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Neural systems underlying photoperiodic time measurement: A blueprint

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Summary. This paper briefly reviews the formal properties of the photoperiodic time measurement apparatus of mammals and presents a hypothetical model for the operation of the neural systems responsible for reading and responding to the nocturnal pineal melatonin signal. The primary melatonin readout mechanism is held to be common to all species responsive to melatonin. It seems likely that this mechanism responds to relative changes in the duration and amplitude of the melatonin signal, rather than the absolute levels of melatonin encountered. A series of neural systems which exploit the calendar information provided by the primary readout is envisaged to vary between and within species, depending upon the neuroendocrine response under consideration. Of particular importance is a mechanism for comparing the relative duration of successive melatonin signals. These more complex elements are responsible for phenomena such as the effects of photoperiodic history and photorefractoriness. The brain may be able to encode an accumulated memory of melatonin signals and thereby define longer term intervals within the annual cycle. A series of response elements within the hypothalamus are engaged by the appropriately processed photoperiodic stimuli. For all elements of this model, their anatomical representations are poorly understood or, in certain cases, completely unknown.
Key words. Melatonin; pineal; hypothalamus; photoperiodism; neural timers.

This paper tries to set out a blueprint for the neural systems that may be concerned with the photoperiodic responses of mammals. This blueprint is, inevitably, drawn in outline only. All we can do at the moment is to consider the properties of the photoperiodic signal and the effects it has on dependent functions, and then try to deduce some features of the neural systems that must be responsible for its effects.

Cognitive vs vegetative time measurement

The brain is concerned with measuring time in at least two distinct ways. The first, which is outside the scope of this paper, involves such functions as conscious estimates of the passage of time or the ability to order events, either in the present or in the future, according to their relationships in time and temporal values. These functions are

conscious, often highly subjective (and hence, have variable scales) and disturbed by lesions which, in the main, are localized to the cerebral cortex; we may call them by the collective name 'cognitive time measurement'. The second group of functions ('vegetative time measurement') has some converse properties of the first. They are not, so far as we know, conscious, though it remains possible that cognitive time measurement may use some of their information. Whereas cognitive time measurement may either be related to some contemporaneous series of events or may be internally generated, vegetative time measurement is linked to external, environmental stimuli which are usually highly predictable. Since it is concerned with the passage of biological time this second system is highly accurate; that is, the internal paradigm(s) bears an invariant relation to the external events which it represents. The measurement of daylength (photoperiodic time measurement: PTM) is one example of this group of functions. Circadian time measurement is another, and the two may have close ties, just as different aspects of cognitive time measurement may also be related. Both cognitive and vegetative time measurement must be represented within the brain by neural processes that act as an internal representation of external events. In the case of the cognitive category, neural processes other than those involved in time measurement may alter the nature of the internal representation of time. For example, under stressful circumstances our perception of external time becomes extremely distorted. I will argue that, in the case of at least one vegetative time measuring device, that concerned with PTM, the internal neural event is invariable, although variable use can be made of this information.

Photoperiodism: The primary readout mechanism

At a given latitude, the annual alteration in daylength is extremely predictable. If the internal neural event tracking daylength is equally predictable, and bears a constant relation to the duration of daylength (or night-time) then the animal will have a logical and reliable reference system representing daylength. This is what Bartness and Goldman [1] refer to as the 'calendar', though, as we shall see, this is an incomplete calendar. All the current evidence, even though it is still based on rather few species, points to the temporal pattern of melatonin secretion from the pineal as the signal that is read by such a neural system. It should be noted that PTM is *not* represented by patterns of melatonin secretion, but by the neural machinery interpreting such patterns. Only in the sheep do we have any extensive knowledge of the actual secretion of melatonin from the pineal, as opposed to changes in intra-pineal levels of melatonin, though the latter are often presumed (with some reason) to represent the former. The relationship between the duration of the scotophase and the length of the melatonin signal shows some interesting and, so far, inexplicable differences between species. In the ewe, the duration of elevated melatonin secretion accurately tracks the duration of the dark period, at least under experimental conditions in which there is a relatively abrupt switch from light to dark [23, 38]. In other species, this may not be so. For example, the onset of melatonin activation in the pineal of the Syrian hamster lags several hours behind that of the dark phase [14]. Nevertheless, within a species at least, if there is a neural mechanism that can measure the duration of elevated melatonin secretion, the animal has accurate information about the current daylength. So the first biological priority is the existence of such a neural machine (the primary readout mechanism), and the first experimental priority is its identification- how is an individual melatonin signal identified and its duration encoded?

