MARCH 2017

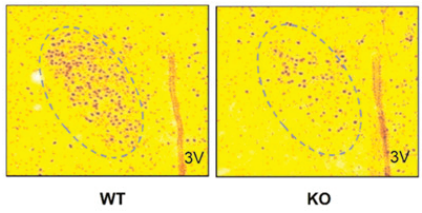
diabetes®

In This Issue of *Diabetes*

By Max Bingham, PhD

A Role for GLUT4 in the Brain in Whole-Body Glucose Homeostasis

The role of the GLUT4 protein in the brain is the subject of a series of experiments by Reno et al. (**p. 587**), and they suggest it may have a critical role in sensing and responding to changes in blood glucose. Although much work has been done on characterizing the role of GLUT4 in muscle and adipose tissue, very little is known about the role of the protein in the brain, even though its presence in the central nervous system has been established for a while. The experiments focused primarily on 8- to 16-week-old mice with a brain-specific knockout of GLUT4 and aimed to then establish a role for the protein in whole-body glucose homeostasis. Using a series of immunohistochemical studies, the authors demonstrate what appears to be a central role for the protein in glucose homeostasis. After verifying that the knockout of GLUT4 resulted in a 99% reduction in brain GLUT4 compared with controls, they show that despite normal feeding and fasting glycemia, the knockout mice had impaired glucose tolerance and insulin resistance and reduced glucose uptake in the brain. Then, after inducing hypoglycemia, the knockout mice had impaired glucose sensing and impaired counterregulation in areas of the brain that are essential to glucose sensing. Subsequent experiments involving the pharmacological inactivation of GLUT4 in the rat brain and electrophysiological studies in neurons from the knockout mice confirmed the findings. Commenting more widely on the study, author Simon J. Fisher told *Diabetes*: "Expanding upon the well-established role of GLUT4 in regulating glucose uptake in peripheral tissues, we now demonstrate that GLUT4 is a brain glucose sensor that serves to regulate whole-body glucose homeostasis. These findings highlight the emerging body of literature linking brain glucose transport/utilization to peripheral glucose metabolism. Altered expression of brain GLUT4 in disease states may therefore contribute to the pathological defects associated with insulin resistance and diabetes."

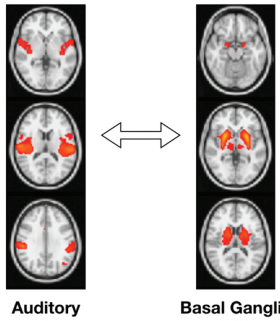


Representative *c-fos* immunostaining of the hypothalamic paraventricular nucleus in wild-type (WT) and brain-specific GLUT4 knockout (KO) mice after 2 h of hypoglycemia.

Reno et al. Brain GLUT4 knockout mice have impaired glucose tolerance, decreased insulin sensitivity, and impaired hypoglycemic counterregulation. Diabetes 2017;66:587–597

Brain Hyperconnectivity in Young Children With Type 1 Diabetes

A neuroimaging study by Saggar et al. (**p. 754**) suggests that young children with type 1 diabetes may have enhanced brain connectivity when compared with age-matched children without diabetes. Consequently, the authors suggest that such hyperconnectivity might play a compensatory role in at least temporarily offsetting the swings in glycemia that characterize the disease at such a young age. Using resting-state functional MRI, the authors examined the connectivity in large-scale brain networks in young children (aged 4–11 years) with and without type 1 diabetes. While observing increased brain connectivity in the children with type 1 diabetes when compared with control subjects, they further report that this increased connectivity was also positively associated with cognitive functioning (specifically executive functioning and processing speed). Although there were no overall group differences in cognitive function, they suggest there may be a putative compensatory role for hyperconnectivity in the brains of children with the disease. According to the article, the hyperconnectivity was observed across several cortical and subcortical regions, as well as within and between some of the large-scale brain networks. The authors go on to propose a number of mechanisms that may explain the outcomes, including the suggestion that hyperconnectivity in several brain regions could be a reaction to loss in connectivity elsewhere. Author Manish Saggar said: "Our findings provide preliminary evidence for functional brain reorganization in young children with type 1 diabetes. As no significant differences in cognitive functioning have yet been observed in our cohort with type 1 diabetes relative to control subjects without diabetes, it is possible that the functional connectivity can be used as a biomarker of adaptation to disease progression. Going forward, longitudinal changes in functional connectivity could provide a clear understanding for the role of type 1 diabetes in young developing brains."



