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REVIEW

Chronohaematology

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Summary
Rhythmic changes in a number of haematological characteristics have been described in many published papers during the 20th and at the beginning of the 21st century. The best known are circadian rhythms, which are mostly correlated with the light/dark regime, inducing rhythmic changes in levels of melatonin, synchronised by a suprachiasmatic nucleus and the retinohypothalamic input. These circadian rhythms in men and diurnal animals have an inverse relationship to rhythms in nocturnal beings. Some haematological rhythms are modified by other synchronisers. Knowledge of circadian rhythms in haematological characteristics is important for both the faultless clinical interpretation of laboratory data and the search for mechanisms participating in rhythm regulation.

Keywords: circadian rhythm – blood cell – haemopoiesis – clinical significance – synchronization

INTRODUCTION

In addition to the spatial structure of organisms (which is studied by anatomy and other disciplines), biorhythms, including periodic changes in the blood, and the haemopoietic system represent the time structure of living organisms. Chronohaematology studies biorhythms in the blood and haemopoietic systems including the rhythm-dependent manifestation of diseases.

The first papers with data showing that leukocyte counts change during the day were written by Japha (1900), Sabin and co-workers (1927), Domarus (1931) and Halberg and Visscher (1950).

Diurnal rhythms in the human bone marrow were first demonstrated in the work of Mauer (1965); Haus and co-workers (1972) and Aardal with Laerum (1983) started experiments on leukaemic mice to explore the circadian rhythms in the sensitivity/resistance of the blood and haemopoietic systems to xenobiotics, and Lasky, with co-workers (1983) was the first to describe circadian rhythmic changes in mouse stem haemopoietic cells.

Currently (cf. Berger 1987, Haus 1996 etc.), we know well that many haematological characteristics must be compared to the non-pathological reference values of the appropriate day time (generally haemopoiesis, the white blood picture and many coagulation components), while several characteristics (e.g. red blood cell counts in human subjects) seem to be so stable during the day that their circadian variations are not detectable or do not have any clinical significance. Human subjects have maximal values of white blood cell counts at midnight, and both bone marrow DNA synthesis and marrow CFU-GM early after noon. The therapeutic dose/infusion speed of a drug may depend on the time of day (e.g. cytotoxic drugs, heparin). Rhythms in coagulation lead to a morning peak of infarcts and cardiac death. Special disorders are also a cause of cyclical changes in peripheral blood cell counts.

Because recent research concentrates on variations during the day and night, and it seems that these rhythms can be keys to the induction and regulation of many rhythms with different periods, we focus below on those rhythms with a period of approx. 24 hrs – the so-called circadian rhythms (circa=about, dian=day). Intensive research is an investigation mechanism causing biorhythms and the role of external stimuli to influence oscillations at molecular, cellular and organism levels.

RHYTHMS IN BLOOD CELLS

Maximal values of human lymphocyte subpopulations with CD8, CD8 dim, CD8 bright, CD16, TcRd and dTcS1 are found in the morning, and CD4, CD4/CD8 ratio, HLA-DR, CD20 and CD25 at night. CD8 bright and TcRd1 presented higher levels in the morning without validation of the circadian rhythm (Akbulut et al. 1999). The numbers of monocytes, NK cells, and counts of lymphocyte subsets (CD19, CD3, CD4, CD8, HLA-DR) were significantly higher in the afternoon and evening than after nocturnal wakefulness (Palm et al. 1996, Born et al. 1997, Zelazowska et al. 1997). Sleep markedly enhanced production of IL-2 by T cells (CD3) but did not influence production of IL-1β and TNF-α, or IL-6 concentrations; the decrease in monocytes, NK cells, and lymphocytes, together with an increased production of IL-2 during sleep, may serve to support ongoing immune defence in extravascular lymphoid tissue during a time of diminished acute antigen challenge (Born et al. 1997).

Nocturnal intensification of some immune functions is correlated to circadian variations in the expression of some adhesion molecules: CD62L(L-selectin) in all classes of leukocytes; CD54 (ICAM-1) in neutrophils and monocytes, and CD11a (LFA-1a) in neutrophils (Niehaus et al. 2002).

Contrary to the data of Kronfol et al. (1997), Born et al. (1997) and Zelazowska et al. (1997), Palm et al.(1996) did not observe the circadian rhythm in NK (CD57) cell numbers, Fukuda et al. (1994) did not find circadian rhythms in three NK subpopulations, while Levi and co-workers (1988) observed the maximum of NK cells in the morning. As reverse circadian rhythms are present in nocturnal animals, findings of the circadian rhythm with a morning peak of NK cells in healthy human subjects is supported by the early dark peak of NK cells in nocturnal rats (McNulty et al. 1990) as well as the increase of NK cell activity in the dark period of nocturnal mice (Yellon and Tran 2002). We suppose that these differences may be explained by the data of Petitto et al. (1992) who showed that diurnal variations in NK cells can be reduced in depressed human subjects as the nervous system exerts its modulatory action upon the immune response (Baciu et al. 2003).

