* Intercellular interactions. Course. Prof. A.Oleskin
* Guest lecturer S. Ostroumov
* Lecture material April 11, 2014
* **Signaling within, between, and among cells is subdivided into the following classifications – by distance**
* [*Intracrine*](http://en.wikipedia.org/wiki/Intracrine) signals are produced by the target cell that stay within the target cell.
* [*Autocrine*](http://en.wikipedia.org/wiki/Autocrine_signalling) signals are produced by the target cell, are secreted, and effect the target cell itself via receptors. Sometimes autocrine cells can target cells close by if they are the same type of cell as the emitting cell. An example of this are [immune cells](http://en.wikipedia.org/wiki/Immune_cell).
* [*Juxtacrine*](http://en.wikipedia.org/wiki/Juxtacrine_signalling) signals target adjacent (touching) cells. These signals are transmitted along cell membranes via protein or lipid components integral to the membrane and are capable of affecting either the emitting cell or cells immediately adjacent.
* [*Paracrine*](http://en.wikipedia.org/wiki/Paracrine_signalling) signals target cells in the vicinity of the emitting cell. Synaptic signaling. [Neurotransmitters](http://en.wikipedia.org/wiki/Neurotransmitters) represent an example.
* [*Endocrine*](http://en.wikipedia.org/wiki/Endocrine_system) signals target distant cells. Endocrine cells produce hormones that travel through the [blood](http://en.wikipedia.org/wiki/Circulatory_system) to reach all parts of the body.
* Comments to the previous
* Autocrine and paracrine – sometimes close types;
* Some signaling molecules can function as both a hormone and a neurotransmitter.
* **Some signaling molecules can function as both a hormone and a neurotransmitter.** For example:
* [epinephrine](http://en.wikipedia.org/wiki/Epinephrine) and [norepinephrine](http://en.wikipedia.org/wiki/Norepinephrine) can function as hormones when released from the [adrenal gland](http://en.wikipedia.org/wiki/Adrenal_gland) and are transported to the heart by way of the blood stream.
* Norepinephrine can also be produced by [neurons](http://en.wikipedia.org/wiki/Neuron) to function as a neurotransmitter within the brain (Cartford et al. 04)
* [Estrogen](http://en.wikipedia.org/wiki/Estrogen) can be released by the [ovary](http://en.wikipedia.org/wiki/Ovary) and function as a hormone or act locally via paracrine or [autocrine](http://en.wikipedia.org/wiki/Autocrine) signaling (Jesmin et al. 04).
* Agents involved in cell signaling
* [**Receptor ligands**](http://en.wikipedia.org/wiki/Ligand_(biochemistry)) **involved in cell signaling**
* A **hormone** (from [Greek](http://en.wikipedia.org/wiki/Greek_language) ὁρμή, "impetus") is a class of regulatory biochemicals that is produced in all [multicellular organisms](http://en.wikipedia.org/wiki/Multicellular_organism) by [glands](http://en.wikipedia.org/wiki/Gland), and transported by the [circulatory system](http://en.wikipedia.org/wiki/Circulatory_system) to a distant target organ to coordinate its physiology and behavior. Hormones serve as a major form of communication between different organs and tissues.
* hormones
* [Vertebrate](http://en.wikipedia.org/wiki/Vertebrate) hormones fall into three [chemical classes](http://en.wikipedia.org/wiki/Chemical_classification):
* [Peptide hormones](http://en.wikipedia.org/wiki/Peptide_hormone) consist of chains of amino acids. Examples of small peptide hormones are [TRH](http://en.wikipedia.org/wiki/Thyrotropin-releasing_hormone) and [vasopressin](http://en.wikipedia.org/wiki/Vasopressin). Peptides composed of scores or hundreds of amino acids are referred to as [proteins](http://en.wikipedia.org/wiki/Protein). Examples of protein hormones include [insulin](http://en.wikipedia.org/wiki/Insulin) and [growth hormone](http://en.wikipedia.org/wiki/Growth_hormone). More complex protein hormones bear [carbohydrate](http://en.wikipedia.org/wiki/Carbohydrate) side-chains and are called [glycoprotein](http://en.wikipedia.org/wiki/Glycoprotein) hormones. [Luteinizing hormone](http://en.wikipedia.org/wiki/Luteinizing_hormone), [follicle-stimulating hormone](http://en.wikipedia.org/wiki/Follicle-stimulating_hormone) and [thyroid-stimulating hormone](http://en.wikipedia.org/wiki/Thyroid-stimulating_hormone) are glycoprotein hormones. There is also another type of hydrophilic hormone called *nonpeptide* hormones. Although they don't have peptide connections, they are assimilated as peptide hormones.
