Neuro-endocrinology BRIEFINGS

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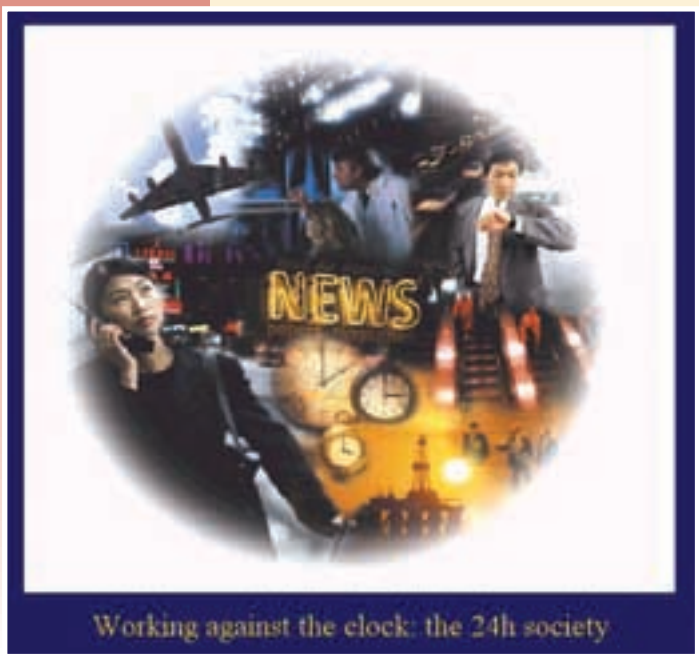
MELATONIN IN HUMANS – IT'S ABOUT TIME

SUMMARY

Melatonin signals night time by its rhythmic profile of secretion. Its measurement provides the best indicator of internal circadian clock timing. Treatment with melatonin induces sleepiness and lowers body temperature during 'biological day' i.e. when its endogenous secretion is minimal, and it acts as a 'chronobiotic' to change the timing of the circadian clock. It has been used successfully to treat disorders of biological rhythms in humans.

No miracles

A few years ago the pineal hormone melatonin was claimed to be the cure for practically every human disease and inconvenience, even old age. This led to a considerable degree of scepticism as to whether it had any useful attributes at all. So what does it really do and has it any uses? It has a number of nicknames: hormone of darkness, circadian glue, the Dracula hormone, and others. Ignoring the latter (a tabloid invention) these attributions are more or less correct. Melatonin is the only solidly established humoral method of signalling time of year and time of day to body physiology.



Working against the clock: the 24h society

Signalling the length of the night

The pineal gland via the profile of melatonin secretion acts as a 'photo-neuroendocrine transducer'. A master clock in the brain, the suprachiasmatic nucleus (SCN), generates approximately 24h rhythmic signals which dictate the timing of virtually all 'circadian' rhythms including melatonin. Interacting negative feedback loops of the so-called 'clock genes' provide the basis for rhythmic output. The light-dark cycle synchronises these rhythms to the 24h day and also changes their characteristics according to daylength. Melatonin is normally synthesised at night in all species and the duration of its secretion reflects the length of the night. This changing signal is rapidly distributed throughout the body and 'read' by target organs and cells primarily through membrane receptors. It then serves to coordinate the appropriate response to daylength. It has been shown to modify peripheral gene expression in target tissues (the pars tuberalis, in animals). Humans retain some seasonal responses (e.g. changes in mood, sleep, immune function, even the success of in vitro fertilisation) in which melatonin may be involved. On a daily basis melatonin serves to define 'biological night' and to reinforce the timing and intensity of night time events, for example sleep, and the night

time decline in core body temperature (cBT) in humans.

Marking time

The rhythmic profile of melatonin in blood, saliva, and its metabolite 6-sulphatoxymelatonin (aMT6s) in urine, are by far the best indicators of human clock timing to date. Attempting to work and sleep when the clock is out of phase is associated with numerous problems including an increased accident rate, poor sleep, and most recently an increased risk of heart disease and cancer. Night shift work is the most obvious situation and has consequences not only for health and safety but also for a nation's economy. Abnormal rhythms also occur for example in jet lag, delayed sleep phase syndrome (DSPS), advanced sleep phase syndrome, non-24h sleep wake cycles (frequent in the blind) and in some psychiatric conditions. Thus it is important to investigate clock timing and attempt to minimise the extent of exposure to such states of 'desynchrony'. Strategies designed to alleviate desynchrony require a knowledge of internal time for optimal timing of treatment.

One of the first demonstrations that light pulses could shift the human circadian clock used melatonin as the marker rhythm. The use of aMT6s as a non-invasive rhythm marker has led to new insights into human clock timing in field studies. It enables diagnosis of the underlying rhythm problem (free-run) of non-24h sleep wake disorder in the blind and these observations have underlined the primordial importance of light for synchronising human rhythms to the 24h day. Melatonin suppression by bright light at night, and its transduction of photoperiodic information in animals, initiated the first light treatments of SAD (seasonal affective disorder). The suppression and phase shifting of melatonin by light has provided endpoints for the recent identification of a novel circadian photoreceptor system maximally responsive to short wavelength light. Possible suppression of melatonin during night shift work has been hypothesised to increase the risk of major disease, since melatonin has some anti-cancer effects and other positive health benefits (however abrupt shifting of the ambient time cues disturbs the whole circadian axis not just melatonin).

" On a daily basis melatonin serves to define 'biological night'. . ."

A substance that changes biological time

Melatonin is not just a 'hand of the clock'. Coordinating daily and seasonal events demands that it act on the timing systems themselves. Melatonin receptors exist within the SCN (inter alia) and it clearly shifts the timing of SCN activity both in vivo and in vitro. In humans, taken during the biological afternoon-early evening it induces sleepiness, lowers cBT and advances the timing of the circadian clock. Taken in the early biological morning it may delay the clock (light pulses, by contrast, act in the opposite sense to shift the clock and light at night lowers sleepiness and increases cBT). These properties have led to its use in the treatment of circadian rhythm disorders. It has been most successful in synchronising blind subjects to the 24h day and normalising sleep time in DSPS. Correct timing of treatment in these conditions is easier than in the cases of shift work and jet lag, where moderate success has been achieved. These observations have inspired new pharmacological approaches to the treatment of health problems through the development of melatonin agonists and antagonists.

In the right circumstances it is possible that by reinforcing and optimising our temporal organisation, melatonin may have substantial benefits for health in general.

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