The Genetic Background of Individual Variations of Circadian-Rhythm Periods in Healthy Human Adults

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Summary

As a group phenomenon, human variables exhibit a rhythm with a period (τ) equal to 24 h. However, healthy human adults may differ from one another with regard to the persistence of the 24-h periods of a set of variables' rhythms within a given individual. Such an internal desynchronization (or individual circadian dyschronism) was documented during isolation experiments without time cues, both in the present study involving 78 male shift workers and in 20 males and 19 females living in a natural setting. Circadian rhythms of sleep-wake cycles, oral temperature, grip strength of both hands, and heart rate were recorded, and power-spectra analyses of individual time series of about 15 days were used to quantify the rhythm period of each variable. The period of the sleep-wake cycle seldom differed from 24 h, while rhythm periods of the other variables exhibited a trimodal distribution (τ = 24 h, τ > 24 h, τ < 24 h). Among the temperature rhythm periods which were either <24 h or >24 h, none was detected between 23.2 and 24 h or between 24 and 24.8 h. Furthermore, the deviations from the 24-h period were predominantly grouped in multiples of ±0.8 h. Similar results were obtained when the rhythm periods of hand grip strength were analyzed (for each hand separately). In addition, the distribution of grip strength rhythm periods of the left hand exhibited a gender-related difference. These results suggested the presence of genetically controlled variability. Consequently, the distribution pattern of the periods was analyzed to elucidate its compatibility with a genetic control consisting of either a two-allele system, a multiple-allele system, or a polygenic system. The analysis resulted in structuring a model which integrates the function of a constitutive (essential) gene which produces the exact 24-h period (the Dian domain) with a set of (inducible) polygenes, the alleles of which, contribute identical time entities to the period. The time entities which affected the rhythm periods of the variables examined were in the magnitude of ±0.8 h. Such an assembly of genes may create periods ranging from 20 to 28 h (the Circadian domain). The model was termed by us "The Dian-Circadian Model." This model can also be used to explain the beat phenomenon in biological rhythms, the presence of 7-d and 30-d periods, and interindividual differences in sensitivity of rhythm characteristics (phase shifts, synchronization, etc.) to external (and environmental) factors.

Introduction

A circadian rhythm is defined as a rhythm having a period (τ) of 24 ± 4 h. On exposure to a natural environmental setting, healthy human adults usually exhibit, as a group phenomenon, circadian rhythms whose period τ equals 24 h (Halberg and Reinberg 1967; Aschoff and

Wever 1981; Moore-Ede et al. 1982; Reinberg and Smolensky 1983a). It is postulated that their endogenous biological clocks (oscillators) are influenced by the periodic changes of a set of environmental factors (also referred to as "synchronizers" or "zeitgebers"). Most plants and animals employ the day/night (photoperiodic) alternation (τ = 24 h) to synchronize their circadian rhythms, using dawn and/or dusk as pertinent cues. Long exposure to bright light (2,500 lux for ≥5 h) may also have a synchronizing effect on human subjects (in comparison, the resetting of circadian oscillators in hamsters can be achieved by a short-pulse 0.5 lux).

Biological rhythms do persist (they are referred to as "free running"), even when organisms are kept in a constant environment without known zeitgebers. In the free-running state the period τ of many circadian rhythms differs from 24 h.

In human subjects, social factors are known to have prominent synchronizing effects (Halberg and Reinberg 1967; Moore-Ede et al. 1982). Our diurnal activity and nocturnal rest are calibrated by a set of imperative hours around which our societal life is built (e.g., work time). Without consciously knowing it, we use a large variety of interhuman relationships and their timing to reset and synchronize our internal clocks. The synchronizing effects of social factors were demonstrated in experiments where groups of subjects were isolated from environmental time cues and clues (Apfelbaum et al. 1969; Aschoff et al. 1974). In these experiments the biologic rhythms of the interindividual interactions involving visual, auditive, and physical signals, all members of the same group, exhibited the same (free-running) circadian periodicity (e.g., $\tau = 24.8$ h). Moreover, when isolation conditions are maintained for several weeks, the biologic time structure of certain subjects (27% among females and 23% among males (Wever 1979; Aschoff and Wever 1981) can split into several components, each free running with a different circadian period, revealing the endogenous (not entrained) period of the variable's rhythm. For example, body core-temperature rhythm may free run with $\tau = 25$ h, while the sleep-wake rhythm will free run with $\tau = 33$ h. Obviously, in such case the acrophase (ϕ; peak time of the best-fitting computed rhythm) will drift daily along the 24-h scale, instead of being stabilized at the same hour. Such phenomena are defined as "internal desynchronization." Furthermore, these experiments have revealed that the rhythms of different variables are controlled by separate oscillators (Moore-Ede et al. 1982).

