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REVIEW

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Diurnal mice (*Mus musculus*) and other examples of temporal niche switching

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Abstract Examples are presented of nocturnal animals becoming diurnal or vice versa as a result of mutations, genetic manipulations, or brain lesions. Understanding these cases could give insight into mechanisms employed when switches of temporal niche occur as part of the life cycle, or in response to circumstances such as availability of food. A two-process account of niche switching is advocated, involving both a change in clock-controlled outputs and a change in the direct response to light (i.e. masking). An emerging theme from this review is the suggestion that retinal inputs have a greater role in switching than suspected previously.

Keywords Diurnal · Masking · Melanopsin · Nocturnal · Rhythms

Abbreviations EGFr: Epidermal growth factor receptor · DD: Constant darkness · LD: Light-dark · SCN: Suprachiasmatic nucleus · vSPZ: Ventral Subparaventricular zone

Introduction

It is generally accepted that one of the reasons for the evolution of circadian rhythms is to confine animals to the temporal niches of night or day, and so allow them to specialise physiologically and otherwise in that niche. In this paper, we review examples of unusual switching of rhythms of activity from the dark to the light phase of a light–dark (LD) cycle, or vice versa. It is already well known that many species are not rigidly confined to being active by day or by night and can adjust their rhythms according to the circumstances. Among stimuli producing these effects are food availability, temperature, social pressures, seasonal cues and developmental changes (reviews in Reebs 2002; Mrosovsky 2003). But the examples of temporal niche switching exhibited in the present paper are not precipitated by such events. Rather they are cases that occur after physiological or molecular manipulations involving sensory input from photoreceptors. As such they may give some insight into the mechanisms of temporal niche switching. At the least they will have to be explained by any mechanistic account of this phenomenon.

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Exhibit 1. Rats with hypothalamic lesions

Richter (1978) found that severing of connections between the optic chiasm and the hypothalamus of rats could result in them becoming active in the light (Fig 1). Unfortunately, his lesions were not characterised in detail. Most often they included but were not confined to the suprachiasmatic nucleus (SCN). The extent of optic tract damage is not clear. Moreover, although in the examples shown there was more activity in the light than in the dark after the lesion, the interpretation of this as a switch from a nocturnal to diurnal state is debatable because even prior to the lesion there was a tendency for the rats to display some wheel running in the daytime. Richter suggested that this was a response to the daytime presence of personnel and disturbance within the animal room, and possibly also to noise from outside. He pointed out that his rats were wild, and especially sensitive to noise. Therefore, it is possible that the damage to the SCN decreased the amount of clock-controlled activity, as is common with lesions in this area, and as a result, activity in the night was diminished. If noise-induced activity was spared by the lesion

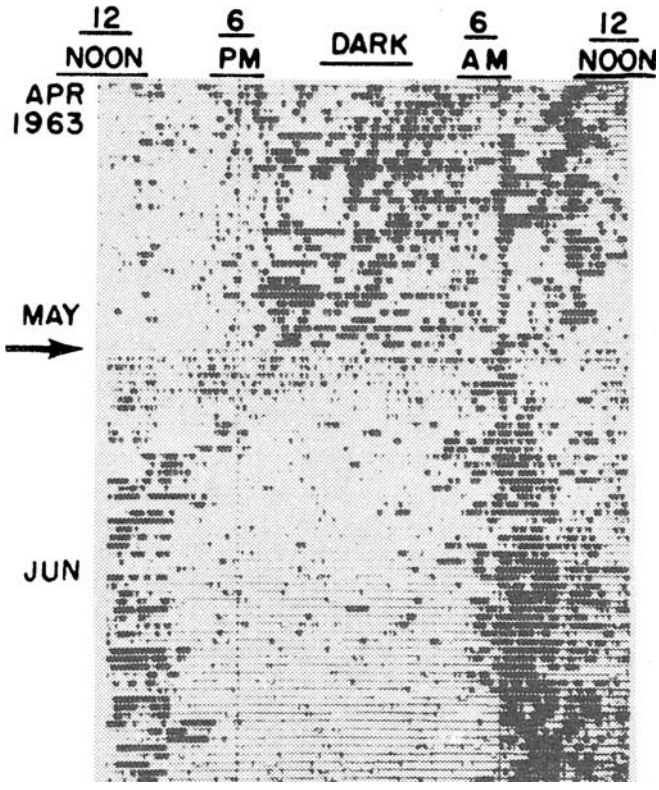

Fig. 1 Actogram of wheel running of a wild rat kept in LD 12:12 h (dark from 6.00am–6.00pm). *Arrow* marks day of cut between the optic chiasm and the hypothalamus (from Richter 1978)

in these wild rats, then the daytime activity would remain, contrasting with the reduced nighttime activity. This would give the appearance of the lesion transforming the rat into a light-active animal.

Despite such uncertainties about the interpretation of these findings, it is historically appropriate to mention this work first here. Richter reported what appears to be a "remarkable and unexpected result". Moreover, he obtained what he called inverted patterns of activity in 63 out of a total of 264 rats lesioned by different methods. That is frequent enough to make it feasible to follow-up these observations.

Exhibit 2. Mice lacking cryptochromes

Cryptochromes are flavin-based pigments found in the inner retina in mammals (Miyamoto and Sancar 1998). Two out of six *mCry1*$^{-/-}$ *mCry2*$^{-/-}$ mice showed a preference for being active in the day phase of LD 12:12 (Van Gelder et al. 2002). In one case, this behaviour occurred on transfer from continuous darkness (DD) to the LD cycle. In the other case, it appeared when a 12:12 h LD cycle was reversed (Fig 2); moreover, when the LD cycle was restored, this mouse maintained a preference for daytime running, although by this stage of the experiment this animal was rather inactive altogether. In subsequent testing, preference for diurnal

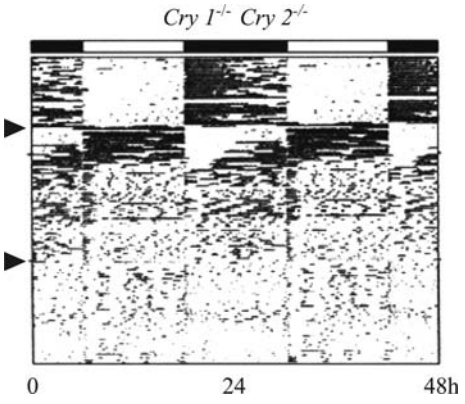

Fig. 2 Double plotted actogram of a *mCry1*$^{-/-}$ *mCry2*$^{-/-}$ mouse showing diurnality of wheel running after a reversal of a 12:12 h LD cycle (*upper arrow*), and maintenance of diurnality after restoration of the original LD cycle (*lower arrow*). *Open and solid bars* at the top show the original and final LD cycle (from Van Gelder et al. 2002)

activity was observed in 4 of 12 animals (Van Gelder et al. 2002); therefore, in total 6 of 18 showed this behaviour at some time or another. Perhaps differences in modifier genes in the mixed background of these mice (a hybrid of 129 and B6 strains) accounts for the phenomenon being evident in only about a third of individuals.

