Sex differences in the therapeutic effects of pioglitazone on type II painful diabetic neuropathy

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Background: Blood levels of methylglyoxal (MG), a glucose metabolite, are elevated in patients with diabetes, and even further elevated in patients with painful diabetic neuropathy (PDN). MG goes onto to form AGEs (Advanced Glycation End Products). AGEs have been characterized as being involved in aging and neurological disorders such as alzheimers (Source). Current strategies to combat the formation of AGEs include using drugs to break down AGEs, or blocking RAGEs (Receptor for advanced glycation end products).

Purpose/Hypothesis: We found that intraplantar and intrathecal injection of MG dose-dependently elicits pain-like behaviors in mice (e.g. licking and lifting of the hind paw) as well as hyperalgesia (mechanical and heat hypersensitivity). Pioglitazone, a PPARγ receptor agonist, is FDA approved for the treatment of type II diabetes and reduced MG-induced hypersensitivity in male mice (Laird, unpublished). We are now testing the hypothesis that pioglitazone is more effective at reducing MG-induced hyperalgesia in female mice than in male mice (Sorge et al, 2015).

Methods: We will be using von Frey filaments to test mechanical sensitivity, and a hot plate assay to test heat sensitivity. Mice of each sex will be given varying amounts of pioglitazone systemically. Our preliminary studies indicated an optimal dose and injection volume for intraplantar administration of MG to be 100ug/5ul for mechanical tests and 100ug/10ul for thermal tests, and 10ug/5ul for intrathecal administration. 30 minutes after injection of pioglitazone or vehicle, MG will be administered into the paw or intrathecal space. Successful intrathecal injection is recognized by a characterized tail flick following insertion.

Results/Conclusions: Our findings suggest that pioglitazone is more effective in female mice than in male mice. We found that doses 100x lower in females reversed MG-induced hypersensitivity than in male mice. Future studies will investigate the contribution of T-cells and microglial cells to this phenomenon, as well as applying pioglitazone therapy to different models of PDN, such as STZ-induced diabetes, db/db mice, and chronic models of diabetes.