Chronobiometric Identification of Disorders of Hunger Sensation in Essential Obesity: Therapeutic Effects of Dexfenfluramine

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In human beings, hunger is a proprioceptive signal that shows intraday (circadian components) and within-day (ultradian components) recursivity. Both periodic components can be investigated by chronobiometric procedures by combining the Cosinor method with spectral analysis. A 24-hour profile of hunger sensation (HS) can be plotted on a 1-to-10 scale of intensity using self-rated scores performed every half-hour of the day. Circadian and ultradian components were studied in 60 patients affected by essential obesity (20 men and 40 women; mean age, 38.4 years; mean body weight, 101 kg) before and after treatment with dexfenfluramine (Isomeride®; Servier, Orléans, France) 15 mg orally twice daily, for 30 days. The control group consisted of 30 clinically healthy subjects (15 men and 15 women; mean age, 37.5 years; mean body weight, 69 kg). Chronobiometric analysis shows three patterns in obese patients, which suggests that HS may be normal (eurectic obesity), exaggerated (hyperrectic obesity), or diminished (hyporectic obesity). After dexfenfluramine administration, HS was showed a substantial decrease in the daily mean level. The spectrum of resolution in circadian and ultradian components was found to be maintained in eurectic obesity and partially readjusted in hyperrectic and hyporectic obesities. This demonstrates that dexfenfluramine acts not only as an anorectic but also as a chronizer by interfering with the recursive components of HS. The anorectic and chronizing effects suggest that dexfenfluramine is a "chronoanorectic drug" that interacts with the chronobiologic properties of the serotoninergic system.

HUNGER IS A proprioceptive signal that in human beings shows an intraday and within-day recursivity. This suggests possible intermodulation of its daily pattern by circadian (cycles with a period of 20 to 28 hours) and ultradian (cycles with a period less than 20 hours) rhythmicities. Because of its repetitive pattern, hunger sensation (HS) can be regarded as a signal that changes periodically in circadian time with given periodicities. Presently, specific chronobiometric procedures allow us to investigate biologic signals in their periodic components. The hunger signal may thus be explored by determining the harmonic components that sustain its circadian and ultradian recursivity. On this basis, the daily pattern of HS in essential obese patients was studied to identify eventual chronotypes, ie, abnormal daily patterns of HS according to the specific temporal structure. A second aim of the study was to verify the effects of dexfenfluramine (Isomeride; Servier, Orléans, France) on HS to better understand its pharmacologic mechanisms and therapeutic indications in the treatment of obesity.

SUBJECTS AND METHODS

Subjects and Protocol

The study was performed on 60 obese patients, 20 men and 40 women, aged 21 to 60 years. Obesity was considered essential if its origin was a primary disorder of eating behavior. Initial body weight varied between 68 and 250 kg, and body mass index ranged from 27.8 to 100, with relative body weight being between +30% and +346%. The control group consisted of 30 clinically healthy subjects, 15 men and 15 women aged 21 to 60 years whose body weight ranged from 65 to 72 kg. All subjects were asked to self-rate and plot every 30 minutes the intensity of HS on a scale from 1 to 10 according to their judgment. The basal score was 1 instead of 0 to avoid division by zero in the computerized analysis. The extremes were as follows: 1, no sensation, to 10, excessive sensation associated with psychophysical disturbances. It was assumed that the nocturnal score was 1 during sleep. Each unitary value of the scale was regarded as a hunger unit (HU). The interpolated values formed a chronogram of HS over the 24-hour span. Obese patients and control subjects were free to follow their daily life-style concerning eating behavior and motor-rest activity. Women were studied between the first and second week of the menstrual cycle. HS in obese patients was recorded twice before and after treatment with dexfenfluramine, which was administered for therapeutic purposes in two oral doses, 15 mg at breakfast and 15 mg at dinner for 30 consecutive days. The treatment was considered effective because weight loss ranged from 1 to 29 kg and final weight ranged from 64.5 to 221 kg, with body mass index between 22.8 and 88.5 and relative body weight between +19% and +294%.