While longitudinally studying biological rhythms in shift workers (Reinberg et al. 1984a, 1984b, 1988; Motohasi et al. 1987), we were astonished to observe (fig. 1) that internal desynchronization of rhythms (e.g., oral temperature, grip strength of both hands, and sleep-wake rhythm) within a given individual was a rather common phenomenon, despite the fact that the examined subjects were not socially isolated from each other or from other persons. The occurrence of this phenomenon (internal desynchronization) was influenced neither by the type of work (different industries were examined) nor by the schedules of the shifts (weekly rotation vs. rapid-rotation shifts [Reinberg et al. 1988]).

Furthermore, internal desynchronization was also found in healthy human adults, even when the environmental settings were not manipulated (Bicakova-Rocher et al. 1984, 1988; Reinberg et al. 1984c, 1985a). The latter observations were also confirmed in a study carried out on 22 young Japanese men and women (Motohashi 1990).

Since deviations from the 24-h period occur in entrained, changing, and constant conditions, it seems that the use of the term "internal desynchronization" to designate the broad spectrum of this variability may be misunderstood. Dealing with a trivial situation— namely, experimentally validated individual variations (e.g., τ) in the circadian time structure—we propose to cluster all the phenotypes of this phenomenon under the term "individual circadian dyschronism." This rather broad cluster includes "internal desynchronization" when the latter is used to refer to deviations from the 24-h period within an individual.

Since, during several experiments, large amounts of individuals' time series have been accumulated (Bicakova-Rocher et al. 1984; Reinberg et al. 1984a, 1984b, 1984c, 1985a; Motohashi et al. 1987), it was decided to analyze these time series in order to quantify the frequency of the variations and to ascertain the ability of subjects to exhibit, even when exposed to natural settings, variations in the circadian time structure which are controlled by genetic entities. More precisely, we wanted to know whether the change in the period τ of the altered rhythms is compatible with a temporal order structured by a genetic control. Furthermore, since internal desynchronization implies the presence of a multioscillatory system, it was tempting to propose a model related to the overall genetic background of the circadian rhythms in human subjects.

