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PHARMACOLOGICAL AND INDUSTRIAL CHALENGE: DECIPHERING EXTRACIRCADIAN RHYTHMIC SIGNATURES IN US AND AROUND US. REVIEW

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A b s t r a c t

The scope of chronobiological diagnosis and treatment in biology and medicine can be extended from a consideration of circadian systems to time structures, i.e., chronomes, and thereby to introduce chronomics, the mapping of chronomes, into applications for medical devices and pharmaceutical industries and the software companies serving them. The task of lifelong monitoring, apart from providing a more solid preventive health care, further serves to a timely and timed treatment and the elucidation of basic aspects of variability in and around us, which may be useful to ecology and chronoastrobiology.

K e y w o r d s

Biological rhythms, Circadian rhythm, Circaseptan rhythm, Cardiovascular parameters

CHRONOMES IN AND AROUND US

Life can be viewed as a transiently self-sustaining organised structure in time and space, consisting of chronomes, made up of irregular changes, rhythms and trends, lasting for duration sufficient to possibly reproduce themselves and to evolve (*1,2*). Chronomes of organisms continuously communicate with the time structures of the environment consisting of similar elements. Indeed, biologists find more and more counterparts of biological cycles in the environment and counterparts of environmental cycles in biology (*3*). The environmental chronomes' rhythmic element consists of photic and non-photic cycles, some of the latter solar and galactic. The rhythmic elements of chronomes in and around us intermodulate functions, i.e., there are interactions among the rhythms in physiological as well as among those in natural physical entities and in intercommunicating open organism-environment systems (*1,2,3,4*). These interactions among two or more biological and/or physical entities are characterized by sequential patterns in time, involving recurrent quantitative or even qualitative changes. The latter can be the changing effect of one entity upon another, entailing a sequence of inhibition, no-effect and stimulation, recurring rhythmically and to that extent predictably (*1,2,3,4,5*).

RULES

Certain procedures, if not rules of chronomes (notably of rhythms in these time structures) are that (*3*):

1. For each inferentially statistically validated rhythm. as an element of a time structure, one can seek a corresponding element in the chronome of a natural physical environmental variable. This is how a 6.74-day component was detected first in a record of geomagnetic disturbance (K_p) covering 59 years (*6*). More specifically, a finding in biology of a built-in near- (but not precisely) 7-day week prompted biologists to search for a geophysical near-match. The near-weekly component was then further specified as to its variation with the solar cycle stage (*7*) and for even longer spans of 110 (*8*) or more (*9,10*) years.

2. For each periodic component in the environment, a near-matching component may be sought, which is how a half-yearly period was found in severe attacks of epilepsy (*6*), as a response to a hint in correspondence from the biophysicist Armin Grafe who described half-yearly cycles in geomagnetics (*11,12*).

3. Biological rhythms without environmental near-matches may point to the disappearance, in the course of life's development on earth, of a natural physical environmental cycle. Accordingly, it would be most interesting if a biological rhythm would have no environmental near-match. A current challenge is the search for a possible environmental counterpart for about 8-hourly rhythms in vasoactive substances such as in the case of endothelin1 (*13,14,15*), a powerful vasoconstrictor, in the population density of endotheliocytes (*16*), and under certain circumstances of a 2-hourly isocaloric diet in epinephrine (*3,17*).

4. In their growth and development, human beings and other multicellulars are living fossils that, in their rhythmic dynamics during ontogeny, may replay the sequences that occurred during the development of life. In this context, humans are a source of information for scholars on the origins of life *par excellence,* in contrast to eukaryotic single cells or prokaryotes whose growth, development and differentiation may not exhibit the time-lapse phenomena observed in more differentiated organisms. In the same context, certain multicellular organisms may be better „fossils“ for certain problems as compared to others. Thus, crayfish may be a better subject of study than human beings, rats or piglets, for the investigation of the biological week, since a circaseptan is present in locomotor activity of crayfish at 6 months of age (*18*). In contrast, by the end of the first month or two of extrauterine life, the about 7-day component of physiological variables compares unfavourably in terms of its (circaseptan) amplitude with the

amplitude of circadian rhythms in rats as well as humans. At old age, circaseptans and ultradians regain some relative prominence, but not necessarily exceed a circadian rhythm in amplitude (*19*).

