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Multi-author Review

Phylogeny and function of the pineal

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Some reflections on the phylogeny and function of the pineal

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Summary. The pineal gland is a universal feature of vertebrate organization and has been implicated in the control of rhythmic adaptations to daily and seasonal cycles. This paper considers three aspects of pineal function; the generation of a rhythmical endocrine signal (the nocturnal synthesis of melatonin) and the use of the signal in the regulation of circadian and photoperiodic functions. The shape of the nocturnal signal is determined by an interaction of afferent neural control and biochemical processes intrinsic to the pinealocyte. The nature of the effect of the signal upon circadian systems is unclear, and in adult mammals may not be a specific, direct influence upon the entrainment pathways of the oscillator. In the foetus, strong evidence exists for a physiological role of the maternal melatonin signal as a true internal zeitgeber, remnants of which may persist in the adult. Photoperiodic time measurement in adult and foetal mammals is critically dependent upon the melatonin signal. Indirect evidence indicates that several neural systems may be involved in the response to melatonin and consistent with this, a variety of central melatonin binding sites have been identified in the brain and pituitary. The intra-cellular actions of melatonin and the properties of melatonin responsive neural systems have yet to be identified, but in the context of photoperiodic time measurement, it is clear that the neural responses to melatonin are not dependent upon the circadian clock. The two central effects of melatonin; photoperiodic time measurement and circadian entrainment are probably mediated through completely separate mechanisms.

Key words. Pineal; melatonin; circadian rhythm; photoperiod; suprachiasmatic nucleus; photoreceptor; seasonality.

Introduction

A widely held view is that the pineal is a vestigial organ. It calcifies early in life, secretes a compound without apparent influence on human physiology and can be removed surgically without deleterious effects on the patient or a requirement for hormonal replacement therapy. Of course, it may be that to focus on the adult human is to look in the wrong place at the wrong time. In lower vertebrates the pineal is involved in regulating behaviours and physiological activities in each and every part of the body. This collection of articles seeks to highlight some of these established functions of the gland but more importantly it contains speculations as to where one should look to put the pineal into a functional perspective. This organ is a universal feature of the vertebrate body plan and so comparative analysis is an essential precondition to understanding. As with all such studies, the problem is to distinguish between general trends and local specializations and recurring throughout the reviews is the striking diversity in function and physiology, not simply between vertebrate classes but also between closely related species. In addition to this taxonomic complexity there is the problem of time. In all vertebrates the pineal synthesizes and secretes a melatonin signal every night. However, the commonality of pineal function, whatever that is, may only be expressed at certain times during the life of an individual and could be essential to a critical decision perhaps only once. For example, in the pinealectomized ewe, melatonin infusions delivered for only a few days are sufficient to generate cycles of reproduction which, once initiated by the signal, will continue spontaneously for months or even years (Ebling and Foster, this issue).

The central theme which emerges from the following chapters is that of timing. How does the vertebrate match internal body state to fluctuating external demands? The environment changes through daily and seasonal cycles

and the pineal has been implicated in adaptation to both. Its origin as a photoreceptor signals its preadaptation to such a function in endotherms but the responses to temperature cycles must also have been an important aspect of temporal control in early vertebrates and are only now being characterized (Falcón and Collin; Underwood, this issue). Investigation of the pineal therefore has general relevance as a model system for understanding oscillator function. All biological clocks appear to be multi-oscillator in nature and the recent recognition that the individual pinealocytes of certain species can function, in vitro, as a combined receptor, circadian oscillator and effector system holds enormous potential for cellular and molecular analysis of vertebrate clocks. Furthermore, on the effector side, the processes which regulate the synthesis of melatonin are excellent examples of the cellular response to external cues and current studies highlight the elegance of the interactions between various intracellular control mechanisms (Sugden, this issue). The aim of these reviews is to produce a biological appraisal of the pineal and its major hormone, melatonin. An understanding of the pineal illustrates one vertebrate solution to the problems of life in a temporally complex environment.

