Association between mammalian lifespan and circadian free-running period: the circadian resonance hypothesis revisited

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Biological rhythms that oscillate with periods close to 24 h (circadian cycles) are pervasive features of mammalian physiology, facilitating entrainment to the 24 h cycle generated by the rotation of the Earth. In the absence of environmental time cues, circadian rhythms default to their endogenous period called tau, or the free-running period. This sustained circadian rhythmicity in constant conditions has been reported across the animal kingdom, a ubiquity that could imply that innate rhythmicity confers an adaptive advantage. In this study, we found that the deviation of tau from 24 h was inversely related to the lifespan in laboratory mouse strains, and in other rodent and primate species. These findings support the hypothesis that misalignment of endogenous rhythms and 24 h environmental cycles may be associated with a physiological cost that has an effect on longevity.

Keywords: circadian; tau; lifespan; free-running; rodent; primate

1. INTRODUCTION

The free-running endogenous circadian rhythm, or ‘tau’ is generated by a network of transcriptional and translational feedback loops controlling the expression of a panel of ‘clock’ genes (Reppert & Weaver 2002), and lies close to 24 h in all animals (Pittendrigh & Daan 1976; electronic supplementary material, tables S1 and S2). Free-running periods that are longer or shorter than 24 h necessitate daily re-entrainment to external time cues that have a 24 h period, such as the light–dark cycle, and this chronic re-entrainment may be associated with a physiological cost that affects survival. There are clear examples of this cost in invertebrates, for example, the lifespan of fruit flies (Drosophila melanogaster) and blowflies (Phormia terranova) were significantly longer when raised on 24 h light dark cycles compared with cycles that were shorter than tau (Pittendrigh & Minis 1972; von Saint Paul & Aschoff 1978). Furthermore, in Arabidopsis strains grown under photoperiods not equal to tau produced less chlorophyll and had reduced growth and survival (Dodd et al. 2005).

The circadian resonance hypothesis was proposed several decades ago by Pittendrigh (e.g. Pittendrigh & Bruce 1959), and states that fitness is enhanced when endogenous periods are synchronized with the period of environmental cycles. Such an adaptive advantage of circadian resonance seems intuitive, but remarkably, this concept is disproved in mammals. Supportive evidence is derived from rather ambiguous epidemiological investigations of prevalence of the disease among human shift workers (Knutsson 2003), and from studies of increased morbidity in rodent models with disruption to the molecular mechanisms of the circadian clock (Martino et al. 2008), neither of which conclusively demonstrates specific beneficial effects of circadian resonance in the healthy, wild-type phenotype.

Ageing is associated with disruption of the circadian timing system, including drifting of tau, reduced entrainment to light, reduced amplitude of clock gene expression and desynchronization of physiological rhythms (Valentinuzzi et al. 1997; Duffy et al. 2002; Hofman & Swaab 2006). Transplantation of the master circadian clock located in the suprachiasmatic nuclei (SCN) of the hypothalamus, from young mice into aged mice restored youthful rhythmicity, and increased lifespan (Hurd & Ralph 1998), suggesting an adaptive advantage of robust circadian timing. This finding, along with the beneficial effects of circadian resonance in plants (Dodd et al. 2005) and invertebrates (Pittendrigh & Minis 1972), led us to investigate whether longer mammalian lifespans are associated with values of tau that are close to 24 h.

The specific hypothesis tested in this study was that values of tau that deviate away from 24 h are associated with reduced lifespan, possibly because they are less easily synchronized with 24 h environmental cycles.

2. MATERIAL AND METHODS

Values for tau, body mass and for lifespan were taken from the literature for strains of laboratory mice (n = 9), primate (n = 13) and rodent species (n = 25) (electronic supplementary material, tables S1–S3). Data for laboratory mice were taken from a single study where tau was measured under identical conditions for each strain (Schwartz & Zimmerman 1990). Linear regression analysis was used to investigate associations between tau, lifespan and body mass using parametric statistical tests. Data were analysed using Minitab software with p < 0.05 taken to indicate statistical significance.

3. RESULTS

Values for the proximity of tau to 24 (tau-24) were significantly related to lifespan (75% failure) in individual strains of laboratory mice (figure 1a; r = 0.83; p = 0.003), with strains with greater values for tau-24 having shorter lifespans. Multiple linear regression analysis confirmed a similar negative relationship between maximum lifespan and tau-24 in 13 species of primate (figure 1b) and in 25 species of rodent.
Based on an estimated phylogenetic tree, as full information for evolutionary relationships among species was maximum lifespan for any species (Speakman et al. 1991). Furthermore, correction for phylogenetic non-independence confirmed a statistically significant relationship between tau-24 and lifespan in the primate group (\(r^2 = 0.43; p = 0.05\)), but not in the rodent group (electronic supplementary material, figure S2).