EXTRAPOLATIONS

The sites of an organism's origins may be distinguished by early ontogeny. Organisms that have a prominent 7-day component early in life on earth may have developed away from the alternations of day/night and night/day recurring each day, on Earth or on Mars, and may have locked into the near 7-day harmonic of the sun's rotation period that may be ubiquitous in the solar system. On Earth there may have been some input from the Moon as well, granted that the latter is reportedly small. Conceivably, the near 7-day period found early in the ontogeny of species such as rats, piglets, humans and crayfish is compatible with life originating anywhere in the solar system, deep at the bottom of the ocean on Earth or inside Mars or in the ice of Europe. As the fourth harmonic of Sun's rotation around its axis, the physical week may have a wide influence, yet only in the absence of a near-daily alternation of light and darkness that may have been the principal driver for organisms evolving on the surface of Earth or Mars.

Galactic and/or photic, thermic and other effects, associated with corpuscular radiation from the Sun, are sufficiently forcing factors to affect microbial (*20*) as well as human variables in a meta-analysis of original data (*21*), morphological ones such as body length and weight, and physiological ones such as heart rate variability that may have some relation to the about 10-year cycle in myocardial infarctions and in vascular and probably other pathologies, notably those related to the brain and heart (*3,6*).

For the study of photic effects from the Sun on the Earth, the amplitudes of periodicities of about 1 year and about 1 day are useful. Conversely, for the study of effects from corpuscular radiation from the Sun, Moon and Cosmos and their effects on biota, the amplitudes of about-half-weekly, about-weekly, about-monthly, about-half-yearly, about 10.5, about 21-year and about 50-year cycles are of interest. The ratio of amplitudes of the latter periodicities related, e.g., to cosmo, helio- or geomagnetics versus the amplitudes of changes with a period of a day or year, may provide a hint about the relative prominence if not the roles played by photic and non-photic corpuscular effects of the Sun, among the diversity of natural physical and environmental factors (*Table 1*), a meta-analysis (3) of thus-interpreted original data (*21*).

Galactic drivers concomitantly cannot be ruled out for life on earth. The effect of cosmic ray flux may actually be a more direct effect as compared to that of a magnetic storm that displaces cosmic ray flux to the earth, and may, for instance, thereby affect the number of bacterial colonies with sectors and thus perhaps of mutations (*20*) in a testable model that may be used in a standardised fashion in

Table 1

Amplitude ratios of non-photic *vs*. photic solar periodicities on human neonatal length and weight*

Period (years)	Double amplitude ± SE		Amplitude ratio[a]	Acrophase (degrees: 360°=period length; 0°=1 Jan 1973)		
A. STATISTICALLY SIGNIFICANT COMPONENTS IN LEAST SQUARES SPECTRA (1-99 CYCLES IN 21 YEARS)[a]						
Length at birth						
21.0	2.20 ±	0.14	3.44	-356°	(-349;	-363)
10.5	0.70 ±	0.20	1.09	-250°	(-216;	-283)
5.25	0.60 ±	0.20	0.94	-298°	(-257;	-338)
1.0	0.64 ±	0.20	1.00	-137°	(-101;	-174)
0.5	0.98 ±	0.18	1.53	-140°	(-118;	-162)
Weight at birth						
21.0	21.35 ±	2.84	1.04	-14°	(-359;	-389)
10.5	8.38 ±	3.10	0.41	-220°	(-173;	-267)
5.25	8.35 ±	3.10	0.41	-336°	(-289;	-383)
1.0	20.56 ±	2.86	1.00	-138°	(-122;	-154)
0.5	19.15 ±	2.90	0.93	-139°	(-121;	-156)
[a]Amplitude ratios computed relatively to the yearly component.						
B. RELATIVE PROMINENCE OF ABOUT-YEARLY AND HALF-YEARLY COMPONENTS AFTER DETRENDING (DATA STACKED OVER IDEALIZED 1-YEAR SPAN)[b]						
Length at birth (all babies)						
1.0	0.956 ±	0.202		-155°	(-131;	-179)
0.5	1.082 ±	0.204		-166°	(-145;	-187)
			$A_{0.5\ y}/A_{1.0\ y} = 1.132$			
Length at birth (babies born at GA=40 weeks)						
1.0	0.392 ±	0.172		-95°	(-46;	-144)
0.5	0.768 ±	0.172		-129°	(-104;	-154)
			$A_{0.5\ y}/A_{1.0\ y} = 1.959$			

