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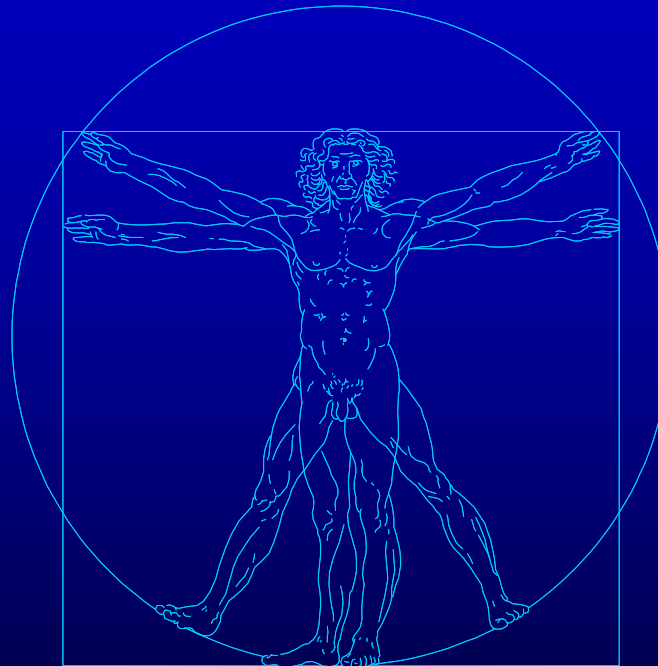
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communication





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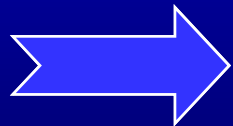
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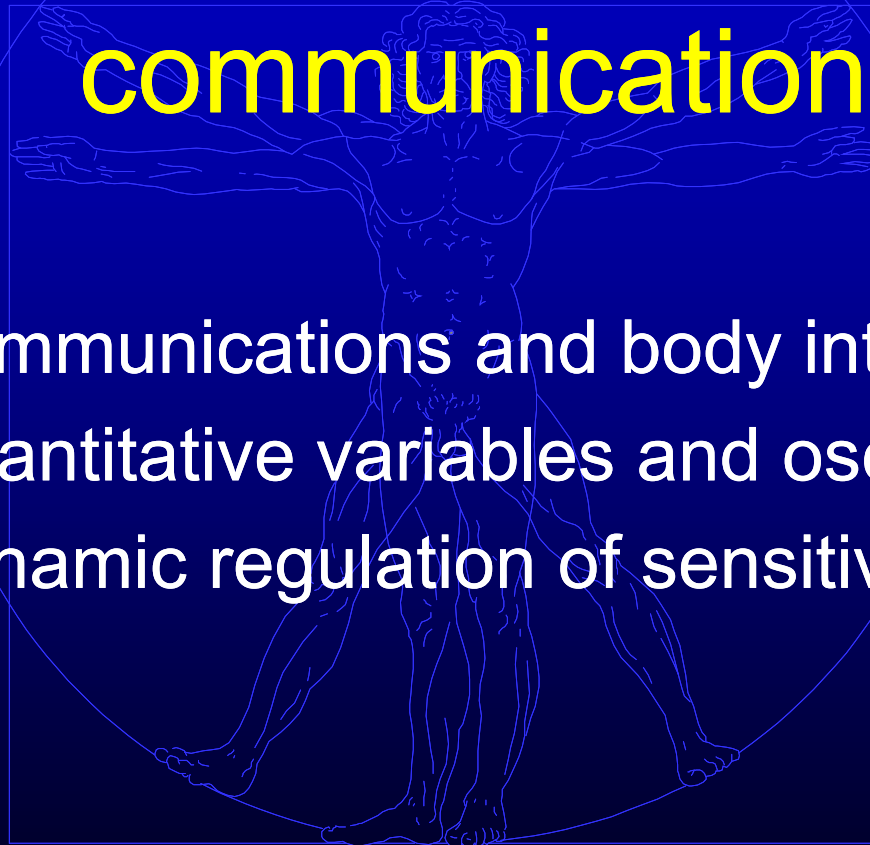
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1.2. Biological communication



- Communications and body integration
- Quantitative variables and oscillations
- Dynamic regulation of sensitivity





INTERACTIONS AND COMMUNICATIONS IN THE BODY

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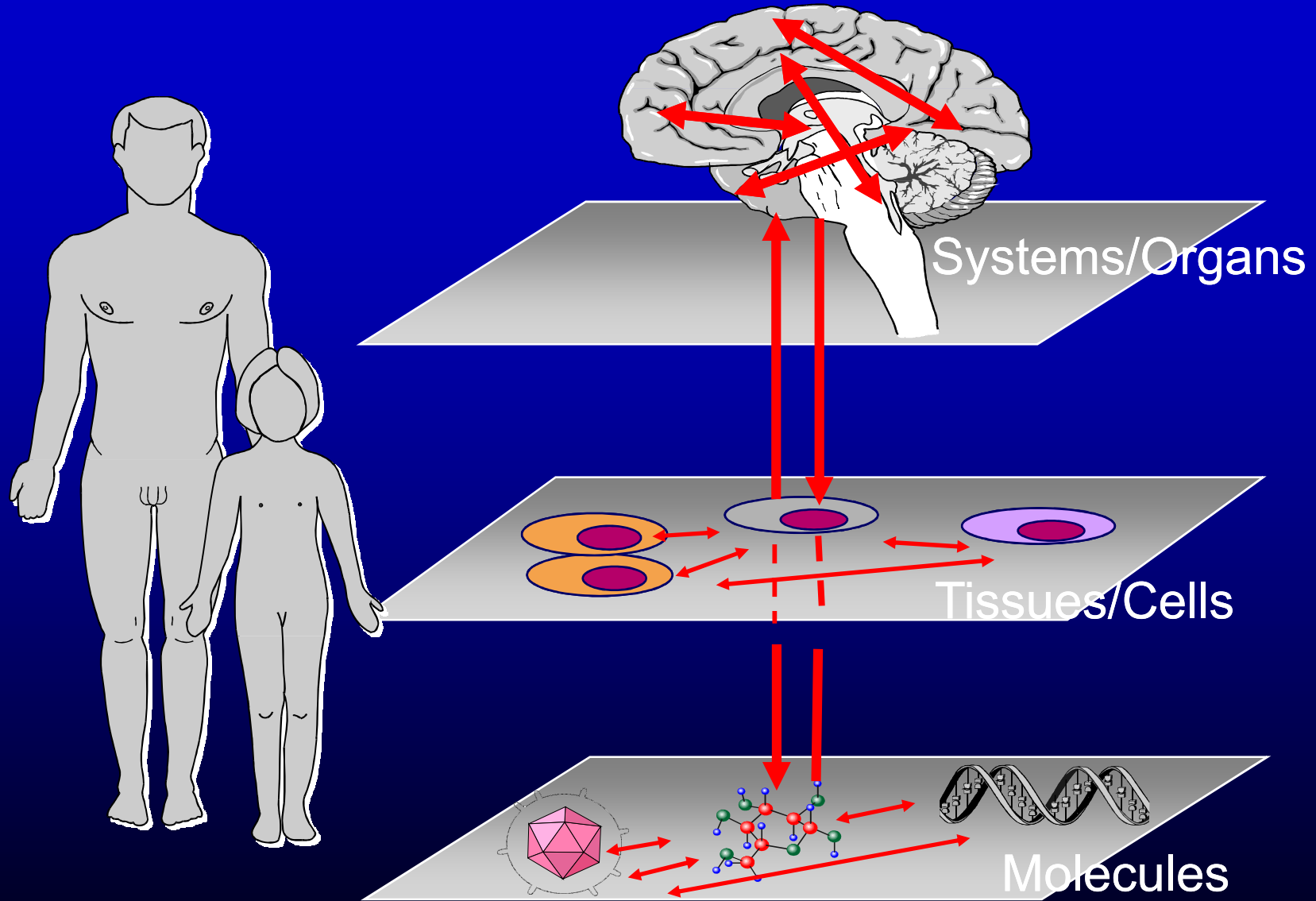
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INTEGRATION OF SYSTEMS IS PROVIDED BY COMMUNICATIONS