**4. DISCUSSION**

The consistent inter- and intra-species relationship between tau and lifespan reported here suggests that this association reflects a biological constraint that limits lifespan when endogenous rhythms do not match the 24 h environmental cycle. The reasons for such a wide inter-species diversity in the values of tau are unclear, but it has been suggested that having a tau that deviates from 24 h confers some additional functional capacity, possibly related to environmental or seasonal adaptation (Pittendrigh & Daan 1976).

Maximum lifespan was the only available index of lifespan in rodents and primates, and because this parameter is often based on a small sample of animals maintained in captivity, it may not represent the true maximum lifespan for any species (Speakman et al. 2002). It is also probable that values for tau in some of the rodents and primates may differ from the true values; many of these measurements were taken using different methods for detection of locomotor activity, and few studies accounted for previous light exposure of the animals, which is known to affect the length of tau (Pittendrigh & Daan 1976). Furthermore, correction for evolutionary relationships among species was based on an estimated phylogenetic tree, as full mitochondrial gene sequences were not available for all animals, also necessitating the assumption of equal branch lengths (Garland et al. 2005). These limitations might account for the lack of association between the phylogenetic independent contrasts in rodents (electronic supplementary material, figure S2). Nevertheless, interpretation of the results in the rodent and primate groups is aided by the concurrent relationship between tau and lifespan among strains of laboratory mice (figure 1), where highly accurate data for tau and lifespan are available (Schwartz & Zimmerman 1990). However, the contribution of strain-related pathology to lifespan cannot be excluded. In this study, tau was measured under identical experimental conditions in all strains, with previous light exposure, age and sex all controlled (Schwartz & Zimmerman 1990), and tau was compared with well-established indices of lifespan (Paigen, Mouse Phenome Database).

The endogenous nature of circadian rhythms was confirmed through SCN lesion studies less than 50 years ago, and evidence to support the enormous significance of circadian control for human health and physiology is now rapidly accumulating. For example, it is evident that circadian clock genes oscillate in virtually all mammalian cells (Peirson et al. 2006), and these genes control the transcription of at least 10 per cent of the human genome (Storch et al. 2002). Most physiological parameters are subject to endogenously generated circadian rhythms, as are demographic factors such as the time of death (Mitler et al. 1987) and birth (Honnebier et al. 1991). Clock genes regulate the cell cycle, cell proliferation and tumour suppression (Fu et al. 2002; Miller et al. 2007; Moriya et al. 2007), and play a central role in metabolic physiology (Rudic et al. 2004; Alenghat et al. 2008). The results of this investigation support the hypothesis that values of tau that deviate from 24 h impose an increased requirement for daily re-entrainment, and this may result in a cumulative physiological cost that negatively affects lifespan.

**Figure 1.** (a) Relationship between tau-24 and lifespan (time to 75% failure, i.e. when 75% of the animals have died) in nine strains of laboratory mouse (values are mean ± s.e.m.; \(r^2 = 0.7; p < 0.01\)). (b) relationship between tau-24 and maximum lifespan of 13 primates (Oreolum garnettii, Aotus trivirgatus, Aotus lemurinus griseimembra, Microcebus murinus, Homo sapiens, Saimiri sciureus, Macaca mulatta, Macaca fascicularis, Calithrix jaccus, Macaca nemestrina, Aotus azarai beliviensis, Galago senegalensis, Eulemur fulus albifrons) (\(r^2 = 0.33; p < 0.05\)). (c) relationship between tau-24 and maximum lifespan of 25 rodents (Mesocricetus auratus, Phodopus sungorus, Mus musculus, Rattus norvegicus, Ammospermophilus leucurus, Arvicanthis nileticus, Cryptomus damarenensis, Georychus capensis, Acomys russatus, Cryptomys hottentotus, Heterocephalus glaber, Rhodamys purnili, Spalax ehrenbergi, Octodon degus, Peromyscus maniculatus, Dipodomys merriami, Tamiasciurus hudsonicus, Tamias striatus, Sigmodon hispidus, Glaucomys volans, Meriones unguiculatus, Peromyscus leucopus, Tamias sibiricus, Lemniscomys barbarus and Spalacopus cyanus) (\(r^2 = 0.16; p < 0.05\)).
Circadian rhythms can no longer be viewed as artefacts of mammalian evolution under a 24 h light–dark cycle, but rather as fundamental molecular synchronizing mechanisms that permeate every aspect of physiology. The relatively recent desynchronization of human life schedules with environmental cycles by increased shift work, trans-meridian travel and electric lighting may have significant implications on human health, and the circadian resonance hypothesis requires timely re-examination.

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