Pineal Gland

Introduction

The pineal gland or epiphysis cerebri is a neuro-endocrine organ. It is one of the major parts of the circadian system, which also includes the eyes and the suprachiasmatic nuclei of the hypothalamus. The pineal gland exerts important regulatory influences by secreting its hormone, melatonin in variable amounts, depending on the time of day; the animal's age; and, in some species, the time of year. The daily rhythm in circulating melatonin is characterized by very low concentrations during the day and high levels at night.

This rhythm persists in constant darkness but can be altered by nighttime light exposure, because light can acutely suppress melatonin production. Normal daily variations in melatonin secretion synchronize numerous body rhythms and, in diurnal species, probably are important for nighttime sleep initiation and maintenance. Since the onset and offset of melatonin production by the pineal gland occur at dusk and dawn, respectively, the length of time per 24-h period that plasma melatonin levels are elevated can synchronize physiologic processes to seasonal changes and, in seasonal animals, can affect season-dependent functions such as body temperature, locomotor activity, and reproductive behavior. Lerner and colleagues first identified melatonin in 1958, as the constituent of bovine pineal glands that lightens isolated frog skin (by causing the melanin granules within the dermal melanophores to aggregate around the cell's nucleus). Initial studies on possible physiologic roles of melatonin focused on its effects on pigmentation (a phenomenon that is not observed in mammals) and on gonadal maturation. Kitay and Altschule had demonstrated that pinealectomy accelerated gonadal maturation in rats, and that administration of pineal extracts had the opposite effect. Melatonin was the constituent of bovine pineal extracts that was responsible for their antigonadal activity and suggested that melatonin thus is a hormone in mammals. Later results confirmed that light indeed suppresses melatonin synthesis, and that the rhythm in melatonin synthesis parallels the natural diurnal rhythm in environmental illumination. Melatonin levels in humans exhibit a characteristic daily pattern; levels are very low during the day (0.5–3 pg/ mL), and can be as high as 200 pg/mL at night, with typical nighttime levels in adults of about 100 pg/mL. The pineal gland and its hormone melatonin apparently are important components of the systems that organize rhythmic biochemical, physiologic and behavioral processes in living organisms. This chapter explores some of the fundamental mechanisms that control pineal function and that mediate melatonin's effects. It also considers possible clinical implications of impaired pineal function.

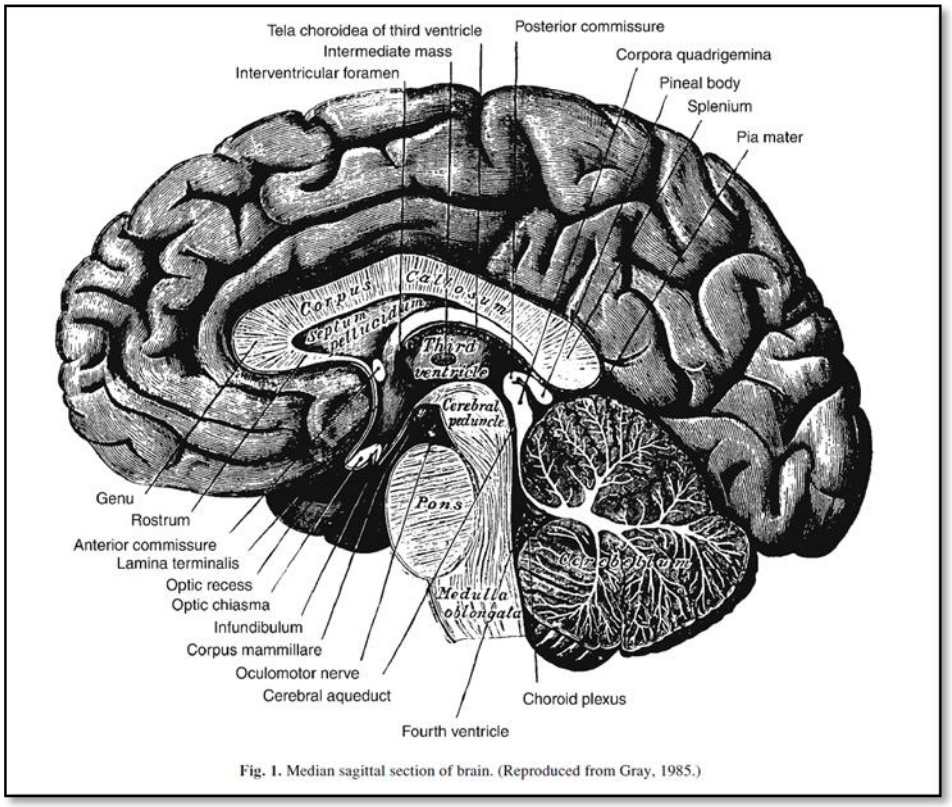

Fig. 1. Median sagittal section of brain. (Reproduced from Gray, 1985.)

