CRC

HANDBOOK of ENDOCRINOLOGY

Volume II
Part A

George H. Gass
Harold M. Kaplan

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CRC Handbook of Endocrinology

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Part A

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PREFACE

The increasing volume of literature in endocrinology usually constricts a single general textbook to a survey which, although broad in scope, tends to be superficial and not sufficiently suitable for research reference or bibliographic use.

This *Handbook of Endocrinology*, Volume II, presents a variety of selected topics, updated to the present by active workers in the field and it offers the diverse opinions of large numbers of current investigators. Many of the chapter reference sections are truly bibliographic in scope. There is no attempt to cover all aspects of the field. This would take more than a single volume.

Among the contributing authors there are clinicians and basic scientists. All are in biomedical research. The clinicians stress the clinical aspects. This is not however, a textbook of therapy. The text is designed for the student at any level, the clinical resident and physician in particular aspects of endocrinology, and the laboratory investigator.

The editors acknowledge the expertise and the amount of time spent by the contributors, This book is their work.

George H. Gass, Ph.D.
Harold M. Kaplan, Ph.D.

THE EDITORS

Dr. George H. Gass (retired) was Chairman, Department of Basic Sciences, of the Oklahoma College of Osteopathic Medicine and Surgery in Tulsa, Oklahoma. Previously he held the position of Director of the Endocrinologic Pharmacology Research Laboratory at Southern Illinois University for 18 years, during which time he was also a professor of Physiology and a professor of Medicine. He has had a very diverse career, spanning industry (Lederle Laboratories), government (Food and Drug Administration), and in university and college higher education surroundings.

Dr. Gass was awarded his doctorate at Ohio State University in 1955. His research was on the effects of androgens and their interrelationships with endocrine organs. Following graduation from Ohio State University, Dr. Gass served in the Endocrine Branch of the Food and Drug Administration in Washington, D.C., where he performed biological assay procedures, biostatistics, and endocrine research for 4 years before leaving to enter higher education. Dr. Gass' best-known work in the Food and Drug Administration was in the co-development of the uterine weight method for estrogen assay and detection. Dr. Gass assumed his duties at Southern Illinois University, Department of Physiology, in the fall of 1959 and almost immediately upon arrival set up the Endocrinologic Pharmacology Research Laboratory. A number of students obtained their research experience under Dr. Gass in the Endocrinologic Pharmacology Research Laboratory, where it was first discovered that a quantitative measure of chemical carcinogen (diethylstilbestrol)—dose response relationship of mammary tumors existed. This work has become a classic, and although published in 1964, has just recently been repeated by the National Center for Toxicological Research with Dr. Gass as a consultant.

Dr. Gass, while a member of the staff at Southern Illinois University, received a large number of honors and served on numerous occasions as a consultant for government and industry. Dr. Gass is a Fellow of the American Association for the Advancement of Science, an Alexander Von Humboldt Fellow, and a Fulbright alumnus.

He was requested to serve as a consultant for the National Center of Toxicology, Food and Drug Administration, to help determine the carcinogenicity and estrogenicity of female sex hormones, both naturally occurring and synthetic. During his 18 years at Southern Illinois University he taught physiology and pharmacology continously. He retired recently from his position as Chairman, Department of Basic Sciences, at the Oklahoma College of Osteopathic Medicine and Surgery where he was in intimate contact with the basic scientists in the college, including those in the disciplines of human anatomy, histology, pharmacology, physiology, behavior, and biochemistry.

Dr. Harold M. Kaplan has had broad experience in many facets of biologic and medical sciences. His publications, over 200 in number, range through a diverse series of research disciplines, spanning a period of 45 years. He is an author of eight textbooks in anatomy and physiology.

Dr. Kaplan completed his doctorate at Harvard University in 1933, his research then centering on the biochemistry of lipids. After one subsequent year on the Harvard staff, he entered teaching as a career, working successively in several universities. In his early activities he chaired the Departments of Physiology at the Middlesex Medical School, at the Middlesex Veterinary School, and then at Brandeis University. He taught at the University of Massachusetts, and then went to Southern Illinois University where he chaired the Department of Physiology for 22 years. He is currently Visiting Professor of Physiology at the Southern Illinois University School of Medicine.