The melatonin-free interval

The discussion so far (see also Bartness and Goldman [1]) has made the important assumptions that we understand the critical parameters of the melatonin pulse, and that the readout mechanism is interested only in its duration. Yet what is meant by a period of 'elevated' melatonin? Studies on serum melatonin in both humans and sheep show that, although daytime melatonin levels are much lower than night-time values, melatonin is not absent. Furthermore, there seem to be considerable differences in the absolute levels of both day- and night-time melatonin levels between individuals. It would have the most important implications for the sort of neural mechanisms for which we are seeking if 'night' were defined not by some absolute (threshold) melatonin level, but by comparing night-time levels with those during the day. The critical experiments to test this hypothesis have yet to be reported. In the sheep, where accurate determinations of serum melatonin levels can be made, administration of constant release implants of melatonin blocks the response to the endogenous pineal signal, even when the release from implants is sufficiently low for the endogenous secretion to be detected by the assay as a clear nocturnal elevation [21]. Elevation alone is therefore insufficient as a stimulus to the primary readout. However, preliminary data in the hamster suggest that melatonin infused into hamsters in a 10-h high: 14-h low pattern can be read as a 'short' day either if the 14-h infusion is a very low dose of melatonin and a somewhat higher dose of melatonin is given for 10 h, or if the latter dose of melatonin is given for 14 h and a much higher amount then infused for 10 h (Hastings, Maywood and Davies, unpublished). Clearly a systematic appraisal of the ability of the brain to read relative and absolute melatonin variations is required, but if the hamster data are confirmed, they tell us that the primary readout neural system is not solely a melatonin detector, but a comparator which requires two stimuli, basal and elevated melatonin levels (comparator 1: fig. 1). Bartness and Goldman [1], point to several similar-

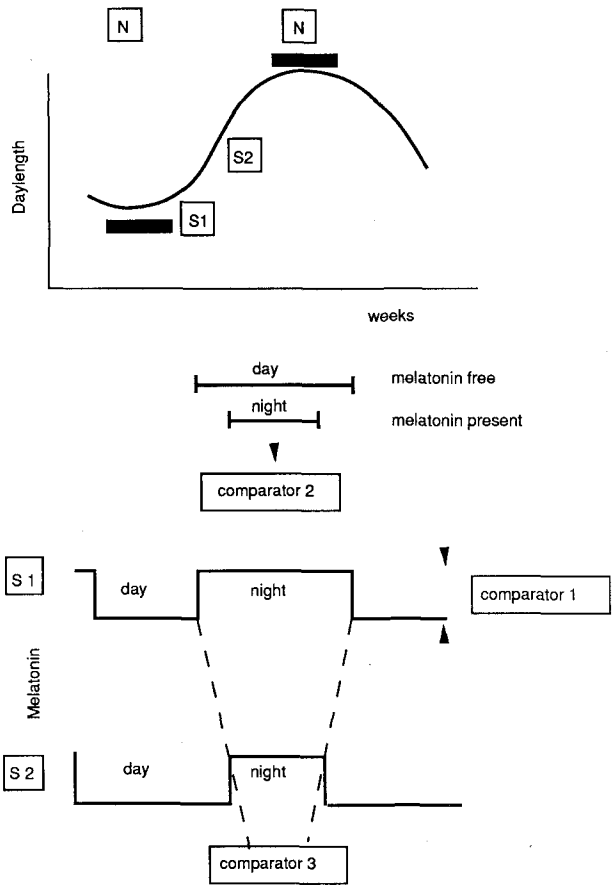

Figure 1. Diagram of the three comparators postulated to be involved in the melatonin decoding system. The upper part of the figure shows the annual change in photoperiod. There are two periods, near the solstices (N) during which alterations in daylength are not read, because either the melatonin signal does not respond to them, or the neural readout cannot detect those changes that occur. It is supposed that the neural system then samples the changing melatonin profile form S1 to S2 (the time interval between the two points is arbitrary). This is the primary readout system. This system has three properties: the first compares the difference between day- and night-time melatonin levels to determine the daily duration of the scotophase (comparator 1), and the second uses the duration of the melatonin-free interval to define the duration of the period of raised melatonin (comparator 2), and the third compares individual signals to determine the direction of the photoperiodic change (comparator 3).

ities between melatonin and steroids; here is another, for there are similar data on the ability of relative increases in serum oestrogen to induce an LH surge [12].

