Chapter

Circadian Synchrony between Mothers and Young in the European Rabbit: Or Not? A Cautionary Tale

Robyn Hudson and Gerard A. Kennedy

Abstract

The European rabbit *Oryctolagus cuniculus*, ancestor of all domestic breeds, has an unusual pattern of maternal care in which females briefly nurse their young just once approximately every 24 h, and where the pups anticipate and prepare for their mother's arrival. Chronobiologists have seen this as a model mammalian system to study the physiological and neurobiological underpinnings of a biologically relevant circadian complex. However, observations of nursing in wild rabbits, together with studies of nursing in domestic breeds allowed free access to their young in laboratory settings, suggest that the rabbit's pattern of daily nursing visits resembles an hourglass rather than a circadian process, well suited to the sudden starts and stops of natural nursing cycles. We consider whether there might be other such cases in the literature, including in human chronobiology, in which failing to consider the organism's natural, evolved daily patterns of behaviour and prematurely studying these under artificially imposed laboratory time schedules might have also led to such patterns being erroneously considered circadian.

Keywords: daily rhythm, circadian, hourglass, maternal behaviour, mother-young synchrony, ontogeny, rabbit, *Oryctolagus cuniculus*

1. Introduction

"Oh dear! Oh dear! I shall be too late". The White Rabbit in Alice's Adventures in Wonderland, Lewis Carroll (1865) [1].

1.1 The rabbit as a model species in mammalian chronobiology

Timing is clearly of the essence in many aspects of the European rabbit's behavioural biology and contributes importantly to this species' proverbial reproductive success. The European rabbit *Oryctolagus cuniculus*, the ancestor of all domestic breeds, has been widely used in the study of mammalian chronobiology. Consistent with various well-studied rodent models, such as the white rat (*Rattus norvegicus*) and the golden hamster (*Mesocricetus auratus*), the rabbit shows circadian (or at least diurnal) rhythmicity in several important behavioural and physiological functions. These include motor activity, feeding, drinking, urination, and defecation, as well as haematological parameters, serotonin concentration in the brainstem, content and absorption of volatile fatty acids in the alimentary tract, visual evoked potentials, and intraocular pressure (review in [2]). In addition, due to the rabbit's abundance, size, and importance as an agricultural pest, it is one of the best-studied laboratory mammals in the wild.

Under natural conditions, the rabbit is a primarily nocturnal or crepuscular species, which is most active during the night with peaks in activity levels at dawn and dusk (in nature: [3–5]; in the laboratory: [6, 7]). Aschoff's rule states that the endogenous free-running circadian period observed in complete darkness (DD) will shorten for diurnal animals and lengthen for nocturnal animals when they are exposed to constant light [8]. Rabbits typically show free-running rhythms in several functions that lengthen in accordance with Aschoff's rule when they are transferred from DD to LL [9]. Furthermore, the phase-response curve of the rabbit's daily pattern of wheel-running activity in response to brief 1-hour light pulses [10] conforms to classic phase-response curves reported for nocturnal rodents [11].

2. The rabbit's unusually limited pattern of maternal care: once-daily nursing

Interest in the rabbit as a mammalian model in circadian studies has been reinforced by this species' unusual pattern of maternal care. In the wild, rabbits give birth to litters comprising several altricial young in an underground nursery burrow that the mother digs either within or close to the communal "warren" [12, 13]. Shortly before giving birth, she constructs a nest in this burrow (or laboratory nest box) of dried grass and fur pulled from her chest and flanks (review in [14]). Parturition usually lasts only a few minutes [15, 16], after which the mother immediately leaves the young, closes and disguises the burrow entrance, and only returns to quickly re-open it and nurse the pups for a few minutes approximately once every 24 hours. The end of nursing is signalled by the mother jumping away from the pups, the pups dropping immediately from the nipples [16, 17], and the mother immediately leaving the burrow (or nest box) and closing the entrance after each visit until the approach of weaning [12, 13].

