Cellular/Molecular

Disintegration of the Sleep–Wake Cycle and Circadian Timing in Huntington's Disease

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Sleep disturbances in neurological disorders have a devastating impact on patient and carer alike. However, their pathological origin is unknown. Here we show that patients with Huntington's disease (HD) have disrupted night–day activity patterns. This disruption was mirrored in a transgenic model of HD (R6/2 mice) in which daytime activity increased and nocturnal activity fell, eventually leading to the complete disintegration of circadian behavior. The behavioral disturbance was accompanied by marked disruption of expression of the circadian clock genes *mPer2* and *mBmal1* in the suprachiasmatic nuclei (SCN), the principal circadian pacemaker in the brain. The circadian peak of expression of *mPer2* was prematurely truncated, and the mRNA levels of *mBmal1* were attenuated and failed to exhibit a significant circadian oscillation. Circadian cycles of gene expression in the motor cortex and striatum, markers of behavioral activation in wild-type mice, were also suppressed in the R6/2 mice, providing a neural correlate of the disturbed activity cycles. Increased daytime activity was also associated with reduced SCN expression of *prokineticin 2*, a transcriptional target of *mBmal1* encoding a neuropeptide that normally suppresses daytime activity in nocturnal mammals. Together, these molecular abnormalities could explain the pathophysiological changes in circadian behavior. We propose that circadian sleep disturbances are an important pathological feature of HD, that they arise from pathology within the SCN molecular oscillation, and that their treatment will bring appreciable benefits to HD patients.

Key words: clock; *per 2*; **suprachiasmatic nucleus; neurodegeneration; polyglutamine repeat; hypothalamus; R6/2 mouse; prokineticin**

Introduction

Severely disturbed sleep is characteristic of progressive neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease (HD) (Askenasy, 2001; Bates et al., 2002; Hatfield et al., 2004). When patients with long-term neurological illnesses have disrupted sleep, this becomes a problem not only for the patient but also for their carers (Bianchetti et al., 1995; Van Someren, 2000). Identification of its origin is essential to rational management of these diseases and should also provide novel insights into the nature of the neurodegenerative process.

In HD, reduced sleep efficiency is characterized by frequent nocturnal awakening and underlying electroencephalographic abnormalities (Wiegand et al., 1991; Silvestri et al., 1995). Severe anxiety and excessive chorea are reported during sleep arousals (Nance and Westphal, 2002) but have both been discounted as primary causes of sleep disturbance (Fish et al., 1991), the origins of which remain unknown. There is some evidence to suggest that the sleep disturbance in HD may be pathological in origin. Although the striatum is the major site of neurodegeneration in early HD, a recent study showed that there is also significant neurodegeneration in the hypothalamus of HD patients (Kassubek et al., 2004). Because the hypothalamus, and specifically the circadian pacemaker of the suprachiasmatic nuclei (SCN), is a key regulator of sleep–wake cycles, it is possible that the sleep deficits in HD are caused directly by hypothalamic dysfunction.

The SCN is the circadian clock that drives sleep–wake cycles (Pace-Schott and Hobson, 2002). This neuronal pacemaker is based on a molecular negative feedback loop in which transcription of the core "clock" genes *Period* (*Per*) and *Cryptochrome* (*Cry*) is driven by heteromeric complexes of the basic helix-loop-helix proteins, CLOCK and BMAL (Reppert and Weaver, 2002). Complexes containing PER and CRY proteins enter the nucleus and suppress CLOCK/BMAL activity, thereby closing the oscillatory loop. HD is accompanied by significant neurodegeneration in the hypothalamus (Kremer, 1992; Kassubek et al., 2004), but the impact of HD on this circadian mechanism is unknown. In this study, we compared sleep–wake disturbances in HD patients and an animal model of HD, the R6/2 mouse (Mangiarini et al., 1996), and examined the impact of disease progression on the circadian molecular oscillation in the SCN.

Materials and Methods

Subjects and actiwatch recording. The Local Research Ethics Committee (Cambridge, UK) granted ethical approval. Eight HD patients, five inde-

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Table 1. Human subject data

Subject	Carer (patient match)	Age^a	Sex	Disease duration (years)	Independence score (% of 100)
HD 1		28	F	6	40
HD 2		68	M	5	90
HD 3		51	F	7	80
HD 4		45	M	11	80
HD 5		62	M	6	65
HD 8		48	M	8	80
HD 9		46	M	14	70
HD 10		47	F	2	60
Cont 1	Yes (HD1)	48	F		
Cont 2	Yes (HD3)	64	M		
Cont 4	Yes (HD5)	60	F		
Cont 7	No	41	M		
Cont 8	No	26	F		
Cont 9	No	59	M		
Cont 10	No	59	F		
Cont 11	No	60	M		

[a]Mean age of patients, 49.4 ± 4.2; mean age of controls, 52.9 ± 4.3; $t_{(14)} = 0.414$, NS. Cont, Control; F, female; M, male.

pendent controls and the carers of three of the patients, were assessed after giving informed consent (HD Research Clinic at the Cambridge Centre for Brain Repair). For details of the subjects, see Table 1.

