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CIRCADIAN RHYTHMS AND NUTRITION

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ABSTRACT

The system of Circadian Rhythms is a mechanism that, in the forms of animal life, has evolved in order to synchronize the behavior and physiological responses to environmental periodical stimuli, so as to allow faster response and better adaptation to environmental changes.

These stimuli (light, food availability, presence of predators, availability of a partner for reproduction) in turn depend on the rotation of the earth on its axis and around the sun.

In mammals, there is a central hypothalamic clock , said Master Clock, directly regulated by light in its periodicity, which therefore plays the role of primary synchronizer, and several peripheral clocks, Slave Clock, synchronized with each other and constantly reset the MC.

Between external stimuli food plays a fundamental role, as capable of take the place of the light in certain conditions.

In recent years there has emerged a direct correlation between alteration of Circadian Rhythm , variously induced, and the development of multifactorial diseases such as obesity and diabetes. The biological clock is involved in the maintenance of energy homeostasis and thus in search of food and in the regulation of body weight.

The recent concept of chrono-nutrition, expressed perfectly the influence of food, through times of intake but also by its specific composition, is able to exert on the expression of regulatory genes of circadian rhythms, and therefore the maintenance or alteration of energy homeostasis of the organism.

Key words*: circadian rhythms, chrono nutrition, Gut Clock, obesity, metabolic syndrome.*

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Circadian rhythms and nutrition

The alternation of light and dark with intervals of 24 hours, affects all forms of life on the globe. In the course of evolution, living things adapted to carry out their activities in accordance with schedules and times, governed by a kind of endogenous circadian clock that can synchronize, according to cadenced rhythms of alternating light and dark, the mechanisms of energy homeostasis (use/conservation reserves) in relation to environmental stimuli, the availability of food, and the probability of reproductive success[1].

Central and peripheral clock

In mammals the existence of a functional structure, the so called Master Clock, has been hypothesized to be probably located in the front of the Hypothalamus, at the level of the Chiasmatic hypothalamic nucleus, composed of pacemaker cells with independent circadian oscillatory activity, daily resettable by a light stimulus, which emits rhythmic signals direct to a Slave Clock, probably located in peripheral tissues (liver, adipose tissue, muscle tissue, heart and retina)[2].

Among the possible environmental synchronizers, light is the main element that can regulate many biological processes, and that interacts with the Master Clock: the light stimulus reaches the retina and the hypothalamus through the retina-hypothalamic tract (RH), and evokes signals through efferent neural and humeral factors[1].

The indiscriminate use of artificial lighting can, in fact, induce a significant effect of de-synchronization of circadian and circa-annual rhythms, creating a mismatch between physiological rhythms and the natural rhythms of the environment[3], a phenomenon classically detectable in the course of trans-meridian plane travel and called Jet-Lag.

In addition to light, another synchronizer of great importance is food, which works through the

Gut Clock (intestinal clock) otherwise defined FEO (Food Entrainable Oscillator)[4] (Figure 1).

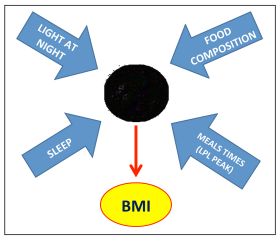

Figure 1: Light and food regulate the Master Clock, which in turn influence the metabolism and physiological responses of peripheral tissues.
CNS: Central Nervous System

Molecularmechanisms of biological clocks

Structurally the Master Clock and Slave Clocks are intracellular mechanisms with identical molecular components. The generation rate of recurrence depends on the coordinated expression of specific genes that are transcribed in response to environmental signals (light and food).

Molecular genetic studies in mice suggest that the activity of the system is regulated by the expression of the Clock genes (Circadian Locomotor Output Cycles Kaput) and Bmal1 (Brain and Muscle Arnt-like protein-1), which encode proteins with stimulatory function and Cry genes (Cryptochrome) and Per (Period) that encode proteins with inhibitory activity[5].

Whenever an organism undergoes a phase shift (de-synchronization between stimulus and endogenous clock), the re-synchronization of the master clock with the environmental stimuli and the peripheral clocks can take a relatively long time (several days), during which the periodic rhythms remain out of phase, sometimes causing unspecified illness[6].