THE PINEAL GLAND

The pineal gland is a small unpaired organ located near the geometric center of the brain. Its function has puzzled researchers for centuries. Postulates regarding this function have ranged from it being a mere vestigial appendage of the brain to Descartes' designation of the pineal gland as the "seat of the rational soul." Experimental investigation over the last half century has revealed that the pineal gland is indeed a biologically significant organ that has undergone profound changes in both form and cytologic differentiation during the course of evolution while retaining a functional role in the temporal organization of animal life.

Embryologically, the pineal organ arises as an evagination of the roof of the diencephalon. The diencephalon also gives rise to the lateral eyes and to the hypothalamus. This common embryologic origin is reflected in a common physiologic property—the capacity to respond to cyclic changes in environmental illumination. A fixed temporal pattern of photic input is a ubiquitous phenomenon, generated by Earth's

daily rotation in reference to the sun. Viewed from an evolutionary perspective, the pineal origin is part of a sophisticated photo-neuro-endocrine system with photoreceptors represented both in the lateral eyes and, in some species (but not mammals), in the pineal organ itself. With development, this organ-system has acquired a unique feature: an endogenous, circadian (*circa* = around, *dian* = day) rhythmic pattern in its metabolic and/or neural activity. In mammals, a neuronal component of this neuroendocrine complex, the suprachiasmatic nuclei of the hypothalamus, displays a regular pattern of spontaneous neuronal discharges, entrained to the cyclic photic input, with a higher frequency during the daylight hours; this pattern persists in the absence of a day-night cycle. In vertebrate classes whose pineal organ possesses true photoreceptors (e.g., birds and reptiles), the pineal organ itself manifests a sustained circadian oscillation in melatonin biosynthesis. In the mammalian pineal organ, the absence of true photoreceptors is accompanied by the loss of this endogenous pace-setting capacity. Mammals thus rely on the suprachiasmatic nuclei for autonomous circadian stimulation. Under natural conditions, the environmental light-dark cycle and the suprachiasmatic nuclei's endogenous oscillator act in concert to produce the daily rhythm in melatonin production. A complex neural pathway has evolved that relays information regarding environmental illumination from the ganglion layer of the retina to pinealocytes via the optic nerve, the suprachiasmatic nuclei, the lateral hypothalamus, and through the spinal cord by preganglionic fibers synapsing in the superior cervical ganglion. Postganglionic fibers reaching the pineal organ via the nervi conarii release norepinephrine at night. This neurotransmitter then activates adenylate cyclase, stimulating production of the second messenger cyclic adenosine monophosphate (cAMP), which accelerates melatonin synthesis. Exposure to sufficiently bright light qiuckly suppresses melatonin synthesis; however, under conditions of constant darkness a circadian rhythm in melatonin production persists, generated by the cyclic suprachiasmatic nuclei output.

Melatonin Synthesis and Secretion

The circulating amino acid L-tryptophan is the precursor of melatonin. Within pineal cells, it is converted to serotonin by a two-step process, catalyzed by the enzymes tryptophan hydroxylase and 5-hydroxytryptophan decarboxylase. Pineal serotonin concentrations in mammals are high during the daily light phase and decrease during the dark phase, when much of this indoleamine is converted into melatonin. This process, which occurs principally but not exclusively in the pineal gland (e.g., also in retina), involves serotonin's N-acetylation, catalyzed by an *N*-acetyltransferase enzyme, and its subsequent methylation by hydroxyindole- *O*-methyltransferase gland.

