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opinion

Bad light stops play

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All animals display profound variations in their physiology over a 24-h period, including changes in locomotor activity, hormone production, metabolism and neural activity. These rhythms are endogenously generated by the circadian system and provide a selective advantage by enabling organisms to anticipate both daily and seasonal changes in the environment. As a result, normal physiology is dynamic, showing constant circadian modulation of homeostatic set-points (Mrosovsky, 1990). Although this is adaptive for the organism, it poses a problem for biological measurement, whether physiological, behavioural or biochemical. For example, in mammals, approximately 10% of the genes expressed in any given tissue show significant circadian variation (Storch *et al*, 2002). Toxicology and pharmacology studies have also demonstrated dramatically different effects at different times of the day (Burns, 2000). As a result, time-of-day and the temporal niche of the animal model need to be taken into consideration in the design of any experiment.

Mice have become the organism of choice in biomedical research due to the availability of extensive genomic information and well-established methods of genetic modification. This has resulted in the production of an enormous range of transgenic and knockout models, which are used widely in attempts to demonstrate genotype–phenotype associations (Crawley, 2008). Much of this research is undertaken in an attempt to understand human physiology and disease. However, the smooth extrapolation of results from mouse to man faces many obstacles, not least that humans are diurnally active primates, whereas mice are nocturnally active rodents. During the daytime a mouse is normally inactive or asleep, and as animal facilities are generally operational between 07:00 and 17:00, most of the data collected from mice is from a mammalian model in the resting state. In the drug development process, many compounds are excluded on the basis of efficacy or adverse effects. One wonders at the potential lost opportunities that have occurred because differences in temporal biology have not been taken into account.

Although there is a growing awareness of the importance of circadian rhythms in experimental design, it is not just time-of-day effects that represent a potential problem. Most behavioural phenotyping is undertaken in the light, when mice are normally inactive or asleep, and when in the wild they would be concealed from light. Several studies have assessed the impact of light and dark on behavioural testing. Mice are photophobic and normally avoid bright light, a phenomenon that is exploited in many tests such as the open-field and light/dark-box paradigms (Crawley, 2008). Open-field testing has demonstrated dramatic differences in exploratory activity in mice in different levels of light (Valentinuzzi *et al*, 2000). In DBA mice, testing in the light has been shown to result in behavioural inhibition and cognitive disruption (Roedel *et al*, 2006). Conversely, testing in the dark results in improved discrimination in a range of behavioural tests, including the widely used SHIRPA test battery (Hossain *et al*, 2004). Collectively, these findings suggest that testing under different light conditions produces differences in behaviour, and that testing in the dark provides superior outcomes. By contrast, there have been relatively few studies that have assessed the effects of circadian phase on performance in behavioural tests (that is, under constant conditions). Beeler *et al* (2006) found no effect of circadian phase on a range of behavioural tests. However, other studies have demonstrated a notable impact of circadian phase on learning and memory, which would be expected to translate into performance (Chaudhury & Colwell, 2002).

To a circadian biologist, it is surprising that testing at different circadian phases does not result in more profound differences in behavioural performance. After all, toxicity effects can vary from 20% to 80% in one day, and changes in gene expression can vary by more than 100-fold. One explanation for this might be that the stimuli involved in many test protocols, including handling, could override the normal circadian gating of arousal. After all, we are not slaves to our internal clocks, and indeed, it would be maladaptive if we were. Environmental factors such as light exert acute effects on arousal. In mice, light exposure during the active phase produces an acute suppression of locomotor activity and induction of sleep (Lupi *et al*, 2008). Conversely, light exposure during the inactive period gives rise to an increase in activity and heart rate (Thompson *et al*, 2008). As levels of arousal are closely linked to performance, a challenge for the future is to determine the way in which time-of-day and responsiveness to environmental stimuli interact to regulate behaviour.

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