[b]The larger $A_{0.5\ y}/A_{1.0\ y}$ amplitude ratio observed for babies born at a gestational age (GA) of 40 weeks by comparison to all babies may be accounted for, at least in part, by the fact that variables such as GA at birth may be primarily characterised by a circannual component, whereas other variables such as length at birth may be primarily characterised by a half-yearly variation. When the influence of factors with a yearly variation such as GA is removed, the half-yearly variation of birth length becomes even more pronounced.

*From the data based on graphs published by Wohlfahrt et al. (16) obtained from the Danish National Birth Registry for all children (N=1 166,206) born from 1973 to 1994. An about 23-year component, resolved nonlinearly for yearly birth weight data in Minnesota and covering the span from 1965 to 1995, cannot be resolved when the shorter span covering 1973-1993 matching the Danish data is correlated. The Minnesotan data preclude the computation of ratios available for the Danish ones since denser-than-yearly data were not available.

long-overdue coordinated biological and physical, including physiological and archival, human monitoring.

Illustrative results from mapping over a wide range of frequencies

Against this background, we find that, in clinical health, about 8-hourly endothelin (ET1) rhythms coexist in the same circulation, with about 24-hour cortisol rhythms (*15*). ET-1 rhythms of about 84 hours are also found in the human circulation, altered in people at high vascular disease risk (*13, 14*). About 8- and ~84-hour rhythms characterise the population density of endotheliocytes in mouse ear dermis (*16*), reproducing, as a temporal pattern, what was previously found for a related variable in the human circulation (*13,14,15,16*). The concept of a time structure or chronome extends the view of a 24-hour clock to conditions wherein more than one rhythmic component is found in more than one species, with some similarity of the findings for the same variable in different species.

The ~1.7 (human REM), ~8, ~84- and ~168-hour components had no known prominent environmental counterpart until the week and half-week were also found in the K_p (*6, 7*) or indices of planetary geomagnetic disturbance (*8,9,10*). As to the circasemiseptan in prolonged human isolation, changes with a period of 81 h, not of precisely 84 h, have been found to characterise both K_p and the heart rate of a 28-year-old woman during isolation from society for 267 days (*22*). The circaseptan period of human neonates correlates with local geomagnetic disturbances (*23, 24*). More generally, human neonates and elderly are characterised in their circulation by an extra-circadian prominence. So is the electrical activity of the giant alga *Acetabularia* kept in continuous light; detrended data reveal a circaseptan with an amplitude larger than that of the circadian of 61.8%, while the circasemi-septan component is of 43.1%, with all three components apparently free-running (*25*).

