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MINIREVIEW

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*We dedicate this study to Vratislav Schreiber, a great Czech endocrinologist, in recognition of his interest in the biological time keeping system and of his sense of humor and fairness*

## Hormones, Subjective Night and Season of the Year

H. ILLNEROVÁ, A. SUMOVÁ, Z. TRÁVNÍČKOVÁ, M. JÁČ, D. JELÍNKOVÁ

*Institute of Physiology, Academy of Sciences of the Czech Republic, Prague, Czech Republic*

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### Summary

Production and release of many mammalian hormones exhibit circadian rhythms controlled by a pacemaker located in the suprachiasmatic nuclei (SCN) of the hypothalamus. Under conditions when the circadian pacemaker free-runs with a period close to, but not equal to 24 h, subjective day and night may not be identical with the environmental day and night. The present study was aimed to define the phase and state of the circadian pacemaker when the circadian system is experiencing subjective night and to ascertain whether and how such a defined subjective night depends on the photoperiod. The results indicate that the subjective night may be defined as the time interval when i) light stimuli can reset the circadian system, ii) pineal melatonin production and photic induction of the c-Fos gene in the ventrolateral SCN are high, and iii) the spontaneous c-Fos protein production in the dorsomedial SCN is low. Such a defined subjective night and, logically, the whole circadian pacemaking system depend on the photoperiod and hence on the season of the year which the animals are experiencing.

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### Key words

Hormones • Circadian rhythms • Suprachiasmatic nucleus • c-Fos • Melatonin

### Introduction

Levels of many mammalian hormones in body tissues and fluids exhibit circadian rhythms, with a maximum of hormone production and release at a certain time of the day (for review see Hastings 1991). Melatonin, ACTH, corticosteroids,  $\beta$ -endorphin, growth

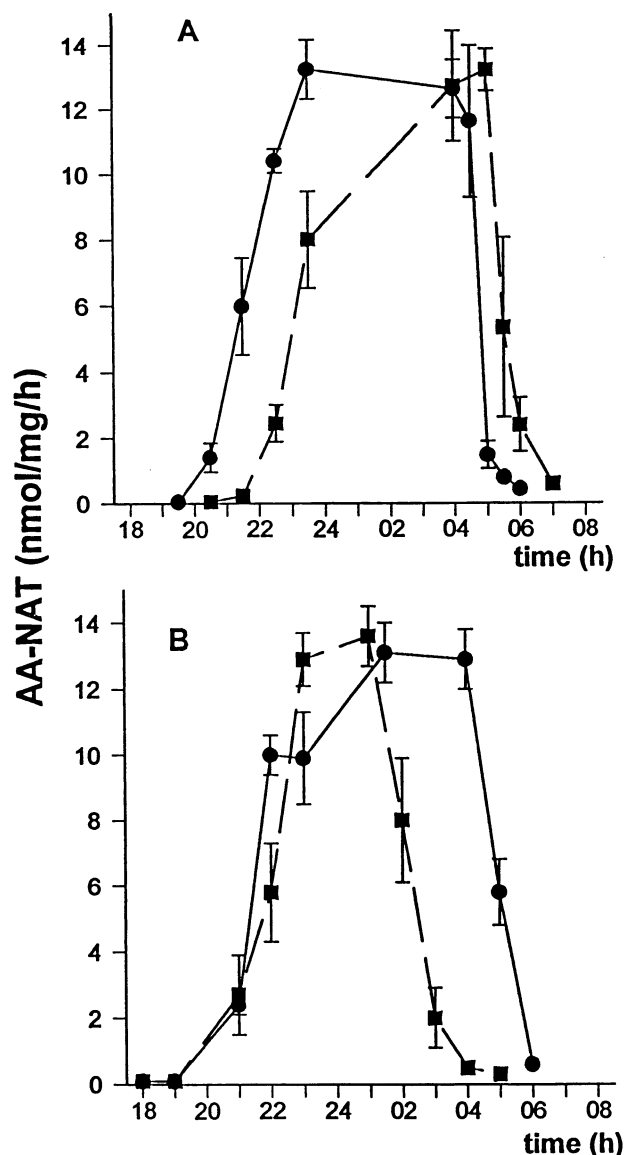
hormone and prolactin belong to this group of hormones; in humans, secretion of the two latter hormones is tightly coupled to central processes which govern slow wave and R.E.M. sleep, respectively. Furthermore, in nocturnal rodents, the ovulatory LH and prolactin surges in the afternoon of proestrous during the 4 to 5 days estrous cycle are under circadian control. In fact, a circadian

influence over the LH surge is still evident in women with normal cycles where repeated sampling of urine revealed that the surge most frequently commences during the mid-morning. Serum testosterone levels may also exhibit daily rhythms.

