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FOR DEBATE

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Neel revisited: the adipocyte, seasonality and type 2 diabetes

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Abstract The modern epidemic of obesity and insulin resistance with cardiovascular risk factor clustering is related to the development of type 2 diabetes and cardiovascular disease. Over 40 years ago, Neel postulated that insulin resistance should confer survival benefit. Extrapolating Neel's hypothesis, we propose that the cluster of associated abnormalities also confers survival benefit and is related to metabolic responses seen in seasonally responsive animals. Weight gain in preparation for winter is accompanied by a range of acute metabolic changes virtually identical to the long-term changes seen in type 2 diabetes. In seasonal animals the responses are acute, physiological and protective. In man, similar responses that would once have conferred survival benefit have become chronic, pathological and harmful in modern life. We hypothesise that type 2 diabetes and cardiovascular disease in man are the result of chronic and inappropriate pineal–hypothalamic–adipocyte interactions biologically related to seasonal change.

Keywords Adipocyte · Cardiovascular disease · Circadian and circannual rhythm · Clock genes · Hypothalamus · Inflammation · Insulin resistance · Melatonin · Metabolic syndrome · Seasonality · Type 2 diabetes

Neel revisited

The world is currently in the midst of an epidemic of type 2 diabetes, and around 300 million individuals are predicted to develop this disorder by the year 2025 [1]. The close biological relationship between diabetes and cardiovascular disease has focused attention on the common genetic and environmental antecedents of these conditions—the common soil hypothesis [2]—but the pathophysiological basis of these associations remains obscure. In 1962, Neel proposed the thrifty genotype hypothesis, which postulated that insulin overproduction must at one time have had a beneficial effect, in that it would provide 'an important energy conserving mechanism when food intake was irregular and obesity rare' [3]. Although Neel recognised insulin antagonism rather than insulin resistance, he hypothesised that the combination of obesity with increased insulin (or the presence of insulin antagonists) would lead to the development of diabetes. With hindsight, Neel was essentially speculating on the potential metabolic benefits of insulin resistance. The recognition in the last 20 years of an insulin resistance risk cluster [4] indicates that, under certain circumstances, elements of the risk cluster should also be beneficial to the survival of the organism, a response that, by analogy with Neel's original hypothesis, may coincidentally lead to the development of cardiovascular disease in times of plenty. The development of both insulin resistance and inflammation are physiological responses to increasing adiposity that, by definition, should be beneficial to the survival of the organism. The observation that the chronic metabolic milieu associated with type 2 diabetes is harmful raises the possibility that the adipocyte response to fat loading is beneficial when acute and short-lived, as is observed in seasonally responsive animals. Modifying Neel's original hypothesis, we propose that the response of the organism to fat loading develops as a result of an ancient metabolic adaptation to seasonal variation regulated by hypothalamic mechanisms. On this hypothesis, maladaption of our relationship with the seasons in modern life leads to a chronic proinflammatory, insulin-resistant, energy-conserving phenotype that underpins the development of both diabetes and cardiovascular disease.

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The adipocyte

The relationship between increasing adiposity and the development of chronic diseases such as type 2 diabetes,

