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Circadian Organization of *tau* Mutant Hamsters: Aftereffects and Splitting

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Abstract   Homozygous *tau* mutant (τ_{ss}) hamsters show an extremely short (20 h) circadian period (τ) that is attributable to altered enzymatic activity of casein kinase 1ε. It has been proposed that coupling of constituent circadian oscillators is strengthened in τ_{ss} hamsters, explaining their tendency to show strong resetting after prolonged exposure to constant darkness. To evaluate further the circadian organization of τ_{ss} hamsters, the authors assessed the extent of shortening of period as an aftereffect of exposure to light:dark cycles whose period (T) is 91% of τ and the ability of constant light to induce splitting. They find that τ_{ss} hamsters show aftereffects comparable to wild types, indicating that normal CK1ε activity is not required for T cycles to shorten τ. This finding also contradicts the proposal that circadian period is homeostatically conserved. However, the authors find that τ_{ss} hamsters rarely show splitting in constant light. Furthermore, LL does not induce lengthening of τ or reduction of activity duration (α) in these mutants. The authors' findings support the conclusion that the τ mutation alters the coupling between constituent circadian oscillators.

Key words   circadian aftereffect, splitting, *tau* mutant hamster, circadian period, casein kinase 1ε

The *tau* mutation in Syrian hamsters, which results in a striking change in entrained phase angle and a dramatic reduction of free-running period (Ralph and Menaker, 1988), has proven useful in a variety of circadian studies. It was essential in neurotransplantation experiments that established the physiological role of the SCN as a master pacemaker (Ralph et al., 1990). Subsequent work established that the *tau* mutant phenotype arises from a single base change in *casein kinase 1ε* that alters enzymatic activity (Lowrey et al., 2000). The effects of mutation of CK1ε are substrate-dependent, and the role of this and other kinases remains to be fully established (Iitaka et al., 2005; Gallego et al., 2006a; Merrow et al., 2006; Vanselow et al., 2006; Yin et al., 2006; Xu et al., 2007). Nevertheless, the discovery that the *tau* mutant is a phenocopy of *Drosophila double time* first established the importance of phosphorylation of clock gene products in determination of circadian period in a mammal. Finally, the discovery that *tau* mutant (τ_{ss}) hamsters show a high amplitude (type 0) phase response curve after several weeks of exposure to DD (Shimomura and Menaker, 1994) suggested that the circadian system is differently organized in these animals.

Although modeling approaches have been used to investigate the nature of circadian organization in τ_{ss} hamsters (Oda et al., 2000; Oda and Friesen, 2002), their susceptibility to splitting and aftereffects has not been studied. The classical observation that constant light can induce dissociation of free-running locomotor

rhythms into 2 components that exhibit different periods before coupling in antiphase was fundamental to the realization that the circadian system is composed of multiple oscillators (Pittendrigh and Daan, 1976b). In this formulation, the pacemaker is composed of 2 populations of cells, one of which is normally phase-locked to dusk and the other to dawn (the evening, E, and morning, M, oscillators, respectively; Daan and Berde, 1978). If coupling of circadian oscillators is affected by the *tau* mutation, the incidence or latency of splitting should be affected.

tau mutant hamsters may also prove useful in addressing the question of the molecular basis of oscillator plasticity. Pittendrigh and Daan (1976a) also described long-lasting reductions and increases in period following entrainment of hamsters and mice to T cycles whose durations were shorter and longer than τ, respectively. The observation that changes in CK1ε activity which lead to hypo- or hyperphosphorylation of clock proteins can alter τ led us to hypothesize that effects of T cycles and photoperiod on activity of CK1ε may be responsible for such aftereffects. The specific direction and degree of the change in τ that may result from modulation of CK1ε expression or activity would depend upon the impact of such changes on phosphorylation of particular clock protein substrates. In any such case, however, we would expect that τ_{ss} mutant hamsters would show changes in the magnitude of aftereffects induced by T cycle exposure. Study of the magnitude of aftereffects in τ_{ss} hamsters also affords an opportunity to test the idea (Pittendrigh and Caldarola, 1973) that circadian period is confined to a limited range by homeostatic processes.

