*Physiol. Res. 41: 335 - 344, 1992*

## EDITORIAL

# Resetting of the Mammalian Circadian Clock Through Lowering of the Amplitude: Rat Pineal N-acetyltransferase Rhythm as a Model

H. ILLNEROVÁ

*Institute of Physiology, Czechoslovak Academy of Sciences, Prague*

*Received April 29, 1992*
*Accepted June 10, 1992*

## Summary

During resetting of the mammalian circadian clock, not only phase of the clock is shifted, but amplitude of overt rhythms driven by the clock may be temporarily reduced or even abolished. The present paper is aimed to elucidate the mechanism of amplitude reduction of the overt circadian rhythm in the rat pineal N-acetyltransferase (NAT). The rhythm has two phase markers, namely the time of the evening NAT rise and that of the morning decline. When the phase relationship between both markers is compressed drastically, the NAT rise may occur just close to or at the time of the decline and consequently the NAT rhythm with a full amplitude cannot be expressed. Such a compression may occur in two ways: either animals are subjected to a considerable advance in the light onset which phase advances the morning NAT decline and at the same time phase delays the evening NAT rise, or they are subjected to a considerable delay in the light offset, which primarily phase delays more the NAT rise than the decline. While in the former case the phase markers move in opposite directions, in the latter case they move in the same direction, but to a different extent. The data suggest a complex structure of the underlying clock.

**Key words**

Circadian pacemaker – Amplitude – Resetting – N-acetyltransferase – Rat

## Introduction

The mammalian circadian clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus (Moore and Eichler 1972, Stephan and Zucker 1972, Rusak and Zucker 1979). In a nonperiodic environment, the clock free-runs with its own period tau close to, but not equal to 24 h (Ashoff 1981). Under natural daylight, the clock is synchronized to the 24-h day by daily cycles in light and darkness: light in each cycle resets the circadian pacemaker, either by phase advancing it when tau is longer than 24 h or by phase delaying it when tau is shorter than 24 h (Pittendrigh 1981). Majority of studies on resetting of the mammalian clock has concentrated only on phase shifting of the circadian pacemaker and of the overt rhythms the pacemaker drives, i.e. on a question how the magnitude and direction of the phase shifts depend on the time when a light stimulus is applied (De Coursey 1964, Illnerová and Vaněček 1982, Davis *et al.* 1983, Hoban and Sulzman 1985), while almost no attention has been paid to a possible change of the rhythm amplitude during the resetting. Recently, the question of amplitude change has become urgent: Czeisler and his colleagues (Czeisler *et al.* 1988, 1989, Jewett *et al.* 1991) reported that resetting of the human circadian clock, namely of cortisol and temperature rhythms, might proceed through a temporal amplitude reduction or even a loss of rhythmicity. Such a depression of clock amplitude or termination of all rhythmicity after a light exposure of a certain strength and duration near or at a specific time termed the "singularity point" had been predicted by Winfree (1970) and later confirmed in unicells, insects and plants (Egelman and Johnson 1978, Saunders 1978, Peterson 1980, Malinowski *et al.* 1985). In mammals, excepting studies on man, only scattered observations on resetting of the rat pineal circadian N-acetyltransferase rhythm through a temporal amplitude lowering and eventually abolishment have been reported (Illnerová and

Vaněček 1987a, Illnerová 1988, 1989, Illnerová *et al.* 1987, 1989, Illnerová and Humlová 1990, Humlová and Illnerová 1990, 1992a, 1992b). The aim of the present paper is to summarize the scattered observations on the amplitude reduction in the rat and to suggest a possible underlying mechanism of such a reduction.

*The N-acetyltransferase rhythm as a model rhythm for circadian studies*

The rat pineal N-acetyltransferase (EC 2.3.1.87) (NAT) rhythm which controls the rhythmic melatonin production (Klein and Weller 1970, Illnerová *et al.* 1983) is driven by the SCN pacemaker as other mammalian rhythms are (Klein and Moore 1979). Oscillatory informations proceed from the SCN to sympathetic nerve terminals in the pineal *via* neuronal pathways. According to the pacemaker's programme, norepinephrine is released at night in darkness and through adrenergic receptors and cAMP system induces and activates NAT and thus increases the melatonin production (Klein 1978). The NAT rhythm is a suitable model for circadian studies and may serve as hands of the underlying circadian clock: it exhibits a high amplitude with night time values 100 fold higher than day time ones and moreover, it has two well defined phase markers, namely the time of the evening (E) NAT rise and the time of the morning (M) decline (Fig. 1) (Illnerová and Vaněček 1987b). It is possible to study motions of both phase markers already during the night when the circadian system is perturbed by light and in subsequent days, during the so-called transient cycles, before the system attains a new steady-state. The phase relationship between the evening NAT rise and the morning decline determines the period of elevated NAT activity and hence of the high nocturnal melatonin production and is photoperiod dependent, i.e. short on long summer days and long on short winter days (Illnerová and Vaněček 1980). Recognition of the melatonin signal duration is involved in the photoperiodic time measurement (Goldman and Darrow 1983). A gradual extension of the phase relationship after a change from a long to a short photoperiod (Illnerová *et al.* 1984, 1986) suggests that memory on long days may be stored in the clock itself, i.e. properties of the pacemaker may change according to environmental lighting regimes.

Existence of the two phase markers of one rhythm, i.e. of the time of the NAT rise and of that of the NAT decline enables to study the dynamics and mechanism of the NAT rhythm resetting.

