"HORMONES" OF THE PINEAL GLAND

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MEDICAL research at the biochemical level necessitates thinking about disease on a wide basis. Incidental knowledge acquired in the study of one disease has often proved to be of great use in the understanding or treatment of another.

The serotonin story is a good example of this, the gradual unfolding of its theme having been undertaken by scientists whose primary interests included mental, cardiovascular, endocrine, dermatologic and neoplastic disease.[1] Serotonin was first isolated from the blood by Rapport, Green, and Page at the Cleveland Clinic because they were interested in its effects on blood pressure. Later it was found to be present in brain and was thought to be a neurohormone. In fact, the hallucinogenic effects of lysergic acid diethylamide (LSD) were thought to be due to the serotonin antagonistic action of this compound.

It was then observed that the carcinoid syndrome was due to large quantities of serotonin produced by the neoplastic tissue, and as an aid to the diagnosis of the condition, Udenfriend, Titus, Weissbach, and Peterson[2] identified the major urinary metabolite 5-hydroxyindoleacetic acid. Other metabolic pathways, however, were unknown.

Since we thought that the metabolism of serotonin might be related to mental and cardiovascular diseases a study of this complex problem was begun at the Cleveland Clinic in 1957. Animals were given radioactive serotonin, and new metabolites including acetyl serotonin were identified. Other studies also indicated that whereas the catecholamines became inactivated, serotonin and its derivatives, in some respects, became more active when O-methylated.

Attention then became focused on the pineal gland when it was learned that the highest concentrations of serotonin occurred in that organ.

The Pineal Gland

The pineal gland was recognized and named at least two thousand years ago. Herophilus believed that the ventricles were the seat of the mind, and that the pineal was a sphincter that regulated the flow of thought. Galen later showed that the organ was not a sphincter, and he thought it to be a gland. There was much interest in the pineal gland during the seventeenth century after Descartes pronounced it to be the seat of the soul.

One idea concerning the pineal, which has persisted, is that it is a gland having endocrine function. This view has been upheld by Kitay and Altschule[3] who, in their excellent review of the literature concerning the pineal, comment ". . . available evidence lends no support to the notion that the pineal gland is a functionless, vestigial organ," and that ". . . findings are consistent with an active rate of metab-

olism in the parenchymal cells which suggest that the gland has a specialized function."

There has been much conflicting evidence concerning the role of the pineal gland. This has arisen from the use of pineal extracts, which might contain more than one factor, the ignoring of the possibility that administration of a factor might cause, for example, the pituitary to secrete an antagonist, and lastly the use of inadequate numbers of animals to obtain significant results.

Nevertheless, the use of the two methods available, pinealectomy or administration of pineal extracts, has left the definite impression that there is a relationship between pineal function and: (1) bodily growth and development, (2) pituitary gonadotropin and the gonads, (3) corticotropin and the adrenal cortex, (4) thyrotropin and the thryoid gland, (5) skin pigmentation, and (6) carbohydrate and electrolyte metabolism. The recent characterization of potent pineal "hormones" should help considerably in clarifying the situation.

Melatonin

The relationship between the pineal gland and skin pigmentation led Lerner, Case, and Takahashi[4] to isolate the hormone responsible. They named it *melatonin* and characterized it as the methoxy derivative of acetyl serotonin (*Fig. 1*).

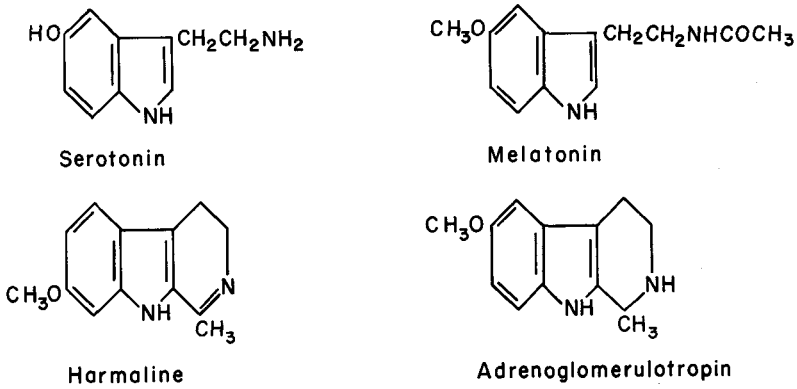

Fig. 1. Chemical structure of some of the indole hormones.

Melatonin is the most potent substance known for lightening the skin color of frogs. It causes an aggregation of melanin around the nucleus of the melanocyte, making the cell appear lighter in color, and antagonizes the action of the melanocyte-stimulating hormone (MSH) which is produced by the pituitary and is responsible for the pigmentation in Addison's disease.

To study the biochemical changes undergone by melatonin in the body, we synthesized radioactive melatonin and found that a minor metabolite no longer had the properties of an indole, and we considered the possibility that by removal

of a molecule of water it might have been converted into an indole alkaloid or carboline.[5] So far, evidence for this cyclodehydration has not been forthcoming, but the concept that carbolines might be formed seemed so important as to merit an extensive study of their actions.

