ROLE OF CATECHOLAMINES IN NEUROENDOCRINE FUNCTION

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THE BRAIN AND THE REGULATION OF THE EXTRACELLULAR FLUID*

THE CELLS of mammals are bathed in a medium, the extracellular fluid, whose temperature and chemical composition are kept within a constant range by regulatory systems. Each such system is composed of multiple organs, usually including the brain. The extracellular fluid is divided into two portions which are in equilibrium: a smaller intravascular portion known as serum, or plasma, and a larger portion that surrounds the cells. When the level of any regulated function in the intravascular portion falls too low (or, in the case of temperature, osmolarity, or calcium concentration, rises too high), this is sensed by specialised cells within or outside the brain, and mechanisms are activated that either add more of the regulated compound to the circulation or decrease the rate at which it is being removed from the blood. The only regulated compound whose plasma concentration does not involve the brain is calcium. Three aspects of the extracellular fluid are regulated: (a) the volume, pressure and temperature of its intravascular compartment: (b) its concentrations of certain essential compounds, such as glucose, water, various ions; and, (c) its concentrations of three hormones, i.e., thyroxine, hydrocortisone (or corticosterone, in the rat) and estradiol or testosterone. These compounds differ in several important ways from the other large class of hormones, the spurt hormones, whose plasma levels are not independently regulated. The regulated hormones are lipid-soluble, and travel in plasma bound to specific globulin proteins; they act to coordinate changes in most cells, including the brain itself, and not in only one or two target organs; their secretion is controlled by hormones released by the anterior pituitary gland.

One result of the brain's involvement in regulation of the extracellular fluid is that the designated concentration (or set-point) of the regulated compound (or the intravascular volume, pressure, or temperature) can be increased or decreased as a function of time or age, or in response to stress or a particular external environment. For example, the apparent set-points for plasma hydrocortisone and body temperature exhibit characteristic daily rhythms; the concentration for plasma hydrocortisone that the system maintains is increased by certain kinds of stress; the set-point for plasma testosterone is very low prior to puberty and rises thereafter (indeed, this change in the sensitivity of the brain may well be the mechanism that *causes* puberty).

* Some of the concepts presented in the following discussions have been described in greater detail elsewhere (Wurtman, 1970a, 1970b, 1971, 1973; ANTON-TAY and WURTMAN, 1971).

NEUROENDOCRINE TRANSDUCERS

The brain has at its disposal three types of output channels for increasing or decreasing the levels of regulated components of the extracellular fluid: The purely neuronal channels of the sympathetic and parasympathetic nervous systems, behavioural channels (for example, hunger in response to hyperglycemia; thirst in response to hyperosmolarity), and neuroendocrine channels. The latter all utilize a special kind of cell, termed the neuroendocrine transducer. These cells differ from both neurons and true endocrine cells in that they convert a neuronal-type input (that is, a neurotransmitter, received at a synapse) to a humoral or endocrine output (a hormone released into the circulation). At least five sets of neuroendocrine transducers have been identified. Two reside within the brain; they are: (1) the cells of the supraoptic and paraventricular nuclei, which respond to such neuronal inputs as pain and suckling by causing the release of vasopressin and oxytocin; and (2) the releasing-factor cells, presumably located within the median eminence of the hypothalamus, which secrete hormones into the hypothalamo-hypophyseal portal vascular apparatus which either cause or inhibit the secretion of anterior pituitary hormones. Neuroendocrine transducers residing outside the brain include: (a) the pineal organ, which synthesises melatonin in response to norepinephrine released from sympathetic nerve terminals; (b) the adrenal medulla, which secretes epinephrine in response to a preganglionic cholinergic input; and (c) the juxtaglomerular cells of the kidney, which, like the pineal, are stimulated by norepinephrine released from sympathetic nerve endings, and respond by releasing renin into the circulation. (Recent evidence suggests that the beta cells of the pancreas receive a sympathetic innervation that physiologically suppresses their release of insulin; this suggests that these cells may constitute a sixth neuroendocrine transducer.) The functional activity of all of the neuroendocrine transducers seems to depend on humoral, as well as neural inputs; thus, the rate at which vasopressin is secreted varies with plasma osmolarity, probably sensed within the hypothalamus: corticotropin-releasing-factor secretion depends on the concentration of plasma hydrocortisone, sensed within the median eminence; epinephrine synthesis depends upon the induction of an adreno-medullary enzyme, phenyl-ethanolamine-*N*-methyltransferase (PNMT), by the very high concentrations of glucocorticoids delivered to the medulla by the intra-adrenal portal circulation. The uniqueness of these cells, however, resides in their capacity to convert synaptic inputs to humoral outputs. Whenever the brain can be shown to influence directly the concentration of a compound within the extracellular fluid, there is good reason to postulate the existence of an intermediary neuroendocrine transducer cell.

