recognition memory. In Experiment 1, rats fed a healthy chow diet (control group) were compared with groups fed CAF for: 3 consecutive days per week followed by 4 days of chow (3:4 group); 5 consecutive days per week followed by 2 days of chow (5:2 group); or 7 days per week (continuous CAF group). Total days of access to CAF diet were matched between the latter three groups so that any group differences were attributable to the pattern of access. The continuous CAF and 5:2 groups had significantly more fat mass and worse short-term spatial recognition memory than the 3:4 and control groups. In Experiment 2, rats consuming CAF diet for 16 days and then returned to chow diet for 11 days displayed intact spatial memory, whereas those returned for 4 days were impaired, despite comparable reductions in adiposity in these two groups. CAF feeding did not impair object recognition memory in either experiment. These results demonstrate that the duration and pattern of access to CAF diet interact to determine effects on obesity and cognition in a graded fashion.

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222

The effect of *ACE* I/D polymorphism on the expression of fatty acid oxidation-related genes in human skeletal muscle after a single session of high-intensity interval exercise

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High-intensity interval exercise (HIIE) is associated with increased fatty acid oxidation, and the majority of fatty acids in skeletal muscle is stored in a form of intramuscular triglycerides (IMTG). The common *ACE* I/D gene polymorphism has been associated with exercise performance, with the I allele more prevalent in endurance-type athletes, who often have more IMTG and more fatty acid oxidation during exercise. We therefore hypothesise that the *ACE* I/D variant is associated with key genes controlling IMTG oxidation.

We analysed sixteen moderately-trained Caucasian males (age = 30.2 ± 7.9) from the Gene Smart cohort (Yan et al., 2017), ten homozygous for the D allele (*ACE DD*), and six homozygous for the I allele (*ACE* II). A graded exercise test (GXT) was used to assess peak power (W_{peak}) and lactate threshold (LT), both key endurance exercise phenotypes. A single session of HIIE (8 2-min intervals with 1 min rest between intervals) was completed by each participant. A muscle biopsy was taken before, immediately after, and 3 hours post HIIE from the *vastus lateralis* muscle and analysed for the expression of PGC1α, PPARα and PPARδ.

The expression of PGC1α was not different between the DD and II individuals at baseline (0.91 ± 0.25 vs 0.71 ± 0.09, $p = 0.08$). There was no difference in PPARα (1.40 ± 0.55 vs 1.90 ± 0.48, $p = 0.09$) or PPARδ (0.82 ± 0.35 vs 0.60 ± 0.11, $p = 0.17$). Three hours post HIIE, the expression of PGC1α, PPARα, PPARδ all increased (by 4.63 ± 2.30, 5.61 ± 3.40, 1.95 ± 1.18 fold, respectively, $p < 0.05$). However, the increase did not depend on *ACE* I/D gene polymorphism (4.11 ± 2.57 vs 5.49 ± 1.57, 5.67 ± 4.22 vs 5.49 ± 1.66, 1.92 ± 1.42 vs 1.99 ± 0.74 between DD and II individuals).

These preliminary results indicate a single session of HIIE significantly increased the expression of PGC1α, PPARα and PPARδ. However, this increase was not associated with the *ACE* I/D genotype. We are currently increasing the sample size to confirm these preliminary findings.

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223

Hepatocyte-specific deletion of Nox4 induces whole-body insulin resistance

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It has previously been shown that hepatic deletion of NADPH oxidase 4 (Nox4) exacerbates the effects of high-fat feeding. In particular, hepatic Nox4 deletion increases adiposity, impairs hepatic insulin signalling *ex vivo*, and also promotes glucose intolerance (via a glucose tolerance test) and impaired insulin sensitivity (via an insulin tolerance test). Here, we examined in more detail the cause(s) of insulin resistance *in vivo*, and hypothesised that hepatic Nox4 deletion would result in whole-body insulin resistance specifically due to impairments in hepatic insulin sensitivity. To test this, male mice with hepatic specific deletion of Nox4 (AlbCre-$Nox4^{fl/fl}$) and wild-type littermates ($Nox4^{fl/fl}$) were fed a high-fat diet (~23% energy from fat) for 12 wk, beginning at 6–7 wk of age. At 18–19 wk of age, mice had catheters placed into the left carotid artery and right jugular vein, and 5d post-surgery a hyperinsulinaemic-euglycaemic clamp was performed at two insulin doses (2.5 and 4 mU/kg/min) in conscious and unrestrained mice ($n = 6$–9 per group). At an insulin infusion rate of 2.5mU/kg/min, glucose infusion rate (GIR), endogenous glucose appearance (endoR_a), and insulin-stimulated glucose disposal rate (IS-GDR) were similar between AlbCre-$Nox4^{fl/fl}$ and $Nox4^{fl/fl}$ mice. In $Nox4^{fl/fl}$ mice, increasing the dose of insulin to 4 mU/kg/min increased GIR (22 ± 2 vs. 11 ± 1 mg/kg/min for 2.5mU/kg/min insulin, $p < 0.001$), enhanced the insulin-induced suppression of endoR_a (75 ± 12 vs. 40 ± 7%, $p < 0.05$), and augmented IS-GDR (12 ± 1 vs. 5 ± 1 mg/kg/min, $p < 0.01$). In contrast, increasing the dose of insulin from 2.5 to 4 mU/kg/min in AlbCre-$Nox4^{fl/fl}$ mice failed to alter GIR (12 ± 1 vs. 11 ± 1 mg/kg/min), an effect that was due to (a) an inability to further increase the suppression of endoR_a (53 ± 6 vs. 53 ± 3%), and (b) a failure to increase IS-GDR (5 ± 1 vs. 3 ± 1 mg/kg/min). Thus, AlbCre-$Nox4^{fl/fl}$ mice are insulin resistant. Furthermore, our findings indicate that the insulin resistance in these mice is due to hepatic and peripheral effects.

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