Another similarity between steroid and melatonin responsive processes concerns the duration of the (relatively) hormone-free interval. Bartness and Goldman [1] and Hastings et al. [13], describe experiments, in Siberian and Syrian hamsters, which show that infusions of melatonin which are effective in inducing gonadal atrophy when given at intervals of 24 h (or less) become ineffective when the interval is lengthened by an increase in the melatonin free period. This cannot be due to a 'resonance' effect whereby the melatonin signal is frame shifted out of a phase of sensitivity, for then the 48-h infusions which coincide with the phase of previous infusions would be effective, whereas 36-h ones would not. In fact, both are ineffective. The provisional conclusion must be that the melatonin-'free' interval is not a neutral event, but that its duration also has some interpretative meaning for the neural system responsive to melatonin. In other words, there is yet another comparator (comparator 2; fig. 1) which computes some relation between the durations of the melatonin-free and the melatonin-present intervals. If this is so, then the neural mechanism may either respond in a progressive but 'opposite' way to melatonin absence and presence (it will be understood in view of the earlier parts of this paragraph that these may be relative rather than absolute conditions), or there may be two systems, each responding to the two phases of the daily melatonin cycle (high vs low) independently, and somehow interacting with each other.

The need for a daylength comparator

The simple calendar-like mechanism described above, in which photoperiodically dependent changes in the duration of the melatonin signal provide a continuous indication of season, lacks one important attribute which qualifies it as a true calendar: the ability to supply prognostic (as well as diagnostic) information. Many physiological systems respond to the change in daylength independently of the pineal signal. Many of these PTM sensitive functions, for example, times of activity, and emergence from burrows etc., predict or anticipate environmental time over a single daily cycle and need only to know the onset and termination of the light and dark phases. With these systems, 'photoperiodism' is reflected in the plasticity of the shape of intrinsically circadian oscillations responding to the changing photoperiod. However, other classically photoperiodic functions need to be able to use current daylength to predict future events and anticipate environmental change. Nowhere is this more obvious than in reproduction, which has been studied more than any other dependent parameter in the context of PTM. In the majority of species living in temperate regions, births occur in the spring, and may continue into the summer. This is the biologically important reproductive event that is controlled by PTM – the classical 'ultimate' factor. Since the gestation interval is fixed by other requirements, animals showing PTM-controlled breeding use one or both of two mechanisms to time births: control of the breeding season, or of the time of implantation. The mechanisms timing these events are the well-known 'proximate' factors. The result is that the period of active breeding (or sexual inactivity – possibly an equally important period in its own right) is, in many species, temporally asymmetrical about the equinoxes. Since the annual light cycle forms an approximately symmetrical mirror-image about the equinoxes, simple measurement of daylength cannot tell the animal whether the photoperiod is increasing or decreasing. Since such information is critical in determining whether it is the summer or the

winter which is approaching at the moment, say, when the ambient photoperiod is 13 h, there must be some method of determining (i.e. a comparator) not only the absolute, but also the directional (or relative) properties of the photoperiod (comparator 3; fig. 1). The second experimental priority within PTM is to understand how this comparator is represented in the neural machinery responding to daylength. It will be important to decide, as Bartness and Goldman [1] point out, whether the comparator is a property of the primary readout (that is, the primary system measuring melatonin secretion), or has a distinct neural system devoted to it alone – a sort of photoperiodic memory. It must be made clear that reproduction, for example, is only one dependent function of PTM, and is not PTM itself: the analogy here between the 'hands' and the 'clock' familiar to students of circadian rhythms is obvious. Other dependent functions, such as the biannual moulting cycle, have timings and photoperiodic signal requirements that are different to those of reproduction [21, 29, 35]. The problem here is to understand whether these various dependent functions are using the same photoperiodic information (which could include a comparator) in different ways, or whether their common use is only for the primary daylength measure and each may have its own comparator. Some dependent functions may not need or use such a comparator at all but simply track current melatonin and therefore ambient photoperiod through the seasons (fig. 2) (see below).

