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Commentary

Impact of anaesthesia on circadian rhythms and implications for laboratory experiments

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ABSTRACT

General anaesthesia is a widely used tool to enable surgery in animal experimentation. There is now convincing evidence that general anaesthesia can cause profound and strongly time-dependant shifts in circadian rhythms of behaviour (sleep-wake cycles), physiology (core body temperature, blood pressure, heart rate and hormone release) and cognitive parameters (learning and memory) in a range of species. These effects have the potential to confound laboratory experiments, and may lead to misinterpretation of results. Here, we summarise these effects and advise caution to those conducting laboratory experiments in which anaesthesia forms part of the protocol.

1. Discussion

General anaesthetic agents are used in animal experimentation to immobilise the animals and/or prevent pain, stress and discomfort for surgery and handling. Unfortunately, this tool comes with some undesirable side effects; one of these is a time-dependent shifting of the circadian clock, which can affect many other parameters such as behaviour and physiology, and thus may lead to confounding or misinterpretation of results.

The circadian clock generates circadian rhythms in all organisms, from prokaryotes (Liu et al., 1995) to humans (Czeisler and Gooley, 2007). In mammals, the central circadian clock is located in the suprachiasmatic nuclei (SCN) of the hypothalamus (Mohawk and Menaker, 2009). The fundamental biochemical basis of circadian rhythms relies on an auto-regulatory feedback loop of circadian clock genes. These genes include amongst others *clock, Bmal1*, *period* and *cryptochrome*, whose expression and protein products oscillate over a period of around 24 h (Duguay and Cermakian, 2009). Any disruption of the circadian clock will have an impact on the circadian rhythms in behaviour and physiology that it drives.

The period of circadian clocks is not exactly 24 h but it is adjusted to exactly 24 h on a daily basis by relevant geophysical cues (such as the light-dark cycle or the daily temperature cycle). The clock can, however, be disrupted by other artificial clock-shifting "chronobiotic" agents. A central characteristic of these chronobiotics is that their influence depends on when they are administered relative to the phase of the clock. A light pulse administered during the early subjective morning to a mouse maintained in constant darkness will cause an advance of the clock to an earlier time zone, whereas the same light pulse administered in the subjective evening will cause a profound phase delay (Pendergast et al., 2010).

There is now a substantial body of evidence summarising the shifting effect of general anaesthesia (GA) on the circadian clock in a range of vertebrate and invertebrate species (Table 1 and (Poulsen et al., 2018)). The proposed mechanism of this effect is via anaesthetic agents acting on the expression of core circadian clock genes (Table 1 and (Poulsen et al., 2018)). Phase shifts in the expression pattern of these genes can then result in shifts in those physiological and behavioural rhythms driven by the clock. A comprehensive summary of the effects of general anaesthesia on circadian rhythms at the whole animal (behavioural and physiological), organ culture, and molecular levels is provided in Table 1 together with details of the duration and administration route of anaesthesia. These effects are substantial enough to be evident in outbred populations of animals of different ages, weights and sex. They persist even when standard anaesthetic dosing (titrated for weight, fat free mass etc.) is conducted.

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Table 1
A comprehensive summary of the published work demonstrating an effect of general anaesthesia on circadian rhythms at the whole animal (behavioural and physiological), organ culture, and molecular levels organised by anaesthetic agent class. Dose and route of administration (inhaled-inhaled, i.v.-intravenous, i.p-intraperitoneal, not stated-administered to tissue culture) is given together with brief experimental details and whether experiments were conducted in the presence of light cycles or in time isolation.

