elderly individuals in the United States[1]. Since our life expectancy has increased concurrently with our predispositions to stroke, it is necessary to find ways to treat acute ischemia. On the forefront, discovering how ischemia affects the brain at the cellular level is critical to discover pharmacological treatments for stroke. Clinical studies have shown lower IGF-1 serum levels are more common in individuals who have increased damage caused by ischemia. There is also an increase in unfavorable outcomes with reduced IGF-1 using the Modified Rankin Scale (MRS) [2]. Other studies have shown an inverse relationship between IGF-1 levels and survival rate of individuals who experienced a stroke [3, 4]. *In vivo* studies have also shown that administering IGF-1 pre or post stroke attenuates damage caused by ischemia [5-8]. In this project, I will try to elucidate IGF-1's role in stroke.

The most difficult task for this project will be learning to perform middle cerebral artery occlusion (MCAO) to induce ischemia on transgenic mice where IGF-1 has been removed in either neurons or astrocytes. To understands the effects of ischemia and IGF-1's role, locomotion, strength, and behavior will be assessed: avoidance memory, grip strength, cat walk, adhesive tape test, cylinder test, pasta test, and rotarod. Neurological deficit score will be assessed immediately after reperfusion as described by Jiang *et* al[8]. After all behavioral test are conducted, the amount of tissue death (infarct) will be quantified using the cresyl violet staining protocol adopted from Rousselet *et al* [9]. Other analysis includes quantifying the number of TUNEL positive cells, the amount of glutamate release by the target cells, and glial cell changes in the infarct and periinfarct zone. Changes in miRNAs (mir33a, 320b,92b,29b,29c,30a, and 15a), caspase3&9, Akt/gsk3b/P70 s6k cascade, and phosphorylated ERK to ERK pathway will also be quantified to see if removal of IGF-1 in neurons and/or astrocytes alters these pathways known to change in ischemia. To achieve a power of 0.8 based on type I error of 5% with a 15% group difference, 16 mice will be needed to detect a significant difference.

External Opportunity:

This proposed research will be submitted to the NIH through the Ruth L. Kirschstein National Research Service Award (NRSA) Individual Predoctoral Fellowship to Promote Diversity in Health-Related Research (Parent F31 -Diversity). My sponsor will be my mentor, Dr. Nicole Ashpole who is currently funded for the NIA for a different research question. The potential funding includes a stipend of $24,323 limited to 5 years of support and 60% of the actual tuition level at the applicant institution, up to $16,000 per year, will be also provided. There are three due dates within the year and my plans are to submit Fall 2020. This award is given to students classified as minorities, disabled, low-income, or come from disadvantage rural/inner-city backgrounds. Receiving this fellowship will give me the foundation needed to apply for the NIH (or other outside) funding. This fellowship will allow me to receive national funding which will start my journey as a well-known scientist which could lead to other national funding sources.

1. Mortality, G.B.D. and C. Causes of Death, *Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015.* Lancet, 2016. **388**(10053): p. 1459-1544.
2. Tang, J.H., et al., *Insulin-like growth factor-1 as a prognostic marker in patients with acute ischemic stroke.* PLoS One, 2014. **9**(6): p. e99186.
3. Roubenoff, R., et al., *Cytokines, insulin-like growth factor 1, sarcopenia, and mortality in very old community-dwelling men and women: the Framingham Heart Study.* Am J Med, 2003. **115**(6): p. 429-35.
4. Denti, L., et al., *Insulin-like growth factor 1 as a predictor of ischemic stroke outcome in the elderly.* Am J Med, 2004. **117**(5): p. 312-7.
5. Sun, C., et al., *Glutamate attenuates IGF-1 receptor tyrosine phosphorylation in mouse brain: possible significance in ischemic brain damage.* Neurosci Res, 2012. **74**(3-4): p. 290-7.
6. Liu, X.F., et al., *Intranasal administration of insulin-like growth factor-I bypasses the blood-brain barrier and protects against focal cerebral ischemic damage.* J Neurol Sci, 2001. **187**(1-2): p. 91-7.
7. Bake, S., et al., *Blood brain barrier and neuroinflammation are critical targets of IGF-1-mediated neuroprotection in stroke for middle-aged female rats.* PLoS One, 2014. **9**(3): p. e91427.
8. Jiang, S.X., et al., *Chlortetracycline and demeclocycline inhibit calpains and protect mouse neurons against glutamate toxicity and cerebral ischemia.* J Biol Chem, 2005. **280**(40): p. 33811-8.
9. Rousselet, E., J. Kriz, and N.G. Seidah, *Mouse model of intraluminal MCAO: cerebral infarct evaluation by cresyl violet staining.* J Vis Exp, 2012(69).