There is no evidence that melatonin is stored in the pineal gland; rather, the hormone is thought to be released directly into the bloodstream and the cerebrospinal fluid as it is synthesized. The pattern of

melatonin secretion in humans is characterized by a gradual nocturnal increase, starting about 2 h prior to habitual bedtime, and a morning decrease in serum concentrations of the hormone. About 50–70% of circulating melatonin is reportedly bound to plasma albumin; the physiologic significance of this binding remains unknown. Inactivation of melatonin occurs in the liver, where it is converted into 6-hydroxymelatonin by the P- 450-dependent microsomal mixed-function oxidase enzyme system. Most of the 6-hydroxymelatonin is excreted into the urine and feces as a sulfate conjugate (6-sulfatoxymelatonin), and a much smaller amount as a glucuronide. Some melatonin may be converted into *N*-acetyl-5-methoxykynurenamine in the central nervous system. About 2 to 3% of the melatonin produced is excreted unchanged in the urine.

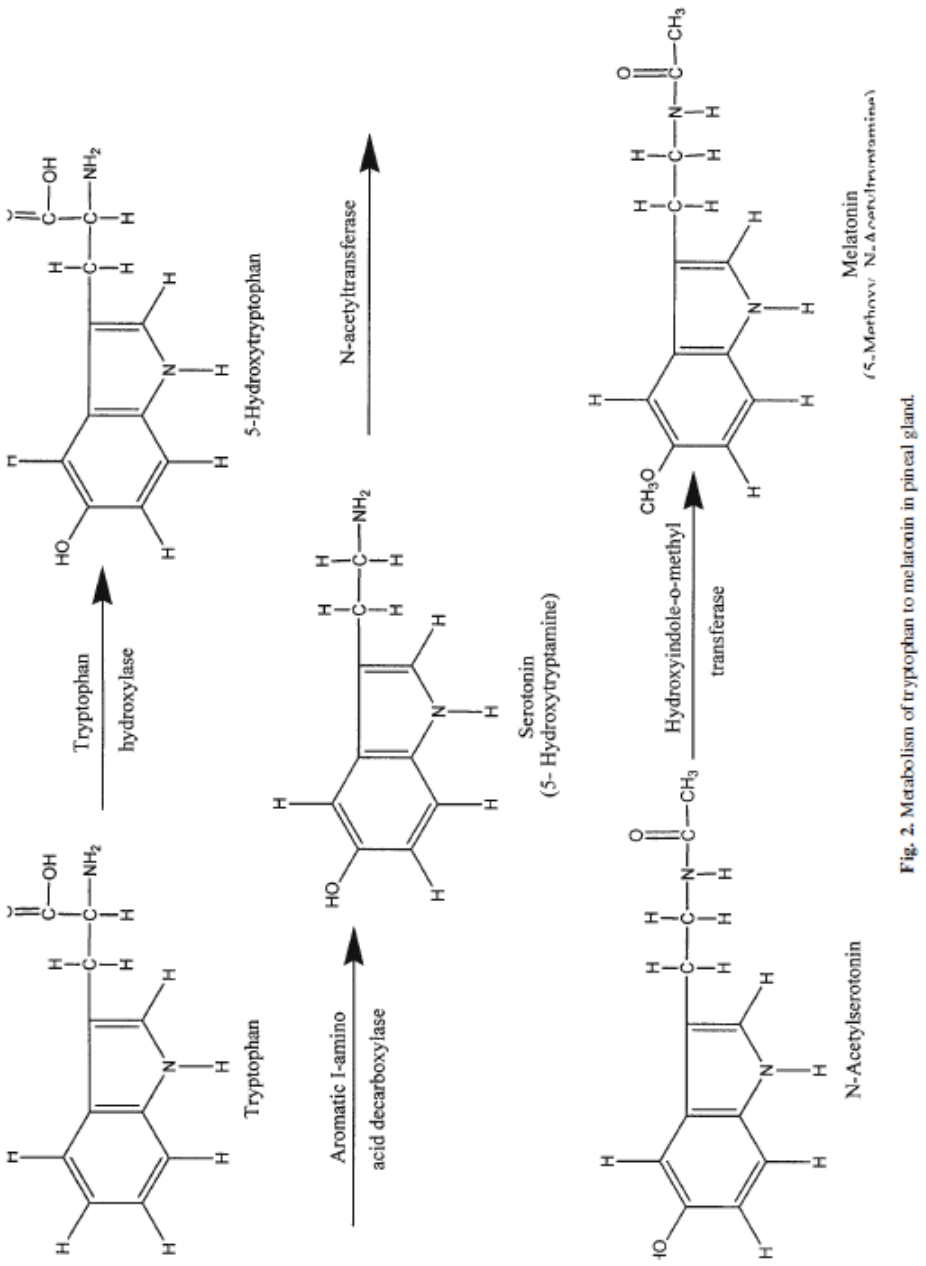

Fig. 2. Metabolism of tryptophan to melatonin in pineal gland.