Dr. Kaplan has served in a large number of capacities on a national scale, including the presidency of the American Association of Laboratory Animal Science, and also of the Illinois State Academy of Science. He was chairman of the Editorial Board of *Laboratory Animal Science* and is currently an associate editor of that journal. He served on the Board of Directors of the Illinois Society for Medical Research and was on the Board of the Illinois State Academy of Science. He was for several years on the Advisory Council of the Institute of Laboratory Animal Resources. He has taught human physiology continuously since 1935.

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TABLE OF CONTENTS

Volume I

Hypothalamic Hormones and Other Factors 1

The Anterior Pituitary 27

Growth Hormone Secretion and Neuroendocrine Regulation 35

Regulation of Thyroid Stimulating Hormone Secretion 61

ACTH of the Anterior Pituitary 71

Gonadotropes 87

Prolactin 111

The Ovary 123

The Testis 145

The Posterior Pituitary 177

The Adrenal Cortex 189

The Adrenal Medulla 229

The Thyroid Gland 241

The Parathyroid Gland 265

Vitamin D 297

Gastrointestinal Hormones 317

Pancreas 335

Index 343

TABLE OF CONTENTS

Volume II

Part A

The Pineal Gland 1

Endocrinology of Bone Formation 31

Endocrinology of the Skin 47

Endocrinology of the Lung 73

Neuronal Peptides of the Gut 93

Endocrine Factors in Ovarian Function 107

Endocrinology of Pregnancy 123

Effects of Nutrition on Reproductive Endocrine Function 143

Hormonal Control of Water and Electrolyte Metabolism 153

Stress Hormones: Their Interaction and Regulation 167

Central Nervous Regulation of the Hypothalamic Neuroendocrine System 181

Index 189

Volume II

Part B

Hypothalamic Regulation of Anterior Pituitary Function 1

Effects of Age on the Neuroendocrine System 23

Genetics of Endocrine Disorders 43

Calcium and Skeletal Metabolism and Aging Bone Loss 85

Environmental Modulation of Neuroendocrine Function 111

Carcinogenicity of Female Sex Hormones, Especially as Related to Use in Pregnancy and in Meat Production 141

Index 159

INTRODUCTION TO THE PINEAL GLAND

Jerry Vriend and Teresa Ralcewicz

INTRODUCTION

The inclusion of a chapter on the pineal gland in this *Handbook of Endocrinology* suggests that the pineal gland has a kinship with the other classical endocrine glands. It is now well documented that the pineal gland secretes at least one active substance, *N*-acetyl-5-methoxytryptamine, melatonin. This indole has been detected both in the pineal gland, from which it was originally isolated,[1,2] and in the circulation of amphibians,[3] birds,[4] fish,[5,6] and a large number of mammalian species including man.[7-16]

A definitive demonstration of the site of action of melatonin at a site distant from the pineal gland is required before melatonin can be regarded as meeting the requirements for classification as a classical hormone. An increasing number of researchers regard the central nervous system (CNS) as a site of action of melatonin. However, general agreement on a specific anatomical location in the CNS is lacking. Furthermore, reports of the diverse effects of melatonin raise the question of whether the various effects of melatonin can be accounted for by an action at a single CNS site. Identification of the site of action of melatonin would be a major landmark in research on the pineal gland.

Research on the pineal gland has become extremely diversified in the last two decades. Basic scientists from a growing list of disciplines, as well as clinicians, have contributed to the literature. The present chapter touches on some of the diversity of pineal research, but more importantly, concentrates on basic aspects of pineal structure and function, with emphasis on the mammalian pineal gland. It is intended as an introduction to the literature, rather than a comprehensive review.

ANATOMY

Phylogenetic Considerations

The vertebrate pineal gland, or epiphysis, develops as an evagination of the roof of the diencephalon. The lumen of the epiphyseal primordium is continuous with the third ventricle. In phylogenetic studies a distinction is made between the diencephalic primordium which develops into the pineal gland and a more rostral primordium which, in some species, develops into a parapineal organ, such as the extracranial, subcutaneous frontal organ of anurans or the parietal eye (third eye) of lacertilian and sphenodon lizards.[17] Some authors regard the pineal gland and the parapineal organs as originating from a common primordium and use the term "pineal complex" to include pineal and parapineal derivatives.[18] Already before the turn of the century the pineal anlage of fish, amphibians, and reptiles was recognized as developing into a photosensory organ[17,19] similar to the retina of the eye. In the pineal gland of these species photoreceptor type cells could be distinguished from supportive cells and sensory nerve cells, all of which originate from the neuroepithelial cell layer of the pineal primordium.[20] Early histological studies suggested that in addition to photoreception, the photosensory cells also had a secretory function.[17] Dense-core, secretory-type vesicles were observed in fish, amphibian, and reptilian pineal cells, supporting this view.[21-26] In the pineal gland of birds, photoreceptor elements are not well developed.[27-32] Secretory vesicles have been demonstrated in avian pineal cells.[33-35]