Some of the above mentioned hormones, namely the pineal hormone melatonin in all mammals, and the growth hormone, prolactin and testosterone in humans, are secreted mostly during the night. ACTH and consequently corticosteroids in man start to be secreted in higher amounts in the late night so that circulating levels of serum cortisol are high prior to wakening.

Endocrine rhythms as well as the rhythms in locomotor activity of animals and in sleep-wake of humans, in body temperature and many other variables are controlled by a circadian pacemaker located in the suprachiasmatic nuclei (SCN) of the mammalian hypothalamus (Klein *et al.* 1991). In a non-periodic environment, the pacemaker free-runs with a period close to, but not equal to 24 h. To the 24-h day, the phase and period of the circadian pacemaker are entrained mainly by the alternation of environmental light and darkness, namely by the light part of the day. Photoc information is conveyed to the SCN by a direct retinal projection, the retinohypothalamic tract, and to a lesser extent also by other pathways, namely the geniculohypothalamic tract (Card and Moore 1991, Moore and Card 1994, Harrington 1997).

When mammals or human subjects are entrained to the 24-h light-dark cycle, i.e. to the 24-h day, it is easy to say, when they are having the night or the day. However, under non-periodic conditions, e.g. in constant darkness or in dim light, without any time-cue, when the circadian pacemaking system free-runs, the subjective day and night may not be identical with the environmental day and night. In nocturnal rodents released into constant darkness, the term subjective night, by convention, designates the active part of the animal's daily cycle. Blind human subjects free-running through time with a period longer than 24 h probably have their subjective night at the time when their blood melatonin is high (Sack *et al.* 1992). The present study was aimed to characterize the mammalian subjective night by different approaches in order to determine whether and how such a subjective night is affected by the length of day, i.e., by the photoperiod or season of the year, and to find how applicable are mammalian data on the subjective night to the human circadian system.



**Fig. 1.** Effect of a light stimulus administered in the early (A) and late (B) night on the arylalkylamine N-acetyltransferase (AA-NAT) rhythm. Rats maintained in LD 12:12 were untreated (circles) or exposed to a 1-min light pulse (squares) at 22:00 h (A) or at 03:00 h (B), then they were released into darkness and the next day the AA-NAT rhythm was followed. After Illnerová and Vaněček (1987).

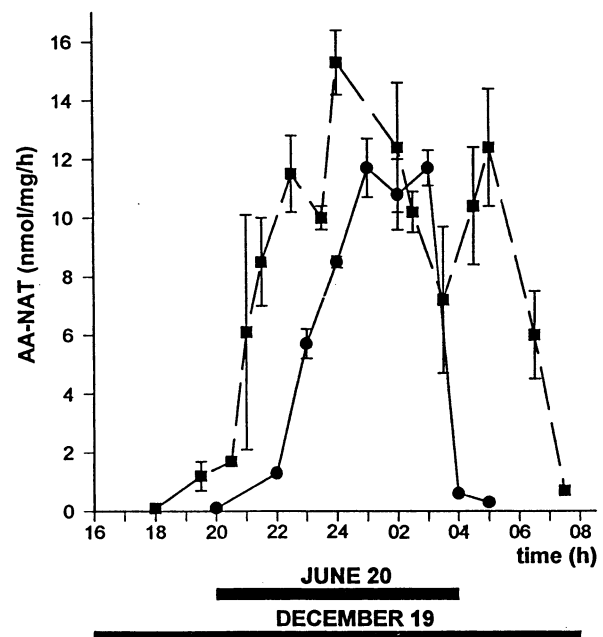
#### **Subjective night 1 – time interval when the pineal melatonin production is high**

