Non-photic synchronization: the effect of aerobic physical exercise

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ABSTRACT

The main alterations, either acute or chronic, caused by aerobic physical exercise (PE) over the body are generally well-known. However, there is a particular effect of PE which started to be elucidated in the beginning of the 90's in humans which has the capacity to alter the temporal relationship of the body with the environment. The modification of the expression of the circadian rhythms caused by PE qualifies it as a synchronizer of the biological oscillators. The main synchronizer of the biological rhythm is the light/dark geophysical cycle. The day/night rotation which occurs through differences in the luminosity levels is perceived through photic ways by the CTS. These stimuli, called photic, provide temporal information to the CTS synchronizing hence the biological oscillators to this environmental cycle. Other stimuli are also capable to synchronize them and are called non-photic synchronizers. This review writes about the effect of PE over the temporization system as well as discusses the possible and probable chronobiological applications of the mentioned knowledge. PE may affect the CTS through non-photic ways, being hence able to benefit health of individuals in several situations, such as transmeridian flights, night shift tasks and sleep disturbs. Moreover, we highlight that further studies should be conducted on individuals' routine in order to better understand the relationship between different synchronizers as well as their contribution in a real context.

Keywords: Circadian temporization system. Sleep/activity cycle. Circadian rhythm. Physical exercise.

INTRODUCTION

Several functions present rhythmicity in most living organisms, such as the sleep/wake cycle, sleep, hormone secretion, heart rate, blood pressure, body temperature, psychomotor performance and perception among others, in different organization levels(1). According to Marques and Menna-Barreto (2003)(2) these physiological phenomena have a regularly repetitive oscillation with a period around 24h, being thus called circadian rhythms.

Some time ago research in the physiology field evidenced the existence of a timing system which generates and synchronizes the different circadian rhythms(3). The body needs external and internal information which acts as pacemakers so that it can adjust its rhythms with the environmental cycles. These two pieces of information of different origins (exogenous and endogenous), are received and transmitted until the main biological oscillator located in the hypothalamus suprachiasmatic nucleus which acts as an integrator(4). The suprachiasmatic nucleus signals for the different effector organs which can be heart, lungs, kidneys, liver, muscles and others. The interaction of this organization- receptors, integrator and effectors- characterizes the circadian timing system (CTS).

Once an organization which articulates the different sectors of the body as time passes exists, which would be the effect of aerobic physical exercise (APE) in this timing system? If this stimulus presents any effect in the CTS, how could we benefit from this situation? This review aims to explain the effect of APE in CTS. Later, we will discuss the application of the chronobiological knowledge in situations in which the individual's health could benefit through synchronization, among them: transmeridian flights (jet lag), night work shifts and sleep disorders.

PHOTIC SYNCHRONIZATION

When isolated from environmental cycles, the body expresses its endogenous rhythmicity, which may easily be detected in sleep and alertness behaviors in humans. Generally, alertness is associated with the light phase of the day, while sleep is expressed in the dark part. In conditions in which regular alternation of luminosity levels and any other time cues do not exist, alertness and sleep still have rhythmic manifestations. However, this cycle (sleep/wake) does not present one more period of exact 24h. The body hence starts to determine the duration of a cycle using an internal clock as orientation, defined as endogenous period. In humans, the usual endogenous period of the circadian rhythms is slightly longer than 24 hours(5). For this reason, individuals need temporal cues in order to synchronize with the environment which oscillates with a 24-hour period. The geophysical light/dark cycle is the main responsible for this synchronization through photic pathways being called photic synchronizer(6). This adjustment requires that our rhythms are daily advanced though a process called drafting. In other situations, for instance, after transmeridian flights, it is necessary that a delay in our rhythms occurs in order to adapt to the new local time. These delays and advances which allow that the body's adjusts to regular changes of the environment are called dislocations or phase alterations.

The natural light/dark cycle is considered the main synchronizer of the circadian rhythms(6). There are specific photo-receptors situated in the retina, probably the ganglionary cells, which present the melanopsin pigment(7). These photoreceptors receive the information of the environment's luminosity levels and send them to the suprachiasmatic nucleus primarily through the retine-hypothalamus pathway and secondarily through the intergeniculate leaflet(4). Alterations are provoked in the main biological clock; the suprachiasmatic nucleus, and through efferent pathways inform other oscillators which are phased, that is, are synchronized with the central oscillator and trigger the functions in a rhythmic and syn-

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chronized way with the environment. This process is called photic synchronization(8).