*Amplitude change after an advance in the morning light onset under a shorter photoperiod*

In rats maintained in a lighting regime with 12 h of light and 12 h of darkness per day (LD 12:12)

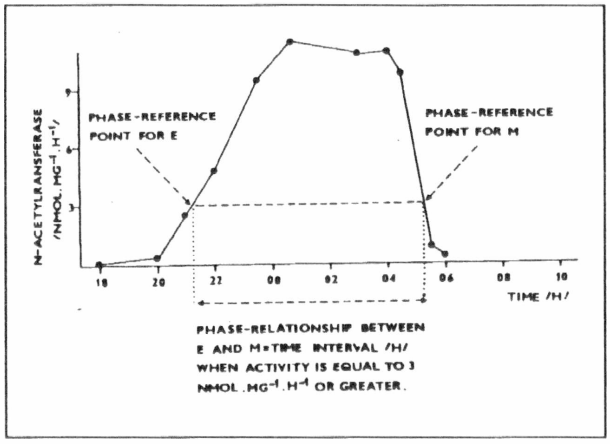


**Fig. 1**

Graphic expression of a hypothetical N-acetyltransferase rhythm. The time when the NAT activity reached the value of 3 $nmol.mg^{-1}.h^{-1}$ which is about 30 times higher than the daytime baseline activity, was arbitrarily chosen as the phase reference point for the evening rise (E). Similarly, the time when the activity declined to the value of 3 $nmol.mg^{-1}.h^{-1}$ was arbitrarily chosen as the phase reference point for the morning decline (M). The time interval between both phase markers represents the phase relationship between them and at the same time indicates duration of the elevated NAT activity.

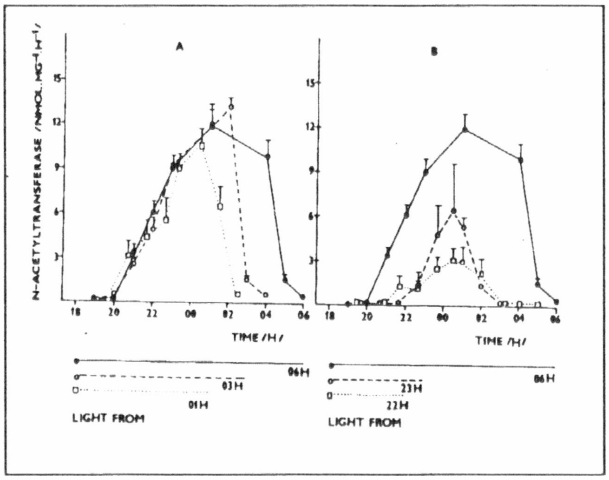


**Fig. 2**

Effect of an advance in the light onset under LD 12:12 on the N-acetyltransferase rhythm the next night. Rats maintained in LD 12:12, with lights on from 06 h to 18 h, were subjected to the usual light offset at 18 h and later that night either to the usual morning light onset at 06 h (full circles) or to bringing forward the light onset A. to 03 h (open circles), 01 h (open squares), B. 23 h (open circles) and 22 h (open squares), respectively. The next day, light was turned off already at 14 h in order to allow an eventual advance of the NAT rise and rats were killed during the subsequent night. Data, taken from Illnerová and Vaněček (1987a), are expressed as means ±S.E.M. of 4 to 8 animals. Lines under the abcissa indicate dark periods during the night when the light onset was brought forward.

and subjected to bringing forward the light onset by 3,5,7 and 8 h, respectively, the morning NAT decline was phase advanced the next day as compared with that in control rats (Fig. 2) (Illnerová and Vaněček, 1987a). The evening NAT rise was either not phase shifted or it was even phase delayed when the light onset was brought forward to before midnight, i.e. by more than 6 h. In the latter case, the NAT rhythm amplitude diminished. Light exposure around midnight might apparently have a dual effect on the NAT rhythm, i.e. a phase advancing effect of the morning NAT decline and at the same time a phase delaying effect on the evening NAT rise. Due to the dual effect, the evening NAT rise might occur near or at the time of the decline and consequently amplitude might temporarily diminish.

A drastic reduction of the NAT rhythm amplitude also occurred after a 4-h light pulse administered around the middle of the night to rats maintained in LD 12:12 (Fig. 3). Apparently, even in this case, light exposure had the dual effect, i.e. a phase advancing effect on the NAT decline and a phase delaying effect on the rise. The rise might occur close to or at about the time of the decline and consequently the amplitude diminished drastically.

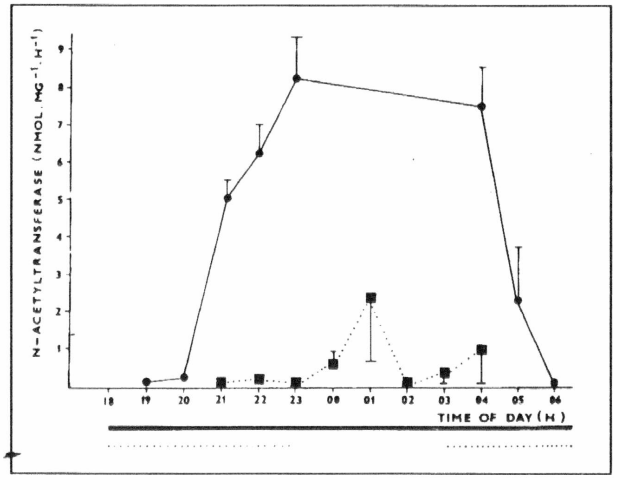


**Fig. 3**

Effect of a 4-hour light pulse on the N-acetyltransferase rhythm the next day. Rats maintained in LD 12:12 were either released into constant darkness at the time of the usual light offset (circles) or were subjected to a light pulse from 23 h to 03 h and only then released into darkness (squares). The NAT rhythm was followed the next night. Data, taken from Illnerová and Vaněček (1987a) are expressed as means ±S.E.M. of 4 animals. Lines under the abcissa indicate dark periods during the night when the rhythm was perturbed by light.

*Amplitude change after an advance shift of the light-dark cycle under a shorter photoperiod*

Advancing of the light-dark (LD) cycle mimics crossing of time zones eastward and involves bringing forward the whole light period. In rats maintained in LD 12:12 and subjected to a 5-h advance of the LD cycle, the NAT rhythm with a normal amplitude persisted following the advance shift, though at the beginning in a compressed waveform (Fig. 4A) (Illnerová and Humlová 1990). However, after a 7-h advance shift of the LD cycle, the NAT rhythm amplitude temporarily diminished and eventually disappeared (Fig.4B). Apparently, in the latter case, the advanced light period had not only a phase advancing effect on the NAT decline, but also a phase delaying effect on the rise. Eventually the rise and the decline might become so close that the rhythm could no longer be expressed. As the NAT rhythm with a normal amplitude persisted after a 5-h, but no more after a 7-h advance shift, it appears that in LD 12:12 a 6-h advance shift of the LD cycle might be a turning point for the persistence or temporal lowering of the NAT rhythm amplitude.