Activity monitoring and data analysis. Locomotor activity was measured using Actiwatch-Neurologica (Cambridge Neurotechnology, Cambridge, UK) over 24–48 hr in their normal home environment and complemented with sleep diaries. Subjects wore the Actiwatch-Neurologica on one wrist, and the watch was only removed when the subject took a bath or shower during this period. Subjects were asked to complete a simple diary indicating for each hour of the 48 hr period whether he or she was awake or asleep. Three HD patients were unable to be monitored for the entire 48 hr period, but the data gathered for 24, 43, and 46 hr, respectively, were suitable for analysis.

The Actiwatch-Neurologica measured total activity in 15 sec epochs over the 48 hr period. Diaries were used to distinguish periods of activity when each individual subject was awake from those when he or she was asleep. The 15 sec epoch readings from the activity monitor were summed to give measurements per minute in the patient and control groups.

Analysis of circadian behavior. Animal studies were conducted under UK Home Office license. R6/2 mice were taken from a colony established at the University of Cambridge using mice obtained from Dr. G. Bates (Guy's King's and St. Thomas' School of Medicine, King's College, London, UK) (Mangiarini et al., 1996). All mice were housed under a 12 hr light/dark (LD) cycle with food and water available *ad libitum* (Carter et al., 1999). For circadian recording, mice were housed individually within a light-tight, ventilated cabinet (Tecniplast UK, Milton Keynes, UK) with passive infrared movement detectors placed on the cage tops, linked to a computerized recording system (Clocklab; Actimetrics, Evanston, IL). In the first study, activity patterns were recorded continuously from 8 until 16 weeks of age. In the first study, mice also had access to a running wheel to monitor their activity patterns that were recorded continuously from 8 until 16 weeks of age. In the second study, mice were transferred from their home cage (under LD lighting cycle) to the circadian recording cabinet at 5 weeks of age. Their activity was recorded by infrared detectors for 1 week (6–7 weeks of age) under LD. The mice were then transferred to constant dim red light (DD) for 1 week (7–8 weeks of age), before being returned to the home cage, where they were reentrained to the LD schedule. This procedure was repeated for the same animals between 13 and 15 weeks, with recording of activity starting at 14 weeks (LD) and 15 weeks (DD) of age. All parameters were compared by *t* test or factorial or repeated-measures ANOVA as appropriate.

In situ hybridization brains were removed rapidly, frozen on dry ice before sectioning at 12 μm, and processed for hybridization as described previously (Field et al., 2000). Antisense riboprobes corresponding to nucleotides 1–638 of *mPer2*, 864–1362 of *mBmal1*, or 603–1172 of *Prokineticin2* (*PK2*) were labeled with [^{35}S]UTP. Sections were apposed to Kodak Biomax MR film (Sigma, Poole, UK) and the intensity of hybridization signal quantified against ^{14}C calibration microscales (Amersham Biosciences, Little Chalfont, UK). The hybridization signal was measured