Several published papers show different findings in the biorhythms of phagocytosis. Sometime circadian rhythms were absent. Comparison of different laboratory procedures suggests that similar differences depend on both the tested phase of phagocytosis and the sensitivity of the laboratory procedures used (Berger and Slapnickova 2003). It was shown that phagocytic activity, the phagocytic index of small particles, and absolute counts of phacytosing cells, are all highest at the end of the subjective day (i.e. night for nocturnal, day for diurnal animals and men) while phases which run after ingestion have later peaks. Neutrophils were taken with blood specimens at different times but subsequent laboratory examinations were processed in vitro and, therefore, the rhythms in phagocytosis cannot be a passive reaction to changes in the environment; they must be an integral part of a gene-based time structure of immunity. Our data was confirmed by Sánchez and co-workers (2004) and they also observed, moreover, that diet tryptophan, i.e. a precursor of melatonin, can modify the circadian rhythm of latex phagocytosis.

Human subjects have maximal values in relative circulating neutrophil counts in the afternoon, absolute circulating neutrophil counts before midnight, total white blood cell counts at midnight, both relative and absolute circulating lymphocyte counts later in the night, bone marrow DNA synthesis (S-phase), marrow CFU-GM and serum cortisol in the early afternoon (Smaaland et al. 1991, 1995), and circulating CFU also in the afternoon (Verma et al. 1980). The delay of peaks of circulating cell counts as compared with the peaks in marrow hemopoietic cells can indicate that circulating leukocyte counts may be dependent on the proliferative activity of their precursors.

As we know that melatonin is an internal synchroniser of circadian oscillations in mammals, we can look for a melatonin influence on blood and haemopoietic cells to explain their rhythms. Melatonin administered in vivo increases leukocyte counts (Karimungi and Joshi 1996), while melatonin administered in vitro has no effect (Rogers et al. 1997). Examinations of ischemic stroke patients detected an impairment of nocturnal excretion of melatonin in the urine, which was associated with an impaired and changed cell-mediated immunity and lymphocyte subsets (Fiorina et al. 1999). As reduced melatonin excretion might be associated with neurological and psychical symptoms (Fiorina et al. 1999), it is possible that neuroimmunological interactions can be a component of the endogenous regulation of circadian rhythms in the blood system.

Although we suggest that melatonin alone does not regulate circadian rhythms in circulating leukocytes, the opposite influence of activated immune cells on the pineal gland is possible (cf. Skwarlo-Sonta et al. 2003).

Visible light (400–700nm) can penetrate epidermal and dermal layers of the skin and may directly interact with circulating lymphocytes to modulate the immune function. In contrast to visible light, in vivo exposure to UV-B (280–320 nm) and UV-A (320–400nm) radiation can alter the normal human immune function only by a skin-mediated response (Roberts 2000). It seems that it is not only periodic changes of immunostimulative impulses that induce rhythmic variations in leukocyte functions but also light can directly modulate immunity.

Table 1. **Summary of literature on acrophases[§] in the circadian rhythm of selected haematological characteristics**

Subjective morning[*]	Subjective afternoon and evening[+]	Subjective night
nucleolar size	total leukocyte counts	eosinophil counts
CD3	monocyte counts	lymphocyte counts
CD4	neutrophil counts	CD2
CD8	phagocytosis	CD4/CD8 ratio
CD8dim	NK cells counts	CD11a (LFA-1a) in neutrophils
CD8bright	CD3	CD20
CD16δ	CD4	CD54 (ICAM-1) in neutrophils and monocytes
CD56	CD8	CD62L (L-selectin)
TcS1	CD19	HLA-DR
platelet adhesiveness	CD45	T
	HLA-DR	B
	marrow DNA synthesis	Th
	marrow CFU-GM	Tγδ
	circulating CFU	Ts/c
	G-CSF	reticulocyte counts
	GM-CSF	platelet aggregation
	platelet counts	APTT
	fibrinolytic activity	thrombin time

[§] acrophase is the position of maximal value of the fitted rhythm
* beginning of the subjective day, i.e. morning for human subjects and diurnal animal, evening for nocturnal mammals
[+] beginning of the subjective night

The size of human lymphocyte nucleoli is mostly greater in the morning than in the evening (Berger and Berger 2004). This non-homogeneity of rhythms is similar to variation in marrow DNA synthesis, which was described by Smaaland and co-workers (1991). The acrophase of lymphocyte subpopulations in the work of both Kronfol and co-workers (1997) and Suzuki and co-workers (1997) is different compared to the data published in several studies published by Mazzoccoli and co-workers (2003). We suppose that these differences can also be caused by various exogenous immune stimuli similar to findings on the rhythm in nucleolar size (Berger and Berger 2004) and exogenous synchronization may be the most important factor for the circadian rhythm in the count and function of white blood cells.