After an 8-h advance of the LD cycle, the NAT rhythm was abolished for 3 subsequent days and reappeared only during day 4 after the shift, though still in a changed waveform (Illnerová *et al.* 1987). The 8-h advance shift was used for clarification of the mechanism underlying the NAT rhythm re-entrainment (Fig. 5) (Illnerová 1989). Rats maintained in LD 12:12 were subjected to the 8-h advance of the LD cycle by shortening of one dark period and were either released into constant darkness after the first advanced light period, after the second advanced light period, and after the third advanced light period, respectively, or were kept in alternating light-dark periods all the time after the shift. After the first advanced light period, the NAT rhythm was expressed in darkness at the time of the original night, though in a compressed waveform and with a lowered amplitude, due apparently to the previous dual effect of the advanced light period (Fig. 5A). After the second advanced light period, the NAT rhythm was still expressed at the time of the original night, though with an even lower amplitude, and the amplitude gradually increased only during the next cycles in constant darkness (Fig. 5B). After the third advanced light period, the NAT rhythm was no longer expressed in the subsequent darkness and appeared only during the next cycle, again at the time of the original night (Fig. 5C). Apparently, after the third advanced light period, the NAT rise and the decline became so close due to the dual effect of advanced light periods, that the rhythm could no longer be expressed even in darkness. Under such a compressed state, after the fourth advanced light period, the NAT activity suddenly phase jumped into the new night (Fig. 5D).

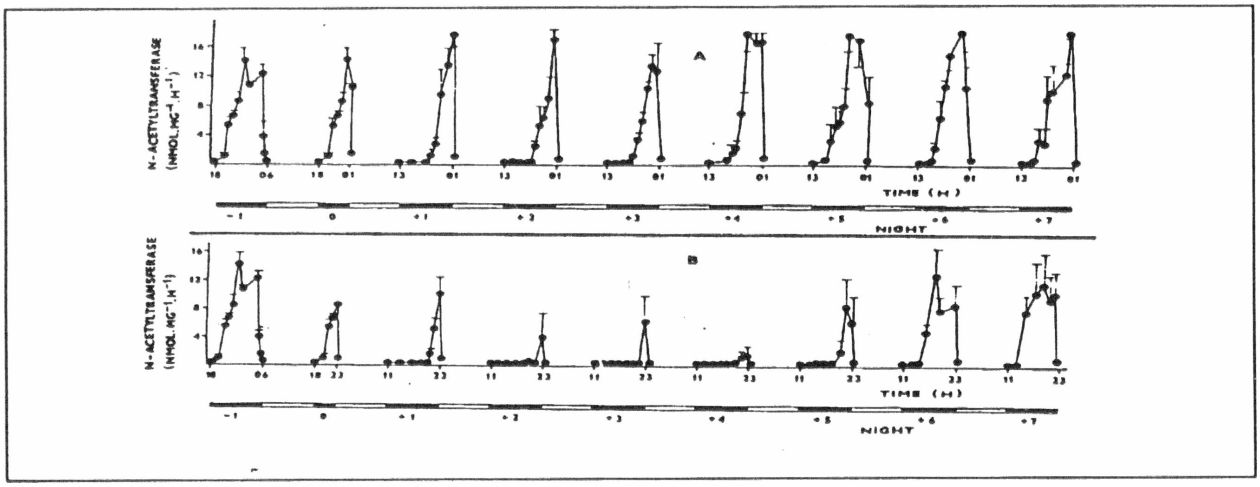


**Fig. 4**

Re-entrainment of the N-acetyltransferase rhythm to a 5-hour advance (A) and a 7-hour advance (B) of the LD 12:12 cycle. Alternating black bars indicate the schedule of advancing the LD cycle by shortening one dark period by 5 hours (A) or by 7 hours (B), respectively. Rats adapted to LD 12:12 were killed during the night before the advance shifts (night -1), during the shortened nights (night 0), and during the subsequent advanced nights (night +1, +2, etc.). Data expressed as means ± S.E.M. of four animals are from Illnerová and Humlová (1990).