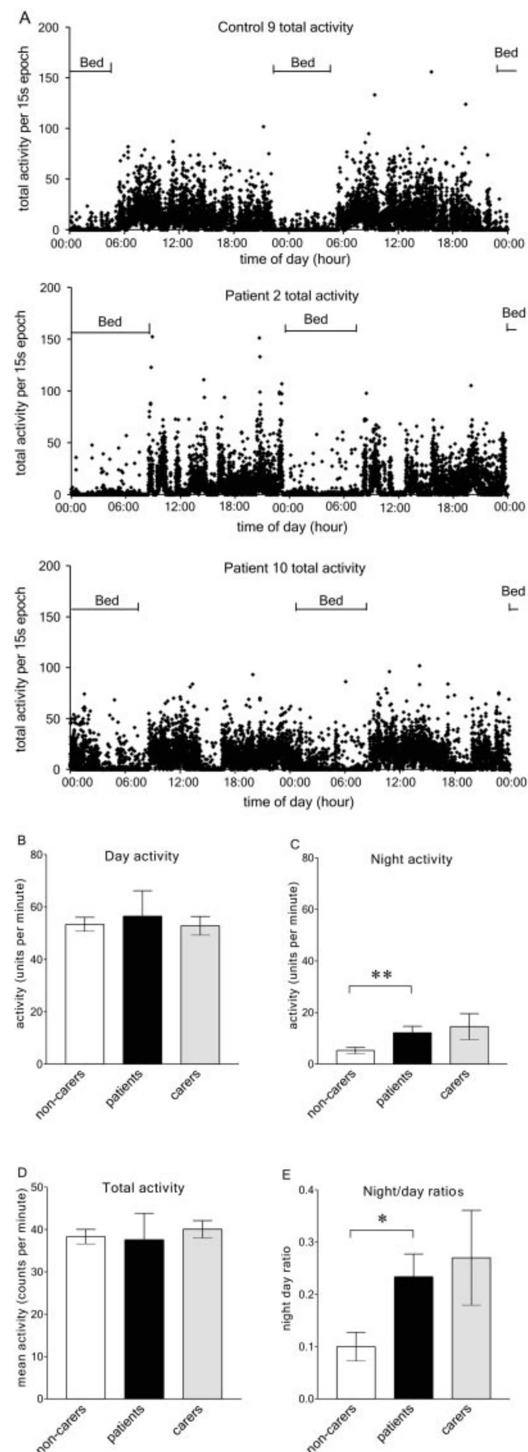

Figure 1. Abnormal circadian activity in HD patients. *A*, Actimetry monitored over 48 hr in representative subjects show data from a neurologically normal control (top), an HD patient with an independence score of 90% (patient 2, middle), and an HD patient with an independence score of 60% (patient 10, bottom). Group activity measures for patients, normal controls, and carers (plotted as mean ± SEM) are shown for daytime activity (*B*), nighttime activity (*C*), total activity (*D*) over 24 hr, and night/day activity ratios (*E*). $*p < 0.05$; $**p < 0.01$.

