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REVIEW ARTICLE

Chronostatic adaptations in the liver to restricted feeding: The FEO as an emergent oscillator

Raúl AGUILAR-ROBLERO[1] and Mauricio DÍAZ-MUÑOZ[2]*

[1]*Department of Neuroscience, Institute of Cellular Physiology, National Autonomous University of Mexico, and* [2]*Institute of Neurobiology, National Autonomous University of Mexico, Querétaro, Mexico*

Abstract

We propose that the mammalian timing system is formed by constitutive clocks, such as the suprachiasmatic nucleus, and emerging clocks build up from the coordinated activity of peripheral oscillators, such as the food entrained oscillator (FEO). This timing system underlies a general regulatory process that modulates the set point of physiological variables in a periodic manner known as chronostasis. In contrast to the suprachiasmatic nucleus, the FEO is a distributed system formed by different brain areas such as the dorsomedial and ventromedial hypothalamus and the paraventricular thalamic nucleus, and peripheral organs such as the liver, adipose tissue, and skeletal muscle, and some endocrine glands. Central to the notion of FEO as an emerging oscillator is the establishment of a series of novel interactions between the molecular circadian clock and the biochemical events that coordinate the metabolic framework by which cellular energy is obtained, stored, and used. In the liver, those metabolic adaptations include changes in the handling of fatty acids, glycogenolysis, cytoplasmic and mitochondrial redox state, balance in the adenine nucleotides pool, intracellular calcium dynamics, and signaling from nuclear receptors. The paraventricular thalamic nucleus (PVT) integrates information from the circadian, feeding, and limbic systems, and thus is in a strategic position to convey different signals from the periphery related to the FEO into central areas related to overt circadian rhythms. The reconfiguration of the circadian system is an example of how biochemical, physiological, and behavioral processes are regulated by chronostasis to optimize the searching, assimilation, and processing of the nutrients during adverse environmental conditions.

Key words: food entrained oscillator, peripheral oscillators, non-photic entrainment, regulatory systems, metabolic integration.

INTRODUCTION

From a physiological perspective, circadian rhythms are the expression of regulatory processes based on a timing system that modulates the set point of physiological variables in a periodic way, which we call chronostasis.[1] Along with homeostasis which operates on a short time basis to maintain physiological parameters within a narrow range of variation,[2] and rheostasis which allows adjusting the set point of physiological parameters to

Correspondence: Dr Raúl Aguilar-Roblero, IFC-UNAM, Apartado postal 70-253, México, D.F. 04510. Email: raguilar@ifc.unam.mx

**The authors' affiliations in their original language are: [1]Departamento de Neurociencias, Instituto de Fisiología Celular, Ciudad Universitaria D.F., and [2]Instituto de Neurobiología, Campus UNAM-Juriquilla, Universidad Nacional Autónoma de México, Querétaro, México*

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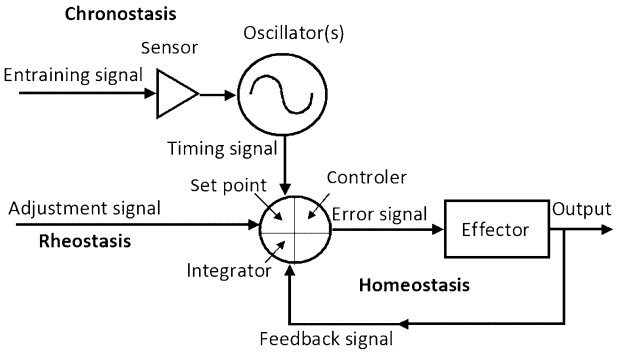

Figure 1 Model of chronostasis. The circadian rhythm of physiological processes can be explained by the action of biological clocks to modulate the set point of the corresponding feed-back control-system. Other regulatory processes include homeostasis aimed at maintaining physiological parameters within a narrow range of variation from a programmed set point, by the action of negative control feed-back loops, and rheostasis aimed at adjusting the value of the set point to changes in either the needs of the organism or its environmental conditions, by the action of feed-forward mechanisms operating on the controller of the feed-back control system.