* [Lipid](http://en.wikipedia.org/wiki/Lipid) and [phospholipid](http://en.wikipedia.org/wiki/Phospholipid)-derived hormones derive from lipids such as [linoleic acid](http://en.wikipedia.org/wiki/Linoleic_acid) and [arachidonic acid](http://en.wikipedia.org/wiki/Arachidonic_acid) and phospholipids. The main classes are the [steroid hormones](http://en.wikipedia.org/wiki/Steroid_hormones) that derive from [cholesterol](http://en.wikipedia.org/wiki/Cholesterol) and the [eicosanoids](http://en.wikipedia.org/wiki/Eicosanoid). Examples of [steroid hormones](http://en.wikipedia.org/wiki/Steroid_hormones) are [testosterone](http://en.wikipedia.org/wiki/Testosterone) and [cortisol](http://en.wikipedia.org/wiki/Cortisol). [Sterol](http://en.wikipedia.org/wiki/Sterol) hormones such as [calcitriol](http://en.wikipedia.org/wiki/Calcitriol) are a [homologous](http://en.wikipedia.org/wiki/Homology_(biology)) system. The [adrenal cortex](http://en.wikipedia.org/wiki/Adrenal_cortex) and the [gonads](http://en.wikipedia.org/wiki/Gonad) are primary sources of steroid hormones. Examples of [eicosanoids](http://en.wikipedia.org/wiki/Eicosanoid) are the widely studied [prostaglandins](http://en.wikipedia.org/wiki/Prostaglandin) and [Lipoxins](http://en.wikipedia.org/wiki/Lipoxins).
* [Monoamines](http://en.wikipedia.org/wiki/Monoamine) derived from aromatic [amino acids](http://en.wikipedia.org/wiki/Amino_acid) like [phenylalanine](http://en.wikipedia.org/wiki/Phenylalanine), [tyrosine](http://en.wikipedia.org/wiki/Tyrosine), [tryptophan](http://en.wikipedia.org/wiki/Tryptophan) by the action of [aromatic amino acid decarboxylase](http://en.wikipedia.org/wiki/Aromatic_amino_acid_decarboxylase) [enzymes](http://en.wikipedia.org/wiki/Enzyme).
* Those classes of hormones are found too in other groups of animals.[[8]](http://en.wikipedia.org/wiki/Hormone) In [insects](http://en.wikipedia.org/wiki/Insect) and [crustaceans](http://en.wikipedia.org/wiki/Crustacean), there is a hormone with an unusual chemical structure, compared with other animal hormones, the [juvenile hormone](http://en.wikipedia.org/wiki/Juvenile_hormone), a [sesquiterpenoid](http://en.wikipedia.org/wiki/Sesquiterpenoid).
* **Neurotransmitters** are [endogenous](http://en.wikipedia.org/wiki/Endogenous) [chemicals](http://en.wikipedia.org/wiki/Chemistry) that transmit signals across a [synapse](http://en.wikipedia.org/wiki/Synapse) from one [neuron](http://en.wikipedia.org/wiki/Neuron) ([brain](http://en.wikipedia.org/wiki/Brain) [cell](http://en.wikipedia.org/wiki/Cell_(biology))) to another 'target' neuron.[[1]](http://en.wikipedia.org/wiki/Neurotransmitter) Neurotransmitters are packaged into [synaptic vesicles](http://en.wikipedia.org/wiki/Synaptic_vesicles) clustered beneath the [membrane](http://en.wikipedia.org/wiki/Cell_membrane) in the [axon terminal](http://en.wikipedia.org/wiki/Axon_terminal), on the presynaptic side of a synapse.