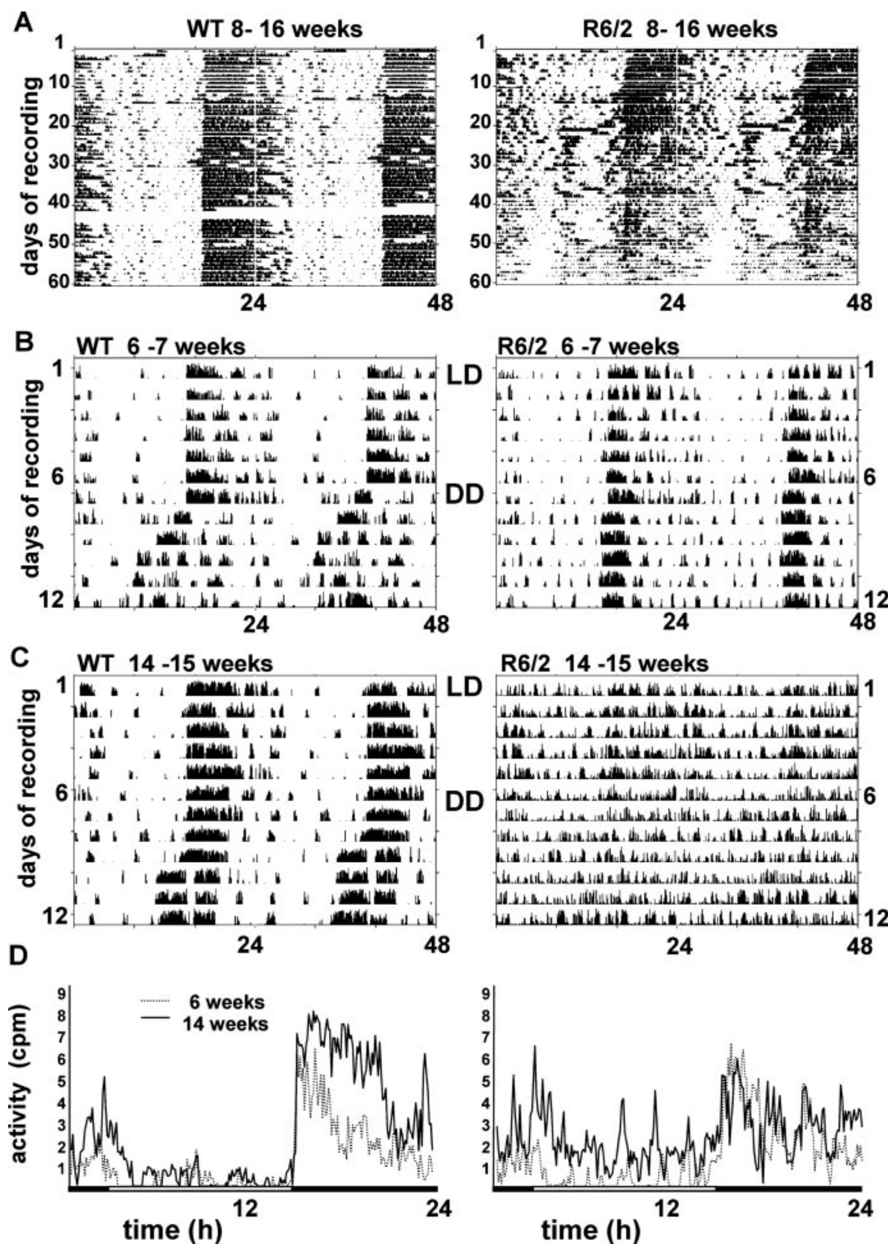

Figure 2. Disruption of circadian activity patterns in R6/2 mice. Representative double-plotted actograms of continuous recordings of a WT (left) and R6/2 (right) mice monitored from 8 to 16 weeks of age, under a LD photoschedule (*A*). Representative actograms from a second study showing activity cycles of mice recorded for 1 week under LD from 6–7 weeks (*B*) or 14–15 weeks (*C*) of age. Mice were transferred to DD at 7 or 15 weeks of age, and their activity was recorded for an additional 7 d. Representative 24 hr activity profiles (averaged counts over 7 d of recording under LD) of an individual WT (left panels) and R6/2 (right panels) mice recorded over weeks 6–7 (gray) and weeks 14–15 (black) (*D*).

in five consecutive sections, and the average value for each mouse was used to calculate the group means. Sense probes generated no specific image.

Results

HD patients show abnormal patterns of day–night activity

HD patients spent significantly longer in bed than did controls (mean ± SEM; controls, 7.30 ± 0.44 hr; HD, 9.88 ± 0.67 hr; $p = 0.017$; *t* test). Actimetry revealed a regular 24 hr profile of rest and activity in control subjects (Fig. 1*A*); however, the daily pattern of activity was markedly different between HD patients and controls, with a significant increase in the number of movements made by the HD patients during nocturnal "bedtime". Whereas some patients had clear "in-bed" intervals but with elevated activity (Fig. 1*A*, patient 2), in others, the normally distinct in-bed phase was masked by the additional nocturnal activity (Fig. 1*A*, patient 10). There was no difference in the total number of movements made by HD patients and control subjects during the daytime (Fig. 1*B*). However, overall, the patients showed significantly higher nocturnal activity ($p = 0.001$ vs controls; unpaired *t* test with Welch's correction) (Fig. 1*C*), and the ratio of nighttime to daytime activity was significantly increased (Fig. 1*E*). This was not attributable to a general hyperactivity because patients, controls, and carers had comparable total activity levels across 24 hr (Fig. 1*D*), nor was it attributable to increased nighttime chorea because, after subtraction of such high-velocity movements, the total activity of HD patients at night was still significantly higher than controls [14.34 ± 2.48 cpm (all patients) compared with 5.36 ± 1.24 cpm (all control subjects); $p = 0.01$; *t* test with Welch's correction]. Notably, the effect of increased nighttime to daytime activity was mirrored in the activity profiles of the patients' neurologically normal carers, indicating a "knock-on" effect of patients' disturbed sleep.

R6/2 mice show progressive disruption of circadian rhythms

To determine whether sleep–wake patterns are similarly disturbed in an animal model of HD, we monitored the spontaneous rest–activity cycle of wild-type (WT) and R6/2 mice continuously from 6 weeks of age (Fig. 2*A*). In presymptomatic (6 weeks old) mice under an LD schedule, the rest–activity cycle was well defined and comparable with that of WT controls (Fig. 2*A*, right). All of the mice showed normal entrainment of their activity rhythms, with activity onset occurring at the time of lights out. Some R6/2 mice had higher daytime levels of activity than the WT controls. However, the overall level of activity over 24 hr was not different between the two groups (mean ± SEM; WT, 482 ± 19 counts; R6/2, 535 ± 28 counts).

By 10–12 weeks of age, when neurodegenerative symptoms typically begin to appear, this pattern became less distinct, with ill-defined activity onset and less consolidated nocturnal activity. By 13–15 weeks of age, the daily cycle in R6/2 mice had started to disintegrate, with increased activity during the light phase and less at night. As a result, 46 ± 6% of their daily activity occurred in the daytime, whereas in the WT, daytime activity represented only 10 ± 3% of total activity recorded over 24 hr.

To test the contribution of the circadian clock to this behavioral disturbance, activity patterns were monitored in a second group of mice exposed to both LD and DD ($n = 16$ R6/2 and 8 WT mice). At 6 weeks, the circadian behavior of R6/2 mice was

