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Characterisation of a novel mouse model of diabetes

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Introduction: Animal models are an essential tool in preclinical diabetes research. We recently detected spontaneous and unexpected diabetes in a colony of C57Bl/6 mice at King's College London. After screening for candidate genes, this was attributed to a novel dominant point mutation in the *Insulin 2* gene (GRCm38/mm10 Chromosome 7:142,679, 440 G>A), a human variant of which causes rare cases of neonatal diabetes (1). The aims of this study were to determine hyperglycaemia onset in these mice, measure islet function, study islet morphology and investigate if the phenotype was reversed by islet transplantation.

Methods: Onset of hyperglycaemia (blood glucose concentration >16.7mM) was assessed from weaning to 20 weeks of age. Islets were isolated at 20 weeks and insulin secretion assessed at basal 2mM glucose and stimulatory 20mM glucose. Insulin secretion and content were assayed by radioimmunoassay. Pancreatic islets were assessed by immunohistochemistry at 20 weeks for insulin and glucagon. To treat the mice, 500 syngeneic islets were implanted under the kidney capsule of diabetic heterozygous males at 12 weeks.

Results: Homozygous male and female mutants had to be killed within days of weaning due to emaciation. Heterozygous males showed onset of hyperglycaemia at 30±1.5 days and by 10 weeks showed blood glucose concentrations of 34.0mmol/l±1.5 vs 8.9mmol/l±0.5 in wildtype littermates ($p<0.001$, t-test, n=11-15). Heterozygous females did not develop overt diabetes but showed substantial glucose intolerance by 10 weeks (intraperitoneal glucose tolerance test area under the curve: 2900mmol/l/120 minutes±180 vs wildtype littermates: 1815mmol/l/120mins±180, $p<0.001$, n=10-11). Heterozygous males at 20 weeks had a 91% reduction in glucose stimulated insulin secretion (0.138±0.03 ng/islet/hour vs wildtype: 1.47±0.41 ng/islet/hour; $p<0.001$, n=5-7) and a 96% reduction in heterozygous insulin content (2.11±0.8 ng vs wildtype: 48.4±10.8 ng; $p<0.001$, n=5-7). Histology showed no signs of autoimmune cells infiltrating the islets and beta cells were present, albeit less numerous than in wildtype mice. Alpha cell hyperplasia was evident, which has previously been described both in diabetes patients and in animal models of diabetes. Diabetes is reversed by islet transplantation showing that peripheral insulin signalling is intact in these animals.

Conclusions: The G32S *Ins2* mutation has been shown to cause severe hyperglycaemia and dramatically impair islet function in heterozygous male mice. Female mice show a milder phenotype, the reason for which is not known. This mouse model may present a novel tool for preclinical diabetes research.

References:

1. ALF Austin et al (2017). Diabetic Medicine **34** : 44-44.