Data Analysis

Circadian recursivity of HS was directly analyzed by the single Cosinor method,[1] which fits a cosine function to time-qualified raw data using the formula

$$Y(t) = M + A \cos\left(\frac{2\pi}{TAU} t + \phi\right),$$

where M, A, and ϕ represent, respectively, the rhythm-adjusted mean (mesor), the extent of oscillation (amplitude), and the clock hour of the oscillatory crest (acrophase). TAU is the fitted period of 24 hours. This method verifies whether there is a significant fluctuation within a 24-hour period, assuming a null hypothesis of zero amplitude for oscillation. The Cosinor method provides an optimal sine wave (cosinorgram) in addition to the quantification of mesor, amplitude, and acrophase.

Ultradian recursivity of HS was analyzed by the least-squares spectral analysis linear in period.[2,3] This method resolves the signal in harmonic components using the formula

$$Y(t) = M + \sum_{i=1}^{N} A_i \cos\left(\frac{2\pi}{TAU_i} t + \phi_i\right),$$

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where N is the number of fitted harmonic waves (N = 27) and i is the fitted harmonic wave number 1, 2, 3 . . ., N, having, respectively, a 2-, 3-, 4- . . . 28-hour period. The amplitude of each fitted harmonic wave constitutes, as a function of its period (TAU) or frequency (F = 1/TAU), the specific power spectrum. With this analysis, the statistical significance of each harmonic component constituting the power spectrum can be determined. Basically, the significant harmonic components that reject the zero-amplitude assumption at a P level less than .05 are regarded as the formants of the spectrum, ie, the constitutive components of the signal. The main advantage of using least-squares spectral analysis linear in period is that it indicates whether the hunger signal shows a deviant pattern. Because the harmonic spectrum is specific, it is highly improbable that different signals might have an identical configuration of significant cyclicities (formants) in terms of period, oscillatory amplitude, and acrophase timing. The power spectrum thus is an objective tool for identifying disorders, any chronotypes, in the recursive pattern of daily HS (pattern recognition).

RESULTS

Clinically Healthy Subjects

The chronogram, cosinorgram, and power spectrum of HS in control subjects are depicted in Fig 1.

The chronogram shows no signal during the night and three salient peaks during the day corresponding to meal times. The cosinorgram displays a well-oscillating profile whose mean level is 2.5 HU per 24 hours with a crest of 4 HU at 13.52. Sinusoidality testing showed the oscillation to reject to null hypothesis of zero amplitude ($P < .001$), which suggests that the HS is a physiologic signal that changes according to a circadian rhythm. The power spectrum shows several harmonic components, the most significant of which are related to the circadian cycles. However, a restricted number of ultradian components also play the role of formants in the physiologic signal of daily HS.

Essential Obese Patients

Chronograms of HS in obese patients are not uniform. In 60% of the cases, the chronogram shows a curve that is almost comparable in its nocturnal plateau, diurnal height, and peaks to that of normoponderal controls (obese patients with apparently normal HS). In 30% of the patients, the chronogram shows a consistent difference, with the profile showing a signal during the night and an abnormally high level during the day (obese patients with an apparently excessive HS). Finally, in 10% of the cases, the chronogram shows a further difference: the curve is flat during the night and poorly pronounced during the day (obese patients with an apparently weak HS).

Because of these three chronograms, the Cosinor method and spectral analysis were applied by category to verify whether HS exhibits differential patterns during the day in obese patients.

Obese patients with an apparently normal HS. The pretreatment chronogram, cosinorgram, and power spectrum of HS in obese patients without evidence of a deviant chronogram are shown in Fig 2 (left panels).