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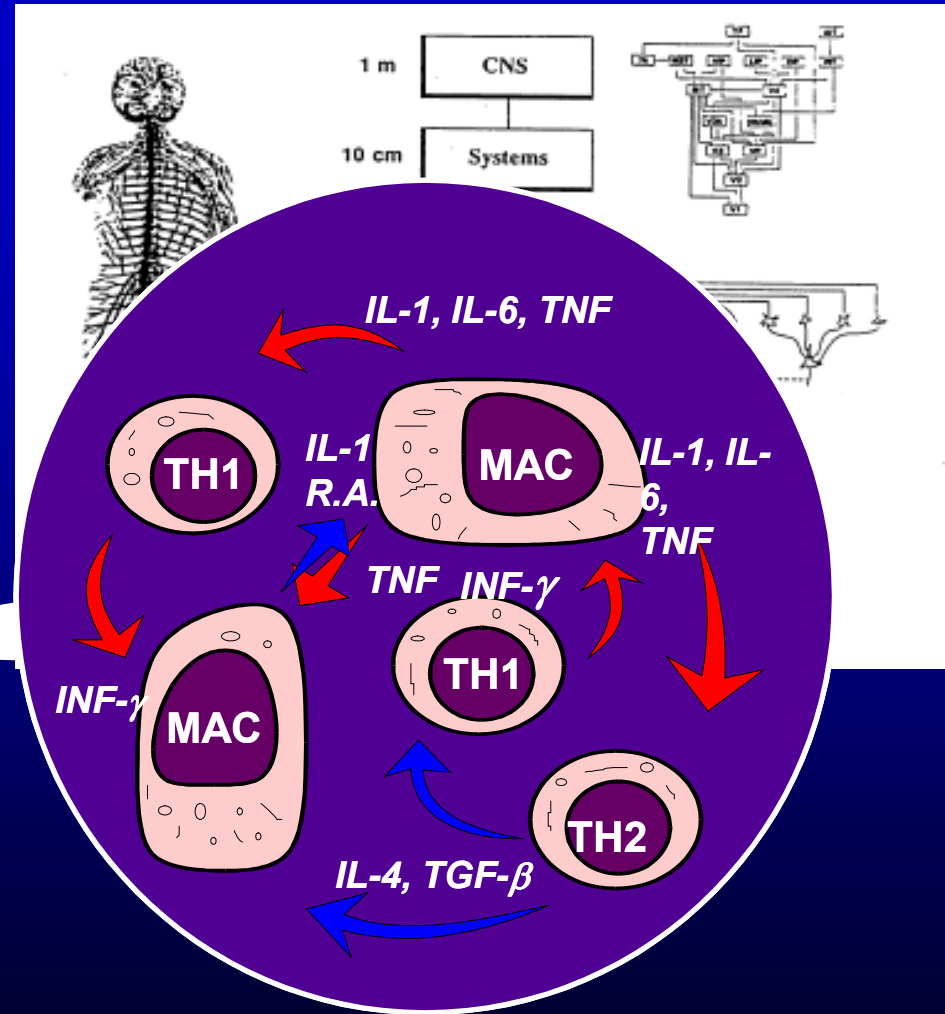
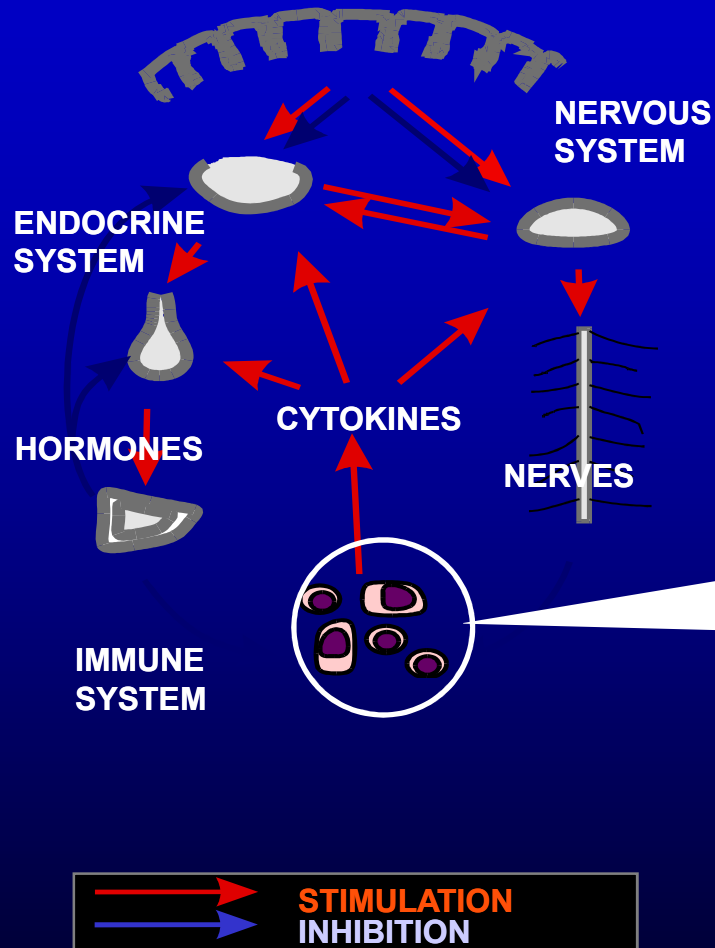
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CYTOKINES: MEANS OF COMMUNICATION

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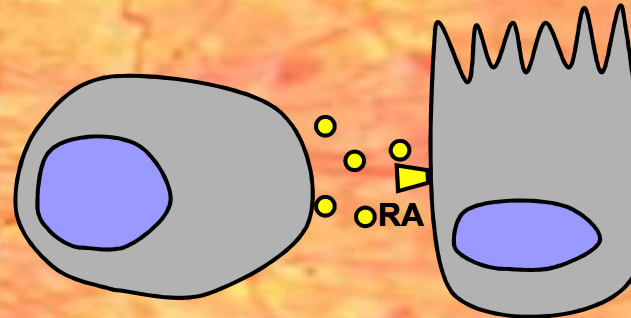
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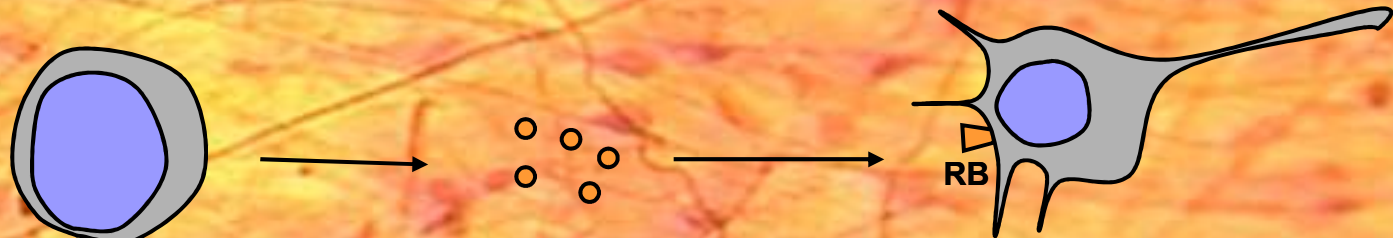
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Juxtacrine
(Contact)



Paracrine
(Distance)



Endocrine
(Through blood)



Producing cells

Target cells





Relax

Music: *Rondino in eb* by Kevin MacLeod (incompetech.com)



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- 
- Communications and body integration
 - Ways and methods of communication
 - Dynamic regulation of sensitivity