MATERIALS AND METHODS

Wild-type and τ_{ss} hamsters were born and raised in 14L:10D. They were placed as adults in plastic tubs with *ad libitum* access to food, water, and running wheels (17 cm diameter). Locomotor activity was continuously monitored, and period was determined by linear regression and chi-square periodogram using ClockLab software (Actimetrics, Evanston, IL). Light was provided by GE F34 CW-RS-WM 34W tubes (intensity approximately 3.2 mmol/m^{-2}/sec at cage level). All experiments were approved by the Animal Care and Use Committee of the University of Massachusetts, Amherst, and the procedures conform to all U.S. federal animal welfare requirements.

Experiment 1: Aftereffects

Animals were placed in DD for assessment of baseline period (τ_1) of locomotor activity for at least 2 weeks. Wild-type and heterozygote (τ_s) animals were then transferred to 10L:14D photoperiods. A group of 6 τ_s control hamsters was maintained on this T24 cycle as a control for effects of aging on free-running period. One group of experimental wild-type hamsters was transferred from DD to 10L:12D and remained in this photoperiod for 8 to 10 weeks. Several of the hamsters in this group exhibited relative coordination. To maximize chances of stable entrainment to short T cycles, a 2nd group of wild-type animals was transferred from DD to 10L:14D, after which T was decreased by 30 min by shortening the dark phase at approximately 2-week intervals over the next 8 weeks by adjustment of Eagle flexopulse timers until a photoperiod of T22 was reached. In both groups of experimental wild-type hamsters, the final T22 zeitgeber period represented an average value of 91% of the free-running period during the preceding (baseline) DD exposure. In each case, the final T cycle was maintained for 3 weeks before animals were returned to DD.

Homozygous *tau* mutants (τ_{ss}) were transferred from DD to a T cycle of 9L:9D, which was maintained for 4 weeks. The T value of this cycle was an average of 91% of the baseline period (τ_1). Our intent was to achieve a comparable proportionate shortening of T relative to τ in the wild-type and τ_{ss} groups. These animals were then returned to DD and τ_2 was measured by linear regression of activity onsets over the final 14 free-running cycles of the experiment.

Aftereffects were statistically evaluated by paired 1-tailed *t* test within each genotype. The percentage by which period shortened (τ_1/τ_2) in each genotype was evaluated by 2-tailed *t* test for independent samples.

Experiment 2: Splitting

Adult wild-type ($n = 10$) and τ_{ss} ($n = 9$) hamsters were transferred from 14L:10D to LL and given access to running wheels. The occurrence and latency of splitting was objectively determined from chi-square periodogram analysis. Estimates of α (from linear regression of activity onset and offset in actograms) and τ assessment were performed on successive 10-cycle epochs over the course of 9 weeks following transfer to LL. Effects of the mutation on group means were evaluated by paired *t* test.
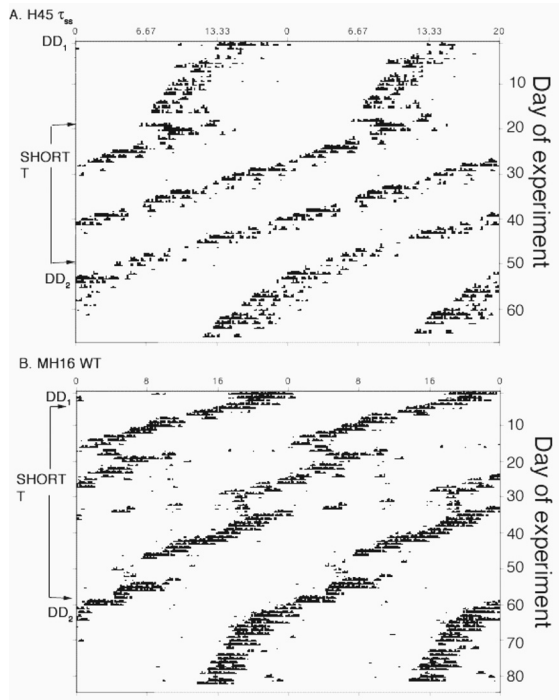
Figure 1. Representative locomotor activity records in a τ_{ss} (*A*, plotted modulo 20 h) and a wild-type (*B*, plotted modulo 24 h) hamster exposed to short T cycles in experiment 1. Intervals over which hamsters were exposed to T cycles whose duration was 91% of τ_1 (Short T) are indicated by arrows. The periods of these light cycles were 18 h in (*A*) and 22 h in (*B*). Note that the *tau* mutant hamster remained stably entrained, while the wild-type hamster broke entrainment on 3 occasions.