As already mentioned, the chronogram shows no signal during the night and the three diurnal peaks corresponding to the periprandial times. The cosinorgram displays a well-oscillating profile with a mean level of 2.5 HU per 24 hours, and a peak at 4 HU at 15.12. Sinusoidality testing showed that the oscillation rejected the zero-amplitude assumption ($P < .001$), which suggests that HS preserved its circadian rhythm in this category of obese patients. The power spectrum shows the circadian harmonic components to be prominent formants. Ultradian components show the amplitude to be slightly more pronounced. Notwithstanding these minor differences, the power spectrum could be compared with that of normoponderal controls, which suggests that neither the mean level nor the recursive components of HS in this group of obese patients had been sensibly impaired.

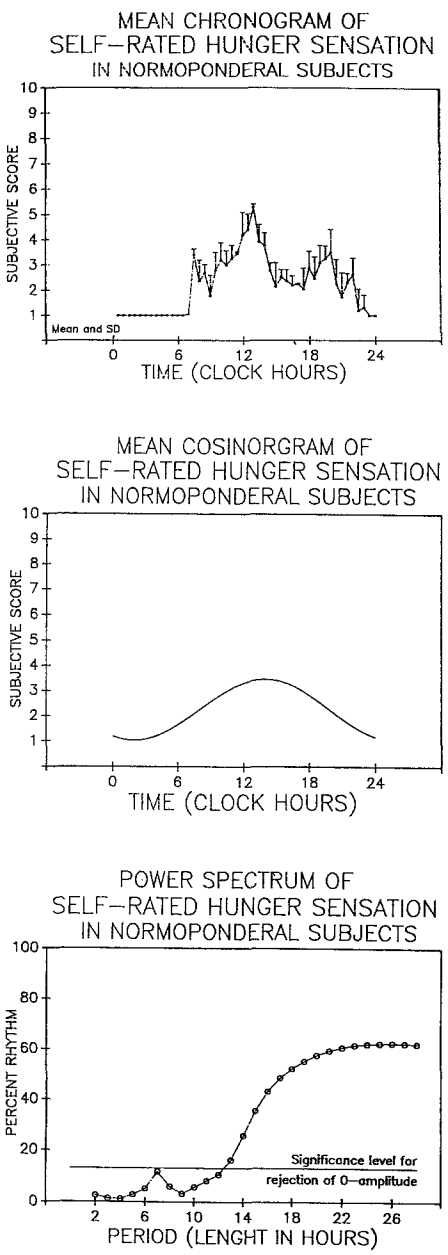

Fig 1. Chronogram, cosinorgram, and power spectrum of HS in normoponderal individuals.