Exhibit 3. Melanopsin knockout mice

A number of instances of unusual amounts of daytime locomotion have been seen in mice lacking melanopsin (*Opn4*$^{-/-}$, also called *mop*$^{-/-}$). The first indication we obtained was in an experiment on masking, that is, on the direct acute response to light, as opposed to the clock-resetting effect of light (Appendix 1). One out of ten melanopsin knockout mice (given as $n = 12$ in error in Mrosovsky and Hattar 2003) started wheel running several hours before dark onset (Fig 3). Since this animal did not show reliable locomotor activity at night, the time when light pulses were given, it could not provide valid data on suppression of nocturnal locomotion by light pulses. It was simply noted that all data from this animal were excluded because its activity at night was too erratic. But really it was more interesting than this. Not only did most of the wheel running of this exceptional mouse occur in the day, but at dark onset, there was often a sharp drop in activity (Fig 3). As the experiments continued, these features became more pronounced. Onset of wheel running occurred earlier in the day, and at dark onset activity ceased altogether (Fig 4). But when 3-h pulses of light were given in the dark, unlike the nocturnal mice that decreased locomotion, this diurnal mouse increased its activity (Fig 4). In a nocturnal species, increased activity when illumination increases is called paradoxical positive masking (Appendix 1). Although modest increases in activity

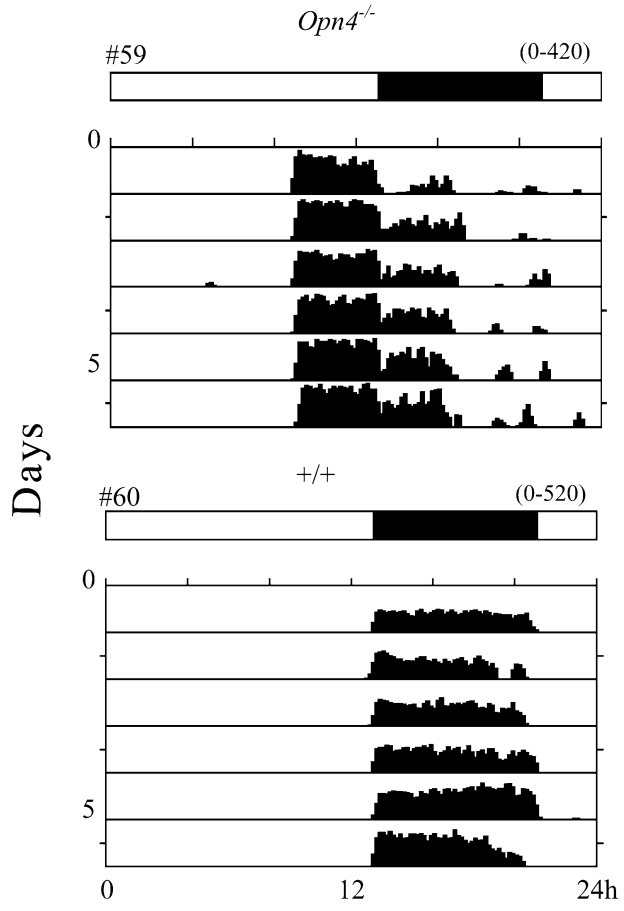

Fig 3 Actogram of wheel running of a melanopsin knockout and a wild-type mouse. *Open and solid bar* shows 16:8 h LD cycle. *Numbers in brackets* show scale for the range of activity on y axis: *absence of solid marks* at a given time indicates that no wheel revolutions occurred in that 10-min bin, highest extent of dark marks indicate that amount in that 10-min bin was equal to the higher value of the range shown in brackets. Actograms were made with ClockLab (Actimetrics, Evanston, Ill). Recording periods shown are from early in the experiment, before the introduction of 1-h light pulses (see Mrosovsky and Hattar 2003 for detailed methods)

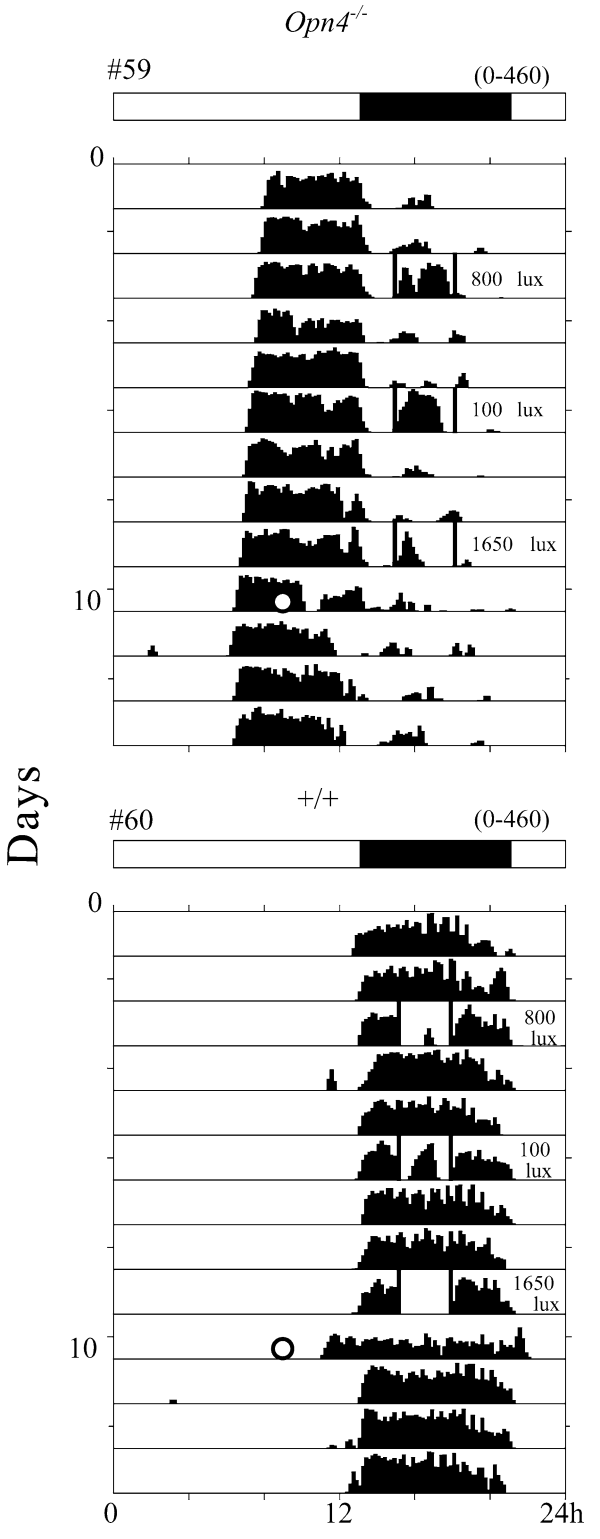

Fig 4 Actograms for days including the tests with 3-h light pulses (time between short vertical lines). Methods for 3-h pulses in Mrosovsky and Hattar (2003). *Open circles* denote cage changes. Other conventions same as in Fig 3. The diurnal melanopsin knockout animal (*top*) and the wild type (*bottom*) differ not only in the phasing of their wheel running with respect to the LD cycle but also in the direction of their masking response to the light pulses. The melanopsin knockout shows positive masking, the wild type shows negative masking

compared to that in dark are common in mice during pulses of dim light, 1 to 0.01 lux (Mrosovsky et al. 1999; Appendix 1), increases in activity during light pulses of 100–1,000 lux are remarkable for a mouse.

