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

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 and phylogenetic independent contrasts were computed to account for evolutionary relationships between the species (see electronic supplementary material for further details of methods and sources). Data for \( \tau \) and lifespan for the rodent and primate species were subjected to a log-transformation in order to comply with the parameters of the normal distribution and to facilitate analysis 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

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 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. 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.

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 (Pearson 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 (Miller 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.
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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