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PARATHYROID GLANDS

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PINEAL ORGAN

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The mammalian pineal organ is a *neuroendocrine transducer*. Like the adrenal medulla, the supraoptic nucleus of the hypothalamus, the releasing factor cells in the median eminence, and the juxtaglomerular apparatus, the pineal converts an input of neuronal signals to a hormonal output. Pineal parenchymal cells receive nerve impulses from sympathetic neurons whose cell bodies lie outside the cranial cavity in the superior cervical ganglia. They respond to these impulses by synthesizing and secreting a family of hormones, the methoxyindoles, of which the prototype is melatonin (*N*-acetyl-5-methoxytryptamine). Melatonin synthesis is controlled by environmental lighting, which acts via the retina. In rats, exposure to darkness stimulates melatonin synthesis, while light suppresses it. Melatonin is secreted into the blood or cerebrospinal fluid and apparently acts on the brain to influence several physiologic processes that share a tendency toward time-dependence (ie, they vary cyclically or with age); these include onset of puberty, ovulation, and sleep. Considerable information is available about the factors that control pineal function; much less is known about the uses to which the body puts melatonin and other pineal secretions.

EVOLUTION OF MAMMALIAN PINEAL. The mammalian pineal is a vastly different organ from the pineals (or epiphyses) of such lower vertebrates as the frog. The frog pineal is a true third eye. It responds directly to light waves by generating nerve impulses, which it transmits to the brain via pineal nerves. The mammalian organ has lost any direct photosensitivity, and it neither generates impulses for transmission to the brain nor receives them from the brain. The biochemical activity of the mammalian pineal continues to be influenced by environmental lighting, but indirectly. Light impinging on the retina generates nerve impulses that travel along the optic nerves to the optic chiasm. Just behind the chiasm a small bundle of accessory optic fibres leaves the main optic tract to run in the medial forebrain bundle of the lateral hypothalamus. These fibers feed into a multisynaptic pathway that extends through the brainstem and down the spinal cord, ultimately reaching the cell bodies of neurons that send presynaptic fibers to the superior cervical ganglia. Postsynaptic fibers from these ganglia enter the pineal and transmit signals directly to the pineal parenchymal cells. The points at which their terminal boutons impinge on pinealocytes satisfy many of the morphologic criteria for synapses. In the rat, a nocturnal species, a shining light on the retina *decreases* the number of sympathetic nerve impulses reaching the pineal. The effects of light on the neural input to the pineal may be opposite in diurnally active animals.

Another important difference between frog and mammalian pineals concerns the uniqueness of the ability to synthesize melatonin. In mammals, only pineal and retinal cells contain the enzyme hydroxyindole-*o*-methyl transferase (HIOMT), which catalyzes melatonin biosynthesis; only the pineal has been shown to be able to synthesize melatonin from its circulating precursor, tryptophan. In frogs, HIOMT is widely distributed throughout neural structures. One can conclude that, with evolution, the pineal has changed from an organ that converts an input of environmental lighting into an output of neurotransmitter substances (released at synapses within the brain) to one whose input is a sympathetic neurotransmitter and whose output is a circulating hormone. The particular neurotransmitter released by the sympathetic nerves in the pineal is norepinephrine. The mechanism by which this substance enhances melatonin synthesis involves a so-called second messenger, cyclic AMP.

LIGHT, PINEAL FUNCTION, AND BIOLOGIC RHYTHM. If rats are kept in a lighted environment, the activity of HIOMT (the enzyme that synthesizes melatonin) declines markedly, and melatonin synthesis and secretion probably show parallel declines. An environment of darkness causes HIOMT activity to increase manyfold. Because the environment in which most mammals live is characterized by light and dark periods during each 24-hour day, melatonin synthesis is also rhythmic, and the pineal provides the rest of the body with a circulating time signal. In rats, melatonin synthesis is least toward the end of the daily light period, and it rises sharply with the onset of darkness. In humans, melatonin excretion is also greatest between 11 P.M. and 7 A.M.

The discoveries that melatonin is the pineal output (or one of the pineal outputs) and that the synthesis of this compound normally varies within a 24-hour rhythm have given physiologists new and relatively fruitful ways of examining pineal function. The question "What do pineal hormones do?" can now be rephrased as "What other organs in the body respond to changes in melatonin secretion?" The answer to this question has been sought in two ways. In one approach, scientists have examined the effects of administered melatonin on neuroendocrine functions, while others have tried to

determine which light-dependent and time-dependent phenomena in the body are altered when the source of melatonin, the pineal, is removed.

