dietary groups despite L-isoleucine treatment (SLD:C,1.58 ± 0.26 g; A,2.40 ± 0.25 g; Ch,2.49 ± 0.34 g; HFD:C,3.19 ± 0.44 g; A,4.59 ± 0.44 g; Ch,4.44 ± 0.85 g; 2 way-ANOVA ($P < 0.0001$) Dietary-effect). At 17 wks, fasting blood glucose was elevated in HFD mice compared to SLD mice but there was no L-isoleucine effect (SLD:C,10.84 ± 0.50 mmol/l; A,10.50 ± 0.31 mmol/l; Ch,11.15 ± 0.48 mmol/l; HFD:C,12.61 ± 0.60 mmol/l; A,12.90 ± 0.70 mmol/L; Ch,12.81 ± 0.66 mmol/l;2way-ANOVA ($P < 0.000$) Dietary-effect). The OGTT blood glucose area under the curve was elevated in HFD compared to SLD mice but there was no L-isoleucine effect within dietary groups (SLD:C,1651 ± 109.0 mmol/l-min; A,1760 ± 95.81 mmol/l-min; Ch,1980 ± 170.8 mmol/l-min; HFD:C, 2228 ± 174.1 mmol/l-min; A,2162 ± 191 mmol/l-min; Ch,2416 ± 232 mmol/l-min;2way-ANOVA ($P = 0.0022$) Dietary-effect).

Conclusion: Acute and chronic supplementation with L-isoleucine had no effect on body weight gain or glucose tolerance in SLD mice or HFD induced-obese mice.

References

[1] (Nutrients 2015, 7, 9573-9589).
[2] (Biol. Pharm. Bull. 2008 31.(3) 469-472).

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Obesity during pregnancy in rats adversely influences brain function in the offspring as adults

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Obesity is a low-grade inflammatory state and a fetus developing in such an inflammatory milieu is susceptible to developing various disorders. After birth, children of obese mothers are at increased risk of obesity, metabolic syndrome and neurodevelopmental abnormalities, eg reduced cognitive capacity, developmental delay, attention deficit hyperactivity disorder schizophrenia, and autism spectrum disorders. Here we used rats to test the effects of maternal obesity on neuronal networking and to determine if establishing a good diet at weaning could rescue deficits.

Rats gestated and maintained on an obesogenic Western diet (WD) had impaired spatial and working memory compared with rats on control chow (CC) at 10 weeks of age. Switching to CC when 3 weeks old completely rescued working memory but had no effect on spatial memory. Brain slices from 15 week old WD male rats had hippocampal epileptiform activity, which reflected current diet. This was supported by epileptiform spike-wave bursts, associated with a "freezing" of movement (absence), in EEG recordings in conscious free-moving animals. Immunohistochemistry revealed a marked reduction in GABA staining, with a reduction in NPY and somatostatin neurons reflecting current diet and somatostatin neurons also very much reduced in rats exposed to WD during gestation and weaning.

Activators of NPY receptors suppress spike-wave activity in absence epilepsies in humans and animal models and the reduction in NPY and occurrence of epileptiform activity in our WD rats supports these observations. A 2017 study of 1.4 million children from Sweden found that the incidence of childhood epilepsy increased with maternal BMI during pregnancy. Our results provide some insights into interpretation of this. Abnormal network and epileptiform activity has been associated with the early stages of Alzheimer's disease. It is alarming to consider that exposure to WD effects as early as *in utero* might predispose to earlier AD.

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Non-humanoid primate model of diet-induced obesity: model validation for biomarker discovery

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Obesity is a leading world health problem. Excess body weight is a major risk factor for developing type 2 diabetes, cardiovascular disease, dyslipidemia and other co-morbidities that ultimately lead to increased mortality rates. While pharmacotherapies can be employed to better manage obesity, they are hindered by their temporary effectiveness and side effects. This highlights the need for a better understanding of the pathophysiological features of human obesity. Non-human primates (NHPs) provide the most suitable pre-clinical model to investigate human obesity and discover novel therapeutic biomarkers. We have generated a high-fat diet (HFD)-induced NHP model of obesity and pre-diabetes in 34 pigtail macaques (*Macaca nemestrina*) consisting of 10 HFD males and 10 HFD females with 8 control males and 6 control females. Body composition analysis, glucose tolerance tests in addition to biopsy (muscle, fat and liver) and blood collections were completed at baseline and then every 3 months for 18 months in all animals. Both male and female HFD-fed animals displayed progressional increases in body weight and total body fat mass compared to baseline or lean controls that was due to largely adipocyte hypertrophy. Both HFD-males and HFD-females also demonstrated significantly increased fasting insulin concentrations and insulin area under the curve (AUC) compared to baseline or lean control counterparts determined via intravenous glucose tolerance tests. These findings suggest HFD-induced changes in insulin-sensitivity and development of insulin resistance at the end of the 18-month study. Obesity-induced changes in liver, muscle and fat morphology (steatosis, fibrosis, immune cell infiltration), circulating lipids (triglycerides, total cholesterol, HDL/LDL), metabolic hormones (leptin, adiponectin and C-peptide) and inflammatory markers (TNF-α, IL-1β, IL-6 and IL-10) are simultaneously being investigated using multiplex assays to further validate our model and provide the basis for future biomarker discovery studies.

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