Material and Methods

A. Subjects and Living Conditions

1. *Shift workers in working conditions (group A).*—Seventy-eight Caucasian males 21–58 years of age (mean age 42 years) were included in this study. Seventy percent of the workers worked in shifts, and 30% were former shift workers assigned to regular (day) work. Sixty percent of the shift workers had rapid-rotation shifts (shift duration 3–4 d; night shift every 3–4 wk), and 40% had weekly rotation shifts (shift duration 7 d; night shift every 4–5 wk). Shift work was well tolerated by 54% of the shift workers and was poorly tolerated by 46%. Seventy-five percent of all workers were oil
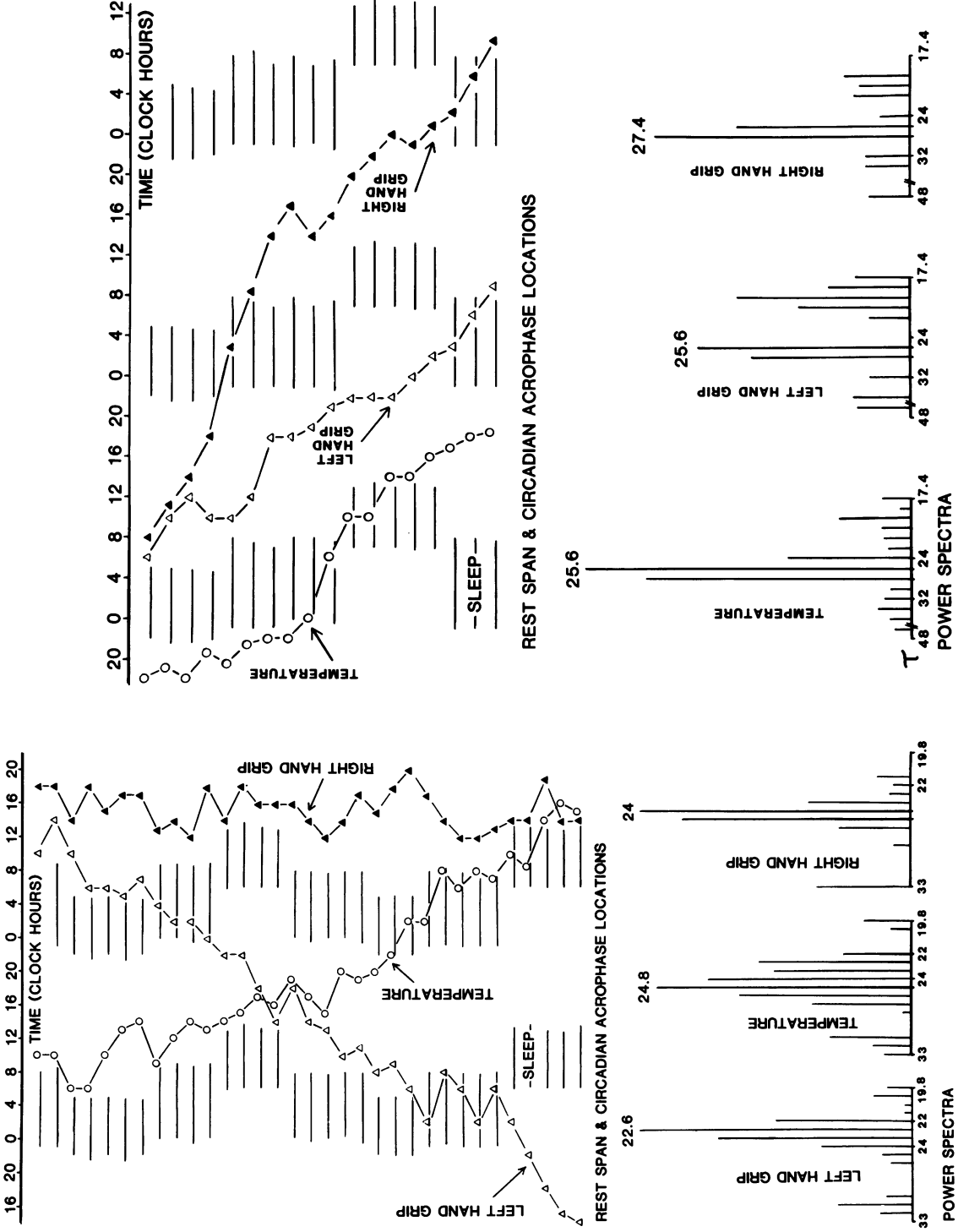
Figure I Rest span and circadian acrophase locations of three variables (top) and the respective power spectra (bottom), as documented in shift workers. Sleep spans (*horizontal lines*) are double plotted. Circles and blackened and unblackened triangles designate the daily rhythm acrophases of the various variables. The highest bar of each spectrum corresponds to the prominent period of each variable (period length [in h] is indicated on the top of that bar). The two panels provide two examples of internal desynchronization or circadian dyschronism.

refinery operators (they constituted the majority of the rapid-rotation shift), while the others came from the steel, film, and chemical industries (Reinberg et al. 1984a, 1984b, 1984c, 1985a, 1988; Motohashi et al. 1987).

2. *Subjects exposed to natural setting (group B).*— Twenty Caucasian males and 19 Caucasian females, with an age range from 19–44 years (mean age 36 years), were examined in this group. They have been involved in studies aimed at documenting circadian rhythms (a) during intensive training in sport (Reinberg et al. 1985a) (b) of controls for chronopharmacokinetic investigations (Bicakova-Rocher et al. 1984, 1988), (c) during a sojourn in the high-arctic summer (Reinberg et al. 1984c), and (d) as individual time series of healthy volunteers leading a regular life (two women and one man; authors' unpublished data). Subjects of both groups followed their spontaneous diet without restrictions on quality and quantity. Meal timing was not taken into account, as its synchronizing effect on the examined variables is nil or very weak (Reinberg et al. 1979; Reinberg and Smolensky 1983a). During the period of the experiment the subjects did not suffer from infectious diseases and were not taking any medications, including placebos (Reinberg and Smolensky 1983b). Subjects were allowed to sleep ad libitum, except during working hours. Only nine subjects took occasional naps, but neither regularly nor frequently. Detailed information regarding waking and retiring times is available in the original publications. Oil refinery operators, chemical workers, and film workers were not allowed to smoke at work. The number of smokers in both groups was small, and their daily consumption of cigarettes did not exceed 10/d. Studies on group A and on sportsmen and sportswomen were carried out between the end of autumn and early winter, and studies on subjects participating in the chronopharmacokinetic investigation were carried out between December and March.

