J Musculoskel Neuron Interact 2003; 3(4):381

Perspective Article

Hylonome

Summary - Estrogen receptors

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The concept of a receptor that mediates the actions of estrogen on hormonally regulated target cells dates back to 1957. As originally envisioned, the estrogen receptor (ER) was a macromolecule having a high affinity for estrogen. Following binding to its ligand, the ER was activated. This altered receptor was then able to regulate gene expression. Specificity was acquired by the amount of ER present in a target cell and the ability of the ER to discriminate estrogen from other potential ligands.

The original concept of the ER has remained remarkably intact. However, it quickly became clear that this simple model was not able to explain the complexity of hormonal action on its many targets, as different from one another as bone and brain.

It is now recognized that there are multiple mechanisms by which the hormone acts. There are two known nuclear receptor subtypes for estrogen, and each is encoded by a separate gene. These receptor isoforms form hetero- as well as homo-dimers. The dimers can bind directly to DNA and thereby function as a transcription factor. Alternatively, they can form complexes with other transcription factors. There are also membrane receptors which are either the same or different from the nuclear ER and influence signal transduction pathways without directly influencing transcription. Finally, there is evidence that some of the effects of estrogen do not require a receptor, as it was originally envisioned. This session revisited the ER in regard to new insights into its role in bone metabolism. The presentations ranged from the molecular biology of ER co-factor interactions to physiology.

Dr. Thomas Spelsberg presented an overview of the mechanisms of action of estrogen with an emphasis on genomic effects. He described the role of the ligand, the receptor isoform and co-regulators in estrogen action. One of the important points of his presentation was that each cell type possesses its own complement of co-activators and co-repressors. These cellular differences may play a key role in establishing the unique tissue specific actions of 17ß-estradiol, as well as estrogen metabolites and selective estrogen agonists.

Dr. Merry Jo Oursler described the actions of estrogen to regulate osteoclast differentiation and apoptosis. In addition to direct ER-mediated actions on the osteoclast, estrogen has indirect actions that are mediated through osteoblasts and other cells. Thus, in order to understand estrogen action on a complex tissue, it is essential to account for paracrine as well as direct endocrine regulation.

Dr. Barbara Boyan's presentation emphasized that estrogen can have actions which do not require nuclear localization of the ligand. This regulation is mediated through a membrane bound ER. ER-ligand binding results in signal transduction through the cell membrane. Activation of these pathways ultimately can lead to transcriptional regulation.

Dr. Avudaiappan Maran described a newly identified estrogen regulated pathway in bone cells which do not contain ER. He has shown that estrogen can activate signal transducers and activators of transcription (stat signaling) independently of the receptor.

Dr. Kim Westerlind discussed metabolism of estrogen as yet another level of regulation. 17ß-estradiol is metabolized to an impressive number of metabolites which differ markedly in their affinity to ER. In addition, cell and tissue level metabolism influences the exposure of target cells to potential ligands. Individual differences in the metabolism of estrogens may play an important role in the relative rates of bone loss during aging in men as well as women.

Dr. Teppo Järvinen described the physiological role of estrogen in increasing the amount of bone in the skeleton at puberty over and above that required for normal mechanical usage. This packing of bone into the skeleton is an adaptation designed to provide adequate calcium for successful reproduction.

The author has no conflict of interest.

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Accepted 15 August 2003