Pharmacodynamics:
(Drug Receptor Interactions, Part 2)

VPT: Unit I; Lecture-22
(Dated 03.12.2020)

Dr. Nirbhay Kumar
Asstt. Professor & Head
Deptt. of Veterinary Pharmacology & Toxicology
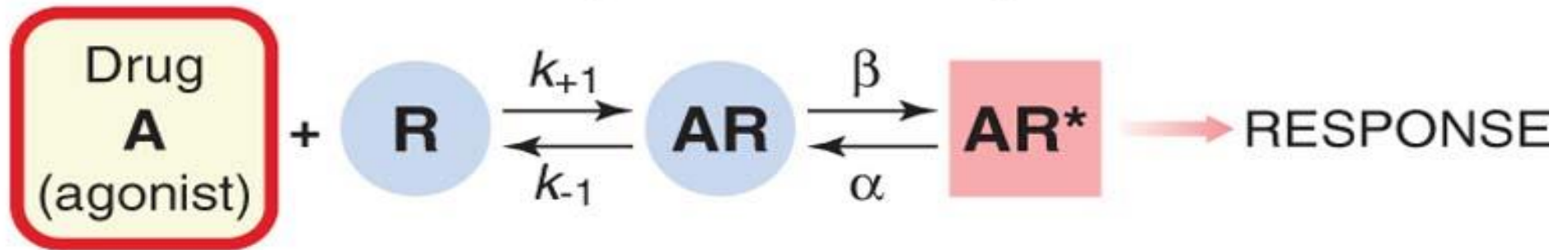Bihar Veterinary College, Bihar Animal Sciences University, Patna

Drug Receptor Interactions

Agonist

✓ **It is a drug that possesses affinity for a particular receptor and causes a <u>change in the receptor</u> that result in an observable effect.**

✓ **Full agonist: Produces a maximal response by occupying all or a fraction of receptors. (Affinity=1, Efficacy=1)**

✓ **Partial agonist: Produces less than a maximal response even when the drug occupies all of the receptors. (Affinity=1, Efficacy= 0 to 1)**

✓ **Inverse agonist: Activates a receptor to produce an effect in the opposite direction to that of the well recognized agonist. (Affinity=1, Efficacy= -1 to 0).**
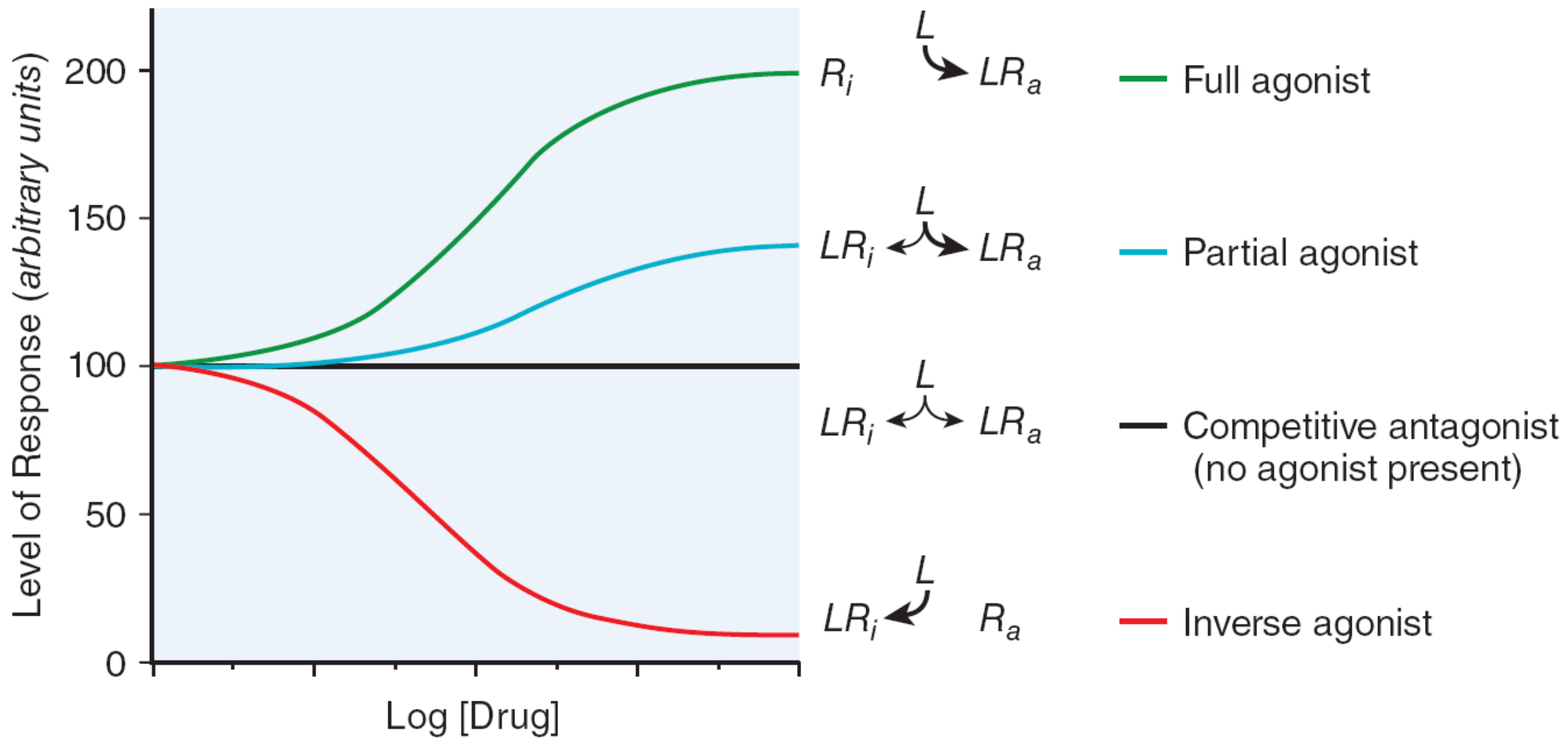
Occupation governed by **affinity**   **Activation** governed by **efficacy**

