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Invited Review

Developmental origins of the metabolic syndrome: Body clocks and stress responses

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ABSTRACT

The prevalence of the metabolic syndrome, which represents a spectrum of metabolic and cardiovascular disorders, continues to increase at an alarming rate in contemporary society. Inadequate responses of an individual to environmental challenges such as unbalanced diet or lack of physical exercise during their life course has been recognised to increase risk of this pathological condition. Recent evidence suggests that this may involve alterations in the settings of the circadian clock system, which consists of oscillating molecular pacemakers found not only in the hypothalamic region of the brain but also in most peripheral tissues, and of the hypothalamic–pituitary–adrenal (HPA) axis which regulates stress responses. These two systems are now known to interact to produce an integrated response to environmental challenges. In this review, we highlight the importance of environmental cues during early development in establishing the homeostatic set-points of the circadian clock and HPA stress systems. These effects can operate within the normal range and are not in themselves pathological, but can nevertheless affect an individual's response to environmental challenges in adult life and thus their risk of the metabolic syndrome.

1. Introduction – the metabolic syndrome

The metabolic syndrome is defined as the clustering of three abnormal metabolic parameters which include being overweight or obese, poor glucose regulation, hypertriglyceridaemia, low high-density lipoprotein (HDL) cholesterol and hypertension. The incidence of the metabolic syndrome has increased dramatically over recent decades, especially in developed countries, but it is also becoming increasingly manifest in developing countries, especially as these go through the economic transition following reductions in infectious diseases. Non-communicable diseases such as the metabolic syndrome are now the focus of much attention at government level internationally (see for example the UN General Assembly resolution of May 2010). This rapid increase in the prevalence of the metabolic syndrome precludes a purely genetic causation for the condition, but nonetheless some fixed genetic variations conferring risk of certain components of the syndrome, such as obesity, have been identified (Frayling et al., 2007). Nor does the condition result purely from adult lifestyle factors such as consumption of high fat, high glycemic index diets and lack of physical exercise (Byberg et al., 2001). Early life factors are increasingly recognised as being of great importance: this is the primary focus of this review.

A focus on early life factors, operating at a time when an individual does not exhibit clear signs and symptoms of disease, raises fundamental questions about how such disease should be viewed. At the simplest level it can be seen from a life course perspective, in which risk builds over many years. In this context there has been much debate about the usefulness of terms such as 'pre-diabetic state' to refer to aspects of the condition (Reaven, 2005) because this implies that the metabolic syndrome, when it does develop in an individual, is the result of a long preceding period of pathological processes.

There is, however, another model of such disease which brings new insights into its early detection, if not its prevention. This model posits that the disease results from repeated exposure to environmental challenges to which the individual is unable to respond adequately to maintain long-term health. In this model, neither the challenges faced by the individual nor the range of their responses need be abnormal in themselves. The challenges may be modest – clearly the case in developing countries in which risk of metabolic syndrome develops under conditions which are far from affluent by Western standards; and the individual's responses may lie within the normal range for the population; all that matters is that these responses are not optimally matched to the challenge.

In this review, we pursue the implications of this second model of disease, focusing on inter-related aspects of metabolic control for which recent evidence suggests that set-points are established in early life. Both circadian clocks and hypothalamic–pituitary–adrenal (HPA) systems are highly relevant in this context, because they influence the balance between energy intake and expenditure,

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affecting appetite, metabolic rate, activity patterns, sleep and arousal and stress responses. These processes together are involved in body composition homeostasis as well as responses to environmental challenges (Fig. 1). There is now substantial evidence from animal experiments that the early developmental environment can affect each of these systems: if this were extended to humans there would be substantial implications for prevention of the metabolic syndrome.

1.1. The role of the developmental environment

A poor environment during fetal life and in early post-natal life can adversely affect the future health of an individual in many ways, including susceptibility to developing the metabolic syndrome. Previous evidence suggests that the early life environment influences adult body composition (Wild and Byrne, 2004), and adds to the effects of unhealthy adult lifestyles to increase risk of the metabolic syndrome (Byberg et al., 2001). These observations are now supported by extensive animal studies showing that an unbalanced diet during pregnancy can induce a phenotype that is associated with features of the metabolic syndrome in adult offspring (Armitage et al., 2004). Moreover, it has been shown that levels of physical activity, appetite, food preference and fat deposition in the offspring can also be determined in part by unbalanced pre- and post-natal nutrition (Vickers et al., 2000).

2. Systems which influence the metabolic syndrome and how they are affected by development

2.1. Circadian clock system

Major components of energy homeostasis, including the sleep-wake cycle, feeding behaviour, thermogenesis and glucose and lipid metabolism, express rhythms with a period of approximately 24 h. These rhythms are driven by circadian (from the Latin words *circa* and *dies*, meaning 'about a day') clocks, which synchronize energy intake and expenditure to temporally relevant signals (*Zeitgeber*) such as the light–dark cycle, temperature, social cues or feeding regime. Thus their definition of internal timing becomes predictive of these external cues.