sustained changes either on the demands of the organism or the environmental conditions which affect it,[3] chronostasis is a general regulatory process which originated from adaptive pressures generated from a cyclic environment (Fig. 1). The core of the circadian timing system involved in chronostatic regulation is built up from transcription – translation loops of genes and proteins, which oscillate with a regular period close to 24 h and are known as the molecular circadian clock. In mammals these clock genes were first found in the suprachiasmatic nuclei (SCN) previously identified as the main circadian pacemaker.[4,5] Clock genes were found later in most tissues from the organism and have been referred to as peripheral oscillators.[6]

The circadian rhythms are entrained by cyclic environmental cues, mainly the light–dark cycle (photic entrainment),[7–9] and in some circumstances also by the alternation of fasting–feeding episodes, increased locomotion, and arousal (non-photic entrainment).[10–16] Periodic feeding is a robust signal to entrain circadian rhythms, so when food access is restricted to a couple of hours once a day, an alternative pattern of rhythmicity emerges (with respect to ad libitum feeding) which reflects a new configuration of the circadian timing system. This phenomenon persists even when the SCN has been completely ablated, and it is considered the result of a circadian oscillator(s) out of the SCN, known as the food entrained oscillator (FEO).[17–21] All attempts to identify the FEO with a single neural structure have failed, but altogether, they suggest that FEO might involve a number of interacting brain areas and peripheral organs related to feeding and energy metabolism, possibly structured as a distributed system arranged as feedback loops.[22]

The SCN controls behavioral (arousal, locomotion, and feeding) and physiological rhythms (autonomic and endocrine) during ad libitum conditions.[23] In contrast, prolonged fasting associated with daily restricted feeding schedules increases the sympathetic tone, triggers the use of energy storages, and shifts metabolic regulation to a catabolic state; the behavioral pattern is disrupted to increase the chance of feeding. After feeding the parasympathetic tone increases, metabolism shifts back to an anabolic state, and the energy storages replete and behavioral arousal decreases.[24] After a relatively small number of cycles of daily restricted feeding, physiological and behavioral adaptations resembling circadian entrainment are observed (Fig. 2): the enormous meal intake that occurs during the feeding access (six times more than in ad libitum feeding conditions)[25] leads to a great distention of the stomach; then gastric distention decreases slowly as the ingested food is processed. The onset of FAA (food anticipatory activity) which occurs 2–3 h before next meal coincides with the emptying of the gastric chamber and release of ghrelin.[26] During this time of FAA different biochemical events take place in the liver, the adipose tissue, and other organs. Thus, free fatty acids are released from adipocytes to the blood, and reach even higher concentration than after 24 h of fasting. Such an increase in free fatty acids promotes active ketogenesis in the liver, while at this time the hepatic glycogen is only partially degraded. This indicates that during the FAA the hepatic energy derives from lipids oxidation rather than carbohydrate catabolism.[27,28] The cytoplasmic ATP-ADP-AMP (adenosine triphosphate- adenosine diphosphate-adenosine monophosphate) ratio which reflects the hepatocyte energy charge increases, whereas the cytoplasmic and mitochondrial NAD/NADH ratios indicate that the hepatic redox state is oxidized.[24] Hence, FEO expression involves the establishment of a generalized "anticipatory state" which optimizes the searching, assimilation, and processing of the nutrients. In the liver and other organs the acrophase of clock genes, hormones, and proteins are shifted toward the time of food accessibility;[29–31] in such condition the SCN maintains its own oscillation and keeps only a partial control of the circadian rhythms in the organism.

