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Gender and the circadian pattern of body temperature in normoxia and hypoxia

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ABSTRACT

Circadian patterns are at the core of many physiological processes, and their disruption can have short- and long-term consequences. This essay focuses on one of the best known patterns, the daily oscillation of body temperature (Tb), and the possibility of its difference between genders. From human and animal studies globally considered, the tentative conclusion is reached that differences in Tb circadian pattern between genders are very small and probably limited to the timing of the Rhythm, not to its amplitude. Such similarity between genders, despite the differences in hormona rhythm (small r) l systems, presumably testifies to the importance that the Tb circadian pattern plays in the economy of the organism and its survival against environmental challenges. The second part of the article presents some previously unpublished experimental data from behaving male and female rats during hypoxia in synchronized conditions. In adult rats hypoxia (10.5% O_2 for three days) caused a profound drop of the Tb daily oscillations; by day 3 they were 55% (♀) and 22% (♂) of the normoxic amplitudes, with a statistically significant gender difference. In pre-puberty rats (26-day old) hypoxia caused a major disruption of the circadian pattern qualitatively similar to the adults but not different between genders. Hence, on the basis of this preliminary set of data, it seems that sex-hormones may be a factor in how the Tb daily pattern responds to hypoxia. The implications of the effects of hypoxia on the circadian patterns, and the possibility that such effects may differ between genders, are matters that could have biological and clinical implications and deserve further investigations.

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1. Generalities

In humans, the daily alternation of periods of sleep and wakefulness is probably the most obvious example of physiological events that cycle with a period close to that of the Earth rotation ("circadian"). Circadian patterns persist in absence of the daily light-dark (L-D) alternation, because they are the overt expression of an intrinsic biological clock the period of which is close, but not quite equal, to 24 h (Refinetti, 2012). Many events, loosely or directly, act as cues to synchronise daily the biological clock to the local L–D pat-

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tern; of all, the morning appearance of light is considered the most powerful synchronizer.

All forms of life, from uni- to pluri-cellular organisms, fungi, plants and animals, have evolved mechanisms equivalent to a biological clock. Such ubiquity is testimony to the survival value in being able to anticipate and prepare for predictable events associated with L-D alternations, rather than simply responding to them once they have occurred. Although probably cells of most tissues have cycling properties, in mammals the master clock is the suprachiasmatic nucleus (SCN), a small neural structure in the anterior portion of the hypothalamus. Lesions in animals or tumors of this region in humans have serious implications on biological rhythms (Schwartz et al., 1986; Cohen and Albers, 1991; Osborne and Refinetti, 1995). The resettability, an essential property of the clock, permits its proper function despite geographical displacements. Furthermore, the magnitude of the daily resetting monitors the changes in L-D duration with the passing of the seasons. This function is integrated by the pineal gland under the SCN control, and cues seasonal phenomena such as migrations and reproductive cycles.

While extensive research from insects to mammals has been focused on decoding the molecular basis of the clock and the genes involved in time-keeping (Allada et al., 2001; Clayton et al., 2001; Jackson et al., 2001; Ko and Takahashi, 2006), how the cycling of the master clock translates into overt physiological and behavioral patterns remains unclear. It is probable that some physiological variables are under the direct control of the SCN; then, either directly or indirectly, their cycles influence the daily pattern of many other functions in a hierarchical manner and in a complex balance with the needs for homeostasis (Ko and Takahashi, 2006; Refinetti, 2012; Zelinski et al., 2014). Body temperature (Tb) is probably at the top of the hierarchy with an extremely robust circadian pattern through a coordinated control of heat production and heat loss; indeed, the Tb daily oscillations have been noted since the early nineteen century (Mellette et al., 1951, for a historical recollection). Experimental temperature oscillations comparable to the natural oscillations of Tb were successful in entraining the circadian rhythms in isolated cells and in unicellular organisms (Brown et al., 2002, also for references). Hence, the Tb rhythm in mammals could serve to synchronize the oscillatory functions of peripheral cell types (Liu et al., 1998; Brown et al., 2002).