* Neurotransmitters are released into and diffuse across the [synaptic cleft](http://en.wikipedia.org/wiki/Synaptic_cleft), where they bind to specific [receptors](http://en.wikipedia.org/wiki/Receptor_(biochemistry)) in the membrane on the postsynaptic side of the synapse.[[2]](http://en.wikipedia.org/wiki/Neurotransmitter)
* Many neurotransmitters are synthesized from plentiful and simple precursors, such as [amino acids](http://en.wikipedia.org/wiki/Amino_acid), which are readily available from the diet and which require only a small number of biosynthetic steps to convert.
* through the careful [histological](http://en.wikipedia.org/wiki/Histology) examinations by [Ramón y Cajal](http://en.wikipedia.org/wiki/Ram%C3%B3n_y_Cajal) (1852–1934), a 20 to 40 nm gap between neurons, known today as the [synaptic cleft](http://en.wikipedia.org/wiki/Synaptic_cleft), was discovered. The presence of such a gap suggested communication via chemical messengers traversing the synaptic cleft, and in 1921 German pharmacologist [Otto Loewi](http://en.wikipedia.org/wiki/Otto_Loewi) (1873–1961) confirmed that neurons can communicate by releasing chemicals.
* a few examples of important neurotransmitter actions
* [Glutamate](http://en.wikipedia.org/wiki/Glutamate) is used at the great majority of fast excitatory synapses in the brain and spinal cord. It is also used at most synapses that are "modifiable", i.e. capable of increasing or decreasing in strength. [Modifiable synapses](http://en.wikipedia.org/wiki/Synaptic_plasticity) are thought to be the main memory-storage elements in the brain. Excessive glutamate release can overstimulate the brain and lead to [excitotoxicity](http://en.wikipedia.org/wiki/Excitotoxicity) causing cell death resulting in seizures or strokes.[[9]](http://en.wikipedia.org/wiki/Neurotransmitter) Excitotoxicity has been implicated in certain chronic diseases including [ischemic stroke](http://en.wikipedia.org/wiki/Stroke), [epilepsy](http://en.wikipedia.org/wiki/Epilepsy), [Amyotrophic lateral sclerosis](http://en.wikipedia.org/wiki/Amyotrophic_lateral_sclerosis), [Alzheimer's disease](http://en.wikipedia.org/wiki/Alzheimer's_disease), [Huntington disease](http://en.wikipedia.org/wiki/Huntington_disease), and [Parkinson's disease](http://en.wikipedia.org/wiki/Parkinson's_disease)[[10]](http://en.wikipedia.org/wiki/Neurotransmitter)
* [GABA](http://en.wikipedia.org/wiki/GABA) is used at the great majority of fast inhibitory synapses in virtually every part of the brain. Many [sedative/tranquilizing drugs](http://en.wikipedia.org/wiki/Sedative) act by enhancing the effects of GABA.[[11]](http://en.wikipedia.org/wiki/Neurotransmitter) Correspondingly, [glycine](http://en.wikipedia.org/wiki/Glycine) is the inhibitory transmitter in the [spinal cord](http://en.wikipedia.org/wiki/Spinal_cord).