B. Examined Variables and Data Gathering

Sleep-wake and temperature rhythms were monitored in all subjects of both groups. Grip strength of left and right hands was recorded in all subjects of group B and in 40 subjects of group A (5 of the latter were left handed). Heart rate (HR) was monitored in the same 40 subjects of group A, and peak expiratory flow (PEF; bronchial patency) was also recorded in the same 40 subjects of group A, as well as in all subjects of group B. The detailed information is presented in table 1. Prior to the experiments the subjects were given data-collecting sheets and monitoring instruments and were trained in their proper use.

The experimental data were recorded for approximately 15 successive days (including one or two night shifts, for subjects involved in shift work). Subjects recorded, on a daily basis, the times of lights on and lights off, as well as, every 3–4 h (except during sleep), the values of the following variables:

1. Oral temperature was measured by a standard large-scale (1/20 of Celsius precision) clinical thermometer. In addition, 13 subjects used a continuous-recording device for axillary temperature (Motohashi et al. 1987).
2. Grip strength of both hands was measured by the use of a Colin-Gentille dynamometer (Paris), in a standardized body and arm position (sitting with the arm and forearm hanging vertically alongside the body). Subjects were asked to exert maximal force, and three measurements were taken for each hand at each time point. The highest value of the three measurements was recorded. The results were expressed in both Newton and kilogram force units.
3. PEF, an index of the bronchial diameter up to the seventh dichotomy of the bronchial tree, was estimated by a Mini-Wright calibrated peak-flow meter (Airmed, England). All measurements were performed in the same way, and the highest value of three consecutive measurements taken at each time point was recorded.
4. Heart rate was determined from the radial pulse counted for 1 min. The procedure of assessment was standardized and identical for all measurements.
5. Sleep-wake rhythm was determined by recording exact times of lights on and lights off.

The above-listed variables were chosen because (a) the procedures of the measurements are easy, do not exert heavy task load, and can be carried out by the examinees; (b) they can be assessed without interruption of normal daily activities and thus are suitable for longitudinal studies; and (c) all of them are measured by noninvasive methods. The use of invasive procedures (such as blood drawing) may induce increased anxiety, which in turn may distort rhythm patterns.

All time points were expressed as hours and minutes. Measurements were performed, in most cases, on the average of four to six times during 24 h. It took 5–10 minutes for a subject to complete the battery of tests. The selection of this sampling methodology was based on both the feasibility of performing a field study and on results from a comparative study where time series

Table I

Prominent Period τ of Variables Examined in Subjects of Groups A and B

GROUP AND VARIABLE (total no. of subjects)	NO. OF SUBJECTS		
	τ < 24 h	τ = 24 h	τ > 24 h
Group A (male shift workers):			
Sleep-wake rhythm (78)	0	78	0
Oral temperature (78)	15	51	12
Grip strength:			
Right hand (40)	12	17	11
Left hand (40)	15	10	15
PEF (40)	11	18	11
Heart rate (40)	10	25	5
Group B:			
Males:			
Sleep-wake rhythm (20)	0	19	1
Oral temperature (20)	5	12	3
Grip strength:			
Right hand (20)	3	12	5
Left hand (20)	7	13	0
Females:			
Sleep-wake rhythm (19)	0	18	1
Oral temperature (19)	4	11	4
Grip strength:			
Right hand (19)	7	9	3
Left hand (19)	10	6	3

were analyzed. Examination of five healthy individuals determined that the circadian-rhythm characteristics of the axillary temperature were similar whether the data were sampled every 15 min or every 4 h during 2 wk (Motohashi et al. 1987).

