

in intracellular adenine nucleotides: ATP closes the channel by binding to Kir6.2, whereas interaction of Mg-nucleotides (MgATP, MgADP) with the nucleotide-binding domains of SUR1 stimulates channel activity and reverses channel inhibition by ATP. Channel activity thus reflects the balance between these excitatory and inhibitory effects.

K<sub>ATP</sub> channels are found in numerous tissues. In neurones they regulate electrical activity in response to glucose, neuropeptides and ischemia; in heart they are important for ischemic preconditioning and the stress response; in smooth muscle they regulate vascular tone and in endocrine cells they mediate hormonal secretion. Our studies focus on their role in insulin secretion. At rest, K<sub>ATP</sub> channels are open, hyperpolarizing the pancreatic beta cell membrane and inhibiting insulin release. When plasma glucose levels rise, K<sub>ATP</sub> channels close, depolarizing the beta-cell and opening voltage-gated Ca<sup>2+</sup> channels. The resulting Ca<sup>2+</sup> influx triggers insulin release. The sulphonylurea drugs used to treat type 2 diabetes stimulate insulin secretion by binding to, and closing the K<sub>ATP</sub> channel.

Gain-of-function mutations in the genes encoding both Kir6.2 (KCNJ11) and SUR1 (ABCC8) can cause neonatal diabetes. Some mutations produce a severe clinical phenotype, characterized by developmental delay, epilepsy, muscle weakness and neonatal diabetes (DEND syndrome). In many patients, sulphonylureas can successfully be used to treat their diabetes, and in some individuals the neurological symptoms can also be alleviated. This lecture will discuss the mechanisms by which nucleotides modulate K<sub>ATP</sub> channel activity, how mutations causing human disease alter K<sub>ATP</sub> channel function, how alterations in K<sub>ATP</sub> channel activity cause the disease phenotype in man and mouse, and why some mutations are susceptible to sulphonylurea therapy and others are not.

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#### SA14

### The role of circadian dysregulation and sleep loss in obesity and metabolic dysfunction

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The discovery just a few years ago that only a few days of partial sleep restriction, in otherwise healthy young men, can induce changes in glucose regulation that are indicative of a trajectory toward insulin resistance and diabetes, introduced a new era of sleep medicine and a new found interest in sleep and metabolism. Indeed, there is now considerable evidence from experimental and epidemiological studies that sleep loss and obesity are “interacting epidemics”. Similarly, the recent discovery that mice carrying a mutation in a canonical circadian clock gene show alterations not just in the timing of sleep and wake, but also in the amount of sleep and sleep architec-

ture, as well as changes in metabolism, has opened up a new era for thinking about how the circadian clock, sleep-wake and energy regulatory systems are integrated at the molecular, genetic and behavioral levels. Further support for the integration of these systems at many levels comes from studies showing that genetic and environmentally induced changes in metabolism can influence sleep and circadian rhythms.

The fact that the core molecular circadian clock machinery is found in most of the cells and tissues of the CNS and periphery and regulates the diurnal timing of expression of hundreds of “clock controlled genes”, and that core molecular circadian genes and proteins are also part of key energy metabolic pathways, has opened up new frontiers for investigating the importance of rhythmicity for mental and physical health. These lines of research are only in their infancy, but nevertheless, have provided a conceptual and experimental framework that potentially has great importance for developing a deeper understanding of complex behavioral and physiological processes. This lecture will review this new and rapidly evolving frontier of neuroscience.

