Hormonal regulation of growth I

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Until 10-15 years ago, hormone actions were thought of as endocrine only, hence the medical specialty endocrinology

### General principles

- **Endocrine**: hormone is produced in a specific gland, secreted into circulation, and exerts specific actions on remote target cells;  
  The SOURCE is remote from the TARGET

- **Paracrine**: hormone is produced by some tissue cells, and diffuse through the extracellular space to exert specific actions on nearby target cells;  
  The SOURCE is near the TARGET

- **Autocrine**: hormone is produced by cells and exerts its actions on the same cells;  
  SOURCE = TARGET

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**Figure 10.1** Different mechanisms of hormonal signaling. From *Physiology, Second Edition* by Robert Berne & Matthew Levy. Copyright © 1968 by C. V. Mosby Company. Reprinted by permission.

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**So, that said…**

Turns out that specific endocrine hormones can also be synthesized as either autocrine or paracrine “factors”:

Some examples of this?

By the way, how can this be so?
Examples of endocrine hormones

The levels of a hormone in the circulation can be a major determinant of final response

- "eu" - normal hormone secretion
- "Hypo-" reduced hormone levels
- "Hyper-" elevated hormone levels

Oh yeah, then what the heck is a "growth factor"?

- Proteins
- Often stimulate growth or other cell processes
- Bind to growth factor receptors
- Often made in many tissues/cell types

It is fair to say that many growth factors are indeed hormones. There are lots of examples:
Growth factor examples:

- Bone morphogenic protein
- Transforming growth factors
- Epidermal growth factor
- Hepatocyte growth factor
- Fibroblast growth factor
- Insulin-like growth factor
- Myostatin
- Erythropoietin
- Etc…

Hormone action involves several steps

1a. Hormone leaves cell (local ECF, circulation)
1b. Hormone may then interact with other molecules
1c. Hormone binds to specific receptors,
2. Binding alters the conformation of the receptor at the target cell.
   - often a “receptor” is 2 molecules that “dimerize” (dimer is 2 molecules combining).

Once a receptor is bound...

Post-receptor signaling events

a) membrane receptors – for non-permeable hormones; peptides, catecholamines
   - 2nd messengers (including cAMP, Ca²⁺, Tyr-P³, etc.)
   - receptor cycling (membrane ↔ cytosol)

b) cytosolic receptors – for membrane-permeable hormones; lipid-soluble, steroids internalization of the hormone-receptor complex
   - transfer into nucleus, produce direct effects on gene expression
Cytokines, growth factors (GF), and hormones are all chemical messengers that mediate intercellular communication. The regulation of cellular and nuclear functions by cytokines, growth factors, and peptide or protein hormones is initiated through the activation of cell surface receptors (Rc). All receptors have two main components: 1) a ligand-binding domain that ensures ligand specificity and 2) an effector domain that initiates the generation of the biological response upon ligand binding. The activated receptor may then interact with other cellular components to complete the signal transduction process. Cytokines and growth factors that stimulate mitogen-activated protein kinase (MAPK) cascades often use G-proteins to couple to PLC. In the presence of cyclic AMP (cAMP), it activates PKA by binding to the regulatory subunit of the enzyme. The G-domain of the receptor is linked to PLC, and activated PLC can generate DAG and IP3, to stimulate Ca2+ release from the ER. Free intracellular Ca2+ can bind to calmodulin, and this Ca2+-calmodulin complex, in the presence of cyclic AMP (cAMP), activates PKA by binding to the regulatory subunit of the enzyme. DAG binds to and activates PKC. Other hormone receptors may be linked through G-proteins to adenyl cyclase (AC) instead of PLC. Activated AC increases the cellular levels of cAMP and, in the presence of the Ca2+-calmodulin complex, will activate PKA. Additionally, some growth factor and cytokine receptors are protein tyrosine kinases (PTK) that are directly activated by ligand-receptor interaction. Activation of any of the protein kinases, PKA, PKC, or PTK, catalyzes the phosphorylation of other proteins within the cell. Enzymes that are activated or inhibited by phosphorylation may mediate functional processes within the cell, while others may be one step in a protein kinase cascade that regulates nuclear events.

Steroid hormones (i.e., estrogen, glucocorticoids), thyroid hormone, vitamin D3, and retinoids are all small lipophilic molecules that easily penetrate both the cellular and nuclear membranes to enter the nucleus where they bind to their respective receptors that are ligand-dependent transcription factors. The ligand-receptor complex binds to specific DNA response elements in the promoter region and regulates gene expression.

References
Kumar, R., Thompson, E.B., The structure of the nuclear hormone receptors. Steroids, 64. 310-319 (1999).
Hormonal mechanisms

- **Homeostatic**: acute, minute-by-minute maintenance of a stable internal environment

- **Homeorhetic**: chronic, coordination of metabolism in support of a dominant physiological process (e.g., growth, lactation)