When nerves and hormones meet

Nerve messages are like phones,
hormone messages like radios.
The messages are now known to cross.

by Joan Arehart-Treichel

Although medical science has come a long way since the early Greeks visualized the nervous and endocrine systems as a network of hollow tubes conducting "animal spirits," there is still, 2,500 years later, a lot to be learned about the two systems. Not until the middle of the past century, in fact, did investigators discover there is a hormone system separate from the nervous one. Scientists then persisted in believing that hormones and nerves have no direct contact with each other. During recent years, though, they have started finding that while the two systems are indeed separate, they interact in marvelously intricate ways.

For all practical purposes, the Age of Neuroendocrinology is just beginning. Not only better understanding of nerve-hormone interplays, such as getting to the origin of the body's 24-hour biological rhythms, but clinical applications, such as birth control through drugs that block brain chemicals, should result from cooperative efforts between neurobiologists and endocrine researchers.

Neuroendocrine findings to date show that nerves and hormones speak two kinds of language. Nerve messages are like telephones; you must have a hookup on both ends for communication signals to be passed. Hormone messages are like radio. There is no need for a hookup, but target tissues throughout the body must have decoding sets to receive the messages.

The nervous system, essentially, is comprised of chains of nerve cells (neurons) that transmit electrical-chemical messages from one to another by means of small, low-molecular-weight, water-soluble chemicals called neurotransmitters. The catecholamines are a major class of neurotransmitter, all made from the amino acid tyrosine. The catecholamino acid L-dopa, for example, is made directly from tyrosine; the catecholamine dopamine is made from L-dopa; the catecholamine noradrenaline (norepinephrine) is made from dopamine. Proposed in 1939, this biosynthetic pathway was not entirely confirmed until 1965.

The gland language, on the other hand, consists of hormone-producing cells that drop messages into the bloodstream that become available to all cells in the body. Since 30 to 40 hormone messages course throughout the bloodstream simultaneously, only cells with the appropriate receptors are able to receive (decode) the messages.

One of the first interactions between nerves and hormones to be confirmed, in the early 1960's, is that the catecholamine chemical factory is active not just in certain nerve cells, but in the core (medulla) of the adrenal gland. This tissue was found to convert the catecholamine noradrenaline to the hormone adrenaline. In 1965 hormones made by the cortex (outer) adrenal gland, such as cortisone, were shown to help synthesize enzymes needed to convert noradrenaline to adrenaline. Here, then, was evidence that hormones act on neurotransmitters.

More recently, during the past two years especially, nerve control over hormones has become of keen interest to neuroendocrine investigators. Neurotransmitter effects on hormones released by the pituitary gland, the master gland of the brain and body, are a particularly hot topic. At the Fourth International Conference of Endocrinology, held in Washington, D.C., in June, Julius Axelrod of the National Institute of Mental Health and a 1970 Nobel Prize winner for helping elucidate nerve cell activities, declared: "Two years ago there would hardly have been any papers on chemicals secreted by nerve cells and their effects on pituitary hormones." Richard Wurtman of the Massachusetts Institute of Technology, and a cochairman of a conference session on neurotransmitter-hormone interactions, concurred.

As research presented at the conference and work going on elsewhere suggest, all hormones released by the pituitary gland are undoubtedly influenced by neurotransmitters in one way or another. For instance, Harold Lebovitz of Duke University has found that the catecholamine L-dopa causes the release of growth hormone from the pituitary. This discovery, he says, might be used as a test to determine whether short children are deficient in growth hormone. William Ganong, physiologist at the University of California at San Francisco, says he is currently studying the effects of neurotransmitters on adrenocorticotrophic hormone (ACTH). His work indicates that biogenic amines (catecholamines plus adrenaline) in the brain inhibit ACTH in response to stress of everyday life. In other words, those neural systems that contain these amines apparently inhibit ACTH secretion. Ganong admits he doesn't yet understand the physiological significance of this control. But since ACTH is known to exert control over stress-combating steroid hormones released by the adrenal gland, brain neurotransmitters might feed messages from outside the body to ACTH, and in turn to the adrenal gland, ordering the production of stress-combating hormones.

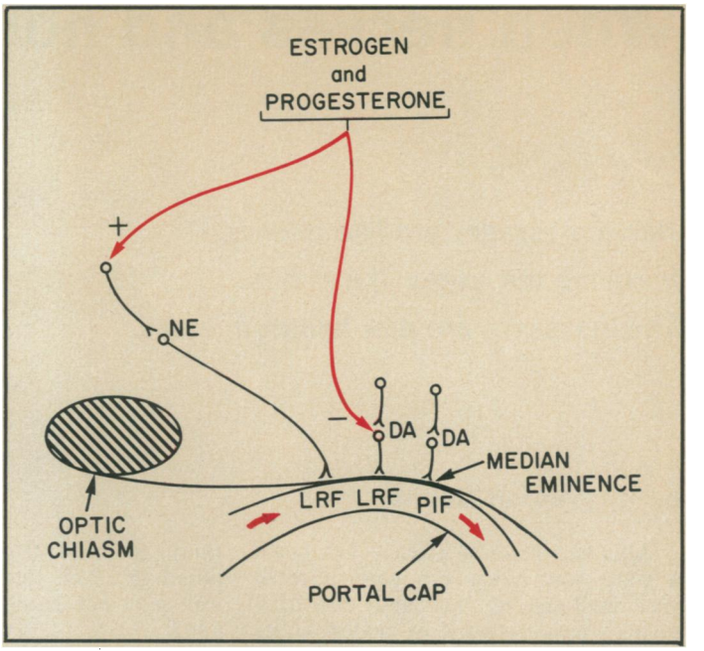
At a July meeting on Drug Effects on Neuroendocrine Regulation, held in Aspen, Colo., Andrew Frantz of the Columbia University College of Physicians and Surgeons presented a particularly interesting paper on neurotransmitter control over the pituitary hormone prolactin. The neurotransmitter dopamine, which is formed when L-dopa is given, was shown by Frantz to inhibit the secretion of prolactin. Since this hormone is now known to be involved in milk secretion and normal breast development, Frantz speculated that the hormone might help right abnormal breast development, such as breast tumors. On the basis of this assumption, Frantz has been giving L-dopa to some women with breast tumors during the past few months. Some

of the tumors, Frantz declares, show signs of regression, thanks to the neurotransmitter treatment.