Cellular processes: Generation of a signal

On morphological grounds, the secretory pinealocyte can be recognized as a modified photoreceptor. The pineal shares with the retina the ability to synthesize melatonin in response to an increase in intracellular c-AMP. Some pinealocytes are spontaneously rhythmic, and in these species the circadian changes in c-AMP which drive the rhythm in melatonin production occur endogenously[15,21]. In the mammalian pinealocyte and in non-rhythmic pineals of lower vertebrates, an external clock acts through noradrenergic or other, unidentified, afferents to regulate intra-cellular levels of c-AMP. In all species, the secretory pinealocyte retains components of the photoreceptive apparatus, including various retinal antigens[11] and also well-developed intracellular c-GMP responses. The relative importance of c-GMP and c-AMP mechanisms in the control of melatonin synthesis and other rhythms within the photoreceptive pinealocyte is unclear. It is tempting to suggest that the melatonin rhythm was originally entrained by the same c-GMP responses which mediate phototransduction but it is equally possible that c-AMP-dependent synthetic capacity evolved independently of c-GMP-dependent phototransduction. Under conditions of darkness, c-GMP content in both secretory pinealocytes and pineal photoreceptors is high. In the retina and pineal, light hyperpolarizes the photoreceptor cell by decreasing c-GMP levels through an activation of phosphodiesterase. It is not known whether the higher levels of c-GMP during darkness influence enzymic activity or cellular metabolism in a fashion comparable to the effects c-AMP in the secretory pinealocyte. In the mammalian pinealocyte, noradrenergic stimulation at night increases c-GMP levels, although the response is probably brought about by stimulation of guanylate cyclase leading to enhanced synthesis of c-GMP. The regulation of c-GMP levels in the two cell lines is therefore not directly comparable and the intracellular basis to photic entrainment of melatonin rhythms remains unclear. Recent evidence in the chick pineal suggests that the two effects of light on the melatonin rhythm; the acute, direct suppression and the indirect, phase shift of the oscillator driving the rhythm, are mediated by different phototransduction mechanisms[21].

A striking feature of the melatonin rhythm in all species is the precise nocturnality. In mammals, initiation of melatonin production involves a complex of biochemical events induced by an initially massive increase in intracellular c-AMP. Synthetic activity is then maintained by a relatively low level of c-AMP stimulation, and indeed a large component of the cellular response following the initial surge of c-AMP is a programmed desensitization to the effects of NA (Sugden, this issue). Even though melatonin synthesis proceeds at a constant rate through the dark phase and the profile of the signal has a smooth and symmetrical appearance, the biochemical status of the pinealocyte changes markedly over the course of the night. The phase of onset to the rhythm is therefore tightly controlled by endogenous processes. However, the end of the signal, the decline in melatonin production, may be more variable. In nocturnal rodents, exposure to light during the dark phase which interrupts noradrenergic stimulation, leads to a precipitous fall in melatonin production[9,19]. This response, which depends upon the lability of the NAT enzyme in the absence of elevated intracellular c-AMP, may well be selected for in nocturnal or crepuscular species. It ensures that at the first exposure to dawn, the signal is truncated and so reflects, as closely as possible, the dark phase. The change in biochemical state of the pinealocyte ensures that the synthetic apparatus is not able to restart should the animal subsequently experience darkness, upon return to the burrow for example. Larger, diurnal species of mammal such as sheep and humans, are inescapably exposed to the complete light-dark cycle and so do not need to rely on intermittent sampling of the photoperiod to entrain the melatonin rhythm. As in nocturnal rodents, interruption of the dark phase by artificial light suppresses melatonin levels immediately, but this may be followed by an increase back to pre-exposure levels[1,4]. Under natural conditions maintained exposure to light following dawn would ensure that melatonin synthesis remained suppressed. The question arises as to whether the difference in responses lies in subtle contrasts in the biochemical machinery of the pinealocyte, for example the lability of the NAT molecule, or in its neural control. To date, most information has been obtained in the rat and comparative studies may highlight inter-specific differences as significant as those reported in lower verte-

brates (Falcón and Collin; Underwood, this issue). What should be emphasized is that the initiation and termination of melatonin synthesis are controlled by two very different processes which interact in the generation of an appropriate melatonin signal. This dual control evolved very early and is seen in all vertebrate groups.