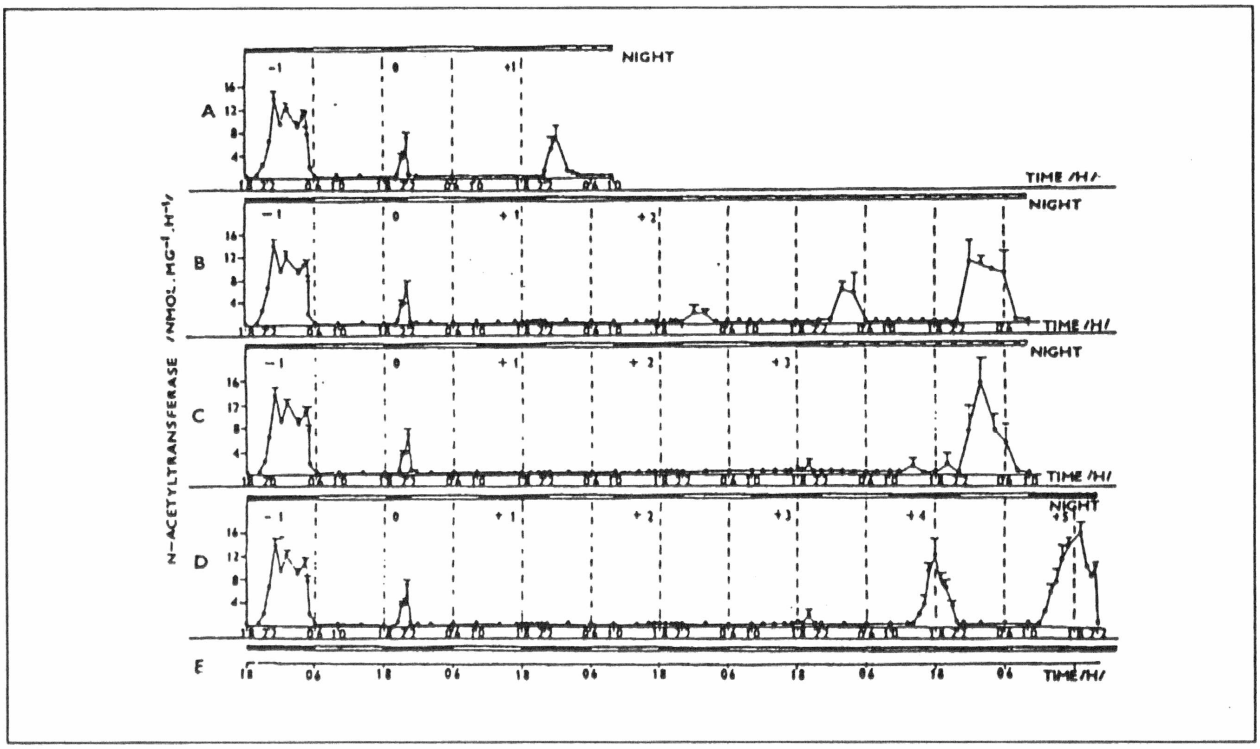


**Fig. 5**

Mechanism of re-entrainment of the NAT rhythm to an 8-hour advance of the LD cycle. Rats maintained in LD 12:12, with lights on from 06 to 18 h, were subjected to the 8-hour advance of the LD cycle, which was accomplished by shortening one dark period by 8 hours. Thereafter, they were either released into constant darkness after the first (A), second (B), or third (C) advanced light period, respectively, or they experienced alternating periods of 12 hours of light and 12 hours of darkness for five consecutive cycles after the advance shift (D). The NAT rhythm was followed before the advanced shift (night -1), during the shortened night (night 0), and after the shift for the next 36 to 120 hours. Black bars above the NAT activity indicate original (-1) and advanced (+1 to +5) nights and crossed bars indicate periods of constant darkness. Black bars in E indicate periods of original nights if they were not advanced. Intermittent lines denote projections of the beginning and of the end of the original night into time axes. Data, taken from Illnerová (1989,) are means ± S.E.M. from 4-12 animals.

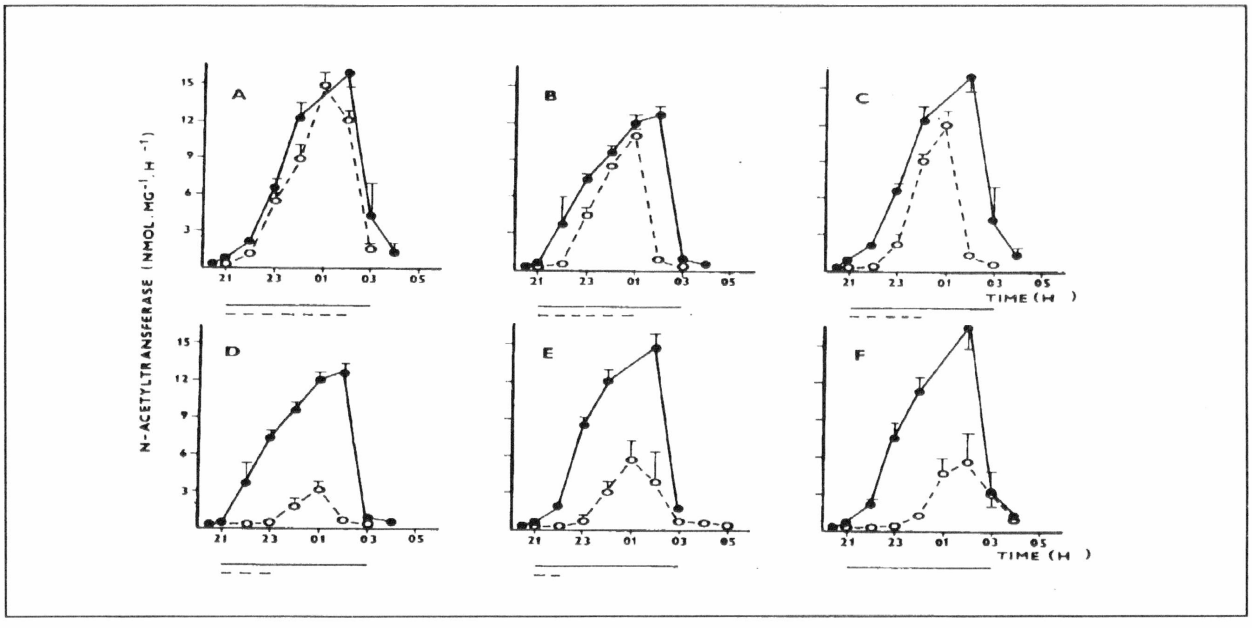


**Fig. 6**

Response of the N-acetyltransferase rhythm under LD 18:6 to an advance in the morning light onset the next night. Rats maintained in LD 18:6 were subjected to the usual evening light offset at 21 h and later that night either to the usual morning light onset at 03 h (full symbols) or to an advance in the light onset to 02 h (A), 01 h (B), 00 h (C), 23 h (D) and 22 h (E) respectively; eventually, light was left on the whole night (F) (open symbols). The next day, light was already turned off at 14 h and the NAT rhythm was followed in the subsequent darkness. Lines under the abcissa indicate dark periods during the previous night. Data, taken from Humlová and Illnerová (1992a), are expressed as means ±S.E.M.