During nursing, the mother stands over the pups without giving them any direct assistance to locate the nipples and suckle (see 2.1). If the mother is pregnant with a subsequent litter, which is often the case due to post-partum oestrus and her mating again immediately after giving birth, she will abruptly stop nursing at around post-partum day 26 and wean her young in preparation for the birth of the next litter several days later ([18, 19], review in [20]). This pattern of brief once-daily nursing visits is shown both by wild rabbits and by domestic breeds in conditions of husbandry and the laboratory (wild rabbit: [13, 21, 22]; domestic rabbit: [23–26]; review in [27]), and has generally been interpreted as a strategy to reduce the risk of the rabbit's many predators locating the open burrow and trapping the nursing mother and young there, and allowing the mother to forage more widely for food [18, 24, 27].

It is a pattern that can also be readily replicated in the laboratory by separating mothers from their pups and only allowing them access to the nest to nurse for a few minutes once each day. Mothers accept this regimen well and raise their young without apparent difficulty (but see Section 2.5). Furthermore, if mothers are given a second opportunity to nurse several hours after the first nursing of the day, they fail to do so [24, 25].

2.1 Synchrony between mothers and young

Such limited maternal care, so different to the extensive care characteristic of most mammalian mothers, is only possible due to several adaptations on the part of the young, synchronising their behaviour with that of their mother. The pups anticipate their mother's nursing visit 1 or 2 hours before her arrival with increased motor activity, resulting in them uncovering from the nest material and thereby gaining unimpeded access to her nipples [25, 28]. They also show an anticipatory rise in body temperature [29] and changes in several endocrine and metabolic parameters [30–33].

Mothers also show a pre-nursing rise in body temperature [34]. In addition, they emit chemical cues from their ventrum, a so-called nipple-search pheromone, which elicits an inborn, stereotyped and highly effective pattern of searching for, attaching to and sucking nipples by the pups immediately the mother positions herself over them ([17, 35]; review in [36]). While nursing, the mother remains motionless, during which she shows a large release of oxytocin into the bloodstream, stimulating a single large milk-ejection reflex, and enabling the pups to drink up to a quarter of their body mass in less than the 3 to 4 minutes, during which she remains positioned over them [17, 37, 38]. At the end of each of the first few visits, she also deposits several hard faecal pellets in the nest, which the pups start to consume after several days, although she never urinates there [19]. Following nursing, the pups simultaneously urinate, become wet, and vigorously dig back under the nest material, fluffing it up and in the process becoming dry again [25].

2.2 A model of circadian rhythmicity including during early development

This unusual pattern of behaviour in such an important aspect of mammalian reproductive biology has attracted the interest of chronobiologists both because of the practical advantages it offers for experimentation, and also as it provides such a clear example of a daily rhythm with a biologically relevant, adaptive function. Interest was soon accompanied by classical chronobiological experiments from various laboratories, seeming to confirm the circadian nature of the mother's nursing rhythm and associated functions, and also of the pups' anticipatory arousal ([25, 28, 39]; reviews in [2, 14, 27]). As mentioned in Section 2.1, mothers allowed access to their pups to nurse at the same time each day show an anticipatory rise in body temperature, and the pups also, while the pups also show an anticipatory increase in motor activity and in uncovering from the nest material. Additionally, in the case of the pups, when the anticipated nursing visit is omitted (possible as pups readily survive missing one nursing, and at later ages even two nursings), they soon return to their baseline behavioural and physiological levels, and then approximately 24 h later (approximately 47 h after the last nursing) again show the usual anticipatory patterns, suggesting these are under the control of endogenous circadian processes ([25, 28, 29, 34]; review in [2]).

Excitement at the seeming evidence for circadian rhythmicity in the relation between mothers and young in the experimentally amenable rabbit quickly resulted in a series of demanding and sophisticated studies of the neural and molecular processes underlying such rhythms, that is, of the regulation of such endogenous biological "clocks", both in mothers and young. These studies, however, have so far provided somewhat equivocal results.

