Other Endocrine Tissues and Hormones

In terms of name recognition, the anterior pituitary, the thyroid and the adrenal glands get a lion's share of the glory. These organs have no significant function other than to produce hormones, and were relatively easy to study years ago using "remove it and see what happens" type of experiments. **There are however a number of other endocrine tissues and hormones that, while less well known, are just as important in controlling vital bodily functions.**

Several of the "other" endocrine cells discussed here are sometimes referred to as the ***diffuse endocrine system*** to reflect that concept that many organs house clusters of cells that secrete hormones. The kidney, for example, contains scattered cells that secrete erythropoietin, a hormone essential for production of red blood cells. Even the heart contains cells that produce atrial naturetic hormone, which is important in sodium and water balance.

Core information on other hormones and endocrine tissues are presented as the following topics:

- **Atrial Naturetic Hormone**
- **Erythropoietin**
- **Pineal Gland and Melatonin**
- **Renin-Angiotensin System**
- **Somatostatin**
- **Vitamin D**

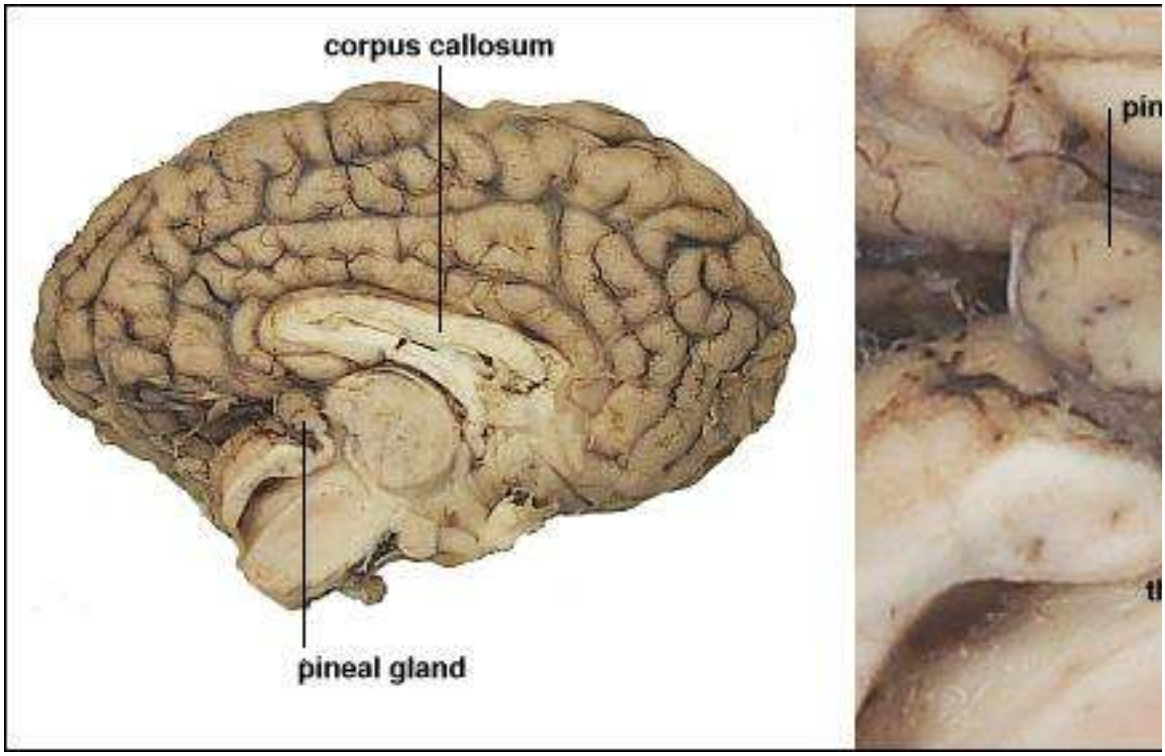
The Pineal Gland and Melatonin

The pineal gland or epiphysis synthesizes and secretes melatonin, a structurally simple hormone that communicates information about environmental lighting to various parts of the body. Ultimately, melatonin has the ability to entrain biological rhythms and has important effects on reproductive function of many animals. The light-transducing ability of the pineal gland has led some to call the pineal the "third eye".

