Investigation of Mechanisms of Action of FGF1 and FGF21 on the Prevention of Diabetic Retinopathy

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Type-2 diabetes results when insulin producing beta-cells cannot compensate for rising insulin resistance. Diabetic pathologies may ensue including retinopathies. Current treatments show adverse effects including weight gain, bone loss and risk of CHF. Studies have shown fibroblast growth factor-21 (FGF21), an endocrine FGF, and fibroblast growth factor-1 (FGF1), a non-endocrine FGF, have therapeutic potential by increasing insulin sensitivity through unresolved mechanisms. In the present study, exogenous FGF1 (0-100ng/mL) and FGF21 (0-100ng/mL), were investigated in the murine-photoreceptor cell line, 661W, attempting to elucidate pathways promoting glucose uptake. Proliferation occurred at 10ng/mL FGF1 ($p<0.05$) and greater than 1ng/mL FGF21 ($p<0.01$). Insulin receptor expression increased at 100ng/mL FGF1 ($p<0.01$) and greater than 1ng/mL FGF21 ($p<0.05$). Glucose uptake increased at 100ng/mL for each FGF ($p<0.001$). GLUT2 expression increased with FGF1, but decreased at greater than 1ng/mL of FGF21 ($p<0.05$), suggesting alternative mechanisms. pAKT expression increased at concentrations greater than 1ng/mL in FGF1 treated cells only, while pERK1/2 expression increased at 100ng/mL in FGF21 treated cells only; supporting alternative pathways ($p<0.001$). LY294002 (PI3K/AKT inhibitor) abolished the FGF1 induced increase in glucose uptake implicating the PI3K/AKT pathway, however the FGF21 increase was unaffected. Inflammatory cytokine, Interleukin-6, decreased across concentrations of FGF21 ($p<0.01$), yet FGF1 did not affect its production. Green opsin photoreceptor expression was inhibited for each FGF at low doses ($p<0.05$), with a high dose restorative effect. Both FGF1 and FGF21 appear to have therapeutic potential in the type-2 diabetic retina through alternate mechanisms.

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