* [Acetylcholine](http://en.wikipedia.org/wiki/Acetylcholine) is distinguished as the transmitter at the [neuromuscular junction](http://en.wikipedia.org/wiki/Neuromuscular_junction) connecting motor nerves to muscles. The paralytic arrow-poison [curare](http://en.wikipedia.org/wiki/Curare) /kjuːˈrɑːriː/ acts by blocking transmission at these synapses. Acetylcholine also operates in many regions of the brain, but using [different types of receptors](http://en.wikipedia.org/wiki/Acetylcholine_receptor), including [nicotinic](http://en.wikipedia.org/wiki/Nicotinic_acetylcholine_receptor) and [muscarinic](http://en.wikipedia.org/wiki/Muscarinic_acetylcholine_receptor) receptors.[[12]](http://en.wikipedia.org/wiki/Neurotransmitter)
* [Dopamine](http://en.wikipedia.org/wiki/Dopamine) has a number of important functions in the brain; this includes regulation of motor behavior, pleasures related to motivation and also emotional arousal. It plays a critical role in the [reward system](http://en.wikipedia.org/wiki/Reward_system); people with [Parkinson's disease](http://en.wikipedia.org/wiki/Parkinson's_disease) have been linked to low levels of dopamine and people with [schizophrenia](http://en.wikipedia.org/wiki/Schizophrenia) have been linked to high levels of dopamine.[[13]](http://en.wikipedia.org/wiki/Neurotransmitter)
* [Serotonin](http://en.wikipedia.org/wiki/Serotonin) is a [monoamine neurotransmitter](http://en.wikipedia.org/wiki/Monoamine_neurotransmitter). Most is produced by and found in the intestine (approximately 90%), and the remainder in [central nervous system](http://en.wikipedia.org/wiki/Central_nervous_system) neurons. It functions to regulate appetite, sleep, memory and learning, temperature, mood, behaviour, muscle contraction, and function of the [cardiovascular system](http://en.wikipedia.org/wiki/Cardiovascular_system) and [endocrine system](http://en.wikipedia.org/wiki/Endocrine_system). It is speculated to have a role in depression, as some depressed patients are seen to have lower concentrations of metabolites of serotonin in their [cerebrospinal fluid](http://en.wikipedia.org/wiki/Cerebrospinal_fluid) and brain tissue.[[14]](http://en.wikipedia.org/wiki/Neurotransmitter)
* [Substance P](http://en.wikipedia.org/wiki/Substance_P) is a [neuropeptide](http://en.wikipedia.org/wiki/Neuropeptide) and functions as both a neurotransmitter and as a [neuromodulator](http://en.wikipedia.org/wiki/Neuromodulator). It can transmit pain from certain sensory neurons to the central nervous system. It also aids in controlling relaxation of the vasculature and lowering blood pressure through the release of nitric oxide.[[15]](http://en.wikipedia.org/wiki/Neurotransmitter)
* [Opioid peptides](http://en.wikipedia.org/wiki/Opioid_peptides) are neurotransmitters that act within pain pathways and the emotional centers of the brain; some of them are [analgesics](http://en.wikipedia.org/wiki/Analgesic) and elicit pleasure or euphoria.[[16]](http://en.wikipedia.org/wiki/Neurotransmitter)
* **Cytokines** (Greek *cyto-*, cell; and *-kinos*, movement) are a broad and loose category of small proteins (~5–20 [kDa](http://en.wikipedia.org/wiki/KDa)) that are important in [cell signaling](http://en.wikipedia.org/wiki/Cell_signaling) - they are released by cells and affect the behavior of other cells, and sometimes the releasing cell itself. Cytokines include [chemokines](http://en.wikipedia.org/wiki/Chemokines), [interferons](http://en.wikipedia.org/wiki/Interferons), [interleukins](http://en.wikipedia.org/wiki/Interleukins), [lymphokines](http://en.wikipedia.org/wiki/Lymphokines), [tumour necrosis factor](http://en.wikipedia.org/wiki/Tumour_necrosis_factor) \nə-ˈkrō-səs, ne-\ but generally not [hormones](http://en.wikipedia.org/wiki/Hormones) or [growth factors](http://en.wikipedia.org/wiki/Growth_factors).
* Cytokines are produced by broad range of cells, including immune cells like [macrophages](http://en.wikipedia.org/wiki/Macrophages), [B lymphocytes](http://en.wikipedia.org/wiki/B_lymphocytes), [T lymphocytes](http://en.wikipedia.org/wiki/T_lymphocytes) and [mast cells](http://en.wikipedia.org/wiki/Mast_cells), as well as [endothelial cells](http://en.wikipedia.org/wiki/Endothelial_cells), [fibroblasts](http://en.wikipedia.org/wiki/Fibroblasts), and various [stromal cells](http://en.wikipedia.org/wiki/Stromal_cells); a given cytokine may be produced by more than one type of cell.
