Photoperiodism

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The male-specific histone variant HTR10 contains ten polymorphic sites/regions compared to canonical histone H3.3, most of them conserved in the HTR10 ortholog from closely related species. Some of these sites might provide specific functions to HTR10 in the zygote/embryo. If this is the case, the effect would have to be almost instantaneous after fertilization, as HTR10 is actively removed from the zygote before the first cell division. However, it remains to be determined whether zygotic HTR10 removal is complete, or whether a small fraction is retained. HTR10 could also affect development of the endosperm, from which it is only passively lost through successive rounds of DNA replication [5].

Ingouff *et al.* [9] demonstrate that the histone H3 content is severely restricted in mature germ cells, and that replication-dependent H3.1 variants appear to be excluded from the chromatin. This suggests that pre-fertilization histone H3 reprogramming in *A. thaliana* is DNA replication-independent. Such a mechanism would release some of the temporal constraints of genome reprogramming, giving more flexibility to the paternal and maternal genomes to reorganize their chromatin. This observation also should help identify the histone chaperone complex responsible for loading the gamete-specific H3.3 variants.

Interestingly, Ingouff *et al.* [9] show that the *Arabidopsis* orthologs of HIRA and CHD1 are not implicated in the process, suggesting that an unknown histone H3.3-loading complex yet to be uncovered exists in plants and acts during male and female germline differentiation. Recently, a new histone H3.3-loading complex (death domain-associated protein (DAXX)) has been discovered in animals [12,13]. Although DAXX orthologs are not present in *A. thaliana*, this finding supports the hypothesis that unknown loading complexes remain to be discovered.

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Photoperiodism: Shall *EYA* Compare Thee to a Summer's Day?

Seasonal changes in day length are used by plants and animals to synchronize annual rhythms in reproduction, physiology, and behavior to the environment. Increasing day length during spring causes sudden changes in the mammalian reproductive system once the critical photoperiod is reached. The molecular mechanism behind this switch is now quickly being elucidated.

Roelof A. Hut

The course of the seasons may not come as a surprise to us anymore. They come and go naturally and seem to have relatively minor influences on human biology in modern societies, but seasonal changes in the environment do have profound impact in nature. Driven by changes in day length and temperature, primary production and reproduction by plants show strong fluctuations over the course of the year. Invertebrates that depend on external temperature for development will arrest their growth or reproduction and go into diapause in the fall. As a result, many organisms higher up in the food chain will also face limited resources during fall and winter. For this reason, terrestrial organisms tend to reproduce only in the spring and summer, when temperature and food conditions are more favourable. In most populations, timing of reproduction is therefore under strong selection pressure: when reproduction starts too early, the growing offspring face low temperatures and resources tend to be scarce, while late reproduction leaves less time for consecutive reproductive attempts and little time to prepare for the following winter. Accurate annual timing is therefore an essential component of life history strategies in organisms living in seasonal environments.

Plants and animals have developed accurate annual timing mechanisms that use changing day length as the

external cue to synchronise endogenous circannual timing, which is especially apparent in long-lived species. In recent years, scientists have made impressive progress to unravel the molecular and physiological mechanisms behind these phenomena. So far, the pars tuberalis (PT) of the pituitary appears to be critical in photoperiod-induced switching between reproductive states, but the precise molecular mechanism behind this switch was unclear. This major gap in our understanding now seems to be closed by two publications in a recent issue of *Current Biology* that describe the molecular mechanism of photoperiodic control of mammalian reproductive timing. In one study, Soay sheep were used as the primary model species [1], and in the other a melatonin-proficient laboratory strain of house mice [2]. Both studies have yielded remarkably similar results in describing the photoperiod-dependent transcription factor mechanism that flicks the reproductive switch at the right time.

This reproductive switch centres on the action of the hormone melatonin on the PT, a highly vascularised part of the pituitary stalk that is intimately apposed to the median eminence at the base of the hypothalamus. Melatonin production by the pineal gland is under the control of the circadian system and can also be directly suppressed by light (Figure 1). The result is that the release of melatonin into the blood is confined to the night, and when day length increases during summer, the duration of the melatonin signal is shortened. Thus, melatonin is the internal mirror representation of day length.