This circadian clock system is composed of transcriptional/translational feedback loops that oscillate with 24-h rhythmicity, and involves a set of core 'clock' genes. The positive drivers to this system are the basic helix-loop-helix PAS domain-containing transcription factors CLOCK (circadian locomotor output cycle kaput) and BMAL1 (brain and muscle aryl 1-hydrocarbon receptor nuclear translocator-like 1), which form a heterodimer complex that activates transcription of genes containing E-box cis-enhancer sequences, including the Period (Per1, Per2, Per3) and Cryptochrome (Cry1 and Cry2) genes. Following translation, Per and Cry form complexes and translocate back to the nucleus where they negatively regulate CLOCK and BMAL1 activity (Reppert and Weaver, 2002). This core transcriptional feedback loop is interconnected with other regulatory loops, providing multiple layers of regulatory control to the circadian clock system. The CLOCK–BMAL1 heterodimer also activates transcription of various clock-controlled genes, such as AVP (arginine vasopressin), DBP (D-site binding protein), TEF (thyrotroph embryonic factor), the nuclear orphan receptor REV-ERBα (reverse erythroblastic leukemia viral oncogene homolog), PAI-1 (plasminogen activator inhibitor 1), LDH-A (lactate dehydrogenase A) and the peroxisome proliferator-activated receptor (PPAR) response element, which in turn are involved in the circadian transcriptional regulation of several metabolic enzymes and processes (Green et al., 2008).

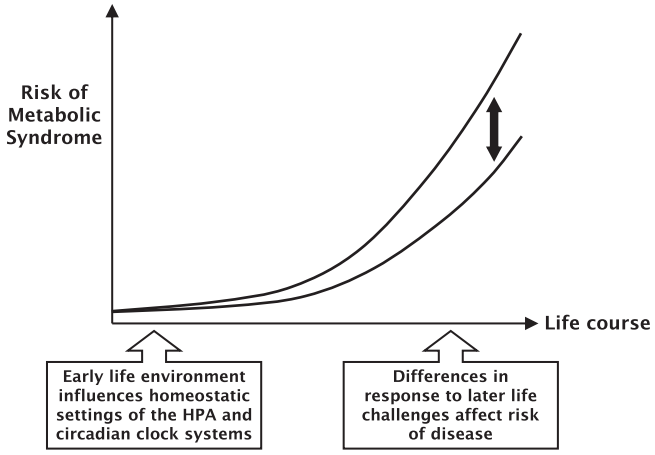

Fig. 1. The trajectory of risk of the metabolic syndrome increasing through the life course is affected (solid vertical arrow) by the differences in settings of the hypothalamic–pituitary–adrenal (HPA) axis and circadian clock systems established in early development.

Just over a decade ago, it was thought that the intracellular circadian clock system resided only in the hypothalamic region of the brain called the suprachiasmatic nucleus (SCN), but it has now been well established that other regions of the brain and peripheral tissues such as the liver, muscle, pancreas, lungs and heart also express these clock genes which oscillate in a circadian fashion (Yoo et al., 2004). This would suggest that circadian, metabolic, respiratory and cardiovascular processes are linked at multiple levels. Nevertheless, the central clock in the SCN, which is reset daily by light stimuli, regulates physiological processes in a tissue-specific manner by entraining clocks in peripheral tissues. The SCN, however, is not essential for driving peripheral oscillators but acts to synchronize them (Yoo et al., 2004). Therefore, the physiological rhythmicity in peripheral tissues may be controlled directly by their own clock genes and could also be separately entrained by stimuli such as food availability and environmental temperature.

Clock genes and clock-controlled genes feature prominently in the regulation of metabolism and energy homeostasis by mediating expression and activity of metabolic enzymes and transport systems involved in cholesterol metabolism, amino acid synthesis, the citric acid cycle, and glycogen and glucose metabolism (Ramsey et al., 2007; Green et al., 2008). In addition, a large number of nuclear receptors involved in lipid and glucose metabolism exhibit circadian changes in expression (Yang et al., 2006). The concentration of many hormones involved in metabolism, including insulin, glucagon, adiponectin, leptin and ghrelin, also exhibit circadian oscillation (Staels, 2006; Green et al., 2008). It is apparent from these studies that there is a cyclical relationship whereby circadian rhythms impact on metabolic activity and metabolism feeds back to the circadian clock system. Thus the disruption of either the central clock in the SCN and/or peripheral clocks has the potential to alter circadian patterns of expression and secretion of peptides and metabolites involved in metabolic processes. This may contribute to the development of the metabolic syndrome, which are associated with dysfunctional responses to environmental stimuli.

In humans it has been suggested that disruption of circadian rhythms leads to manifestations of the metabolic syndrome (Staels, 2006). Shift work and sleep deprivation are associated with increased incidence of cardiovascular and metabolic disease (Karlsson et al., 2001). The most compelling experimental evidence linking metabolic syndrome with disturbance of the circadian clock is based on the phenotypes of clock gene mutation or gene knockout in mice. Homozygous CLOCK$^{-/-}$ mutant mice have an attenuated diurnal feeding rhythm, are hyperphagic and obese,