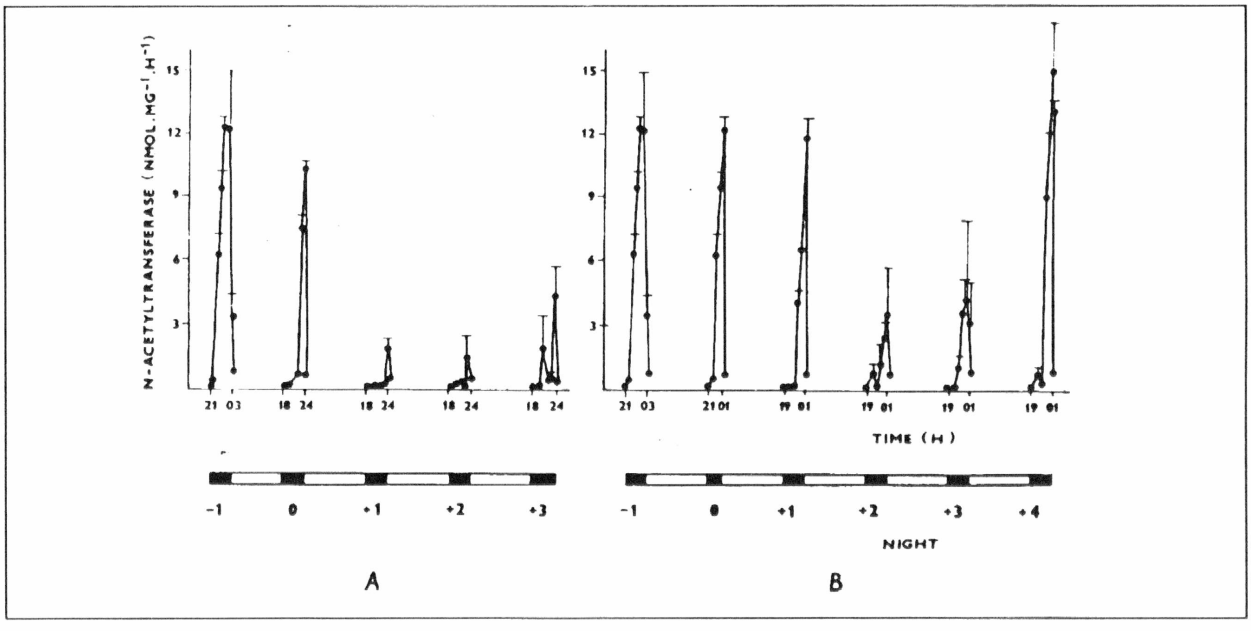


**Fig. 7**

The effect of a 3-hour (A) and 2-hour (B) advance of the LD 18:6 regime on the NAT rhythm. Rats adapted to LD 18:6 were subjected either to the 3-hour advance of the LD cycle accomplished by shortening of one light period by 3 hours (A) or to the 2-hour advance of the LD cycle accomplished by shortening of one dark period by 2 hours (B). The NAT rhythm was followed before the advance shifts (night -1), during the shifts (night 0), during night +1, +2 and +3 after the advance shifts and eventually during night +4. Bars under the abcissa indicate dark periods. Data, taken from Humlová and Illnerová (1992b) are expressed as means ±S.E.M. of 4 animals.

*Amplitude change after an advance in the morning light onset under a longer photoperiod*

Resetting of the mammalian circadian clock does not depend only on the time when a light stimulus is presented but on the photoperiod under which animals are maintained as well (Illnerová and Vaněček 1985, Illnerová and Humlová 1990, Humlová and Illnerová 1992a, 1992 b, Elliot and Pittendrigh, personal communication). When rats maintained under a very long photoperiod, in LD 18:6, were subjected to bringing forward the light onset, the morning NAT decline the next day was phase advanced in all cases, while the evening NAT rise was phase delayed (Fig. 6) (Humlová and Illnerová 1992a). Under such a long photoperiod, even a mere 1-h advance in the light onset, had the dual effect on the NAT rhythm, i.e. it phase delayed the evening NAT rise and phase advanced the morning decline. Whereas phase delays of the NAT rise gradually increased with the increasing advance of the light onset, phase advances of the NAT decline first increased and later, when the light onset was brought forward to before midnight, decreased again. Eventually, the NAT rise and the decline became so close that the amplitude diminished.

*Amplitude change after an advance shift of the light-dark cycle under a longer photoperiod*

In rats maintained in LD 18:6 the NAT rhythm amplitude temporarily decreased after a 3 h advance of the LD cycle (Fig. 7A) and even after a mere 2-h advance shift (Fig. 7B): while the NAT decline was phase advanced, the NAT rise became gradually phase delayed (Humlová and Illnerová 1992b). The data are in consonance with the fact that under a long photoperiod, even a very short advance of the light onset has the dual effect on the NAT rhythm.

*Amplitude change after a delay in the evening light offset under a shorter photoperiod*

In rats maintained in LD 12:12 and subjected to a 10-h delay in the evening light offset, the next day the NAT rhythm was phase delayed as a whole by more than 6 h as compared with the rhythm in control rats subjected to the usual lights off (Fig. 8A) (Illnerová and Vaněček 1987a). After a 12-h delay in the evening light offset, the next day the NAT rhythm amplitude decreased dramatically as compared with that in control animals (Fig. 8B). The NAT rise was phase delayed to a much larger extent than the decline so that it occurred close to or at about the time of the decline; consequently, the NAT rhythm could not be fully expressed.

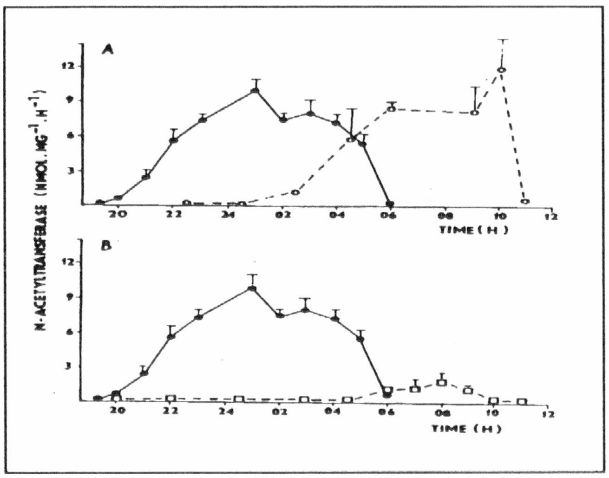


**Fig. 8**

Effect of a 10-hour (A) and a 12-hour (B) delay in the light offset under LD 12:12 on the N-acetyltransferase rhythm the next day. Rats maintained in LD 12:12 were either released into constant darkness at the time of the usual light offset (full symbols) or were subjected to a 10-hour (A) and a 12-hour (B) delay in the light offset, respectively (open symbols) and only then released into darkness; the NAT rhythm was followed the next day. Data, taken from Illnerová and Vaněček (1987a), are expressed as means ±S.E.M. of 4 animals.