PHYSICAL EXERCISE AS A NON-PHOTIC SYNCHRONIZER

There are other synchronizing agents besides the light/dark cycle which also influences the circadian rhythms. Among them, we may mention work and school schedules(4,9-10). The eating times also may cause drafting of phase in the individuals(11-12). The process through which synchronization occurs in these cases is called non-photic.

It is known that PE practice acts in the prevention of coronary arterial diseases, diabetes mellitus, metabolic syndrome, different types of cancer, obesity, among other conditions, through distinct mechanisms and many of them are still unknown(13). Likewise, PE has demonstrated to be a non-pharmacological intervention for individuals who wish to improve quality of sleep(14-16).

There is massive evidence that PE may act as a non-photic synchronizer, being able to dislocate the circadian rhythms phase(17-24). This phenomenon may be observed when PE is applied in constant situations, in which the influence of other synchronizers both photic and non-photic are tried to be blocked. Generally, the so called constant routine protocol is used in these studies. This protocol consists of the removal of the influence of the known synchronizers in order to guarantee that the only factor that may transmit temporal information to the body is the given stimulus, namely the PE. The individual then starts to constantly eat (e.g. 200 kcal intravenous glucose infusion every 2 hours), remains still on a reclined chair (45º), is taken to the restroom on a wheelchair and luminosity conditions are kept constant at low intensity.

It is already well-characterized in rodents, namely hamsters, that the activity/rest cycle (PE) may effectively cause the phase change(25-26). Generally, in these experiments rodents are kept at constant conditions and activity is induced in different ways. Although the performance of forced PE on treadmill is the means that is most similar to human PE(27), the one performed on the activity wheel is widely used. It is possible to precisely quantify activity by counting the number of laps in a given time. Due to the amount of observations performed, the intensity, duration and time of the day needed to cause specific phase dislocation in rodents is already known. Such research stimulated investigations on the PE influence on CTS in humans.

Although PE acts as a synchronizer in humans, some factors such as intensity, duration, most suitable time, whether followed by light or not, and if the same effect is experienced for all ages, are still being elucidated. Some researchers who have tried to answer some of these questions initially used extrapolation of observations in rodents to determine the intensity and duration of PE.

Van Reeth *et al.* (1994)(24) followed such standard and tried to determine whether one single session of nocturnal PE is able to affect the expression of thyreotropin and melatonin rhythms[1] one day after exposition. Seventeen male healthy individuals, age range 20/30 years were studied. The individuals were studied twice under constant conditions (reclined position at 45º during alertness, exposition to low luminosity intensity < 300lx and constant caloric intake through glucose intravenous infusion). The first step was the control situation without PE application in order to verify the CTS situation before stimulation. In the second step a three-hour session of uninterrupted PE was applied (5 36'-30' exercise cycles – 6' rest) which varied from 40 to 60 % of $\dot{V}O_2$max in cycle ergometer, at the moment in which it coincides with the nadir (moment of greatest probability to find minimum values) of rectal temperature of each individual. The monitoring of the beginning of the increase (baseline) of the plasma levels of thyreotropin and melatonin determined the circadian phase before and after the stimulus presentation. The PE application in the nocturnal phase demonstrated a clear phase delay of one to two hours one day later, both of melatonin and thyreotropin secretion. The longest phase delays could be observed when the stimulus was presented three to five hours before the temperature nadir.

Buxton *et al.* (1997)(22) investigated the role of the intensity and duration of nocturnal PE in the modification of the thyreotropin and melatonin rhythms expression. The authors studied a group of 8 male healthy adult subjects (20-30 years), who received two pulses of PE at one o'clock in the morning at different days. One pulse consisted of one hour of PE at 75% of $\dot{V}O_2$max in a stairclimber (instrument which simulates the act of climbing up stairs) and another oe in three hours alternating at every 15 minutes between hand and leg cycle ergometer, between 40 and 60% of $\dot{V}O_2$max for both types of PE, with 6-minute intervals. A constant routine protocol was applied before and after each PE pulse in order to verify the CTS phase with the biological markers mentioned above. It was verified that the high intensity one-hour PE caused phase delay apparently as effective as the three-hour one at moderate intensity. Since the one-hour PE practice is much closer to reality and seems to be more easily inserted in people's routine, this finding is fairly interesting concerning applicability.