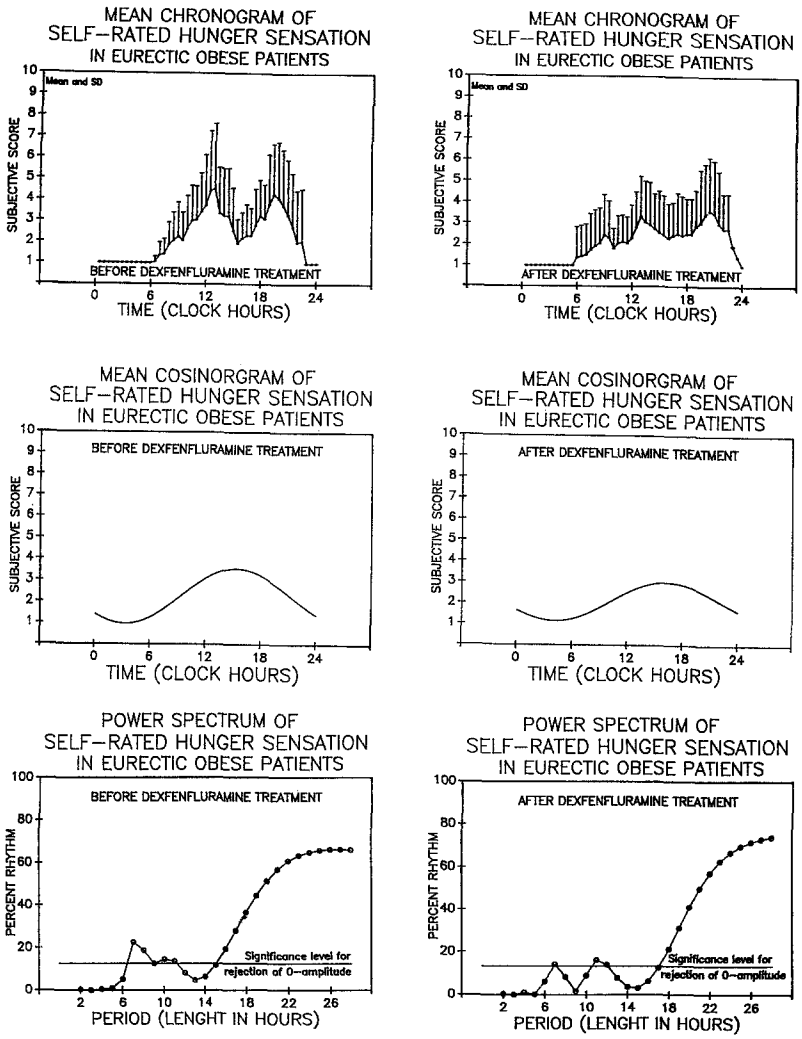

Fig 2. Chronogram, cosinorgram, and power spectrum of HS in eurectic obese patients before (left panels) and after (right panels) therapy with dexfenfluramine.

The posttreatment chronogram, cosinorgram, and power spectrum of HS are displayed in Fig 2 (right panels).

The chronogram shows a daily profile reduced in height, with the three periprandial peaks still observable. The cosinorgram displays a well-oscillating profile with a mean level less than 2 HU per 24 hours, and a peak of 3 HU at 16.04. Sinusoidality testing showed that the oscillation rejected the null hypothesis of zero amplitude ($P < .001$), which demonstrates that HS preserves its circadian rhythm in this category of obese patients treated with dexfenfluramine. The power spectrum shows all circadian components to be preserved and ultradian components to be slightly deamplified. Consequently, this spectrum was much more comparable in its configuration with that of normoponderal subjects. This suggests that dexfenfluramine exerted an anorectic effect by tonic inhibition without affecting the recursivity of HS in these obese patients who presented a normal hunger signal before treatment.

Obese patients with an apparently excessive HS. The pretreatment chronogram, cosinorgram, and power spectrum of HS in obese patients with evidence of an excessive HS are reported in Fig 3 (left panels).

The chronogram shows a peculiar pattern because of the persistence of the signal until late into the night and an exaggerated height with adjunctive intradiem peaks. The cosinorgram displays a well-oscillating profile with an increased mean level at 4.5 HU per 24 hours, and a crest of 6.5 HU at 15.56. Sinusoidality testing showed that the wave rejected the zero amplitude assumption ($P < .001$), which suggests that HS preserves its circadian recursivity in this category of obese patients. The power spectrum shows less pronounced circadian components and more prominent ultradian components. The additional number of ultradian formants along with the deamplified circadian components caused the power spectrum to be totally different from that of normoponderals. This suggests that HS was excessive because of a surplus of ultradian components sustaining the signal during the 24 hours.

The posttreatment chronogram, cosinorgram, and power spectrum of HS are reported in Fig 3 (right panels).

The chronogram still shows the abnormal presence of the signal during the night. However, the curve shows both a lower level and better-defined periprandial peaks. The cosinorgram displays a well-oscillating profile with a mean