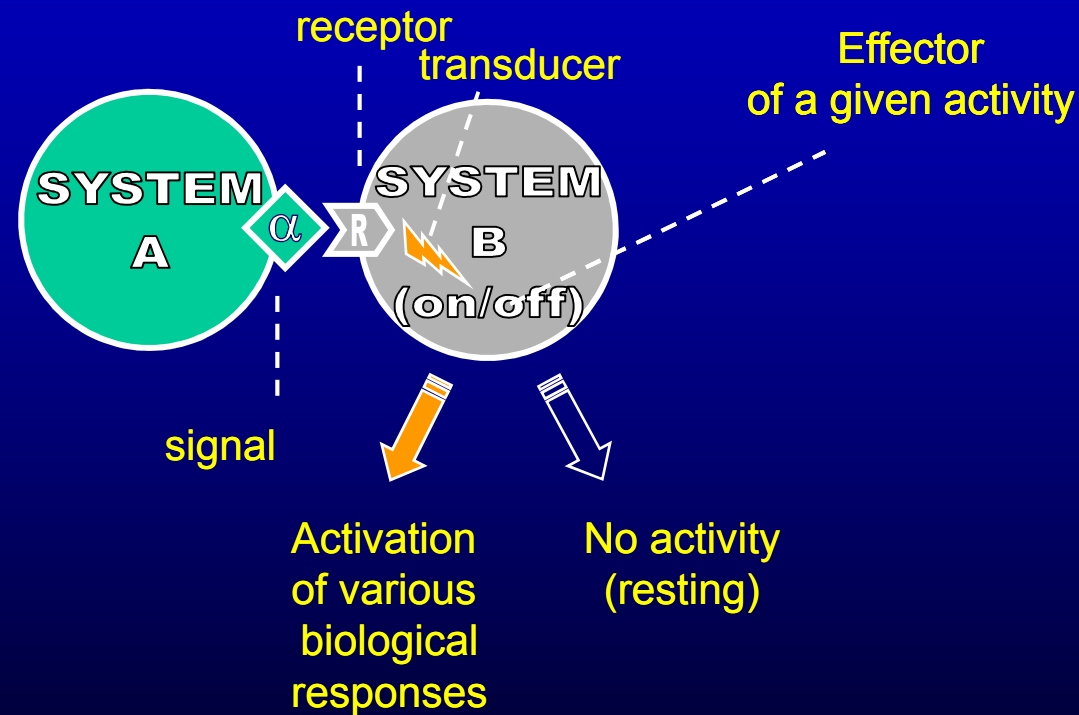


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Communication through direct contact





KEYWORDS OF BIOLOGICAL INFORMATION

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Information is structured, by the transmitting system, in a **signal code** (language), whose **chemical-physical structure** can interact with the receiver.

The **effect** of interaction (information transfer) depends on:

- a) the **correspondence** between **signal** and **receiver** (receptor affinity, sensitivity)
- b) the degree of **freedom** of the receiver (programmed capacity of different choices)
- c) the **context** (network of other signals)





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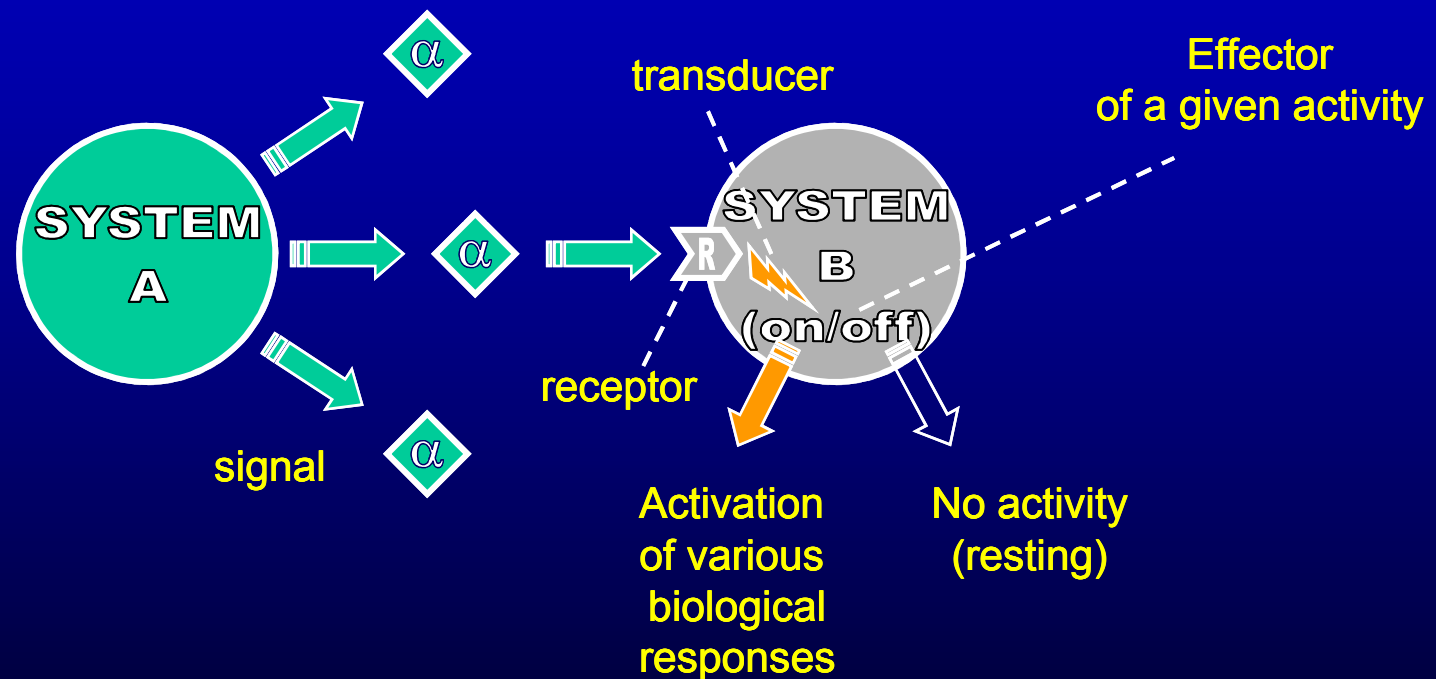
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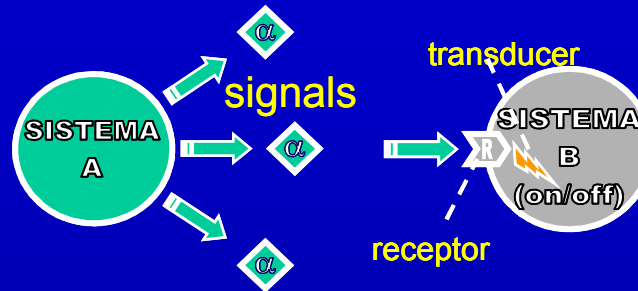
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Communication through signal molecules





INTER-CELLULAR COMMUNICATION SIGNALS



| SIGNALS | EXAMPLES |
|----------------------------|---------------------------------------------|
| Local mediators | Histamine, CO ₂ , H ⁺ |
| Hormones (often pulsatile) | Cortisol, ACTH, estrogens |
| Cytokines | Interferons, interleukins |
| Neurotransmitters | Acetylcholine, noradrenaline |
| Membrane molecules | HLA, adhesion molecules |
| Low-frequency e.m. fields | Cell growth |
| Piezoelectricity | Bone trabeculae |
| Light | Leukocytes, DNA (biophotons) (?) |