Edwards *et al.* (2002)(28) studied the effect of PE performed at different moments over the rectal temperature rhythm, another circadian marker. Sedentary individuals with only one day of PE were studied. A phase delay was found when the PE session was between 4 hours prior and 1 hour post the rectal temperature nadir. When the session was performed between 3 and 8 hours after the nadir, a phase advance was observed. Nonetheless, these results were not presented by all the volunteers and should be further investigated.

What would be the best time to change the CTS phase and in which direction, advance or delay? Usually, in the studies in which PE was applied between the middle and the ending of the nocturnal phase, the researchers found a phase delay(17-20,22,24). When PE was performed both in the morning and in the afternoon, it was possible to verify a phase advance in a study(20). Klerman *et al.* (1998)(21) found a phase advance when the PE was performed 6 hours after wake up time. Buxton *et al.* (2003)(18) also verified an advance. However, the PE was performed at the beginning of the night, about 6:30 p.m.

It is known that the CTS responds differently to light pulses depending on the administration time. When the light pulse is administered at night, a delay of the biological 'clocks' is usually observed, which is expressed in a phase delay of the measured rhythms. When the light pulse is given in the morning though, an advance in the rhythms phase is produced. In two studies, the interaction of the effects of intense light and PE in human circadian rhythms was investigated. Baehr *et al.* (1999)(29), simulated a night shift protocol with 9h delay in the sleep and wake times. The authors verified if the association of intense light (5000lx) with PE intermittently applied in the nocturnal phase would produce a longer delay of the rhythms than if both stimuli were presented alone. The PE consisted of 6 series of 15 minutes in cycle ergometer with intensity between 50 and 60% of maximal heart rate. The PE neither helped nor inhibited the synchronizing effects of light. The intensity and duration of the PE may have not sufficient to cause an effect in the circadian rhythms of the subjects.

Youngstedt *et al.* (2002)(30) investigated the effects of three hours of intense light (3000lx) alone or combined with PE applied at night. The PE was performed in a cycle ergometer at the intensity of 65 to 75% of reserve heart rate. The observation of the body temperature nadir demonstrated a significant phase delay when only intense light was applied; the acrophase (moment of highest proba-

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[1] In this case, the melatonin and thyreotropin hormones represent circadian markers, since they express the rhythm of the circadian oscillators. The baseline of these hormones, in this study, was the phase or the moment used as reference of the Circadian Timing System.

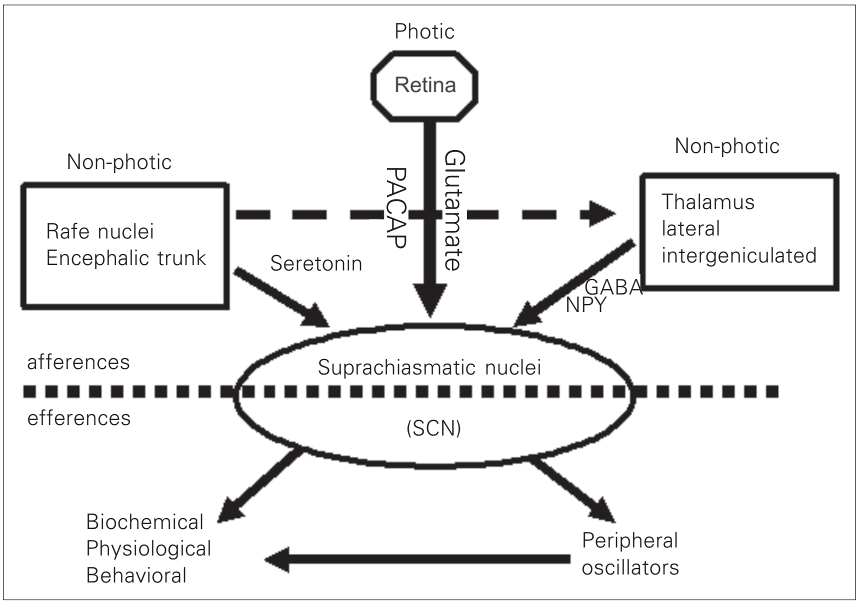

***Figure 1** – The retina is the main afferent (retino-hypothalamus tract) using glutamate and PACAP (pituitary adenylate cyclase-activating polypeptide) as neurotransmissors which signal the photic data for the SCN. Concerning the non-photic data, the two main afferent ways are: lateral thalame intergeniculate tract using gaba and NPY (neuropeptide-Y) and rafe nuclei which use serotonin as neurotransmissor.*