One of overt rhythms controlled by the SCN circadian pacemaker is the rhythm in pineal melatonin production, which is driven in the rat by a circadian

rhythm of the pineal arylalkylamine N-acetyltransferase (AA-NAT, E.C. 2.3.1.87) (Illnerová 1991, Klein *et al.* 1997). In the evening in darkness, according to the pacemaker's program, norepinephrine starts to be released from nerve endings in the pineal gland and *via* cAMP and other signaling mechanisms, AA-NAT gene is activated and consequently AA-NAT mRNA, protein and activity are induced (Klein *et al.* 1997). In the morning, neural activation may be switched off, norepinephrine release and cAMP levels may decline and AA-NAT protein and activity decrease rapidly due to selective adrenergic-cAMP controlled proteosomal proteolysis (Gastel *et al.* 1998).

Light stimuli applied to rats in the evening and early night primarily phase-delay the evening AA-NAT rise. However, the next day the whole AA-NAT rhythm is already phase-delayed (Fig. 1A) (Illnerová and Vaněček 1987, Illnerová 1988, 1991, Illnerová and Sumová 1997). Light stimuli administered in the late night and morning primarily phase-advance the morning AA-NAT decline and it takes 3-4 days before the evening AA-NAT rise also starts to be advanced (Fig. 1B). On long summer days, light intruding into the late evening hours phase-delays the evening AA-NAT rise, light intruding into the early morning hours phase-advances the morning AA-NAT decline. Consequently, the interval when AA-NAT activity and melatonin levels are high is shorter in long summer days than in short winter days (Fig. 2) (Illnerová and Vaněček 1980, Illnerová 1988, 1991). In all mammals so far studied, the melatonin signal depends on the photoperiod and may thus transduce information about the length of day (Illnerová 1988). Following a change from a long to a short photoperiod, the melatonin signal in nocturnal rodents becomes extended just gradually (Illnerová *et al.* 1984, 1986, Hastings *et al.* 1987). This finding suggests the existence of a memory trace of long days, which is likely stored upstream from the pineal gland.

Similarly to the rhythmic melatonin production, the locomotor activity of nocturnal rodents, which is also controlled from the SCN, depends on the photoperiod (Elliot and Tamarkin 1994). However, whereas nocturnal mammals are active during the night and diurnal mammals during the day, melatonin is produced mostly during the night, in both nocturnal and diurnal animals. Hence the subjective night may be designated as the time interval when the melatonin production is high; duration of such a subjective night depends on the previous photoperiod to which the animals had been entrained.



**Fig. 2.** Effect of photoperiod on the arylalkylamine N-acetyltransferase (AA-NAT) rhythm. Rats were maintained under a natural photoperiod and the AA-NAT rhythm was followed on June 20 (circles) and December 19 (squares). Full bars indicate dark periods. After Illnerová and Vaněček (1980).

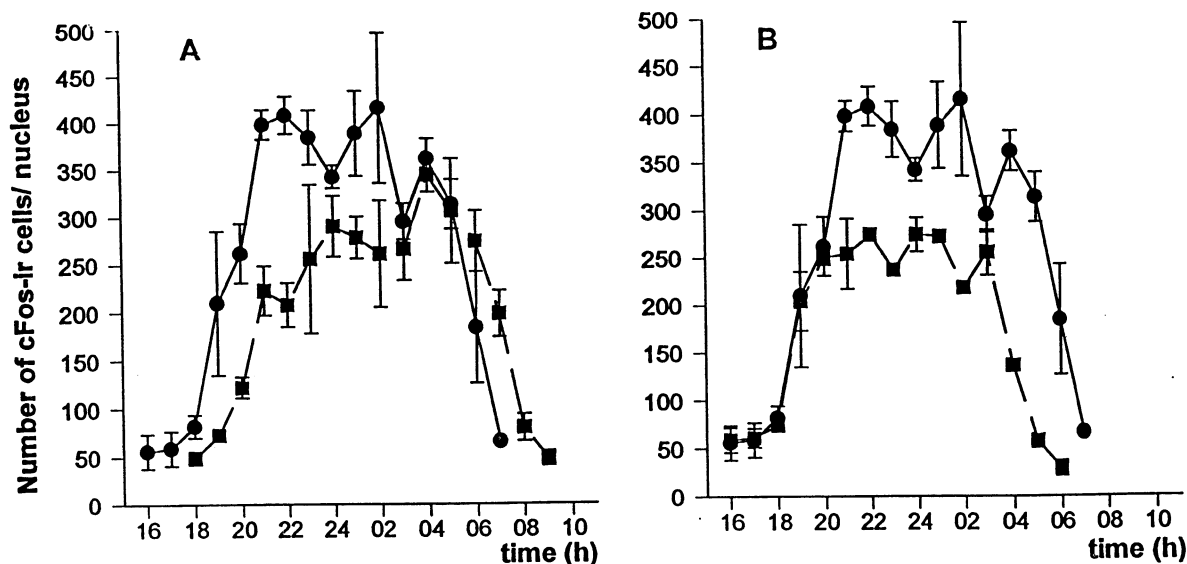
#### **Subjective night 2 – time interval when *c-fos* gene in the SCN is inducible by light**