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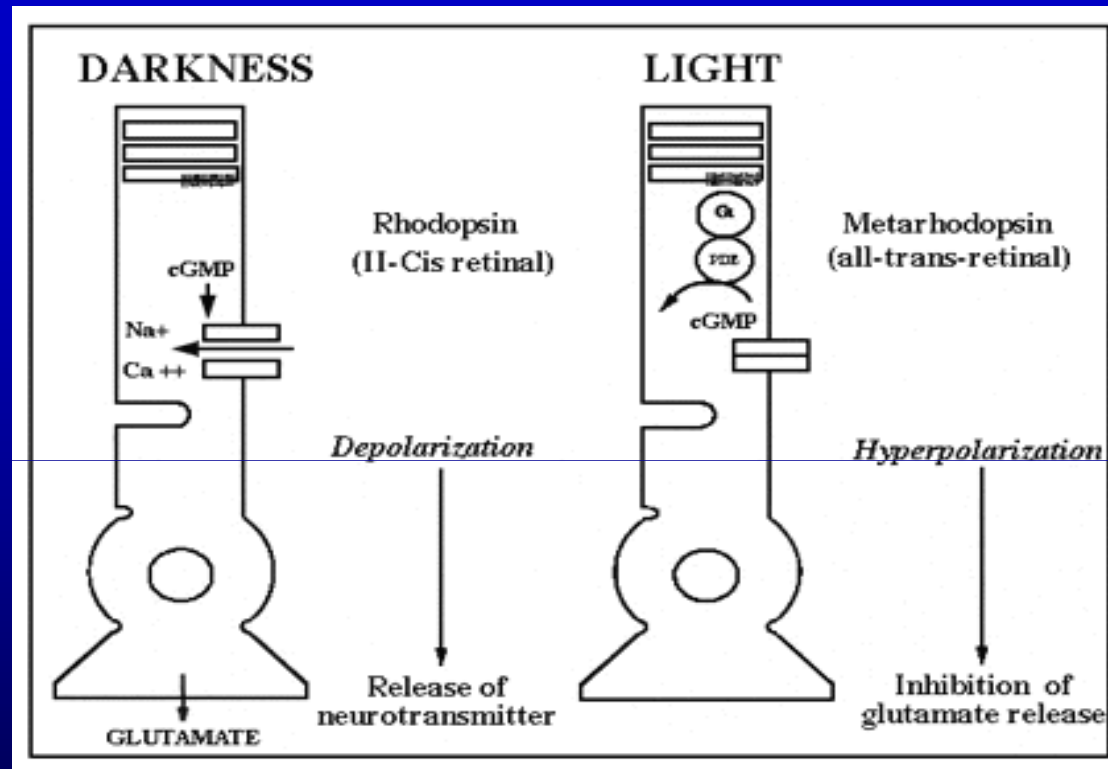
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BIOLOGICAL COMMUNICATION

Communication through light



A stimulus is an agent that produces a response in a living organism. One stimulus has no significance per se but acquires one particular meaning, becoming a message, when applied to one particular biological system. Stimuli can be of very different natures; they can be physical, chemical, static or dynamic. Ultimately, the absence of stimulus can be a stimulus by itself if we consider the environment of the living organisms.

As an illustration of this paradox, darkness is a stimulus as far as the retinal photoreceptors are concerned, since sensory cells are very active in the absence of light in terms of metabolism and synaptic transmission! Actually, under this condition, rhodopsin, the photosensitive pigment located in the outer segment disks of the cell, does not interact with cation channels of the membrane. These channels are maintained in the open configuration by cyclic GMP and consequently, the membrane is depolarized and the neurotransmitter, glutamate, is continuously released (Figure). Obviously, light is also a stimulus for these cells. When a photon interacts with rhodopsin, the conformation of retinol, a component of the pigment, changes from eleven-cis to all trans. This event allows rhodopsin to bind another protein (G_t), a G-Protein also called transducin, which activates an enzyme (PDE) able to metabolize cGMP. Without cGMP, cation channels are closed, the cell becomes hyperpolarized and the synaptic transmission is stopped (Pugh and Lamb, 1993). This is a good illustration of a stimulus transformation into a message, through the activation of a receptor, a transduction and an effector system.

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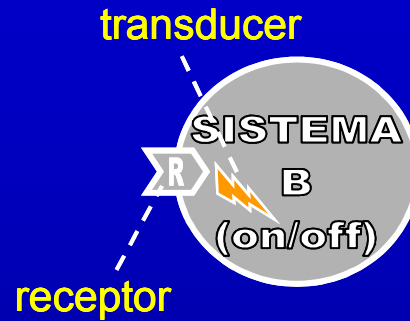
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INTRA-CELLULAR COMMUNICATION SIGNALS (transducers)



| SIGNALS | EXAMPLES |
|---------------------------|----------------------------------------|
| Molecule concentration | H ⁺ , Na ⁺ , ATP |
| Molecule oscillations | Calcium, cAMP |
| Phosphorylation | Kinases → enzymes, receptors |
| Lipid composition changes | Arachidonate, phosphoinositides |
| Electric potentials | Ionic channels, nerve fibers |
| Mechanical waves | Actin fibers, muscle |
| Low-frequency e.m. fields | G-proteins, membrane pumps |
| Dimerization, binding | Receptors, DNA/mRNA |

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EXAMPLE OF INTRACELLULAR COMMUNICATION SIGNALS AND PATHOGENIC FACTORS AFFECTING THEM

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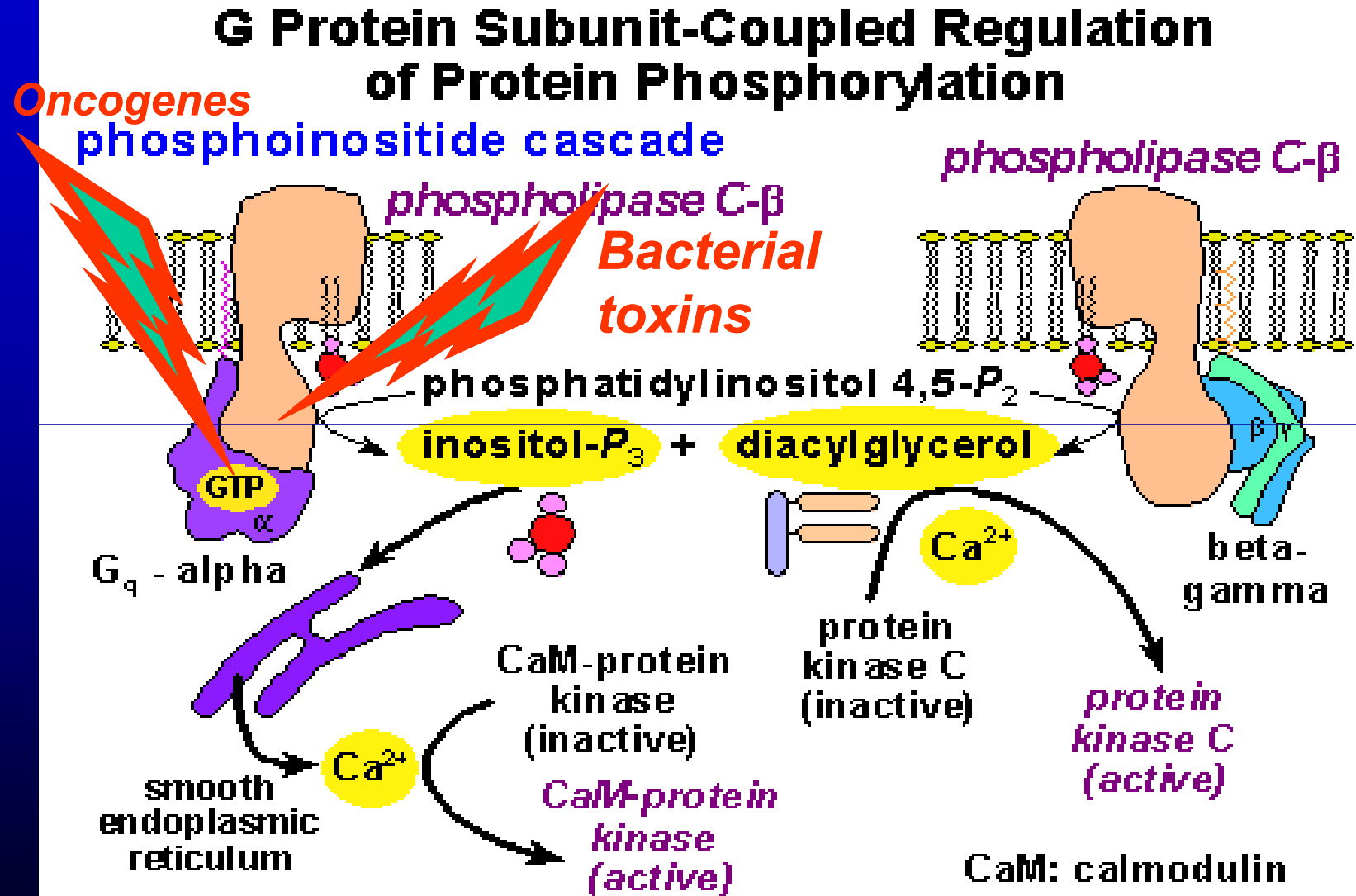
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Information is therefore contained not only in molecules, but also in the “way” molecules relate to the receiver systems. The quantity of the signal is very important, but so is its quality.