Figure 2. Circadian period (τ, in hours, mean ± SEM) of τ_{ss} and wild-type (WT) hamsters before (pre) and after (post) several weeks of exposure to T cycles whose duration was 91% of the mean baseline free-running period. Hamsters in the group that experienced gradual shortening (far right) were entrained to T cycles in which the duration of the dark phase was reduced by 30 min every 2 weeks. This reduced the incidence of relative coordination but did not influence the magnitude of the aftereffect. Regardless of genotype and method of shortening T (gradual vs. abrupt), τ_2 was significantly reduced ($p < 0.02$) in each of the "post" groups when compared with τ_1.

RESULTS

Experiment 1: Aftereffects

The initial free-running periods (mean ± SEM) of wild-type hamsters during initial maintenance in DD (τ_1) was 24.07 ± 0.05 h. Subsequent to maintenance in T cycles whose period was 91% of τ_1, these hamsters exhibited statistically significant aftereffects (τ_2 = 23.66 ± 0.06 h; Figs. 1 and 2). This aftereffect represented a free-running period of 98.3 ± 0.3% of baseline (τ_1). Each of these wild-type animals broke entrainment 2 or 3 times during the interval of exposure to the T22 cycle to which they had been abruptly transferred. To determine whether this affected induction of aftereffects, a 2nd group of wild-type hamsters was subjected to gradual shortening of T through adjustments of the LD cycle every 2 weeks. As expected, this reduced the incidence of relative coordination to 1 episode in most animals. Nevertheless, the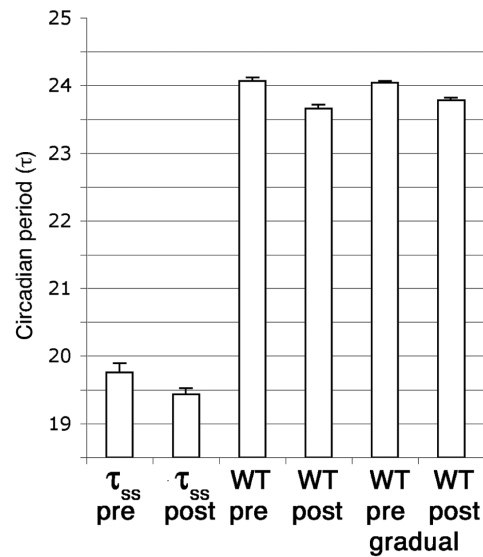 magnitude of the aftereffect was unaffected: free-running period shortened from 24.04 ± 0.03 to 23.78 ± 0.04. This statistically significant change ($p = 0.001$) represented a shortening of τ to 98.9% of the initial value.

In contrast, τ_{ss} hamsters exhibited initial free-running periods of 19.76 ± 0.14 h. They maintained a stable phase angle after abrupt transfer to the 9L:9D cycle, with only 1 instance of relative coordination among 7 animals. Mutant hamsters showed statistically significant ($p = 0.02$) aftereffects that were proportionally similar to those of wild-type animals: after return to DD, the final free-running period (τ_2) of τ_{ss} hamsters was 19.43 ± 0.09 h, which was 98.3% ± 0.6% of baseline. The percentage by which τ shortened after exposure to T cycles whose length was 91% of the initial free-running period did not differ between wild-type and τ_{ss} hamsters ($p = 0.96$).