An important property of the melatonin signal of mammals is that its duration varies as a direct reflection of the length of the night (fig. 1). The longer melatonin profile parallels the increased duration of other circadian functions such as nocturnal locomotor activity and the plasticity of the pineal signal appears to be a property shared by the rest of the circadian system driven by the suprachiasmatic nuclei (SCN)[7]. However, the neural basis to the change in shape is unresolved and it is not clear whether similar changes in duration of the signal occur in those species where the pineal is a self-sustaining oscillator, although this would be necessary if the melatonin signal were to be used for the photoperiodic control of seasonality (see below). One selective advantage in the loss of autonomous rhythmicity and the development of the neural control observed in representatives of all vertebrate classes may be that it allows the signal to change shape in response to a variety of stimuli and therefore provide both daily and seasonal cues. This advantage may explain why the same trend has occurred independently in several vertebrate classes. The effect of photoperiodic stimuli on the duration of daily activity cycles can be explained by a dual oscillator model developed by Pittendrigh and Daan[16]. This hypothesizes the existence of separate oscillators controlling onset and offset to activity. This model has been applied experimentally to the melatonin rhythm generating system by Illnerova and Vanacek[10]. If the on and off signals to melatonin synthesis are provided by separate oscillators, their anatomical location and neurochemical properties are unclear. The recognition that several neural inputs to the pineal may influence the basic NA response, in particular VIP and potentially NPY (Sudgen, this volume), offers some scope for speculation about multiple signalling to the pinealocyte. However, the origin of photic control to such systems remains obscure and the temporal patterning of neural activity within the sympathetic afferents to the pineal is unknown. Although the SCN are definitely a major source of the 'on' signal, the description of numerous retinal terminations within the hypothalamus[25] provides a number of candidates for the 'off' control. In rodents, melatonin synthesis can be interrupted by light pulses significantly below the threshold required for phase shifts of locomotor rhythmicity (Menaker, personal communication), echoing the dual response to light in lower species[21] and lending support to the hypothesis of two separate control systems. The 'on' signal may be tightly linked to the circadian clock, whereas the more photosensitive 'off' mechanism may be independent of the circadian system.

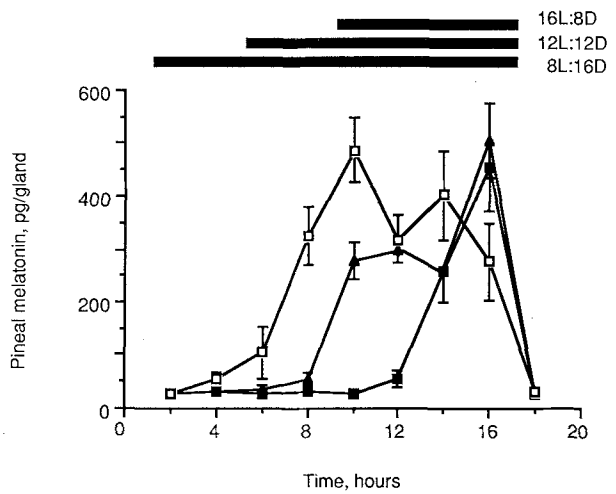

Figure 1. Pineal melatonin content (mean + SEM) of male Syrian hamsters following prolonged exposure to photoperiods of 16L:8D (■-■), 12L:12D (▲-▲) or 8L:16D (□-□). Bars indicate periods of darkness for the 3 schedules. Redrawn from Hastings et al.[8] and unpublished data.

Using the signal; circadian effects

Melatonin provides a chemical definition of darkness which is clearly important to circadian control in a variety of lower vertebrates. The chemical nature of the signal means that it can address an extensive variety of rhythmic processes but why should such a signal be necessary to an organism? During the light phase, oscillators and entrainment pathways will remain under environmental control and it could be argued that the role of the melatonin signal is to compensate for the absence of precise neural stimuli during the dark phase. This would be particularly important when the controlling elements of the circadian system were dispersed throughout the body and involved non-neuronal components. What melatonin actually does to such oscillators remains unclear. It is widely held that melatonin influences coupling between oscillators, although the endocrine or neurochemical basis to such coupling is not known. One problem is that many studies have customarily focussed upon a single overt rhythm, locomotor activity. If the hypothesis of internal synchronization is to be tested effectively, a significant number of other rhythmical functions must be monitored. How melatonin may affect coupling can only be a subject for speculation. Melatonin can influence the period of a biological rhythm (Underwood, this issue) and so it may produce changes in angular velocity of an oscillator during the potential free-running interval of darkness, such that it remains within the entrainable range of other systems. Melatonin may induce or sustain responsivity of a tissue to endocrine or neural zeitgebers. Alternatively, the effects of melatonin may be generalized, causing changes in the global metabolic activity of the oscillator rather than disturbing specifically its timekeeping properties or the cellular systems through which oscillators communicate. Indeed, if melatonin does act on a variety of oscillatory components, its common effect