Anatomy of the Pineal Gland

The pineal gland is a small organ shaped like a pine cone (hence its name). It is located on the midline, attached to the posterior end of the roof of the third ventricle in the brain. The pineal varies in size among species; in humans it is roughly 1 cm in length, whereas in dogs it is only about 1 mm long. To observe the pineal, reflect the cerebral

hemispheres laterally and look for a small grayish bump in front of the cerebellum. *The images below shows the pineal gland of a horse in relation to the brain.*

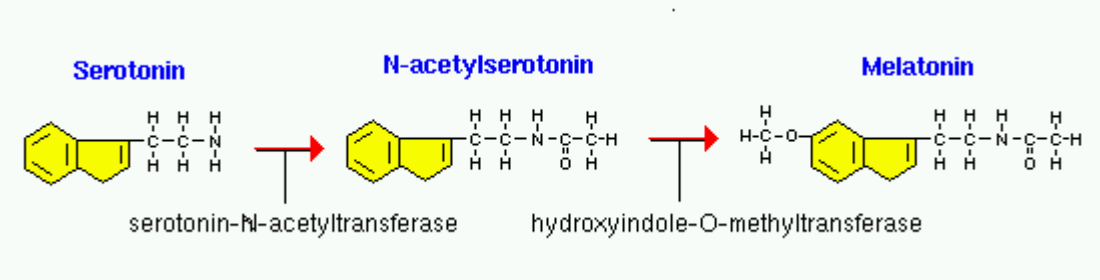


Histologically, the pineal is composed of "pinealocytes" and glial cells. In older animals, the pineal often is contains calcium deposits ("brain sand").

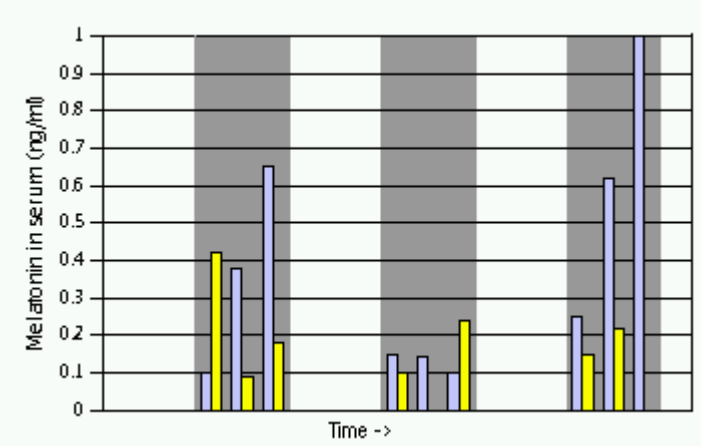
How does the retina transmit information about light-dark exposure to the pineal gland? Light exposure to the retina is first relayed to the suprachiasmatic nucleus of the hypothalamus, an area of the brain well known to coordinate biological clock signals. Fibers from the hypothalamus descend to the spinal cord and ultimately project to the superior cervical ganglia, from which post-ganglionic neurons ascend back to the pineal gland. Thus, the pineal is similar to the adrenal medulla in the sense that it transduces signals from the sympathetic nervous system a hormonal signal.

Melatonin: Synthesis, Secretion and Receptors

The precursor to melatonin is serotonin, a neurotransmitter that itself is derived from the amino acid tryptophan. Within the pineal gland, serotonin is acetylated and then methylated to yield melatonin.