bility of finding maximal values) of the urinary 6-sulfatoximelatonin did not present difference. In the protocol in which PE added to intense light was applied, a significant phase delay of the urinary 6-sulfatoximelatonin was produced, but this delay was not significantly different from the phase alteration produced in the protocol in which only intense light was used.

Klerman *et al.* (1998)(21) investigated 15 visually-impaired individuals, who besides not being able to see (without visual photo correction), did not present circadian photoreception (detection of the temporizing stimulus, luminosity levels, through the melanopsins). Even in the lack of photic data, 9 of these subjects were synchronized with the environment. Later, one of these individuals was separately studied. A pulse of PE was daily applied, six hours after the beginning of the wake cycle during 38 consecutive days. The PE was performed during ten minutes in ergometric bicycle at an average velocity of 66% of the maximal heart rate. The authors found a rhythm phase advance of the core body temperature and of the melatonin secretion baseline. It can be concluded from this result that the synchronization which occurred in the 9 visually impaired individuals at a 24h period, was performed through the non-photic pathways. In the trial to explore the application of the possible synchronizing effect of PE, some authors implemented it in simulations of nocturnal work shifts. Eastman *et al.* (1995)(23) used PE in order to promote a circadian adaptation to nocturnal work shift. Sixteen subjects were studied, being 8 from the control group. The individuals from the experimental group performed 15 minutes of PE in stationary cycle ergometer, with intensity of 50 to 60% of $\dot{V}O_2$max, at every hour of the three first nights of the eight study days. The rhythm phase of the core body temperature could be more delayed in the group which performed PE. The circadian rhythm of the core body temperature presents great influence in the mechanisms which lead to sleep(31). The decrease in the temperature corresponds to the moment in which the individual's chance to sleep increases(32). Since the temperature reaches minimum values in the early morning (around three or four a.m.), it makes sleep tendency maximal at this time. The phase delay caused by PE made the temperature decrease which occurs in the early morning, occur later, adjusting better to the sleep episodes at the diurnal phase. The subjects presented improvement in sleep, alertness levels and mood.

Recently, Barger *et al.* (2004)(17) applied PE in the trial to facilitate a circadian adaptation after 9h delay in the sleep/wake cycle times. Eighteen healthy male young individuals participated in the 15 days of experiment. The circadian phased of these individuals was estimated in the first and last days through a constant routine protocol. The luminosity intensity levels were controlled and remained at ~0.65lx at the retina height of the individuals. Melatonin was used as a circadian marker. The subjects performed three 45-minute series of PE, at 65 to 75% intensity of $\dot{V}O_2$max, in cycle ergometer during 7 nights. The experimental group demonstrated a phase delay significantly higher than at the beginning, from the mean point and the end of the melatonin release when compared with the control group (without PE). These data suggest that PE may facilitate a circadian adaptation when a delay in the sleep/wake cycle times is needed. The authors discussed as well a possible synergic effect of light and PE.

Cardinalli *et al.* (2002)(33) investigated the PE effect in the adaptation after a transmeridian flight (jet lag). They evaluated professional soccer athletes who flew from Buenos Aires to Tokyo. The results demonstrated that the melatonin rhythm and the times of sleep beginning of the athletes adapted more rapidly than expected if no intervention had occurred. Moreover, the athletes reported increased alertness during the day in the new environment (Tokyo). However, this effect cannot be only attributed to PE, since the athletes were exposed to natural luminosity and were treated with melatonin. The diurnal PE performance in the new environment may have contributed to accelerate the athletes' adaptation to the new time, giving evidence hence of smaller jet lag effects.