We did not observe clinically significant circadian rhythms in red blood cell counts (Berger 1983). We think it was due to the erythrocyte life span of approx. 110 days in human subjects or 60 days in laboratory rats. This life span is too long to allow a detectable influence of the circadian rhythms on erythropoiesis as it cannot influence more than one percent of their circulating pool. In addition, variations in erythrocyte counts are also limited by rheological characteristics (Berger 1981).

RHYTHMS IN HAEMOPOIESIS

The concentration of both human CFUc and CFU-GEMM exhibits a significant circadian rhythm (Aardal and Laerum 1983, Lasky et al. 1983). Human marrow CFU-GM, cells in DNA S-phase, CD34 stem progenitor cells as well as circulating neutrophils and lymphocytes also represent significant circadian rhythms (Haus 1996,

Smaaland et al. 2002). A similar phasing in DNA synthetic activity with maximal DNA synthetic activity during the day and minimal between midnight and 04:00 were documented for myelopoietic and erythropoietic cells in the human bone marrow (Abrahamsen et al. 1997). Circadian variations were also documented for cord blood haematopoietic progenitors (Baudoux et al. 1998).

The significant correlation shown in healthy volunteers between the serum granulocyte-macrophage colony-stimulating-factor (GM-CSF), the cortisol and melatonin level with peripheral white blood cell, neutrophil, and the lymphocyte counts during day and night (Akbulut et al. 1999), indicates the influence of these humoral factors on both the proliferation and release of mature blood cells into the blood. As only lymphocyte counts correlate with GM-CSF, with cortisol and with melatonin levels in early breast cancer patients (Akbulut et al. 1999), we can assume the participation of other factors in the modification of the circadian rhythm in the haemopoietic and blood system, particularly in circulating neutrophil counts.

This finding is also supported by correlation between circadian changes in human serum haemopoietic growth factors G-CSF (Jilma et al. 1999) GM-CSF (Abdelaal et al. 2000, Dincol et al. 2000) and lymphocyte and total white blood cell counts as well as the correlation between variations in the number of human CFU-GM and circulating neutrophil counts (Morra et al. 1984, Smaaland et al. 2002) during the day and night. Thus, much data supports the above-mentioned opinion on the important influence of growth factors on marrow proliferation which seems to be fundamental for the rhythms of circulating leukocytes.

As melatonin alone do not affect lymphocyte proliferation but potentiate corticosteroidal inhibition of lymphocyte proliferation (Rogers et al. 1997), melatonin together with corticosteroidal can regulate some biorhythms in the haemopoietic and blood system.

Granulocyte and lymphocyte subsets (natural killer cells, extrathymic T cells, γδT cells, and CD8) with a maximum during daytime, carry a high density of adrenergic receptors, and lymphocyte subsets (T cells, B cells, αβT cells, and CD4). With the maximum at night they carry a high proportion of cholinergic receptors (Suzuki et al. 1977). This data can explain the modification of circadian rhythms which are not in correlation with factors influencing the cell cycle of their proliferating precursors.

Chen et al. (2000) found the expression of clock genes mper1 and mper2 in mouse bone marrow. Thus, marrow cells contain their own genetic oscillators but we do not know if a marrow clock gene has a crucial or complementary/peripheral role.

PATHOLOGICAL RHYTHMS

Cyclic neutropenia and thromocytopenia at six-week intervals or lasting for five to six months have been documented (Tefferi et al. 1989, Abe et al. 2000, for review). Weiden et al. (1974) found that cyclic neutropenia are caused by a defect in the marrow stem cell. Mutations in ELA2, the gene encoding neutrophil elastase was observed in disease (Horwitz et al. 2004). These mutations seem to be implicated in the accelerated apoptotic process of the bone marrow myeloid cells (Papadaki and Eliopoulos 2003). Using a mathematical model (Østby and Winter 2004), impaired effective cytokine elimination by cell receptors may enforce these oscillations. Some cyclic neutropenia and thrombocytopenia have immune mechanisms involving T lymphocytes (Abe et al. 2000, Fureder et al. 2002).

Rhythms in the leukocyte function can alternate during several diseases as malignant growths (cf. Filipski et al. 2002), asthma (Carandente et al. 1988, Koh et al. 2002), urticaria (Grattan et al. 2003), alcoholism (Redwine et al. 2003), and HIV (Rabson 1995) etc. Such relationships are a consequence of the disruption of the circadian structure and/or changes which are a component of the immune defence during a disease without primary damage to the circadian system.

CONCLUSION

Circadian rhythms in many haematological characteristics have such large amplitudes that knowledge about them is important for good clinical interpretation. Rhythms can be modified by physiological regulation disabled during disease, and some defects in haemopoietic stem cells can induce a cyclic decrease in circulating cell counts. The investigation of circadian rhythms in peripheral blood and hemopoietic cells seems to be a suitable model for understanding the fundamental machinery of oscillations and their disorders in various organs.

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