A pineal nerve, or tract, homologous to the optic nerve, has been described in studies of a variety of fish, amphibian, reptile, and avian pineals. Descriptions of synaptic connection of photoreceptor cells with fibers of the pineal tract are well documented,[36] but the central

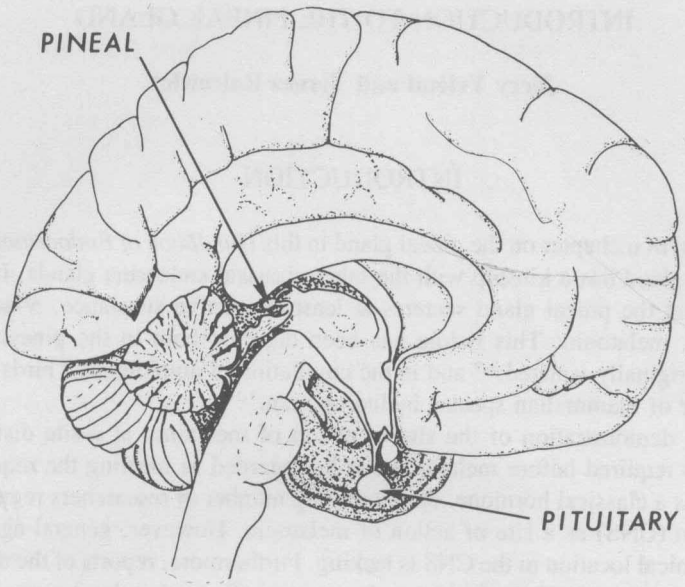

FIGURE 1. Location of the human pineal gland.

projections of the pineal tract have been studied in any detail by few investigators. The central projections of the pineal tract reported for these species include the lateral habenular nucleus, pretectal area, and periventricular gray matter.[36-39]

The Mammalian Pineal Gland

The mammalian pineal gland appears to have no direct photosensory function; yet from a phylogenetic point of view, the mammalian pinealocyte appears to be a photoreceptor cell modified to become a secretory cell. In pineal glands of some mammalian species, rudimentary photoreceptor cells and cells intermediate between photoreceptor and secretory cells have been described,[40] raising the question of whether the "pinealocyte" comprises a heterogeneous population of cells, only some of which are derived from a rudimentary photoreceptor cell. Dense-core secretory vesicles have been observed in mammalian pinealocytes.[41,42] Although the mammalian pineal gland does not appear to be directly photosensitive, it does respond to changes in environmental lighting, via a rather circuitous route (see below). The secretory vesicles increase in number in blind mice and decrease in number in mice subjected to constant light.[43,44] Light restriction is therefore thought to result in increased secretion of the pineal gland.

The mammalian pineal gland (Figure 1) is a solid parenchymal structure (in contrast to the pineal of submammalian species which may be saccular or follicular in structure) surrounded by a capsule of connective tissue and pia mater. In many mammals, including humans, it is located under the splenium of the corpus callosum; rodents are an exception, having a more superficial pineal gland, which is embedded in the dura of the confluence of sinuses. The mammalian pineal gland is connected to the brain via a stalk which is attached dorsally to the habenular commissure and ventrally to the posterior commissure. The cavity between the dorsal and ventral roots of the stalk is the pineal recess of the third ventricle.

In the developing pineal of mammals, modified ependymal cells may be found, not only lining the pineal recess, but in some species, forming follicular-like structures with cilia and microvilli on the apical surface.[41] The pineal anlage becomes invaded by connective tissue and blood vessels forming a highly vascular structure that has been likened to the capillary glomerulus of the kidney.[41] Since the pineal recess retains its lining of ependymal cells, there is apparently no direct contact of pineal parenchymal cells with cerebrospinal fluid.