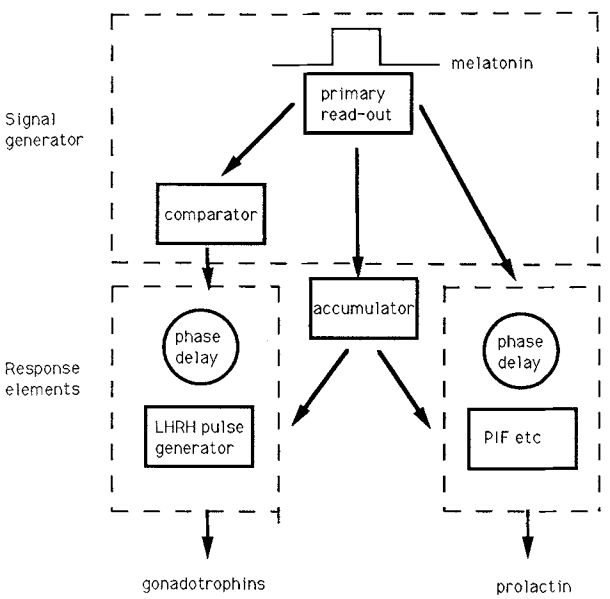

Figure 2. Diagram of the components of the melatonin readout system and the response elements to it. The signal generator consists of two components, though they may be combined (see text). The first reads the daily duration of the melatonin signal, according to the comparators 2 and 3 in figure 1. There is a 'history' comparator (comparator 1 in fig. 1), and an accumulator, which may be used by some (but not all) response elements. One of each sort is shown. Each dependent function (there may be many) has its own response element, which also consists of two parts. The first is the phase delay, which determines the interval between the detection of a photoperiodic signal and the onset of the response to it; the second is the neural mechanism that activates the dependent response itself (in these cases, either LHRH or the prolactin-inhibiting/release factors). Photorefractoriness is supposed to reside in the response elements reading the accumulator, not the signal generator.

Photoperiodic directionality and the importance of the solstices

It is standard experimental practice to expose animals to photoperiods of constant length for predetermined periods, measure some dependent variable (such as gonadal condition, or hormone level), then, perhaps, transfer the animal to another, also constant photoperiod, differing in length from the previous one, and so on. This general strategy has given an enormous amount of the most valuable information; in fact, practically all of our inferences about the nature of the neural systems involved in PTM are derived from such experiments. Yet such light treatments have no place in the natural world, for animals living in temperate climates never experience constant photoperiods, and therefore should not need a neural mechanism to detect them. What they do experience is changing photoperiods, and thus it would be easy to deduce that the primary neural machinery should be concerned not only with the length of the melatonin pulse but its direction of change. Yet countless experiments have shown that constant photoperiods are very effective in altering photoperiodically-dependent parameters. Clearly either there is some ability to measure absolute length, as well as direction of change, or constant photoperiods are intrepreted in the same way as changing ones. However, if the latter is true, the animals must always interpret a constant 'long' day as 'increasing' and a 'short' day as 'decreasing', rather than the other way round. Abrupt reductions in photoperiod do indeed result in a gradual expansion of the melatonin pattern, which adjusts to the new photoperiod over many days [14]. Such changes may mimic, perhaps in a modified form, what occurs under more natural conditions of decreasing daylength. However, with acute transfer to longer daylengths, the melatonin signal will be immediately truncated by the direct masking effect of light on pineal synthetic activity and the acute increase in daylength will be mirrored by an acute reduction in the melatonin signal. Under these circumstances, only one large amplitude relative change in successive signals occurs.

