Estrogen receptors and central osmotic regulation

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MAINTENANCE OF CONSTANT OSMOLALITY in body fluids depends on a precise balance between intake and excretion of sodium and water and is maintained primarily by vasopressin, which is released from the neurohypophysis after increases in plasma osmolality. Vasopressin acts to promote insertion of aquaporins in the kidney collecting ducts and thereby helps to conserve water. Variations in the osmolality of blood plasma are picked up in the brain by small areas that lack a blood-brain barrier. These areas, the circumventricular organs, surround the ventricular system. Three of these are involved in body fluid homeostasis: the subfornical organ (SFO) and organum vasculosum laminae terminalis (OVLT), which are located in the anteroventral third ventricle, and the area postrema, which is located at the transition between the fourth ventricle and the central canal of the spinal cord (reviewed in Ref. 5). The osmoreceptors that trigger vasopressin release are located in the OVLT and SFO and project directly or indirectly through the median preoptic nucleus (MnPO) to the magnocellular neurosecretory cells in the supraoptic nuclei (SON) and paraventricular nuclei (PVN) of the hypothalamus. The SON contains only magnocellular neurons, which produce vasopressin and oxytocin and project to the neurohypophysis. The PVN contains, in addition to magnocellular neurons, parvocellular neurons that have a number of neuroendocrine and autonomic functions. In addition to being controlled by plasma osmolality, release of vasopressin from the magnocellular neurosecretory cells is stimulated by a variety of other signals, such as ANG II, hypovolemia, and a fall in arterial blood pressure.

Estrogens are sex steroid hormones, but the demonstration of estrogen receptors in a variety of tissues that have no relation to reproduction have prompted investigations into nontraditional effects of estrogens. Estrogen receptors (2) are found in the magnocellular neurosecretory cells of the hypothalamus and are likely to mediate inhibitory effects of gonadal steroids on release of vasopressin (6). The estrogen receptors are nuclear receptors, of which two types exist, ER-α and ER-β, with identical DNA-binding domains. When not activated the receptors are present within the cell nucleus.

After activation, the receptors form homodimers (α/α or β/β) or heterodimers (α/β), which bind to estrogen response elements in target genes. Alternatively, the activated receptors may exert indirect actions through transcription factors residing on target promoters or may interact with other nuclear factors in a manner that does not require DNA binding (1). Transcriptional regulation at the level of the target gene is accomplished by recruitment of specific coactivator proteins by the ER-ligand complex to form multiprotein complexes that may interact with chromatin structure, stabilize the preinitiation complex, and help recruit RNA polymerase II. Differences in recruitment of coactivators or corepressors by ER-α and ER-β as well as variations in coactivator protein expression may explain differences in responses elicited by ER-α and ER-β and response differences in different tissues (1). The vasopressin magnocellular neurosecretory cells of the hypothalamus express ER-β. The expression of estrogen receptors in cells that are involved in osmoregulation and not in reproduction led Somponpun and Sladek (4) to ask if the expression of ER-β in vasopressin magnocellular neurosecretory cells was influenced by osmotic challenges. They found that plasma hyperosmolality decreased ER-β receptor expression, whereas hypoosmolality enhanced expression. The response seemed to be specific, because ER-β expression was affected only in the magnocellular and not in the parvocellular cells of the PVN.

In the present issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, Somponpun and coworkers (3) examined the hypothesis that regulation of ER-β requires monitoring of changes in plasma osmolality by the circumventricular organs. To test this hypothesis, the authors lesioned the anteroventral wall of the third ventricle, thereby destroying the OVLT, the ventral MnPO, and fibers passing from the SFO. Such lesions are documented to disrupt osmotic regulation of vasopressin secretion, and their well-performed study shows that, after lesion of the pathway that transmits information on plasma osmolality to the hypothalamus, an increase in plasma osmolality (induced by 48 h thirst) no longer suppresses ER-β expression in the hypothalamus.

As pointed out by the authors, the exact physiological significance of the observations remains to be established. Although activation of hypothalamic estrogen receptors tends to inhibit vasopressin release, the presence of gonadal steroids certainly does not eliminate osmotic control of vasopressin release, suggesting that estrogen is a modulator of this process, which may act in long-term adaptation processes. Another unanswered question is whether the endogenous ligands for the hypothalamic estrogen receptors are derived from the circulation or produced locally. In any case, the complexity and importance of estrogen actions and effects in normal physiology and in diseases ranging from osteoporosis to breast cancer will ensure great future interest in these topics.

REFERENCES

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