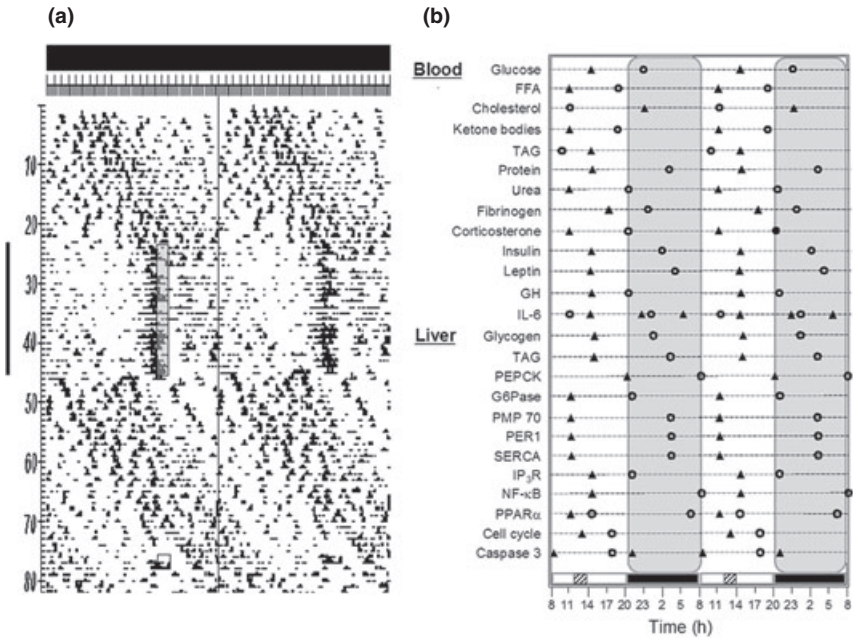

Figure 2 Phase angles among different rhythmic parameters in animals under ad libitum- and restricted-feeding schedules. (a) Drinking behavior recorded under ad libitum feeding in constant darkness (days 1–20). From days 21–45 food was available only from 12 to 14 h every day (shadowed area). Food was provided ad libitum from day 46 to the end of the recording. During days 75–78 the animal was fasted and a burst of activity was found at the time of feeding during the restriction interval (open square). (b) Acrophase of metabolic and endocrine parameters measured in the blood (top) or the liver (bottom) from ad libitum fed animals (filled circles) maintained under light–dark cycles; daily food restriction (12–14 h, dashed bar at bottom) induced shifts in most parameters to the time of feeding (open triangles). It is clear that daily food restriction induced an anticipatory state which included behavioral and physiological parameters.

The coordination of the physiological and metabolic processes of the organism from SCN control to the assembly of the FEO that involves the uncoupling and independent operation of peripheral oscillators from the SCN illustrate the concept of chronostasis. Chronostatic regulation allows different configurations of the timing system to cope with changes in the environment as well as the physiological demands of the organism. Thus, the circadian system allows an optimal timing of cellular events to provide energy, support the metabolism, and make possible the coordinated display of biochemical, endocrine, and behavioral processes during a 24-h cycle and at the same time prevent the disruption of homeostatic processes operating in a short time scale. Chronostatic regulation requires the reciprocal relationship between the molecular components underlying the molecular clock and the signaling pathways that control the metabolic networks, which includes how the cellular energy is obtained, stored, and used. Some of the interaction points between the molecular circadian clock and energy metabolism are briefly reviewed next (Fig. 3).