For example, the receptor system of cells is often capable of distinguishing the *kinetics* whereby the signal is received, namely whether it is a sudden signal or a signal of slow onset, whether the concentration is stable or oscillating, whether the signal is single or accompanied by other concomitant or preceding signals, whether it is the first prompting or a repetition of something *dejà vu*.

Thus, information is not merely quantitative, but essentially *spatiotemporal*. It has recently been suggested that one of the most important intracellular signalling systems, the increase in calcium ions, performs its function by means of pulsations, or rather oscillations of concentration, which constitute a kind of “digital code” for the various sensitive systems: for a response process to be activated, what counts is the frequency of the spatiotemporal oscillations (waves) in the calcium concentration rather than the actual amount of calcium present.





OSCILLATING CALCIUM TRANSIENTS IN NEURONS

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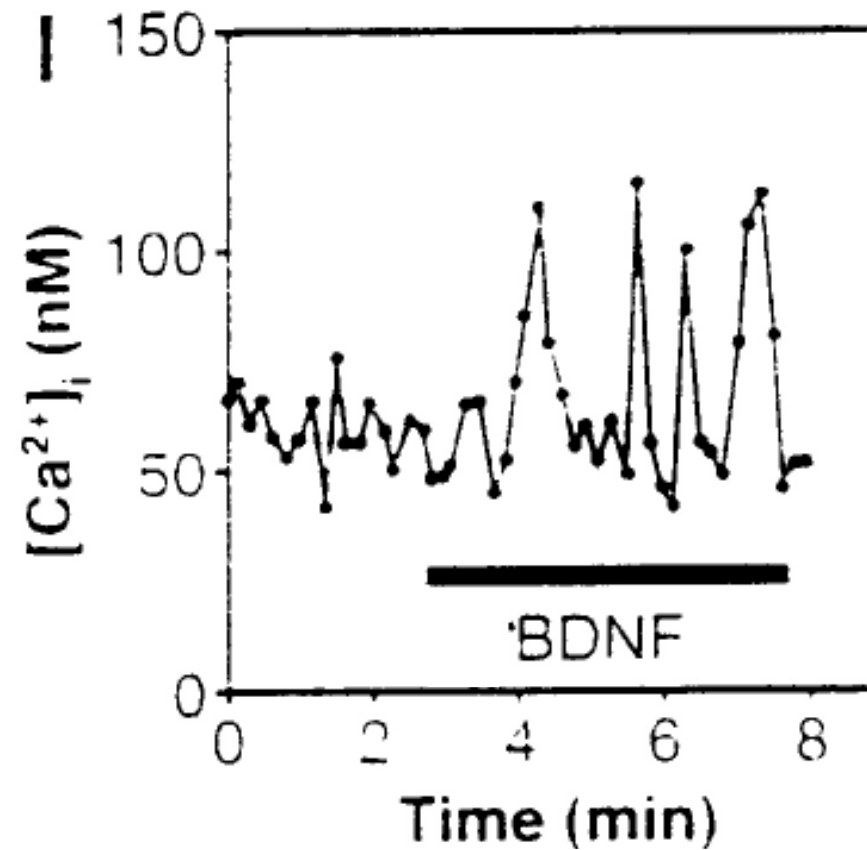
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Time course of oscillating calcium transients in a dendrite in the absence and in the presence of BDNF
Science 270, oct. 1995





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Single-cell measurements have shown that many hormones trigger a series of calcium *spikes* and that these spikes show a rise in frequency with increasing hormone concentrations. It has been suggested that many cell responses are controlled by *frequency-modulated* rather than *amplitude-modulated* signals, analogous to the transmission of information between neurons by changes in frequency of action potentials. Such digitally encoded signals could more precisely regulate the cell response to changing hormone concentrations.

Calcium waves can also propagate in tissues and organs, providing a long-range signalling system, as observed in ciliated epithelial cells, in vascular endothelial cells, in hepatocytes, and in monolayers of cultured astrocytes. It has been suggested that this mechanism of cell to cell communication may contribute to the synchronization of large cell assemblies.

In vivo, various hormones are secreted with oscillatory rhythms. In healthy people, insulin is secreted with pulsations that are repeated every 12-15 minutes, controlled by a pancreatic *pacemaker*, probably influenced by the vagus nerve.

The insulin secreted in pulsations is metabolically more efficient in maintaining normal glucose levels, and it is significant that irregularity or even the loss of these oscillations is the earliest abnormality detectable in insulin secretion in patients with type 2 diabetes.





CALCIUM OSCILLATIONS IN CHROMAFFINE CELLS. EFFECT OF CAFFEINE (D'Andrea et al., J.B.C. 268, 15213, 1993)

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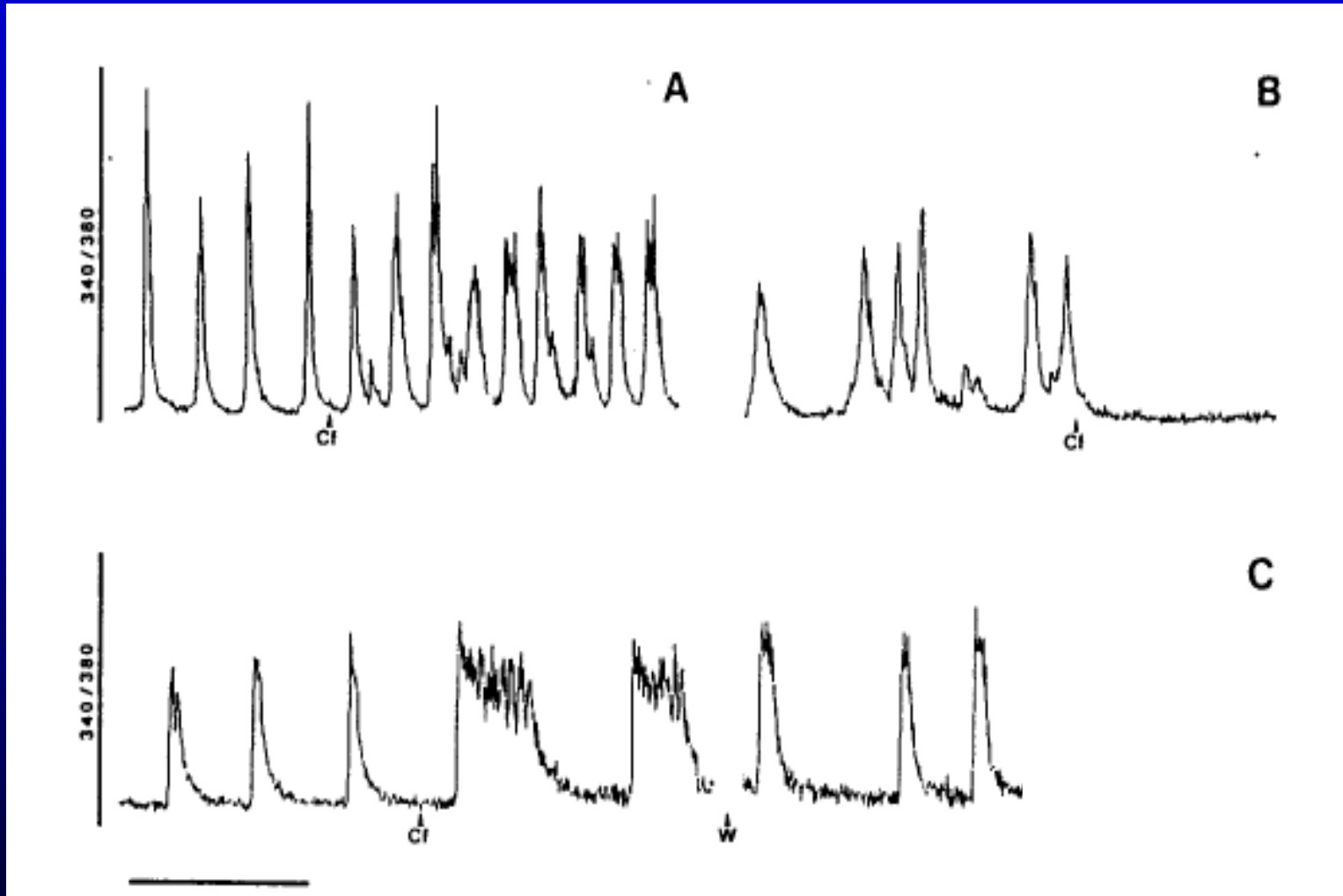
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Complex calcium-dependent regulation of an oscillator. Administration of caffeine (1-3 mM) to oscillating cells gives rise to a variety of responses: increase in the oscillation frequency (above), marked increase in the duration of individual oscillations (below). W: washing for 20 min in Krebs-Ringer solution.