The previous designation uses an overt rhythm of melatonin production for the subjective night definition. A question arises whether it is also possible to define the subjective night by a rhythm expressed in the SCN circadian pacemaker itself. The SCN exhibits circadian rhythms of electrical (Gillette 1991) and metabolic activity (Schwartz 1991), of arginine vasopressin (AVP) secretion (Majzoub *et al.* 1991, Kalsbeek *et al.* 1998, Jin *et al.* 1999) and, to a certain extent, of intestinal vasoactive peptide production (Inouye and Shibata 1994). Furthermore, the SCN exhibits a circadian rhythm in the photic induction of immediate early genes (for review see Kornhauser *et al.* 1993, Schwartz *et al.* 1995). After a light stimulus, in addition to other processes, immediate early genes, especially *c-fos* and *jun-B* genes, are transcriptionally activated mostly in the retinorecipient (ventrolateral) part of the SCN. These genes are believed to function in coupling short-term signals elicited by extracellular events to long-term changes in the cellular phenotype by

mediating subsequent changes in gene expression (Hughes and Dragunov 1995). After stimulation of a cell and subsequent transcription of *c-fos* and *jun-B*, corresponding protein products *c-Fos* and *Jun-B* are produced and may, as transcription factors, regulate the transcription of late response genes (Kornhauser *et al.* 1993, Schwartz *et al.* 1995). Presence of *c-Fos* in the cell may thus serve as a marker of neuronal activation. Importantly, light induces *c-fos* and *jun-B* expression and elevates *c-Fos* and *Jun-B* in the mammalian SCN only during the subjective night, when it also phase-shifts circadian rhythmicity.

We used the rhythm in *c-Fos* photoinduction as an *in vivo* marker of SCN intrinsic rhythmicity. Rats were

entrained to a light-dark regime with 12 h of light and 12 h of darkness per day (LD 12:12). A 30-min light pulse started to induce high levels of *c-fos* mRNA and *c-Fos* protein in the evening and stopped to induce them in the morning (Fig. 3). Administration of a light stimulus in the early night phase-delayed the whole rhythm in *c-Fos* photoinduction within one day, but the evening rise was more affected than the morning decline (Fig. 3) (Sumová and Illnerová 1998, Illnerová *et al.* 1999). Administration of a light stimulus in the late night primarily phase-advanced the morning decline; the next day following this stimulus, still only the morning decline was phase-advanced.



**Fig. 3.** Effect of a light stimulus administered in the early (A) and late (B) night on the rhythm in *c-Fos* immunoreactivity photoinduction in the SCN. Rats maintained in LD 12:12 were untreated (circles) or exposed to a 1-h light pulse (squares) from 23:00 h to 24:00 h (A) or from 02:00 h to 03:00 h (B) and then they were released into darkness. The next day, they were exposed to a 30-min light pulse at various times and the rhythm in *c-Fos* photoinduction was followed. After Sumová and Illnerová (1998).

