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Circadian rhythms – daylight saving time, health, and body clocks

Each year we are reminded of our body clocks with the change in “daylight saving times”. At those times we are forcefully reminded of our bodily clocks and need to plan our daily schedules more carefully. In contrast, we like to deny our clocks becoming a 24/7 type, since we are “*homo sapiens*” (Latin – “wise man”) as Carl Linnaeus, also known after his ennoblement as Carl von Linné, described us in his biological classification.

Daylight savings time has been implicated in many events e.g. even in myocardial infarctions, yet daylight does not change that day[1], while there is certainly a winter predominance in acute myocardial infarction[2].

The recognition of the biological clock is old, but it was put forward as chronobiology by Franz Halberg [3], introducing the term “circadian” derived from the latin “circa” [around] and “dies” [day] and by Jürgen Aschoff[4]. Seymore Benzer, stimulated by his postdoc time in Max Delbrück’s lab at California Institute of Technology in genetics, discovered together with his student Ron Konopka the first *clock* mutants in Drosophila melanogaster[5]. In the following decade Jeffery C. Hall, Michael Rosbash and Michael W. Young accomplished the genetic analysis of the circadian behavior of Drosophila with the discovery of *per* and *timeless*. Based on these achievements the Nobel Committee for Physiology or Medicine awarded jointly to Jeffrey C. Hall, Michael Rosbash and Michael W. Young "for their discoveries of molecular mechanisms controlling the circadian rhythm[6].

The circadian clock regulates sleep and rest / activity and feeding via the superchiasmatic nucleus (SCN). It has now become evident that the molecular core-clock machinery affects every cell in the body[7] with disturbances of these pathways leading to significant

pathophysiological consequences far beyond the regulation of sleep. The SCN projects to various locations including the thalamus, hypothalamus and the basal forebrain[8]. In this issue Burish et al[9] describes the emerging evidence of circadian rhythms in headaches and neuropathic pains. Cluster headaches are an intermittent pain disorder with links to several circadian components like the melatonin system, cortisol secretion, and single nucleotide polymorphism changes in the *clock* genes. Pain medication for cluster headaches are known to affect the circadian clock such as lithium, valproic acid, melatonin and corticoids.

In the Meeting of the International Union of Physiologica Sciences (IUPS) in Rio de Janeiro, Brazil, last year under the scheme "Rhythms of Life" the "Circadian rhythm of the intestine" was discussed. Glucose tolerance and insulin sensitivity vary during the 24 hr cycle. The team of Joseph Bass has shown previously that disruption of the clock components *CLOCK* and *Bmal1* leads to hypoinsulinaemia and diabetes[10]. The same group found that along with circadian oscillation of insulin secretion, the genes encoding for secretory machinery components and signaling factors for insulin release exhibited rhythmic expression[11]. Petrenko and Dibner demonstrated that along with insulin, its counter-hormone glucagon produced by α-cells is regulated by the cell-autonomous clocks. Surprisingly, the oscillators operative in α- and β - cells differ in their circadian phase, which possibly facilitates a temporal fine-tuning of the islet hormone secretion[12]. Same authors presented in the meeting their results on the differential synchronizing effects of glucagon, glucagon-like peptide 1 (GLP-1) and somatostatin on α and β - cellular clocks[13]. The pro-glucagon derived hormones seem to reset β-cell clocks via a cAMP/CREB pathway. Thus, timing of α- and β – cell function is of essence for optimal insulin and glucagon secretion and overall glucose homeostasis.

Western diet impairs rhythmic GLP-1 release, but the mechanisms underlying this effect had been unclear. Martchenko et al[14] investigated the pathway(s) by which palmitate, a major component of the Western diet, impairs circadian GLP-1 secretion. The team of Patricia L. Brubaker[14] could demonstrate that palmitate reduced expression of the *Bmal1* downstream target, nicotinamide phosphoribosyltransferase (Nampt), with decreased nicotinamide adenine dinucleotide levels and impaired ATP production in mGLUTag cells, an established

model of intestinal L-cells, while activation of Nampt restored GLP-1 secretion in the presence of palmitate.

In the last talk of the session, Guillaume de Lartigue[15] summarized the current knowledge on the synchronization of behavioral and internal processes with daily circadian cycles distinct from the SCN. The food-entrained oscillator in the dopaminergic neurons of the dorsal striatum seems to enable animals maintained on a restricted feeding schedule to anticipate food arrival. The review provides arguments that the dopamine oscillations in the dorsal striatum exhibits all the necessary hallmarks of a secondary food-entrainable oscillator. The entrainment mechanisms by which nutritive information is communicated to promote food anticipatory activity when food is restricted to one daily mealtime remain poorly understood, but a putative role for ghrelin, PYY, insulin, leptin and the vagus nerve as mechanisms of food anticipation is suggested.

The internal time-keepers should not be ignored by the *homo sapiens* of today any longer, if we wish to be "wise man" and stay healthy. Our problems with the change of just one hour in the "daylight saving time" in spring and autumn undoubtedly illustrates a significant effect of even very mild circadian misalignment on our well-being!

Conflict of Interest

There is no conflict of interest to declare.

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