Considerable variability exists in the morphology of the pineal gland of mammals. Vollrath[45] has classified pineals as to their proximity to the habenular and posterior commissures, the site of the pineal anlage during ontogenesis. Animals with a large pineal gland, relative to brain size, include the walrus, seal, and sea lion;[46,47] animals with a small pineal include the anteater, sloth, and armadillo.[18,48] Some mammals such as the rhinoceros[18,48] reportedly have no pineal. Ralph[48] has related the size of the pineal gland of mammals to the seasonal reproductive pattern; many species with a highly restricted seasonal pattern of breeding were observed to have well developed pineal glands.

A pineal nerve has been described in studies of sheep, rabbit, and human fetuses.[49,50] This nerve was described as extending from the pineal gland to a group of nerve-cell bodies dorsal to the subcommissural organ. Similar pineal nerves have not been reported in adult mammals.

Ultrastructure of Mammalian Pinealocytes

The mammalian pinealocyte is difficult to classify. Although the pineal gland is attached to the brain it is not typical neural tissue; nerve cells are not commonly found in the adult mammal. In spite of the endocrine role of the pineal gland, pinealocytes do not look like cells which secrete either peptide or steroid hormones. Although the pinealocyte is thought to derive from ependymal cells,[51] the pinealocyte must be considered as a cell type in its own right.

Ultrastructural studies have shown that the mammalian pinealocyte characteristically possesses one or more cytoplasmic processes.[52-54] These cellular processes possess expanded endings which terminate in pericapillary spaces or between other pinealocytes. Pevet and Collin[40] have compared the shape of the mammalian pinealocyte to that of the photoreceptor cells in pineals of lower vertebrates; their work suggest that the mammalian pinealocyte retains characteristics of the basal part of submammalian photoreceptor cells.

Most of the organelles of the mammalian pinealocyte do not differ substantially from those of other mammalian cells. In most species, the endoplasmic reticulum is described as being primarily smooth (lacking ribosomes), but Wolfe[52] pointed out that in the rat the endoplasmic reticulum is not typical smooth endoplasmic reticulum. Although mitochondria are generally reported as normal in mammalian pinealocytes, some very large mitochondria have been reported.[52,55] Considerable variation in shape has also been reported.[56,57] Centrioles, although not present in great numbers, have been reported to differentiate into structures called microtubular sheaves (microtubules arranged in sheaves).[52,58] The presence of cilia depends on the developmental period and the species studied. Clabough[59] observed cilia in pinealocytes of fetal and neonatal rats, but cilia are absent or very rare in pinealocytes of adult rats.[52,60] In some species, such as the mole, for example, cilia may be a characteristic of each pinealocyte.[40] In this species, the cilia were reported as having filaments in a 9 + 0 arrangement in the shaft, an arrangement also found in photoreceptor cells.

A cell organelle found in pinealocytes, but not usually found in other mammalian cells, is the synaptic ribbon,[61] which consists of an electron-dense rod surrounded by vesicles. It has been suggested that this structure is involved in cell-to-cell communication between adjacent pinealocytes.[62] Similar structures have been found in the retina.[63] Although the precise function of synaptic ribbons is not known, they are present in all mammalian pineal glands studied.

Secretory granules are much rarer in mammalian pinealocytes than would be expected of an organ which is primarily secretory in function. Dense-core vesicles, presumably secretory vesicles, have been observed in many species both in perikarya and in pinealocyte processes. Dense-core vesicles have been reported in rat, mouse, hamster, cat, sheep, cow, monkey, and seal pinealocytes, just to mention a few.[41,54,64,68] In vitro evidence that the dense-core vesicles represent a secretory product was provided by Romijn and Gelsema;[69] they found

that norepinephrine, which stimulates melatonin production, also produces a great increase in number of dense-core vesicles. In vivo studies have shown that there is a 24-hr rhythm in dense-core vesicles of several species.[70,71] Thyrotropin releasing hormone (TRH) administration in rats was reported to increase the number of dense-core vesicles in pinealocytes.[72] Although researchers have concentrated on the dense-core vesicles as a morphological correlate of secretion, a second type of secretory process has been postulated from ultrastructural studies of the rat pineal; this process has been described as release of flocculent material from the endoplasmic reticulum.[73] The chemical nature of either the dense-core vesicles or the "flocculent" material remains to be determined. Investigators have considered them to contain either melatonin or a peptide.

Unlike other endocrine glands, the pineal gland shows little ultrastructural evidence that it is storing a hormonal product. Its secretory product, melatonin, appears to be released almost immediately after it is synthesized.

Other well known structures found in the human pineal are the corpora arenacea, calcium-containing concretions[74] which increase in number with age. Although thought to be characteristic of human pineals, these structures have been reported in an increasing number of species including the monkey, horse, gerbil, and aged rat.[75-77] Functionally these structures are not well understood.