All of the neuroendocrine transducers identified thus far utilise a catecholamine as one of their input or output signals. Thus, norepinephrine causes the pineal to synthesise melatonin, the juxtaglomerular cells to secrete renin, and suppresses insulin secretion from the pancreas; the adrenal medulla secretes the catecholamine epinephrine as its hormone. The precise roles of catecholamines in the functional activities of the neuroendocrine transducers within the hypothalamus (the supraoptic and paraventricular nuclei, and the median eminence hypophysiotropic cells) have been very difficult to characterise, inasmuch as the presynaptic inputs to these cells cannot easily be isolated. However, considerable evidence, described below, suggests that catecholamines participate in controlling the secretion of releasing factors

and, thereby, the hormones of the anterior pituitary, thyroid, adrenal cortex and gonads.

INVOLVEMENT OF BRAIN CATECHOLAMINES IN CONTROL OF ANTERIOR PITUITARY FUNCTION

The roles of catecholamine-containing brain neurons in the control of pituitary function have been studied experimentally in several ways: (1) Animals or human subjects have received drugs that are presumed to act selectively at catecholaminergic synapses, and changes in endocrine function have been measured. For example, L-dopa administration has been shown to stimulate the secretion of growth hormone, and suppress that of prolactin. Even assuming that a particular drug did act selectively on brain synapses utilising dopamine or norepinephrine (an assumption that clearly is unwarranted in the case of L-dopa), its specific site of action in producing its neuroendocrine effect would still be difficult to identify, inasmuch as it could act on monoaminergic neurons at some distance from the releasing-factor cells (i.e., within the medial forebrain bundles or on peripheral sympathetic synapses) as well as on the releasing-factor cells themselves. Studies on the endocrine effects of drugs presumed to act on brain catecholamines are discussed in other papers in this Symposium. (2) Animals have been given hormones, or glands have been removed surgically, and changes in the synthesis, turnover, or levels of brain monoamines have been measured. For example, as described below, ovariectomy has been shown to accelerate the synthesis and turnover of catecholamines in rat brain. (3) Changes in endocrine function and in the synthesis or turnover of brain catecholamines have been studied in parallel in unoperated animals (e.g., during the various phases of the vaginal estrous cycle). This "natural history" approach can be used to determine whether, for example, major changes in brain catecholamine synthesis normally *precede* puberty or coincide with the critical period that occurs on the day of proestrus.

BRAIN CATECHOLAMINES AND GONADAL FUNCTION IN RATS

The rates at which the brain of the female rat synthesises and turns over catecholamines are influenced by the secretion of pituitary gonadotropins and gonadal steroid hormones. Ovariectomy has been shown to elevate the norepinephrine content (DONOSO *et al.*, 1967) and tyrosine hydroxylase activity (BEATTIE *et al.*, 1972) of the anterior hypothalamus, and to accelerate the accumulation of brain ^{3}H-catechols following systemic administration of ^{3}H-tyrosine (ANTON-TAY *et al.*, 1970); all of these effects can be suppressed by treating the ovariectomised animals with estradiol, or with estradiol plus progesterone (BEATTIE *et al.*, 1972; DONOSO and STEFANO, 1967; BAPNA *et al.*, 1971). Ovariectomy also accelerates the turnover of ^{3}H-norepinephrine taken up into the brain from the cerebrospinal fluid (ANTON-TAY and WURTMAN, 1968; ANTON-TAY *et al.*, 1969). Since this acceleration is not observed in hypophysectomised animals, but can be reproduced in intact or hypophysectomised-ovariectomised rats by treating them with follicle-stimulating hormone (FSH), it has been suggested that FSH may affect the catecholamine-containing neurons directly, as well as by controlling the rates of secretion of gonadal steroids. (See Fig. 1.)