Relax

Music: Orchestra One by Kevin MacLeod (incompetech.com)



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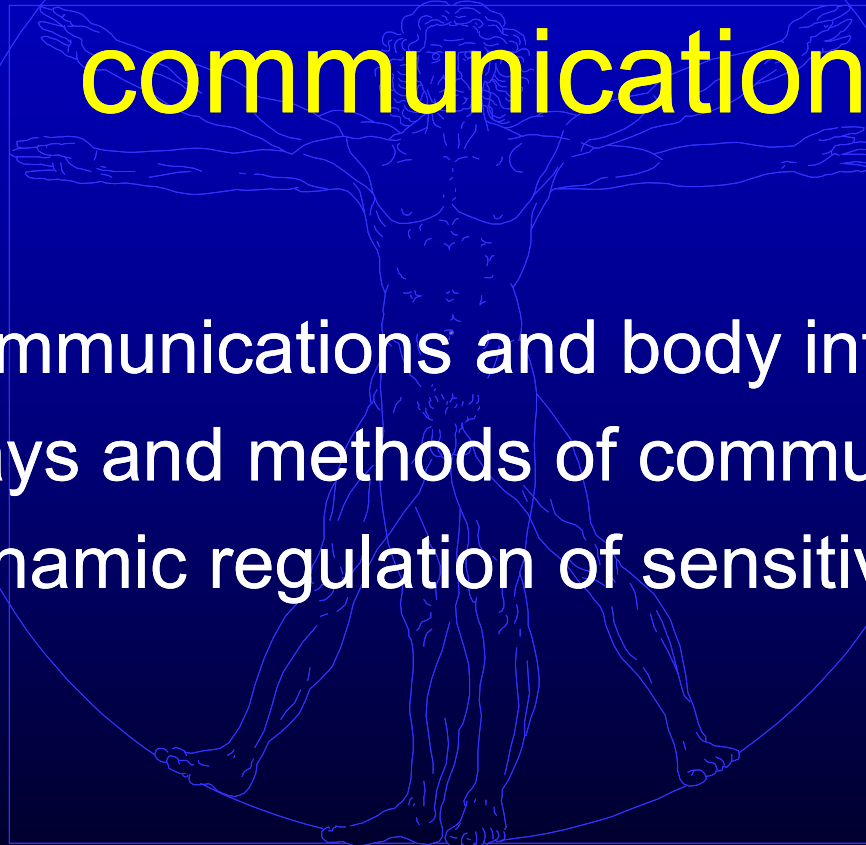
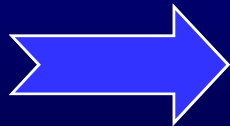
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- Communications and body integration
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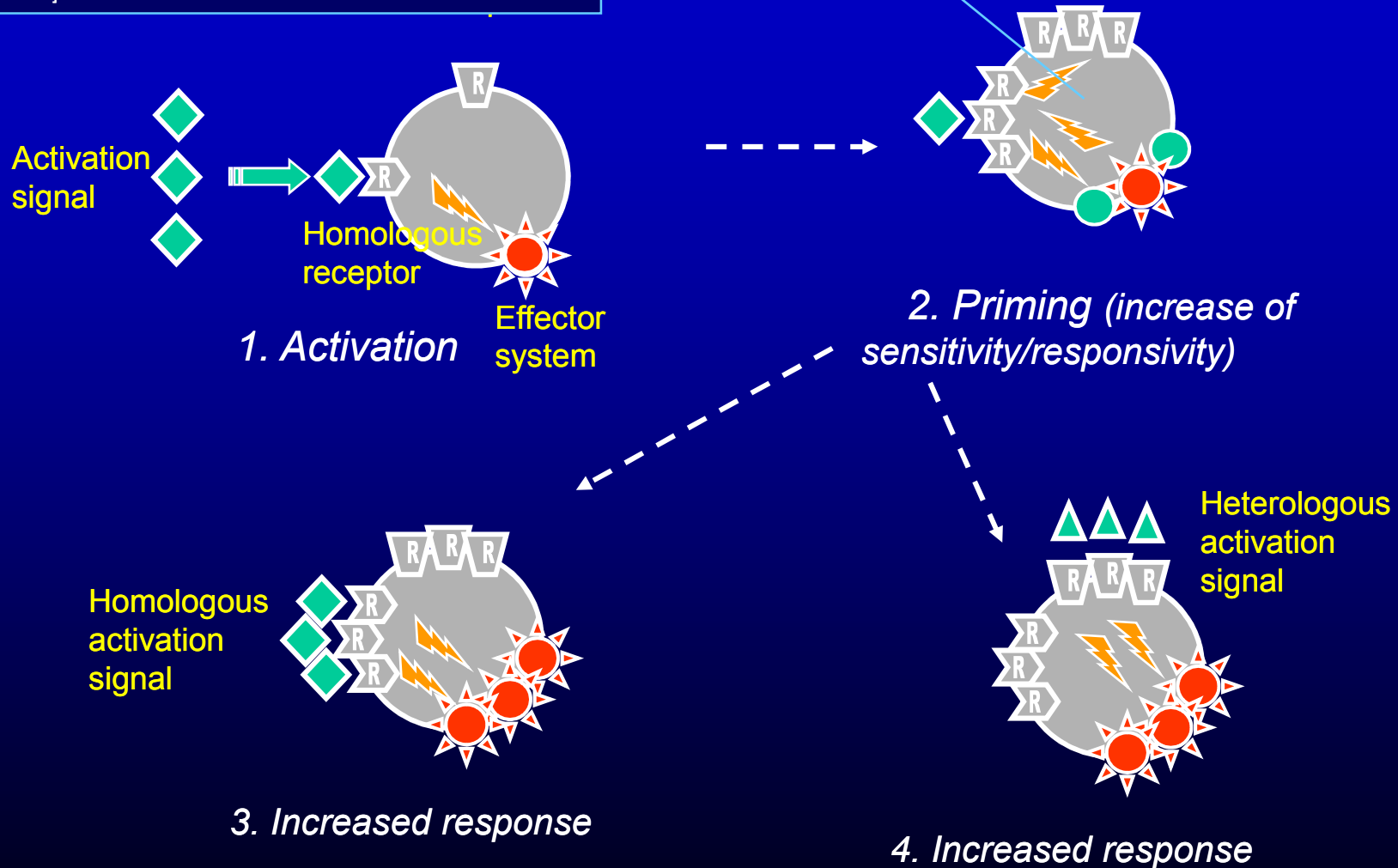
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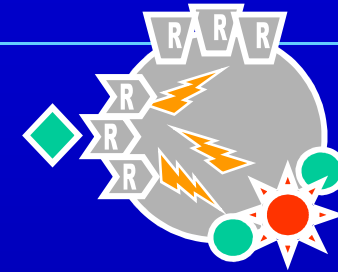
What is meant by priming is a state of hyperactivation in response to a given stimulant, which characterizes a cell after it has received pretreatment with low doses of the same stimulant (homologous priming) or of other stimulants of a different type (heterologous priming). The priming is due to exposure of new receptors, to activation of the same receptors and/or to a number of changes in the intracellular communication or enzyme systems. It is worth noting that priming has been described not only at the cell level, such as in leukocytes, but also in tissue and organs, such as in the airways of allergic individuals after repeated challenge with allergens [Koh et al., 1994].