* Cytokines: **Difference from hormones**
* Classic hormones circulate in nanomolar (10-9M) concentrations that usually vary by less than one order of magnitude. **In contrast, some cytokines (such as IL-6) circulate in picomolar (10-12M) concentrations that can increase up to 1,000-fold during trauma or infection.**
* The widespread distribution of cellular sources for cytokines may be a feature that differentiates them from hormones. Virtually **all nucleated cells, but especially endo/epithelial cells and resident** [**macrophages**](http://en.wikipedia.org/wiki/Macrophage) **(many near the interface with the external environment) are potent producers** of [IL-1](http://en.wikipedia.org/wiki/Interleukin_1), [IL-6](http://en.wikipedia.org/wiki/Interleukin-6), and [TNF-α](http://en.wikipedia.org/wiki/TNF-%CE%B1). (Boyle JJ , 05 )
* In contrast, classic hormones, such as insulin, are secreted from discrete glands (e.g., the [pancreas](http://en.wikipedia.org/wiki/Pancrea)).
* As of 2008, the current terminology refers to cytokines as **immunomodulating** agents. However, more research is needed in this area of defining cytokines and hormones.
* Part of the difficulty with distinguishing cytokines from hormones is that some of the immunomodulating effects of cytokines are systemic rather than local. For instance, to use hormone terminology, the action of cytokines may be [autocrine](http://en.wikipedia.org/wiki/Autocrine) or [paracrine](http://en.wikipedia.org/wiki/Paracrine) in [chemotaxis](http://en.wikipedia.org/wiki/Chemotaxis) or [chemokinesis](http://en.wikipedia.org/wiki/Chemokinesis) and [endocrine](http://en.wikipedia.org/wiki/Endocrine) as a [pyrogen](http://en.wikipedia.org/wiki/Fever). Further, as molecules, cytokines **are not limited to** their immunomodulatory role.
* Growth factor
* *Growth factor* is sometimes used interchangeably among scientists with the term [*cytokine*](http://en.wikipedia.org/wiki/Cytokine)*.*[[2]](http://en.wikipedia.org/wiki/Growth_factor) Historically, cytokines were associated with [hematopoietic](http://en.wikipedia.org/wiki/Hematopoietic) (blood forming) cells and [immune system](http://en.wikipedia.org/wiki/Immune_system) cells (e.g., lymphocytes and tissue cells from [spleen](http://en.wikipedia.org/wiki/Spleen), [thymus](http://en.wikipedia.org/wiki/Thymus), and [lymph nodes](http://en.wikipedia.org/wiki/Lymph_node)). For the [circulatory system](http://en.wikipedia.org/wiki/Circulatory_system) and [bone marrow](http://en.wikipedia.org/wiki/Bone_marrow) in which cells can occur in a liquid suspension and not bound up in solid [tissue](http://en.wikipedia.org/wiki/Tissue_(biology)), it makes sense for them to communicate by soluble, circulating protein [molecules](http://en.wikipedia.org/wiki/Molecule). However, as different lines of research converged, it became clear that some of the same signaling proteins the hematopoietic and [immune systems](http://en.wikipedia.org/wiki/Immune_system) used were also being used by all sorts of other cells and tissues, during development and in the mature organism.
* While *growth factor* implies a positive effect on cell division, *cytokine* is a neutral term with respect to whether a molecule affects proliferation. While some cytokines can be growth factors, such as [G-CSF](http://en.wikipedia.org/wiki/G-CSF) and [GM-CSF](http://en.wikipedia.org/wiki/GM-CSF), others have an inhibitory effect on cell growth or proliferation. Some cytokines, such as [Fas ligand](http://en.wikipedia.org/wiki/Fas_ligand), are used as "death" signals; they cause target cells to undergo programmed [cell death](http://en.wikipedia.org/wiki/Cell_death) or [*apoptosis*](http://en.wikipedia.org/wiki/Apoptosis).