After the tests with pulses of light in the night were completed, these animals were placed in a 3.5:3.5-h LD cycle (Table 1). This cycle has been developed as a test for masking that eliminates or greatly attenuates confounding factors from entraining effects of light, because mice and hamsters cannot normally entrain to this cycle, or to multiples of this cycle such as 21 and 28 h (Redlin and Mrosovsky 1999). It was found that only 29.8% of the wheel running of the exceptional mouse took place in the dark phases of the 3.5:3.5-h cycle, whereas, for wild-type mice with this hybrid background 97.8% ± 0.7 SEM ($n = 12$) of the activity took place in the dark phases, as might be expected with a nocturnal species. Thus, the exceptional mouse exhibited diurnal behav-

Table 1 Lighting schedules and number of days each prevailed

LD cycle	Days	Figure
Melanopsin knockout and wild-type mice		
16:8	36[a]	Fig 3
16:8, 1-h light pulses	42[a]	
DD	2[a]	
16:8	14	
16:8, 3-h light pulses	7[a]	Fig 4
16:8	5	
3.5:3.5	14[a]	
12:12 800 lux	24	Figs. 5, 6
12:12 1.5 lux	25	Figs. 5, 6
12:12 800 lux	7	Figs. 5, 6
12:12 .04 lux	50	Figs. 5, 6
DD	3	Figs. 5, 6
Melanopsinless-rodless mice and triple heterozygotes		
16:8	23[b, c]	
3.5:3.5	19[b, c]	
16:8	13	Fig 8
DD	3	Fig 8
Melanopsinless-rodless and melanopsin knockouts (animals from the end of the two experiments above)		
16:8	124	Fig 8
16:8 advanced by 8 h	49	Fig 9

Figure number denotes an illustration in the present paper of this part of the experiment. Age of melanopsin knockouts and wild types at start of experiments listed was 21.5 ± 4 weeks. Age of melanopsinless-rodless was 9.6 ± 5 weeks, and of triple heterozygous was 24 ± 14 weeks
[a]Details and results in Mrosovsky and Hattar (2003)
[b]Details and results in Hattar et al. (2003)
[c]A few additional days after those used in tests in Hattar et al. (2003)

iour both in an LD 16:8 h cycle and on the special masking test with the ultradian 3.5:3.5-h LD cycle.

For the other nine melanopsin knockouts, 75.3% ± 5.2 SEM of their running occurred in the dark phase, consistent with them being nocturnal on LD 16:8 h, but having an impaired masking response to light pulses (Mrosovsky and Hattar 2003). However, one of these animals, although nocturnal on the LD 3.5:3.5 h cycle, was only barely so with 55.0% of its activity in the dark. It was therefore not so surprising in retrospect that when back on an LD cycle, after the experiments reported by Mrosovsky and Hattar (2003) were finished, this mouse developed a pattern of running with a greatly advanced phase angle and much of its activity in the light. Whether the experience on the ultradian cycle had actually precipitated this change, or whether it simply had occurred after that time, cannot be said.

An alternative interpretation of the activity patterns of these two mice should perhaps be considered. Although more than half of the wheel running occurred in the light for the days shown in Fig 3, this pattern could perhaps be thought of as nocturnal with a strongly positive phase angle, possibly resulting from being on a schedule with only 8 h of darkness, or from unusually short free-running periods. However, there is no evidence that mice lacking melanopsin have particularly short free-running period (Panda et al. 2003; Hattar et al. 2003). Moreover, this interpretation does not account for the lack of nocturnal masking scores on the 3.5:3.5-h cycle. Nor does it account for the decrease in activity when lights go out (Fig 3). For a nocturnal animal, a sharp decrease in activity each day when the lights go out is paradoxical (Appendix 1). So the activity pattern in Fig 3 is certainly unusual for a nocturnal species, with wheel running starting several hours before dark onset and paradoxical suppression of locomotion when the lights do go off.

In further tests (Table 1) on this group of melanopsin knockout mice, not covered in Mrosovsky and Hattar (2003), the animals were kept in LD 12:12 h for varying periods with different levels of illumination in the L phase (see Table 1, Figs. 5, 6). These tests were rounded out with 3 days in continuous darkness (DD).

On LD 12:12 h, the mouse whose initial running pattern is illustrated in Fig 3 was more clearly diurnal, with very little running in the dark (Fig 5). Although its phase angle of entrainment was unstable, the animal was entrained, as revealed by the similarity of its activity onset when put into DD for a few days (Fig 5). The second animal, the one that developed an early phase angle only after the tests on the 3.5:3.5 h cycle, also had a clearly diurnal pattern on LD 12:12 when there was 800 lux in L, but failed to entrain when the light was 1.5 lux or dimmer.

These additional investigations were made to confirm diurnality in these two melanopsin knockout mice, and show that it was not a short-lived aberration. These aims were achieved, but the tests provided some surprises: three other melanopsin knockout mice failed to maintain entrainment on LD 12:12 when the L was only 0.04 lux, but then, after free running with a short tau, realigned their activity with the LD cycle, but with their running predominantly in the day (e.g. Fig 6 left). This realignment presumably reflected the entrainment because the activity onsets in DD were close to those on the LD cycle. The three mice that became diurnal in the dim LD cycle had previous masking scores of 77.6, 57.4 and 84.5%, respectively, on the ultradian 3.5:3:5 h cycle, i.e. although they had run more in the dark on those tests, they were not as nocturnal as the wild types with a mean score of 97.8% in the dark (Fig 7 left).

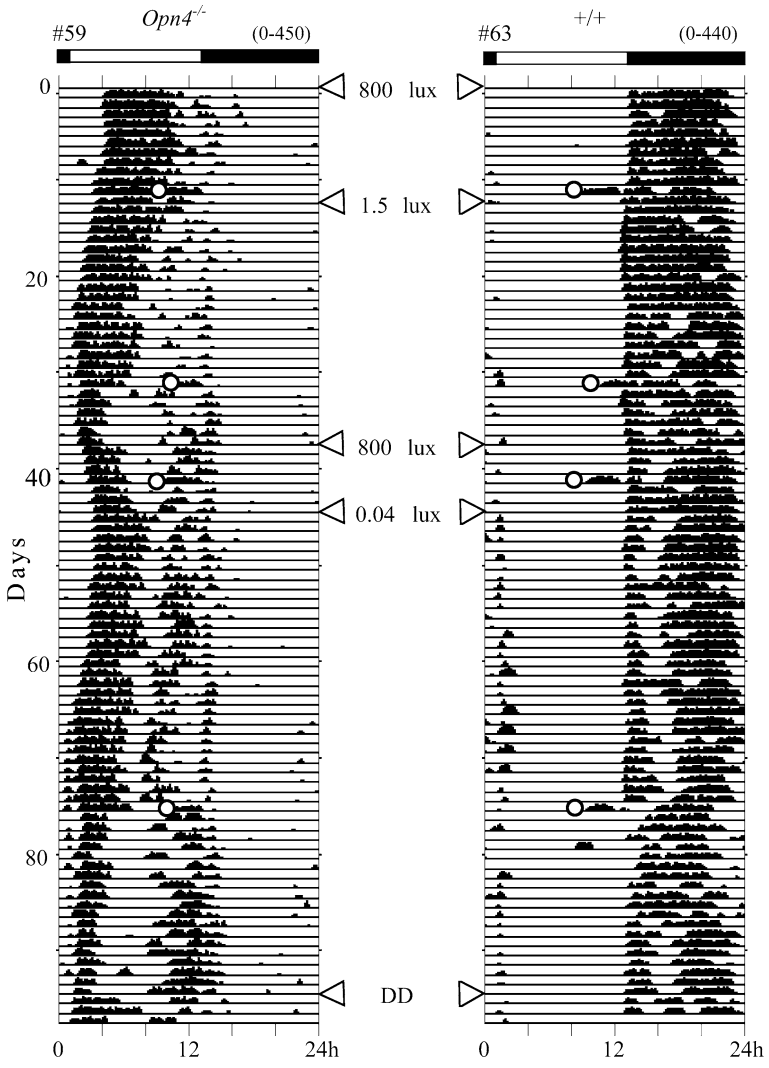

Fig 5 Left: Actogram showing the persistence of diurnality over many days in the melanopsin knockout mouse illustrated in Figs. 3 and 4. *Right*: wheel running of a wild-type mouse is shown for comparison. *Open arrows* show when illumination during the L part of the LD 12:12 h cycle was changed. The *bottom of the actograms* show data for a 3-day test in continuous darkness (DD). Conventions same as in Figs. 3 and 4

Summarising the findings with melanopsin knockouts, a total of 5 of 10 of these mice exhibited periods of diurnality at some stage or another in these investigations. This suggests that lack of melanopsin can predispose to or precipitate diurnality. Although the available evidence suggests that this is probably true, there was one more surprise: one of the 12 wild-type mice also became diurnal (Fig 6 right) after free-running for awhile on LD 12:12 h (0.04 lux in the L), even though it had been highly nocturnal on LD 3.5:3.5 h, with a score of 99.4%. Perhaps in some individuals different backgrounds related to the cross between B6 and 129 mice might modify the reactions to light (see also Hattar et al. 2003).

