COMMENTARY

A perinatal signature of light on chronobiology? If so, numerous questions arise and experimental animal research must provide more information

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Abstract

That light and melatonin rhythms provide both clock and calendar information in humans and numerous other species is beyond dispute; this holds true for all stages of life, including the very early ones. Experimental evidence elucidates that exposure to light and melatonin titres are keys for the very development of circadian and seasonal rhythms. As evinced by a 2011 publication in Nature Neuroscience such awareness could impact considerably on the design and conduct of experimental studies as well as their subsequent analyses, interpretations and comparisons. Therefore "when and how experimental animals were bred, developed and raised" may be critical when experimenting with animals generally, and not just rodents. As long as the suggested imprinting of circadian system stability via light cues is not falsified, the perinatal season or perinatal experimental light:dark [L:D] conditions that an animal was kept under should be routinely recorded, published and considered in analysing and interpreting study data.

At least for mice, a recent report in *Nature Neuroscience* (Ciarleglio *et al.* 2011) suggests that perinatal photoperiods, which resemble winter light or summer light conditions, may imprint circadian clocks and systems and may determine their stability with regard to light exposures later in – and possibly throughout – life. In these experiments, perinatal summer light conditions (L:D 16:8) appeared to imprint timing relationships between circadian organization and light/dark transitions later in life, which were stable and robust. Perinatal winter light-dark ratios (8:16) contributed to large fluctuations in phasing or timing the animals' circadian systems relative to the light/dark transitions experienced later in life. Importantly, this is not the only report of its kind. Ohta *et al.* (2006), albeit using far more extreme light conditions postnatally (L:D 24:0), showed that circadian systems remained disrupted over observational periods of many months. The lasting effects of this extreme environmental intervention may be interpreted as a demonstration that postnatal light exposures can indeed imprint the responsiveness of circadian clocks and systems to

light, and possibly to other *Zeitgebers* (Aschoff 1951; 1955) later in life and may thus determine the very stability of circadian systems to light and a host of other experimental stimuli in test animals.

This is precisely why one ought to consider publishing information on perinatal L:D conditions together with other details of experimentation and it might then actually be(come) a *conditio sine qua non* to understand and compare experiments, which may be critically influenced by the seasonal photoperiods under which the study animals were bred, developed and raised in the first place.

The alternative may be disconcerting: as long as rigorous research has not falsified the hypothesis of a perinatal signature of light on circadian system stability, conclusions regarding experiments into determinants of health and disease may be disallowed without the perinatal L:D information. It is conceivable that such information may be relevant to understand individual experiments on their own and when several experiments are compared with each other.

That it can be critical to understand why a series of "identical" experiments can fail to show the same or similar results may be evinced by an example from research into possible effects of electric and magnetic fields [EMF] on the development of cancer. In 2004, Fedrowitz and colleagues (2004) resolved through systematic work "Why different labs doing what appear to be identical experiments, produce conflicting results" (Slesin 2004). The authors concluded from diligent analyses that "Probably the most important difference between our and the Battelle studies was the use of different substrains of SD [Sprague-Dawley] rats" (Fedrowitz *et al.* 2004) when investigating whether power-line frequency (50-Hz) magnetic fields have co-carcinogenic or tumour-promoting effects or not. Slesin summarized the long-lasting controversy of conflicting replication studies in EMF research between 1993 and 2004, albeit in a somewhat provocative way, as "It's genetics, stupid" (Slesin 2004). In a similar vein we may postulate today "It's when and how they were raised" when trying to explain results in animal experimentation regarding biomedical results. Indeed, unless proven otherwise, the non-consideration of the biologically plausible perinatal imprinting of circadian clocks and systems and thus differential susceptibility to a host of exposures may leave us with animal experiments that are not interpretable.