Similarly as in the case of rhythmic melatonin production, the window enabling high *c-Fos* photoinduction depended on the photoperiod: in rats maintained previously under a long LD 16:8 photoperiod, the window enabling high *c-fos* mRNA (Fig. 4) and *c-Fos* protein photoinduction was by 5-6 h shorter than that in rats maintained previously under a short LD 8:16 photoperiod (Sumová *et al.* 1995a). The main difference between the waveform of the rhythm in *c-Fos* photoinduction under a long photoperiod and that under a short photoperiod concerned the time of the morning *c-Fos* photoinduction decline; under the a photoperiod,

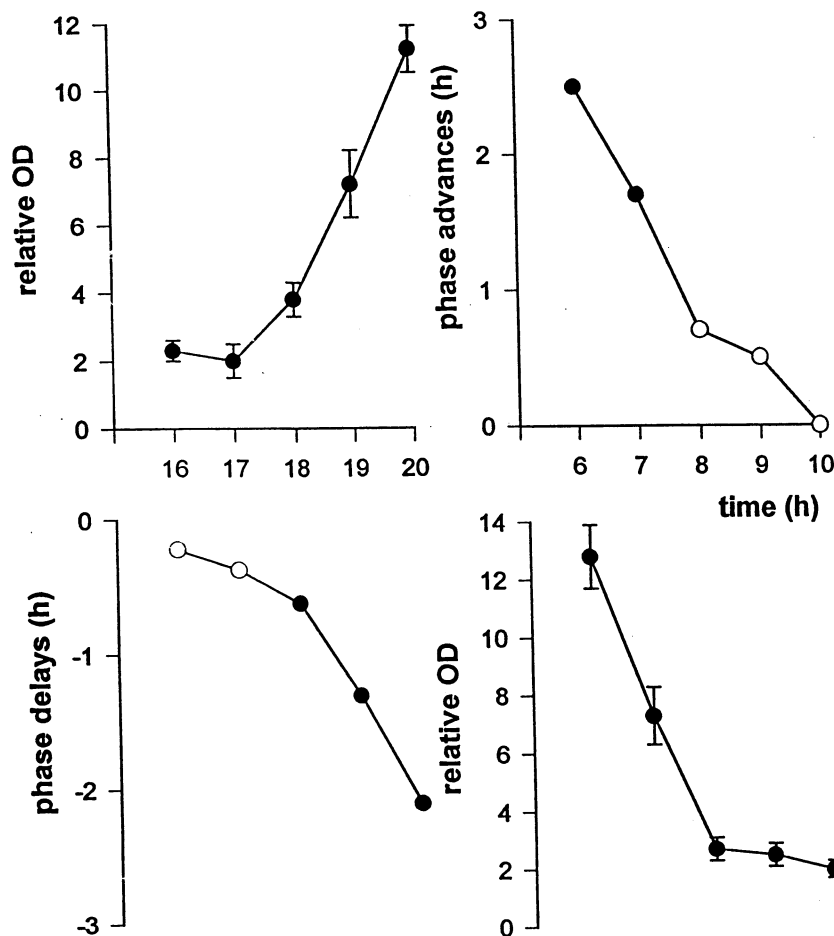
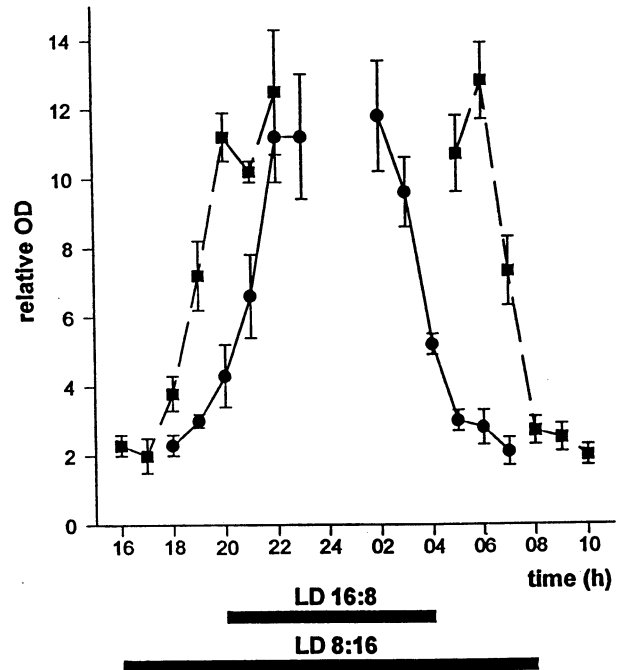
the decline occurred 4 h earlier than under a short one. The findings underscore the importance of the morning onset of light for entrainment of the rat circadian system to the external light-dark cycle; the evening light offset may serve rather as a photoperiodic signal.