Exhibit 4. Mice lacking melanopsin and functional rods

Data from these animals have not been published previously. They were six male animals, engineered to knock out both melanopsin ($Opn4^{-/-}$) and rod function by targeted deletion of rod transducin alpha subunit, $Gnat1^{-/-}$ (Calvert et al. 2000; Hattar et al. 2003).

The mice were aged approximately 10 weeks at start of the tests. They were initially studied along with triple knockouts ($Opn4^{-/-}$, $Gnat1^{-/-}$ and $Cnga3^{-/-}$), the latter preventing cone function also, by knocking out cyclic GMP-gated channel-A subunit 3 (Biel et al. 1999; Hattar et al. 2003). Mice triply heterozygous for these genes served as a comparison group ($n=6$). Initially, the animals were kept on LD 16:8 h for 19 days, and then on LD 3.5:3.5 h, with scoring based on the last 7 of 11 days on this cycle (Table 1); some further details are in Hattar et al. (2003).

In three melanopsinless-rodless animals, entrainment status was ambiguous by the end of the 19 days in LD 16:8: they did not entrain fairly rapidly as did the triple heterozygotes (Hattar et al. 2003). Two of the melanopsinless-rodless mice were nocturnal, though one had a positive phase angle of about 4 h. And one animal most definitely ran more in the light (Fig 8). This is the most striking case of a diurnally active common or

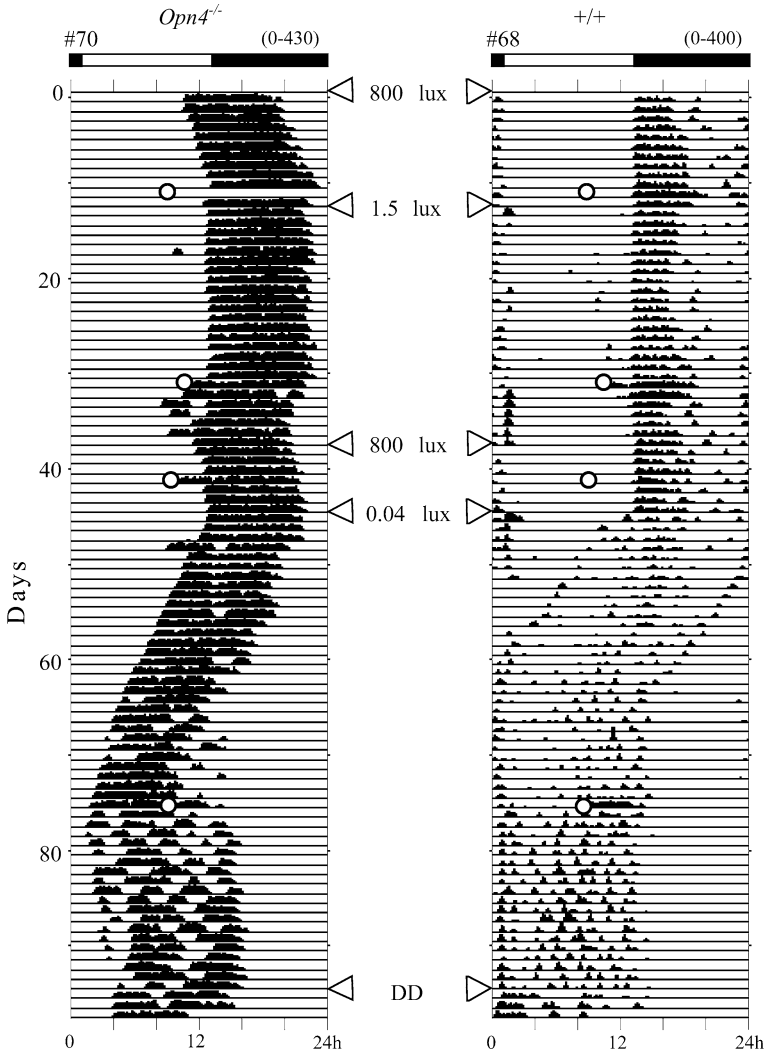

Fig 6 Actograms of melanopsin knockout (*left*) and wild-type mouse (*right*) that failed to maintain entrainment on an LD 12:12 cycle when the light was dim (0.04 lux) but subsequently reentrained as diurnally active animals. Note the continuation of activity during the 3-day test in DD at the end. Conventions same as in Fig 3

house mouse (*Mus musculus*) of which we are aware. On the subsequent 3.5:3.5 h test, this animal made only 15.6% of its wheel turns in the dark, the most diurnal score obtained yet with mice tested in this way, and a further indication that this ultradian cycle is useful for revealing the masking component contributing to diurnality or nocturnality.

Relying then on this cycle for a quantitative summary of nocturnal and diurnal masking responses, Fig 7 plots the percent of running that took place in the dark for all six melanopsinless-rodless individuals and compares those to scores for the triple knockouts and triple heterozygotes tested at the same time. Compared to the 43.2% mean score of triple knockouts, which lack the putative irradiance detector(s) and had scores close to the random level of 50% of activity in dark phases, the mice lacking melanopsin and functional rods showed more diurnality (mean 37.6% of activity in the dark).

However, it may be questioned whether this diurnality can be attributed solely to the melanopsinless-rodless state, because 2 of 6 triple heterozygous mice showed masking scores indicating diurnality (see Hattar et al. 2003); moreover, a two-tailed *t*-test between the scores of the triple heterozygous and the melanopsinless-rodless groups did not quite reach significance ($P = 0.07$, Fig 7).

On the other hand, previous to the ultradian cycle test, the triple heterozygotes had been kept on LD 16:8 h at 800 lux for about 3 weeks (Table 1). None had shown diurnal behaviour then. Even if they had done so, it may be argued that triple heterozygotes are an inappropriate control group for melanopsinless-rodless mice because triple heterozygotes probably also have a deficit in melanopsin. Some evidence in support of this is that in homozygous melanopsin knockout animals having instead two copies of the tau-lacZ marker gene, the expression of tau-β-Galactosidase as revealed by X-gal staining, is stronger than in animals that are heterozygous for melanopsin and the tau-lacZ marker gene (Lucas et al. 2003). Also, in mice that have both rod and cone transduction disabled, the size of pupillary light response depends on whether the melanopsin locus is wild type or heterozygous. These points suggest that melanopsin expression could have

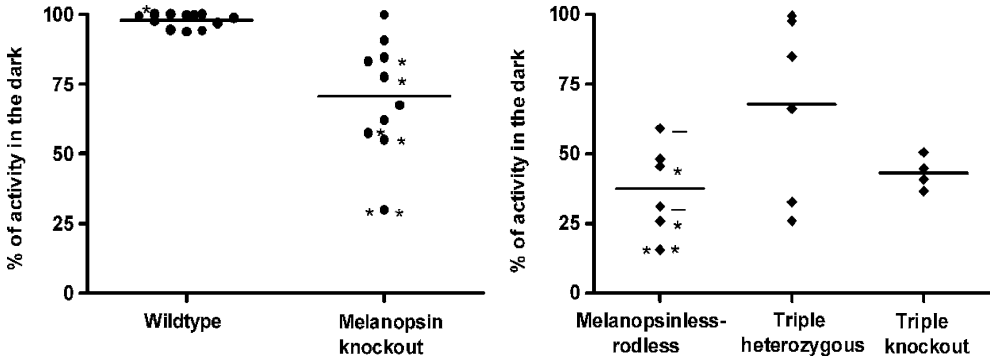

Fig 7 Masking scores (% occurring in the dark out of total wheel running) for individual mice over 7-day durations in a 3.5:3.5 h LD cycle. *Left*, experiment described in Mrosovsky and Hattar (2003). *Right*, experiment described in Hattar et al. (2003). Illumination during L was ca 800 lux in both experiments. *Horizontal lines* are means. *Star on left of point* indicates individual was diurnal when on LD 16:8 h prior to being put on the ultradian cycle; *star on right of point* indicates that it was diurnal at some stage subsequent to having been on the ultradian cycle. *Small horizontal dash at right of point* indicates that both a free-running and a lights-on component of activity were present. None of the triple heterozygous or triple knockouts received additional testing in 16:8 h after the tests on the 3.5:3:5 h LD cycle

been attenuated in the triple heterozygous group (Hattar, unpublished).