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#### SA15

### Developmental origins of metabolic syndrome

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The ‘metabolic syndrome’ develops when an individual makes inappropriate responses to their environment, predisposing to obesity, dyslipidaemia, Type 2 diabetes and vascular endothelial dysfunction. Whilst there is debate about the definition of the syndrome and its usefulness as a descriptor, it is associated with increased risk of coronary heart disease. Much research has focused on potential genetic determinants of the phenotypic components of the syndrome on one hand and lifestyle and nutritional factors on the other. There is however a third component of how individual risk is created, namely the interaction between genotype and environment during development. Such developmental origins of health and disease (DOHaD) accounts for a substantial fraction of risk. This is part of a broader picture in mammals, in which developmental plasticity sets many phenotypic traits during prenatal and infant life based on cues about the environment, transduced by the mother and transmitted to her offspring across the placenta or in her milk. Developmental plasticity is also utilised to produce polyphenisms in many other species too. In humans, mismatch between predicted and eventual environment can arise through unbalanced maternal diet or disease and migration or socio-economic development (1). This pathway is involved in the dramatic increases in metabolic syndrome between generations in both developing and developed societies. The effects are also exacerbated by demographic changes in reproductive behaviour,

such as the tendency for women to have children at the extremes of their reproductive age and for more primiparous pregnancies. A second set of developmental pathways also exists, by which fetal or infant overnutrition affects development, to become manifest later as metabolic syndrome in the offspring. Such overnutrition may originate as maternal diabetes, maternal obesity or infant overfeeding (2). Thus the risk which starts with mismatch can be perpetuated into new cycles of risk in successive generations. Low socioeconomic status and educational attainment underpin many aspects of these cycles.

The processes underlying these developmental effects involve various components of non-genomic inheritance. Particular interest concerns epigenetic processes, involving DNA methylation, histone structure and small non-coding RNAs (3). Other processes relate to parental physiology, for example maternal adaptations to pregnancy, or behaviour such as suckling and grooming of offspring (4, 5). In addition recent animal data reveal that the changes induced by dietary change or endocrine challenges in pregnancy can be passed to the grand-offspring (F2) without additional challenge in the F1 generation, and can affect a range of cardiovascular, endocrine and metabolic functions (e.g. 6). We have now shown that these effects may be due in part to epigenetic changes (7). Current emphasis on the metabolic syndrome is focused on screening and interventions in adults. We believe that understanding the epigenetic and other processes which operate early in life to determine risk holds greater hope for future detection of those individuals and population groups most susceptible and for design of appropriate interventions.

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II diabetes and stroke. Some of these obesity-related complications (e.g. type II diabetes) have been linked to changes in inflammation, as obesity is characterised by chronic low-grade inflammation (1). Obesity is also associated with an increase in the prevalence and severity of infections. Genetic animal models of obesity, such as leptin-deficient (ob/ob) and leptin receptor-deficient (db/db) mice display altered centrally-mediated sickness behaviour in response to acute systemic infections (2-4). Although obese ob/ob and db/db mice are useful models of obesity, genetic mutations leading to leptin or leptin receptor deficiency have been only identified in a small subset of the obese population in humans, and to date diet-induced obese (DIO) rodents remain the most relevant model for human obesity. We have shown recently that DIO mice display a heightened and prolonged response to infection caused by lipopolysaccharide (LPS), and these observations maybe due to changes in the inflammatory response.

Growing evidence suggests that inflammation modulates the response to acute brain injury (5). Peripheral inflammatory stimuli, such as infection, increase the risk of stroke and are associated with poorer outcome (6,7). As obesity is a risk factor for stroke, and is associated with changes in the inflammatory response, we determined the effects of obesity on the outcome of stroke, and if changes in inflammation maybe involved. Ischaemic damage was exacerbated in obese ob/ob mice compared to lean controls 24h after experimental stroke and this effect was independent of leptin. This enhancement in damage was accompanied by an increased susceptibility of haemorrhagic transformation in ob/ob mice. We also observed changes in the number of inflammatory cells in the obese mice. These data demonstrate that obesity is detrimental to the outcome of stroke, and is associated with an increased risk of haemorrhagic transformation. Furthermore, the altered inflammatory state associated with obesity maybe involved in the detrimental affect this condition has on neuronal injury.

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SA16

### Effects of obesity on the brain-mediated inflammatory response and recovery from neuronal injury

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Obesity is a major cause of morbidity and mortality and is a risk factor for many diseases such as cardiovascular disorders, type

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