C. Statistical Analysis

The time series of each individual were analyzed separately, for the following reasons: (a) Pooling or averaging data may obscure certain features of the rhythm (Reinberg and Smolensky 1983a, 1983b; De Prins et al. 1986), especially when large interindividual differences are expected (Kerkhof 1985). (b) Manipulation of zeitgebers usually leads to transient alterations of rhythm parameters such as period, amplitude, and acrophase (computed parameters of a cosine curve, best fitting to the observed data) (Aschoff et al. 1975). (c) Short data-gathering spans make it difficult to distinguish between a continuous transient phenomenon and instability of a rhythm or to estimate accurately the rhythm parameters. In our experiments the latter was avoided, since data were collected for 15 d. Special consideration was given to gender analysis (with regard to grip strength and temperature) to elucidate sex-related differences in periods when internal desynchronization occurred.

The following analytical methods were used for computing rhythm parameters:

1. The cosinor method (Nelson et al. 1979) using the best-fitting cosine function approximating the data for a given period τ. This analysis provides three rhythm parameters: (1) Acrophase φ, computed peak or crest time, which in these studies was referenced to midnight; (2) amplitude, half the total variability between the value at the acrophase and the value at the trough; and (3) Mesor, the rhythm-adjusted mean. Acrophase and amplitude values are given with 95% confidence limit, and the mean values are given with the standard error of the mean (SEM). In this method a rhythm is validated when its amplitude differs from zero with a $P < .05$. The cosinor was used to determine, for each day for each variable of each individual, the location of the acrophase. It should be noted that in some circumstances (where not enough time points per 24 h were available) data of two consecutive days were pooled; their acrophases were considered to be similar (Reinberg et al. 1988). The computed acrophases of different variables for a given individual are displayed as a function of time (on a double-24-h scale, to facilitate readings), day by day, one beneath the other. This kind of

graphic presentation visualizes clearly the acrophase drift (demonstrated in fig. 1).

2. Power spectrum analysis. Value of the prominent periods τ expressed in hours was obtained from individual time series by using a power-spectra method developed by De Prins et al. (1986) (examples are demonstrated in fig. 1, lower part). For six daily measurements the determined precision, in hour and minutes, for the prominent period τ is 0.031, 0.025, and 0.0.017 for follow-up of 8, 10, and 15 d, respectively. Furthermore, this method can be applied to time series with missing time points (e.g., due to sleep), as well as to unequally spaced time points, which occurred in this study. τ Values obtained by the two different methods (acrophase drift and power spectra) were either similar or very close.

Other statistical methods, such as cross-correlation, ANOVA, and χ^2 analysis, were used to test the validity of various conclusions. Each of these methods has its own limitations, and therefore it was of interest to test whether each provided concordant and complementary results (De Prins et al. 1986).

D. Genetic Analysis

Conventional methods applicable for analysis of population genetics were used, such as histograms of the frequency distribution of the periods, χ^2 tests, Hardy-Weinberg (Hardy 1908; Stern 1943) computations, etc. Each one (or more than one) was used at various stages throughout the analysis and will be referred to in the Results section.

Results

A. Sleep-Wake Rhythm

Two methods were applied to quantify the period τ of the sleep-wake rhythm. In the first method, the power spectrum of the sleep-wake pattern was computed by analyzing the sleep-wake rhythm of each individual as a step function with the arbitrary assignment of 1 = wake, 0 = sleep, and time unit = 15 min. In the second method, mid sleep of each individual was taken as a phase reference, and the sleep-wake rhythm was first computed on a daily basis and then averaged. For example, when the latter analysis was applied to the sportsmen and sportswomen (eight subjects, included in group B; table 1), the resulting respective periods τ ± SEM were 24.14 ± 0.41, 24.12 ± 0.51, 24.4 ± 0.35, 24.02 ± 0.14, 24.1 ± 0.06, 24.26 ± 0.41, 23.93 ± 0.29, and 24.31 ± 0.39. None of these periods differed signif-
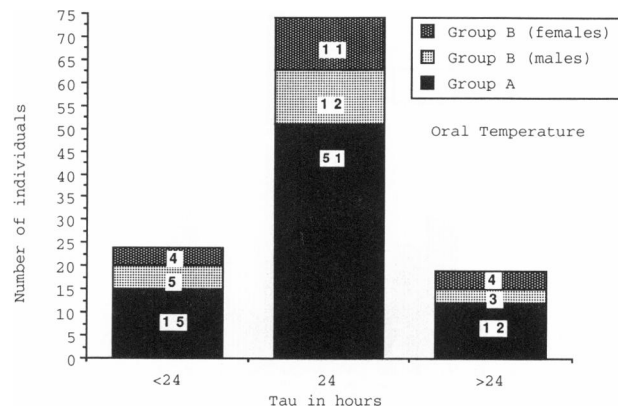