A more appropriate comparison group for melanopsinless-rodless mice would probably be wild-type mice. These were not available within the very same experiment, but comparison to another similar experiment strongly suggests that melanopsinless-rodless mice have greater tendencies toward diurnality than wild types (Fig 7), although the latter occasionally may show more activity in the day in very dim LD cycles (Fig 6).

After the tests on the 3.5:3.5-h LD cycle, and a short test in DD, the rodless-melanopsinless mice were returned to LD 16:8 h (ca 800 lux in L) This LD 16:8 cycle was then advanced by 8 h, starting with an advance in dark onset (Fig 9). Four melanopsin knockout mice, two predominantly diurnal, two predominantly nocturnal, were studied along with the melanopsinless-rodless animals. Of the latter, one of six was predominantly nocturnal, albeit with a ca 3-h positive phase angle at times, and two individuals used their wheels mostly in the day, and were considered to be diurnal. Both the nocturnal and the two diurnal animals showed advancing transients when the LD cycle was advanced, indicating entrainment had occurred on the 16:8-h cycle (e.g.

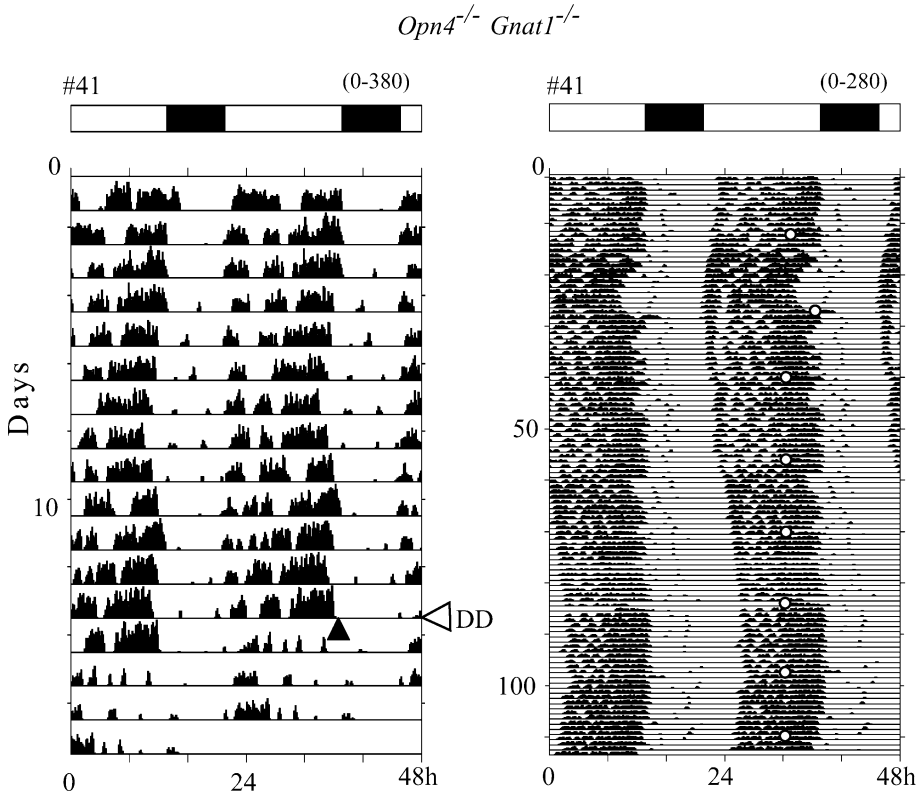

Fig 8 Actogram of mouse lacking both melanopsin and functioning rods. *Left*: data in 16:8 h LD cycle shortly after tests with a 3.5:3.5 h LD cycle, described in Hattar et al. (2003). At bottom are data for 3 days in DD; *open triangle* shows day of start of DD, *solid triangle* shows time of start of DD. Two aspects of diurnality are evident. Activity occurring at roughly the same time in DD as previously in LD indicates entrainment had occurred in LD. The weaker expression of activity in DD indicates that the direction of masking is characteristic of a diurnal animal. Right: persistence of diurnality in the same mouse over many days. Conventions same as Figs. 3 and 4, except that actograms have been double plotted on the *x* axis

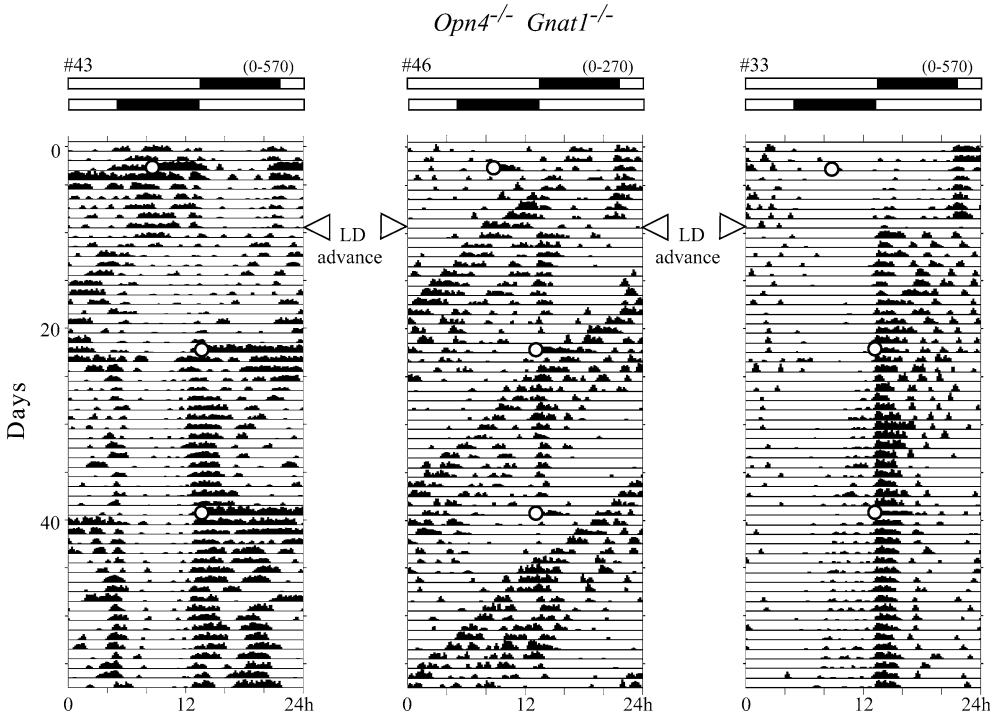

Fig 9 Actograms of 3 mice lacking both melanopsin and functional rods, illustrating varied reactions to a phase advance of the 16:8 h LD cycle. *Upper and lower open and solid bars* show LD cycle before and after the phase advance, respectively. *Left*: a diurnally active mouse that was entrained to the LD cycle both before and after the phase advance. Re-entrainment was not achieved immediately, but after a number of days of advancing transients. *Middle*: a mouse that showed both a free-running component and another occurring at light onset. The free-running component continued after the advance; the light-onset component shifted immediately without transients. In this animal the free-running component was relatively strong. *Right*: another animal with two components, but in this case the free-running component was relatively weak. The light-onset component shifted rapidly, without advancing transients. Conventions same as in Fig 3

Fig 9). Paradoxical masking was not noted in any of these three entrained mice. The other three mice displayed two components of wheel running, one free-running and one occurring at lights on. The strength of the two components varied both within and among animals. Thus, in the records shown in Fig 9 right, the free-running component is relatively weak. In contrast, in Fig 9 middle, it is relatively strong. These two components behaved differently when the LD cycle was advanced. The free-running component continued to free-run: the lights-on component adjusted to the new cycle almost immediately, indicating that it was a masking response to light. This is an example of paradoxical positive masking because there was an increase in activity at lights on in a supposedly nocturnal species (Appendix 1). The four melanopsin knockouts showed normal adjustment to the phase advance with advancing transients and re-establishment of phase angles of entrainment similar to those present before the shift.