*Amplitude change after a delay in the evening light offset under a longer photoperiod*

In rats maintained in LD 18:6, subjected to a 2-h delay in the evening light offset and thereafter released into darkness, only the NAT rise was phase delayed in the subsequent darkness but not the decline; consequently, the NAT rhythm waveform was compressed (Fig.9A) (Humlová and Illnerová, 1992a). After a 4-h (Fig. 9B) and a 6-h (Fig. 9C) delay in the light offset, no NAT rhythm with a normal amplitude was expressed during the same night. The next night, the NAT rhythm with a normal amplitude persisted and was phase delayed after a 4-h delay in the evening light offset (Fig. 10A), but not after an 8-h delay (Fig. 10B) or a 10-h delay (Fig. 10C). After the 8-h delay, only the evening NAT rise was phase delayed and occurred thus close to the time of the morning NAT decline.

*Model of resetting of the circadian N-acetyltransferase rhythm through reduction or abolition of the amplitude*

All presented data suggest that reduction of the NAT rhythm amplitude may proceed through two ways (Fig. 11). First, an advanced light period or exposure to light at a specific night time may have a dual effect on the NAT rhythm, i.e. may phase delay

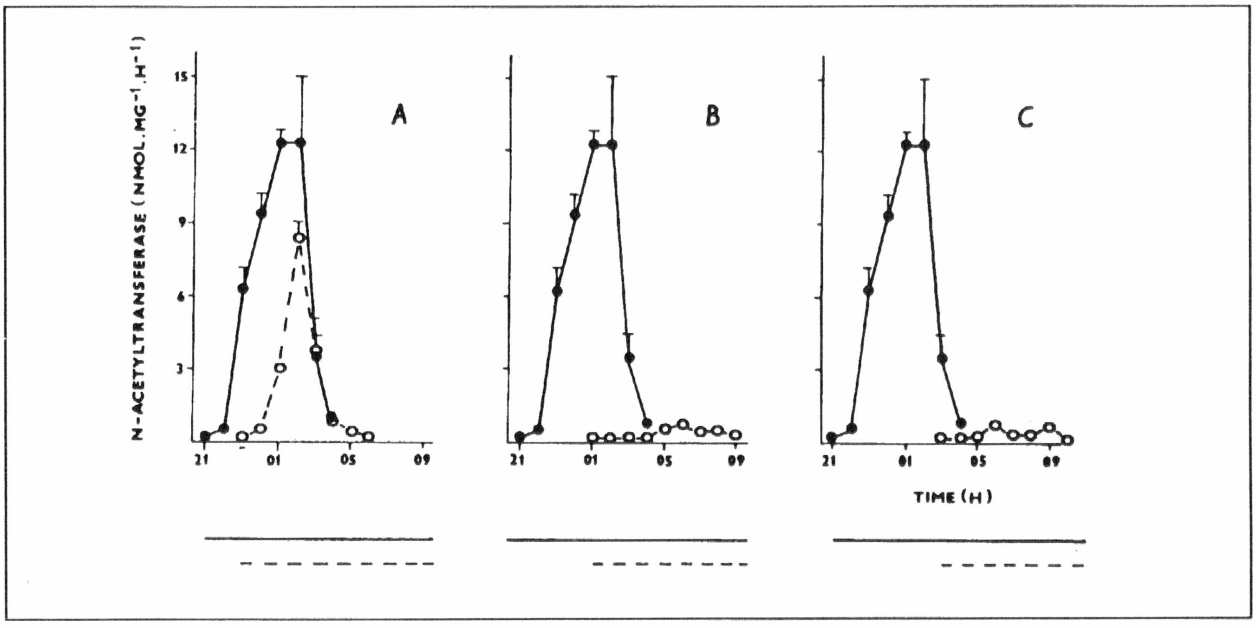


**Fig. 9**

Response of the N-acetyltransferase rhythm under LD 18:6 to a delay in the evening light offset during the same night. Rats maintained in LD 18:6 were either subjected to the usual evening light offset at 21 h (full symbols) or to a delay in the light offset till 23 h (A), 01 h (B), and 03 h (C), respectively (open symbols). Thereafter, they were released into darkness and the NAT rhythm was followed immediately. Lines under the abcissa indicate periods of darkness. Data, taken from Humlová and Illnerová (1992a) are expressed as means ±S.E.M. of 4 animals.

