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GUEST EDITORIAL

Does anaesthesia stop the clock?

Anyone who has undergone general anaesthesia (GA) remembers the strange state of disorientation lasting for quite some time after waking up. Until recently, the idea that one's biological clock had just "paused" for a few hours was not a concept that was considered to explain (part of) this discombobulation. Yet it seems that when we go into the operating room, we come out in another time zone, or rather, time stands still: in other words, GA induces jet-lag. Post-operative recovery may be hindered by circadian disruption and the resulting sleep disturbances, and may also impair mood, alertness, cognitive performance, and even immune function. What is the evidence for this novel explanation?

This review [1] collates a number of studies of a wide variety of anaesthetic agents, acting on a disparate group of living organisms, both in vitro and in vivo, comparing the anaesthetic effect with neurotransmitters involved in circadian function. The neurochemical pathways of light via the eye entraining the circadian pacemaker in the suprachiasmatic nuclei (SCN) are known, as are its molecular components. GABA and NMDA are crucial to this entrainment mechanism and most anaesthetics (except ketamine) are GABA agonists and/or NMDA receptor antagonists, via which they may inhibit expression of a core clock gene. Within the SCN it appears that jet-lag occurs between subsets of neurones in the ventral core (directly innervated by the retinohypothalamic tract) and the dorsal region driving peripheral clocks – the former reentraining quickly to shifted light–dark cycles, the latter much slower. Thus, a key interaction of GA is with the light–dark cycle, and maybe even with the photoperiod. More disrupted rest-activity cycles occur with GA during an animal's active phase. If the active phase is short, the jet-lag induced might be greater – leading the authors to postulate that the post-GA symptoms will be worse in the short days of winter than in summer.

As acknowledged in the discussion, a major problem in confirming these effects is the mechanistic differences, and indeed clinical effects, of the anaesthetic agents used, which may contribute to the variability in their effects on rhythms and the sleep homeostat. The agents tested belong to different groups of drugs: for instance, ketamine causes loss of consciousness and has effects that are qualitatively dissimilar to other anaesthetic agents in common use, while the barbiturate pentobarbital is generally used for sedation rather than for anaesthesia. The only thing they have in common is that they cause unconsciousness, some requiring clinically impractically high doses. It is important to be cautious when comparing the effects of different anaesthetic agents, not only because of their different molecular targets but also because they are cleared differently from the body and thus may be acting for different durations, which may modify the resultant effect on the timing and structure of sleep.

In summary, caution needs to be applied in reaching conclusions when looking at too many variants in type of anaesthetic used (including inhalational anaesthetics, intravenous anaesthetic agents, sedatives, and dissociative hallucinogenic psychotomimetics) and models of living organisms tested (nocturnal and diurnal, bees and rodents). The effects documented of anaesthesia on the circadian clock and sleep-wake cycle are intriguing, but not yet proven. Further studies are required to increase our understanding in this area.

Of course, other effects from the anaesthesia, as well as illness, hospitalisation, the stress of an operation, often-found lack of clear light–dark cycles in intensive care wards, and multiple entries of staff into bedrooms to check condition of their patients – all these are additive factors contributing to any direct effects of GA on circadian rhythms and sleep homeostasis. Can one counteract such post-operative phase shifts and sleep disruption by ensuring the patient's recovery in a room with bright daytime summer-long light and nocturnal darkness i.e., provide a strong zeitgeber signal to enable faster reentrainment? Importantly, the authors set out a research agenda that addresses the relevant missing issues in this multidisciplinary approach to a fascinating clinical problem.

Reference

[1] Poulsen RC, Warman GR, Sleigh J, Ludin NM, Cheeseman JF. How does general anaesthesia affect the circadian clock? Sleep Med Rev 2018;37:35–44.

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