The rate of brain ^{3}H-catechol synthesis during the afternoon of proestrus (i.e., during the critical period), measured in untreated female rats killed 10 min after

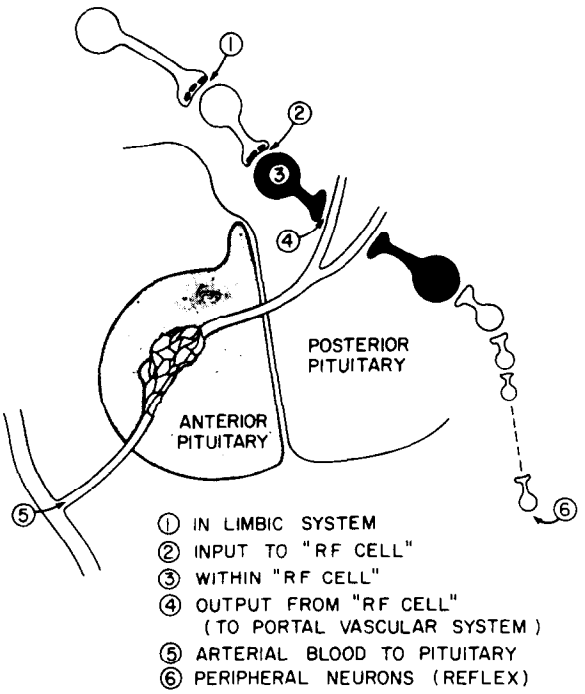

FIG. 1.—Some possible loci at which drugs might act via catecholaminergic neurons to affect the secretion of pituitary hormones. Releasing-factor (RF) cells, shown in dark, presumably secrete hormones into the hypothalamo-hypophyseal portal circulation, which preferentially delivers them to the anterior pituitary. The anterior pituitary also receives arterial blood from the systemic circulation. (1) The drug could act at a catecholaminergic synapse within the limbic system (e.g., in the medial forebrain bundle). (2) It could modify the release, reuptake, or receptor interactions of norepinephrine or dopamine liberated by neurons synapsing with RF cells. (3) It could act within the RF cells (i.e., it is possible that these cells contain both monoamines and nonmonoaminergic releasing factors, and that the former compounds affect the secretion of the latter. (4) It could cause or suppress the release of a catecholamine from the RF cells (i.e., the identity of one or more of the releasing factors might be norepinephrine or dopamine). (5) It could increase the amounts of norepinephrine or epinephrine released into the general circulation from sympathetic neurons or the adrenal medulla, and thereby increase the concentration reaching the pituitary via its arterial blood supply. (6) It could act peripherally to alter the level of one of the regulated aspects of the extracellular fluid (e.g., blood pressure; blood glucose), leading to reflex changes in central catecholaminergic function and pituitary secretion. (Figure is redrawn from Fig. 12.1 in "Brain catecholamines and the control of secretion from the anterior pituitary gland" by R. J. WURTMAN, in *Hypophysiotropic Hormones of the Hypothalamus*, J. MEITES, ed., Williams & Wilkins, Baltimore, 1970, p. 186.

receiving a tracer dose of ^{3}H-tyrosine, is almost four times as great as during diestrus and twice that during estrus (ZSCHAECK *et al.*, 1973). The location of the specific groups of catecholaminergic Neurons affected by the estrous cycle awaits identification, as does their neurotransmitter (dopamine or norepinephrine, both of which are found in the hypothalamus). Presumably, these cyclic changes in brain catecholamine synthesis could be part of the mechanism that causes the estrous cycle, or could be a consequence of the changes in concentrations of circulating hormones. They might underlie some of the behavioral and autonomic correlates of cyclic ovarian function.

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