BIOLOGICAL COMMUNICATION: "PRIMING"





PRIMING: Increase of SENSITIVITY or of RESPONSE to a second stimulus after the challenge with a first stimulus



EXAMPLES

- Cellular models (e.g. Leukocytes)
- Tissues (e.g. Bronchial reactivity)
- Organs (e.g. Liver induction, heart)
- Systems (e.g. Nervous and immune hypersensitivity)

MECHANISMS

- Receptors increase
- Positive gating (signal transduction)
- Decrease of inhibitory pathways
- Increase of genes expression
- Pre/post synaptic conditioning
- Organ hypertrophy

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THE "RULES" OF BIOLOGICAL COMMUNICATION: "DESENSITIZATION"

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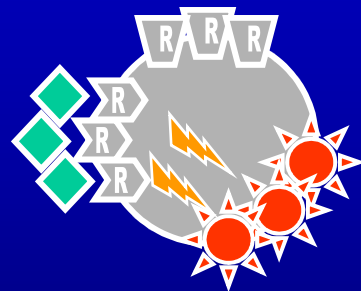
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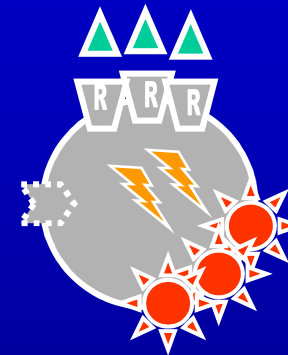
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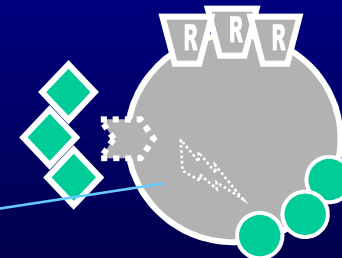
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1. *Continuous strong homologous stimulation*



3. *Heterologous priming*



2. *Homologous desensitization*

What is meant by desensitization is a state characterized by lack of cell responsiveness to a given stimulus after the cell has received pretreatment with low, medium or high doses of the same stimulant (homologous desensitization) or of different stimulants (heterologous desensitization). Generally speaking, desensitization (whether homologous or heterologous) may be due to many mechanisms, including consumption or inactivation of receptors, decoupling of receptors from transduction systems, and de-activation of cell effector systems. Homologous desensitization is incompatible with heterologous priming.





DESENSITIZATION

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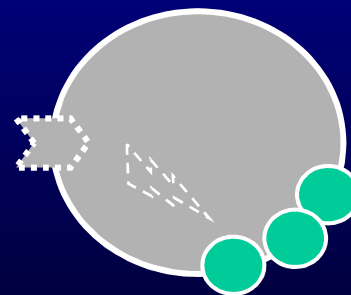
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*is a state characterized by lack of responsiveness to a given stimulus after the cell or the organism have received pretreatment with the same stimulant (**homologous** desensitization) or with different stimulants (**heterologous** desensitization)*





REGULATION OF RECEPTOR SENSITIVITY

Example of how a receptor can be inactivated by a negative feedback mechanism triggered by its own activation

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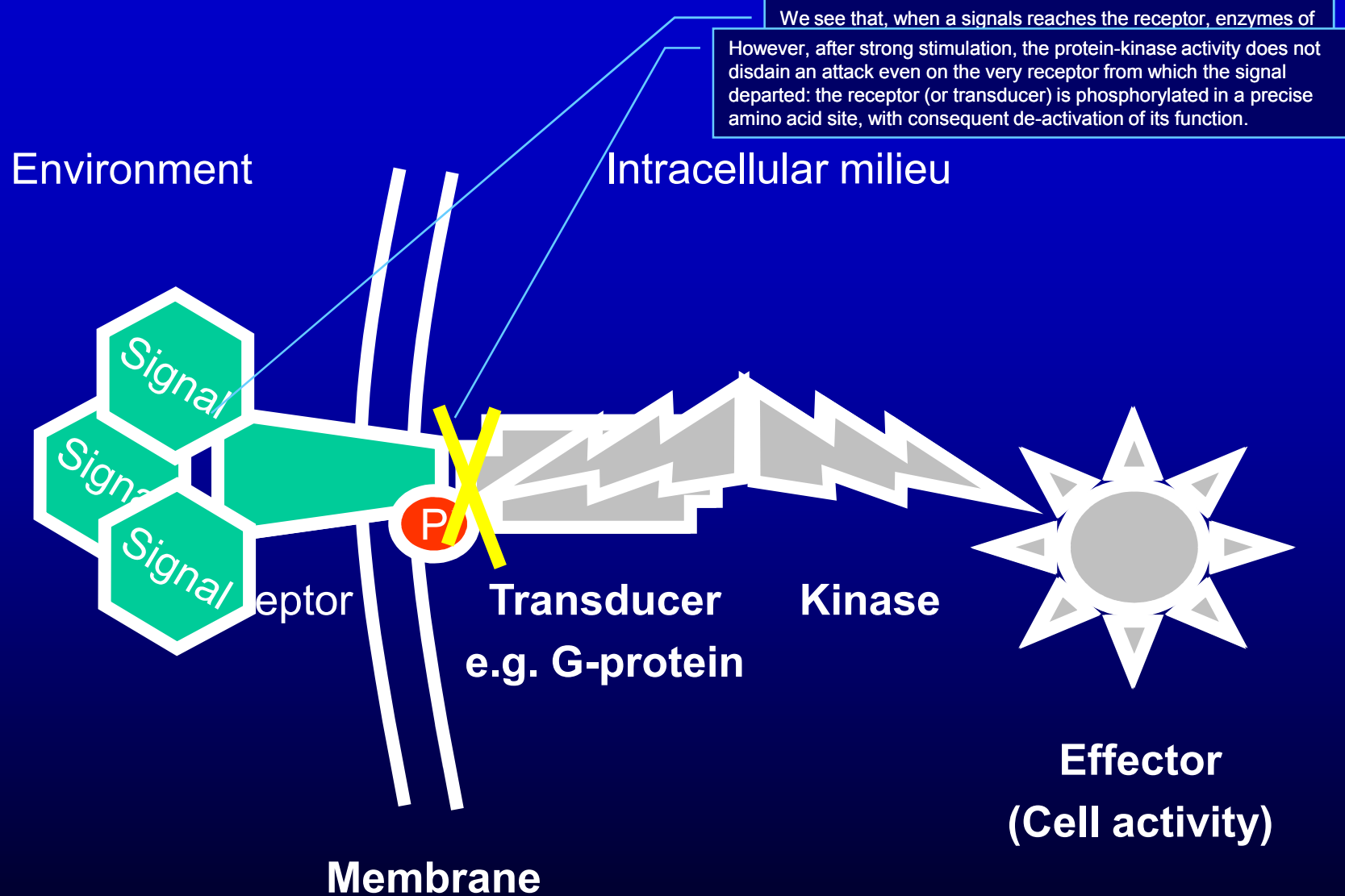
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DOSE-RESPONSE CURVES OF THE EFFECT OF INCREASING DOSES OF THE BACTERIAL PEPTIDE fMLP ON O_2^- PRODUCTION AND ON ADHESION OF HUMAN BLOOD NEUTROPHILS