Following transition of the rats from a long to a short photoperiod, the decompression of the rhythm waveform occurs gradually (Sumová *et al.* 1995b), similarly as in the case with the decompression of the waveform of the rhythm in melatonin production (Illnerová *et al.* 1986). The data suggest that memory on long days is stored in the long photoperiod entrained state

of the SCN circadian pacemaker, in this case namely in the ventrolateral SCN.

The subjective night may be designated as the time interval enabling high *c-Fos* photoinduction; duration of such a subjective night depends on the previous photoperiod to which the rats had been entrained.

**Fig. 4.** Light-induced *c-fos* gene expression in the SCN under long and short photoperiods. Phase-dependent photic induction of *c-fos* mRNA, measured by *in situ* hybridization, was followed in the SCN of rats previously maintained in either a long (LD 16:8, circles) or a short (LD 8:16, squares) photoperiod and exposed to a single dark period. After Sumová et al. (1995).



**Fig. 5.** Evening rise (left, upper part) and morning decline (right, lower part) of the light-induced level of *c-fos* mRNA and phase delays of the evening AA-NAT rise (left, lower part) and phase advances of morning AA NAT decline (right, upper part) under a short, LD 8:16 photoperiod, plotted as a function of the time of onset of a 30-min light pulse. *c-fos* mRNA was measured by *in situ* hybridization and expressed as relative optical density. Phase delays are expressed as negative hours, phase advances as positive hours. After Trávníčková et al. (1996).

### ***Subjective night 3 – time interval when the circadian system may be reset by light***

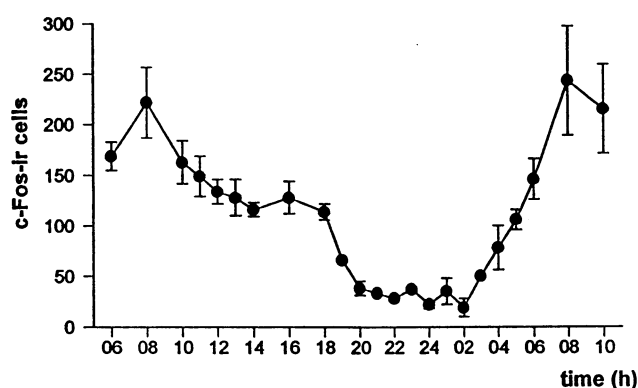
The above discussed rhythm in the light-elevated c-fos mRNA and c-Fos protein may also represent the endogenous rhythm of SCN sensitivity to light. The interval enabling high c-Fos photoinduction may thus be similar to that enabling the resetting of the circadian system by a light stimulus. In rats maintained under a short LD 8:16 photoperiod, the window for c-Fos photoinduction and that for photic resetting of the overt rhythm in the pineal AA-NAT rhythm were indeed almost identical (Fig. 5) (Trávníčková *et al.* 1996). However, in rats maintained under a long LD 16:8 photoperiod, the window for the AA-NAT rhythm resetting appeared to be wider than that for the high c-fos photoinduction. This discrepancy prompted us to study again resetting of the circadian pacemaking system under the long LD 16:8 photoperiod, but this time directly by resetting the intrinsic SCN rhythmicity, namely the rhythm in the light-induced c-Fos. The window for photic resetting of this rhythm under a long photoperiod was the same as the window enabling high c-Fos photoinduction (Jelínková *et al.* in preparation). This close similarity between the c-Fos induction and the resetting effect of light at night indicates that c-Fos expression might be a part of the pathways transducing information on photic stimuli into the resetting mechanisms of the circadian pacemaking system (Wollnick *et al.* 1995, Hastings 1997).