Although the pinealocyte is the most numerous and most extensively studied cell type in the mammalian pineal, other cell types have been observed. Glial cells have been estimated to account for up to 12% of the total number of cells in the rat pineal.[78] Immunocytochemical studies of glial cells in the rat pineal provide evidence that the glial cells are primarily astrocytes.[79] Astrocytes may be either fibrous or protoplasmic.[53]

Blood Supply

The pineal gland is supplied by unnamed branches of the posterior choroidal arteries, which derive from the posterior cerebral arteries.[80-82] It has been estimated that the mammalian pineal gland has a blood flow (per gram of tissue) that is exceeded only by the kidney.[83] The pineal is drained by venules which join the great cerebral vein of Galen and the internal cerebral veins.[83] The perivascular spaces of the mammalian pineal are the site of termination of pinealocyte processes as well as sympathetic nerve fibers. Melatonin is thought to be secreted into the perivascular spaces. The extent of the relationship between pinealocyte processes and perivascular spaces may vary considerably from species to species, but is considered to be of basic structural importance.[53]

Innervation

Although the pineal gland is attached to the brain, the primary innervation of the mammalian pineal is via peripheral sympathetics. The sympathetic innervation was definitively demonstrated in the albino rat,[83-85] and was since demonstrated in many other mammalian species by a variety of methods. Kappers[83] showed that after surgical removal of the superior cervical ganglia, the sympathetic nerve fibers in the rat pineal disappeared. The sympathetic nerves release norepinephrine into pericapillary spaces; norepinephrine in turn, via β-receptors on pinealocytes, stimulates the synthesis of melatonin from serotonin.[86-88] This mechanism is mediated by an adenylate cyclase system[89,90] in the pinealocyte.

The effects of light on pineal secretion of melatonin depend on intact postganglionic sympathetics to the pineal gland. The pathway by which information about light reaches the pineal has been partially demonstrated by experimental methods: light information is converted to neural information in the retina and travels via the optic nerve through the optic chiasm. Following the decussation, the fibers involved in the photoregulation of melatonin leave the neural pathway involved in vision. Impulses are transmitted by direct retinohypothalamic pathway to the suprachiasmatic nuclei (SCN).[91-93] The SCN project caudally into

the hypothalamus, reach the lateral hypothalamus via one or more neurons, and synapse with central sympathetic fibers running through the medial forebrain bundle.[91,92] These fibers project to the intermediolateral cell column of the thoracic cord, the source of preganglionic fibers to the superior cervical ganglia. The preganglionic neurons travel up the sympathetic trunk to synapse with postganglionic neurons in the superior cervical ganglia. These fibers reach the pineal gland via the tentorium cerebelli and enter the pineal gland as the nervi conarii.[83] Sympathetic fibers distribute themselves in the pineal to terminate among pinealocytes or in pericapillary spaces.

Parasympathetic innervation of pinealocytes is not common in mammals.[83] Such fibers, however, have been reported in the monkey and in the rabbit.[94,95] There is no evidence for parasympathetic innervation in the mammalian pineal. Ganglion cells have been found in primates,[96] in rabbits,[95,97] and in the ferret.[98,99] The relationship of the ganglion cells to other autonomic fibers is not clear.

In addition to autonomic fibers, an innervation of the pineal from the habenular area has been noted[83,100,101] in several species. Electrophysiological studies have confirmed a habenula-pineal connection.[102,103] It has been suggested that the habenular nuclei play a role in linking pinealocytes with the olfactory system.[83,104,105] Fibers entering the pineal from the posterior commissure have been described in studies of the dog pineal.[106]

Neurosecretory fibers have been reported in the mammalian pineal gland.[18,75,106,107] These fibers are considered to originate in the brain and enter the pineal through the stalk. Peptidergic neurons, demonstrated by immunocytochemistry of oxytocin and vasopressin in hedgehog brains, have been reported to enter the pineal gland via the habenular commissure.[108] In both the guinea pig and hedgehog, such fibers have been reported to originate in the paraventricular nuclei of the hypothalamus, a conclusion based on horseradish peroxidase tracing methods.[108,109] The presence of vasopressin and oxytocin in the mammalian pineal has been confirmed by radioimmunoassay.[110] Results demonstrating the presence of oxytocin and vasopressin in the mammalian pineal are interesting findings that deserve more attention than researchers have given them.