would be expected to be a generalized one. In the absence of melatonin, independent oscillators may well uncouple and lead to chaotic disorder in a formerly ordered programme. Only small changes in oscillator properties are needed to produce global effects on rhythmic function and they would not necessarily be based on a phasic response to melatonin. Although rhythmic sensitivity to melatonin has been postulated in both circadian and photoperiodic systems, it is not a necessary requirement for melatonin to be effective in either context (see below). The influence of melatonin on the circadian system of the adult mammal remains controversial, although it is clear that in the laboratory rat, melatonin can induce phase-dependent phase shifts, a primary requisite for any potential zeitgeber (Armstrong, this issue). An intriguing feature of these phase shifts is that they occur at a circadian phase (CT 10, 11) at which melatonin is not normally synthesized by the pineal and they are advances whereas light pulses at this phase would induce phase delays. Although a more extensive responsiveness to melatonin may be revealed in pinealectomized animals, the adult mammal is perhaps an inappropriate subject in which to investigate melatonin's effects. The neural networks regulating circadian function are fully developed and pinealectomized individuals exhibit perfectly normal PRCs to light [2]. If melatonin is viewed as chemical darkness, then it is perhaps inappropriate to attempt to fit melatonin into models implicitly related to photic as opposed to scotopic entrainment. It becomes necessary to ask what types of influence does darkness have on rhythmic activity. Dark pulses can induce phase shifts in animals exposed to constant light although this may not be a direct effect of darkness on the oscillator. An alternative interpretation is that darkness has a behavioural effect on the animal's locomotor activity and that this in turn has a feedback effect on the oscillator [18]. If responses to melatonin and darkness are mediated by similar mechanisms, the role of melatonin as an internal zeitgeber awaits further definition.

The developing mammal is possibly a more fruitful subject for investigation of the biological role of melatonin [20]. The neural systems regulating circadian function are undeveloped and an immature visual system denies the animal photic cues. Nevertheless, it is critically important that during gestation the physiology of the foetus is synchronized with that of the mother and as parturition approaches, synchrony with the physical environment should be established. The chemical stimulus of melatonin provides an ideal vehicle for such entraining effects and because the ontogenetic process, in part, reflects evolutionary origins, the circadian effects of melatonin are probably one of the few and presumably the earliest of such temporal cues available to the foetus. Both circadian and photoperiodic effects of melatonin have been shown to occur in utero (Armstrong; Bartness and Goldman; Ebling and Foster, this issue) but it remains to be determined whether the phase control exerted by melatonin on the foetal circadian system, which must influence the entire circadian cycle, bears any relationship to the restricted phase shifts reported in the adult. The melatonin binding sites described in the foetal and adult SCN are presumably important for melatonin to exert these effects but a striking feature of their distribution is that they extend throughout the entire nucleus. In contrast, the distribution of other receptor molecules and neurotransmitters generally differentiates dorso-medial and ventro-lateral compartments [5, 17]. The latter is concerned primarily with photic input whereas the dorso-medial division is the origin of most of the efferent projection systems. The distribution of binding, although not yet attributable to defined neuronal populations, suggests that whatever the nature of melatonin's actions, they are unlikely to be equivalent to photic entrainment but are probably a more global modulation of nuclear function.