Drug **A** (agonist) + R $\xrightarrow[k_{-1}]{k_{+1}}$ AR $\xrightarrow[\alpha]{\beta}$ AR* → RESPONSE

Drug **B** (antagonist) + R $\xrightarrow[k_{-1}]{k_{+1}}$ BR → NO RESPONSE

© Elsevier. Rang et al: Pharmacology 6e - www.studentconsult.com

Source: Rang & Dale's Pharmacology, Elsevier

Source: Good & Gilman's The Pharmacological Basis of Therapeutics, 13th Edn.

Antagonist

✓ **An antagonist is a drug that blocks the response produced by an agonist.**

✓ **Antagonists interact with the receptor or other components of the effector mechanism, but antagonists are devoid of intrinsic activity (Affinity=1, Efficacy=0).**

Antagonist contd...

✓ **Competitive Antagonism:** It is completely reversible; an increase in the concentration of the agonist in the bio-phase will overcome the effect of the antagonist.

Example: Atropine (Antimuscarinic agent)

Diphenhydramine (H1 receptor blocker)

✓ **Non-competitive antagonism:** The agonist has no influence upon the degree of antagonism or its reversibility.

Example: Platelet inhibiting action of aspirin (The thromboxane synthase enzyme of platelets is irreversibly inhibited by aspirin, a process that is reversed only by production of new platelets).

Drug Action & Effect

✓ **Drug action:** **It is the initial combination of the drug with its receptor resulting in conformational change in the latter (in case of agonist), or prevention of conformational change through exclusion of the agonist (in case of antagonists).**

✓ **Drug effect:** **It is the ultimate change in biological function brought about as a consequence of drug action, through a series of intermediate steps.**

Chemical Bonds

Five types of chemical bonds can be formed between a receptor and a drug. They are :-

- ✓ **Covalent bond**: Strongest chemical bond and is commonly associated with a drug that interacts irreversibly with a receptor. Most drugs do not form covalent bonds.