cardiovascular disease and some cancers has been recognised for many years. Although much interest has been generated in the genetic approach to these disorders, it is intellectually attractive to think of the adipocyte as one of the conduits through which the environment translates into clinical disease. Although the adipocyte was traditionally thought of as a passive storage cell, it is now known to have a critical role in the manifestation of insulin resistance under conditions of adipocyte fat loading [5]. Several novel proteins (adiponectin, leptin and resistin), and others such as TNF-α, C-reactive protein, plasminogen activator inhibitor-1 (PAI-1), renin and angiotensinogen, are produced and regulated by the fat-loaded adipocyte [6]. Under these circumstances, the adipocyte generates a metabolic and proinflammatory phenotype that is central to the development of insulin resistance and vascular disease [7, 8]. Obesity, type 2 diabetes and TNF-α downregulate adiponectin synthesis, whereas increased levels of adiponectin are seen with weight loss and glitazone use [9]. Adiponectin could potentially reduce insulin resistance through a number of mechanisms, although the principal effects seem to be achieved through a reduction in hepatic glucose production and increased fatty acid oxidation [9]. Recent clinical studies implicate low levels of adiponectin in the pathogenesis of both insulin resistance and cardiovascular disease [10, 11]. Leptin production, on the other hand, is upregulated by the fat-filled adipocyte [6] and has an important role in the regulation of appetite through inhibitory effects on appetite stimulatory pathways in the arcuate nucleus [12]. Levels of leptin are increased in obesity, but this is accompanied by central resistance to the action of leptin [13]. As the adipocyte modulates adiponectin and leptin secretion, tightly linked proinflammatory changes occur that augment and magnify the development of insulin resistance both locally and systemically. The enhanced secretion of TNF-α from the fat-filled adipocyte has been implicated in insulin resistance by direct suppression of insulin signalling [14], and indirectly through suppression of adiponectin expression. TNF-α increases adipocyte lipolysis, thus increasing the output of fatty acids [15], which act directly to suppress the insulin signalling pathway, whilst enhancing fatty acid synthesis in the liver. TNF-α also has direct inflammatory effects on the macrophage and the endothelial cell, which promote the development of atherosclerosis. Recent studies support the view that a 'paracrine loop' exists between the adipocyte and macrophages to enhance inflammatory responses. This seems to be driven from the macrophage by TNF-α and from the adipocyte by increased NEFA [16]. TNF-α also enhances the production of PAI-1 from the adipocyte and other cell lines [17].

PAI-1 is the fast-acting inhibitor of tissue plasminogen activator and has a primary role in inhibition of fibrin clot lysis. Circulating levels of PAI-1 increase with obesity and predict cardiovascular events and mortality. There is also some evidence that PAI-1 may have a role in adipocyte insulin signalling, although this is an area that needs further investigation [18]. The adipocyte has a fully intact renin–angiotensinogen system, which is involved systemically in blood pressure control through vasoconstrictive effects. This may further enhance peripheral insulin resistance, as well as leading to hypertension [19]. Angiotensin II, for example, causes a reactive oxide species-dependent suppression of adipocyte adiponectin secretion, a mechanism that might explain the reported reduction in conversion to type 2 diabetes in large epidemiological studies of patients treated with ACE inhibitors.

The responses of the adipocyte to fat loading raise interesting questions as to why this happens under these circumstances, and what the physiological benefit of such responses might be. Lazar commented that 'there are no known survival benefits of morbid obesity' [20], a view that does not consider the potential benefits of short-term weight gain, as against the adverse consequences of chronic weight gain. All the short-term responses of the adipocyte would potentially enhance insulin resistance locally and systemically to direct glucose metabolism to the brain, an essential prerequisite for survival during seasonal adaption. Over the longer term, these same metabolic responses would predispose to beta cell failure and type 2 diabetes, and the inflammatory response would additionally lead to the development of cardiovascular disease. Most free-living mammals have circannual responses that mimic these changes on an acute seasonal basis; only man has developed chronic obesity and the associated consequence of chronic disease.

Seasonal and circadian responses in mammals

If we take the hibernating mammal as one end of the spectrum of seasonal changes seen in animals, its metabolism is evidently exquisitely attuned to the changing seasons (Fig. 1). During the longer summer days, pineal melatonin secretion is suppressed [21] and food intake maximised, leading to fat loading of the adipocyte in anticipation of winter. This leads to suppression of the phosphatidylinositol 3-kinase/protein kinase B insulin signalling pathway [22, 23] and the development of insulin resistance [24]. This is associated with hyperleptinaemia and suppression of adiponectin [25] together with a proinflammatory [26, 27] and prothrombotic phenotype [28] as the mammal enters winter. One might hypothesise that, in the seasonal animal, the suppression of adiponectin and increased leptin secretion are co-ordinated to develop insulin resistance and suppress appetite as food availability diminishes. During long winter nights, melatonin secretion is increased, enhancing adipocyte insulin sensitivity and energy availability whilst the animal is dormant [23, 29], leading to an animal that is lean and insulin sensitive once more on re-awakening in spring [23, 24]. The seasonally responsive mammal cycles obesity and insulin resistance in response to food availability and photoperiod to generate energy conservation. The autocrine and endocrine effects of adipocyte secretion of cytokines and other inflammatory proteins augment this locally and systemically. Hibernation is beneficial to the animal both in prolonging life expectancy and in protecting against insults during

dormancy, such as infection and ischaemia. It might be expected that disruption of these finely regulated processes would have detrimental effects. In support of this, when exposed to unseasonally moderate temperatures in winter and fed ad libitum, the edible dormouse develops insulin resistance and diminished beta cell function as compared with control animals [30], whilst hamsters that are unseasonally exposed to long-day photoperiods maintain their body fat [31].