Melatonin forms a critical component of the photoperiodic response and it has a profound action in the PT. The PT is packed with melatonin receptors [3] and responds under long photoperiod by increasing expression of the gene coding for thyroid stimulating hormone subunit-β (*Tshβ*; Figure 1). TSHβ forms, together with glycoprotein subunit-α (GSUα), thyroid stimulating hormone (TSH, or thyrotropin), which in turn regulates thyroid hormone deiodinase type-2 (*Dio2*) expression in the adjacent medial basal hypothalamus. Here, *Dio2* is expressed in a specialized population of ependymal cells lining the cerebral ventricles known as tanycytes. The DIO2 enzyme transforms the inactive form of thyroid hormone (T4) to its active form (T3), and hence it appears that tanycytes control local T3 actions in the basal hypothalamus. T3 was shown to ultimately influence the activity of gonadotropin releasing hormone (GnRH)-producing neurons, which are the critical element that drives gonadal activation. Direct evidence that this regulation of T3 availability is crucial for seasonal control of reproduction comes from earlier studies in mammals [4,5], as well as in birds [6]. How T3 impacts on the reproductive system is still unclear (see dashed arrow in Figure 1), but direct or indirect actions on the GnRH neurons, which drive anterior pituitary secretion of the gonadotropins (follicle stimulating hormone and luteinizing hormone), must be crucial (Figure 1). Here it deserves attention that not all circannual rhythms depend on T3 for their synchronisation. The circannual prolactin rhythm in sheep driving moult depends on the action of melatonin in the PT [7] but seems independent of thyroid hormone [5].

Until recently, it was thought that TSH production was specific for the pituitary (pars distalis) to drive TH production in the thyroid gland. The discovery of hypothalamic paracrine TSH and TH (T3) production as a critical element of photoperiodic regulation has been a major step forward, and the molecular components are now being resolved.

The two papers by Dardente *et al.* [1] and Masumoto *et al.* [2] focus on the molecular mechanism of the long

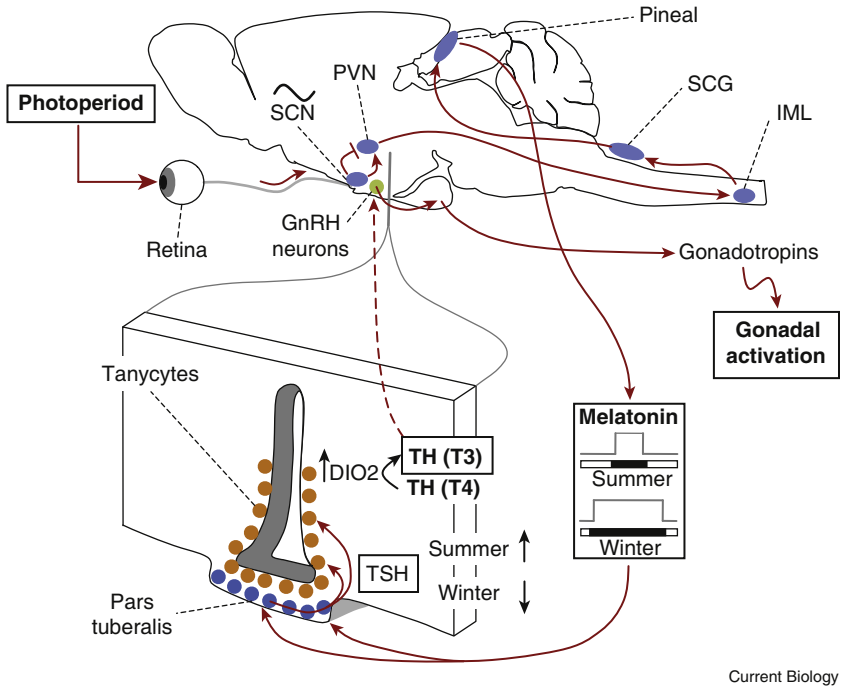

Figure 1. The photoperiod input pathway to the mammalian reproductive system.

Photoperiod is perceived by photoreceptors (melanopsin-containing ganglion cells) in the retina, which project directly to the suprachiasmatic nucleus (SCN). The SCN generates circadian rhythms that alternate between stimulatory and inhibitory signals to neurons in the hypothalamic paraventricular nucleus (PVN), which drive pineal melatonin production via autonomous projections (via the intermediolateral column of the spinal cord (IML) and the superior cervical ganglion (SCG)). Pineal melatonin is released in the bloodstream at night and forms the internal mirror image of day length. It binds to the melatonin receptors in the highly vascularised pars tuberalis (PT), where it induces TSH production under long photoperiod. The high levels of TSH cause the hypothalamic tanycytes in the third ventricle wall to produce the active form (T3) of thyroid hormone from the inactive form (T4) through increased expression of the enzyme DIO2. The dashed arrow indicates a rather unknown part of the pathway (see text) which is either a direct or indirect effect of T3, and possibly other hypothalamic signals, on GnRH-producing neurons, which subsequently drive gonadotropin production in the anterior pituitary gland, leading to gonadal activation in spring when day length increases beyond a specific critical photoperiod. Arrow connectors indicate stimulatory connections; flat connectors indicate inhibitory connections.