2.3 Mothers

In the case of the mothers, several studies have been undertaken to locate the nuclei of the neural circuits thought to represent the substrate for the mother's nursing rhythm, although without finding strong support for this being regulated by the rabbit's circadian system. Findings have included both the lack of nursing-induced expression of the "clock" gene protein PER1 [40, 41] or enhanced c-Fos expression in the suprachiasmatic nucleus of the hypothalamus [42], generally considered to be the master clock regulating circadian rhythms in mammals [43]. One reason for these equivocal findings might be that the rabbit's nursing rhythm, despite early assumptions, is not part of the rabbit's circadian system and is regulated by processes largely independent of this (see Section 2.5).

2.4 Young

Despite the value of a developmental approach to understanding biological systems, there have been relatively few studies of the development of circadian phenomena in neonatal mammals (but see [44–46]). One reason for this is the extensive maternal care shown by most mammals that makes it difficult to exclude the contribution of the mother, or other caregivers, to patterns of activity observed in the young. Partly for this reason, the behaviour of rabbit pups was early proposed as a model to study the ontogeny of the rabbit's circadian system [28, 39, 47]. Again, various molecular biological techniques such as the expression of c-Fos and various "clock" genes in the pup hypothalamus have been used in the attempt to identify the structures in the developing brain potentially regulating the anticipatory behaviour and physiological functions associated with the once-daily nursing, and the persistence of such patterns in the absence of the mother's nursing visit [48–51]. Interesting though the findings of these studies are, their significance for an understanding of the development of the rabbit's circadian system is unclear. This is because as outlined below (Section 2.5), the pups' anticipation of and preparation for their mother's daily visit seems to be the product of an hourglass mechanism, reset at each nursing, rather than of an endogenous circadian process.

2.5 Truly circadian or rather an hourglass process?

Despite the circadian enthusiasm, reports started to emerge quite early suggesting that perhaps the female rabbit's daily pattern of nursing and the accompanying daily pattern of pups' anticipatory arousal were not, in fact, a circadian-regulated package. One cause for doubt were observations in wild rabbits that mothers did not return to their pups on a 24-hour basis, but rather during the days following parturition returned with a periodicity shorter than 24 hours, arriving a little earlier at each visit. As mothers typically give birth early in the day, this resulted in their nursing visits drifting back into the night ([13, 21, 22]; review in [27]). A second cause for doubt was the timing of nursing by mothers in the laboratory allowed free access to their young. They showed the same pattern as wild rabbits, giving birth in the daylight hours and arriving to nurse a little earlier on each visit, and so with their visits also drifting back into the night-time ([27]; cf. [52]). This gradual shift apparently does not disrupt the synchrony between mothers and their young, since the pups anticipate their mother's arrival by an hour or so, allowing them to be prepared for her earlier arrival each time. Following nursing, they then apparently reset their "clock" a little earlier in anticipation of her next visit.

Additional experiments then suggested why this gradual separation between the timing of birth and the timing of nursing might be physiologically important to mothers, and that nursing visits might be timed so as not to interfere with physiological processes associated with pregnancy and parturition. Specifically, there is evidence [52] that this might be to avoid the large surge in the release of oxytocin into the mother's bloodstream during nursing ([37]; see also ([18]) from provoking premature parturition in pregnant mothers at a time of day when the (pregnant) uterus is maximally sensitive to oxytocin [53], and when the swift parturition characteristic of the rabbit [16] is made possible by a single large release of oxytocin into her bloodstream [15].

The above findings are consistent with the results of a further series of experiments in which rabbit mothers maintained under controlled laboratory conditions were allowed scheduled or free access to their young, and their nursing visits compared to the circadian pattern of their feeding behaviour. When allowed free nest box access, mothers' nursing visits also had a periodicity shorter than 24 hours, cutting across, and apparently independent from the circadian regularity of their daily pattern of feeding [54]. Furthermore, when the pups were permanently removed from the nest before the normal age of weaning and the box left open, mothers stopped visiting the nest within 1 or 2 days, showing little evidence of an endogenous, self-sustaining circadian nursing rhythm.