* The growth factor was first discovered by [Rita Levi-Montalcini](http://en.wikipedia.org/wiki/Rita_Levi-Montalcini), which won her a Nobel prize.
* **Rita Levi-Montalcini** (Italian pronunciation: [[ˈrita ˈlɛvi montalˈtʃini]](http://en.wikipedia.org/wiki/Help:IPA_for_Italian); 22 April 1909 – 30 December 2012) was an Italian [neurologist](http://en.wikipedia.org/wiki/Neurology) who, together with colleague [Stanley Cohen](http://en.wikipedia.org/wiki/Stanley_Cohen_(biochemist)), received the 1986 [Nobel Prize in Physiology or Medicine](http://en.wikipedia.org/wiki/Nobel_Prize_in_Physiology_or_Medicine) for their discovery of [nerve growth factor](http://en.wikipedia.org/wiki/Nerve_growth_factor) (NGF). Also, from 2001, until her death, she served in the [Italian Senate](http://en.wikipedia.org/wiki/Italian_Senate) as a [Senator for Life](http://en.wikipedia.org/wiki/Senator_for_Life).
* Rita Levi-Montalcini had been the oldest living [Nobel](http://en.wikipedia.org/wiki/Nobel_Prize) laureate and the first ever to reach a 100th birthday.On 22 April 2009, she was feted with a 100th birthday party at [Rome](http://en.wikipedia.org/wiki/Rome)'s city hall.
* **Classes of growth factors.** Individual growth factor proteins tend to occur as members of larger families of structurally and [evolutionarily](http://en.wikipedia.org/wiki/Evolution) related proteins. There are many families:
* [Adrenomedullin](http://en.wikipedia.org/wiki/Adrenomedullin) (AM)
* [Angiopoietin](http://en.wikipedia.org/wiki/Angiopoietin) (Ang)
* [Autocrine motility factor](http://en.wikipedia.org/wiki/Autocrine_motility_factor)
* [Bone morphogenetic proteins](http://en.wikipedia.org/wiki/Bone_morphogenetic_protein) (BMPs)
* [Brain-derived neurotrophic factor](http://en.wikipedia.org/wiki/Brain-derived_neurotrophic_factor) (BDNF)
* [Epidermal growth factor](http://en.wikipedia.org/wiki/Epidermal_growth_factor) (EGF)
* [Erythropoietin](http://en.wikipedia.org/wiki/Erythropoietin) (EPO)
* [Fibroblast growth factor](http://en.wikipedia.org/wiki/Fibroblast_growth_factor) (FGF)
* [Glial cell line-derived neurotrophic factor](http://en.wikipedia.org/wiki/Glial_cell_line-derived_neurotrophic_factor) (GDNF)
* [Granulocyte colony-stimulating factor](http://en.wikipedia.org/wiki/Granulocyte_colony-stimulating_factor) (G-CSF)
* [Granulocyte macrophage colony-stimulating factor](http://en.wikipedia.org/wiki/Granulocyte_macrophage_colony-stimulating_factor) (GM-CSF)
* [Growth differentiation factor-9](http://en.wikipedia.org/wiki/Growth_differentiation_factor-9) (GDF9)
* [Hepatocyte growth factor](http://en.wikipedia.org/wiki/Hepatocyte_growth_factor) (HGF)
* [Hepatoma-derived growth factor](http://en.wikipedia.org/wiki/Hepatoma-derived_growth_factor) (HDGF)
* [Insulin-like growth factor](http://en.wikipedia.org/wiki/Insulin-like_growth_factor) (IGF)
* Migration-stimulating factor
* [Myostatin](http://en.wikipedia.org/wiki/Myostatin) (GDF-8)
* [Nerve growth factor](http://en.wikipedia.org/wiki/Nerve_growth_factor) (NGF) and other [neurotrophins](http://en.wikipedia.org/wiki/Neurotrophins)
* [Platelet-derived growth factor](http://en.wikipedia.org/wiki/Platelet-derived_growth_factor) (PDGF)
