However, it is not entirely clear whether ectopic lipid accumulation plays a causal role in the development of insulin resistance or whether this is simply an associative relationship. We have conducted a number of studies to explore this relationship. Firstly, to further understand the role of muscle lipids in mediating insulin action, we generated a muscle-specific knockout of a key enzyme in phospholipid synthesis, CTP:phosphoethanolamine cytidylyltransferase (ECT), which resulted in marked (2—3-fold) increases in both diacylglycerol and triacylglycerol content in muscle. Despite this increase in lipid content, whole body and skeletal muscle insulin sensitivity, as determined by euglycemic hyperinsulinemic clamp, was not altered. These findings demonstrate that lipid accumulation in muscle is not always associated with insulin resistance. To examine the role of hepatic lipids, we performed a study where chronically (8 wk) high-fat, high-sucrose fed (HFSD) mice were switched back to a standard chow diet for 7 days. Upon the switch, energy intake was reduced, resulting in reductions of fat mass and hepatic diacylglycerol and triacylglycerol content. However, these parameters were still elevated compared to chow-fed mice, thus representing an intermediate phenotype. Nonetheless, glucose intolerance and hyperinsulinemia were completely normalised in mice that underwent the 7 day diet switch. This indicates that lipotoxicity per se does not necessarily maintain the glucose intolerant and insulin resistant state in HFSD fed mice. Rather, it appears that persistent over nourishment is likely to be the major factor responsible for causing defects in glucose metabolism. Together, these findings dissociate tissue lipid accumulation from the development of insulin resistance and glucose intolerance.

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Invited talk: Do factors secreted from the fatty liver cause diabetes?

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Obesity is a risk factor for the development of secondary complications including dyslipidemia, non-alcoholic fatty liver disease, cardiovascular disease and type 2 diabetes. An accumulation of lipid in the liver, which is clinically known as hepatic steatosis, is a pathologic abnormality that is common in obese and type 2 diabetes patients. Hepatic steatosis occurs when fatty acid supply outweighs fatty acid demand and occurs in a time-course that usually precedes the induction insulin resistance and type 2 diabetes. In this presentation, we describe how 'omics' approaches are used to delineate the hepatocyte protein and lipid secretome in health and obesity. Further, we report on the pre-clinical validation of several liver secreted factors that cause insulin resistance and disturbances in systemic metabolic homeostasis.

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Invited talk: Diabetes surgery — Has the time arrived?

John Dixon

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Bariatric-metabolic (BM) surgery as a treatment for type 2 diabetes (T2DM) has progressed rapidly. There is now high quality evidence of efficacy, safety, reduced morbidity and mortality, and very favourable health economic profile. Yet surgery is rarely performed as a treatment for Type 2 diabetes and has been slow to enter the treatment algorithms of managing diabetes. The International Diabetes Federation has provided a position statement, and the NHMRC and NICE have included BM surgery in their algorithms for managing weight in patients with obesity and T2DM.

An international consensus conference was convened in collaboration with leading diabetes organisations to develop guidelines to inform clinicians and policy makers about benefits and limitations of metabolic surgery for T2DM. The evidence collected, the process used to reach consensus, and the level of international acceptance will be presented.

Key points of consensus:

Given its role in metabolic regulation, the gastrointestinal tract constitutes a meaningful target to manage T2DM.

There is now sufficient clinical and mechanistic evidence to support inclusion of metabolic surgery among anti-diabetes interventions for people with T2DM and obesity.

Metabolic surgery should be recommended to treat T2DM in patients with Class III obesity (BMI $\geq 40\,kg/m^2$) and in those with Class II obesity (BMI 35.0—39.9 kg/m^2) when hyperglycaemia is inadequately controlled by lifestyle and optimal medical therapy. Surgery should be considered for patients with T2DM and BMI 30.0—34.9 kg/m^2 if hyperglycaemia is inadequately controlled despite

treatment with either oral or injectable medications.

Our challenge now is to understand where this fits into real world management of T2DM in Australia.

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Invited talk: Prediabetes phenotypes improve prediction and prevention of type 2 diabetes

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The prevalence of prediabetes is increasing world-wide. Prediabetes is not only associated with an increased risk of type 2 diabetes and cardiovascular disease (CVD), but also of dementia and cancer, and, therefore, has recently gained much attention in the field of clinical research. In prediabetes lifestyle and pharmacological intervention can prevent diabetes and possibly CVD. Thus, the implementation of interventions in this condition is of major importance. However, prediabetes is a very heterogeneous metabolic state, both in respect to its pathogenesis and prediction of diseases. Thus, better understanding of its pathophysiology and stratification of the risk should be done. This can be achieved by applying precise phenotyping strategies. It will be discussed how stratification of individuals with prediabetes at baseline into a high-risk and a low-risk phenotype, based on corrected insulin secretion and insulin-resistant NAFLD, may help to determine the effectiveness of a lifestyle intervention to revert individuals to normal glucose regulation. By addressing evidence that has derived from lifestyle intervention studies the further aim is to clarify whether these phenotypes can be used for individualised prediction and prevention of cardiometabolic diseases in prediabetes.

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Invited talk: Metabolic syndrome: Sympathetic (neural) perspectives

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The sympathetic nervous system (SNS) plays a pivotal role in both cardiovascular and metabolic regulation. Prospective cohort, offspring and clinical studies indicate that elevated SNS activity is an early pathophysiological phenomenon that predicts future metabolic abnormalities (insulin resistance, hyperglycaemia, type 2 diabetes, dyslipidemia and adiposity), increases in blood pressure and cardiovascular risk. In established obesity several factors act in concert to maintain chronic elevation of central sympathetic drive to skeletal muscle, the kidneys and the heart. Primary amongst these are hyperinsulinemia, impaired baroreflex function, sleep apnoea and elevated adipokine levels.

Using the techniques of clinical microneurography to quantify sympathetic nerve firing rate in skeletal muscle vasculature and isotope dilution to estimate total body noradrenaline spillover rate, our group has demonstrated associations between SNS activity and insulin resistance and insulin clearance (inverse) in obese cohorts. Furthermore, insulin resistant obese individuals display blunted postprandial sympathetic response to oral carbohydrate loading compared with age- and body mass index-matched insulin sensitive controls. This is relevant to body weight homeostasis, given that facultative thermogenesis accounts for 3—4% of daily energy expenditure. The sympathetic neural signal is also modified by the rate of removal of noradrenaline from the neuroeffector junction and plasma compartment. We recently reported reduced plasma noradrenaline clearance in obese treatment naïve type 2 diabetic patients compared with controls with impaired glucose tolerance. This was attributed to reduced peripheral noradrenaline transporter (NET) expression, and haemoglobin A1C was an independent inverse predictor of NET levels.

Weight loss and exercise are first line treatments for the metabolic syndrome that elicit sympathoinhibitory effects and reverse blunted postprandial sympathetic response in insulin resistant states. The magnitude of sympathoinhibition is greatest in hyperinsulinemic subjects. Insulin-sensitising, oral hypoglycaemic and sympathomoderating drugs may offer other approaches to modify sympathetic