Figure 2 Distribution of periods (<24 h, 24 h, and >24 h), as detected in the temperature rhythms of the examined subjects. For definitions of groups A and B, see sections 1 and 2 of Subjects and Living Conditions.

icantly from τ = 24. Thus, the analyses by both methods yielded τ = 24 as the prominent period in 115 of the 117 examined individuals (table 1).

B. Rhythms of Other Variables

Individual τ values of oral temperature, heart rate, grip strength (each hand separately), and PEF rhythm were obtained by using the power-spectrum analysis according to the method of De Prins et al. (1986). The pooled frequency distributions of periods τ equals 24 h, and those >24 h and <24 h are detailed in table 1.

C. Dissected Analysis of the Oral Temperature Circadian Rhythm

The three classes of periods (24 h, >24 h, and <24 h) observed in the time series of oral temperature are exhibited in figure 2. As can be seen, the ratios of the three classes—group A, group B males, and group B females—were similar. The dissected analysis of these observations was then carried out as follows: In the first step, the results related to the oral temperature rhythm of group A were arrayed according to actual observed periods of the examined individuals by using period differences of 0.1 h (e.g., 23.1, 23.2, . . . 24, 24.1, 24.2, . . . , etc.), from τ = 19.6 h to 28 h. It was astonishing to observe that none of the examined individuals exhibited an oral temperature rhythm with a period value falling between 23.25 h and 24.75 h.

In the second step, the results were arranged as absolute differences from 24 h (observed period minus 24 h or 24 h minus observed period). It was found that the prominent deviations were those of either 0.7 h or 0.8 h
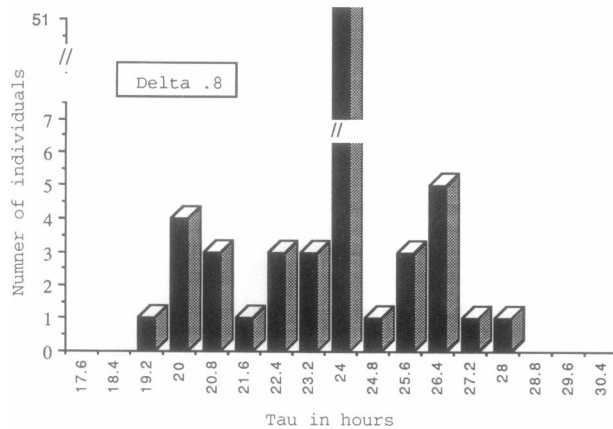
Figure 3 Distribution of periods (grouped in 0.8-h intervals), as detected in the temperature rhythms of the examined subjects.

Figure 4 Distribution of period length, as detected in the rhythms of males' and females' right-hand grip strength.

and their multiplications (e.g., 22.4, 23.2, 24, 24.8, 25.6, etc.). Consequently, the results were classed according to period differences of 0.7 h (not exhibited) or 0.8 h (fig. 3).

D. Dissected Analysis of the Grip-Strength Circadian Rhythm

Time series of grip strength (each hand separately) were analyzed in the same manner as was the temperature rhythm, and the results were similar to those obtained for the latter variable. The prominent period of both right- and left-hand grip-strength circadian rhythms was $\tau = 24$ h, but the periods which were >24 h or <24 h exhibited significant deviations in the magnitude of 0.8 h (or 0.7 h) or its multiplication.

It should be stated that differences exist between the frequencies of the various periods of the left- and the right-hand grip-strength rhythms. However, valuation of the influence of the dominant hand on the relative distribution of the detected periodicities could not yield conclusive results, as the right hand was the dominant one in most of the examinees.

Variability in period length was also observed in PEF and heart rate rhythms. Yet, no dissected analysis was applied to these variables, since (a) they were not monitored in both groups and (b) they are highly prone to influence by environmental factors.