Together, these findings suggest that rather than the mother rabbit's nursing rhythm (and by implication the associated behaviour of her pups) being regulated by a circadian mechanism, it corresponds to an hourglass process more appropriate to, more adaptive for "stop and go" functions such as nursing and weaning than to the inertia of a self-sustaining rhythm. For certain functions, an hourglass mechanism, allowing a quick response to rapidly changing short-term contingencies may be more adaptive than an enduring, self-sustaining circadian mechanism. In the rabbit, such contingencies include the abrupt cessation of nursing visits in late lactation by mothers pregnant with a further litter [18, 19], or in response to nest mortality, in which mothers may lose an entire litter, for example, due to predation, infanticide or flooding [55–57]. Under such circumstances it would be presumably maladaptive for mothers to repeatedly return to raided or flooded nests, and when they should return to breeding as soon as possible.

2.6 What you get out is what you put in. Circularity?

To the extent that the above is correct, it suggests that supposed circadian rhythmicity in the rabbit's daily pattern of nursing and associated patterns of behaviour in the young might be an artefact of protocols that have applied experimental procedures giving the animals little option other than to confirm the experimenters' assumptions of the operation of circadian mechanisms in the regulation of the behaviour and physiology of mothers and young in the nursing context. Thus, when given no choice, mothers show anticipatory behaviour as reported previously, enter the nest box (sometimes somewhat frantically, e.g. [54]) to nurse their young every 24 hours, and the young anticipate this as previously reported. However, this line of evidence involves a certain circularity; mothers (and again by extension their young) are typically given no choice other than to confirm the assumption of circadian regulation upon which experimental protocols of limited, 24-hour access to the young have been based. When allowed free access to their young, whether under natural conditions in the field or the laboratory, mothers arrive with a period somewhat less than 24 hours and show a nursing rhythm that drifts back, cutting across their well-established, approximately 24-hour rhythm in feeding activity [54]. This is further confirmed by Apel et al. [54] in nursing mothers exposed to LD cycles at the limits of their range of entrainment [10], where nursing visits show a periodicity of around 23 hours irrespective of the LD cycle period. Furthermore, when the young pups are permanently removed from the nest, thereby removing feedback to the mother from stimuli associated with suckling such as stimulation of the nipples ([58, 59]; see also [19, 60, 61]), nursing visits abruptly cease within approximately 24 hours. As suggested in Section 2.4, the regular diurnal nursing visits of rabbit mothers thus correspond better to the operation of an hourglass than to a circadian process ([54]; see review in [62]).

3. Conclusions

The caution implied in our title refers to the danger of not considering a study species' natural behaviour and the ecological conditions under which it evolved when designing experimental procedures under often highly artificial laboratory conditions and in interpreting the results obtained from these within highly reductionist frameworks. In the present case of the rabbit's unusual daily pattern of nursing, this has arguably involved jumping too quickly to assume that this and associated patterns of behaviour and physiological and neural functions, including in the young, to have a circadian basis, and then investing considerable time and money to explore underlying physiological, neural and molecular mechanisms based on these possibly erroneous assumptions. At times, it has also involved an important confusion in the use of terminology between circadian and diurnal processes in article titles and abstracts, and thus in the interpretation of results. If our above historical analysis of the case of the rabbit's nursing rhythm is correct, it raises the question that in how many other models of "circadian" function, including in humans, might such bias also be the case? In mammalian studies, and in contrast to studies in invertebrates, the adaptive advantages of flexible hourglass processes, set to start and stop by immediate environmental events, have been little considered in contrast to the benefits but also costs of the inertia, the lag in adjustment, of circadian processes (review in [62]). Speculatively, in the human case, one can think of the ease (and pleasure) with which many of us transition from workday routines to often very different weekend or holiday schedules. And to complicate things, since we are dealing with the regulation of biological functions in complex organisms leading complex lives, perhaps we need to consider that diurnal functions may be regulated by a combination of circadian and hourglass processes working in tandem?

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