Between-network connectivity differences were examined for all combination of resting-state networks (RSNs) extracted using independent component analysis (corrected for multiple comparisons). Out of all between-network connectivity examinations, connectivity between the auditory and basal ganglia RSNs was found to be significantly different between groups, such that children with type 1 diabetes had significantly higher connectivity (than control subjects without diabetes) between the two RSNs.

Saggar et al. Compensatory hyperconnectivity in developing brains of young children with type 1 diabetes. Diabetes 2017;66:754–762

MARCH 2017

diabetes®

Population-Based Cohort Study and Meta-analysis Reveals Associations Between Sex Hormones and Risk of Type 2 Diabetes in Women

According to the outcomes of a large prospective cohort study in the Netherlands, lower levels of sex hormone–binding globulin (SHBG) and higher levels of estradiol are independent risk factors for type 2 diabetes in postmenopausal women. The relationship, reported by Muka et al. (**p. 577**), suggests the sex hormones may indicate risk independently of other established risk factors for diabetes, such as BMI and glucose and insulin levels. A systematic review and meta-analysis reportedly then further established validity, and according to the authors, this suggests that both SHBG and total estradiol are robust risk markers for the disease. The study, which is based on the Rotterdam Study prospective cohort, identified 3,117 postmenopausal women without diabetes at baseline, of which, 384 incident cases of type 2 diabetes subsequently developed in 11 years of follow-up. Following analysis of blood samples collected over time for a range of sex hormones and other related biochemical markers, the authors established that SHBG was inversely associated with risk of type 2 diabetes, whereas total estradiol was associated with increased risk. Testosterone, meanwhile, was not associated at all with risk of type 2 diabetes. As a result of their analysis, the authors suggest that if the outcomes can be replicated in further studies, the two hormone markers might be used to identify high-risk postmenopausal women in a clinical setting. They also speculate on possible mechanisms behind the result but stress that further work is needed to properly address that angle. Author Taulant Muka commented: "The findings of an increased risk of diabetes associated with high estrogen support the concern for the safety of hormone replacement therapy use in postmenopausal women. Also, our results should encourage future research to investigate whether plasma sex hormone levels may have clinical utility in patient stratification and intervention based on the risk of developing diabetes in women."

Muka et al. Associations of steroid sex hormones and sex hormone–binding globulin with the risk of type 2 diabetes in women: a population-based cohort study and meta-analysis. Diabetes 2017;66:577–586

AMPK Mediates Improvements in Muscle Insulin Sensitivity After Exercise

The search for molecular links behind the insulin-sensitizing effects of acute exercise goes on with fresh evidence now emerging from a study by Kjøbsted et al. (**p. 598**). The study suggests that AMPK is a necessary component of the signaling pathway involved in increasing insulin sensitivity for glucose uptake in muscle after exercise and that subsequently whole-body insulin sensitivity may also be enhanced. The data will add to the growing body of evidence that exercise likely induces activation of AMPK, which, in turn, potentiates insulin to increase phosphorylation of TBC1D4, thus leading to enhanced muscle glucose uptake: the so-called AMPK-TBC1D4 signaling axis. As a result of the outcome, the authors suggest that AMPK likely represents a target for both physiological and pharmacological interventions for both the prevention and treatment of muscle insulin resistance, which will of course be relevant in type 2 diabetes and likely other conditions. The experiments center on mouse knockout models where AMPK was deleted in skeletal muscle only. The authors examine how either contraction of hindlimb muscles or treadmill exercise affects muscle and whole-body insulin sensitivity in the presence or absence of AMPK. Using a combination of techniques, they demonstrate the likely molecular outcomes of the deletions, establishing a causal link between contraction-regulated signaling involving AMPK and TBC1D4 and subsequent improvements in muscle insulin sensitivity. Author Jørgen F.P. Wojtaszewski said: "We are fascinated by the health-beneficial effects of exercise in general. Our study illuminates one of the molecular mechanisms involved. If this mechanism can be further substantiated in man, our new insights hold great clinical potential. Our observation strengthens the idea of targeting AMPK in skeletal muscle to combat insulin resistance and suggests that other non-exercise, yet physiological AMPK stimuli may also increase muscle insulin sensitivity in man. Such scientific progress would make significant contributions to the health of many for whom physical activity is not an option in daily life."

Kjøbsted et al. Enhanced muscle insulin sensitivity after contraction/exercise is mediated by AMPK. Diabetes 2017;66:598–612

DOI: 10.2337/db17-ti03