Furthermore, an about 10-year cycle characterises several composite series constituted from 12 years of experimentation on *Acetabularia;* the endpoints analysed are the circadian average and circadian phase and the durations of an initial standardisation and of the total experiment spans, constituting primarily features of algal growth. Concomitant processing of 100 series of noise at the intervals at which biological data are available does not reveal such rhythms more often than anticipated by chance. The chronomes around us, notably their multi-frequency rhythms, have counterparts in the chronomes within us, including the about 10-year cycles long known under the guise of secularity, but revealed as characterising even myocardial infarctions among other variables of major biomedical interest (*3,6,26,27,28*). The further international mapping in the BIOCOS project (*3,29*) should have a high priority if phenomena that today are confounders are identified as predictably rhythmic and dealt with as a source of important information for the development of countermeasures as needed. The propositions of a preventive chronobiology and its implementation by long-term physiological monitoring, as a basis for diagnosis and treatment, may fit into an ongoing discussion of evolutionary health promotion (*30*). Exploitation by chronomics of the time structures, which we acquired through an integrative (*31*) as well as adaptive evolution, is a challenge, as is the task of assessing how we modify this ecological inheritance, as in the case of anthropogenic magnetic pollution also assessed as a purely physical phenomenon (*32*).

TODAY'S APPLICATIONS IN HEALTH CARE WITH A CIRCADIAN FOCUS

In view of the foregoing, as yet a greatly restricted focus, the parametric section of the sphygmochron (*33*), a blood pressure and heart rate summary, enables a test of the statistical significance of the outcomes of an intervention on an individualized patient basis. A reduction in sodium intake was possibly useful for some patients (*1,2,4,6,11*), of negligible effect for other patients (*8,10*), or possibly undesirable for still other patients (*3,5,7,9,13*). The confirmation of the blood pressure-lowering effect of dietary caloric restriction was also assessed by sphygmochron.

It cannot be overemphasized that a 7-day record is recommended only as a start. The display of CHAT (**c**ircadian **h**yper-**a**mplitude-**t**ension) present most of the time on a given treatment (R_X-1). Following a change in treatment (to R_X-2) for the ensuing week, CHAT seems to be cured (the dark areas are absent). Thereafter, however, the dark areas indicating CHAT (that disappeared for a week) reappear. The graph indicates why even a 7-day span can be very deceptive when there is a problem, as reported repeatedly earlier elsewhere (*33,34,35,36*).

DISCUSSION

There is no long-term compromise with restricted monitoring only of circadians. There is a broad spectrum of rhythms in and around us. We need transdisciplinary agreements on the terms we use to eliminate confusion, as we undertake aligned physical, environmental and physiological monitoring. Some tentative suggestions may serve for discussion (*37*).

Broad spectra of rhythms are generated by seemingly chaotic, some of them deterministic, changes in us and the trends they undergo are basic science today. They are essential for the planning of monitoring and treatment devices and administration schemes to be optimised for these devices, whether we deal with diagnostics based upon rhythm alterations, as in the case of altered variability in heart rate or blood pressure (*36*), or with changes in the spectrum of breast surface temperature (*38*), as warnings of pre-disease, or with treatment of actual disease when intermodulations among frequencies can lead to opposite outcomes, as a function of administration patterns, unless more than rhythms with a single frequency are taken into account (*39*).

A c k n o w l e d g e m e n t s

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FARMAKOLOGICKÁ A PRŮMYSLOVÁ VÝZVA: ROZŠIFROVÁNÍ EXTRACIRCADIÁNNÍCH RYTMICKÝCH PODPISŮ V NÁS A KOLEM NÁS

S o u h r n

Rozsah chronobiologické diagnózy a léčení v biologii a medicíně může být rozšířen z přihlédnutí k circadiánním systémům na časové struktury, chronomy, mapování chronomů, do aplikací pro výrobu lékařských přístrojů a farmaceutický průmysl a do společností vyrábějících programové vybavení, které slouží těmto odvětvím. Celoživotní monitorování slouží podle potřeby kromě poskytování důslednější preventivní zdravotní péče dále pro včasné a v nejvhodnější době poskytované léčení a pro objasnění základních aspektů variability v nás a kolem nás, které mohou být užitečné pro ekologii a pro chronoastrobiologii.

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