

## REVIEW

# Advances in chronohaematology

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### Summary

The circadian rhythms of the haemato-immune system seem to be synchronized by two clocks: the hypothalamic endogenous, and the exogenous which is based on environmental stimuli. The suprachiasmatic nucleus is not only a circadian clock, it also synchronizes peripheral oscillators and integrates light information through the retino-hypothalamic tract. The role of the “peripheral” clock genes in mature leucocytes still remains an unanswered question as well as the role of clock proteins in “non-clock” physiology. The circadian rhythms may be a basis for circannual variations, although the molecular bases of such rhythms remain a mystery. There are several hormones which have a significant impact on haematological characteristics; the finding of a lower superoxide release from granulocytes at higher melatonin levels opens up new research opportunities for melatonin therapy. Discrepancies between circadian changes in mRNAs and the appropriate protein participating in haemocoagulation and fibrinolysis may indicate that we do not know their control processes or their genetic background well, although this problem has now opened up a new area for pharmacological research. The endogenous clock facilitates an alternation in the immune system which counters external attacks in daytime and induces repair and development by night.

*Keywords:* circadian – seasonal – clock gene – haemostasis – immunity – melatonin – superoxide

### INTRODUCTION

A biorhythm is a periodically repeated change in living systems. It is a time-keeping system that anticipates environmental alterations. The rhythms most studied are circadian, with a period of about

24 ( $\pm 2$ ) h. The mechanism of biorhythm control has now been intensively studied at the molecular, cellular and organism levels for some tens of years. The circadian rhythms have most often been described in terms of their phases and amplitudes, and how these respond, in both health and disease, to a single exposure to synchronisers.

There is a reciprocal relationship between the robustness of the endogenous circadian timing system and its dependency on regularly timed synchronisers (light, physical activity, and feeding); this relationship can be damaged during disease or by ageing (Van Sommeren et al. 2007). Eventual therapeutic intervention can also embrace circadian synchronisation (cf. Lader 2007, Maharaj et al. 2007).

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In addition to circadian rhythms, there are important circannual variations and many more new frequencies, with the newest being an 0.42 year periodicity not only in solar flares and in solar activity generally and in sudden cardiac death (Halberg et al. 2006), but even in the circulating melatonin of patients.

The aim of this contribution is to choose and highlight the advances in chronohaematology (Halberg et al. 2003, Berger 2006) in the two years after our last review of this topic.

Table 1. Summarizing table that conveys main areas of advances in chronohaematology during last two years

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*Clock control*

two clocks system  
environmental changes  
suprachiasmatic nucleus and peripheral oscillators  
photoc and nonphotoc synchronization

*Molecular timing*

the role of genes in timing  
*per* genes in cancer development  
clock proteins in “non-clock” physiology

*Haemato-immune rhythms*

hypothalamo-immune communication  
genetic background  
melatonin synchronization  
correlation between activity of antioxidant enzymes and hormones  
circadian changes in leucocyte and erythrocyte functions  
stem cell harvest

*Hemostasis*

the risk state of thromboembolic events  
clock genes control

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## CLOCK CONTROL

Recent studies suggest that the control system of the circadian rhythm is composed of two parts: the rigid master circadian clock and the more flexible peripheral oscillators (Berger 2004a, Kronfeld-Schor and Dayan 2008). Mammals, including humans, synchronize the master clock in the brain (Ko and Tkahashi 2006) to environmental changes through photic stimuli or the little known non-photoc entrainment (Halberg et al. 1953, Cornelissen et al. 2007, Salazar-Juarez et al. 2007, Challet 2007, Mendoza 2007, Novak et al. 2008).

The circadian rhythms of the haemato-immune system seem to be synchronized by two clocks, the first of which is endogenous, based on clock gene activity in the suprachiasmatic nucleus. The second is exogenous, based on environmental immune stimuli (Berger 2004a). Interactions between these two clocks can explain both the frequently observed

individual differences in circadian rhythms and the more subtle role of the clock genes in peripheral organs (Berger 2008).

The endogenous clock facilitates an alternation in the immune system which counters external attacks in daytime and induces repair and development by night. The suprachiasmatic nucleus is not only a circadian clock, it also synchronizes peripheral oscillators and integrates light information through the retino-hypothalamic tract (Lamont et al. 2007). Shift work and jet lag, which modify circadian rhythms, may be factors contributing to an increase in certain cancers, cardiovascular, gastrointestinal disease, reproductive difficulties and mortality (Mormont et al. 2000, Haus and Smolensky 2006, James et al. 2007a, Lamont et al. 2007).

The circadian rhythms may be the bases of circannual variations with a period about 1 year ( $\pm 2$ months). Vertebrates can anticipate seasonal

changes in weather using a set of interconnected neural elements (retina, hypothalamus, pineal melatonin production and receptors in mammals) and endocrine elements (prolactin secreting cells in mammals) that govern photoperiodic responses (Hazlerigg and Wagner 2006, Lincoln et al. 2006). Seasonal photoperiodism facilitates transition from winter to summer phenotypes, physiology and behaviour (Wagner et al. 2007).