These findings indicate that under both a short as well as a long photoperiod, the window enabling photic resetting of the circadian system is very similar to that enabling high c-Fos photoinduction. The subjective night may be designated as a time interval, when a light stimulus can reset the circadian pacemaking system; the duration of such a subjective night again depends on the photoperiod to which rats had originally been entrained.

### ***Subjective night 4 – time interval when spontaneous c-Fos immunoreactivity in the SCN is low***

As was mentioned above, the rhythm in c-Fos photoinduction is expressed mostly in the ventrolateral or ventral part of the SCN, also called the core, which receives direct or indirect photic inputs (Card and Moore 1991, Moore and Card 1994, Harrington 1997, Leak *et al.* 1999). Besides the ventrolateral part, the SCN is composed of a dorsomedial or a dorsal part called the shell. The dorsomedial SCN mostly receives a nonphotic

input from the cortex, basal forebrain and hypothalamus (Leak *et al.* 1999) and contains many AVP-immunoreactive cells (Inouye and Shibata 1994). The rat dorsomedial SCN exhibits a rhythm in the spontaneous c-Fos immunoreactivity (Fig. 6) (Sumová *et al.* 1998). The immunoreactivity is low during the night and starts to increase before the morning light onset. The higher c-Fos immunoreactivity during the day than during the night may be an expression of elevated dorsomedial SCN neuronal activity during the day. The hamster SCN exhibits a similar rhythm in c-Fos immunoreactivity (Guido *et al.* 1999).



**Fig. 6.** Spontaneous c-Fos immunoreactivity in the dorsomedial SCN. Rats maintained in LD 12:12 were released into constant darkness at the time of the usual light onset at 06:00 h and c-Fos immunoreactivity was followed in darkness. After Sumová *et al.* (1998).

In rats maintained under a long photoperiod and then released into darkness, the interval, when c-Fos immunoreactivity in the rat dorsomedial SCN is low, is by 5-6 h shorter than the interval in rats maintained previously under a short photoperiod (Sumová *et al.* 1999, Sumová *et al.*, in preparation). Following a change from a long to a short photoperiod, the delay of the morning rise of c-Fos immunoreactivity in the dorsomedial SCN occurs only gradually. These findings suggest that the memory on long days may not only be stored in the ventrolateral SCN, but also in the dorsomedial SCN. Hence both parts of the SCN may act as memory store. Alternatively, the ventrolateral SCN may mostly store the memory on long days, as the ventral part projects densely to the dorsal part, but there is little reciprocal innervation (Leak *et al.* 1999).

The subjective night may be designated as the time interval when the spontaneous c-Fos

immunoreactivity in the dorsomedial SCN, indicating neuronal activity, is low. The duration of such a defined subjective night depends again on the previous photoperiod.

#### Further definitions of subjective night

Subjective night might also be a time interval when the SCN electrical activity measured by multiunit activity recordings is low (Meijer *et al.* 1997) or an interval when the SCN metabolic activity determined by  $^{14}\text{C}$ -labelled deoxyglucose uptake is low (Schwartz 1991) or an interval when AVP mRNA and peptide levels in the SCN are low (Majzoub *et al.* 1991, Kalsbeek *et al.* 1998, Jin *et al.* 1991). Until now, the effect of the photoperiod on the duration of above mentioned intervals has not been studied. Quite recently, mammalian core clock genes, namely mClock, BMAL1, mPer1, mPer2, mPer3, Tim, mCRY1 and mCRY2 have been described (for review see Dunlap 1999, Kume *et al.* 1999). Some of these genes and their mRNAs and proteins, e.g. mRNAs of mPer1, mPer2, mPer3, mCRY, proteins mPer1, mCRY1, mCRY2, BMAL are expressed in a circadian manner in the mouse SCN and are part of the mammalian clock feedback loop (Honma *et al.* 1998, Hastings *et al.* 1999, Jin *et al.* 1999, Kume *et al.* 1999). The waveform of the rhythm of PER1 protein in the hamster SCN depends on the photoperiod to which the animals are entrained (Hastings, personal communication). The latter finding on the effect of the photoperiod on the core clock protein rhythm suggests that the whole SCN pacemaking system and hence also the subjective night defined by various ways are modulated by the photoperiod.