τ_s hamsters maintained on T24 experienced a small lengthening of free-running period (τ_1 = 22.29 ± 0.13, τ_2 = 22.46 ± 0.10h). τ_s hamsters exposed to T22 exhibited a slight shortening (τ_1 = 22.29 ± 0.17, τ_2 = 21.94 ± 0.96 h; $p = 0.03$ for both groups, 1-tailed t test).

Table 1. Characteristics of Splitting in Wild-Type and *tau* Mutant Hamsters, as Estimated by Chi-Square Periodogram, on Days 90 through 120 of LL

Genotype	Proportion Splitting	τ_1	Amp_1	χ^2_1	τ_2	Amp_2	χ^2_2
WT	9/10	12.60 ± 0.44	298.58 ± 154.47	119.69 ± 3.30	24.15 ± 0.03	760.6 ± 166.86	202.9 ± 0.29
τ_{ss}	3/9	11.98 ± 1.15	78.5 ± 26.56	114.67 ± 8.65	19.51 ± 0.18	367.14 ± 0.89	169.86 ± 1.22

Values are mean ± SEM. Mean τ_1, amplitude$_1$, and χ^2_1 values are given only for those individuals that showed statistically significant power at a subharmonic of the fundamental circadian period.

Experiment 2: Splitting

Chi-square periodogram analysis confirmed the conclusion from visual inspection that splitting occurred in 9 of the 10 wild-type hamsters that were transferred from 14L:10D to LL for 9 weeks, but only in 3 of 9 τ_{ss} hamsters (Table 1).

Tau consistently lengthened through the duration of LL exposure in wild-type hamsters, showing a highly significant increase over the course of the experiment (from 24.03 ± 0.02 to 24.51 ± 0.08 h, $p < 0.001$; Fig. 3). In contrast, τ actually *shortened* in τ_{ss} animals, changing from 20.43 ± 0.14 to 19.80 ± 0.18 h, $p = 0.01$; Fig. 3). Alpha (proposed to reflect the phase relationship between constituent circadian oscillators) decreased over the interval of exposure to LL in the wild-type hamsters (from 6.21 ± 0.54 to 2.94 ± 0.68 h, $p = 0.001$). There was no consistent or statistically significant change in α over the same interval in τ_{ss} hamsters (2.59 ± 0.71 vs. 2.64 ± 0.87; $p > 0.4$; Fig. 4).

DISCUSSION

The present results indicate that although the *tau* mutation does not interfere with the generation of aftereffects of T cycles, it profoundly influences splitting in constant light. These findings extend the usefulness of τ_{ss} mutants in understanding circadian organization.

The circadian pacemaker is plastic: endogenous period is altered by long-term entrainment to extreme photoperiods or T cycles (Pittendrigh and Daan, 1976a, 1976b). The molecular basis of this phenomenon, and the limits to which τ may be driven, are unknown. Upon surveying the literature in finches, mice, and humans, Pittendrigh and Caldarola (1973) concluded that individuals with longer circadian periods show smaller lengthening of τ in response to light, stress, or electrostatic fields. In experiments on cockroaches, they found that exposure to higher temperatures, which lengthens τ, reduces effect of D_2O to increase period. Furthermore, they found that the
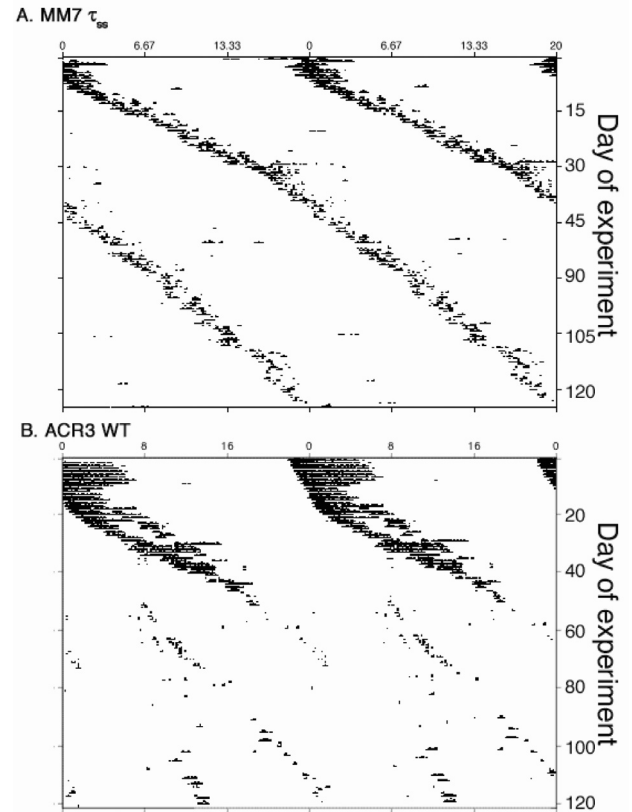

