Abnormalities of circadian rhythmicity in liver disease

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Under normal conditions, a wide range of biological processes exhibit a diurnal rhythm of approximately 24 h (the term circadian arises from the Latin, circa=approximately, diem=day). The most obvious rhythm is the one related to variations in the sleep/wake cycle, but almost all aspects of the internal environment undergo such changes over a 24-h period. This oscillation occurs in parallel to the daily alteration in external conditions that our rotatory planet imposes on all species. Thus, a teleological perspective of circadian function would posit that such internal organization allows adequate adaptation to the changing external environment. However, there is ample evidence to indicate that circadian rhythms arise from an internal time-keeping system that functions even in the absence of external cues (1). The existence of a “biological clock” with its afferent/efferent connections allows the organism to foresee and anticipate the modifications in the external environment that occur during the day/night cycle.

Abnormal rhythms of several biological parameters have been described in patients with cirrhosis. The robustness of these findings will be influenced by the frequency of recording, and few studies have utilized continuous or very frequent samples in patients with liver disease. Furthermore, a diurnal variation cannot be truly termed circadian until it is shown that the rhythm persists under conditions of a constant external environment. However, there is ample evidence to indicate that circadian rhythms arise from an internal time-keeping system that functions even in the absence of external cues (1). The existence of a “biological clock” with its afferent/efferent connections allows the organism to foresee and anticipate the modifications in the external environment that occur during the day/night cycle.

Abnormal rhythms of several biological parameters have been described in patients with cirrhosis. The robustness of these findings will be influenced by the frequency of recording, and few studies have utilized continuous or very frequent samples in patients with liver disease. Furthermore, a diurnal variation cannot be truly termed circadian until it is shown that the rhythm persists under conditions of a constant external environment. Still, most biological oscillations are shown to persist under controlled circumstances, and diurnal variations under natural conditions can be viewed as reflecting circadian processes. Reports of abnormal rhythmicity in liver disease include such diverse processes as the lack of diurnal variation of arterial pressure in continuous 24-h recordings (2), the blunted rhythm of several hormones, such as angiotensin and aldosterone (3), the nocturnal rise in portal pressure (4) and alterations of the rhythm of plasma melatonin (5) and sleep patterns (6) in patients with compensated cirrhosis. The clinical observations suggest a generalized abnormality of circadian function in cirrhosis. Our experimental observations suggest a complex pathogenesis for these abnormalities.

Circadian Dysfunction and Hepatic Encephalopathy

A common symptom of patients with early hepatic encephalopathy is the inability to sleep during the night, while exhibiting sleepiness during the daytime. It was logical then to examine whether experimental models of hepatic encephalopathy exhibit changes in circadian rhythmicity. It had been previously shown that rats after portacaval anastomosis, a model that reproduces some features of hepatic encephalopathy, exhibit alterations in the distribution of activity during the 24-h day (7). In our studies, we went one step further by choosing the rhythm of circadian locomotor activity to characterize potential abnormalities in circadian function. In this paradigm, animal cages include an attached wheel where rodents will initiate running activity during the nighttime hours. This behavioral rhythm can be easily measured for many weeks without disturbing the animal’s environment via a computerized analysis of wheel revolutions.

Experiments in this model were performed under strict conditions of entrainment to the light/dark cycle and in a setting that allowed expression of “free-running” circadian rhythms (constant low level illumination). These animals exhibited a spectrum of abnormalities in circadian function, ranging from a blunted capacity to entrain to the light/dark (LD) stimulus to an absence of endogenous circadian rhythm of locomotor activity (8,9). We also observed that the abnormal entrainment to the L/D cycle is affected by the extent of portal-systemic shunting (9) and is ameliorated by a low-protein diet (10), by the administration of neomycin (11) and is less conspicuous with a stenosed portacaval shunt (12). These interventions, known to improve an abnormal mental state in human liver disease, suggest that abnormalities of circadian func-

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Circadian rhythmicity in liver disease may arise from neurochemical alterations seen in hepatic encephalopathy. Preliminary observations indicate that hyperammonemia in the absence of liver disease can result in abnormalities of circadian locomotor activity in the rat (13). Under this light, the derangement of circadian function could arise from the effects of neurotoxins implicated in hepatic encephalopathy on specialized areas of the brain.

Anatomical Considerations
The anatomical pathways that subserve the circadian timekeeping system are well defined (14) (Fig. 1): (a) The suprachiasmatic nucleus (SCN) of the anterior hypothalamus is the pacemaker, a “biological clock” that can generate “endogenous” self-sustained rhythms in the absence of external clues. (b) Afferent pathways, related to photic and non-photic stimuli, travel (in the case of the former) from the retina via the retinohypothalamic tract to the SCN. (c) Efferent pathways, a complex array of connections to other structures in the hypothalamus, thalamus and basal forebrain, link the SCN to different effector systems and neurohumoral connections.

Where could the abnormality lie in patients with liver disease?

Afferent pathways
Anatomical changes in the retina have been described in patients with cirrhosis (15). These are characterized by abnormalities in Müller cells, glial cells of the retina, that parallel the morphologic alterations in astrocytes seen throughout the brain (16). It has been postulated that these changes could add to deficiencies in vitamin A (17) and translate into functional abnormalities of phototransduction (18). However, it is unknown whether the subset of retinal cones that serve as photoreceptors for the circadian system may be affected.