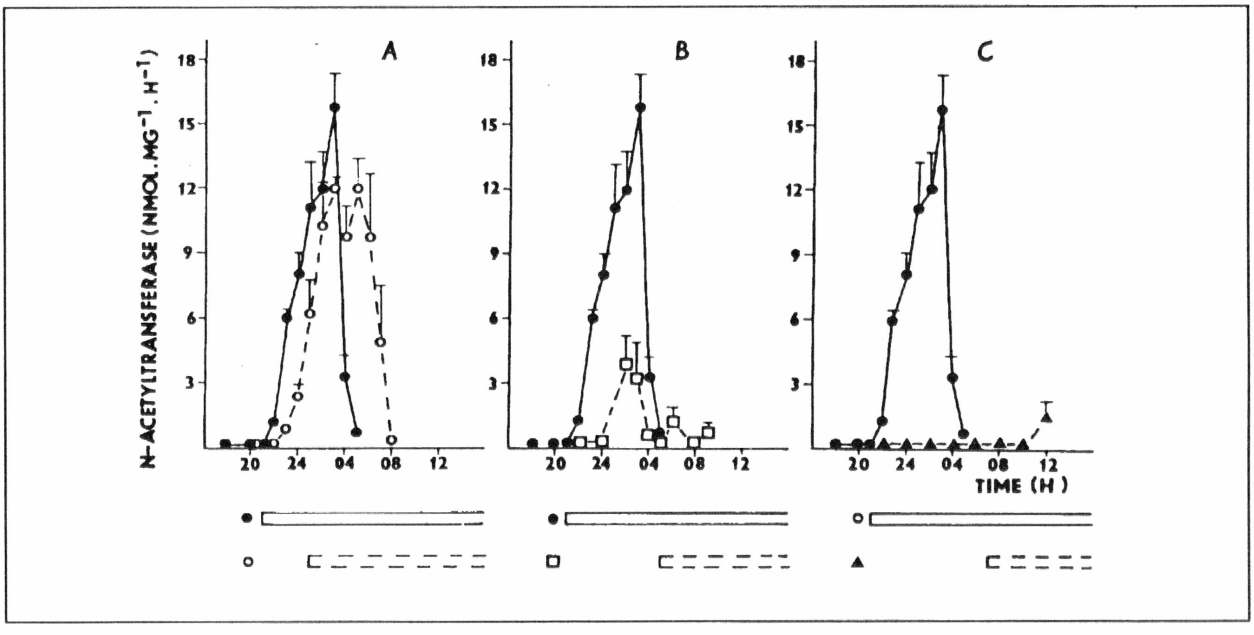


**Fig. 10**

Response of the N-acetyltransferase rhythm under LD 18:6 to a delay in the evening light offset the next night. Rats maintained in LD 18:6 were either subjected to the usual evening light offset at 21 h (full circles), or to a delay in the light offset till 01 h (A; open squares), 05 h (B; open squares), and 07 h (C; full triangles), respectively. Thereafter, they were released into darkness and the NAT rhythm was followed the next night. Bars under the abcissa indicate dark periods during the previous night. Data, taken from Humlová and Illnerová (1992a) are expressed as means ±S.E.M. of 4 animals.

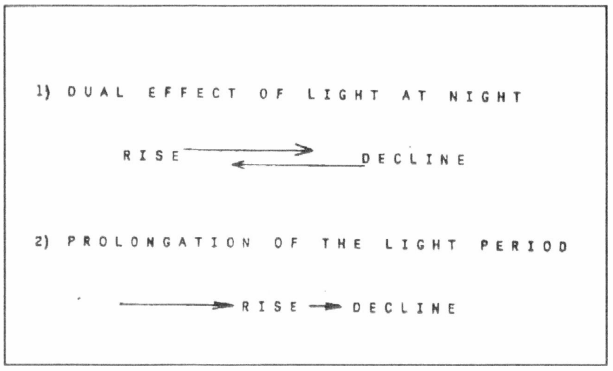


**Fig. 11**

Two ways of compression of the phase relationship between the evening N-acetyltransferase rise and the morning decline which may lead to the NAT rhythm amplitude reduction. For details see text.

the evening NAT rise and phase advance the morning NAT decline. The rise and the decline thus move in opposite directions and eventually they may become so close that the rise may occur just near to or at the time of the decline. In such a case, the NAT rhythm amplitude diminishes or the rhythm ceases to be expressed. Secondly, a considerable extension of the light period into the night hours may phase delay the evening NAT rise more than the morning NAT decline. Though in this case the rise and the decline move in the same direction, they may eventually become so close that the NAT rise may occur just close to or at the time of the NAT decline. Consequently, the NAT rhythm amplitude again diminishes or the overt rhythmicity is abolished. Under a longer photoperiod, amplitude reduction occurs after smaller light perturbations than under a shorter photoperiod, as in long days the phase relationship between the evening NAT rise and the morning decline is already compressed (Illnerová 1988).

The model may explain amplitude reduction during resetting of the NAT rhythm. This rhythm represents a unique model in that it involves two phase markers and thus makes it possible to follow a phase relationship between them. The phase relationship might reflect a phase relationship between two components of an underlying circadian pacemaker (Pittendrigh and Daan 1976, Illnerová and Vaněček 1982). At present it is not possible to say whether the model is also valid for other circadian rhythms. Though they are controlled by the same pacemaker as the NAT rhythm (Rusak and Zucker 1979), usually only one phase marker may be followed. Eventually, amplitude reduction and abolishment during a specific circadian clock resetting may be explained by a concept and even mathematical necessity of the phase-free singular condition of a physiological rhythm generator (Winfree 1970).

**Acknowledgements**

The research was partly supported by the Czechoslovak Academy of Sciences grant number 71118.

## References

ASHOFF J.: Freerunning and entrained circadian rhythms. In: *Handbook of Behavioral Neurobiology, Vol. 4, Biological Rhythms.* J. ASCHOFF (ed), Plenum Press, New York and London, 1981, pp. 81–93.

CZEISLER C.A., ALLAN J.S., KRONAUER R.E., DUFFY J.F.: Strong circadian phase resetting in man is affected by bright light suppression of circadian amplitude. *Sleep Res.* **17**: 367, 1988.

CZEISLER C.A., KRONAUER R.E., ALLAN J.S., DUFFY J.F., JEWETT M.E., BROWN E.N., RONDA J.M.: Bright light induction of strong (Type 0) resetting of the human circadian pacemaker. *Science* **244**: 1328–1333, 1989.

DAAN S., PITTENDRIGH C.S.: A functional analysis of circadian pacemaker in nocturnal rodents: II. The variability of phase response curves. *J. Comp. Physiol.* **106**: 252–266, 1976.

DAVIS F.C., DARROW J.M., MENAKER M.: Sex differences in the circadian control of hamster wheel-running activity. *Am. J. Physiol.* **244** *(Reg. Integr. Comp. Physiol.* **13**): R93–R105, 1983.

DE COURSEY P.J.: Daily light sensitivity rhythm in a rodent. *Science* **131**: 33–35, 1960.

ENGELMAN W., JOHNSSON A., KOBLER H.G., SCHIMMEL M.L.: Attenuation of Kalanchoe's petal movement rhythm with light pulses. *Physiol. Plant.* **43**: 69–76, 1978.

GOLDMAN B.D., DARROW J.M.: The pineal gland and mammalian photoperiodism. *Neuroendocrinology* **37**: 386–396, 1983.

HOBAN T.M., SULZMAN F.M.: Light effects on circadian timing system of a diurnal primate, the squirrel monkey. *Am. J. Physiol.* **249** *(Reg. Integr. Comp. Physiol.* **18**): R274–R280, 1985.

HUMLOVÁ M., ILLNEROVÁ H.: Rate of re-entrainment of circadian rhythms to advances of light-dark cycles may depend on ways of shifting the cycles. *Brain Res.* **531**: 304–306, 1990.

HUMLOVÁ M., ILLNEROVÁ H.: Resetting of the rat circadian clock after a shift of the light-dark cycle depends on photoperiod. *Neurosci. Res.* **13:** 147–153, 1992.

HUMLOVÁ M., ILLNEROVÁ H.: Entrainment of the rat circadian clock controlling the pineal N-acetyltransferase rhythm depends on photoperiod. *Brain Res.*, in press.