Figure 3. Actograms of representative τ_{ss} (*A*, *top*, plotted modulo 20 h) and wild-type (*B*, *bottom*, plotted modulo 24 h) hamsters following transfer to LL. Note that splitting occurred in the wild-type (WT) but not the mutant animal. Furthermore, τ gradually lengthened in the WT animal and alpha decreased prior to the split. No such changes were observed in the τ_{ss} hamster.

individuals with longest τ show smallest standard deviation of period values. This led them to suggest that τ has an upper limit and that period is homeostatically conserved within a certain range. In testing this idea in hamsters, Fitzgerald et al. (1978) found that lengthening of τ by exposure to LL did *not* reduce the effect of D_2O to further increase circadian period. Thus, the idea of an upper limit on circadian period is controversial. The finding of Oklejewicz et al. (2000)
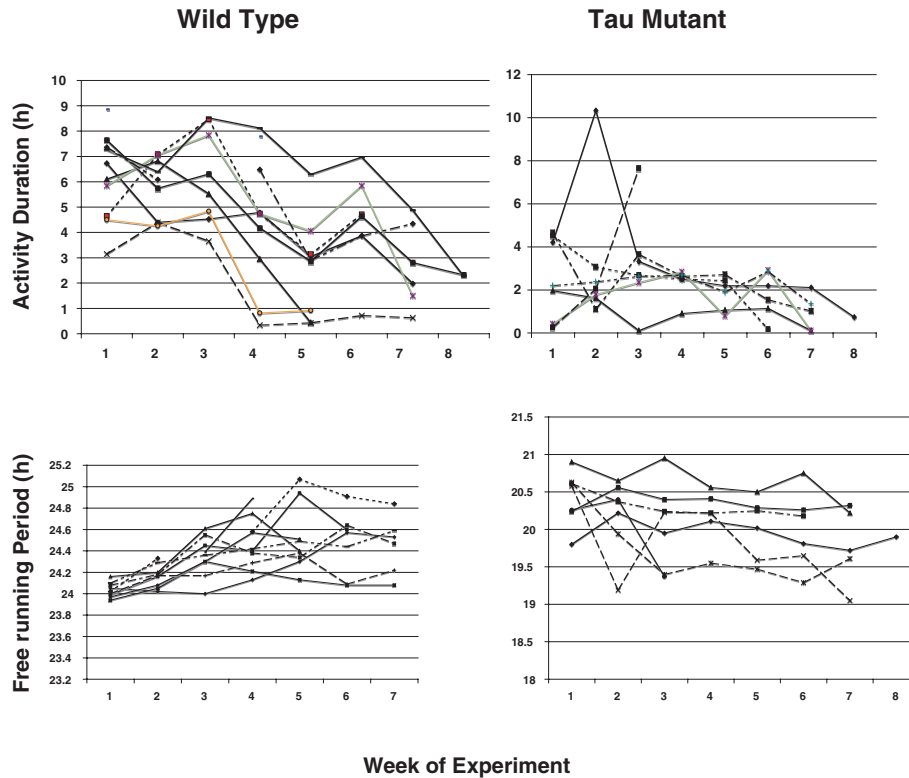
Figure 4. Effects of LL exposure on alpha (in hours, *top*) and tau (in hours, *bottom*) in individual wild-type (*left*) and τ_{ss} (*right*) hamsters. Each line represents values over successive 10-day intervals in a single animal.