* [Thrombopoietin](http://en.wikipedia.org/wiki/Thrombopoietin) (TPO)
* [Transforming growth factor alpha](http://en.wikipedia.org/wiki/Transforming_growth_factor_alpha)(TGF-α)
* [Transforming growth factor beta](http://en.wikipedia.org/wiki/Transforming_growth_factor_beta)(TGF-β)
* [Tumor necrosis factor-alpha](http://en.wikipedia.org/wiki/Tumor_necrosis_factor-alpha)(TNF-α)
* [Vascular endothelial growth factor](http://en.wikipedia.org/wiki/Vascular_endothelial_growth_factor) (VEGF)
* [Wnt Signaling Pathway](http://en.wikipedia.org/wiki/Wnt_Signaling_Pathway)
* [placental growth factor](http://en.wikipedia.org/wiki/Placental_growth_factor) (PGF)
* [(Foetal Bovine Somatotrophin)] (FBS)
* IL-1- Cofactor for IL-3 and IL-6. Activates T cells.
* IL-2- T-cell growth factor. Stimulates IL-1 synthesis. Activates B-cells and NK cells.
* IL-3- Stimulates production of all non-lymphoid cells.
* IL-4- Growth factor for activated B cells, resting T cells, and mast cells.
* IL-5- Induces differentiation of activated B cells and eosinophils.
* IL-6- Stimulates Ig synthesis. Growth factor for plasma cells.
* IL-7- Growth factor for pre-B cells.
* Signaling molecules
* Signaling molecules can belong to several chemical classes: [lipids](http://en.wikipedia.org/wiki/Lipid), [phospholipids](http://en.wikipedia.org/wiki/Phospholipid), [amino acids](http://en.wikipedia.org/wiki/Amino_acid), [monoamines](http://en.wikipedia.org/wiki/Monoamine), [proteins](http://en.wikipedia.org/wiki/Protein), [glycoproteins](http://en.wikipedia.org/wiki/Glycoprotein), or [gases](http://en.wikipedia.org/wiki/Gas).
* Signaling molecules binding surface receptors are generally large and [hydrophilic](http://en.wikipedia.org/wiki/Hydrophilic) (e.g. [TRH](http://en.wikipedia.org/wiki/TRH), [Vasopressin](http://en.wikipedia.org/wiki/Vasopressin), [Acetylcholine](http://en.wikipedia.org/wiki/Acetylcholine)),

while those entering the cell are generally small and [hydrophobic](http://en.wikipedia.org/wiki/Hydrophobic) (e.g. [glucocorticoids](http://en.wikipedia.org/wiki/Glucocorticoid), [thyroid hormones](http://en.wikipedia.org/wiki/Thyroid_hormone), [cholecalciferol](http://en.wikipedia.org/wiki/Cholecalciferol), [retinoic acid](http://en.wikipedia.org/wiki/Retinoic_acid)),

but important exceptions to both are numerous, and a same molecule can act both via surface receptor or in an intracrine manner to different effects.

* In intracrine signaling, once inside the cell, a signaling molecule can bind to [intracellular receptors](http://en.wikipedia.org/wiki/Intracellular_receptor), other elements, or stimulate [enzyme](http://en.wikipedia.org/wiki/Enzyme) activity (e.g. gasses). The intracrine action of [peptide hormones](http://en.wikipedia.org/wiki/Peptide_hormone) remains a subject of debate.
* [Hydrogen sulfide](http://en.wikipedia.org/wiki/Hydrogen_sulfide) is produced in small amounts by some cells of the human body and has a number of biological signaling functions. Only two other such **gases** are currently known to act as signaling molecules in the human body: [nitric oxide](http://en.wikipedia.org/wiki/Nitric_oxide) and [carbon monoxide](http://en.wikipedia.org/wiki/Carbon_monoxide)