Many seasonal changes in the laboratory characteristics (Berger 1980a, Haus 1996, Sher et al. 2005, Kiank et al. 2007) and behaviour of both human and animal subjects cannot however be explained by the above mentioned circannual mechanism. The molecular bases of the control of circannual rhythms remain a mystery.

## MOLECULAR TIMING

Some oscillator components in animals may be related to tumour growth and it is known that *per* genes can suppress tumour growth or formation (Fu et al. 2002, Chen et al. 2005, Gery et al. 2006, Krugluger et al. 2007, Lamont et al. 2007, Zeman et al. 2008). Circadian proteins such as BMAL play a role in age-related pathologies (Kondratov 2007). The clock gene mutant in laboratory mice has increased tumours (Fu et al. 2002). A proper relationship between the rhythmic expression of clock components and their absolute values may play a role in cancer development, and their deficit or absence may negatively influence the progress of the disease (Zeman et al. 2008). Clock genes also play a role in mental disorders (Lamont et al. 2007).

Historically, the molecular mechanisms of circadian rhythms have been studied in micro-organisms and *Drosophila* because the entire circadian system can be contained in a single cell. The transcription/translation feedback model in micro-organisms (Lakin-Thomas and Brody 2004, Lakin-Thomas 2006) reflects an evolutionary conserved mechanism and may therefore give us insight into the molecular basis in both prokaryotic and eukaryotic organisms.

Circadian rhythms are generated by molecular clock genes whose proteins rhythmically modulate transcription of nearly 10% of the genome: the so-called clock 'controlled' genes (Tsinkalovsky et al. 2006, for review). Mammalian clock genes are active in both the hypothalamus central clock and peripheral tissues including human blood cells (Berger 2006, Tsinkalovski 2005, 2007, James et al. 2007b, Dardente and Cermakian 2007, Haus 2007a,

for review). The second and third control points of clock gene regulation represent post-translational modifications of the clock proteins and chromatin remodelling (Dardente and Cermakian 2007).

It has been hypothesized that cell cycle points are gated to an intrinsic circadian clock for protection from circadian exposure to mutagens, e.g., UV radiation peaks with daylight and dissolved genotoxins that fluctuate with feeding periods (Shadan 2007). Perhaps, we can now – following publication of the literature summarised above – look forward to the discovery of a new role for clock proteins in “non-clock” cellular physiology.

## HAEMATO-IMMUNE OSCILLATIONS

Circadian changes in circulating blood cells have been recognized in various species and ages (Haus 1996, Berger 2004b). Cerutti and co-workers (2006) described the creation of the circadian during ontogenesis of calves. Circadian rhythms in the number of mammalian leucocytes can reflect oscillations in haematopoietic proliferation activity in the bone marrow (Berger 1980b, Smaaland et al. 1992). Recent findings show that haematopoietic stem cells also exit the bone marrow into the periphery in a circadian rhythm with a peak at five hours of light (Alcivar 2008). Clinicians may now need to pay attention to the time of day in which they harvest stem cells from the blood.

Last year, Ohkura with co-workers (2007a) revealed the influence of different genetic backgrounds on the circadian rhythmicity of leucocytes, erythrocytes and erythropoietin. Periodic changes in the number of peripheral blood cells can influence their functions. The fact that the autonomous nervous system and the neuroendocrine system have been shown to modulate leucocyte physiology supports the concept that circadian timing is an important aspect of hypothalamo-immune communication (Arjona and Sarkar 2008).

There are several hormones which have a significant impact on haematological characteristics one of the more important of which is melatonin which regulates and synchronizes many circadian rhythms (Haus 2007a).

Circadian and circannual variations in erythropoietin production and release, stimulate rhythms in erythropoietic proliferation (Gunga et al. 2007) but there are some papers that demonstrate, and others that simply did not find, a rhythm in

erythropoietin activity. Further research on this topic is desirable.

Melatonin plays an important role in the regulation of various body and cellular functions including immunity. It can induce changes in the intracellular calcium concentration that modulates proliferation and its circadian alteration (Wronka et al. 2008). This hormone serves as an inhibitor of myeloperoxidase which catalyses oxidant formation, which has been implicated in both immune reactions and the pathogenesis of various diseases. It modulates the formation of myeloperoxidase intermediates (Galijasevic et al. 2008). It prevents inflammation and oxidative stress and the circadian rhythm of the melatonin level correlates with variations in both neutrophil accumulation and its protective effect (Guney et al. 2007).

The endogenous level of melatonin is highest during the night or during the second half of the night – it is the so-called ‘nocturnal’ hormone – and higher melatonin levels are associated with better sleep. Ageing changes these rhythms; in older individuals, treatment with melatonin and tryptophan at the concentrations and times of administration considered suitable for improved nocturnal rest also reverses the immuno-suppressory and oxidative effects accompanying phagocytosis (Paredes et al. 2007).

Human leucocyte reactive oxygen species show circadian variations and they might possibly influence the occurrence of cardiovascular incidents (Larsen and Lyberg 2006). The finding of lower superoxide release from granulocytes at higher melatonin levels opens up new research opportunities for melatonin therapy (Geron et al. 2006). Some patients with low melatonin activity may benefit from both improvement in their sleep quality and a reduction of granulocyte mediated oxidative stress after melatonin administration.