that the magnitude of this effect of heavy water was comparable in wild-type and τ_{ss} hamsters also suggests that the plasticity of circadian period is not dependent upon its baseline value. The idea of a limit on the *minimal* value of τ has not been tested. According to the logic of Pittendrigh and Caldorola (1973), hamsters whose circadian period is shortened by the τ mutation might be expected to experience proportionately smaller aftereffects than wild types as a limit of the rate at which feedback loops that set circadian period run is approached. Our finding that τ_{ss} and wild-type hamsters experience similar shortening of τ after entrainment to T cycles whose length is 91% of endogenous period is inconsistent with the conclusion that homeostatic mechanisms limit the degree to which circadian period can shorten.

The factors that determine the upper and lower limits of circadian period are not known. Up- or down-regulation of the expression of any of several genes that control circadian period may contribute to aftereffects. Gallego et al. (2006a) argue that CK1ε*tau* is a gain of function mutation with respect to phosphorylation and degradation of PER1 and PER2, but a loss of function mutation with respect to BMAL1 phosphorylation. The

observation that the *tau* mutation in hamsters, which results in free-running periods of 20 h, is attributable to altered activity of CK1ε led us to hypothesize that this enzyme participates in the generation or maintenance of aftereffects. If this hypothesis is correct, the ability of short T cycles to reduce τ should be altered in τ_{ss} hamsters, and induction of aftereffects should be accompanied by changes in kinase activity. Our finding that these mutants experience a degree of shortening of τ after entrainment to short T cycles that is comparable to wild types indicates not only that normal CK1ε activity is not necessary for such aftereffects, but also that the mechanism for their induction is undisturbed by changes in CK1ε that dramatically alter the baseline period. It is possible that entrainment to T cycles alters autophosphorylation of CK1ε to change its activity in a way that contributes to aftereffects, and that the mutant form of the enzyme is equally subject to such changes so that τ values change proportionately around the lower baseline. We cannot rule out the possibility that other kinases and/or phosphatases can determine τ and that their regulation contributes to aftereffects (Gallego et al., 2006a; Gallego et al., 2006b; Iitaka et al., 2005; Merrow et al., 2006; Vanselow et al.,

2006; Yin et al., 2006). In addition to phosphorylation, numerous other posttranslational events (e.g., ubiquity-lation, nuclear-cytoplasmic shuttling; Cardone et al., 2005; Kwon et al., 2006) may be regulated by T and con-tribute to aftereffects. It is also possible that aftereffects result from interactions between autonomous oscilla-tors and are thus a network property that is unaffected by changes of period within individual cells among a population. It would be useful to determine the range of τ values in individual SCN neurons in wild-type vs. τ_{ss} hamsters, as this might provide insight into the cou-pling strength, amplitude, and range of entrainment.

We observed that τ_{ss} hamsters showed much less rel-ative coordination upon abrupt transfer to T cycles whose duration was 91% of their endogenous period than did wild-type animals subjected to a comparable transition. Since the amplitude of the PRC is believed to dictate the range of entrainment, this observation could suggest that τ_{ss} hamsters have a higher ampli-tude PRC under entrained conditions. This is not consistent with the observations of Shimomura and col-leagues (Shimomura and Menaker, 1994; Shimomura et al., 1998), who found that the amplitude of the PRC increases in τ_{ss} hamsters relative to wild types only after several weeks of exposure to DD. This indication that τ_{ss} hamsters have a greater range of entrainment merits further exploration by examining locomotor activity over a wider range of T cycles.