Hypoxia depresses heat production and shifts the regulation of Tb toward lower ambient temperatures in all animals studied (Mortola and Maskrey, 2011). Furthermore, hypoxia affects the expression of genes involved in time-keeping (Chilov et al., 2001; Ghorbel et al., 2003; Guillaumond et al., 2008; Burioka et al., 2009). Therefore, one may expect hypoxia to interfere with the normal circadian pattern of Tb and, possibly, with many other daily cycles that depend on Tb. Indeed, the studies that have addressed this issue (notably in humans and in rats) found that hypoxia caused profound modifications of the circadian pattern of Tb and other physiological variables (reviewed in Mortola, 2007). The circadian disturbances caused by hypoxia are potentially important from a clinical perspective. In fact, disruptions of the circadian patterns, as with frequent crossings of multiple time zones or alternations in day and night work-shifts, have been associated to a growing list of ailments, depression and mental disorders (Winget et al., 1984; Bunney and Bunney, 2000; Bovbjerg, 2003; Davidson et al., 2006; Touitou et al., 2010; Zelinski et al., 2014). Because the SCN outputs to hypothalamic nuclei responsible for hormone release (which in turn regulate SCN function in a reciprocal manner), rhythm desynchronization affects multiple organ systems, and the implications are not necessarily similar in males and females (Ferrari et al., 1990; Santhi et al., 2016).

While several experiments have indicated that hypoxia can alter profoundly the Tb circadian pattern, whether such effects may differ between genders has never been addressed. Some previously unpublished experimental data in this direction are presented in the second part of this essay, after a review of what is currently known on the normal daily cycling of Tb in males and females.

2. Gender and the circadian pattern of Tb: normoxia

2.1. Studies in humans

The daily oscillations of Tb are usually quantified from their period, the chronological time of the daily peak (or acrophase) and trough (or nadir) and the amplitude (peak-trough difference). Despite the simplicity in data collection and analysis, a definitive conclusion on whether or not the Tb pattern differs between men and women can get complicated by methodological and physiological factors.

Because the L-D alternation has a powerful synchronizing effect on the SCN, the intrinsic (or endogenous) period of the rhythm can be appreciated only in 'free-running' conditions, under constant level of light or darkness. A common methodology is the constant routine (CR) protocol; the subject remains awake for 24–36 h by reading or listening to music in semi-recumbent position in an isolated and lighted room, with frequent evenly distributed small isocaloric intakes (Mills et al., 1978; Duffy and Dijk, 2002). This approach eliminates the confounding effects of activity-rest and sleep-wake cycles (Waterhouse et al., 1999) although, by necessity, the duration of data collection is brief; hence, the accurate detection of the intrinsic period of the Tb rhythm can be complicated by noise of various sources, including oscillations of short periods (Refinetti and Menaker, 1992). Differently, field measurements on subjects allowed to follow their usual routines can be continued for many days or weeks, but include the confounding variables of the activity and sleep cyclic patterns.

In addition to methodological issues, physiological factors, like age and body mass, if unaccounted for, can raise variability and confuse the comparison between women and men. With aging, the period, mean values and amplitudes of the Tb oscillations decrease and the acrophase and nadir fall at earlier chronological times (Weitzman et al., 1982; Vitiello et al., 1986; Campbell et al., 1989; Refinetti and Menaker, 1992; Prinz et al., 1993). With respect to body weight, the mean Tb value is inversely related to body mass (Adam, 1989), but whether this inverse relationship applies also to the amplitude of the Tb oscillation does not seem to be known. If it did, as it is among species of different body sizes (Aschoff, 1982; Mortola and Lanthier, 2004), it would complicate in the interpretation of the Tb-rhythms of same-age men and women.

It is well known that in women the value of the 24-h Tb mean is higher in the luteal (postovulatory) phase, but whether or not the circadian pattern of Tb varies with the phase of the menstrual cycle is still unresolved. Several past studies have noted a dampening of the Tb amplitude during the luteal phase (Lee, 1988; Kattapong et al., 1995; Coyne et al., 2000). However, a more recent work (Baker et al., 2001) did not confirm those differences nor could detect differences in the amplitude of the Tb oscillations between women normally cycling and those making use of hormonal contraceptive (and therefore with no menstrual cycles). Finally, inter-individual differences in the physical activity and wake-sleep cycles (i.e., the morning-type or evening-type personality) can cause entrainment and be a confounding factor in the appreciation of the endogenous rhythm (Kerkhof, 1985; Baehr et al., 2000; Weinert and Waterhouse, 2007; Refinetti, 2012).

In brief, the answer to the seemingly straightforward question "*does the Tb circadian pattern differ between men and women?*" finds a variety of methodological and physiological obstacles, which, if not resolved or at least accounted for, can be the source of inconsistent