E. Genetic Analysis

A sex-dependent difference was found with regard to the internal desynchronization of grip-strength rhythms. In group B (non–shift workers) there were 20 males and 19 females. When the periods' distributions
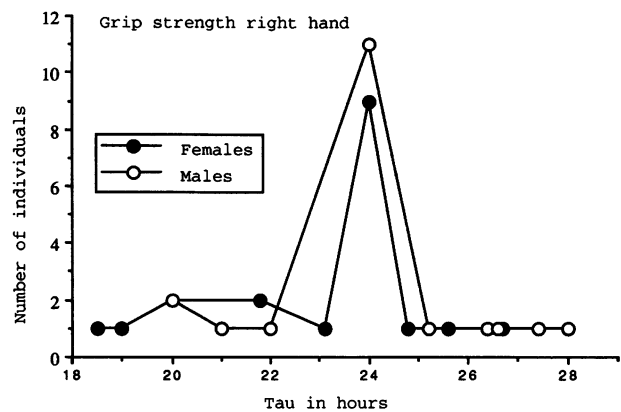
obtained for the grip-strength rhythm of the right hand were compared between the genders, no significant difference was observed (fig. 4; χ^2 test, $P > .05$). However, when the respective distributions, monitored in the left hand, were compared (fig. 5), a statistically significant difference was found between the genders ($\chi^2 = 6.1$, $P < .05$). There was a predominant fraction of circadian rhythms in which $\tau < 24$ h.

The distribution of the periods of the oral temperature rhythms suggested that the variability is genetically controlled. The equal size of the classes having either $\tau < 24$ h or $\tau > 24$ h (fig. 2) suggested, as the most simple explanation, the presence of a two-allele system with codominant expression (heterozygote = 24-h period). However, neither the Hardy-Weinberg analysis nor
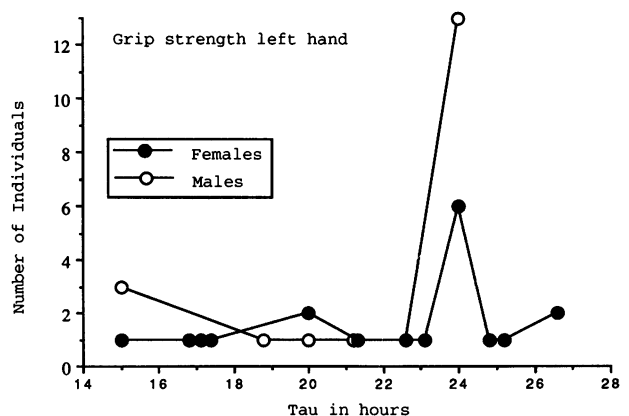

Figure 5 Distribution of period length, as detected in the rhythms of males' and females' left-hand grip strength.

contingency analysis could support the two-allele assumption.

The clustered distribution of the periods was then analyzed by assuming the control of either a multiple-allele system or a polygenic one. A multiple-allele system will contribute to the population an assortment of alleles each adding or subtracting, from the 24-h period, one of the following (for the 0.8 multiplicity): 0 h, ±0.8 h, ±1.6 h, ±2.4 h, etc. Yet, in each individual there will be only two of these alleles controlling the rhythm period of a specific variable.

The polygenic assumption calls for the presence of a series of genes, in each individual, responsible for the expression of a period of a given variable. Each of these genes will contribute either a 0.8-h (or 0.7-h) period or a −0.8-h (or −0.7-h) period. The resulting length of a period will be determined by the relative proportion of the +0.8-h or −0.8-h genes residing in the genome.

To examine which of the two periods (±0.7 h or ±0.8 h) is more compatible with the actual distribution, the 0.7-h and 0.8-h clusters were tested, by using scattergrams, polynomial regression, and associated statistics. The 0.8-h multiplicity unit was found to be statistically significant as compatible with the actual distribution of the periods, while the 0.7-h multiplicity was rejected.

Discussion

The genetic control of circadian rhythms has been demonstrated for some variables in various plant (Feldman 1982) and animal species (Konopka and Benzer 1971; Bargiello and Young 1984). In Drosophila, at least two genes which are located on the X chromosome were found to be involved in the activity rhythm. In man, studies with twins (MZ vs. DZ) were used by Barcal et al. (1968) (measuring blood pressure and heart rate), by Hanson et al. (1984) (measuring heart rate), and by Reinberg et al. (1985b) (measuring adrenal activity), to suggest the presence of genetic control of interindividual differences in the pattern of circadian rhythms. The observed difference between the genders, with regard to the frequency of individual circadian dyschronism between sleep-wake rhythm and temperature, as shown by Wever (1979) during isolation experiments, further reflect the presence of a genetic control.