Pittendrigh and Daan (1976b) argued that splitting reflects a change in the coupling state of E and M oscil-lators, in which transient decoupling is followed by establishment of a stable antiphase relationship. Although anatomical data indicating LL-induced split-ting reflects lateralization of pacemaker function (de la Iglesia et al., 2000) has raised questions about the orig-inal E-M dual oscillator model, reciprocal coupling of constituent circadian oscillators is also indicated by responses of hamsters to LDLD cycles (Gorman and Steele, 2006). Oda and Friesen (2002) proposed that τ_{ss} and wild-type hamsters differ in the amplitude of their circadian oscillators and in the coupling between the morning and evening oscillators. They argue that cou-pling strength decreases in τ_{ss} hamsters but not wild-type hamsters with duration of DD exposure. It was proposed that this change explained differences in PRC between the 2 hamster genotypes after prolonged exposure to DD.

Our 2nd experiment was designed to examine the circadian organization of τ_{ss} hamsters by comparing the time course of splitting with that of wild-type hamsters that were released into LL after entrainment to T24. We reasoned that if τ_{ss} hamsters are prone to weaker coupling of constituent oscillators, splitting might occur earlier after transfer to LL. Surprisingly, τ did not lengthen in LL among τ_{ss} hamsters as it did in wild types. This contradicts the observation (Johnson, 1939), subsequently formalized as Aschoff's rule (Aschoff, 1960), which stipulates that circadian period lengthens in nocturnal animals as the intensity of con-stant light increases. This reinforces the doubts raised by our 1st experiment concerning the concept of a homeostatic limit on τ, in that such a mechanism would predict a greater lengthening of circadian period in ani-mals that start with a shorter τ. We did not expect to find that α would fail to shorten in τ_{ss} hamsters exposed to LL, as it does in wild types. Our experiments allowed further tests of the proposition of Pittendrigh and Daan (1976b), Daan and Berde (1978), and Oda and Friesen (2002) that α and interoscillator coupling strength are inversely correlated. The Oda simulations were based on effects of prolonged DD on the phase-shifting behav-ior of τ_{ss} hamsters; our findings suggest that they also have predictive validity for hamsters exposed to LL.

Although we expected a low value of α in the more tightly coupled (non-split) τ_{ss} than in the wild-type hamsters, we did not anticipate that α would be so much shorter after transfer to LL. Interdependence of τ and α was cited by Pittendrigh and Daan (1976b) as a feature of Aschoff's rule, and this has been incorporated in subsequent models (Daan and Berde, 1978; Oda et al., 2000). Our finding that both τ and α remain stable over many weeks in τ_{ss} hamsters maintained in LL (Figs. 3 and 4), and that these mutants fail to split, provides empirical confirmation of this interdependence. Our observations indicate that the coupling of circadian oscillators is dependent upon CK1ε activity. However, we cannot exclude the alternative possibility that the impact of constant light on alpha and the persistence of unsplit rhythms in τ_{ss} hamsters is independent of the effects of the mutation. For example, it is conceivable that the mutation of CK1ε alters α through an influence on the turnover or translocation of clock proteins within SCN cells but retards splitting through some effect on communication between cell populations within the SCN (Yan et al., 2005). Furthermore, the failure of circa-dian locomotor patterns of τ_{ss} hamsters to split in LL may be attributable, at least in part, to their short circa-dian period, irrespective of its genetic basis. This could be tested by transferring wild-type hamsters showing aftereffects of entrainment to T22 to LL: Perhaps all ani-mals with short periods show an increased latency of splitting.

In conclusion, analysis of the response of τ_{ss} hamsters to short T cycles and constant light extends their use in understanding circadian organization. Our results indicate that the capacity of circadian period to be shortened through aftereffects is not homeostatically limited and that modulation of CK1ε activity is not likely to be a necessary step in this phenomenon. Furthermore, the short α and failure of splitting to occur in τ_{ss} hamsters exposed to LL are consistent with the hypothesis that period shortening arising from this CK1ε mutation is accompanied by increased oscillator coupling.

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