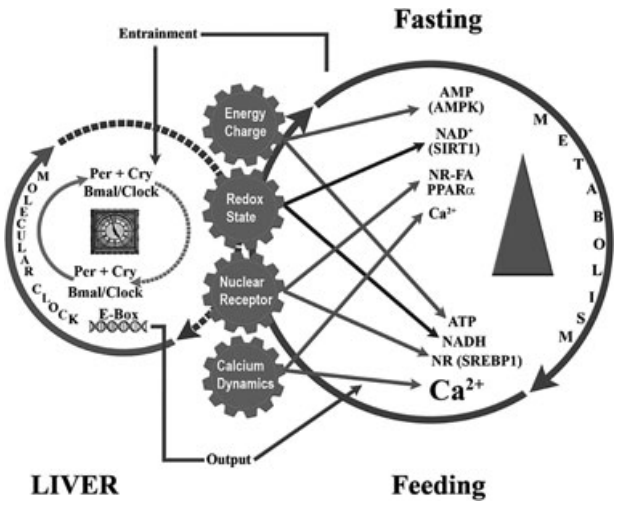

Figure 3 Schematic representation of the interaction points between the molecular circadian clock and the energy metabolism, see text for explanation.

CLOCK GENES AND METABOLIC REGULATION

Redox state

The cellular redox state functions as a switch between metabolic pathways, which alternates from reduced to oxidized as the animal feeds or fasts. Direct control of the loop of clock genes and proteins by redox state has been documented: the reduced coenzymes NADH and NADPH enhance the formation of the heterodimers CLOCK-BMAL1 and NPAS2-BMAL1 and promote their interaction with DNA. Oxidized forms of these coenzymes have the opposite result.[32] Hence, the availability of food and the metabolic transformation of nutrients may influence the functioning of the molecular clock by redox modulation. Furthermore, the family of enzymes with deacetylase activity known as sirtuins also modulates the molecular clock in a redox-dependent manner:[33,34] sirtuin 1 is a histone deacetylase whose activity requires an oxidized redox state since it depends on NAD+ as cofactor. Removal of acetyl groups by sirtuin 1 is in equilibrium with protein CLOCK that shows acetylase activity.[35] Hence, the timing system is regulated at this level by the metabolic role of sirtuin 1 that inhibits transcription in conditions of oxidized redox state, and counteract the action of CLOCK.

Energy charge

The intracellular relation of adenine nucleotides (ATP, ADP, and AMP) is another relevant parameter of metabolic control in the cells. Anabolic or synthetic reactions are favored when the proportion of ATP is high whereas catabolic or degradative reactions occur when AMP levels are increased. In this context, a regulatory kinase that is controlled by AMP has been gaining importance. AMP-K is a key enzyme that orchestrates the switch between antagonistic processes: from active ATP utilization to enhanced ATP production. A relation between AMP-K activity and the molecular clock has been documented: phosphorylation of casein kinase ε by AMP-K promotes faster degradation of mPER2 (mouse protein Period 2) that causes a shorter circadian cycle. In addition, active AMP-K is necessary in the transcriptional balance of clock-related genes in skeletal muscle.[36] These examples demonstrate clearly the metabolic control that link the energetic status of the cell with the circadian molecular clock.

Intracellular calcium dynamics

Calcium is a ubiquitous intracellular messenger that regulates diverse metabolic networks (glycogen catabolism, mitochondrial oxidative reactions, production of reactive oxygen species) and cellular events (excitation-contraction coupling, excitation-secretion coupling). Studies aiming to unravel the link between intracellular calcium dynamics and the functions of the molecular clock in the hepatocytes are in still in course. Experiments with liver explants have shown that pharmacological treatment with drugs that affect the release and uptake of calcium from internal deposits modify significantly the circadian rhythm of PER1 (protein Period 1). The data shows that the shift in the expression of PER1 associated with restricted feeding schedules (RFS) is abolished by thapsigargin (an inhibitor of the calcium ATPase from endoplasmic reticulum) and 2-APB (a blocker of IP_3-dependent calcium release). These results are indicative of a relationship between the timing system and status of calcium handling by the calcium pool associated with the endoplasmic reticulum.