Using the signal; photoperiodic effects

As daylength changes through the year, photoperiodic species exhibit a variety of adaptive neuroendocrine and behavioural changes. Early studies on the control of photoperiodism concentrated on the effects of light and identified a 'rhythm of photosensitivity' [6]. Light breaks administered into subjective night induced long day responses, indicating that the 24-h patterning of light, rather than the total exposure to light, was the critical stimulus in photoperiodic control. Following the identification of a role for the pineal in these responses, it was shown that exogenous melatonin could induce short day effects i.e. act as an extension of the dark phase, but only if administered at certain phases of the light dark cycle; either during the afternoon [23] or just before lights on. With the conceptual framework of a clear rhythm of sensitivity to light, the diurnal variation in the response to melatonin was interpreted as evidence for a 'circadian rhythm of neural sensitivity to melatonin'. This hypothesis implies that the photoperiodic effects of melatonin are mediated in some way through the circadian system. However, as stated previously, melatonin and light should not be viewed as different manifestations of the same stimulus. The rhythm in the effectiveness of melatonin delivered at various phases probably arose as a consequence of the interaction between endogenous and exogenous melatonin. At the 'phases of sensitivity', the injected melatonin induced short day responses because it added onto the beginning or end of the endogenous signal, thereby increasing its duration to reflect that associated with shorter daylengths (Bartness and Goldman, this issue). In pinealectomized animals, melatonin infusions are equally effective at all phases of the light-dark cycle, provided they are of an appropriate duration. Moreover, to be effective, consecutive signals do not

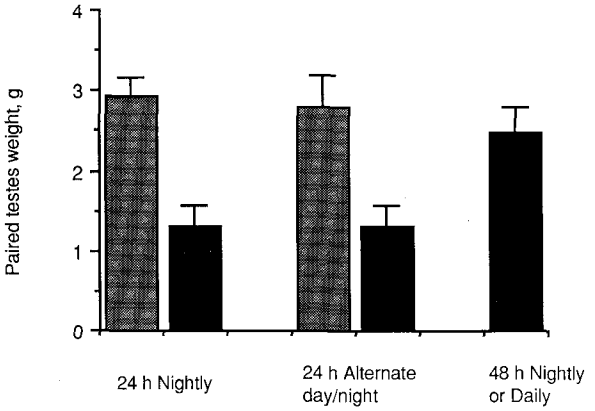

Figure 2. Paired testes weights (mean + SEM) of pinealectomized Syrian hamsters following 5 weeks of infusion with saline (stippled) or melatonin (solid) (250 ng in 500 µl per night delivered over 10 h). Infusions were given during subjective night, every 24 h, or during alternate subjective night and subjective day (signal every 24 h), or on every alternate subjective day or subjective night, i.e. every 48 h. Light cycle 16L:8D, night infusions commenced 3 h before lights off, day infusions 1 h after lights on.

need to fall within the same phase of the light-dark cycle. Pinealectomized Syrian hamsters, receiving daily 10-h infusions of melatonin for 5 weeks undergo gonadal involution (fig. 2). This effect is seen not only in groups infused during each subjective night but also in groups infused alternately during subjective night and subjective day. Animals which receive the signal every second day fail to respond, demonstrating that the animal is able to use both diurnal and nocturnal signals in combination to elicit an appropriate photoperiodic response.

Once the duration dependent mode of action had been revealed, it became clear that the physiological basis to the rhythm of photosensitivity was the truncation of the melatonin signal caused by exposure to light delivered during subjective night; the 'photosensitive phase'. Moreover, it immediately drew a sharp contrast between circadian and photoperiodic effects of melatonin which are fundamentally different. The former is an acute, phase-dependent effect whereas the latter is phase independent and chronic. To be effective as a short day signal the melatonin pulse must be continuous, persist for over 8 h and several exposures to the signal are necessary to induce a response. However, the phase of the signal is not important (Bartness and Goldman, this issue) in stark contrast to the expected properties of a potential zeitgeber.

