A Role for Central PPARγ in the Regulation of Glucose Homeostasis?
Matthew M. Johnson, Karen K. Ryan, Darleen Sandoval, Stephen C. Woods and Randy J. Seeley; *University of Cincinnati, Obesity Research Center*

PPARγ is a nuclear receptor found in various peripheral tissues including fat and liver that has modest binding affinity to various endogenous fats and fat metabolites. Once activated, gene products of this receptor play significant roles in adipogenesis, lipid storage, and improved glucose homeostasis. Therapeutic agonists such as thiazoladinediones (TZDs) benefit glucose homeostasis in type II diabetic patients, but also cause significant weight gain. PPARγ is also found in the CNS but its function there remains unknown. The CNS plays an important regulatory role in both energy and glucose homeostasis. Therefore, we hypothesized that central activation of PPARγ by TZDs play a role in regulating the observed changes in energy and glucose homeostasis. To test this hypothesis rats had a cannula permanently implanted into the third cerebral ventricle, and we performed various studies to test the role of the CNS PPARγ system in energy and glucose homeostasis. We found that i3vt administration of Rosiglitazone, a well-known TZD, caused marked increases in food intake when compared with rats receiving vehicle injections. Likewise, Rosiglitazone blunted the weight loss effects in the treatment group when considering the larger weight loss observed in the control group. These effects seen in energy metabolism led us to expand our investigation of central PPARγ to determine its role in the regulation of glucose homeostasis. Our data showed no significant effect of central PPARγ activation by Rosiglitazone on glucose tolerance. These data suggest that TZD's act peripherally to benefit glucose homeostasis, but centrally to cause weight gain. Understanding the mechanisms behind this weight gain, which is arguably contraindicated in these patients, could lead to development of a more targeted pharmacological agent that benefits glucose homeostasis without the adverse weight gain. This study was supported in part by NIH grants T35 DK 60444.