Summarising the findings with melanopsinless-rodless animals, as a group they lacked the strong negative masking normally seen in wild-type mice on LD 3.5:3.5 h. When studied subsequently on other LD cycles with periodicities of 24 h, 5 out of 6 mice also showed signs of diurnality on those cycles, either being entrained, or free running with a paradoxical positive masking component at lights on.

Exhibit 5. Vitamin-A depleted mice

Plasma retinol-binding protein knockout mice (*rbd* $^{-/-}$) are unable to synthesize vitamin A. When placed on a vitamin-A deficient diet, retinaldehyde in the eye becomes barely detectable. A few mice in this condition exhibit diurnal locomotor activity, some in light as strong as 500 lux (Thompson et al. 2004). This is consistent with the instances of diurnality reported in previous sections for mice lacking melanopsin, since vitamin-A depletion should at least have impaired the function of melanopsin-containing cells. However, both opsins and flavin based pigments may be involved because on a vitamin-A deficient diet the % of activity occurring in the daytime and the incidence of diurnality were higher in *rbd* $^{-/-}$ mice also lacking cryptochromes (*rbd* $^{-/-}$ *Cry1* $^{-/-}$ *Cry2* $^{-/-}$) than in *rbd* $^{-/-}$ mice (Thompson et al. 2004).

Exhibit 6. Mutant fruit flies

In mutant fruit flies lacking compound eyes (eyes absent *cli*^{eya}, and *sine oculis so*^{1}), some of the entrained individuals—not all such mutants entrain—undertake more of their activity in the night than in the day. Although the tendency is stronger in photoperiods with short days, it is

evident in LD 12:12 h in some individuals (Rieger et al. 2003).

Moreover, in flies without compound eyes, normal masking responses are deficient: the bursts of activity occurring at lights on, and the inhibition of activity at lights off are diminished or absent. In *histidine decarboxylase* (hdc^{JK910}) mutant flies, with dysfunctional compound eyes, at lights off there is a paradoxical increase of activity (Rieger et al. 2003). Paradoxical masking can be manifest in mutants even without entrainment. Decreased activity at lights on and increased activity at lights off occurs in $glass^{60j}$ cry^{b} mutants freerunning in an LD cycle to which they fail to entrain (Helfrich-Förster et al. 2001). Thus, just as in mice the entraining and masking effects of light can be distinguished by using the 3.5:3.5 h cycles to which they do not entrain, so in $glass^{60j}$ cry^{b} flies masking responses, albeit paradoxical, can be obtained in the absence of entrainment to LD cycles. These various findings show that entrainment and masking are separable, different phenomena and can occur in various combinations.

Exhibit 7. Smith-Magenis syndrome

In this rare syndrome occurring in children, melatonin is high in the daytime, and low at night. This is especially remarkable when one recalls that in both nocturnal and diurnal mammals melatonin is high at night. Patients with Smith-Magenis syndrome may suffer from falling asleep in the day, and from bouts of wakefulness in the night, suggesting that the sleep-wake cycle as well as the melatonin rhythm is phased abnormally.

Treatment with a combination of beta blockers in the morning, and melatonin in the evening can be quite successful in normalising these symptoms, making it much easier for the parents (De Leersnyder et al. 2003). Whether or not an underlying rhythm had been rephased is unclear as tests immediately after withdrawal of therapy were not reported. Ophthalmological examination of children with Smith-Magenis syndrome has revealed a variety of defects, sometimes including iris anomalies and retinal detachment (Finucane et al. 1993; Chen et al. 1996).

Discussion

Downstream or upstream from the clock?

All the examples from studies of animals mentioned above involve interference in sensory systems. Even in the case of Richter's experiments, although the retina was not targeted, it is likely that the optic tract and/or retino-hypothalamic fibers were damaged. Sensory control of preferred temporal niche is thought provoking, since a commonly held current view is that differences in phasing between nocturnal and diurnal mammals are not a reflection of differences within the oscillator but rather in some downstream mechanism. This arises from studies of the SCN in diurnal mammals: cycles of metabolic activity (Schwartz et al. 1983), electrical activity (Sato and Kawamura 1984) and gene expression (Mrosovsky et al. 2001; Lincoln et al. 2002; Caldelas et al. 2003; see also Yoshimura et al. 2001) are phased in a similar way with respect to the LD cycle as in nocturnal species. Also, in crickets, electrical discharges in the optic lobes are greatest at night both in the nymphs, which are nocturnal and in the adults which are diurnal (Tomioka and Chiba 1992). A comparison of the sequences of BMAL1 and CLOCK proteins in nocturnal owls to those of diurnal birds did not reveal any distinguishing features (Fidler and Gwinner 2003).

However, the possibility that intrinsic features of oscillators differ between nocturnal and diurnal species has not been ruled out. Oster et al. (2002) report that profiles of period gene expression differ between diurnal and nocturnal individuals of blind mole rats, *Spalax ehrenbergi*. Media worker ants, *Componotus compressus*, that are diurnal have longer circadian periods than those that are nocturnal (Sharma et al. 2004). This suggests that oscillator function may differ in some respects between the nocturnal and diurnal state.

Some other points that hint at but fall short of establishing differences within the oscillator mechanisms themselves now follow. Novak and Albers (2004) found that, in contrast to the phase advances seen in laboratory rats, GABA agonists produced delays when injected into the SCN of Nile rats (*Arvicanthis niloticus*), a predominantly diurnal species. However, it is debatable whether a difference in the direction of phase shift represents a fundamental difference in the function of the oscillatory system, or one in input or output mechanisms. Some would include the paper of Jiao et al. (1999) in this list of hints that oscillators may differ between diurnal and nocturnal species. They reported that the circadian rhythm of firing in SCN cells, often seen in rats, was absent in degus, *Octodon degus*, which are diurnal rodents. However, that study was focussed on responses to light; the numerous photic stimuli might have affected baseline firing rates.

In considering the neural basis of being active by day or by night, it should be kept in mind that diurnality in rodents has probably evolved several times; there could well be a variety of mechanistic routes to diurnality (Smale et al. 2003). What is needed is more comparative work with several nocturnal and diurnal species studied by the same methods (Lee 2004). As it is at present, in many studies on this topic comparisons are made between only two species, one diurnal one nocturnal. Whether the findings of such studies reflect differences in temporal niche or in some other characteristics of the species involved remains uncertain.

As it stands now, although it is premature to dismiss intrinsic features of SCN clocks being responsible for specifying diurnality or nocturnality in some cases, no clear differences in the SCN that distinguish groups of diurnal and nocturnal mammals have as yet been found

(Smale et al. 2003). So this leads back to the idea that "a 'switch' may reside somewhere along the direct line from SCN cells to target cells" (Smale et al. 2003). Others have also suggested that essential differences between nocturnal and diurnal species lie on the output side of the SCN oscillator (Kas and Edgar 1999; Mrosovsky et al. 2001; Dardente et al. 2002; Fidler and Gwinner 2003).