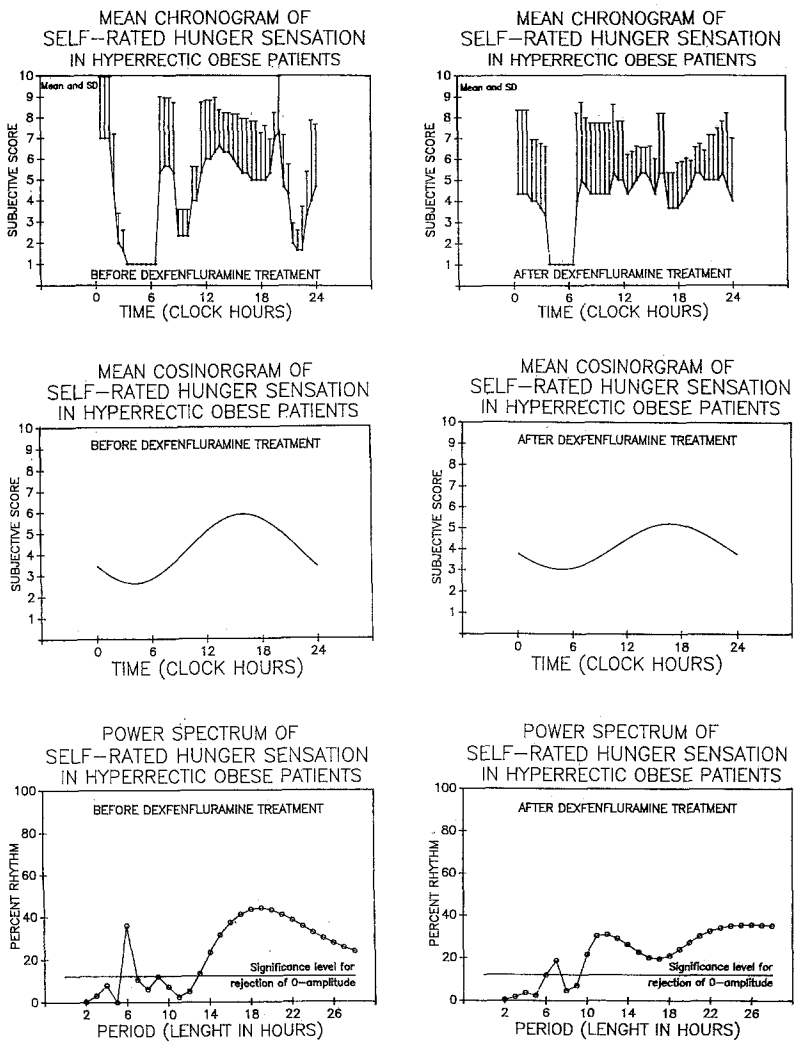

Fig 3. Chronogram, cosinorgram, and power spectrum of HS in hyperrectic obese patients before (left panels) and after (right panels) therapy with dexfenfluramine.

level less than 4 HU per 24 hours and a crest of 5.5 HU at 16.40. Sinusoidality testing showed that the oscillation rejected the null hypothesis of zero amplitude ($P < .001$), which demonstrates that HS still exhibited a circadian rhythm despite the anorectic therapy. The power spectrum shows that the circadian components recovered a prominent amplitude and that the ultradian cycles were deamplified. This suggests that dexfenfluramine not only tonically decreased the level but also cyclically demultiplied the high-frequency formants at the origin of an excessive repetitivity of the signal during the day.

Obese patients with an apparently weak HS. The pretreatment chronogram, cosinorgram, and power spectrum of HS in obese patients with an apparently weak signal are reported in Fig 4 (left panels).

The chronogram shows a low profile characterized by small peaks scattered during the day. The cosinorgram shows an observable oscillation with a mean level of 1.5 HU per 24 hours, and a crest of 2 HU at 13.56. Sinusoidality testing showed that the oscillation rejected the zero amplitude hypothesis ($P < .001$), which demonstrates that HS preserves its circadian rhythm in this category of obese patients. The power spectrum shows the almost-absolute lack of circadian components and the relative prevalence of ultradian cycles. This suggests that HS was poorly and episodically perceived because of the weak modulation sustained by recursive components of the signal with a slower frequency.

The posttreatment chronogram, cosinorgram, and power spectrum are reported in Fig 4 (right panels).