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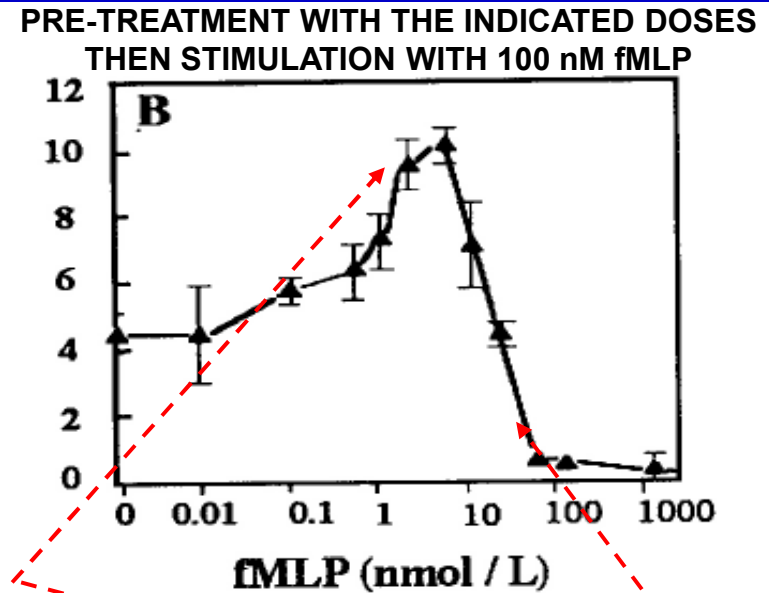
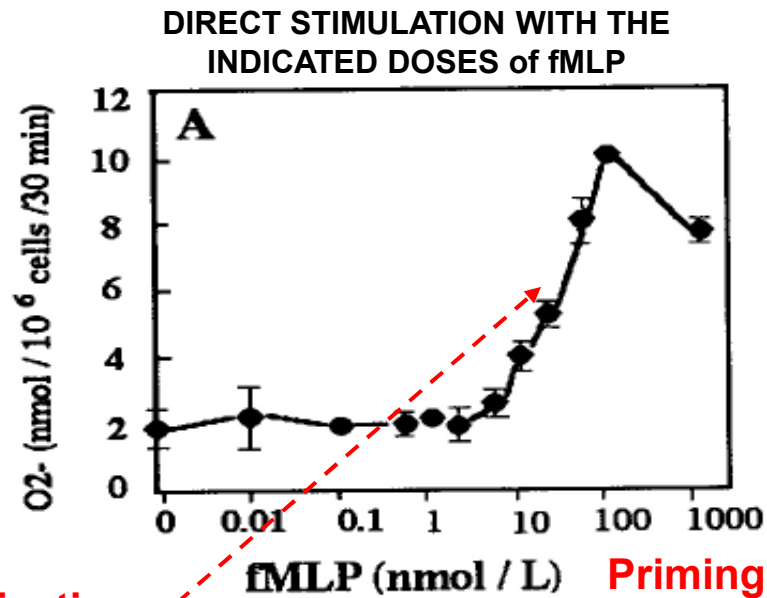
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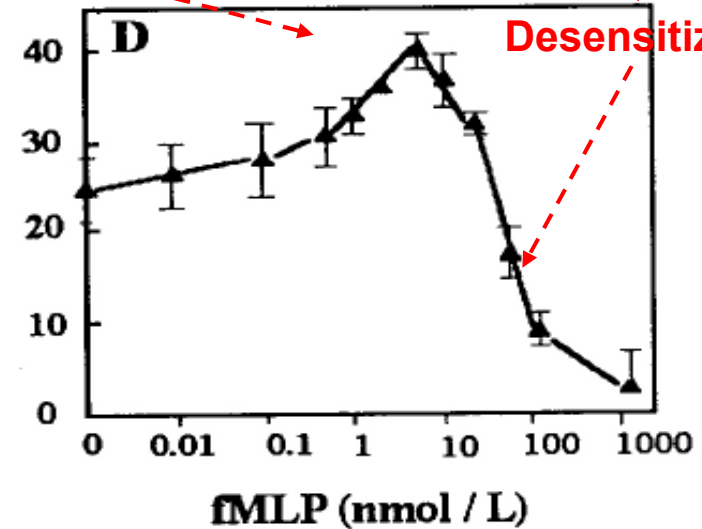
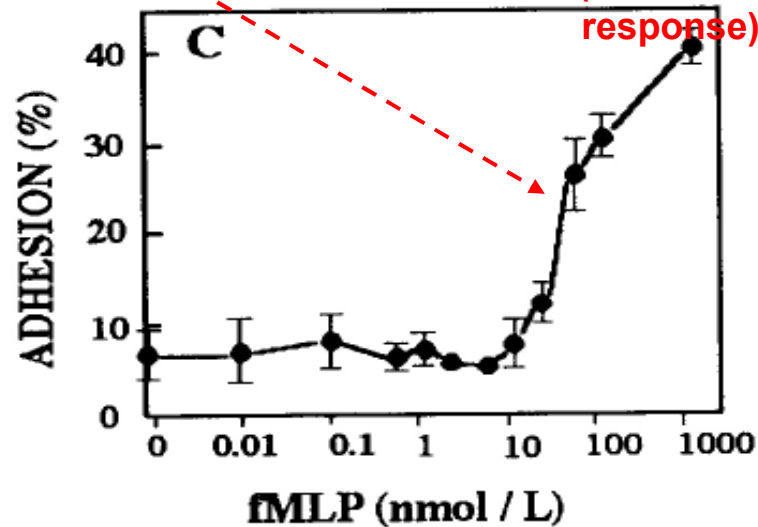
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Activation

Priming
(increased
response)

Desensitization





EXPERIMENTAL DEMONSTRATION OF HOMOLOGOUS AND HETEROLOGOUS PRIMING, HOMOLOGOUS DESENSITIZATION

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Effect of pre-treatment 15 minutes with different doses of fMLP on the O₂⁻ production induced by fMLP and PMA in human neutrophils.

From Bellavite, P. et al, Signals and Images (M. Bastide ed.). Kluwer Acad. Publ., Dordrecht, 111-119, 1997

| Pre-treatment (15 min) | O ₂ ⁻ production (nmol/30 min/10 ⁶ cells) | | |
|------------------------|----------------------------------------------------------------------------|-----------------------------------------------------------|-----------------------------------------------------|
| | (NO stimulants) | Stimulant: fMLP (100nM) | Stimulant: PMA (10ng/ml) |
| Buffer (control) | - (no increase of activity) | 4.1 ± 0.5 (=Normal response to fMLP) | 13.6 ± 0.3 (=Normal response to PMA) |
| fMLP (5nM) | - (no increase of activity) | 10.1 ± 0.9 (=Homologous priming to fMLP) | 18.4 ± 1.3 (=Heterologous priming to PMA) |
| fMLP(100nM) | - (no increase of activity) | 0.4 ± 0.4 (=Homologous desensitization to fMLP) | 35.5 ± 2.2 (=Heterologous priming to PMA) |

On the other hand, the desensitization induced by high doses of fMLP is exclusively homologous, because the response to PMA was not inhibited but, instead, was further augmented.

of O₂⁻ after pretreatment with 100nM fMLP followed by PMA is further augmented because the burst by fMLP is short-lasting (<10 min).





1.2. BIOLOGICAL COMMUNICATION - END OF THE LECTURE

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