Nuclear receptors

The nuclear receptor superfamily consists of nearly 50 different transcriptional factors. At least one clock protein, REV-ERB $\propto$, is itself a nuclear receptor. These transcriptional activators direct an extensive variety of genetic programs that regulate lipid and sugar metabolic transformation by sensing fat-soluble hormones, vitamins, and especially dietary lipids. In contrast with glucocorticoid and steroid receptors, the nuclear receptors recognize their ligands with relatively low affinity. Some ligands are fatty acids (arachidonic and linolenic acids), peroxidized fatty acids, prostaglandins, protacyclines, vitamin D, retinoic acid, thyroid, and some steroidal molecules. Direct interaction of the circadian clock machinery with two sets of nuclear receptors has been reported: the peroxisome proliferator-activated receptor family (PPARα, β/δ and γ) and peroxisome proliferator-activated receptor γ coactivator 1 $\propto$ (PGC-1$\propto$). It has been shown that both nuclear receptors stimulate the expression of the clock genes *CLOCK* and *BMAL-1*.[37–39] Hence, the relationship between nuclear receptors and the molecular clock can be considered another form of interaction between the timing system and ongoing cellular metabolic activity.

METABOLIC AND BEHAVIORAL INTEGRATION

How do peripheral (metabolic, endocrine, and neural) signals induce anticipatory behavior during restricted feeding schedules? An obvious answer is hunger; very likely the neural mechanisms involved in triggering seeking behavior during hunger are involved in triggering FAA when FEO express independently from the SCN. A number of forebrain areas, such as the ventromedial (VMH), lateral (LH), and dorsomedial hypothalamus (DMH), as well as the nucleus accumbens, have been implicated in the expression of FEO; for all these brain regions the data is contradictory regarding their possible role regulating FAA. A detailed critical analysis of the available evidence is beyond the scope of this work, but for our present purpose we will enunciate the most illustrative information on the role of hypothalamic nuclei and FAA and FEO expression (Fig. 4).

An electrolytic lesion of the VMH disrupted FAA, but later follow-up of the effects of the lesion indicated recovery of the anticipatory activity, once the metabolic effects of the lesion were compensated.[40–43] The LH has also been involved as a possible dampen oscillator related to FAA, but neurotoxin lesions of this area or analysis of c-Fos expression in relation to RFS failed to support the notion that the nucleus might be the locus of the FEO;[44,45] nevertheless, recent data indicate that orexinergic neurons from LH might have some role in FAA.[46–48] The DMH has also been recently implicated in the expression of the FAA because of c-Fos expression induced by RFS and the effect of cell-specific lesions in the DMH on eliminating anticipatory activity,[49,50] while others studies involving complete SCN lesions point in the opposite direction.[51]

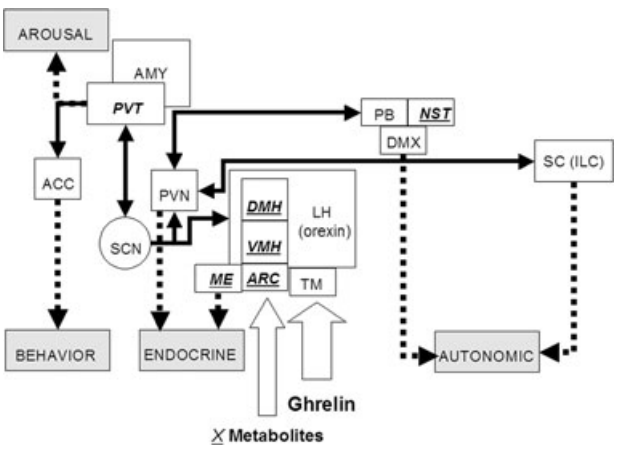

Figure 4 Diagram showing different brain structures involved in the regulation of food anticipatory activity. Solid lines indicate some of its neural interactions. Dashed lines indicate regions involved in some of the system outputs (shadow boxes). Areas indicated in underlined italics indicate possible input regions to different metabolic and endocrine signals from the periphery (open arrows). Acc, n. acumbens; Amy, amygdala; Arc, arcuate n.; DMH, dorsomedial hypothalamic n.; DMX, doral motor nucleus of the vagus; LH, lateral hypothalamus; ME, median eminence; NST, n. solitary tract; PB, n. parabrachialis; PVN, paravetricular hypothalamic n.; PVT, paraventricular thalamus; SC (ILC), spinal cord (intermedio lateral column); SCN, suprachiasmatic n.; TM, tubero mammilar n.; VMH, ventromedial hypothalamic n.