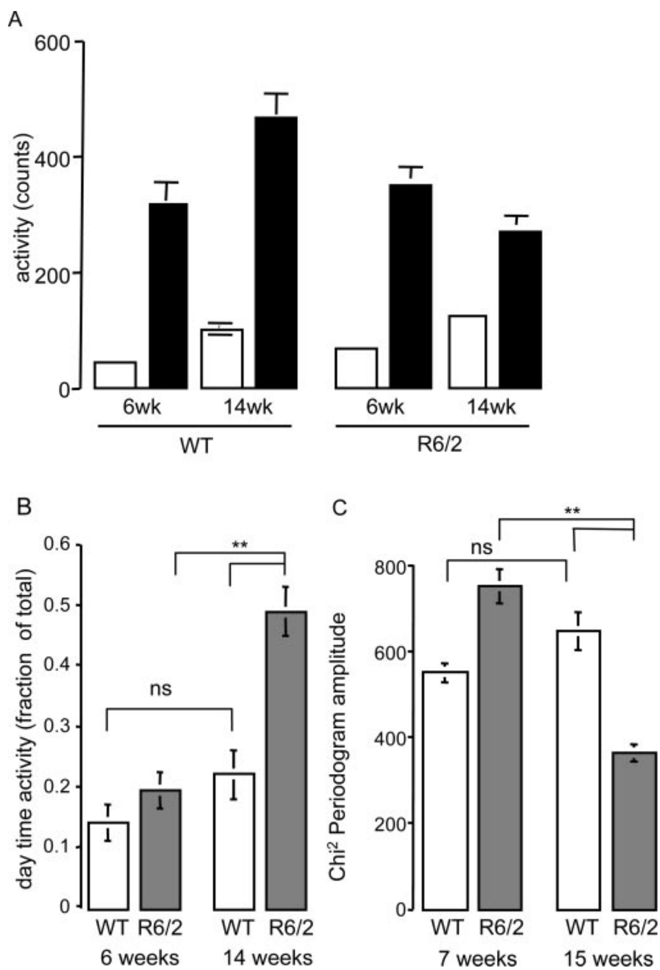

Figure 3. Increased daytime activity and impaired circadian control over rest–activity cycle in R6/2 mice. *A*, Daytime (white columns) and nighttime (black columns) activity levels in WT ($n = 8$) and R6/2 ($n = 16$) mice recorded for 7 d at 6 and 14 weeks of age on an LD schedule. *B*, Daytime activity measured as a fraction of total activity in WT (white columns) and R6/2 (gray columns) mice at 6 and 14 weeks of age. *C*, Amplitude of χ^2 periodogram of peak circadian periodicity (22–26 hr) measured in free-running WT (white columns) and R6/2 (gray columns) mice at 7 and 15 weeks of age. All data are mean ± SEM; $^{**}p < 0.01$; *post hoc* Dunnett's *t* test. ns, Not significant.

similar to that of WT mice on LD (Fig. 2*B*). Synchronization was normal, with activity onset coincident with lights out, and the total level of activity over 24 hr was not different between the groups (mean ± SEM; WT, 352 ± 46 counts; R6/2, 404 ± 35 counts). Under DD for 7 d, the activity rhythm of both WT and R6/2 mice free-ran with indistinguishable periods (period ± SEM; WT, 23.85 ± 0.06 hr; R6/2, 23.85 ± 0.04 hr).

When monitored between 13 and 15 weeks of age, WT mice showed a robust rhythm of activity in both LD and DD conditions (Fig. 2*C*). In contrast, the R6/2 mice exhibited a marked deterioration in their circadian rhythm, with a significant redistribution of activity from the dark to the light phase (two-way repeated-measures ANOVA; day–night, $p < 0.0001$; age, not significant; interaction, age vs day–night, $p < 0.001$ as a result of redistribution of activity in R6/2 mice). Total activity levels of the R6/2 mice were unchanged between 6 and 14 weeks (mean ± SEM; week 6, 404 ± 35 counts; week 14, 379 ± 37 counts), but the proportion of activity occurring in the light phase was significantly increased in the R6/2 mice (Fig. 3*A*,*B*). This obscured the clear definition of rest and activity phases (Fig. 2*D*). The R6/2 mice also had severely disrupted free-running activity rhythms when transferred to DD at week 15 (Fig. 2*C*). Whereas all eight WT mice showed clear circadian activity patterns, 4 of 16 R6/2 mice were completely arrhythmic. Of the remaining 12 R6/2 mice, although circadian period was not significantly changed (mean period ± SEM; WT, 23.65 ± 0.07 hr; R6/2, 23.37 ± 0.22 hr), its coherence as determined by the periodogram amplitude was significantly reduced compared with WT controls and with the same mutant animals aged 7 weeks (Fig. 3*C*).