Lower vertebrates start secreting melatonin at an early embryonic age. However, in mammals, including humans, the fetus and the newborn infant do not produce their own melatonin but rely on the hormone supplied via the placental blood and, postnatally, via the mother's milk. The few studies of the development of circadian functions in full-term human infants, including the melatonin secretory rhythm, the sleep-wake rhythm, and the body temperature rhythm, reveal an absence of circadian variation neonatally until 9–12 wk. Preterm babies display a substantial delay in the appearance of rhythmic melatonin production. Total melatonin production rapidly increases during the first year of life, with highest nighttime melatonin levels observed in children ages 1–3 yr. These high levels start to fall around the time of onset of puberty, decreasing substantially with physiologic aging (Fig. 4). Marked, unexplained inter individual variations in "normal" melatonin levels are observed in all age groups, so some elderly people do still exhibit relatively high serum melatonin levels. Several factors may explain the decline in melatonin concentration during the life-span, such as the increase in body mass from infancy to adulthood (which results in a greater volume of distribution and, therefore, a decline in the melatonin concentration in body fluids even if melatonin production is almost constant); the calcification of the pineal gland with advancing age (which may suppress melatonin production); or a reduction in the sympathetic innervation of the pineal gland, which is essential for melatonin's nocturnal secretion (which may result in diminished melatonin production). High variability in melatonin production among individuals of the same age group could reflect, among other things, genetic predisposition, general health, and particular environmental lighting conditions.

Melatonin and Physiologic Functions

Diversity in the adaptive strategies employed by particular mammalian species may dictate how each species responds to the circadian signal provided by the release of melatonin. The effects of melatonin on behavioral rhythmicity, sleep, reproduction, and thermoregulation have been studied most extensively. Some investigators have also proposed that melatonin might affect immune function, intracellular antioxidative processes, aging, tumor growth, and certain psychiatric disorders.

Homeostatic and Circadian Regulation of Sleep

The concurrence of melatonin release from the pineal gland and the habitual hours of sleep in humans had led to the hypothesis that the former might be causally related to the latter. The effects of the

administration of melatonin made it clear that melatonin can affect both homeostatic and circadian sleep regulation (i.e., the need to sleep after having been awake for a sufficient number of hours, and the desire to sleep at certain times of day or night), and that it does so at normal plasma melatonin levels. Although the acute sleep-promoting effect of doses of physiologic melatonin has been documented only in diurnal species (e.g., humans, fish, birds, monkeys), the circadian effects of melatonin appear to be similar in both nocturnal and diurnal species.

This phenomenon can be explained by temporal organization of the circadian system in diurnal and nocturnal species and its relation to habitual hours of sleep. Activation of the SCN and synthesis of melatonin in the pineal gland vary inversely in both nocturnal and diurnal species, with the metabolic and neuronal activity of the SCN high during the day, and the production of pineal melatonin low. This pattern is reversed during the night, when the SCN is relatively inactive and melatonin production is substantially increased. Acute exposure to light stimulation, mediated through the lateral eyes, produces an excitatory response in SCN neurons and inhibits melatonin production. On the other hand, melatonin itself exerts an acute inhibitory effect on SCN neuronal activity. When environmental light or melatonin is applied at an unusual time of day, such as bright light at the beginning of the night or melatonin in the afternoon, the phase of the circadian activity of the SCN shifts and, thus, advances or delays other circadian rhythms. Such circadian effects are similar in nocturnal and diurnal species. By contrast, the temporal relationship between sleep and activation of the circadian system is different in diurnal and nocturnal species. Nocturnal melatonin secretion is concurrent with habitual hours of sleep in diurnal animals and with peak activity levels in nocturnal animals. As a result, melatonin is linked to sleep initiation and maintenance in diurnal but not nocturnal species. Indeed, physiologic melatonin levels promote sleep in humans, diurnal primates, birds and fish, but not in rats or mice.