Synthesis and secretion of melatonin is dramatically affected by light exposure to the eyes. ***The fundamental pattern observed is that serum concentrations of melatonin are low during the daylight hours, and increase to a peak during the dark.***


The duration of melatonin secretion each day is directly proportional to the length of the night. *Just think of melatonin as a hormone of the dark force.*

The mechanism behind this pattern of secretion during the dark cycle is that activity of the rate-limiting enzyme in melatonin synthesis - serotonin N-acetyltransferase (NAT) - is low during daylight and peaks during the dark phase. In some species, circadian changes in NAT activity are tightly correlated with transcription of the NAT messenger RNA, while in other species, post-transcriptional regulation of NAT activity is responsible. Activity of the other enzyme involved in synthesis of melatonin from serotonin - the methyltransferase - does not show regulation by pattern of light exposure.

Two melatonin receptors have been identified from mammals (designated Mel1A and Mel1B) that are differentially expressed in different tissues and probably participate

in implementing differing biologic effects. These are G protein-coupled cell surface receptors. The highest density of receptors has been found in the suprachiasmatic nucleus of the hypothalamus, the anterior pituitary (predominantly pars tuberalis) and the retina. Receptors are also found in several other areas of the brain.

Biological Effects of Melatonin

Melatonin has important effects in integrating photoperiod and affecting circadian rhythms. Consequently, it has been reported to have significant effects on reproduction, sleep-wake cycles and other phenomena showing circadian rhythm.

Effects on Reproductive Function

Seasonal changes in daylength have profound effects on reproduction in many species, and melatonin is a key player in controlling such events. In temperate climates, animals like hamsters, horses and sheep have distinct breeding season. During the non-breeding season, the gonads become inactive (e.g males fail to produce sperm in any number), but as the breeding season approaches, the gonads must be rejuvenated. Photoperiod - the length of day vs night - is the most important cue allowing animals to determine which season it is. As you've probably deduced by now, the pineal gland is able to measure daylength and adjust secretion of melatonin accordingly. A hamster without a pineal gland or with a lesion that prevents the pineal from receiving photoinformation is not able to prepare for the breeding season.

The effect of melatonin on reproductive systems can be summarized by saying that it is anti-gonadotropic. In other words, melatonin inhibits the secretion of the gonadotropic hormones luteinizing hormone and follicle stimulating hormone from the anterior pituitary. Much of this inhibitory effect seems due to inhibition of gonadotropin-releasing hormone from the hypothalamus, which is necessary for secretion of the anterior pituitary hormones.

One practical application of melatonin's role in controlling seasonal reproduction is found in its use to artificially manipulate cycles in seasonal breeders. For example, sheep that normally breed only once per year can be induced to have two breeding seasons by treatment with melatonin.

Effects on Sleep and Activity

Melatonin is probably not a major regulator of normal sleep patterns, but undoubtedly has some effect. One topic that has garnered a large amount of interest is using melatonin alone, or in combination with phototherapy, to treat sleep disorders. There is some indication that melatonin levels are lower in elderly **insomniacs** relative to age matched non-insomniacs, and melatonin therapy in such cases appears modestly

beneficial in correcting the problem.

