Introduction

Prader-Willi syndrome (PWS) is a genetic syndrome, characterized by low birth weight and neonatal failure-to-thrive, mental retardation, gross hyperphagia and obesity developing in childhood, hypogonadism and growth hormone (GH) deficiency contributing to short stature. PWS arises from lack of expression of imprinted genes within the paternally derived chromosome 15q11-q13. Patients with PWS have reductions in lean tissue and increased body fat, but unusually a selective reduction in visceral adiposity, as determined by whole body magnetic resonance imaging (MRI) which protects against metabolic complications of obesity. This could be related to the neonatal failure-to-thrive in PWS. Studies in the Dept. of Pediatrics and McKnight Brain Institute, University of Florida, using 3-D MRI have identified neuroanatomical abnormalities in patients with PWS, including cortical defects and ventriculomegaly. Others have reported abnormalities in the parietal cortex using MR spectroscopy, consistent with neuronal loss. Reduced neuronal number has also been seen in certain nuclei in post-mortem human PWS hypothalami. These findings could be related to learning difficulties, feeding, neuroendocrine and behavioral problems in PWS. Previous work in Dr. Brannan’s lab at the University of Florida has generated a mouse model for PWS which displays neonatal failure-to-thrive. Mice that paternally inherit a 35kb deletion of the PWS imprinting control center (ΔPWS-IC) lack expression of similar paternally expressed genes, including Mcm3, Ndn, Stuaf-Snrpn, Magel2 and several snoRNAs. Others have also identified embryonic abnormalities of axonal development and neuronal tracts in the Ndn knockout mouse. Breeding males (C57BL/6J strain) harboring a maternally inherited ΔPWS-IC (and hence unaffected) to wild-type females (FVB/NJ strain) results in mutant offspring that develop poor feeding and failure-to-thrive, but with increased survival of mutant offspring reaching >80% if wild type pups are removed and fostered to reduce competition. Surviving adult ΔPWS-IC mice remain small compared to fostered wild-type littermates, with body weights reduced by up to 50-60% at 1 year of age. We have also recently identified behavioral defects in adult ΔPWS-IC mice.

Experimental

We have performed brain and metabolic phenotyping in adult ΔPWS-IC mice (1 year old, 4 wild-type and 4 PWS of each sex) using the AMRIS facility in the McKnight Brain Institute, University of Florida, including:
1. in vivo 3-D whole brain MRI to look for anatomical defects (11T machine),
2. in vivo diffusion tensor imaging (DTI) to look for defects in fiber tract mapping (11T machine),
3. in vivo magnetic resonance spectroscopy of hypothalamus, frontal and parietal cortex (11T machine),
4. ex vivo 3-D whole body composition to determine fat content and distribution, and tibial length (4.7T machine).

Results and Discussion

Preliminary examination of the data has suggested evidence for ventriculomegaly and reduced brain size in male PWS mice. Data analysis is currently ongoing to identify and measure in more detail the presence of neuroanatomical defects, including variations in size of different brain regions, fiber tract misroutings using DTI and regional brain choline / NAA / creatinine ratios using spectroscopy. Adult ΔPWS-IC mice of both sexes have evidence of reduced total body fat. Examination of whole body MR scans will be performed to formally measure total, subcutaneous and intra-abdominal fat volumes, and parameters of growth.

Conclusions

The use of MRI for phenotyping ΔPWS-IC mice will allow assessment of the role of imprinted genes in the PWS region in a variety of physiological processes, and how mouse models of PWS and humans with PWS differ phenotypically.

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