Males rats born small have elevated resting metabolic rate despite being less active and do not have exacerbated insulin resistance on a high fat diet

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Obesity is associated with an increased risk of developing a number of noncommunicable diseases including diabetes. One subset of the population who are at an increased risk of obesity are individuals who were born small. Growth restricted males have reduced pancreatic β-cell mass and are prone to developing diabetes, which may be exacerbated if they become obese. This study investigated the effect of obesity on the metabolic health of growth restricted male rats.

Uteroplacental insufficiency was induced by bilateral uterine vessel ligation (Restricted) or sham (Control) surgery in anaesthetized (4% isoflurane and 650ml.min^{-1} oxygen flow, reduced to 3.2% isoflurane and 250ml.min^{-1} oxygen flow when suturing) Wistar-Kyoto rats on embryonic day 18 (term = 22 days). Male Control (sham surgery) and Restricted (ligation surgery) offspring were randomly allocated to receive a Chow or high fat diet (HFD; 43% kcals from fat) from 5 weeks of age until 6 months. Rats underwent an insulin challenge (IC; 4.5 months), intraperitoneal glucose tolerance testing (IPGTT; 5 months), and were individually placed in an indirect open-circuit calorimeter chamber (CLAMS; 5 months for 36 hours) to determine their energy expenditure and spontaneous physical activity. Data were analysed using a two-way ANOVA.

Restricted males were born small (-17%; $P < 0.0001$) but caught up by 6 months. Consumption of a HFD increased body weight from 3 months (+8%), irrespective of birth weight. HFD males had increased basal insulin (+111%; $P < 0.0001$) with no changes in basal glucose, irrespective of birth weight. Similarly, HFD males had increased insulin area under the curve (AUC; +76%; $P < 0.0001$) and first phase insulin secretion (+74%; $P = 0.002$) during IPGTT despite no changes in glucose AUC which was irrespective of birth weight. Homeostatic model assessment of insulin resistance (HOMA-IR) was increased in HFD males (+111%; $P = 0.001$) which was irrespective of birth weight. Glucose AUC following an IC was increased in Restricted males on a HFD (+14%; $P = 0.03$) compared to their Chow-fed counterparts indicating insulin resistance.

Restricted males had a higher VO_2 (+15%; $P < 0.0001$) and VCO_2 (+18%; $P < 0.0001$) compared to their Control counterparts irrespective of diet, during the dark cycle. Interestingly, Restricted males produced more heat (+10%; $P = 0.001$) during the dark cycle irrespective of diet compared to their Control counterparts which was independent of their activity. Specifically, Restricted males performed less stereotypy movements (such as grooming and scratching) on both diets compared to Control counterparts (-18%; $P = 0.027$). A HFD reduced VO_2 (-8%; $P = 0.006$) and VCO_2 (-16%; $P < 0.0001$), irrespective of birth weight. Stereotypy was additionally reduced with HFD (-22%; $P = 0.008$), irrespective of birth weight. However, there were no changes in rearing or jumping movements in Control and Restricted offspring on either diet.

These data suggest that growth restricted male rats, whose body weight caught up to Controls, have an increased resting metabolic rate despite being less active which may be protecting them from developing glucose intolerance and insulin resistance on a Chow diet. However, consumption of a HFD leads to altered insulin profile in male rats irrespective of their birth weight, which is suggestive of insulin resistance. Thus, a HFD results in insulin resistance which is not further exacerbated by low birth weight in this cohort. It is possible that aging these animals further or challenging them with a HFD with more enegry from fat may promote metabolic dysfunction.