Over the last decade a more complete understanding of the mechanisms that underpin the relationship animals have with the seasons has been achieved. Many different forms of life, including mammals, demonstrate cyclical responses that regulate reproductive, metabolic and behavioural changes. This is predominantly organised by light exposure, interpreted through the supra-chiasmatic nucleus, leading to regulation of melatonin secretion. Melatonin affects hypothalamic clock gene expression and has systemic effects on other tissues in the body [32]. Within the hypothalamus, a complex system of positive and negative feedbacks occur on the clock genes that lead to the development of an oscillating system that essentially regulates the cyclical phenotype in response to day length and the seasons [32–34]. One remarkable finding has been the recognition that peripheral tissues have intrinsic clock activity (critically, including the adipocyte [35]), suggesting a hierarchy of regulatory mechanisms that keep the organism in time with its environment [33]. A second equally astonishing finding is that there appear to be two clock pathways, one involving the pineal gland, which regulates short photoperiodicity, and a second involving pituitary calendar cells, which has much longer term effects [34]. The latter process seems to be more embedded in longer living animals, and there is evidence that this cycle survives migration from the tropics to the northern hemisphere and even through subsequent generations [36].

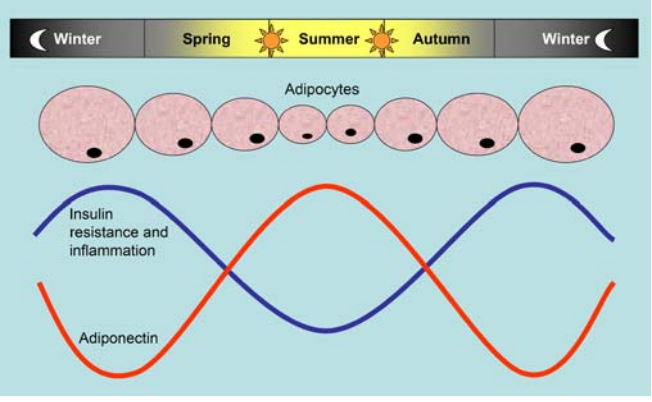

Fig. 1 Changes in adipocyte function, insulin resistance and inflammatory responses in seasonal animals in response to increased food availability in summer and autumn and decreased food availability in winter. Cycling of these responses secondary to alterations in adipocyte fat filling provides a mechanism for conserving the organism in winter by diverting glucose away from peripheral organs to the brain. Humans possess the same fundamental biological mechanisms but have lost contact with seasonal variation and instead chronically accumulate fat. The result in man is chronic insulin resistance leading to the development of type 2 diabetes and chronic inflammatory responses leading to cardiovascular disease

Two important pieces of information have emerged to support the relationship between the seasons, clock regulation and the development of type 2 diabetes. First, it has been demonstrated that altering the expression of the clock genes that coordinate seasonal and circadian rhythms leads to changes in glucose homeostasis and features of the metabolic syndrome, including hypertriglyceridaemia and hyperleptinaemia [37, 38]. Second, adipocytes have fully intact clock machinery that alters in response to daytime, and which appears to correlate with the expression of a number of other genes [35]. This mechanism is attenuated in the presence of obesity to suggest that fat loading blunts intrinsic cellular clock activity [35]. Bearing in mind that adipocytes express melatonin receptors through which melatonin is able to phosphorylate and co-activate the insulin receptor to enhance insulin sensitivity [29, 39], there appears to be complex circadian regulation of adipocyte function, which, when interrupted, may contribute to the insulin resistance phenotype.