Expression of circadian rhythm genes is abnormal in R6/2 mice

The progressive breakdown in circadian rhythmicity in R6/2 mice is consistent with a pathological involvement of the SCN. To test this, brains were collected at 8 or 16 weeks of age on the second cycle of DD and processed for *in situ* hybridization. At 8 weeks of age, mice of both genotypes exhibited a significant rhythm in expression of *mPer2* mRNA in the SCN, levels being high at circadian time 9 (CT9) and low at the expected nadir at CT21 (data not shown). WT mice were also highly rhythmic after 16 weeks, again showing peak levels at CT9 and nadir at CT21 (Fig. 4*A*). However, at 16 weeks, expression of *mPer2* in the SCN of mutants was significantly reduced, falling to a nadir at CT15, considerably in advance of the WT mice (genotype, $F_{(1,23)} = 31.1$, $p < 0.01$; time, $F_{(3,23)} = 69.6$, $p < 0.01$; interaction, genotype vs time, $F_{(3,23)} = 15.7$, $p < 0.01$). Rhythmic expression of *mBmal1b* mRNA was also disrupted in the SCN of the R6/2 mice (Fig. 4*B*). Whereas WT mice showed a clear circadian profile in anti-phase to *mPer2*, R6/2 mice failed to show a statistically significant rhythm, and *mBmal1b* mRNA levels never reached the WT peak (genotype, $F_{(1,23)} = 0.5$, NS; time, $F_{(3,23)} = 19.5$, $p < 0.01$; interaction, $F_{(3,23)} = 10.8$, $p < 0.01$). Impaired *mBmal1b* expression may account for the truncated *mPer2* peak. It may also explain the disorganized locomotor behavior in the older R6/2 mice.

PK2 is a transcriptional target of BMAL1, and its product is proposed to suppress daytime activity in nocturnal rodents (Cheng et al., 2002). As expected, *PK2* mRNA was high in the SCN of WT mice during circadian daytime and low at night. However, the peak was reduced in mutants by 8 weeks (data not shown) and severely blunted at 16 weeks (genotype, $F_{(1,23)} = 73.4$; time, $F_{(3,23)} = 60.3$; interaction, $F_{(3,23)} = 21.6$; all p values < 0.01) (Fig. 4*C*). This is likely to account for the increased daytime activity in the R6/2 mice that precedes the complete breakdown in circadian rhythm.

The altered behavior of R6/2 mice was also reflected in a blunted circadian expression of *mPer2* in the striatum and motor cortex at 16 weeks (Fig. 4*D*) (striatum: genotype, $F_{(1,23)} = 12.4$, $p < 0.01$; time, $F_{(3,23)} = 31.9$, $p < 0.01$; interaction, $F_{(3,23)} = 8.1$, $p < 0.01$; motor cortex: genotype, $F_{(1,23)} = 4.6$, $p < 0.05$; time, $F_{(3,23)} = 16.6$, $p < 0.01$; interaction, $F_{(3,23)} = 5.4$, $p < 0.01$). Circadian gene expression in these sites is normally driven by periodic motor activity. It would be of interest to determine whether the disturbances that we observe in these motor centers of R6/2 mice are solely a consequence of altered circadian behavior or whether they arise from pathology intrinsic to these tissues. Either way, our findings highlight the extensive loss of circadian function across the brain as the disease progresses.

Discussion

We show here that HD patients have disrupted night–day activity patterns and that this disruption is mirrored in a line of transgenic mice carrying the HD mutation (R6/2 line). In R6/2 mice, the disruption of night–day activity worsened as the disease pro-

