In amphibian melatonin is a skin-lightening hormone and is secreted in response to light to assist the camouflage of the animal. In mammals, it is a reproductive hormone and, paradoxically, it is secreted in response to dark.

The synthesis of melatonin

Tryptophan, provided in the diet and brought to the pineal gland by the blood supply, is converted into 5-hydroxytryptamine (serotonin) and then to N-acetyl-5-hydroxytryptamine (N-acetylserotonin) and then to N-acetyl-5-methoxytryptamine (melatonin).

Abbreviations used: HIOMT, hydroxyindole O-methyltransferase; NAT, N-acetyltransferase; CNS, central nervous system; GnRH, gonadotropin-releasing hormone; L.H, luteinizing hormone.

The pineal specific enzyme, hydroxyindole O-methyltransferase (HIOMT) permits the conversion of N-acetylserotonin into melatonin. The enzyme N-acetyltransferase (NAT) permits the conversion of serotonin into N-acetylserotonin. NAT is the rate-limiting enzyme and, consequently, NAT controls the rate of synthesis (and secretion) of melatonin.

The control of NAT

NAT is activated by dark and inhibited by light. The nervous pathway starts at the retina and passes through the central nervous system (CNS) via the supra chiasmatic nucleus (SCN) to the lateral horn of the thoracic spinal cord. It exits from the CNS as pre-ganglionic sympathetic fibres to synapse in the superior cervical ganglia, and re-enters the brain along the blood supply as post-ganglionic sympa-
Biochemical Society Transactions

The duration of the night-time secretion of melatonin is longer in winter than in summer. Consequently it also follows that the duration of the night-time secretion of melatonin is longer in winter than in summer.

**Seasonal breeding and the biological activity of melatonin**

A change in the duration of the night-time release of melatonin consequent upon a change of season, activates or inactivates the hypothalamic gonadotrophin-releasing hormone (GnRH) pulse generator, which in turn activates or inactivates the pituitary gonadal axis.

In long-day breeding animals the sequence of events which follows a change of season is as follows: In summer the nights are short and the duration of the night-time secretion of melatonin is equally short. As a consequence the GnRH pulse generator is active, i.e. it is pulsing GnRH at a rate of approximately 6 min every 60 min. The pulsatile release of GnRHI causes a pulsatile release of the pituitary gonadotrophins, particularly luteinizing hormone (LH). The pulsatile release of LH from the pituitary causes either spermatogenesis and the secretion of testosterone in the testis, or the cycle of oestrogen, progesterone and ovulation in the ovary. In winter, the nights are long and the duration of the night-time secretion of melatonin is equally long. As a consequence of this change in the duration of the night-time release of melatonin from summer to winter, the GnRH pulse generator is inactivated and the pituitary gonadal axis is quiescent [1–5].

**Man and the biological activity of melatonin**

Man is not a seasonal breeding animal and the hypotheses which could explain this are either: (a) darkness does not cause a night-time release of melatonin, i.e. there is an impairment in the neural control of NAT by light and dark; or (b) a change in the duration of the night-time release of melatonin does not control the GnRH pulse generator.

There are two pieces of evidence which support the first hypothesis. First, in seasonal breeding animals the night-time release of melatonin is universal, i.e. there are no substantial inter-animal variations, and the amplitude of nocturnal circulating melatonin exceeds 500 pmole/l. In adult humans, the night-time release of melatonin is erratic, i.e. there is substantial inter-individual variation, and the amplitude of nocturnal circulating melatonin is less than 500 pmole/l. This suggests that, in man, there is an impairment in the neural control of NAT by light and dark. Secondly, there are three examples in man where the nocturnal circulating concentration of melatonin exceeds 500 pmole/l. The three examples are: (i) children before puberty; (ii) hypogonadotropic hypogonadal infertility and (iii) high-dose melatonin as a contraceptive. In these examples there is also an inhibition of the GnRH pulse generator, suggesting that melatonin may be able to control the GnRH pulse generator in man, as much as in seasonal breeding animals [6].

**Puberty and melatonin**

From birth to puberty the GnRH pulse generator is inactive and puberty can be defined as the moment at which it becomes activated. Hence the problem is: what causes the GnRH pulse generator to be activated?

The secretion of melatonin may provide the clue. We now know that there is a dramatic fall in the nocturnal circulating concentration of melatonin throughout childhood. We also know that the daily production rate of melatonin by the pineal gland is constant throughout life. Given that body mass increases as the child grows, it follows that the circulating concentration of melatonin must fall. In other words, a constant daily production of melatonin by the pineal gland plus an increasing body mass equals a decreasing circulating concentration of melatonin [7, 8].

Consequently, the elements are in place for a ‘catastrophe’ theory of puberty [6]. As body mass increases and as the circulating concentration of melatonin declines, melatonin levels eventually drop below a critical concentration (approximately 500 pmole/l) and the GnRH pulse generator is activated, thereby activating all the endocrine events which accompany sexual maturation.

**Hypogonadotropic hypogonadal infertility and melatonin**

Hypogonadotropic hypogonadal infertility, or hypothalamic amenorrhoea, is a condition characterized by an inactive GnRH pulse generator leading to a failure of pituitary gonadotrophins and gonadal steroids. It can be treated by the pulsatile infusion of GnRH. Recently, there have been two studies investigating the levels of circulating melatonin in...
Control of N-Acetyltransferase

this condition [9, 10]. Both studies reported significantly higher levels of melatonin at night (exceeding 500 pmole/l) in this condition compared with normal controls. If the high melatonin levels are responsible for the inactivation of the GnRH pulse generator in this condition, it opens the possibility that the condition can be treated by inhibiting the secretion of melatonin.

Contraception and melatonin

Melatonin is a comparatively cheap and readily synthesized drug which has been administered to human volunteers since the early 1960s without ill effect. It has also been without biological effect, which is unsettling if it is meant to control the GnRH pulse generator.

However, past studies have been conducted using an inappropriate regimen of administration. Either the drug was administered for too short a period (one or two days) or at too low a dose to sustain high circulating levels for several hours each night. For example, the nightly ingestion of 2 mg of melatonin produced a maximum nocturnal concentration within 1 h of more than 4000 pmole/l, but by 3 h the circulating concentration had dropped below 500 pmole/l [11].

Recently a melatonin-based contraceptive has been developed (AMR Pharm Holland BV, 2514 BI the Hague, Netherlands) which uses a nightly dose of 75 mg of melatonin. Presumably the efficacy of this preparation is due to the fact that the nocturnal concentration of melatonin is maintained above 500 pmole/l for 8–12 h.

Conclusion

It is possible that melatonin controls the GnRH pulse generator in humans as it does in seasonal breeding animals. Therefore two strategies are required if melatonin is to be used therapeutically: (1) there has to be a method for the administration of melatonin whereby it can be provided as a controlled-release preparation, ensuring a circulating concentration of more than 500 pmole/l for 10–14 h; (2) means should be sought to control the activation or inactivation of NAT, the rate-limiting enzyme in the syntheses of melatonin, so that the circulating concentration of melatonin can be manipulated endogenously rather than exogenously.


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