					Effect on behaviour		Effect on overall activity		Effect on clock gene expression		Other effects		
Anaesthetic	Organism	Tissue	Light cycles	GA Duration (hours)	GA during active phase	GA during rest phase	GA during active phase	GA during rest phase	GA during active phase	GA during rest phase	GA during active phase	GA during rest phase	Reference
Isoflurane (2%) (inhaled)	Honey bee	whole animal + brain	absent	6	Delay	None	–	–	Delay in *per* and *cry* expression profiles	No change	–	–	Cheeseman et al. (2012); Ludin et al. (2016)
Isoflurane (1.4%) (inhaled)	Rat	whole animal + hippocampus	present	4	Advance	None	–	–	–	–	–	–	Kikuchi et al. (2013)
Isoflurane (1%) (inhaled)	Mouse	whole animal + SCN	present	6	–	–	Increase during subsequent rest period	–	–	–	–	–	Xia et al., 2016)
Isoflurane (2%)	Mouse	SCN + Peripheral mononuclear blood cells	present	6	–	–	–	–	Delay in *cry1* and *per2* expression in the SCN	–	Expression of clock genes in peripheral mononuclear blood cells delayed	–	Xia et al. (2015)
Isoflurane (1.3%) (inhaled)	Mouse	Whole animal + SCN	present	5	Delay				Delay in *cry* expression, advance in *Bmal* and *Clock*				Song et al. (2018)
Isoflurane (1.5%) (inhaled)	Rat	Whole animal	absent	6						Suppression of clock gene expression in brain and liver			Gökmen et al. (2017)
Sevoflurane (2.5%) (inhaled)	Mouse	whole animal + SCN	absent	4	Delay	Delay	–	–	*mper2* repression	–	–	–	Kadota et al. (2012)
Sevoflurane (4%) (inhaled)	Rat	whole animal + brain	absent	8	–	None	–	Decrease	Suppression of *per2* expression, phase delay	–	–	–	Anzai et al. (2013)
Sevoflurane (2.5%) (inhaled)	Mouse	whole animal + brain	absent	4	–	Delay	–	Decrease		Delay	–	–	Ohe et al. (2011)
Sevoflurane (2.5%)	Mouse	Brain	absent	1–4	–	–	–	–	Suppression of *per2* expression	–	–	Decrease in clock protein binding and acetylation of histone H4 of *per2* promoter	Mori et al. (2014)
Sevoflurane (4.5%) (inhaled)	Rat	Multiple	present	0–6	–	–	–	–	–	Decrease in *per2* mRNA	–	–	Sakamoto et al. (2005)
Sevoflurane (4%)	Rat	Brain	present	2–6	–	–	–	–	–	Suppression of circadian gene expression	–	–	Kobayashi et al. (2007)
Sevoflurane (2.2%)	Rat	SCN	present	8	–	–	–	–	Advances/delays in *per2* mRNA	No effect in *per2* mRNA	–	–	Matsuo et al. (2016)
Sevoflurane (4%)	Mouse	Cell lines (hypothalamic)	N/A	8	–	–	–	–	Suppression of *per2* expression	–	–	–	Nagamoto et al. (2016)
Sevoflurane (1.97%) (inhaled)	Rat	Whole animal	present	6	–	–	–	–	–	–	Decrease in melatonin levels	–	Ocmen et al. (2016)
Desflurane (5.7%) (inhaled)	Rat	Whole animal	present	6	–	–	–	–	–	–	–	Increase in melatonin levels	Ocmen et al. (2016)

(*continued on next page*)

Table 1 (*continued*)