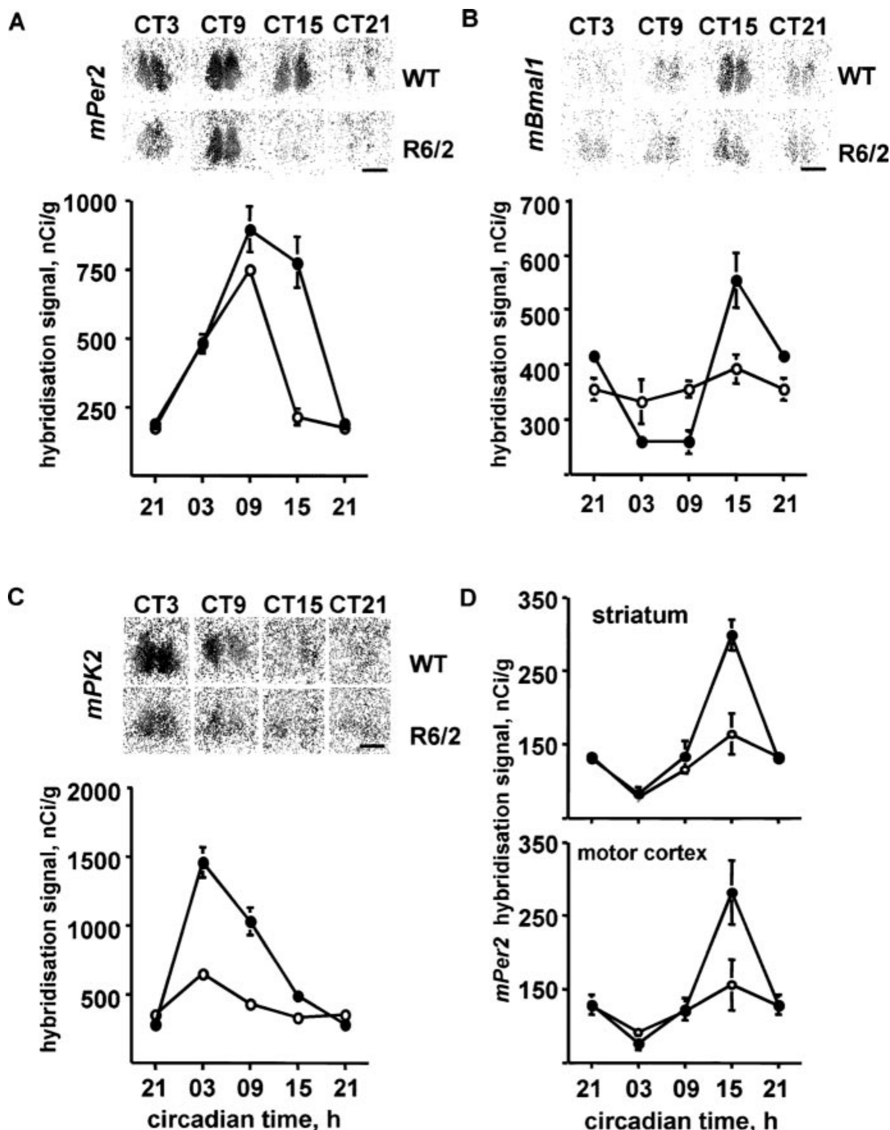

Figure 4. Impaired circadian gene expression in SCN of R6/2 mouse. Representative images and corresponding semiquantitative analysis of *in situ* hybridization for *mPer2* (*A*), *mBmal1* (*B*), and *mPK2* (*C*) in SCN and *mPer2* in motor cortex and striatum (*D*). Tissue was taken from 16-week-old WT (filled symbols) and R6/2 (open symbols) mice. Mice were killed at 6 hr intervals over one 24 hr period in the second cycle after release to DD. Note that data for CT21 are double plotted for clarity. All data are mean ± SEM. Scale bar, 500 μm.

gressed, eventually leading to the complete disintegration of circadian behavior. This was accompanied by marked disruption of expression of the circadian clock genes *mPer2* and *mBmal1* in the suprachiasmatic nuclei, as well as in the motor cortex and striatum. Increased daytime activity was also associated with abnormal SCN expression of *prokineticin 2*. Together, our data strongly suggest that disturbance of the rest–activity cycle in R6/2 mice, and by implication the HD patients, arises from impaired circadian regulation by the SCN. With progression of the disease, dysregulated activity within the molecular oscillation of SCN neurons would perturb circadian output signals mediated by PK2 and possibly other clock-controlled factors, leading to disorder of sleep–wakefulness.

The origin of altered clock gene expression in the SCN is unclear. A large number of genes are dysregulated in HD (Luthi-Carter et al., 2000; Chan et al., 2002; Luthi-Carter et al., 2002), although changes in the clock genes have not been reported. Furthermore, there is no known association between mutant huntingtin, the causative factor in HD, and PER or BMAL. However, it is notable that the molecular feedback loops of the SCN that govern circadian time are dependent on alternating phases of PER protein synthesis and degradation, with proteasomal breakdown of clock proteins determining the period of the circadian oscillator (Yagita et al., 2002). This is interesting because it has been suggested that ubiquitin-proteasome dysfunction in HD contributes to the pathogenesis of HD (Zoghbi and Orr, 2000). Ubiquitinated inclusions are widely distributed in HD brain (Bates et al., 2002), and subunits of the proteasome are found in inclusions in both *in vitro* and *in vivo* models of HD (Tarlac and Storey, 2003). Furthermore, impairment in the proteasome has been shown in cellular models (Jana et al., 2001) and in the R6/2 mouse (Gong et al., 2001). The observation of inclusions within the SCN of symptomatic mice by us (A.J.M., unpublished data) and others (Obrietan and Hoyt, 2004) supports the idea that proteasomal dysfunction may contribute to the changes in clock gene expression reported here.

Although it has been shown that there is retinal degeneration in R6/2 mice (Helmlinger et al., 2002), it is unlikely that this is a direct cause of the disrupted circadian rhythm. The behavioral impact of the mutation was more obvious under continuous darkness, when only endogenous mechanisms regulate circadian functions, rather than under LD schedules when photic stimuli will also govern these molecular processes. Furthermore, it has been demonstrated using a transgenic mouse carrying a CRE (cAMP response element)-reporter gene that the SCN of the R6/2 mouse remains sensitive to light and therefore potentially entrainable by LD cycles (Obrietan and Hoyt, 2004). Indeed, the attenuated peak of *mPer2* mRNA expression in the SCN on the second cycle of continuous darkness may represent a dampening of a stronger oscillation initiated and maintained by the previous lighting schedule.