The duality of effect (circadian vs photoperiodic) implicates a diversity of neural systems in the responses to melatonin. Seasonal adaptations involve a variety of behavioral and neuroendocrine processes, individual systems using the photoperiodic cue in distinctly different ways. For example, although reproductive activation may occur at any season depending upon species, the secretion of other hormones, e.g. prolactin, bears a common phase relationship to the annual cycle. This leads to a dissociation in the controlling stimuli for the two axes and the implication that different neural pathways subserve these functions[8]. Furthermore, within a single neuroendocrine system, it is possible for a particular melatonin signal to evoke contrasting responses, depending upon context and the photoperiodic history of the individual (Bartness and Goldman; Ebling and Foster; Herbert, this issue). It is clear then, that neural systems must interpret the duration of the signal, once it has been recognized, against a background photoperiodic memory and the nature of this interpretation varies for different neuroendocrine responses. This flexibility in use of the photoperiodic cue is presumably important for the elaboration of seasonal strategies appropriate to local conditions. The significance of small adjustments should not be overlooked. Earlier this century attempts to restock hunting areas in Czechoslovakia failed because native European ibex were mixed with Turkish and Nubian stocks which were adapted to more southerly climates. The hybrid offspring rutted earlier in the year and the kids were consequently born in the cold winter months, rather than spring, and so perished[24]. This plasticity in the use of photoperiod and the melatonin signal clearly has a genetic basis and must be incorporated into any model for photoperiodic control.

The involvement of the circadian system in photoperiodic time measurement, so clearly signalled by the rhythm of photosensitivity, may reside solely in the role played by the circadian clock in generating a melatonin signal appropriate to ambient daylength. Although it is tempting to speculate that the reading of the melatonin signal may be accomplished by individual neurones, its interpretation must be a property of a neuronal network. The neural machinery behind the responses to melatonin is completely unknown. The mechanism for identifying the length of exposure to any one melatonin signal must, by definition, operate as an interval timer. Non-circadian timers capable of defining intervals of the order of several hours have been implicated in other temporal mechanisms, including responses to steroids (Bartness and Goldman, this issue) and anticipatory feeding behaviour[13]. It is not clear how many such timers are involved in photoperiodic time measurement and whether they bear any relationship at all to the circadian system.

One particular aspect of photoperiodism warrants special mention. Photorefractoriness is the condition developed following prolonged exposure to a single photoperiod, whereby initial neuroendocrine responses are reversed. For example, although exposure of Syrian hamsters to inhibitory photoperiods leads to gonadal involution, recrudescence will occur spontaneously following prolonged exposure to short days. This loss of response to photoperiod has been taken as evidence that the brain has lost its sensitivity to melatonin. It is certainly the case that administration of exogenous melatonin to refractory animals will not induce a further bout of gonadal regression. For example, pinealectomized Syrian

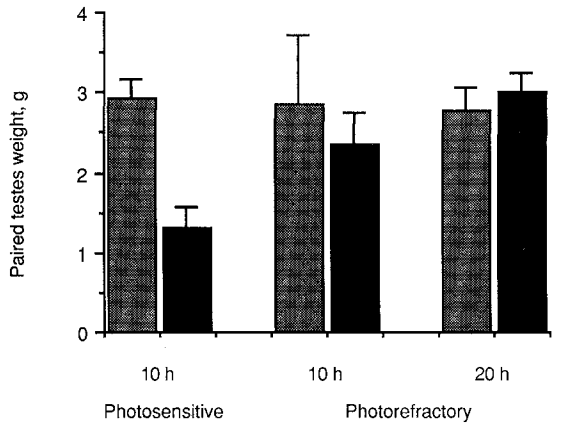

Figure 3. Paired testes weights (mean + SEM) of pinealectomized photosensitive or photorefractory (30 weeks in 8L:16D) Syrian hamsters following 5 (photosensitive) or 6 (photorefractory) weeks of infusion with saline (stippled) or melatonin (solid) (250 ng in 500 µl) delivered over 10 or 20 h. Light cycle 16L:8D for photosensitive animals, 8L:16D for refractory animals. All infusions terminate 1 h before lights on.

hamsters refractory to the inhibitory effects of short days and infused daily for 6 weeks with melatonin for 10 or 20 h will maintain full gonadal function (fig. 3).