					Effect on behaviour		Effect on overall activity		Effect on clock gene expression		Other effects		
Pentobarbital (4 mg/100 g) (i.v.)	Rat	Whole animal	absent	N/A	Delay	Delay	–	–	–	–	Phase delay in temperature rhythms	–	Ehret et al. (1975)
Pentobarbital (50 mg/kg) (i.v.)	Mouse	Whole animal	absent	N/A	Delay	Advance	–	–	–	–	–	–	Ebihara and Hayakawa (1990)
Ether (20 ml) (inhaled)	Rat	Whole animal	present	1	–	None	–	None	–	–	–	–	Prudian et al. (1997)
Ketamine (100 mg/kg)(i.p.)	Rat	Whole animal	present	1	–	None	–	None	–	–	–	–	Prudian et al. (1997)
Ketamine (150 mg/kg) (i.p.)	Rat	Whole animal	present	4–4.5	Delay	Advance	Decrease	None	–	–	Phase delay in melatonin rhythm	Phase advance in melatonin rhythm	Mihara et al. (2012)
Ketamine (10 mM +1 mM)	Mouse	Fibroblasts	N/A	1	–	–	–	–	Phase shift in *bmal1 and dbp* expression + reduced amplitude of *cry1* and *dbp*		–	–	Bellet et al. (2011)
Propofol (120 mg/kg)	Rat	SCN	absent	1–3	–	–	–	–	–	Reduction in *per1* and *per2* expression (transient)			Ben-Hamouda et al. (2018)
Propofol (120 mg/kg) (i.p.)	Rat	Whole animal	present	0.5	Advance	Advance	–	–	–	–	Melatonin phase advance	–	Dispersyn et al. (2010)
Propofol (120 mg/kg) (i.p.)	Rat	Whole animal	present	0.5	Advance	Advance	–	–	–	–	–	Phase advance in temperature rhythms	Dispersyn et al. (2009)
Propofol (60 mg/kg) (i.p.)	Rat	Whole animal	absent	0.5	Advance	Advance	–	–	–	–	–	–	Challet et al. (2007)
Propofol (600 μg/kg/min)	Rat	Brain	–	6	–	–	–	–	–	Reduction in *per2* expression			Yoshida et al. (2009)
Propofol (10 mg/ml) (i.v.)	Rat	Whole animal	present	0.5	–	–	–	–	–	–	Period of rhythm of core body temperature lengthened	Period of rhythm of core body temperature shortened	Touitou et al. (2016)
2,2,2-tribromoethanol (240 mg/kg) (i.p.)	Mouse	whole animal + brain	absent	1–4	None	None	–	–	Phase advance in *per2* expression	Phase delay in *per2* expression			Kubo et al. (2012)

While the effect of GA on the circadian clock holds interest primarily for chronobiologists, scientists using GA as a part of their protocols should consider controlling for these effects to increase study power (by reducing the potential confounding effects of phase shifts which only occur at sometimes of the day). By ignoring clock effects of GA and conducting anaesthetics at different times of the day in different study animals, biological parameters such as physiology, behaviour and cognition can inadvertently be shifted in some treatment groups (Table 1).

By way of example, the anaesthetic agents isoflurane, sevoflurane, propofol and ketamine have all been shown to cause time-dependent shifts in daily behavioural rhythms in rodents and other animals (see Table 1). Ketamine, a NMDA receptor antagonist, has been shown to produce 60 to 150 min phase advances when administered to rats during the resting phase (Table 1). In contrast, ketamine administered during the active phase produces 40 to 200 min phase delays (Mihara et al., 2012). GABA agonists such as sevoflurane, propofol and isoflurane elicit different effects on circadian behaviour (Table 1). Sevoflurane anaesthesia administered to mice causes a phase delay of the rest-activity rhythm independent of the time of administration (Kadota et al., 2012). Propofol administered to rats appears to provoke one hour phase advances when given at the transition from sleep to wakefulness (Challet et al., 2007), but no phase shifting effect at other times of the day (Challet et al., 2007; Dispersyn et al., 2009). Isoflurane anaesthesia produces two hour phase advances of rest-activity cycles only when administered during the active phase in rats (Kikuchi et al., 2013). In contrast, isoflurane administered to the honeybee early in the morning (active phase) causes a profound phase delay, but no shift when administered during the subjective night (rest phase) (Cheeseman et al., 2012; Ludin et al., 2016) (Table 1).