Perturbed SCN gene expression was accompanied by disrupted rest–activity cycles, raising the possibility that altered behavioral feedback may affect the clock of the mutant mice. First, R6/2 mice show less locomotor activity than WT mice at 16 weeks of age (Carter et al., 1999; this study). We do not think, however, this is a likely direct cause of the changes in SCN gene expression because the mutant mice did not show any overall change in total daily activity between 6 and 14 weeks, during which time gene expression became dysregulated. Second, the altered daily pattern of activity seen in R6/2 mice, rather than its total level, might affect the SCN because intense locomotor activity during circadian day can suppress *Period* gene expression in the SCN and shift circadian rhythms in a "nonphotic" manner, i.e., opposite to light

(Maywood et al., 1999, 2001). The activity levels observed in this study with R6/2 mice during circadian day, however, fell well outside the limits of intense activation needed to induce these nonphotic effects on the SCN. In addition, such activity-dependent effects are opposed by the light/dark cycle (Maywood et al., 2001), whereas we observed the changes in temporal patterning of behavior in both DD and light/dark cycles. Our preferred interpretation, therefore, is that changes in SCN gene expression are upstream and possibly causative to changes in circadian behavioral cycles.

Rhythmic expression of *mPer2* mRNA is observed in other brain regions in rodents, in particular the motor cortex and striatum, in which it peaks after the onset of the daily activity bout in both nocturnal and diurnally active species (Field et al., 2000; Mrosovsky et al., 2001). Although we propose that the dampened rhythms of gene expression in cortex and striatum are a consequence of disrupted activity patterns rather than a cause of this disruption, our findings highlight the fact that gene expression across the brain and periphery is not static. Rather, it follows a predetermined tissue-specific circadian program involving transcriptional waves of large parts of the genome, including transcripts encoding many rate-limiting factors (Akhtar et al., 2002; Panda et al., 2002; Hastings et al., 2003). This is a critically important feature in seeking to unravel the molecular genetic basis of the sleep disorder in HD in particular, and the molecular pathology of HD in general, because analyses of transcriptional and proteomic profiles only at single time point may be misleading, especially when circadian time of sampling is not rigorously controlled.

The hypothalamus is responsible for a large number of symptoms of neuroendocrine, neurological, and psychiatric diseases. The progressive breakdown in circadian rhythmicity in R6/2 mice is consistent with a pathological involvement of the SCN in the progressive neurological phenotype. In fact, the rhythm of the R6/2 mice is similar to that seen in WT mice with lesions of the SCN (King et al., 2003; Kriegsfeld et al., 2004). It is not known whether there is neurodegeneration in the SCN in HD patients. However, there is widespread neurodegeneration in other hypothalamic nuclei. For example, there is extensive degeneration in the nucleus tuberalis lateralis of the hypothalamus in postmortem HD brains (Kremer, 1992) that has been suggested to cause appetite and feeding abnormalities in HD. Furthermore, a knock-out mouse for HAP-1 (huntingtin-associated protein 1, one of the binding partners for huntingtin) shows degeneration in the hypothalamus (Li et al., 2003). Finally, a recent study using voxel-based morphometry in early HD patients showed significant hypothalamic atrophy in early stages of the disease (Kassubek et al., 2004). One important circadian output pathway from the SCN is to the dorsomedial hypothalamus, which contains orexinergic neurons that maintain arousal (Pace-Schott and Hobson, 2002; Chou et al., 2003). Sleep disturbances have been reported in rats expressing a polyglutamine repeat transgene in these neurons (Beuckmann et al., 2004). Interestingly, progressive death of orexin-containing neurons with the gradual development of narcoleptic-like behavior in R6/2 mice as well as loss of orexin neurons in HD patients have recently been found (Petersén et al., 2004). It remains to be determined whether HD patients have disrupted function within the SCN. In other dementias, altered activity–rest cycles can occur with various degrees (marked, limited, or none) of disturbance to other SCN-dependent physiological rhythms, such as core body temperature (Mishima et al., 1997; Harper et al., 2001) and cortisol secretion (Davis et al., 1986). Dementia may also be associated with neuropathology within the SCN (Stopa et al., 1999). The data from R6/2 mice suggest that HD patients may well suffer pathology within the SCN that leads to sleep disturbance.

Sleep deficits in humans can cause serious neurological problems. Furthermore, when patients with long-term neurological illnesses have disrupted sleep, this becomes a problem not only for the patient but also for their carers (Bianchetti et al., 1995; Van Someren, 2000). The pronounced increase in nighttime activity of both carers and HD patients suggests that more attention should be paid to the management of the sleep disorder in HD. Focused management of disturbed sleep in patients with progressive neurological illnesses such as HD and Parkinson's disease could mean the postponement of the institutionalization of the patient, as well as allowing the spouse or the caregiver a quiet night's sleep. Thus, any therapies that will delay the onset of symptoms in neurodegenerative diseases, even briefly, will have a major impact on public health.

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