However, this does not mean that the brain is globally blind to melatonin. Indeed, to break refractoriness and restore sensitivity to inhibitory daylengths and their accompanying melatonin signal, the animal must be exposed to the opposite, i.e. stimulatory, photoperiod and its accompanying melatonin signal[3,22]. The brain is therefore still able to read and differentiate between melatonin signals. However, it is not known where or how melatonin acts to terminate refractoriness nor, indeed, is it clear what aspect of the melatonin signal induces refractoriness after the appropriate interval of exposure to inhibitory daylengths. In the pinealectomized ewe, maintained expansion of the melatonin signal may delay the onset to refractoriness, suggesting that the temporal sequence of changes in the duration of the signal are important[12,14] (Bartness and Goldman, this issue). However, the results in the Syrian hamster indicate that once established, the refractoriness to inhibitory photoperiods and their corresponding melatonin signal is an absolute rather than a relative condition. The recognition of the importance of the duration of the signal in the photoperiodic control of neuroendocrine function is therefore only an initial step towards understanding the complexities of neuronal responses to melatonin.

One final point should be made. The entrainment of the neural circadian system of mammals ensures that the duration of the melatonin signal reflects the length of the night. There is adaptive value in using a self-sustaining, oscillatory mechanism for this purpose. It is able to interpolate between samples of the light dark schedule to define subjective day and night. It will not be compromised by intermittent exposures to darkness and will define daylength as an average function accumulated over several cycles of entraining pulses. But why use melatonin when the SCN already has processed the photoperiodic information into a neuronal signal? One obvious reason is that by broadcasting a generalized endocrine representation of the signal, it may potentially be exploited by many different organs and systems without the requirement for a specific neural address. Another feature relates to the evolutionary origin of the signal. The melatonin signal appears to be capable of providing both circadian and photoperiodic information to the foetus at a time when other avenues of temporal control are not open (Bartness and Goldman; Ebling and Foster, this issue). Evolution has not displaced melatonin from this position of primacy over photoperiodic function possibly because its early pre-eminence has precluded the development of alternatives. The role of melatonin in the control of recurrent fertility in the adult may therefore be the expression of an essentially foetal mechanism which natural selection has drawn forward into adult life. The continued expression of the signal in non-seasonal adults may still be of adaptive value insofar as it coordinates foetal activity when necessary, although in those species which are not seasonal and, in the case of man, have acquired control over their photic environment, the signal is of little consequence in adult physiology.

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Photoreceptors in the pineal of lower vertebrates: Functional aspects

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Summary. The pineal of lower vertebrates characteristically contains true and modified photoreceptors with functional und structural homologies to retinal photoreceptors. Afferent nerves convey photic information from the pineal to sensory areas of the brain stem. Light also influences synthetic activity within the organ, controlling the rhythm in melatonin production which is generated endogenously. The molecular mechanisms underlying this rhythmic event are described and the hypothesis advanced that the pineal transduces several forms of environmental stimulus involved in the regulation of rhythmic function.
Key words. Circadian rhythm; pineal; melatonin; c-AMP; fish.

Introduction

In vertebrates, as in most living organisms, many functions are rhythmic in their occurrence. Rhythms with a periodicity of 24 h (nyctohemeral) or one year (annual) represent major components of the adaptation of organisms to their environment. Such synchronization to environmental factors is mediated by the circadian system which is composed of sensors and of circadian oscillators, and which drives a number of behavioural and physiological functions.

The pineal organ of vertebrates is a component of the circadian system, primarily influenced by the light/dark (LD) cycle[2,4,5,16]. It elaborates rhythmic signals, amongst which is the hormone melatonin which is considered as an internal 'zeitgeber' of many organisms (see Underwood; Armstrong, this issue). Melatonin secretion is low during daytime and high during night-time. Despite this apparent homogeneity within the vertebrate phylum, the pineal and its chief cells display a distinct evolutionary trend[2,4,5]. Typical photoreceptors are mainly found in the pineal of ectotherms. During the course of evolution, they are gradually replaced by modified photoreceptors (e.g., reptiles, birds) and then by the pinealocytes stricto sensu (snakes, mammals). These stages of differentiation exhibit a corresponding plurality in the mechanisms involved in the photic control of the production of the melatonin and other signals. The general acceptance is that the direct control by light, as seen in the pineal of primitive vertebrates, has been completely replaced in mammals by an indirect one mediated by the retina of the lateral eyes[2,4,5,16]. Most of our knowledge on the mechanisms of control of melatonin production by the pineal refers to studies on the rat (Sugden, this issue) and on the chick. The present review outlines the most essential functional characteristics of the pineal photoreceptor cells as they emerge from recent studies on lower vertebrates, in particular lampreys, fish and frogs.