As with the previous brain structures, different lines of evidence suggest that the paraventricular thalamic nucleus (PVT) may be involved in the expression of FEO, but experiments directly aimed at testing whether PVT is indispensable to FEO expression are conflicting.[52–54] Nevertheless, PVT integrates information from the circadian timing system (SCN in particular), hypothalamic and brain stem involved in feeding, and the limbic system.[55,56] In turn, PVT projects to the SCN, amygdala, and nucleus accumbens among other brain areas.[57,58] Thus PVT is in a strategic position to convey different signals from the periphery related to the FEO into central areas related to the circadian expression of locomotion, feeding, and metabolism.[59] Furthermore, PVT modulates the SCN response to light; and its stimulation with glutamate induces a phase response curve similar to that induced with light pulses.[60] Thus, PVT input to the SCN may contribute to coordinate the timing under SCN control and the timing under FEO regulation, which is necessary to achieve a new configuration of the timing system adequate to different demands of the organism. An unexpected and puzzling finding is the possible co-release of GABA (gamma amino butyric acid) and glutamate from the synapses between PVT terminals and SCN neurons (Alamilla *et al.*, unpublished manuscript, 2009). This is the first time that co-release of two fast neurotransmitters has been found in the adult brain. Although its physiological relevance is yet to be established, the possibilities of synaptic plasticity of such a mechanism may well be of value in explaining the plasticity of the circadian timing system we have previously outlined.

FEO AS AN EMERGENT OSCILLATOR

Why is the expression of FEO concealed during ad libitum feeding? One possible explanation is that under

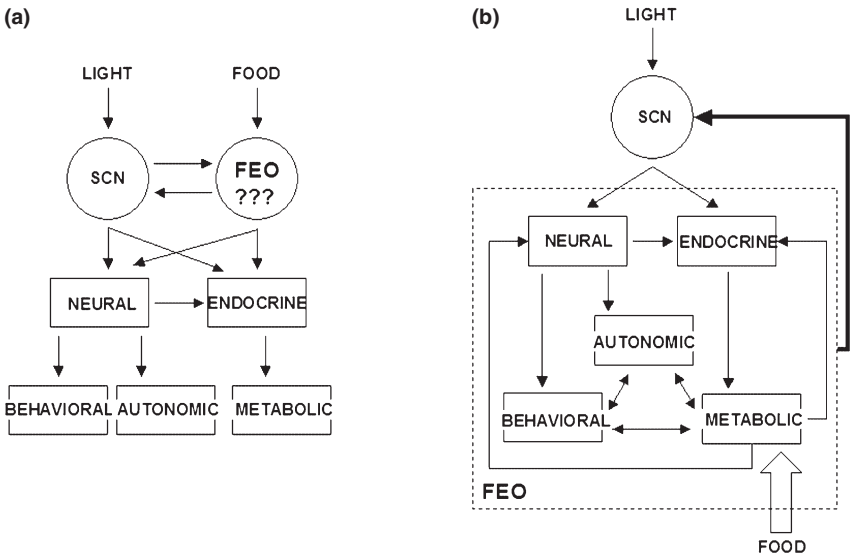

Figure 5 Alternative conceptual models to explain the effects of restricted feeding schedules (RFS) on circadian rhythms. (a) The food entrained oscillator (FEO) is a "constitutive" circadian oscillator coupled to the suprachiasmatic nucleus (SCN) clock during ad libitum conditions and entrained to feeding during RFS. (b) The FEO is an emerging oscillator resulting from the regulation of peripheral clock genes by nutritional signals triggered by daily RFS; in this model the effector systems generating the rhythmic outputs are a dynamical part of the FEO, and its oscillatory properties may be bound to the time constants of the emerging system.