Cortisol and stress response

Cortisol and sympathetic-mimetic amines, while representing the two major hormonal systems involved in stress, show a mode of response to stressful stimuli regulated by anatomical and functional hypothalamic structures: among them the Master Clock modulates the rhythmic release of neuro-hormonal signals (Releasing Factors, RF: CRH, GHRH, TRH etc.) on the one hand by influencing the activity of the hypothalamic-pituitary-adrenal axis (HPA), and the other by changing the rhythms of oscillator slave clocks located in peripheral tissues and organs (liver, kidneys and heart)[2].

Biological clocks and obesity

The Biology of Adipose Tissue

The adipose tissue, or better the adipose organ, is an endocrine organ with specific functions primarily related to the synthesis of adipokines, belonging to the group of cytokines, which include growth factors, angiogenic factors, acute phase proteins and the response to stress proteins of the alternative pathway of complement proteins in homeostasis, coagulation, and vascular tone; many of these factors are regulators of energy balance and lipid and glucose metabolism[7]. Of special interest are pro-inflammatory cytokines due to the role they play in causing the condition of insulin resistance in obesity with abdominal visceral fat[8], and obesity-related diseases: hypertension, hyper-triglyceridemia, low HDL cholesterol, abnormal glucose metabolism, hyper-homocysteinemia, hyperuricemia, type-2 diabetes, and consequently the initiation of processes of atherogenesis, the most significant clinical manifestation of which consists of the cardio-vascular diseases[9].

Rhythms of adipose tissue

Recent studies have highlighted the rhythmic expression of specific genes of visceral adipose tissue, such as Resistin, Adiponectin and Visfatin[1], PAI1, Leptin, and pro-inflammatory cytokines IL-6 and TNFα, Lipoprotein Lipase (LPL), Pyruvate Dehydrogenase Kinase, and the factor responsible for the synthesis of cholesterol (SREBP1)[10].

The relationship between Lipoprotein Lipase insulin-sensitive (LPL) and adiposity appears complex and suggestive. In humans, peak plasma levels of LPL, highest in the post-prandial, are for breaking down adipocyte deposits of the diet lipids. If the intake of fat does not coincide with peak plasma levels of LPL (for example in terms of destruction of the adipocyte biological clock), most of the diet triglycerides, and free fatty acids (FFA) based on them, are carried to other organic structures (liver and muscle), manifesting a real toxic effect (organ lipotoxicity), of which the most clinically detectable conditions of hepato-steatosis and accumulation of fat in the intramuscular myofibrillar are expressions[10,11].

Circadian rhythms and metabolism

Intestinal biological clock: Gut Clock

In humans, the feeling of hunger and satiety is controlled not only by the central pacemaker, but also by the Gut Clock, identifiable by pacemaker cells arranged along the intestinal tract, between the layers of longitudinal and circular muscle, and this, together with the activity of the gastro-entero-pancreatic (GEP) hormone system is the so-called migrating motility complex (MMC), which regulates the periodicity of the peak functions (secretory and motor) of the digestive tract. It is also conceivable that the de-synchronization of the Gut Clock, provoked by work activity during night hours, reduced sleep times, food restriction and aging related phenomena, can result, in some subjects, in functional bowel disorders (dyspepsia and dysfunctional colon disorders)[12] (Figure 2).

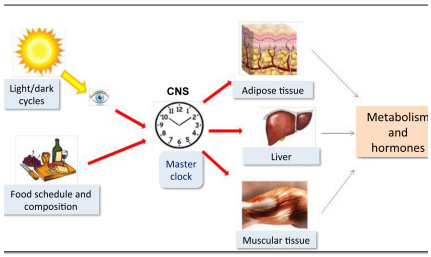

Figure 2: Light at night, the amount and quality of sleep, hours of intake of meals, probably because of nutrient transporter, as well as the composition of foods, influence changes in BMI (body mass index) indirectly, via endogenous clock.

