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## A24. Hyperinsulinaemia in subjects with impaired glucose tolerance and Type 2 diabetes.

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Type 2 diabetes is associated with hyperinsulinaemia. Conventional assays have been shown to overestimate insulin levels due to cross-reaction with proinsulin and proinsulin-like molecules. In order to determine if the apparent hyperinsulinaemia is, in part, due to cross-reacting molecules we used an in-house, amplified, end-point enzymoimmunometric assay (IEMA) for specific measurement of human insulin. The assay was sensitive to 2.0 pmol $l^{-1}$ with intraassay coefficient of variation (CV) less than 10% and interassay CV less than 15%. Recovery of insulin from spiked plasma was 96% (range 88 to 105%). The assay was used to measure fasting insulin levels in 107 caucasian subjects with no evidence of heart disease (60 normal glucose tolerance, NGT; 17 impaired glucose tolerance, IGT and 28 newly discovered diabetics, DM). There was a stepwise increase in fasting insulin concentrations from NGT to IGT and to DM [median 28 (range 3-179); 54 (16-232), $p=0.003$; 82.5 (15-241), $p=0.0001$]. Following a 75 g glucose challenge given to non-diabetics, in normal subjects the 2 hr plasma insulin increased by 299% (interquartile range 85-528%) over fasting, while in IGT this increase was 426 (267-811%). In conclusion subjects with IGT and Type 2 diabetes are not insulin deficient in the fasting state, even using specific assays of insulin, suggesting that insulin resistance must contribute to the aetiology of Type 2 diabetes.

## A25. MODY is a dominantly inherited disorder of β-cell function.

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Maturity Onset Diabetes of the Young (MODY) is characterized by the diagnosis of Type 2 diabetes before the age of 25 and a dominant inheritance. The pathophysiology of MODY is uncertain. We studied 62 members of 5 large multigeneration MODY pedigrees to determine if there was a single pathophysiology and its relationship to common Type 2 diabetes (diagnosis >40 yrs, without dominant inheritance).

21 MODY patients were compared with 21 Type 2 diabetic patients individually matched for fasting glucose (7.6: 7.5 mmol), treatment and gender. Statistical analysis was Paired t and Student t-tests on logged data. The MODY patients had a lower fasting plasma insulin [5.7 (4.6-7.7) median (interquartile range): 13.2 (9.2-14.9) mU $l^{-1}$ $p=0.013$]. Using HOMA analysis MODY patients showed reduced β-cell function [%B 50 (28-67): 69 (40-94) $p=0.005$] and increased insulin sensitivity [%S 59 (43-67): 27 (22-34) $p<0.001$]. The marked absence of obesity in the MODY patients, in part explains the difference in sensitivity. [BMI 22.8 (21.6-24.7): 27.4 (24.5-33.5) kg $m^{-2}$, $p<0.001$].

41 unaffected subjects from the MODY pedigrees showed significantly better β-cell function [%B 125 (113-157): 50.2 (28-69) $p=0.005$] than the MODY subjects but were not more insulin sensitive [%S 61 (44-76): 59 (43-67) $p=0.02$] or less obese [23.7 (22.5-25.3): 22.8 (21.6-24.7) kg $m^{-2}$ $p>0.05$]. In the MODY pedigrees β-cell function but not insulin sensitivity allowed differentiation of affected from unaffected. We conclude that MODY results from the dominant inheritance of a single gene affecting β-cell function.

## A26. Acute hyperinsulinaemia causes an increase in neuropeptide Y (NPY) concentrations in the hypothalamic arcuate nucleus of the rat.

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NPY, a major hypothalamic peptide, stimulates feeding, insulin secretion and weight gain when injected intrahypothalamically. NPY synthesis in the arcuate nucleus (ARC) and levels in NPY-sensitive hypothalamic regions rise in diabetes and starvation, possibly stimulated by insulin deficiency. High pharmacological intracerebroventricular insulin levels inhibit NPY synthesis in the ARC, but the effects of hyperinsulinaemia have not been studied. We therefore measured regional hypothalamic NPY levels in rats during a hyperinsulinaemic, euglycaemic clamps.

Male Wistar rats with implanted jugular cannulae, fasted for 24 hrs, were infused with insulin (128.2 mU $l^{-1}$ at 780 μl $hr^{-1}$ ($n=7$) together with variable-rate glucose to maintain euglycaemia ($3.9\pm0.1$ mmol $l^{-1}$), or saline ($n=8$; glycaemia, $4.0\pm0.5$ mmol $l^{-1}$), for 2.5 hrs. Insulin levels were $80.2\pm10.4$ mU $l^{-1}$ in insulin-infused rats and $16.7\pm11.7$ mU $l^{-1}$ in saline-treated controls ($p<0.001$). NPY levels were measured by radioimmunoassay in the ARC and 7 other hypothalamic regions. NPY levels in the ARC were significantly higher in hyperinsulinaemic than in control rats ($4.80\pm1.17$ *vs* $2.54\pm0.58$ fmol μg protein$^{-1}$; $p<0.001$), but comparable with controls in all other regions.

Acute physiological hyperinsulinaemia therefore increase NPY levels selectively in the ARC. Insulin may cause NPY accumulation in the ARC by blocking its transport to NPY-sensitive areas, consistent with the suggested inhibition by insulin of NPY and the postulated role of insulin as a satiety factor.

## A27. Effect of insulin on intracellular pH in cultured myoblasts from insulin-resistant spontaneously hypertensive rats.

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One postulated mode of insulin action in muscle is the elevation of intracellular pH by stimulation of the $Na^+/H^+$ antiport leading to increased glycolysis. Such an action in the kidney would also lead to $Na^+$ retention. As spontaneously hypertensive rats (SHR) and hypertensive humans are insulin resistant, we studied the *in vitro* effect of insulin (1 mU $ml^{-1}$) on intracellular pH in cultured myoblasts from SHR and normotensive Wistar Kyoto rats (WKY). Insulin led to a progressive fall in intracellular pH of WKY myoblasts (0 min: mean ± SD $7.17\pm0.10$; 15 min $7.09\pm0.14$, $p<0.007$; 30 min $7.062\pm0.13$, $p<0.001$), resembling the response of normo-