The chronogram shows a profile with a further decreased but less-fragmented level that mimics the three peripprandial peaks detectable in the physiologic curve. The cosinorgram displays an oscillating profile whose mean level is 1.5 HU per 24 hours, with a crest of 2 HU at 16.08. Sinusoidality testing showed that the oscillation rejected the zero amplitude assumption ($P < .001$), which suggests that HS maintained its circadian rhythm in these obese patients treated with dexfenfluramine. The power spectrum shows a relative magnification of the blunted circadian components, which partially returned to be the formants, and deamplification of the unusual ultradian components. This suggests that dexfenfluramine restored an intraday and within-day recursivity that corresponded more closely to the physi-

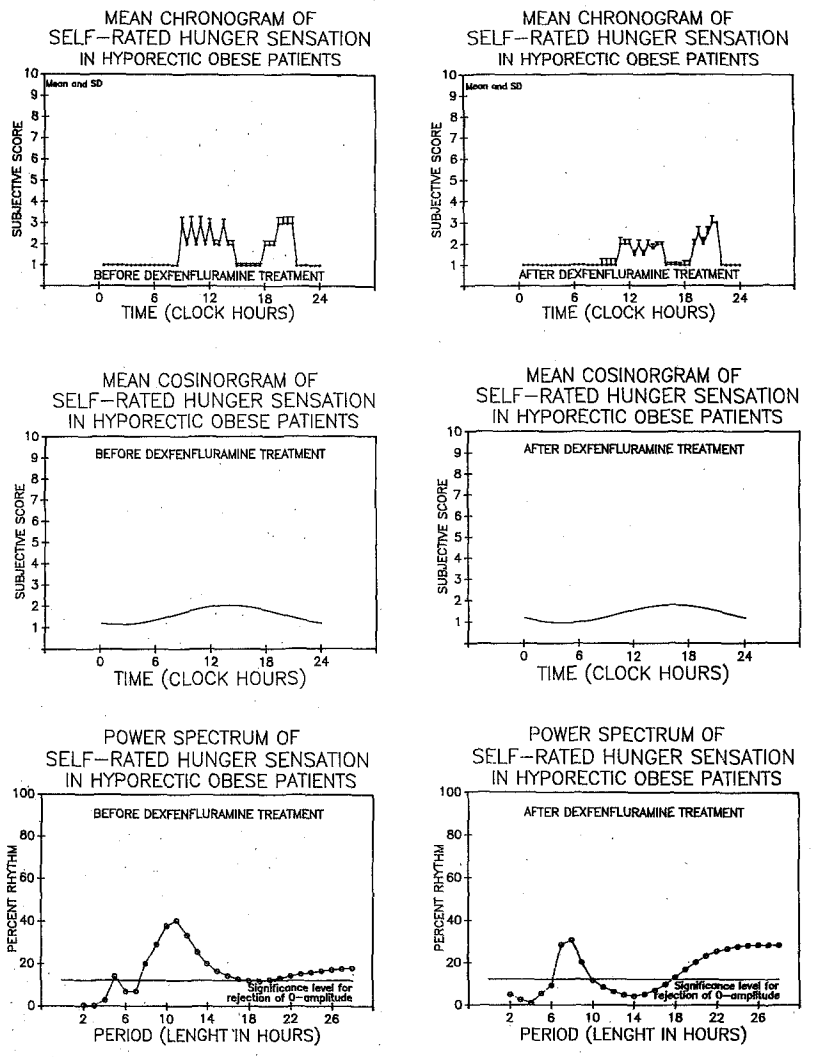

Fig 4. Chronogram, cosinorgram, and power spectrum of HS in hyporectic obese patients before (left panels) and after (right panels) therapy with dexfenfluramine.

ologic patterns despite tonic inhibition of HS in this category of obese patients.