Other experiments have shown that the distinction between 'long' and 'short', which must always be in terms of some output (dependent) parameter, is itself arbitrary, and depends upon the duration of the current photoperiod relative to the preceding one (the photoperiodic 'history' effect) [15, 20]. The melatonin pattern changes direction at the solstices; this strongly suggests that these (rather than the equinoxes) are the critical time of year for photoperiodic responses, for it is at these times that the 'baseline' is set against which subsequent photoperiods will be compared. A number of constraints operate on the system detecting changes in photoperiod. For

example, there are limits to the way that the melatonin pattern can follow very short or very long photoperiods. Another factor may be the ability of the primary readout mechanism to detect accurately small changes in day (night) length. Although an ability to discriminate between photoperiods with a precision to within 30 min has been demonstrated, change at the solstices is of the order of a few min per day. So how does the animal know it has reached a solstice? All that is needed is a neural system to differentiate between the two photoperiodic directions. At the solstice, the 'directional signal' changes from one state to the other. This, it is postulated, has two effects: it 'sets' the current photoperiod as the baseline, if there are physiological parameters that need a baseline, and it generates either a 'photoperiod increasing' or 'decreasing' signal, by use of the comparator already discussed. This signal would serve as the primary regulator in a large number (perhaps all) of photoperiodically-regulated events, though extra neural signals may be required by some.

Photorefractoriness

Any model attempting to explain the neural basis of PTM has to contend with refractoriness. It is important to note how refractoriness is usually studied. Animals are exposed to a constant photoperiod ('long' or 'short') that either induces or suppresses some photoperiodically-dependent function, usually gonadal activity. After the passage of some interval – usually several weeks – the initial response is replaced by the converse one, and this may persist until the animal is switched to the 'opposite' photoperiod [30, 36, 40]. Studies of the melatonin profiles in photorefractory animals point to these effects not being due to alterations in the pattern of melatonin itself, but some neural process responsive to it, since melatonin secretion patterns continue to follow the ambient photoperiod in the same way as in the photosensitive animal [22]. Because the pineal is required if altering the photoperiod is to 'break' photorefractoriness [3], and because injections of melatonin can substitute for the appropriate photoperiod [37], it is clear that the primary readout mechanism continues to function during the refractory state. What has become refractory is not the animal's ability to read the melatonin signal [2], but the way that some dependent function responds to the primary readout. Other systems may not become refractory, and even those that do may show different times of onset of the refractory state. Photorefractoriness may also occur if the change of photoperiod stays in the same direction for a critical period [28]. That period will, it is suggested, be determined not by the primary melatonin readout mechanism, but by some secondary neural process that is able to assess the direction in which melatonin is changing, and the duration (in days) for which this occurs; that is, an accumulator. The biological importance of refractoriness is clear: it enables two sets of responses (say the start and end of the breeding season) to occur without melatonin changing direction, thus allowing (for example) the breeding season to end before the solstice. Does this mean that the animals must be able to count the number of melatonin pulses? There are precedents for such mechanisms. For example, the duration of pseudopregnancy in the rat and mouse is controlled by the animal apparently counting the number of days elapsing since the copulation responsible for it [8, 25, 31]. An obvious experiment would be to induce gonadal regression in pinealectomized hamsters by the appropriate daily infusion of melatonin, and then, if the atrophic state could be maintained by, say, infusions given every other day, determine whether the onset of photorefractoriness was delayed. Alternate 'long' and 'short' infusions of melatonin could be used to test whether the animal counts only the presence of melatonin, or the presence of a pulse of effective duration.

Species and sex differences in photoperiodic responses

It has been argued elsewhere [7, 19] that the historic distinction between 'long' and 'short' day breeders is no longer valid. This, of course, has implications for our ideas of the neural control of PTM, since it is no longer necessary to postulate some essential difference in the way that the primary readout is used by the two sets of species. Clear evidence for abandoning the old distinction comes from a variety of sources. First, the same species may appear to be a 'long' or 'short' day breeder depending on latitude (though the operation of modulating or 'masking' factors, such a temperature or food supply should not be discounted). Second, it is generally found that the male of a species begins to show annual reproductive activity before the female, though there are problems about comparing exactly the stages of gonadal activity in the two sexes [19]. Third, exposing animals to alternating photoperiods with periodicities other than 12 months changes the phase of photoperiodic responses relative to the ambient light cycle, so that the same species can appear as either a 'long' or 'short' day animal under different conditions [11]. Fourth, as Ebling and Forster [7] show, and a recent paper reinforces [24], even in animals (e.g. sheep) in which reproduction can be activated by shortened photoperiods, lengthening ones play a crucial controlling role in the timing of the following breeding season, establishing a sensitivity to the inductive photoperiod [18]. Animals, particularly those with a longer life span, have evolved to operate within a complete seasonal cycle and so it is perhaps misleading to develop theories of PTM based upon responses to single photoperiods. Finally, the timing of either the onset or the end of the season can be due as much to developing refractoriness to the current direction of the photoperiod as to its stimulating effect [19, 28, 39]. How should this information be placed in the context of the neural mechanisms responsible for PTM? If we limit ourselves, for the moment, to the annual reproductive cycle, we can postulate that the primary