photoperiod (LP) induction of *Tshβ* in the PT in sheep and in mice, respectively. Although their initial methodological starting points differ considerably, their conclusions are remarkably similar. Both studies find that *Tshβ* is induced via the synergistic action of the transcription factors EYA3, SIX1, and TEF (and to a lesser extent HLF). Both studies also indicate interesting regions of the *Tshβ* promoter that are either strongly conserved or highly polymorphic across a range of species. One of these regions is the D-element (or D-box) in the *Tshβ* promoter that binds TEF and HLF. This D-element was found to be essential in tuning TEF-driven *Tshβ* expression when various forms of the D-element, occurring in different species, were screened for their efficiency to drive transcription [1,2]. This suggests that much of the transcription factor binding efficiency has been shaped by species-specific selection pressures.

The finding that TEF is strongly involved in this PT-based photoperiodic mechanism is interesting since TEF was found to play a role in the circadian timing system [8]. Since the early days of circadian biology, scientists have hypothesised on the role for circadian clocks in photoperiodism, leading to basically three models: the hour glass model, the external coincidence timing model (or 'Bünning's hypothesis') [9], and the internal coincidence timing model (or 'Pittendrigh's hypothesis') [10]. In short, these hypotheses formulate that photoperiodism involves either no role for circadian clocks, but rather some accumulating process that increases as a function of day length (hour glass); an interaction between a circadian clock that drives a photosensitive phase and light (external coincidence); or an interaction between two circadian oscillators, one following dawn and the other following dusk (internal coincidence; see [11] for review). The mammalian photoperiodic pathway (Figure 1) involves several places in which a circadian mechanism may play a role, but it has been best described for the suprachiasmatic nucleus (SCN) and the PT [12]. In the SCN there is molecular [13–16] and electrophysiological evidence [17,18] that different single-cell oscillators are simultaneously entrained either to dawn or to dusk, consistent with Pittendrigh's internal coincidence timing model. In the PT, however, the studies of Dardente *et al.* [1] and Masumoto *et al.* [2] suggest a mechanism that is similar to Bünning's external coincidence timing mechanism (see Figure 4 in [1]), in which *Eya3* expression is always timed ~12 h after dark onset and sets a 'photosensitive phase'. Taken together, it seems that the circadian system uses both internal and external coincidence timing mechanisms simultaneously to stabilize the photoperiodic response mechanism in mammals. The balance between the two mechanisms may vary between species, enabling functional tuning to variation in the light environment to which different species are exposed.

So far, the story on the photoperiodic system seems to be wonderfully converging to a conserved system in vertebrates involving hypothalamic thyroid hormone (T3) availability, but the Devil seems to be in the details again. In fact, the combined findings in the Dardente *et al.* [1] and Masumoto *et al.* [2] studies raise two interesting issues. Firstly, Masumoto *et al.* [2] describe that the photoperiodic induction system seems to be preserved in house mice all the way down to T3 production (Figure 1), yet the reproductive system of house mice (even the melatonin-proficient ones) is normally not responsive to photoperiod. Moreover, Dardente *et al.* [1] come to the surprising finding that the mouse form of the D-box is by far the most efficient one to drive TEF-dependent gene expression of *Tshβ*. Both findings seem unexpected because mice are usually classified as having an 'opportunistic' reproduction strategy: they seem to reproduce whenever enough food is available. On the other hand, sheep were found to have about 50% lower D-box efficiency, but sheep have strong photoperiodic induction of their reproductive system and established circannual rhythms [7]. This opens the possibility that house mice are in fact a photoperiodic species, but only when other factors like food or temperature are considered to play an additional interacting role. It seems fair to say that the mechanisms behind such interactions deserve more attention in future research.