Frantz has also confirmed that L-dopa acts not directly on prolactin, or the pituitary, but via a prolactin-inhibiting factor that is made in the nearby hypothalamic region of the brain. Over the past decade or so, endocrine scientists have come to realize that while the pituitary may be the master gland per se of brain and body, hypothalamic chemicals probably dominate hormones released from the master gland. Now it appears, from Frantz' work, that the master switchboard may not even be the hypothalamus but neurotransmitters. Work by other researchers, such as Lebovitz, also suggests that L-dopa's control over growth hormone is mediated by the hypothalamus.

If pituitary hormone control by neurotransmitters takes place through the hypothalamus, then feedback communication between hormones throughout the body and neurotransmitters might also be expected. S. M. McCann and his colleagues at the University of Texas Southwestern Medical School have indeed found evidence for such feedbacks—at least between catecholamines released in the brain and estrogens released by the ovaries. As the Dallas physiologist pointed out at the Aspen meeting, there is a big discharge of pituitary sex hormones (gonadotropins) when ovulation occurs. This release is triggered by steroid hormones put out by the ovaries. McCann and his team have found that these steroids feed signals to catecholamines in the brain when it is time for ovulation, rather than feed signals directly to the pituitary. The catecholamines then pass the messages from the steroids on to the hypothalamic chemicals, which in turn tell the pituitary to release gonadotropins.

The crucial catecholamine in this communications relay, the Dallas researchers have found, appears to be norepinephrine released from nerve cells in the preoptic region of the brain. When asked about the clinical implications of his group's findings, McCann replied, "There is no doubt we can block ovulation with catecholamine-blocking drugs." However the drugs he and others are using in their research have serious side effects, so he doubts whether they will be used as a means of birth control any time in the near future. He doesn't rule out the possibility of neurotransmitter contraceptives, however. Wurtman underscores this possibility. "We now know," he says, "that drugs that act on neurotransmitters are capable of altering hormonal activity. If we give transquilizers to women, for example, the drugs stop ovulation or cause lactation in some of the patients. Consequently some of us think we might be able to develop birth control drugs that act on hormones via the neurotransmitters."



Possible catecholamine connections between steroids and hypothalamic factors (LRF, PIF).

S. M. McCann
Univ. of Texas

While a number of neuroendocrine investigators are tackling the more general physiological effects of neurotransmitters on hormones, others are getting down to the biochemistry of these interactions. One of the more elegant interactions to be elucidated in recent months, for example, shows how the neurotransmitter norepinephrine causes the synthesis of the neurotransmitter seratonin, and of the hormone melatonin, in the pineal gland. The interaction has been worked out by several research groups—Axelrod and David Klein and co-workers at the National Institutes of Health; Wurtman and co-workers at MIT; Samuel Strada and Benjamin Weiss of St. Elizabeths Hospital in Washington, D.C.; Harvey Shein and colleagues at the Harvard Medical School.

What the Boston, Bethesda and Washington scientists have confirmed is that norepinephrine acts on receptors of the membranes of cells in the pineal gland. The receptors activate adenyl cyclase, which in turn prompts the synthesis of cyclic AMP, now known to serve as a secondary messenger in many kinds of tissues. Cyclic AMP then turns on several enzymes needed to synthesize melatonin and seratonin in the pineal gland.

These findings, Shein believes, are exciting for several reasons. They may shed light on the origin of the 24-hour biological rhythms that many physiological processes in man and animals adhere to. They may serve as models for neurosecretory cell action in other parts of the brain and body. Neurosecretory cells are generally distinguished from regular nerve cells because they make neurotransmitters and/or hormones. They don't just transmit neurotransmitters. Because thousands of nerve cells undoubtedly synapse (connect) with neurosecretory cells, and use the chemicals the neurosecretory cells produce, the findings may also be a basis for further clarification of basic nerve cell activities.

Although present emphasis in neuroendocrine research lies more with neurotransmitter effects on hormones, both at the general physiological and more intimate biochemical levels, some neuroendocrine scientists are looking at the effects of hormones on neurotransmitters. W. J. Shoemaker of the University of California at San Francisco, for instance, reported at the June hormone conference that abnormal responses to stress, reflected through imbalances in adrenal steroids, are not the only effects of malnourishment in rats. He also cited studies performed at MIT showing that malnutrition caused decreases in the neurotransmitter norepinephrine and in some of the enzymes that make norepinephrine. Shoemaker would like to know whether the hormonal upset precedes the neurotransmitter upset, or vice versa. Axelrod is currently attempting to see how hormones affect enzymes in neurosecretory cells that induce the synthesis of neurotransmitters.

Ganong predicts that the next five years of the Neuroendocrine Age will bring more insight into the biochemistry of neurotransmitter-hormone interactions. As basic knowledge expands, he asserts, clinical applications will be the offshoot. There is no doubt, Axelrod prophesized at the June International Conference of Endocrinology, "The wedding of endocrinology and catecholaminology will produce tremendous offspring." □