DISCUSSION

The present study provides evidence that the daily pattern of HS can be biometrically quantified in its intraday and within-day recursivity by applying the Cosinor method associated with spectral analysis. By Cosinor analysis, it was demonstrated that in clinically healthy subjects HS is a signal with a well-structured circadian rhythm whose mean level and oscillatory extent can be precisely measured and timed. In detail, biometric estimates indicate that the physiologic sensation of hunger reaches an average 2.5 HU per 24 hours, and fluctuates up to 4 HU in the early-afternoon hours. Spectral analysis shows that the physiologic signal of HS is prevalently sustained by circadian components, the low frequency of which modulates intraday recursivity, while the high frequency of the few ultradian formants acts to confer within-day repetitivity with its characteristic three periprandial peaks.

The present study also demonstrates that on the basis of the power spectrum with which the signal can be explored, self-rated HS can be objectively analyzed to detect eventual disorders of its daily pattern. It must be remarked here that spectral analysis is universally used for recognizing signals (pattern recognition) because of the fact that any spectrum of resolution is specific in terms of constitutive formants. Therefore, the power spectrum can be taken as an objective tool for experimentally demonstrating whether a given signal conforms to its physiologic pattern.

The present study demonstrates that the daily HS shows three different patterns in patients affected by essential obesity. These profiles indicate that HS may be classified as normal, excessive, and poorly perceived in essential obesity.

Cosinor analysis of the hunger chronogram in patients with an apparently normal signal estimates the circadian mean level at 2.5 HU per 24 hours and oscillatory maximum at 4 HU. Spectral analysis, on the other hand, detects a power spectrum whose configuration in harmonics is almost identical to that of normal subjects. Consequently, it can be said that some obese patients really do feel a normal sensation of hunger. This reinforces the idea that essential obesity may coexist with the eurectic variety.

Interestingly, the Cosinor analysis of hunger chronogram

in obese patients with an excessively high signal provides evidence that the HS is higher in both its circadian mean level (4.5 HU per 24 hours) and its diurnal crest (6.5 HU). Spectral analysis, on the other hand, demonstrates that the power spectrum is composed of unusual ultradian components, the high frequency of which justifies the abnormal persistence of HS during the night and its exaggerated increase during the day. The specificity of the power spectrum leads us to argue that some obese patients really feel a more intense and prolonged HS over the day. This substantiates the idea that essential obesity may coexist with the hyperrectic variety.

Finally, the Cosinor analysis of hunger chronogram in obese patients with a negligible signal estimates a very low circadian mean level (1.5 HU per 24 hours) and oscillatory crest (2 HU). Spectral analysis in turn provides a power spectrum that eminently consists of high-frequency ultradian components, for which the low level and the pulsatility of the signal can be justified. The specific configuration of the resolution spectrum leads us to assume that some obese patients really do feel a low sensation of hunger during the entire day. This means that essential obesity may coexist with the hyporectic variety.

Whatever the chronotype may be, it is important to stress that neither eurectic nor hyporectic obese patients were seen to restrain themselves from overeating. This implies that eating behavior in eurectic and hyporectic obese patients is not at all mediated by an overstimulus to eat. Therefore, a psychodynamic mechanism of "psychovegetative dissociation" can be advocated in these chronotypes of essential obesity.

Given the three chronotypes, it is interesting to see how dexfenfluramine interacts with the daily pattern of HS in eurectic, hyperrectic, and hyporectic obesities. The present study shows that the drug invariably reduced the daily mean level of HS in all three chronotypes. This common effect leads us to suggest that dexfenfluramine exerts an anorectic action by tonically inhibiting the hunger signal. However, the present study also demonstrates that the anorectic effect in eurectic obesity is not accompanied by a negative rebound on the spectrum of harmonic components that sustain the recursivity of the signal over the 24-hour span. Accordingly, it can be said that in eurectic obesity, the anorectic drug acts as an agent that substantially preserves the intraday and within-day recursivity of HS.