readout, which we will assume gives information on the direction of the photoperiod, is essentially the same in all species, and the two sexes. This assumption is heavily qualified by the lack of comparative information. The reproductive cycle needs only two control parameters (though, in reality, more may be used): the phase of the onset of breeding to the critical ambient light cycle, and the duration of the subsequent breeding season. Note that for 'onset' we could substitute 'end', and 'non-breeding' for 'breeding', and we would still have a valid control system.

The neural systems

We must now try and turn the description of the neural systems required for PTM into neural realities. The previous paragraphs have suggested that, as a minimal requirement, the translation of the melatonin signal into photoperiodically-driven events needs the following components, summarized in figure 2:

1) *A primary readout mechanism.* This mechanism would compute the duration of the melatonin pulse, though whether the pulse itself is defined in absolute or relative terms is uncertain and the cellular nature of the responses to melatonin presence and/or absence is unknown. If this system measures melatonin duration on a relative scale, it may have two comparison scales: one with the daytime levels of melatonin, the other with the duration of the melatonin-free interval. It may be important that there is a relatively rapid rise in the titres of melatonin during darkness (which seems to be the case), allowing the brain to separate scoto- and photophase distinctly.

2) *A comparator,* determining the direction of the change in the duration of the melatonin pulse. It is not clear whether this property is intrinsic to (1) above, although it is equally likely to be property of a neuronal network. Since all photoperiods must be experienced in relation to previous ones, it could be plausibly suggested that such a comparator might serve as the primary readout itself. This comparator must have some mnemonic ability, since it has to store some representation of the duration of an earlier photoperiod. The duration of the 'memory' itself is not known, nor is there any information (at the moment) which allows us to estimate it.

3) *A set of response elements,* each specific to a photoperiodically- dependent function. This requirement follows from the fact that individual functions (such as LH or prolactin secretion) show distinct responses to a common photoperiodic cycle or treatment within a species, and because between species there is no correlation between the effects of the photoperiod on one dependent function (e.g. moulting, prolactin) and that upon others such as gonadotrophins. The nature of the response elements will be responsible for two important photoperiodically-related properties: the phase (or delay) between the onset of a given set of photoperiodic conditions (normally a melatonin pulse change in a given direction) and the neuroendocrine response, and the time to the expression of refractoriness. It is at this stage that other internal and external stimuli will become integrated with the photoperiodic signal, ensuring that photoperiodic responses which do occur are appropriate to the status of the individual.

4) *An accumulator.* Both the phase delay between initial photoperiodic stimulation and change in neuroendocrine status and the time to the establishment of refractoriness may depend on the ability of the response elements to count the number of melatonin cycles. Early experiments on ferrets showed that exposure to a minimum number of days was needed to reset the gonadotrophic response to lengthened photoperiods, and more recent studies suggest the same for the formation of the refractory state[17]. Species differences in photosensitivity, or in the parameters of the photoperiodic response, would reside in these response elements, which are to be thought of as functionally distinct from each other. So far, it has not been possible to identify the relative time courses of the operation of the accumulator and the inertia involved in recruiting a neuroendocrine response once an appropriate signal has been registered. Although some responses may be very rapid, for example prolactin secretion in sheep[21] and FSH secretion in photoinhibited hamsters[5], the gonadal responses to photoperiodic stimuli require several weeks for their full expression.