BIOCHEMISTRY

Purification and Identification of Melatonin

In 1917, McCord and Allen[111] reported that cattle pineal glands contained a substance that was very effective in causing melanin concentration in tadpole melanophores. This substance was isolated in 1958 from extracts of bovine pineals by Lerner, a melanin biochemist.[1] It was subsequently identified as *N*-acetyl-5-methoxytryptamine, a derivative of serotonin.[2] Because of its skin-blanching effects on tadpole skin it was termed melatonin. Melatonin is the best studied of substances found in the mammalian pineal gland. Soon after it was isolated and identified, Wurtman and Axelrod[112] proposed that the endocrine effects of the mammalian pineal gland were attributable to melatonin. According to this hypothesis, the pineal was considered as an endocrine organ, secreting a substance, melatonin, into the blood to effect an action at a distant site.

Peptides in the Pineal Gland

An alternative to the melatonin hypothesis of pineal function is the hypothesis that the pineal gland produces one or more proteins or polypeptides which are responsible for the endocrine-like actions of the pineal gland. A variation of this view is that melatonin acts via a pineal polypeptide. Much of the research on peptides in the pineal gland arose out of the search for a natural antigonadotropic substance. Despite numerous preliminary reports of pineal peptide and polypeptide "factors", the hypothesis that the pineal synthesizes and secretes a physiologically active peptide hormone has very little critical evidence to support it.

One substance that received some attention several years ago is arginine vasotocin (AVT), a nonapeptide which occurs naturally in the neurohypophysis of nonmammalian vertebrates. Although AVT was reported as present in the mammalian pineal,[113-117] and accepted as a pineal hormone by a number of researchers,[118,119] subsequent studies with adequate controls have made it clear that this substance is not present in the mammalian pineal gland.[110,120,121] AVT was found to cross-react, in radioimmunoassay and immunocytochemistry, with antibodies to vasopressin and oxytocin, nonapeptides which are present in the mammalian pineal gland and are structurally similar to AVT. This would account for the preliminary reports of AVT in extracts of pineal glands and in tissue sections of pineal glands. Although AVT may have some interesting endocrine actions when administered to animals,[122-123] the evidence shows that it is not a hormone of the mammalian pineal gland.

Studies of partially purified fractions of pineal extracts have led to a large number of reports of hormonally active "factors" in the mammalian pineal. Although some of the techniques used to purify hypothalamic hormones have been used on pineal extracts, no one has reported a convincing amino acid sequence for a peptide or polypeptide that could qualify as a pineal hormone. Many of the peptide "factors" reported from in vitro and in vivo testing of fractions of pineal extracts are artifacts. We include as probable artifacts "anestrina",[124] "anovulin",[125] Neacsu's peptide E5,[113] the Milcu extract,[126,127] the Orts factor,[128,129] the pineal antigonadotropin (PAG) of Ebels and co-workers,[130-132] the Ota factor,[133] the Cheesman extract,[134] a TRH inhibitor,[135,136] a luteinizing releasing hormone (LHRH) inhibitor,[137] and a prolactin inhibitory factor.[138] One problem faced by all researchers working with pineal extracts is that these extracts contain significant amounts of hypothalamic-hypophysiotropic hormones; these hormones could account for some of the reported effects of the extracts. Convincing evidence for the presence of TRH and LHRH in extracts of mammalian pineal glands has been reported.[139-141] Unpublished data from the author's laboratory show that in methanol extracts of approximately 600 rat pineal glands, LHRH could be detected by radioimmunoassay; results showed approximately 1 pg LHRH per rat pineal. Compared to the levels in the rat hypothalamus (3000 to 8000 pg), the levels in the pineal gland are not great. Studies of extracts of large numbers of bovine pineal glands, however, confirmed the presence of LHRH by radioimmunoassay and by bioassay (release of luteinizing hormone (LH) by pituitary cells in culture) in fractions of extracts separated on Sephadex G-25.[136] Oxytocin, vasopressin, and their neurophysins, have also been reported as present in extracts of pineal glands of a number of mammalian species.[110,142-145] It is not clear to what extent these substances have interfered in the various assays for pineal peptide "factors". Oxytocin has been reported in the human pineal in concentrations 200 times less than in the neurohypophysis.[146]