The potential effects of GA are not limited to those associated with rhythmic activity. There are other behavioural parameters that are profoundly influenced by clock phase, such as learning and memory (Liu et al., 2014). For instance, we have previously demonstrated that the clock-shifting effect of isoflurane anaesthesia persists in time-place learning in honeybees maintained in strong daily light cycles for at least three days (Cheeseman et al., 2012). Acquisition and memory retention have also been reported to be impaired by the administration of different anaesthetic agents. In 18-month male rats and 10-week male mice, isoflurane administered at 1 MAC (minimum alveolar concentration of an inhalational anaesthetic that prevents movement in 50% of the subjects in response to a painful stimulus) for two hours impaired cognitive performance in the Barnes maze. Animals which had been anaesthetised for two hours showed poorer acquisition and learning skills in comparison with the controls (Cao et al., 2012). This effect was also observed in young (three month old) and middle aged (12 month old) male rats. A recent study by Song et al., 2018 claims that 5 h exposure to 1.3% isoflurane during the active phase of mice impairs memory and disrupts circadian rhythms, with the effect lasting longer in aged (18-month old) mice than young mice. Further, they show that melatonin treatment (10 mg/kg intragastrically) for seven days prior to general anaesthesia may prevent isoflurane-induced cognitive impairments via a suggested effect clock gene expression. Isoflurane at 1MAC administered for four hours impaired acquisition and memory retention in the Morris Water Maze (MWM) a week after the treatment (Callaway et al., 2012), whereas sevoflurane did not impair acquisition learning and retention memory in young adult (8–10 week old) or aged rats (15–21 month old) (Callaway et al., 2012). In this study, it should be noted that the experiments were conducted at different circadian times and therefore were not directly comparable. Sevoflurane administered for four hours in concentrations between 3 and 5% in seven day old male rats has been reported to affect spatial reference memory and locomotor activity performance. The performance of seven day old male rats in the MWM temporarily deteriorated six weeks after sevoflurane anaesthesia treatment (Fang et al., 2012). In contrast, there was no effect found on the performance of young adult male mice (nine week old) in MWM after a single four hour exposure to sevoflurane (and desflurane), nor after shorter (two hour) exposure during five consecutive days (Kilicaslan et al., 2013).

Currently, there are no comprehensive reports of a phase, dose or duration response curve for the clock-shifting effects of general anaesthetics administered to small mammals, hence, it is not possible yet to advise a “safe” circadian time, dose or duration at which GA can be performed without confounding any post-anaesthesia experimental measures. In experimental animal protocols it is commonplace for subjects to receive multiple different anaesthetic and analgesic drugs, and frequently antibiotics. All of these different agents can shift the central circadian clock controlling locomotor activity when administered individually (Table 1; Takahashi and Turek, 1987; Meijer et al., 2000; Beauchamp and Labrecque, 2007) but there is currently no information on the potential synergistic effects of combined administration of different agents.

The effect of multiple periods of GA within a relatively short time frame are potentially additive and will certainly exacerbate rhythm disruption. The phase shifting effects of GA (and surgery) in mammals and invertebrates have been shown to persist for up to five days (Farr et al., 1988; Barrett et al., 2001; Leon et al., 2004; Jensen et al., 2009; Cheeseman et al., 2012; Touitou et al., 2016). Indeed protocols for the accurate measurement of physiological parameters in sheep and rodents at Auckland University employ a five day period to allow for the re-establishment of normal rhythmicity prior to experimentation (Jensen et al., 2009). The maintenance of animals in strong, regular daily light-dark cycles following anaesthesia will expedite the recovery of normal rhythmicity following anaesthesia.

The lack of information on the specific effects of duration, dose and phase responses of anaesthetics on the clock reflects the fact that this is a relatively recent area of study. One generalisation that can be made is that the administration of anaesthesia at the beginning of the active phase tends to elicit the largest phase shifts of the clock (Poulsen et al., 2018). Complete phase and dose response curves for the clock effects of commonly used general anaesthetics will provide a useful tool to allow specific recommendations on “safe” doses and times of anaesthesia that minimise variation due to shifting.

In conclusion, the consequences of GA on daily variations in animal behaviour and physiology (Table 1) are real. Failure to consider this can lead to misinterpretation of experimental results. To avoid confounding effects due to clock shifting, some precautions can be applied, such as conducting anaesthesia at the same time of the day across repeated experiments. This may improve the reliability of results and also the reproducibility of experimental protocols.

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Competing interests

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Author contributions

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