

Chronobiology

PETER H. REDFERN

School of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY

The constancy of the internal environment and homeostasis, the processes through which the constancy is maintained, are basic tenets of physiology.

But even cursory observation shows that biological processes are not constant over time. They vary as a result of unpredictable internal imbalances and external insults.

Homeostatic processes are designed to restrict these random variations within fixed limits. It is equally clear that in addition to random, unpredictable fluctuations, biological processes also display rhythmic variations of fixed period. These periods range from fractions of a second in the case of electrical fluctuation across excitable membranes to around a year in the case of hormonal patterns in seasonal breeding species.

Most prominent are rhythms with periods approximating to 24 hours which arise partly as a direct response of the organism to the pervading 24 hour, day-night pattern of the environment. However it has been known for almost half-a-century that in the absence of external time cues organisms including man continue to exhibit rhythms with periods that approximate to 24 hours, and hence are called circadian rhythms [*circa diem* about a day]. Persistence of circadian rhythms in the absence of all external time cues is strong evidence for the existence of an endogenous pacemaker. It is now known that this 'biological clock' is located in the suprachiasmatic nuclei of the hypothalamus and over the past decade there have been major

advances in our understanding of how this endogenous pacemaker works. Examination of mutants exhibiting rhythms outside the normal range has led to identification of specific 'clock' genes first in *Drosophila* and *Neurospora* and more recently in hamster and mouse. At the same time we are beginning to build up a picture of the neurochemistry of the nerve pathways involved in generating the circadian oscillation, in transmitting the signal to remote parts of the nervous system and thence to the organism as a whole, and in providing the internal clock with external time cues. These latter, of which light is pre-eminent, are essential if the biological clock is to be effectively readjusted to a period of exactly 24 hours.

Circadian periodicity impinges on pharmacology and therapeutics in many ways. First it may significantly influence the symptomatology of the disease process under consideration. Secondly, the pharmacokinetics of drugs may be affected by circadian variation in physiological processes responsible for absorption, distribution, metabolism and excretion. Thirdly circadian rhythms in pharmacodynamic processes can result in altered drug efficacy and altered intensity of side effects.

Increased understanding of basic clock mechanisms has been paralleled by a widening awareness of their importance in biology and medicine and the benefits of application of chronobiological principles to clinical situations are beginning to be identified.