Prior to assessing the usefulness of the present observations for genetic studies, whether the observed variability in the length of the periods is due to masking effects should be considered. When this possibility is assessed, it should be emphasized that all the presented variables were measured at the same time points in each of the examined individuals. Yet, the distribution of the various periods τ differed between right hand, and left hand, and temperature. One would expect that masking effects would induce similar or close distribution patterns of the periodicities. As this was not observed in the presented data, it is permissible to assume that the role of masking effects in the present study is negligible. The present study (a) further establishes the presence of individual circadian dyschronism between various variables and (b) extends the study of such a dyschronism between genders, pointing to the existence of this type of a difference in the circadian rhythm of the left-hand grip strength (figs. 4 and 5).

An additional support for the involvement of a genetic control on the periodicity of circadian rhythms resides in our observations. It is evident that the interindividual differences of the periods τ during such a dyschronism are not randomly distributed in the circadian domain (20–28 h). Instead, we observed that the differences in the periods deviating from 24 h, either to lower or higher periodicities, are in the magnitude of ±0.8 h and its multiplications. This was observed for oral temperature (fig. 3) and for grip strength.

The conventional way to explain the dual capacity of the rhythm—namely, exhibiting a free-running or entrained 24-h rhythm of the same variable—suggested the idea of one oscillator (for each variable) under which free-running conditions can exhibit a period >24 h or <24 h and under which another set of conditions may be entrained to show a period equal to 24 h. Affecting the orientation of the rhythm are the characteristics of the oscillator and the zeitgebers (strong or weak for both entities).

On the basis of our observations, we were tempted to formulate the dual behavior of the rhythm's period (free running or entrained), by applying some basic models drawn from the genetic discipline. The assumptions are as follows: (a) A constitutive gene is responsible for τ = 24 h (the Dian gene). Mutations of this gene in the natural population will be strongly selected out, since they carry a negative adaptive value (they may be found, though rarely, in laboratory-kept species). (b) The genome contains, in addition (for each variable or for a set of variables), a series of genes (polygenes) each adding or subtracting a fixed time to the period (the circadian genes). In the two variables examined by us, the fixed time was ±0.8 h. (Another version of this assumption, though less likely, is that, instead of a polygenic series, the control of the +/− deviations from the 24-h period is governed by a multiple-allele system

whose alleles add or subtract a multiplication of a fixed time (e.g., 0.8 h, 1.6 h, etc.). (*c*) These polygenic (multiple-allele) systems are usually repressed in normal settings when natural synchronizers (zeitgebers) are present. Induction of these genes will occur under conditions which distort or weaken the intensity, the timing, or the perception of the zeitgebers. The system does not behave like a "flip flop" control, but its output depends on the "concentration" of the zeitgeber (e.g., the time taken for a prone individual to become "internally desynchronized" during isolation is about 14 d [Wever 1979]).

Such a model (named by us the "Dian-Circadian model") can be suitable to explain the occurrence of internal desynchronization in various settings, the various durations of being in a free-running state, as well as the occurrence of free running, even when there is exposure to what seems to be a natural setting. Furthermore, this model also explains why some subjects are prone to circadian dyschronism and why others exposed to the same environment are not. For example, the total output of the polygenic (multiple-allele) system may be 0 (nil), even when induced to function, if the number (or total length) of + time-period units equals the number (or total length) of the − time-period units.

This model is also capable of generating beat phenomena leading to occurrence of infradian rhythms (τ > 24 h; e.g., circamensual rhythms with $\tau \approx$ 30 d, and circaseptan rhythms with $\tau \approx$ 7 d). A 30-d period may result from beat between oscillations of τ = 24 h and either τ = 24.8 or τ = 23.2 h. A 7.5-d period may result from beats of oscillations with τ = 27.2 h or τ = 20.8 h. Rhythmicities with both τ = 30 d and τ = 7.5 d have been demonstrated in human subjects (Haus and Touitou 1992).

From a practical point of view, it is of interest to know that some individuals in a natural setting may exhibit a circadian dyschronism of their biological rhythms. It is no longer possible to state that the biological rhythm of a healthy subject has a period of 24-hours, unless that subject is examined.

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