ILLNEROVÁ H.: Entrainment of mammalian circadian rhythms in melatonin production by light. *Pineal Research Reviews* **6:** 173–217, 1988.

ILLNEROVÁ H.: Mechanism of re-entrainment of the circadian rhythm in the rat pineal N-acetyltransferase to an eight-hour advance of the light-dark cycle: phase jump is involved. *Brain Res.* **434:** 365–368, 1989.

ILLNEROVÁ H., HUMLOVÁ M.: The rat pineal N-acetyltransferase rhythm persists after a five-hour, but disappears temporarily after a seven-hour advance of the light-dark cycle: a six-hour shift may be a turning point. *Neurosci. Let.* **110:** 77–81, 1990.

ILLNEROVÁ H., VANĚČEK J.: Pineal rhythm in N-acetyltransferase activity in rats under different artificial photoperiods and in natural daylight in the course of a year. *Neuroendocrinology* **31:** 321–326, 1980.

ILLNEROVÁ H., VANĚČEK J.: Two-oscillator structure of the pacemaker controlling the circadian rhythm of N-acetyltransferase in the rat pineal gland. *J. Comp. Physiol.* **A 145:** 539–548, 1982.

ILLNEROVÁ H., VANĚČEK J.: Entrainment of the circadian rhythm in rat pineal N-acetyltransferase activity under extremely long and short photoperiods. *J. Pineal Res.* **2:** 67–78, 1985.

ILLNEROVÁ H., VANĚČEK J.: Entrainment of the circadian rhythm in the rat pineal N-acetyltransferase activity by prolonged periods of light. *J. Comp. Physiol.* **A 161:** 495–510, 1987a.

ILLNEROVÁ H., VANĚČEK J.: Pineal N-acetyltransferase: a model to study properties of biological clocks. In: *Fundamentals and Clinics in Pineal Research, Sereno Symposia 44.* G.P. TRENTINI, C. DE GAETANI, P. PEVET (eds), Raven Press, New York, 1987b, pp. 165–190.

ILLNEROVÁ H., VANĚČEK J., HOFFMANN K.: Regulation of the pineal melatonin concentration in the rat (Rattus norvegicus) and in the Djungarian hamster (Phodopus sungorus). *Comp. Biochem. Physiol.* **74A:** 155–159, 1983.

ILLNEROVÁ H., HOFFMANN K., VANĚČEK J.: Adjustment of pineal melatonin and N-acetyltransferase rhythms to change from long to short photoperiod in the Djungarian hamster Phodopus sungorus. *Neuroendocrinology* **38:** 226–231, 1984.

ILLNEROVÁ H., HOFFMANN K., VANĚČEK J.: Adjustment of the rat pineal N-acetyltransferase rhythm to change from long to short photoperiod depends on the direction of extension of the dark period. *Brain Res.* **362:** 403–408, 1986.

ILLNEROVÁ H., VANĚČEK J., HOFFMANN K.: Adjustment of the rat pineal N-acetyltransferase rhythm to eight-hour shifts of the light-dark cycle: advance of the cycle disturbs the rhythm more than delay. *Brain Res.* **417:** 167–171, 1987.

ILLNEROVÁ H., VANĚČEK J., HOFFMANN K.: Different mechanisms of phase delays and phase advances of the circadian rhythm in the rat pineal N-acetyltransferase activity. *J. Biol. Rhythms* **4:** 187–200, 1989.

JEWETT M.E., KRONAUER R.E., CZEISLER C.A.: Light-induced suppression of endogenous circadian amplitude in humans. *Nature* **350:** 59–62, 1991.

KLEIN D.C.: The pineal gland: a model of neuroendocrine regulation. In: *The Hypothalamus.* S. REICHLIN, R.J. BALDESSARINI, J.B. MARTIN (eds), Raven Press, New York, 1978, pp. 303–327.

KLEIN D.C., MOORE R.J.: Pineal N-acetyltransferase and hydroxyindole-O-methyltransferase: control by the retinohypothalamic tract and the suprachiasmatic nucleus. *Brain Res.* **174:** 245–262, 1979.

KLEIN D.C., WELLER J.L.: Indole metabolism in the pineal gland. A circadian rhythm in N-acetyltransferase activity. *Science* **169:** 1093–1095, 1970.

MALINOWSKI J.R., LAVAL-MARTIN D.L., EDMUNDS L.N.: Circadian oscillators, cell cycles, and singularities: light perturbations of the free-running rhythm of cell division in Euglena. *J. Comp. Physiol.* **B 155:** 257–267, 1985.

MOORE R.Y., EICHLER V.B.: Loss of a circadian adrenal corticosterone rhythm following suprachiasmatic lesions in the rat. *Brain Res.* **42:** 201–206, 1972.

PETERSON E.L.: Phase-resetting a mosquito circadian oscillator. I. Phase resetting surface. *J. Comp. Physiol.* **138:** 201–211, 1980.

PITTENDRIGH C.S:: Circadian systems: entrainment. In: *Handbook of Biological Neurobiology, Vol. 4, Biological Rhythms.* J. ASCHOFF (ed), Plenum Press, New York, 1981, pp. 95–124.

PITTENDRIGH C.S., DAAN S.A.: A functional analysis of circadian pacemakers in nocturnal rodents. V. Pacemaker structure: A clock for all seasons. *J. Comp. Physiol.* **106:** 333–355, 1976.

RUSAK B., ZUCKER J.: Neural regulation of circadian rhythms. *Physiol. Rev.* **59:** 449–526, 1979.

SAUNDERS D.S.: An experimental and theoretical analysis of photoperiodic induction in the flesh-fly, Sarcophaga argyrostoma. *J. Comp. Physiol.* **124:** 75–95, 1978.

STEPHAN F.K., ZUCKER J.: Circadian rhythms in drinking behavior and locomotor activity of rats are eliminated by hypothalamic lesions. *Proc. natl. Acad. Sci. USA* **69**: 1583–1586, 1972.
WINFREE A.T.: An integrated view of the resetting of a circadian clock. *J. Theor. Biol.* **28**: 327–374, 1970.

---

**Reprint Requests**
RNDr. H. Illnerová, Institute of Physiology, Czechoslovak Academy of Sciences, CS-142 20 Prague 4, Vídeňská 1083.