Importantly, the present study shows that dexfenfluramine exerts specific effects on HS in hyperrectic obesity. Besides showing tonic reduction, spectral analysis revealed that the signal is restructured, since its spectrum appears to be much more similar to that of controls and eurectic patients because of the amplification of low-frequency circadian components. This suggests that the effect of the drug is not only anorectic but also chronizing, since the spectrum is partially readjusted in its harmonic formants. Consequently, it can be stated that the drug interacts with the recursivity of HS, causing its daily pattern to be more physiologic.

Finally, the present findings provide further evidence that dexfenfluramine is a chronizer of HS in hyporectic obesity. The power spectrum in this category is characterized by high-frequency ultradian components. After therapy, the spectrum shows a clear amplification of circadian harmonics. This demonstrates that the drug works as a chronizing agent on the low-frequency components that sustain the intraday recursivity of HS. The chronization of the signal leads to a more physiologic pattern, emphasizing that dexfenfluramine exerts its beneficial effects as a chrononanorectic agent in essential obesity.

Considering its chronopharmacologic properties, it can be argued that the interaction between dexfenfluramine and the serotoninergic system[4-6] may be effective due to a mechanism of tonic and phasic modulation. This implies that future studies should explore the use of dexfenfluramine in a chronotherapeutic scheme in the specific chronotypes of HS in essential obesity.

APPENDIX

Glossary of Methodologic and Technical Terms

Chronizer (or *chronizing drug*): A drug that is able to restore some periodicities in a biologic function that has lost its rhythmic pattern.

Chrononanorectic drug: The term "chrononanorectic," related to a drug, derives from three Greek roots, ie, "chrono," "an," and "orexis." The prefix chrono literally means "time," but in this context it is used as an abbreviation of the word "chronizing" to indicate a chronizer (see above). The prefix an is the Greek "alpha privative," which means "without," and orexis means "hunger." Therefore, the combined word chrononanorectic is related to a drug that shows the combined actions of being contemporarily a chronizing and anorectic agent, in the sense of being able to restore periodicities in HS and to reduce the hunger.

Chronobiometric procedures: Methods of statistical-mathematical analysis applied to temporal series of biological data to objectively detect, statistically validate, and biometrically estimate the occurrence and properties of cycling patterns.

Cosinor method: A method of periodic regression analysis set up by Halberg et al,[1] which is used worldwide for statistically validating and biometrically estimating biorhythmic events whose period is "a priori" postulated. It consists of the best-fitting of a cosine function to experimental time data series by minimizing the sum of residuals by the least-squares method.

Cosinorgram: The optimal waveform profile fitted to experimental time data series by the Cosinor method.

Eurectic obesity: The term eurectic, related to obesity, derives from the combination of two Greek roots, ie, "eu," which means "normal," and "orexis," which means "hunger." Eurectic obesity thus identifies a variety of body weight excess characterized by a normal HS.

Formants: The harmonic components whose oscillatory amplitude (power) has been validated as statistically significant in the spectrum of periodicities detected in a time data series by means of chronobiometric procedures (least-squares spectral analysis). Because of their significant power, the formants are the waves with a role of constituents in the construction of the wave resulting from the sinusoidal sum of all the significant cyclic components. The resultant wave returned by the formants represents the periodic trend of the time data series as it is expressed by its significant spectrum of resolution.

Harmonic components: The cycles of a given period that can be found in a time series of biologic data by adopting chronobiometric procedures for detecting and validating bioperiodicities.

Hyperrectic obesity: The term hyperrectic, related to obesity, derives from the combination of two Greek roots, ie, "hyper," which means "exaggerated," and "orexis," which means "hunger." Hyperrectic obesity thus identifies a variety of body weight excess characterized by an exaggerated HS.

Hyporectic obesity: The term hyporectic, related to obesity, derives from the combination of two Greek roots, ie, "hypo," which means "reduced," and "orexis," which means "hunger." Hyporectic obesity thus identifies a variety of body weight excess characterized by a reduced HS.

Ultradian components: Cyclicities with a period less than 20 hours that can be found in a time data series by applying chronobiometric procedures for detecting and validating periodic recursivities in biologic events.

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