Superoxide dismutase activity in erythrocytes changes the circadian rhythm in correlation with corticosteroid levels, although other enzymes participating in oxidative stress seem to be rather constant (Goncharova et al. 2006). It seems that hormones melatonin and corticosteroids play an essential role in the regulation of superoxide dismutase activity which is assumed to participate in many cellular processes.

Following the dissociation of sleep from the effects of circadian rhythms it has been documented that sleep alone can enhance adaptive immune responses. Sleep is associated with an increase in pre-dendritic cells, i.e. myeloid dendritic cell precursors, producing interleukin-12, activity of

interleukin-6 (but not the concentration of monocytes producing this cytokine) and decreased numbers of CD14(dim)CD16+ and interleukin-10, producing monocytes, plasmacytoid dendritic cells and T cells (Lange et al. 2006, Dimitrov et al. 2006, 2007). Sleep alone enhances adaptive immunity and stimulates circadian alterations in immunity, but high prolactin and low cortisol levels also contribute to some of these changes during sleep.

Lymphocytes and neutrophils participate in allergic-inflammatory processes. One of the effects of their activation is increased binding to histamine which reaches a peak in the afternoon for healthy subjects’ and is lowered in the night, while their amplitude in asthmatic subjects was not significant (Zak-Nejmark et al. 2006). The different circadian histamine binding to leucocytes in atopic from healthy subjects may participate in the nocturnal exacerbation of disease symptoms.

Erythrocyte superoxidase, catalase and glutathione peroxidase show seasonal variations (Balog et al. 2006) which can be important in relation to the circannual rhythm in oxidative stress and cardiovascular events (cf. Touitou and Bogdan 2007). Circannual rhythms in the enzymes of oxidant-antioxidant balance can be positively influenced following regular physical activity (Balog et al. 2006). New results (Yerer and Aydogan 2006) have revealed rhythms in erythrocyte deformability, one of the impact factors participating in the rhythms of cardiovascular events.

A significant leucocytosis after elevated cortisol concentration has been noted several times, recently in horses by Quaranta et al. (2006): training programmes must consider the circadian rhythms of cortisol as its elevated concentration can cause stress disease and the ‘overtraining’ syndrome. Cortisol has an important immunosuppressive activity and its alternations could be considered to be the ground of the circadian rhythm in the circulating lymphocyte count. No similar correlation was found in colorectal cancer patients (Mussi et al. 2006).

In summary, new details concerning oscillations in blood cells have been brought to light in the last two years, while the chronobiology of haematopoiesis has concentrated on clock gene activity.

## **HAEMOSTASIS**

The haemostatic system has multiple components in an intricate organization; the interaction of the

rhythms of the variables participating in haemostasis determine the transient risk states of thromboembolic events, including myocardial infarction and stroke, and of haemorrhage and haemorrhagic events, each with a unique timing and coinciding with rhythms in fibrinolytic activity (Haus 2007b, for review). It has been known for many years that the myocardial infarction peak usually occurs in the morning between 7 and 12 a.m. (Touitou and Bogdan 2007). Ohkura and co-workers (2007b) have described circadian rhythms in the plasma plasminogen activator inhibitor-1 in all examined mice strains, and in plasma antithrombin and protein C only in the strain Jcl:ICR, whereas plasma prothrombin, factor VII, X, prothrombin time and activated partial thrombin time remained constant in all strains. They also found circadian fluctuations of mRNA, although an appropriate coagulation factor expresses constant activity. The clock gene was found to be involved in the regulation of fibrinolysis through plasminogen activator inhibitor-1 production (Oishi et al. 2005, 2006).

The CLOCK protein forms heterodimers with BMAL1 and then activates another clock gene via E-box elements in their promoters (Reppert and Weaver 2002). Understanding the molecular mechanism of plasminogen activator inhibitor-1 alterations could lead to the discovery of new pharmaceutical targets (Oishi et al. 2006). A new research area could be found in the mechanism of the coagulation and fibrinolytic system.

## CONCLUSION

The circadian rhythms of the haemato-immune system are synchronized by two clocks. The suprachiasmatic nucleus also synchronizes peripheral oscillators and integrates light information through the retino-hypothalamic tract. Current findings indicate the important role of “peripheral” clock genes in the immune system but the role of clock genes in mature leucocytes is unknown. The molecular bases of circannual rhythms also remain a mystery.

Melatonin and erythropoietin have a significant impact on rhythms. The autonomous nervous system and the neuroendocrine system have been shown to modulate leucocyte physiology and this supports the concept of circadian timing as an important aspect of hypothalamo-immune communication. The different circadian histamine binding to leucocytes in atopic from healthy

subjects may participate in the nocturnal exacerbation of disease symptoms. Some oscillator components in animals may be related to tumour growth.

The interactions among the rhythms of the variables participating in haemostasis determine transient risk states of thromboembolic events. Discrepancies between circadian changes in mRNAs and appropriate proteins participating in haemocoagulation and fibrinolysis indicate that we do not know the control of these processes or their genetic background well.

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