If melatonin is administered chronically to young rats, they experience a delay in gonadal growth and a subsequent disturbance in the ovulatory cycle, as indicated by changes in the vaginal estrous cycle. Melatonin implants in certain brain regions, such as the median eminence and the midbrain, block the rise in pituitary levels of luteinizing hormone (LH) that follows castration; hence the pineal hormone might produce part of its gonadal effects by interfering with gonadotropin secretion from the pituitary. 5-Methoxytryptophol, another compound produced uniquely in the pineal through the action of HIOMT, also influences pituitary gonadotropin levels when implanted in the brain. Unlike melatonin, this compound acts primarily on follicle-stimulating hormone (FSH) secretion. It is possible that the mammalian pineal produces a family of hormones that influence gonadal function and that are chemically unique in that they are methoxyindoles, synthesized through the action of HIOMT. Recent studies suggest that the pineal may also synthesize characteristic biologically active peptides such as arginine vasotocin.

Since HIOMT acts to convert hydroxyindoles, which enter the brain with some difficulty, to methoxyindoles, which have free access to the brain, and since melatonin implants in the brain modify pituitary gonadal function, it is generally held that the locus at which melatonin acts in producing its neuroendocrine effects resides within the brain. This hypothesis is supported by evidence that melatonin injections alter the levels of serotonin (believed to be a neurotransmitter substance) in the hypothalamus and midbrain and that the pineal hormone can induce changes in the electroencephalogram and in behavior that resemble sleep.

When most birds and mammals are blinded, or when they are exposed to continuous light or darkness, marked changes are observed in the timing of gonadal maturation and in subsequent ovulatory cycles. Blind humans exhibit a significant acceleration of menarche; blind rats show the opposite response. Hamsters kept in continuous darkness show a pronounced atrophy of the gonads; this effect is blocked by pinealectomy, which suggests that it is mediated by dark-induced changes in secretion of melatonin or some other pineal hormone. Gonadal maturation is accelerated in most avian species by exposure to artificial long days (ie, days in which light is presented for at least 14 hours). The stimulatory effect of light on the Japanese quail is blocked by removing the pineal; hence in this species the pineal must normally *stimulate* gonadal maturation. The two procedures of exposing a rat to continuous light and removing its pineal produce comparable increases in ovarian weight. The effects of the procedures are not additive, thus suggesting that both operate by depressing the amount of an inhibitory pineal substance (melatonin) that acts on the neuroendocrine axis.

Very little information is available about the role of the pineal in producing the 24-hour rhythms observed in glandular secretion and other functions (eg, body temperature, urine production). The pineal could provide the rhythmic signal that generates rhythms in functions such as adrenocortical secretion. More likely, it might serve to modify the phasing of an intrinsic rhythm.

HUMAN PINEAL AND DISEASE. Heubner, a German pathologist, first noted that certain pineal tumors were associated with precocious puberty in young boys; he postulated that the pineal normally secretes a hormone that suppresses the onset of sexual maturation, that tumors that destroy the pineal remove this brake, and that precocious puberty soon follows. Pineal tumors composed of cells that resemble true pinealocytes might be expected to cause a delay in sexual maturation or an inhibition of gonadal function. This correlation has, in fact, been observed in a small number of patients.

This thesis has not been confirmed, inasmuch as no pineal substance that inhibits gonad function has been shown to be present in the body fluids of normal prepubertal children or absent in children with precocious puberty induced by destructive pineal tumors. Melatonin or a related methoxyindole appears to be a good candidate for Heubner's inhibitory hormone. However, no assays are currently available for measuring melatonin or its chief metabolites in clinical material; thus this hypothesis has not yet been tested. It should be noted that diencephalic tumors unrelated to the pineal can also lead to precocious puberty; thus it is possible that some, if not all, of the gonadal sequelae of pineal tumors result not from changes in the secretion of pineal hormones but from pressure exerted by the tumor on other brain areas. This pressure hypothesis fails to explain the correlation between the endocrine effects of a given tumor and its histologic appearance. Most cases of pineal tumors associated with precocious puberty in the male have involved pineal teratomas, which secrete an LH-like hormone, while true pinealomas composed of cells that resemble pinealocytes have more commonly caused a delay in sexual maturation. Tissue samples from 2 children with parenchymal pinealomas and delayed pubescence were found to synthesize large amounts of melatonin in vitro. Progress in evaluating the role of the human pineal in health and disease might be expected to accelerate now that good assays are finally available for the melatonin levels in human body fluids.

Human pineal organs typically show radiologically observable calcification by the end of the second decade of life. Microscopically identifiable calcification may be noted soon after birth. The etiology and physiologic significance of pineal calcification remain obscure. Pineal calcification does not alter the activity of any pineal enzyme yet examined, and it probably has no effect on the ability of the pineal to synthesize its characteristic indolic hormones.

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