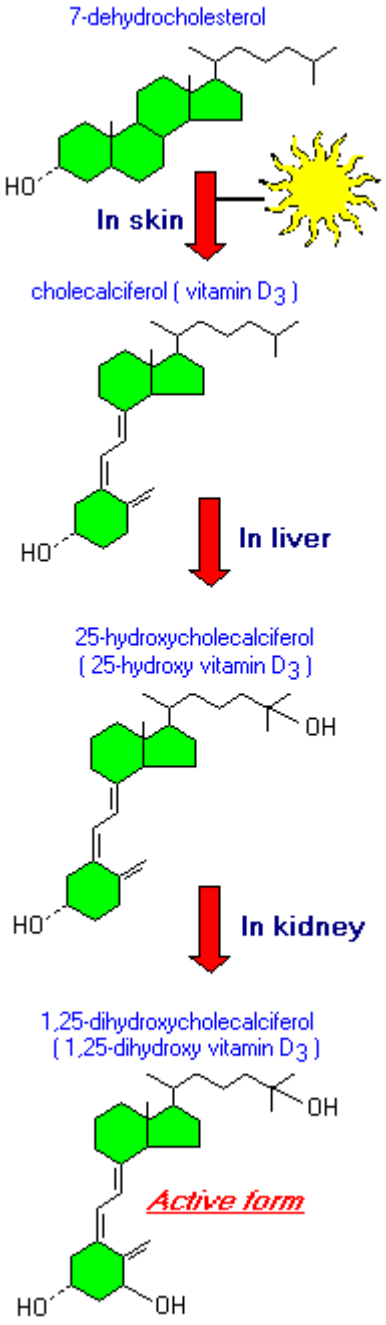
Another sleep disorder is seen in **shift workers**, who often find it difficult to adjust to working at night and sleeping during the day. The utility of melatonin therapy to aleviate this problem is equivocal and appears not to be as effective as phototherapy. Still another condition involving disruption of circadian rhythms is **jet lag**. In this case, it has repeatedly been demonstrated that taking melatonin close to the target bedtime of the destination can alleviate symptoms; it has the greatest beneficial effect when jet lag is predicted to be worst (e.g. crossing many time zones).

In various species including humans, administration of melatonin has been shown to decrease motor activity, induce fatigue and lower body temperature, particularly at high doses. The effect on body temperature may play a significant role in melatonin's ability to entrain sleep-wake cycles, as in patients with jet lag.

Other Effects of Melatonin

One of the first experiments conducted to elucidate the function of the pineal, extracts of pineal glands from cattle were added to water containing tadpoles. Interestingly, the tadpoles responded by becoming very light in color or almost transparent due to alterations in melanin pigment distribution. Although such cutaneous effects of melatonin are seen in a variety of "lower species", the hormone does not have such effects in mammals or birds.

Vitamin D (Cholecalciferol)



Vitamin D is a steroid hormone that has long been known for its important role in regulating body levels of calcium and phosphorus, and in mineralization of bone. More recently, it has become clear that receptors for vitamin D are present in a wide variety of cells, and that this hormone has biologic effects which extend far beyond control of mineral metabolism.

Structure and Synthesis

The term vitamin D actually refers to a group of steroid molecules. Vitamin D_3, also known as *cholecalciferol* is generated in the skin of animals when light energy is absorbed by a precursor molecule 7-dehydrocholesterol. Vitamin D is thus not a true vitamin, because individuals with adequate exposure to sunlight do not require dietary supplementation. There are dietary sources of vitamin D, including egg yolk, fish oil and a number of plants. The plant form of vitamin D is called vitamin D_2 or ergosterol. However, natural diets typically do not contain adequate quantities of vitamin D, and exposure to sunlight or consumption of foodstuffs purposefully supplemented with vitamin D are necessary to prevent deficiencies.

Vitamin D, as either D_3 or D_2, does not have significant biological activity. Rather, it must be metabolized within the body to the hormonally-active form. This transformation occurs in two steps, as depicted in the diagram to the right:

1. **Within the liver**, cholecalciferal is hydroxylated to 25-hydroxycholecalciferol by the enzyme 25-hydroxylase.
2. **Within the kidney**, 25-vitamin D serves as a substrate for 1-alpha-hydroxylase, yielding ***1,25-dihydroxycholecalciferol*, the biologically active form of vitamin D.**

Each of the forms of vitamin D is hydrophobic, and is transported in blood bound to carrier proteins. The major carrier is called, appropriately, vitamin D-binding protein. The halflife of 25-hydroxycholecalciferol is several weeks, while that of 1,25-

dihydroxycholecalciferol is only a few hours.

Control of Vitamin D Synthesis

Hepatic synthesis of 25-hydroxycholecalciferol is only loosely regulated, and blood levels of this molecule largely reflect the amount of amount of vitamin D produced in the skin or ingested. In contrast, **the activity of 1-alpha-hydroxylase in the kidney is tightly regulated and serves as the major control point in production of the active hormone.** The major inducer of 1-alpha-hydroxylase is parathyroid hormone; it is also induced by low blood levels of phosphate.