#### Subjective night in humans

Under certain conditions, e.g. in blind subjects, the human circadian system may free-run with a period longer than 24 h (Sack *et al.* 1992, Czeisler *et al.* 1999). The subjective night of such free-running human subjects may be designated as the time interval when plasma melatonin and thyrotropin levels are increased, sleep propensity is high whereas body temperature is low; plasma cortisol starts to rise in the late night (Van Cauter *et al.* 1994, Shochat *et al.* 1997). The best marker of a circadian phase appears to be the melatonin rhythm, as other rhythms may also be affected by sleep, stress and activity, besides the circadian pacemaker (Lewy *et al.* 1999). Determination of the phase of the circadian system and of the actual subjective night of an individual is important not just in blind subjects, but also in everyday life; e.g. in two normal subjects entrained to the 24-h day,

the phase of their subjective nights may be more hours apart (Fig. 7). The phase of the circadian system and hence of the subjective night is given mostly by the light-dark cycle (Boivin *et al.* 1996). Shifting of the sleep period at home may also induce phase shifts of the human circadian system; however, such shifting is usually coupled with a change in light exposure (Jelínková-Vondrašová *et al.* 1999).

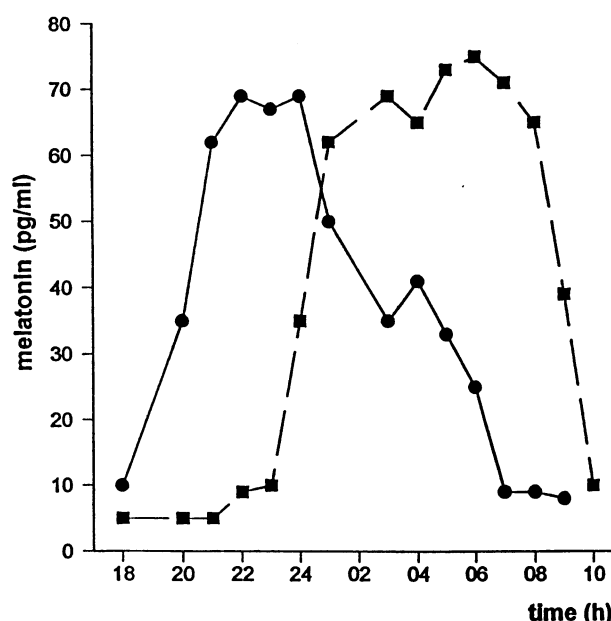


Fig. 7. Serum melatonin profiles of student 1 (circles) and student 2 (squares) from the same class during their examination period. After Illnerová (1995).

When human subjects experience an artificial or natural LD 16:8 regime, the melatonin signal duration is shortened by about 2 h as compared with the pattern under a LD 10:14 regime with forced inactivity during the dark period (Wehr *et al.* 1993). The exposure of human subjects in summer to a natural 16 h bright light photoperiod still shortens their nocturnal melatonin signal by 2 h (Vondrašová *et al.* 1997). However, following a shortening of the natural summer photoperiod, the melatonin signal duration extends markedly within one day (Vondrašová-Jelínková *et al.* 1999). All these findings suggest that even in humans the melatonin signal and hence the subjective night duration is photoperiod-dependent and indicate that the human circadian system is capable of retaining a memory on a 16 h artificial and ambient natural light photoperiod, but not on the summer 16 h natural photoperiod.

## Conclusions

The term subjective night may designate the time interval i) when the circadian pacemaking system is sensitive to light, i.e. when light is capable of inducing the c-fos gene in the ventrolateral SCN and reset the circadian system, ii) when c-Fos immunoreactivity in the dorsomedial SCN indicating neuronal activation is low, and iii) when pineal melatonin production controlled by

the SCN is high. The duration of such defined subjective nights depends on the photoperiod to which the animals had been entrained.

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#### Reprint requests

Dr. Helena Illnerová, Institute of Physiology, Academy of Sciences of the Czech Republic Vídeňská 1083, 142 20 Prague 4, Czech Republic. Tel.: +420-2-475 2437. Fax: +420-2-475 2488 E-mail: illner@biomed.cas.cz