Moreover, having a switching mechanism downstream from the principal oscillator may have adaptive value. An endogenous clock has a number of functions, including synchronisation with conspecifics, anticipation of important events concerning prey and predators, gating of physiological changes such as oestrous to suitable times of day, tracking day length in photoperiodic species, and use in sun-compass orientation. A change in oscillator function to cope with a particular need, for instance switching from nocturnal to diurnal in response to availability of food, might diminish the value of the clock for other uses. But if adjustments are made downstream of the clock, flexibility is retained to alter the timing of particular behaviours without altering that of others (Mrosovsky 2003). A downstream location of a switching mechanism does not exclude the role for sensory factors as will now be discussed.

Possible mechanisms

If, downstream of the oscillator, there were some switching mechanism whose state determines whether the animal is active by day or night, it could be that inputs from specific sensory receptors hold that switch in a particular state, perhaps by controlling whether $GABA^A$ receptor signalling is inhibitory or excitatory. Such plasticity in $GABA^A$ receptors is known in other contexts in which phenomena are conceptualised in terms of switches and switching (Wagner et al. 1997; Laviolette et al. 2004). If this specific suggestion is incorrect, there could be other ways in which sensory receptors might inhibit directly or indirectly any diurnality in a nocturnal species. Removal of such inhibition could then make diurnality possible. For instance, it has been pointed out that a projection from melanopsin-positive retinal ganglion cells to the ventral subparaventricular zone (vSPZ) is well positioned to "modify (or mask) photic circadian entrainment" by acting downstream of the circadian oscillator (Gooley et al. 2003).

The vSPZ is mentioned here only to provide an example of a candidate area downstream of the SCN that could depend on the correct input from the retina to maintain nocturnal activity. It is an area that would be likely to have sustained some damage in Richter's (1978) lesions. And a report of more recent work with lesions damaging the SCN and adjacent structures tells of impaired negative masking (Li et al. 2005). If the vSPZ is a switch area, it may be more likely that the main input for masking responses is based on melanopsin rather than growth factors. In this laboratory, we have been unable to confirm the results of Kramer et al. (2001) on impaired masking in mutant mice with deficiencies in epidermal growth factor receptor (EGFr) function. In contrast, triple knockout mice lacking functional rods, cones, and melanopsin-containing retinal ganglion cells fail to show negative masking in response to light (Hattar et al. 2003; Panda et al. 2003).

Since both negative and positive masking have been found in *Mus musculus*, it is natural to wonder if a strengthening of positive masking relative to negative masking might be responsible for a switch to diurnal patterns of activity in this species (Van Gelder et al. 2002). Since positive masking occurs in dim lights, perhaps interference with sensory mechanisms in the eye would make bright light be treated as dim light. However, for mice lacking cryptochromes, no differences in masking responses from wild types, in either dim or bright light, have been detected (Mrosovsky 2001). Although more extensive tests of this point are desirable, from the available data it seems unlikely that any differences in masking between mice lacking cryptochromes and wild types would be great. Likewise, for mice lacking melanopsin, although negative masking is diminished, there is no evidence of enhancement of positive masking (Mrosovsky and Hattar 2003).

Nevertheless, the possibility remains that some cases of switching to diurnality in mice might be linked to paradoxical positive masking. To understand this it should be recalled that the processes underlying negative and positive masking are different. Negative masking depends on an irradiance detection system that remains functional in mice with severe degeneration of classical photoreceptors in the outer retina (Mrosovsky 1994). Melanopsin is required for sustained negative masking (Mrosovsky and Hattar 2003). In contrast, positive masking is absent in retinally degenerate mice lacking most or all rods, and in mice with lesions of the dorsal lateral geniculate. The implication is that form vision mediated by the classical visual system is necessary for positive masking (Mrosovsky et al. 1999; Edelstein and Mrosovsky 2001). Being able to discern objects, even if only dimly, facilitates movement compared to being in total darkness, just as night vision goggles improve mobility in people with night blindness (Hartong et al. 2004).

With different processes mediating negative and positive masking, it is conceivable that diurnality could arise in different ways, one by reversing negative masking, another by enhancing positive masking. Interactions between the influence of irradiance detection and of form vision on locomotor activity might also change. Even if lack of melanopsin does not actually enhance positive masking, it could still be that the diminution of negative masking in melanopsin knockout mice (Fig 7) leaves positive masking unopposed, and sufficiently strong to make some individuals become active in dim light and rest in darkness. This might occasionally occur even in a wild type if lights were sufficiently dim, for instance 0.04 lux (Fig 6). A wild type receiving only very

dim light may be looked upon as an animal without melanopsin; 0.04 lux may be too low to activate melanopsin-containing cells sufficiently to produce negative masking.

Working with migratory birds, Bartell and Gwinner (Bartell pers comm) found that in dim lighting there could be two components of activity, free-running with different periods. Zugunruhe, manifest by stereotyped wing whirring, was associated with the oscillator having the longer period. However, when the two components coincided with each other, Zugunruhe was inhibited. It was suggested that in the non-migratory state the output of the Zugunruhe oscillator was inhibited by its being in phase with an oscillator promoting daytime activity, but that in the migratory state a different phase relationship allowed the output of the Zugunruhe oscillator to be manifest in the night.

Extending this line of thought, one could suggest that, in addition to migratory birds, many species have both an oscillator that promotes activity in the night, and another that promotes activity in the day. Temporal niche would reflect which one of these oscillators dominates.

Whether or not one of these speculative accounts contain some truth or not is debatable. But in any case, they are certainly all incomplete because for a nocturnal animal to become diurnal, or vice versa, two conditions must be met. First, there must be a loss of the usual masking response to light. If strong negative masking to light remains intact and the light is reasonably bright, then activity in the day will be suppressed in a nocturnal species, and it could not become day-active.

Loss or weakening of the normal negative masking response is not, however, sufficient to produce a temporal niche reversal. There must be something else that results in the now no longer suppressed activity moving from the nighttime into the daytime. Taking away (or overwhelming) negative masking is only one component of temporal niche switching. It leaves the daylight hours open to colonisation by activity, but does not in itself insure that the second step of activity moving into that available territory will actually take place. There are various ways in which running in the hours of daylight might be promoted. There might be changes in the phase relationship or coupling between the oscillator and downstream mechanisms. Non-photic factors could also be involved. Sounds or other stimuli from other mice with nocturnal patterns could be a factor.

Two process account of temporal niche switching

Whatever the specific mechanisms, the evidence presented here suggests that when a mouse becomes diurnal, there are changes not only in masking but also in some factor controlling the relationship of locomotion to clock phase. The data are consistent with a two-process account of switching temporal niches.

This should not be too surprising if it is kept in mind that the direct masking effects of light and the clock-resetting entraining effects of light are different and separate phenomena, as exemplified by the persistence of masking in SCN-lesioned hamsters (Redlin and Mrosovsky 1999) and in cryptochrome knockout mice (Selby et al. 2000; Mrosovsky 2001), neither of which display a persisting endogenous locomotor rhythm in constant conditions, and therefore can not display an entraining effect of light. Similar dissociations can occur in flies (Helfrich-Förster et al. 2001). If both the direct masking response to light and the phasing of endogenous rhythms relative to the LD cycle change when a nocturnal animal becomes diurnal, it is debatable whether we should be searching for a single toggle switch for temporal niche.

Theoretically, it is conceivable that only one process (entrainment or masking) is involved. A change in phasing of outputs from the circadian clock could be so dominant as to overwhelm masking responses that remained the same. However, in some of the cases above, this seems unlikely because paradoxical masking occurs (e.g. abrupt changes at dark onset, Fig 3). Also telling is the greater tendency for those mice showing diurnality on 3.5:3.5 h LD cycles to show diurnality when on LD cycles adding to 24 h (Fig 7). Because the circadian rhythm of the mice did not entrain to the 3:5:3.5-h LD cycle, diurnality (low scores for % running in the dark) seen on such cycles presumably contributes to the diurnality seen in LD 16:8 h cycles.