ad libitum conditions FEO expression is coupled to the SCN, but restricted feeding would be a stronger stimulus to activate and entrain the FEO, which then uncouples from the SCN and reveals independently (Fig. 5, panel a). An alternative possibility is that FEO is an emerging phenomenon of the organism related to the daily alternation of fasting–feeding episodes; by this we mean that the different organs involved in this process are assembled as a circadian oscillator as a result of the daily restricted feeding (Fig. 5, panel b). Both processes would involve peripheral oscillators, but in the first hypothesis FEO is a constitutive clock resulting from the *coupling of peripheral oscillators* to the SCN, and at least one of them can be entrained by food; while in the alternative hypothesis peripheral oscillators are driven by the SCN but do not interact among them, and thus the FEO is not present until it builds up as a relaxation oscillator by *recruiting peripheral oscillators* in response to nutritional signals triggered by the fasting–feeding cycles. In either case, FEO will lead to a generalized anticipatory state aimed at optimizing the handling of nutrients and energy production by the organism. Although both hypothesis are very similar and present some difficulties to discriminate, the latter hypothesis is consistent with evidence which indicates that after complete SCN lesions FEO does not take control, and most circadian rhythms are disrupted unless RFS are established;[17,18] and that anticipatory activity only occurs when animals go into a catabolic state by the RFS.[22] Furthermore, recent evidence indicates that during restricted feeding access at variable intervals, some metabolic parameters are reset by the last meal episode. This response would be expected from a relaxation oscillator, but does not induce FAA unless a periodic RFS is imposed.[61] This observation is consistent with the hypothesis that peripheral oscillators need to be recruited and phase locked for the FEO to be expressed.

With respect to the neural regulation of food anticipatory activity, the hypothesis of FEO as emergent oscillators imply the driving of the neural circuits involved in hunger, feeding, and even motivation by different metabolic signals, coordinated by the restricted food access, in order to generate the anticipatory behavior. Therefore, the apparently conflicting results found in the literature could be related to the actual interpretation of the data in order to provide evidence of a food-related clock, instead of addressing the dynamical interplay of the neural structures participating in the control of behavior.

To summarize, we propose that the role of peripheral oscillators, rather than playing a key role as a chronometric element of the FEO, is to assure that each organ involved in metabolism resonates at a circadian frequency with periodic feeding. The actual chronometry

involved in FEO results from the time constant of the system, which results from feedback and feed-forward interactions among peripheral organs related to handling of energetic storages and neural structures involved in control of behavior.

CONCLUSIONS

The coordination of behavioral, physiological, and metabolic processes of the organism from SCN control to the assembly of the FEO that involves the uncoupling and independent operation of peripheral oscillators from the SCN illustrates the concept of chronostasis. Chronostatic regulation allows different configurations of the timing system to cope with changes in the environment as well as the physiological demands of the organism, and guarantee an optimal timing of cellular events to provide energy, support the metabolism, and make possible the coordinated display of biochemical, endocrine, and behavioral processes during a 24-h cycle, and at the same time prevent the disruption of homeostatic processes operating on a short time scale. Chronostatic regulation requires the reciprocal relationship between the molecular components underlying the molecular clock and the signaling pathways that control the metabolic networks, which includes how the cellular energy is obtained, stored, and used. With respect to the timing of behavior, a number of forebrain areas, such as VMH, LH, DMH, the nucleus accumbens, and the PVT have been implicated in the expression of FEO, but none of these structures is indispensable for display of FAA. This clearly suggests a distributed system arranged in a non-hierarchical manner to control food anticipatory activity, which is consistent with our proposition that the FEO is an emergent system built up in response to daily periodic feeding.

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