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Receptor regulation

Down regulation: It is the decrease in number &/or sensitivity of receptors due to prolonged stimulation by agonist.

In some receptors, **continued stimulation of the receptors with the same dose of agonist** results in decreased synthesis of new receptors or a state desensitization (also referred to as adaptation, refractoriness).

Up-regulation: It is the increase in number & or sensitivity of receptors **due to prolonged inhibition by antagonist.**

Prolonged contact of receptors with an antagonist leads to **synthesis of more new receptors.**

The number of certain receptors is regulated by **regulatory factors and hormones** that do not bind to these receptors at all (e.g. **thyroid hormone excess in patients suffering from hyperthyroidism causes increase the number of cardiac beta- adrenoceptors**).

The number and function of receptors **can be affected by diseases like autoimmune antibodies** which destroy the receptor itself or affect the coupling efficiency. Examples: **diabetes due to destruction of insulin**

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Drug Tolerance

repeated administration of some drugs, the intensity of response may decrease during the course of therapy.

- 1- "**pharmacodynamic**" due to downregulation of receptors ,drug holiday may solve the problem.
- 2- "**pharmacokinetic**" tolerance occurs due to increased rate of drug metabolism , increasing the dose of the drug is required to get the same response

Tachyphylaxis: When tolerance happens rapidly after the first few doses

Cross tolerance: development of tolerance to a chemically or pharmacologically related drugs

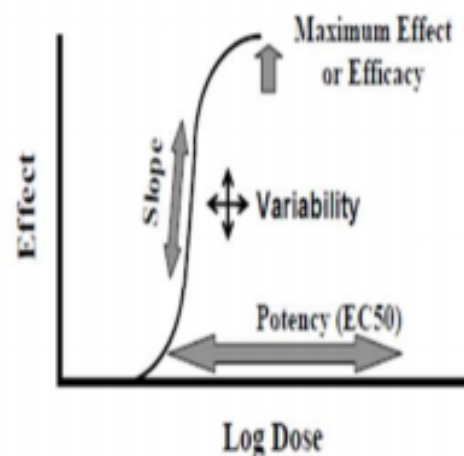
Types of dose response curves

Characteristics of graded dose-response

four characteristic variables can be identified: **potency, efficacy, slope and biological variation.**

Graded ,quantitative: measured on a continuous scale

Quantal (qualitative): All or non- response. the response is measured by the percentage of occurrence of these events



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Summary of graded dose response curve



Potency: a comparative measure which refers to the different doses of two drugs needed to produce the same effect. For comparison of potency, ED50 is used.

Efficacy: is the maximum effect of a drug. For comparison of efficacy, the maximum ceiling effects are compared.

Slope: The slope of the central linear part of the curve. When the slope is steep, it means that the ratio between the therapeutic dose and toxic dose of the drug is low i.e., the drug has a narrow margin of safety.

Variability: of effects among different or the same individual at different times.

Quantal dose response curve

All or non-response are measured in percentage. Like occurrence of deaths, convulsions or arrhythmias. It is used to determine the dosage causing toxicity and lethality to experimental animals.

Median effective dose (ED50) of quantal response = dose which produce a specific response in 50% of population.

Median Toxic dose (TD50) = dose which produce a specific toxicity in 50% of experimental animals.

Median lethal dose (LD50) = dose which produce death in 50% of experimental animals.

Therapeutic index (TI)

- Therapeutic index (TI) is a quantitative measurement of the relative safety of drugs. It is the ratio of TD50 or LD50 to ED50.

$$TI = TD_{50} / ED_{50}$$

Therapeutic index should be greater than 1.
the drug is a poison