How near are we to knowing the anatomical locations of these neural components? The current evidence points to the anterior hypothalamus as the site of the melatonin readout. Lesions here prevent the effects of either photoperiods or melatonin[5], though we should note it is difficult to separate destruction of the readout from that of a response element if only one dependent variable (e.g. gonadal state) is measured. However, implants of melatonin in this region also interfere with the reading, but not the generation, of the endogenous melatonin signal[9,10,16]. The fact that melatonin binds to this area (see Morgan and Williams[27]) is consistent with its postulated role. However, which structure responds to melatonin is not agreed. Although lesions outside the SCN, but within the POA/AHA prevent melatonin dependent effects[5], SCN lesions themselves are also claimed to give the same results although others find SCN lesions ineffective and this remains a controversial area[4,33]. The problem is partly technical. It is hard to be sure that lesions to adjacent structures do not affect their neighbours[10]. Thus lesions to the SCN may encroach on a critical part of the POA; the converse complication is reduced by the demonstration that 'free-running' circadian rhythms are still present in animals rendered melatonin-insensitive by hypothalamic lesions. The balance, at the moment, favours the POA, as distinct from the SCN. If this is so, the role of the POA in many other 'vegetative', chemically-coded activities should be noted (e.g. sexual and maternal

behaviour, thermoregulation, water balance and ingestive behaviour, control of the pituitary); it seems likely that the melatonin-readout system may be part of a neural 'family', its specificity residing, perhaps, in the chemical identity of the molecule to which it responds (in this case, melatonin). It has already been noted how another detector in the POA, that for steroids, shares many of the properties of the melatonin sensitive system.

There is hardly any information on the identity of the postulated response elements. It is possible that an opioid-containing system (POMC) may be involved in that regulating the gonadotrophins, since opiates can mimic some of the photoperiodic effects on gonadotrophins, and levels of opioids (specifically β-endorphin) alter with the photoperiod[6, 31]. As far as reproduction is concerned, the response element must read information from the primary readout and then translate this into relatively simple patterns of LHRH output from the portal system. There ought to be parallel response elements for other functions, such as the control of prolactin.

Finally, what of the mechanism for melatonin readout at the level of the cell? The properties of the system outlined above may reside within each of its neurones, or be a property of some sort of neural network. At the cell level, there are precendents for suggesting that a time-dependent intracellular event may occur during continuous exposure to a chemical signal. Steroid-receptor complexes, which act directly on DNA, may progressively enhance their own DNA binding as a time-dependent function[32]. Whether or not this can account for the interval timer actions of steroids is not known. More exact comparisons are limited by current results suggesting a very different intracellular role for melatonin, which has been shown to have an action on cAMP dependent mechanisms, rather than directly on DNA, although it remains possible that a DNA binding mechanism is involved somewhere along the chain of response to melatonin[26] (see Morgan and Williams[27]). Alternatively, and perhaps more probably, the known and predicted properties of the melatonin readout may depend upon the activities of a multi-neuronal complex. Whereas the detection of the melatonin signal is likely to be achieved by individual neurones, it is possible that the integration of this signal into the comparators and accumulators postulated in this paper depends upon changes in activity of a neural network (the same may be true of other functions of the POA). If this is so, we remain entirely ignorant of the nature of such a structure, though understanding it is likely to have importance beyond that of a clearer view of the neural basis of photoperiodism.

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Reviews

The evolutionary conservation of eukaryotic gene transcription

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Summary. The basic components required for eukaryotic gene transcription have been highly conserved in evolution. Structural and functional homology has now been documented among promoters, promoter factors, regulatory proteins, and RNA polymerases from eukaryotes as diverse as yeast and mammals. The ability of these proteins and DNA sequences to function across phylogenetic boundaries demonstrates that common molecular mechanisms underlie gene control in all eukaryotic cells, and provides the basis for powerful new approaches to the study of eukaryotic gene transcription.
Key words. Eukaryotic gene transcription; evolutionary conservation; common motifs; new experimental approaches.

Introduction

Transcription is the cellular process by which RNA is synthesized from a DNA template. Like other cellular processes such as DNA replication and RNA splicing, gene transcription is mediated by both protein and nucleic acid constituents. The basic components required for accurate, efficient and regulable eukaryotic transcription initiation include two types of DNA elements known as promoters and upstream regulatory sequences, two sets of proteins known as general promoter factors and regulatory proteins, and the RNA synthesizing enzyme termed RNA polymerase. Recent experiments indicate that many of these basic components have been structurally and functionally conserved in eukaryotes as diverse as yeast and mammals, indicating that similar molecular mechanisms probably underlie gene transcription in all eukaryotes.

The purpose of this review is to summarize the topic of the evolutionary conservation of eukaryotic gene transcription. I shall discuss, in turn, the functional conservation of promoters, general promoter factors, RNA polymerase, activator proteins, and the regulation of activator proteins. I shall then present an overview of some