# Neuro-endocrinology

# 10 BRIEFINGS

## BIOLOGICAL TIMEKEEPING

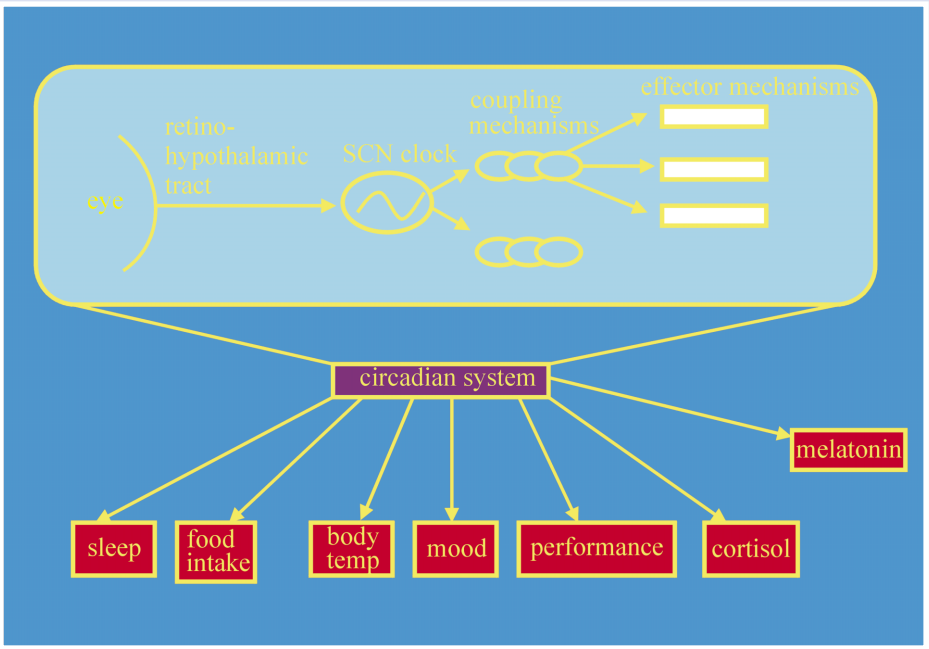

### SUMMARY

The existence of biological clocks was once the subject of considerable debate. However, research has confirmed that a 24 hour (circadian) clock in our brain has a pronounced influence on when we sleep, eat, drink, etc. Disruptions in clock function compromise normal daily patterns of hormone release, sleep, and body temperature and can affect mental and physical well-being. The recent identification of clock genes and the neural pathways to the clock will facilitate the development of effective strategies to treat disorders of circadian function.


*Information on environmental light level is conveyed directly to the SCN circadian clock via the retino-hypothalamic tract. Acting via coupling and effector mechanisms, the SCN clock influences the temporal organisation of a wide range of physiological and behavioural processes.*

## Times of our lives

Everyday, we routinely organise our activities so that we awaken, work, eat, and sleep at approximately the same times during 24 hours. Over the past 50 years, compelling evidence suggests such temporal organisation in our behaviour and physiology is not simply due to socio-cultural influences, but is partly set biologically. The existence of internal temporal programmes or biological clocks is now well accepted. Biological clocks function across a range of periodicities and their synchronisation with environmental cues governs the timing of our physiology and behaviour. A biological clock producing a complete oscillation every 24 hours is called a circadian clock. Circadian clocks can be reset by changes in the timing of external events so that they are synchronised or entrained to recurring signals in the environment such as the diurnal variation in levels of daylight. These clocks are thought to have evolved to anticipate metabolic demands so that we are physiologically and behaviourally prepared for probable needs in our environment. Thus, our core body temperature increases before we awaken and falls prior to sleep onset. Mismatches between circadian clock phase and environmental cues are thought to produce feelings of malaise (or jet-lag) which accompany rapid transition through many time zones.



# Neuro-endocrinology Briefing 10: Biological timekeeping

## Are clocks good for us?

In mammals, the main circadian clock is localised to a small cluster of nerve cells located in the anterior hypothalamic region of the brain, the suprachiasmatic nuclei (SCN). This clock is synchronised to changes in environmental light levels; information of which is relayed directly to the SCN through a neural pathway from the retina of the eye. In turn, the SCN form numerous direct and indirect neural connections through which the timing of many physiological and behavioural processes are regulated. In rodents, damage of the SCN disrupts the normal patterns of gonadotrophin-releasing hormone neuronal activity, the elicitation of appropriate reproductive behaviours, rhythmic function of the pineal gland, and overt rest-activity rhythms. Thus the suprachiasmatic circadian clock appears to regulate the timing of some neuroendocrine hormonal pulses as well as brain regions controlling complex behavioural patterns. Damage to the human SCN region, as occurs from pituitary tumours, evokes profound disruptions in sleep-wake cycles, neuroendocrine function, and surprisingly cognition. A functional SCN circadian clock thus appears to have an important influence on our personal well-being.

## Signals to the brain and body?

Studies with cell grafts from the SCN achieve restoration of behavioural rhythms only. In a fascinating study, Rae Silver and colleagues at Columbia University showed that SCN transplants successfully communicate phase information to target sites via a diffusible coupling factor without forming neuronal contacts with the host tissue. The identification of this diffusible compound will be a critical step in the development of pharmacological treatments for circadian disorders. In contrast, transplanted clocks do not restore circadian rhythms in corticosterone, cortisol, or melatonin. These neuroendocrine rhythms appear to require intact neural pathways from the SCN clock that are only partly understood.

*"Our bodies might be composed of millions of cellular clocks"*

## What makes the clock tick?

Over the last two years, a clearer understanding of the molecular machinery of the mammalian circadian clock has emerged. The levels of candidate clock genes, such as *mper* and *mtim* and their associated proteins oscillate with a 24-hour period in the rodent SCN. Expression of these putative clock genes shows evidence of autoregulatory feedback similar to some neuro hormone synthesis/release mechanisms. Moreover, these clock gene proteins directly regulate the temporal transcription of the arginine-vasopressin gene, the major peptide neurotransmitter of the SCN clock. Homologues of *mper* and *mtim* are present in circadian clocks from insects to mammals, suggesting that the molecular components of the circadian clock are evolutionarily conserved.

## Clocks in all body tissues?

One groundbreaking finding by Steven Reppert and associates at Harvard University is that individual SCN neurones produce circadian rhythms in electrical signals. The implication is that the SCN is actually composed of several thousand cellular clocks and the massed output of the SCN is then the resultant symphony of activity of these clocks. The identification of putative clock genes has further enabled scientists to search for evidence of other circadian clocks in the body. Scientists in California and Switzerland have recently shown cellular clocks present throughout the body of fruit flies and in cultured rat fibroblasts respectively. These findings suggest that our bodies might be composed of millions of cellular clocks whose activity is in some manner coupled to outputs from the master circadian clock in the SCN. Identifying these SCN output factors will be vitally important in the development of effective strategies for the treatment for sleep-wake disorders. Our physical and mental well-being may thus depend on the appropriate synchronisation of these circadian clocks with our environment.

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