The Vitamin D Receptor and Mechanism of Action

The active form of vitamin D binds to intracellular receptors that then function as transcription factors to modulate gene expression. Like the receptors for other steroid hormones and thyroid hormones, the vitamin D receptor has hormone-binding and DNA-binding domains. The vitamin D receptor forms a complex with another intracellular receptor, the retinoid-X receptor, and that heterodimer is what binds to DNA. In most cases studied, the effect is to activate transcription, but situations are also known in which vitamin D suppresses transcription.

The vitamin D receptor binds several forms of cholecalciferol. Its affinity for 1,25-dihydroxycholecalciferol is roughly 1000 times that for 25-hydroxycholecalciferol, which explains their relative biological potencies.

Physiological Effects of Vitamin D

Vitamin D is well known as a hormone involved in mineral metabolism and bone growth. Its most dramatic effect is to facilitate intestinal absorption of calcium, although it also stimulates absorption of phosphate and magnesium ions. In the absence of vitamin D, dietary calcium is not absorbed at all efficiently. Vitamin D stimulates the expression of a number of proteins involved in transporting calcium from the lumen of the intestine, across the epithelial cells and into blood. The best-studied of these calcium transporters is *calbindin*, an intracellular protein that ferries calcium across the intestinal epithelial cell.

Numerous effects of vitamin D on bone have been demonstrated. As a transcriptional regulator of bone matrix proteins, it induces the expression of osteocalcin and suppresses synthesis of type I collagen. In cell cultures, vitamin D stimulates differentiation of osteoclasts. However, studies of humans and animals with vitamin D deficiency or mutations in the vitamin D receptor suggest that these effects are perhaps not of major physiologic importance, and that **the crutial effect of vitamin D on bone is to provide the proper balance of calcium and phosphorus to support mineralization.**

It turns out that vitamin D receptors are present in most if not all cells in the body.

Additionally, experiments using cultured cells have demonstrated that vitamin D has potent effects on the growth and differentiation of many types of cells. These findings suggest that vitamin D has physiologic effects much broader that a role in mineral homeostasis and bone function. This is an active area of research and a much better understanding of this area will likely be available in the near future.

Disease States

Vitamin D deficiency: The classical manifestations of vitamin D deficiency is rickets, which is seen in children and results in bony deformaties including bowed long bones. Deficiency in adults leads to the disease osteomalacia. Both rickets and osteomalacia reflect impaired mineralization of newly synthesized bone matrix, and usually result from a combination of inadequate exposure to sunlight and decreased dietary intake of vitamin D.

Vitamin D deficiency or insufficiency occurs in several other situations, which you might predict based on the synthetic pathway described above:

- **Genetic defects in the vitamin D receptor**: a number of different mutations have been identified in humans that lead to hereditary vitamin D resistance.

- **Severe liver or kidney disease**: this can interfere with generation of the biologically-active form of vitamin D.

- **Insufficient exposure to sunlight**: Elderly people that stay inside and have poor diets often have at least subclinical deficiency. Ironically, it appears that hypovitaminosis D is very common in some of the most sunny countries in the world - the cause of this problem is the cultural dictate that women be heavily veiled when outside in public.

Sunscreens, especially those with SPF ratings greater than 8, effectively block synthesis of vitamin D in the skin. However, people that use such sunscreens religiously live in industrial countries where many foods are supplemented with vitamin D, and vitamin D deficiency is thereby averted by dietary intake.

Vitamin D toxicity: Excessive exposure to sunlight does not lead to overproduction of vitamin D. Vitamin D toxicity is inevitably the result of overdosing on vitamin D supplements. *Don't do this!* Ingestion of milligram quantities of vitamin D over periods of weeks of months can be severely toxic to humans and animals. In fact, baits laced with vitamin D are used very effectively as rodenticides.