It was found that the carboline obtained by the cyclization of melatonin was a potent serotonin antagonist, and also had a profound effect on the avoidance-escape behavior of trained rats.[6] This led to the formulation of a biochemical concept of mental disease, which will be more fully discussed later.

Adrenoglomerulotropin

Dr. G. Farrell had demonstrated the presence of a factor, which he named adrenoglomerulotropin, in pineal tissue, which could cause secretion of aldosterone by the suprarenals. The minute amounts make isolation extremely difficult; however, Doctor Farrell and I obtained sufficient adrenoglomerulotropin in a purified form to allow an attempt at characterization. We found that it had chromatographic, fluorescent, and biologic properties similar to those of the carbolines in general, and 1-methyl-6-methoxy 1,2,3,4 tetrahydrocarboline in particular[7] (*Fig. 1*). Doctor Farrell also found that the synthetic compound caused secretion of aldosterone in dogs that had been hypohysectomized and had part of the brain removed. In this effect, the synthetic carboline proved to be more potent than adrenocorticotropin (ACTH). These findings led us to comment, "From an evolutionary point of view, transition from an aqueous to a terrestrial environment may have made necessary simultaneous adjustments in electrolyte balance and skin color in response to solar radiation. The finding of chemically related hormones for these functions in the same anatomical location (the pineal) and perhaps controlled by similar neural mechanisms, is not entirely unexpected."[7]

Hitherto it had been assumed that carbolines like other alkaloids only occurred in plants, and in which their function is still obscure. After administering a radioactive precursor to rats, and using enzyme-blocking agents to prevent its rapid degradation, we isolated a radioactive derivative, from the urine, which strongly suggests the formation of a carboline in vivo.[8]

These indications that carbolines may be present in the mammalian central nervous system open up a field of speculation concerning the actions of what may prove to be a new class of hormones.

A Biochemical Concept of Mental Disease

Woolley and Shaw[9] put forward the idea that serotonin participated in mental processes, and that the psychotomimetic action of LSD might be due to its ability to block the action of serotonin. We found that the carbolines derived from serotonin also possess this property, and also profoundly affect the avoidance-escape behavior of trained rats.[6] The close resemblance of adrenoglomerulotropin,

a carboline derived from serotonin, to harmaline can be seen in *Figure 1*. Harmaline has long been known to be the active agent in *caapi*, a potion made from a jungle vine and ingested by Peruvian Indians to induce hallucinations and delusions. While carbolines derived from serotonin probably play an important physiologic role in neural tissue, possibly by regulating neural transmission mediated by serotonin or norepinephrine, it can, nevertheless, be easily imagined that a psychotic state might result from the accumulation of abnormal amounts of such potentially psychotomimetic compounds. In addition, being potent monoamine oxidase inhibitors, once the balance were upset there would be a tendency for serotonin metabolism to be shunted along pathways favoring the production of increasing amounts of the toxic agent.[10]

Psychosomatic Factors in Cardiovascular Disease

In a recent paper, Fischer[11] has reviewed the relationship between the psyche and hypertension. He discusses the findings of workers who have studied the similarity of symptoms in early hypertension and neurosis and the occurrence of hypertension in relationship to social settings of emotional stress.

The effect of emotions on electrolytes in heart failure was recently reviewed.[12] The onset of cardiac failure has been related to emotional disturbance in many patients. Sodium and water retention during periods of emotional tension has been found to be followed by diuresis after emotional relaxation. A careful metabolic study of patients with congestive heart failure implicated emotion as playing an important part in determining urinary sodium output. In one case the patient was able to excrete thirty-two times more sodium during strenuous activity than at rest under emotional tension. Increased secretion of aldosterone due to emotional stress might account for the reduced urinary volume and sodium excretion.

In this context it is interesting to speculate on the role that carbolines produced by the pineal gland might have. Certainly there is evidence that aldosterone secretion might be effected by this mechanism,[7] but in addition, carbolines liberated into the circulation might be expected to have other actions including an effect on blood pressure. The carbolines might be expected to exert this effect either by a direct action or indirectly by potentiating the effect of other vasopressor substances, e.g., the catecholamines.

Conclusion

It would seem that the mysterious pineal gland, which has been the source of so much speculation, is at last yielding its secrets. Whether the agents it contains are really hormones remains to be seen, and their roles in physiologic and diseased states require much clarification.

Nevertheless, the conflicting evidence of the past, due no doubt, to the use of extracts containing many active compounds, should soon be resolved by the use of

single compounds. Now that we know the chemical structure of some of these active agents and have been able to synthesize them, progress should be rapid.

It might prove ironic that it should have taken two thousand years for us to come full cycle to agree with the philosophic concept of the ancient Greeks that the pineal gland is the seat of the emotions. However, from the practical point of view it may well be that the recently discovered hormones of the pineal gland may prove to be a real key to a better understanding of the cause of some types of mental, cardiovascular, and other diseases.

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