Non-photic signals can influence circadian function in several vertebrate species. Changes in ambient temperature, periodic presentation of food and changes in physical activity/inactivity will affect the “biological clock” of rodents (19). In the case of humans, factors such as social cues, the sleep/wake state and physical exercise are important synchronizing agents (20). It is possible that the impact of chronic disease on general well-being may affect such non-photic stimuli in liver disease. However, when we compared the sleep patterns of patients with cirrhosis to those of another chronic ailment, chronic renal failure, we noted differences in the choice of bedtime and awakening between the two diseases (6). Nonetheless, the role of chronic disease in circadian dysfunction is still a distinct possibility and studies are needed to explore the role of non-photic signals in chronic liver disease.

Suprachiasmatic nucleus
Translation of the photic signal utilizes neurotransmitter systems known to be affected in the brain of patients with liver disease. Exposure to light results in glutamate release from the endings of the retinohypothalamic tract, acting through both N-methyl-D-aspartic acid (NMDA) and non-NMDA glutamate receptors on neurons of the SCN (21). Inhibitory influences on the SCN arise among others from the intergeniculate leaflet, a process that involves GABA neurotransmission and the mid-brain raphe nucleus, via serotoninergic neurotransmission. However, the mechanisms that generate circadian rhythms are still incompletely understood. The recent isolation of the Clock gene, whose mutation results in a complete loss of the rhythm of locomotor activity in the mouse (22), points to molecular mechanisms that control the generation of circadian rhythmicity.

Individual neurons from the SCN independently express circadian firing rates (23), suggesting that an integrated response occurs in the SCN itself. Astrocytes, whose multiple end-foot processes establish a dense connection with neurons and endothelial cells, may play an important role in this integration (24). The rich glial content of the SCN can be identified using stains for glial-fibrillary acidic protein. Current views of the pathogenesis of hepatic encephalopathy point not only to abnormalities in astrocyte anatomy and function but to a deranged astrocyte-neuronal interaction (25,26). A working hypothesis is that such abnormalities in the SCN may underlie the genesis of abnormal circadian function in liver disease.

Efferent pathways
The complexity of pathways that link the SCN to the multiple biological processes that undergo circadian variability is starting to be unraveled. The best char-

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Fig. 1. A schematic depiction of circadian organization. SCN=suprachiasmatic nucleus. RHT=retinohypothalamic tract. PN=pineal gland.
acterized efferent connection is the multisynaptic path-
way that directs the synthesis and release of melatonin
from the pineal gland during darkness (27). Melatonin
is derived from tryptophan→serotonin and, once syn-
thesized, is released into the circulation, as the hor-
mone is not stored in the pineal gland. In plasma, mel-
tonin has a short elimination half-life (ca. 30 min)
and undergoes hepatic elimination via cytochrome P-
450-mediated hydroxylation, with subsequent sul-
phation. Not unexpectedly, the plasma clearance of
melatonin is reduced in cirrhosis (28).

The biological role of melatonin is still being defined
(29). One effect is on the circadian system itself. The
presence of melatonin receptors within the SCN of
mammals points to a feedback loop where melatonin
influences the activity of the circadian pacemaker (30).
Thus, two factors are important in the control of the
output from the SCN: light and melatonin. While the
endogenous pacemaker may cycle with a circadian
period of more than 24 h, light and melatonin provide
synchronization to the external conditions and entrain
the SCN to a 24-h day. The effects of light and mela-
tonin on the SCN are in opposite directions and occur
within a window of time, around dawn or dusk, where
phase advances or delays occur. Thus, shining bright
light in the evening and administering melatonin in the
morning delay the output from the SCN; morning
light and evening melatonin result in a phase advance
(31).

When measured at frequent intervals, the rhythm of
plasma melatonin is markedly altered in patients with
compensated cirrhosis, (Fig. 2) (5). These abnormali-
ties can be summarized as a delayed onset of nocturnal
rise (21:20 vs 19:45 in well-matched controls), a delay-
ed peak nocturnal time (00:30 vs 05:30) and elevated
levels during the day. The latter is of particular interest
as administration of exogenous melatonin in the morn-
ing hours will delay the phase of circadian rhythms.
Thus high morning melatonin levels could explain the
delayed phase of the melatonin rhythm in liver disease.
Our more recent evaluation of sleep patterns of com-
penated cirrhotic subjects and age/sex matched controls. Reproduced
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Therapeutic Implications
In essence, we have proposed two explanations for the
alterations in circadian function seen in chronic liver
disease. First, abnormalities of circadian rhythms arise
from the effects on the SCN and/or its afferent/efferent
connections of neurotoxins implicated in the patho-
genesis of hepatic encephalopathy. Second, the im-
paired hepatic metabolism of melatonin results in elev-
ated morning plasma levels that cause a phase shift of
the output from the circadian clock. It is possible that
both explanations, that combine the effects of hepato-
cellular dysfunction and portal-systemic shunting, are
responsible for the circadian abnormality in liver dis-
ease. A better understanding of the pathogenetic mech-
nisms should lead to novel therapeutic interventions
aimed at ameliorating the disturbance in circadian
function.

On one hand, the impact of long-term therapy of
hepatic encephalopathy needs to be re-examined. Non-
absorbable disaccharides are administered over a pro-
longed period to patients with chronic or recurrent
encephalopathy; if long-term therapy improves circadian parameters, a rationale for a more widespread use for these agents would arise. On the other hand, treatment with bright light, administered in the morning hours, may provide a method to phase advance the output from the circadian clock and correct abnormalities that arise from this shift (31). Treatment of circadian dysfunction is not an attempt to correct a biological curiosity but a measure that may impact on areas of daily functioning that profoundly affect the circadian output from the circadian clock and correct abnormalities that arise from this shift (31). Treatment of circadian dysfunction, a rationale for a more widespread use of these agents would arise. On the other hand, treatment with bright light, administered in the morning hours, may provide a method to phase advance the output from the circadian clock and correct abnormalities that arise from this shift (31).

References