Secondly, both studies indicate that mice and sheep share essentially the same photoperiodic induction mechanism upstream of the GnRH neurons (Figure 1). But, small mammals have short gestation times (weeks) and are so called 'long day breeders'; *i.e.* they mate in spring time when days are lengthening. Larger mammals like deer and sheep have much longer gestation times (months) and are so called 'short day breeders'; *i.e.* they mate in autumn when days are shortening. The offspring of both 'long day breeders' and 'short day breeders' will be born in spring time due to the difference in gestation time. If long and short day breeders share a similar photoperiodic induction mechanism for T3, then the surprising conclusion could be that the difference between long and short day breeders lies in the impact of T3 on GnRH neurosecretory activity. So far, it is unknown how this might occur, but one possibility is that neuropeptidergic pathways controlling GnRH neuronal activity differ in their sensitivity to T3. In particular, the RF-amide signals Kisspeptin and gonadotrophin inhibitory hormone (GnIH) seem to be central to this process, possibly exerting mutually antagonistic actions on GnRH activity [19]. Nonetheless, the precise mechanism that distinguishes long and short day breeders remains to be elucidated.

With the discovery of more and more molecular bits of the photoperiodic timing mechanism puzzle, we head towards ever more exciting times. It seems to me that in the not too distant future we can take the molecular genetics of seasonal timing back to the field and explore precisely how selection pressures on reproductive timing act in nature. Evolutionary biologists have been telling us for decades how important such selective pressures are for our understanding of population dynamics, life history traits, maximisation of fitness, and last but not least, nature's adaptation to climate change [20].

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Photoreceptors: Unconventional Ways of Seeing

Animals perceive light typically by photoreceptor neurons assembled in eyes, but some also use non-eye photosensory neurons. Multidendritic neurons in the body wall of *Drosophila* larvae have now been shown to use an unconventional phototransduction mechanism to sense light.

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For animals, visual information is vital for detecting potential mates, food, predators or prey. Light is primarily sensed by image-forming photoreceptors in eyes or eye-like structures. Photoreceptor neurons detect photons and generate electrical responses, through a process called 'phototransduction'. However, eyes are not the only organs perceiving light. Unconventional types of non-image-forming light perception are crucial for regulating physiological functions such as circadian rhythms, pupillary reflex or acute suppression of locomotor behaviour in rodents [1–3]. Such non-image-forming photoreceptors have been known to exist since the 1930s in invertebrate species such as the marine gastropods *Aplysia* and *Onchidium* [4]. More recently, similar photoreceptors, the so-called 'intrinsically photosensitive retinal ganglion cells' (ipRGCs) have also been described in mammals [5,6]. Perhaps more surprising was the discovery of non-image-forming photoreceptors in the eyeless nematode *Caenorhabditis elegans*, which has no morphologically distinguishable photoreceptors and lacks genes encoding opsins — the light-sensitive G-protein coupled receptors (GPCRs) used in canonical phototransduction pathways of animal photoreceptors [7]. Now, in a recent paper, Xiang and colleagues [8] show that the *Drosophila melanogaster* larval body wall possesses non-image-forming photoreceptors. In *C. elegans* as well as in *Drosophila,* non-image-forming photoreceptors seem to play a central role in light-avoidance behaviour. Even more surprising is the finding that neither of these non-image-forming phototransduction pathways involves an opsin-related light-sensing protein.

Animal photoreceptor cells come in two principal types characterised by distinct specialized structures that harbour the light-sensing proteins. In ciliary photoreceptors, the light-sensing proteins are housed in a folded ciliary membrane, while in the rhabdomeric type they sit in a folded apical cell membrane forming a rhabdom. While both photoreceptor types may coexist in the same organism, ciliary photoreceptors are typically found in vertebrates and rhabdomeric ones in invertebrates (Figure 1A,B) [9]. The canonical phototransduction pathway in the ciliary photoreceptors of vertebrates involves the ciliary-opsin (c-Rh). Light brings c-Rh to an excited state, in which it activates the G-protein alpha subunit ($G_{t\alpha}$), thereby stimulating a phosphodiesterase (PDE) that hydrolyzes cyclic GMP (cGMP) to GMP. Consequently, free cGMP decreases, causing the closing of the cyclic-nucleotide-gated (CNG) ion channels that are open in darkness. As a final response, the cell hyperpolarizes, thus reducing or arresting the release of the neurotransmitter glutamate [9].
In invertebrates, another canonical pathway operates, established mainly based on the *Drosophila* photoreceptor as a model. It involves the rhabdomeric photoprotein r-opsin (r-Rh). Absorption