Synthesis and Regulation of Melatonin Secretion

Melatonin is synthesized in the pineal gland from serotonin via a two-step procedure (Figure 2). Acetylation of serotonin is the first step. This requires the enzyme serotonin *N*-acetyl transferase (SNAT) and an acetyl donor, acetylcoenzyme A.[147] The second step is the transfer of a methyl group to *N*-acetyl serotonin from *S*-adenosylmethionine, using the enzyme hydroxyindole-*O*-methyltransferase (HIOMT).[148,149] HIOMT was initially purified from extracts of bovine pineal glands.[150] It has been found in the pineal glands of all mammalian species studied. The enzyme SNAT has been reported in other brain areas.[151,152] Initial studies with the enzyme HIOMT suggested that it is found only in pineal gland,[153] but more recent studies suggest that in many vertebrates, including rats, HIOMT may also be found in the retina.[154,155]

Serotonin is produced in the pinealocytes from circulating tryptophan, which is hydroxylated by tryptophan hydroxylase to produce 5-hydroxytryptophan; 5-hydroxytryptophan, in turn is converted to serotonin by the enzyme 5-HTP decarboxylase.[150,156] The mammalian

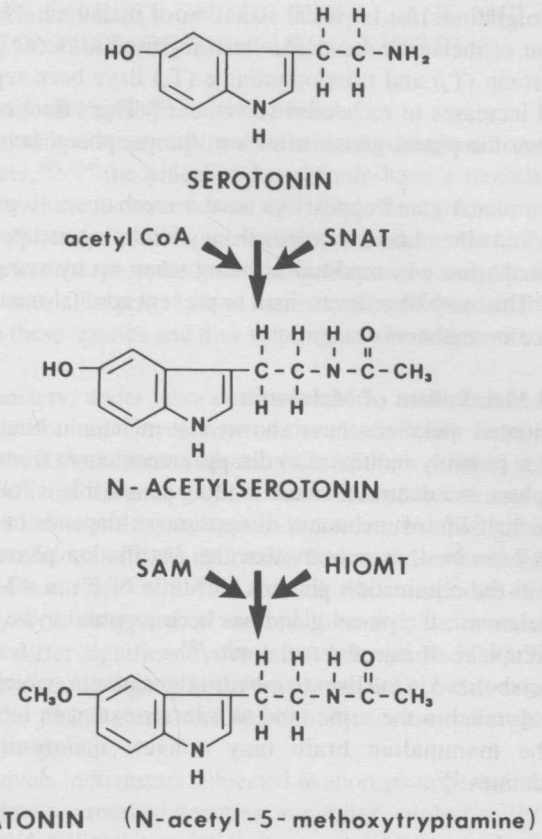

FIGURE 2. Synthesis of melatonin.

pineal gland contains a higher concentration of serotonin than other brain tissue.[157] Other methoxyindoles found in the pineal include 5-methoxytryptophol, 5-methoxyindole acetic acid, and 5-methoxytryptamine.[158]

Melatonin synthesis from serotonin is stimulated by sympathetic input via the nervi conarii.[83-85] In both plasma and pineal gland, melatonin levels follow a distinct circadian pattern cued to the daily light cycle. In all mammals studied to date, the photoperiodic rhythm in melatonin is characterized by a nighttime rise in melatonin. This has been reported in rat, hamster, squirrel, sheep, cattle, donkey, pig, camel, monkey, and in humans.[159-166] In the rat, a 60-fold increase in SNAT was measured during the dark phase of the daily light-dark cycle of the rat.[167] If lights are turned on during the dark phase a rapid decrease in SNAT and melatonin occurs.[168,169] The nighttime rise in melatonin has been extensively studied since melatonin was identified in the mammalian pineal gland (over 100 reports of this phenomenon could be cited), and continues to attract attention.

In organ culture, norepinephrine stimulates the secretion of SNAT (and to a lesser extent HIOMT) and melatonin.[170,171] In humans, administration of propranolol, a beta-adrenergic blocker, inhibits or prevents melatonin secretion.[172-174] Thus it is clear that melatonin secretion in mammals, including man, is under noradrenergic control. The beta-adrenergic stimulation of SNAT and melatonin is regulated by cyclic AMP.[175-177]

Several investigators have suggested that the output of melatonin by the pineal is significantly influenced by peripheral hormones. The hormones of the adrenals, thyroid, and gonads have all been studied for their effects on the pineal. Studies of endocrine organ ablation showed that hypophysectomy, thyroidectomy, and adrenalectomy resulted in small