Circadian rhythms and metabolism of food fats

PPARs (Peroxisome Proliferator Activated Receptor) are nuclear receptors that are activated upon binding with circulating FFA and regulate the transcription of genes coding for enzymatic protein structures related to lipid and glucose metabolism[5]. A rhythm in gene expression of nuclear receptors has recently been detected in fat cells, which interacts with the gene expression induced by exposure to high levels of lipids and vitamins consumed in the meal, and by high plasma levels of fat-soluble hormones. In other words, in the condition of eu-synchronization of the biological clock, dietary fats activate transcription of PPAR, which in turn regulate the transcription of the genes of lipid and glucose metabolism. Conversely, in conditions of de-regulation of the system, an exaggerated intra-adipocyte lipid synthesis[1] is detected, and follows a different metabolic fate of dietary fat intake in relation to different times of the day.

The effects of the biological clock in the control of energy balance become particularly evident during seasonal changes when adjusting to variations in the photo-period. It is possible to observe changes in body weight in response to the activation of regulatory mechanisms of energy expenditure, the consumption of food and body temperature[13].

Sleep, shiftwork and obesity

In humans, exposure to light at night and the reduction of hours of sleep cause alterations in lipid and glucose metabolic pathways[14]. It is interesting to speculate that a reduction in hours of sleep, as measured by the hypothalamus-like change in photoperiod, induces the body to eat more food to cope with a likely condition of intense physical activity[13]. However, since the change is only fictitious, the increased caloric intake, if it occurs in a context of potential genetic metabolic type, can result in phenotypic expansion of adipose compartments with preferential location in the abdominal viscera. Clinical studies have shown that a reduction in hours of sleep, even for a few days, can promote the occurrence of metabolic disorders[13]. Similarly, in patients with sleep apnea syndrome (OSAS), the qualitative and quantitative disturbances of sleep can induce effects favoring weight gain with likely expansion of the fat component in the supra-diaphragmatic, mediastinal and paratracheal sites[15].

Molecular biology studies emphasize the pro-obesogenic genetic polymorphisms involved in the regulation of circadian rhythms[10]; the determination of the genetic profile could allow, in some subjects, the development of nutritional intervention associated with a therapeutic behavioral tendency to re-synchronize biological rhythms.

Chrono-nutrition

The digestion and absorption of nutrients are regulated by the circadian rhythms of the dedicated factors (digestive enzymes, membrane transporters, the activities of the migrating motility complex etc.) As well as the consumption of daily meals[16]. Food can become the main synchronizer, as demonstrated by some experiments on rodents[17], predominantly nocturnal animals, fed during the hours of exposure to light; under these conditions a change occurs in some metabolic activities normally regulated by light, which become dependent on the

availability of food[18].

It is widely accepted that the timing of meal intake can modify the expression of clock genes[18,19] suggesting that a de-regulation of circadian rhythms can lead to an abnormal absorption of nutrients. In addition, regardless of the time of intake, the composition of the meal seems to cause a phase shift in the rhythm of expression of Per2 in the liver[20].

Foods with a high glycemic index, adherence to ketogenic diets, or excess salt in the diet, may cause a shift of the slave clock which can result in increased intestinal absorption of nutrients through the over-expression of some transporters[21].

Obesity-diabetes: a chronobiological disease?

The mechanism that links obesity to chrono-disruption of biological rhythms is not yet clear. It has been proposed that the abuse of snacks, the reduction of hours of sleep and the increased exposure to light at night, leading to a lower sensitivity in the coordination between internal and external rhythms favoring an excessive, often unconscious, caloric intake which favors the occurrence of obesity and some metabolic alterations. On the other hand it is possible that obesity and diabetes may itself lead to a de-regulation of biological rhythms; it is sufficient to consider the possible role of glycemic variability on changes in endocrine-metabolic parameters.

Regardless of reciprocal causal relationships, obesity and chrono-disruption of the rhythms are closely related, and in any case diversified interventions that can re-structure the system can produce positive clinical effects.

To summarize, indications for the prevention of diseases related to the alteration of circadian rhythms can be schematized in the acquisition and maintenance of a lifestyle encompassing:

• Regularity of meals, trying to consume the main meals during peak hours of the LPL (hours of light);

• Avoid excess consumption of dietary fat;

• Minimize stressors;

4• Sleeping a sufficient number of hours (at least 7) and maintain schedules of natural sleep/wake cycle;

• Limit excessive exposure to light at times when the body is physiologically predisposed to rest (for humans at night).

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