It is also theoretically possible that only masking could change, but be so dominant as to overwhelm output signals from clocks that remain functioning in their usual way. If the normal masking response in a mouse were not merely weakened or lost, but changed into paradoxical masking, then the activity could be driven to occur in the day by masking alone. But this too is unlikely; for the mice shown in Figs. 4 and 5, the endogenous rhythm is also phased to give daytime activity, as the DD test shows. If diurnality had simply been a matter of powerful paradoxical masking both promoting daytime activity and also suppressing clock-controlled nighttime activity, then the latter should have reappeared in DD. So both masking and something in a switch downstream from the oscillator are involved. The transients seen in diurnal mice when the LD cycle is shifted (e.g. Fig 9), and in one of the diurnal mice lacking cryptochromes (Van Gelder et al. 2002; Fig 2), further exemplify a change in clock controlled activity as well as a change in masking.

So it appears probable that both entrainment and masking are changing in these examples of diurnal mice. Normally, entrainment and masking are complementary (Aschoff 1988; Mrosovsky 1999). Both serve to confine the animal to a particular temporal niche. Both entrainment and masking will make it less likely for a mouse to be active in the day. Yet there are cases in which masking and entraining responses pull in opposite directions. In the Nile rat, *Arvicanthis niloticus*, tested in the laboratory, activity may start before dawn, and be

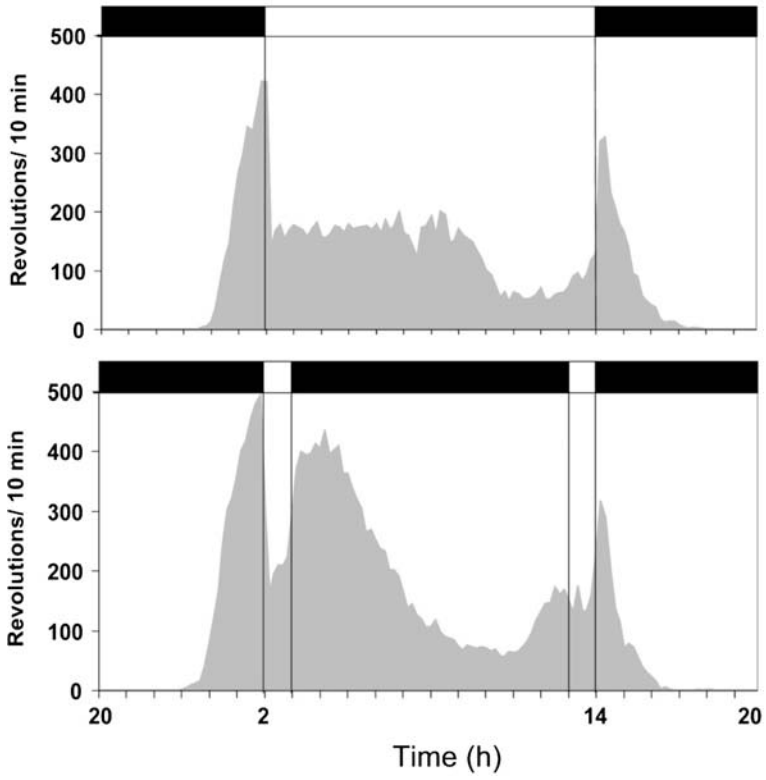

Fig 10 Wheel running of a group of Nile rats on LD 12:12 h (*top*) and on a skeleton photoperiod, LDLD 1:10:1:12 h (*bottom*). Data from Redlin and Mrosovsky (2004)

present throughout the day, and cease after dusk. Yet when given a running wheel, these animals exhibit paradoxical masking (Fig 10). Bursts of activity occur at lights off and, at lights on, there is a sharp inhibition of the anticipatory activity that was building up in the dark before then. In addition, the amount of activity throughout the subjective day is greater when there is a skeleton photoperiod than a full LD cycle. So masking and entrainment are exerting opposite effects on activity levels. There are also other instances of bursts of paradoxical activity at dawn or dusk in animals whose activity otherwise remains in the normal phase relationship to dawn and dusk (Redlin et al. 2003; Pickard et al. 1995); these cases reinforce the point that entrainment and masking are not indissolubly complementary in their actions.

If changes in masking and in phase of outputs from a clock can occur in varying degrees separately or together in different individual mice, this might account for why in a batch of mice only some animals show diurnality overtly. Involvement of two processes would provide two sources of variability.

The most striking examples of diurnality above come from mice with a hybrid B6/129 background. Perhaps particular background compositions are important. In preliminary studies, we have tested 12 male 129S6/SvEvTac mice on LD 16:8 and 12:12 h (ca 800 lux), as well as on 3.5:3.5 h (10 lux) cycles, and did not find diurnal individuals or paradoxical masking. These tests were not nearly extensive enough to demonstrate a negative, and do not exclude diurnality manifesting itself in dim LD cycles. However, with melanopsinless-rodless transgenic mice, it may be that enough individuals show tendencies to diurnality to make planned studies attractive. Even though not manifest in all individuals, the fact is that diurnality has been a reoccurring feature of studies of mice with melanopsin dysfunction.

Role of the retina

The appearance of some striking instances of diurnality in mutant mice with genotypes affecting the retina (Exhibits 2–4 above) suggest that the state of photoreceptors can play an important role in determining temporal niche. This is unexpected since it has been thought that different phasing of activity in diurnal and nocturnal species depends on some mechanism downstream from the clock. Evidently such a mechanism can be much influenced by retinal input. It may be surprising that such a role should be vested in a sensory organ. On the other hand, eyes and retinas are specialised for nocturnal or diurnal function in numerous ways, from size to relative numbers of receptor types. It may be reasonable then that such specialisations should also extend to some influence on whether an animal prefers to be active by day or by night, whichever is best for the sensory equipment it possesses.

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Appendix

Explanation of masking terminology used in this review

Masking: a direct acute effect of light on a variable, for example suppression of locomotion in a nocturnal mammal by illumination occurring in the night. Masking of locomotion differs from the phase-shifting effect of light on locomotor rhythms: the latter depends on light resetting an endogenous clock which in turn controls activity. Masking can occur in animals not displaying circadian locomotor rhythms (e.g. after SCN lesions, and in cryptochrome knockout mice).

Negative masking: a decrease in activity, often occurring during relatively bright illumination in a nocturnal species.

Positive masking: an increase in activity, often occurring in mice during periods of dim light against a background of complete darkness.

Paradoxical positive masking: an increase in activity occurring in a nocturnal animal during illumination, or an increase occurring in a diurnal species after a decrease in illumination. Thus, the increase in activity seen in the common mouse during a dim illumination qualifies as paradoxical positive masking because this is a nocturnal species. The term paradoxical does not imply anything abnormal or maladaptive, any more than does the term paradoxical sleep imply pathology.

Paradoxical negative masking: a decrease in activity in a diurnal species when there is an increase in illumination or a decrease in a nocturnal species when there is a decrease in illumination. Again, this is not necessarily maladaptive. For instance, the nocturnal owl monkey (*Aotus lemurinus*) reduces its activity when it becomes too dark (Erkert and Gröber 1986), presumably a valuable response for an animal that must be able to jump safely from branch to branch.

For further definitions and history of terminology, see Mrosovsky (1999).

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Note added in proof: A recent abstract (Doyle S et al. 2005 IOVS 46: ARVO E-abstract 3989) reports diurnality in mice with defective rod function ($Rpe65^{-/-}$) combined with knockout of melanopsin ($Opn4^{-/-}$).