Although there is no doubt about the synchronizing effect of PE in humans, the mechanisms responsible for this synchronization are still unknown. Some researchers suggest through experiments with rodents, the participation of secondary neural pathways which would be informing the suprachiasmatic nucleus. The thalamic intergeniculate leaflet and the rafe nuclei, the main proposed ways, would transmit data of non-photic stimuli for the suprachiasmatic nuclei, promoting thus synchronization(34-35). Mikkelsen *et al.* (1998)(36) also found an increase of the c-fos expression in the intergeniculate leaflet in response to non-photic information, in this case in the activity wheel, strengthening even more this hypothesis.

Marchant *et al.* (1997)(37) injured two neural structures (intergeniculate leaflet and rafe nuclei) in blind rats and tried to synchronize them through PE. The animals did not present synchronization of the activity/rest rhythm with exposition to PE cycles. This study suggests the importance of these pathways for non-photic synchronization, corroborating other mentioned articles.

Yannielli and Harrington (2004)(35) proposed a schematic representation which illustrates the interaction of the areas of the circadian temporization system with photic and non-photic afferent ways. This scheme represents the afferent ways for the suprachiasmatic nuclei (SCN) of hypothalamus (figure 1).

CONCLUSION

This review demonstrated that PE in appropriate circadian times may cause alterations in the CTS phase, being added as extra non-pharmacological stimulus for action on circadian rhythm. For instance, in nocturnal workers who face difficulty in adapting to times of inverted sleep/wake cycles opposite from the rest of the society. PE could be performed at night in order to provoke a phase delay of circadian rhythms. Such delay would facilitate the adaptation to nocturnal work shift, increasing alertness and improving mood. Parallel to this, the improvement in sleep quality would minimize the harmful effects of nocturnal work. Moreover, a study recommended moderate physical activity for workers in rotating shifts after the nocturnal shift and before the afternoon nap, aiming with this, improvement in sleep quality(38).

The workers' situation is similar to that in which the individual crosses several local times east bound (delaying the times). For instance, in the case of an individual who leaves Brazil and flies to the Middle East, changing the sleep/wake cycle times. A change about 6 to 8 hours in his/her circadian rhythms is necessary so that the individual adapts to this condition. PE could be performed in order to delay the circadian rhythms phase before and after the trip, thus synchronizing more rapidly.

Another situation in which PE could help would be the case of older individuals who tend to advance their sleep/wake times cycles(39). Possibly, for older individuals who still work and present the extreme diurnal chronotype[2], the phase's delay would be desired. Therefore, these older individuals would synchronize better with their work shifts.

Other circumstances in which the PE could beneficially act would be in the sleep circadian rhythm disturbs. In these disturbs, the individuals have difficulty to align the sleep times with the sleep/wake cycle desired or imposed by society. Among these disturbs, we have the sleep advanced and delayed phase syndromes. In the former, similarly to older individuals, these individuals sleep and wake up very early because they present an advance of the circadian rhythms. In the latter, on the contrary, the subjects sleep and wake up very late.

Physical activity has been associated with prevention of different types of chronic-degenerative and psychological diseases, metabolic dysfunctions and currently sleep-related problems as well. PE practice or the simple performance of physical activity has been recommended in order to improve the quality of life of general population for these reasons. Therefore, PE joined with these potential benefic effects mentioned above, presents a synchronizing effect of the circadian rhythms and can aid in the prevention and treatment of disturbs related with CTS. However, as a synchronizer, PE may add undesirable effects, as when the individual needs to sleep earlier and exercise close to sleep time, provoking a phase delay. Likewise, if the PE is performed at times in which the temporizing system is not responsive to this non-photic stimulus, the direct effect of its performance over the circadian rhythms is indifferent.

PERSPECTIVES

The results obtained in laboratorial conditions allow us to attribute to PE a characteristic of synchronizer of the circadian rhythms. Nonetheless, we should observe how this synchronization happens in real contexts, describing the pattern of light exposure in the routine and also considering social factors such as work, school and leisure shifts.

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[2] Classification of the individuals concerning time preference of the sleep/wake cycle. The individuals are classified according to the points resulting from the chronotype questionnaire's data created by Horne and Ostberg (1976). The higher the punctuation, the higher the degree of diurnicity; the lower the punctuation, the higher the degree of nocturnicity.

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