Man, diabetes and cardiovascular disease

So what of man? In an elegant review on the mechanisms of seasonal rhythymicity in mammals, Lincoln et al. [34] stated that ‘humans express all elements of photoperiodism and circannual rhythm generation, albeit in a relatively weak fashion compared with many non-primate species’. This rhythmicity is reflected in man by changes in carbohydrate metabolism and weight gain, as well as behavioural and reproductive responses [34]. Substantial interest has developed in the general effects of disruption of this rhythmicity on health in man [40, 41]. Human responses to seasonal changes in the natural photoperiod were more robust prior to the Industrial Revolution and have subsequently been increasingly suppressed by alterations in the physical environment [42, 43]. Disruption of these processes is exemplified by the extreme circumstances of reversal of day/night working patterns seen in some shift workers. Lund et al. [40] reported that maladaption of endogenous circadian rhythms in shift workers was associated with increased insulin resistance and elevated postprandial triglyceride levels, findings consistent with other studies in this field [44–47]. In addition, shift work is associated with an increased risk of cardiovascular disease [46, 47], reported in one study as conveying a 1.6- and 3.0-fold increased risk for men and women, respectively, in the 45–55 year age group [46, 48]. As noted earlier in this article, it is particularly interesting to note that, in some mammals, migration north is accompanied by a chronic retention of circannual photoperiodicity appropriate for the region from which the animal is derived, rather than that in which it has settled [36]. This maladapted cycle can be transmitted through subsequent generations, even when the original animal and its offspring remain in the northern hemisphere [34, 36]. It

would be intriguing to know whether humans from the tropics who have migrated to the northern hemisphere similarly retain aspects of periodicity that are more appropriate for a tropical environment. If this were the case, it would indicate that Asians and Africans living in Europe are chronically maladapted to seasonal variation, which might, analogous to the shift workers, generate higher levels of insulin resistance and contribute to the increased risk of type 2 diabetes and cardiovascular disease in these populations.

Conclusions

It appears that the acute hypothalamic/adipocyte responses described in this article are ubiquitous within the animal kingdom, and are employed in the short term to protect against the vagaries of food shortages and other environmental hazards. There is evidence to suggest that cycling of these processes is protective in the short term and extends the life expectancy of the organism in the longer term. As Neel indicated, the development of insulin resistance should be a short-term response to protect man against future energy deprivation. The associated release of inflammatory cytokines and other adipokines could be in place to promote this metabolic switch by enhancing peripheral insulin resistance. Modern, westernised man has a substantially reduced ability to cycle these processes, probably because of attenuation of the rhythmicity of the environmental triggers (light exposure, food intake) that regulate these responses, and which, to some extent, will be seasonally related. As a result, our biology is attempting to cope with an environment for which it is not suited, and which predisposes to the chronic overexpression of a range of metabolic, pro-inflammatory and vasoactive proteins by the adipocyte. In modern man, the metabolic adaptation will develop into type 2 diabetes, and the pro-inflammatory and vasoactive responses will promote the development of co-existent cardiovascular disease.

Over 40 years ago, Neel postulated that insulin resistance must be beneficial and would operate in times of famine. He may well have been correct in pointing out the benefit of insulin resistance, but he was unaware of the cluster of adipocyte responses involved in generating this phenotype, as the full implications of the insulin resistance risk cluster were unknown in 1962. There is an exquisitely regulated link between the seasons, food intake and the requirement to preserve the organism during deprivation. What we call a cardiovascular risk cluster in association with insulin resistance is thus in fact a normal response in an abnormal setting. We hypothesise that disruption of seasonally related, rhythmical signalling through a pineal–hypothalamic–adipocyte pathway, and the metabolic changes incurred, explains the pathophysiology of obesity in modern man, complements Neel's hypothesis, and explains the basis of the common soil hypothesis. Testing this hypothesis to identify the cause of type 2 diabetes will require cross-disciplinary research involving hibernation biologists, neuroscientists, and adipocyte and vascular biologists in collaboration with endocrinologists and cardiovascular clinicians. Both genetics and proteomics will be key to a full understanding of this association. Genes in the human have been identified that are homologous to hibernation genes in true hibernating animals [23, 49]. It will be intriguing to find out whether manipulation of this group of genes holds the key to the prevention of both type 2 diabetes and cardiovascular disease in man.

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