How the suggested imprinting of the circadian system works in detail is unfortunately not yet understood. It is, however, reasonable to expect that melatonin will play an important role, for instance as a messenger of environmental time in whatever time window of – early or late – developmental stages. In humans, scattered evidence is compatible with the notion that both pregnant and breast-feeding mothers' melatonin may be a critical determinant of the developing perinatal circadian timekeeping system by relating it to environmental signals (Illnerova *et al.* 1993; Cubero *et al.* 2005). And moreover, beyond melatonin contributing to synchronizing seasonal functions (Simmoneaux 2011), recent experiments suggest that melatonin signals also determine daily functions via entraining circadian clocks in rats during foetal life (Torres-Farfan *et al.* 2011). Overall, it was suggested that "data indicate that newborn animals are sensitive to the photoperiodic history encountered during the prenatal period and that maternal melatonin may be the clock/calendar signal that primes the developing biology of the foetus during the prenatal period" (Simmoneaux 2011).

Now, with the question no longer appearing to be "*Is* early light exposure relevant in determining subsequent biological rhythms, behaviour, physiology, et cetera?" but rather "*How* do perinatal light exposures impact on the developmental stages of newborns' circadian system stability and determine long-term sequelae?", numerous avenues for research, and possible angles for prevention, open up and should be explored. To exemplify, one of us (RJR) recalls discussing a related issue many years ago with a group of students. The question considered then was "how does the reproductive system of hamsters respond to short day exposure when they are born in the laboratory (under a light dark cycle like, e.g., 14:10) compared with responses of hamsters born in the wild (where they are born under constant darkness in underground burrows, and remain in that environment until they are weaned)?" No researcher has ever tested this or similar issues.

Targeted studies in humans would be just as relevant. Throughout evolution, babies were raised by necessity in an alternating light:dark environment from birth. Currently, with the availability of artificial light, the period of darkness for newborns may be repeatedly interrupted by bursts of light (perhaps in some cases of rather long duration) at night which could well have physiological consequences. Moreover, some children are allowed to sleep with the light on at night because they are "scared of the dark" or they fall asleep at night with the TV on. How does this influence their subsequent behaviour, e.g., does it relate to the increase in developmental disorders such as Attention Deficit Hyperactivity Disorder (ADHD)?

Even with regard to EMF and cancer studies, where the book was considered to be closed by many (Erren 2003), differential responses to magnetic field exposures in different categories of animals may be very relevant. Someone might consider doing these and related experiments.

Taken together, the experiments by Ohta *et al.* (2006) and by Ciarleglio *et al.* (2011) may have significant implications for understanding human physiology and pathophysiology. In this vein, the reported insights have already prompted the suggestion of a specific hypothesis, a corollary and a set of predictions regarding links between perinatal photoperiods, circadian system stability and their possible impact on sleep in

children (Erren *et al.* 2011), on facets of "morningness or eveningness" orientation (Erren *et al.* 2012) and on the development of mood disorders (Erren *et al.* 2011) and cancers (Erren *et al.* 2011) in adults. The validity of such rationale should be rigorously investigated in future epidemiological studies.

With regard to experimental research, the quoted works by Ciarleglio *et al.* (2011) and Ohta *et al.* (2006) will, clearly, have to be replicated and extended. Equally clearly, our advice above to publish perinatal season or perinatal experimental light:dark [L:D] conditions that the animals were kept under may have to be considered by journals which invite experimental animal studies. After all, not only melatonin but most, if not all, animal responses to experimental conditions are – until proven otherwise – exhibiting some circadian rhythmicity and/or are affected by biological rhythms. Taking note of the suggestive experiments in 2011 (Ciarleglio *et al.* 2011) and 2006 (Ohta *et al.* 2006) and as long as a perinatal imprinting of circadian system stability via L:D cues is not convincingly falsified, the *Neuroendocrinology Letters* may want to take the lead and discuss with and/or ask authors to routinely provide information on "*when* and *how* experimental animals were bred, developed and raised" when reporting experiments in animals for biomedical science. Authors who recorded such information in the past may want to revisit their work in the light of the possible impact of such perinatal imprinting of circadian system stability on study results and their interpretation.

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