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Neuroendocrine systems as targets for environmental endocrine-disrupting chemicals

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Incontrovertible scientific evidence demonstrates that environmental endocrine-disrupting chemicals (EDCs) affect reproductive function (1). Nevertheless, the mechanisms for these effects remain elusive, in part because the control of reproductive physiology is so complex. The reproductive axis of all vertebrates comprises three interdependent levels of organization: the brain (specifically the hypothalamus), the anterior pituitary gland, and the gonad (ovary or testis). Each of these levels produces unique hormones, and each level also responds to the hormones produced by the other levels. Recent studies demonstrate that the three reproductive levels are also responsive to environmental EDCs. Here, I will discuss the compelling evidence that the neuroendocrine level of the reproductive axis, namely the hypothalamus, is a target for endocrine disruption.

Reproductive neuroendocrine function is driven by about 1000 neurons in the brain that synthesize and secrete a ten-amino acid peptide, gonadotropin-releasing hormone (GnRH) (2). GnRH release drives reproduction throughout the life cycle and this is the primary stimulus to the rest of the reproductive axis. Using a GnRH cell line, the GT1-7 cells (3), we found that polychlorinated biphenyls (PCBs) (4) and organochlorine pesticides such as methoxychlor and chlorpyrifos (5) altered GnRH gene expression, GnRH peptide release, and the morphology of the GT1-7 cells. Animal models also identify GnRH neurons as targets for both natural environmental estrogens such as coumestrol (6) and for industrial contaminants and pesticides (7). Interestingly, some of these studies reveal non-linear dose-response curves that are typical of hormonally active substances (8,9).

The hypothalamus is abundant in neurotransmitter and sex steroid hormone receptors that, together with GnRH neurons, form a neural network controlling reproductive physiology and behavior (10–12). Direct effects of EDCs have been shown on hypothalamic neurotransmitter systems, on the size of specific hypothalamic regions, as well as on numbers of cells expressing the estrogen receptor beta (13–15). These actions may underlie observations that prenatal exposure to low-doses of PCBs (16), or postnatal treatment with soy (17), significantly affected

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aspects of mating behavior in female rats. These studies demonstrate a functional outcome for effects of EDCs in the neuroendocrine hypothalamus.

In conclusion, GnRH cells, and their regulatory neural network, are targets of EDCs. As a consequence, exposure to EDCs, particularly during critical developmental windows, results in impaired reproductive physiology and behavior. Importantly, the reproductive axis is only one of five neuroendocrine systems, the others being thyroid/metabolism, growth, stress, and lactation. These five neuroendocrine systems all play regulatory and homeostatic roles in the control of vertebrate physiology. In addition, there is cross-talk among these systems because the function of one neuroendocrine system impacts the functions of all the others. While this may increase the complexity of studying effects of EDCs it is also an important consideration for how an EDC may exert complex and diverse effects on the exposed individual. There is considerable need for additional research on effects of EDCs in neuroendocrine systems in order to better understand how the environment regulates basic physiologic processes.

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