- ✓ **Electrostatic bond**: This type of bonding is very common type of bond between a receptor and a drug.
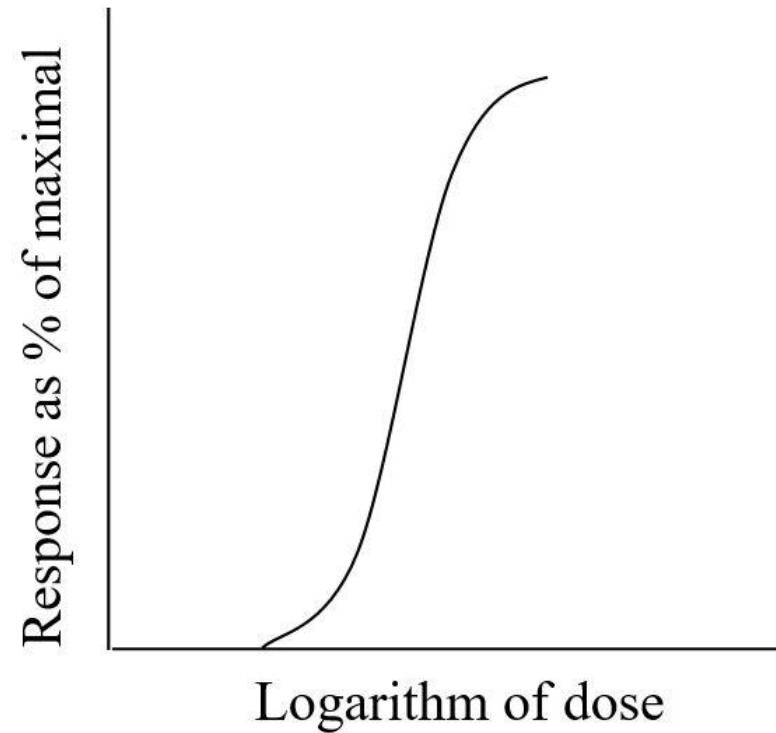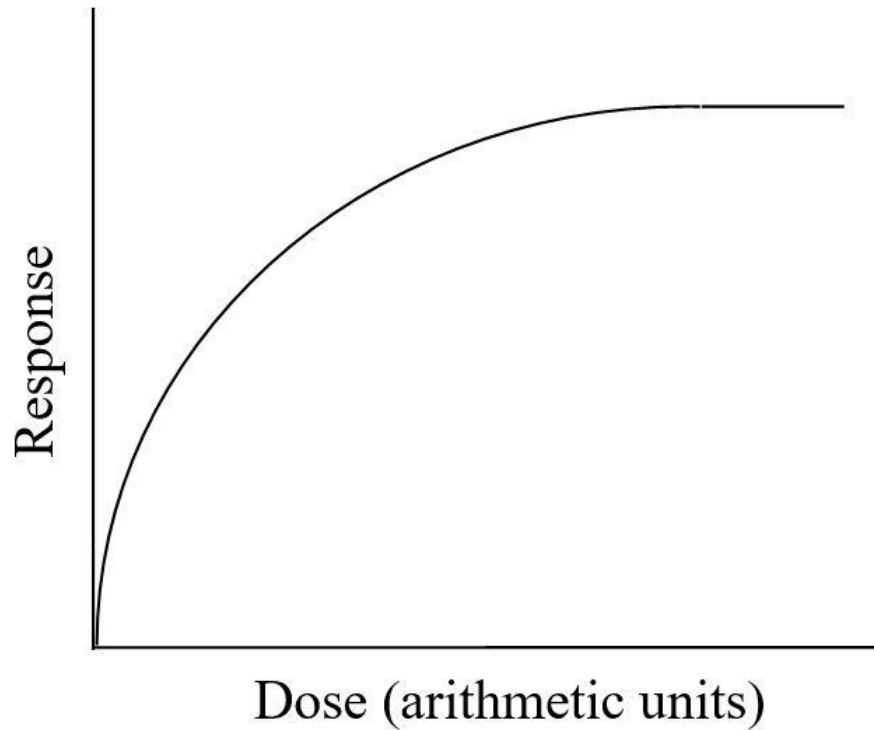
Chemical Bonds   contd...

- ✓ **Hydrogen bond:** It represents a strong interaction between drug and receptor arises from a sharing of the hydrogen atom between an acidic group and a basic group.

- ✓ **Van der Waals bond:** It is a weak attraction between either polar or non-polar molecules. It is essentially electrostatic in nature and varies with distance.

- ✓ **Hydrophobic bond:** Interaction of non-polar with water is unfavourable and that by removing two non-polar surfaces from an interaction with water a net attractive force is produced.

DOSE RESPONSE RELATIONSHIP

The response to a drug varies according to its dosage i.e. the magnitude of the drug effect is a function of the dose administered. The relation between the response produced by different dosage is expressed by graphical representation called Dose Response Curve (DRCs). These are of two types:

(i) Graded dose response curve

(ii) Quantal dose response curve

Graded Dose Response Curve

Graded Dose Response Curve   contd...

✓ It gives the relation between dose of a drug and the intensity of response in a **single biological unit**.

✓ The curve depicts that when the dose exceeds a critical level (threshold dose), the response also increases progressively until it reaches a steady level (**ceiling effect-ceiling dose**).

✓ The **threshold dose** may be defined as the minimum dose required to produce an observable response.

✓ The dose producing ceiling effect may be called as **ceiling dose**, which may be defined as the minimum dose producing the maximum response.

Graded DRC

✓ **Any further increase in the dose above the ceiling dose will not increase the level of response.**

✓ **The graded dose response represents the relationship between dose and response in a single unit or animal, but it does not indicate the normal biological individual variation on a population basis.**

✓ **When the graded response is plotted as a graph, a hyperbolic curve is obtained.**

✓ **When the response is expressed as a % of maximum instead of in absolute units, and is plotted against the logarithm of the dose, the curve adopts a sigmoid shape characteristic of a log-dose-percent response curve.**

Graded DRC   contd...

- ✓ **The central portion of such curves is more or less linear.**

- ✓ **When two or more different dilutions of the same drug are applied in sequence to the same test tissue in increasing volumes to obtain for each response the minimal to maximal range, the curves resulting from each dilution are parallel.**

- ✓ **In such a quantitative bioassay, the separation between the curves gives the ratio of the concentrations of the dilutions tested.**

Quantal Dose Response Curve

✓ It represents the percent response of animals in a group of population to the doses of a drug.

✓ Each animal receiving a dosage is characterized as responding or non-responding. The percentages responding to each dose are recorded (i.e. 0% dead, 0% alive, % responded or % not responded etc.).

✓ The relation is based on all-or-non phenomenon, which cannot be quantitatively measured such as occurrence of death, convulsions, emesis, oestrous etc.

✓ This type of curve is used for estimating ED_{50} or LD_{50} values of a drug.

✓ For a quantal response, both the dose response and the log dose response curves are sigmoid.
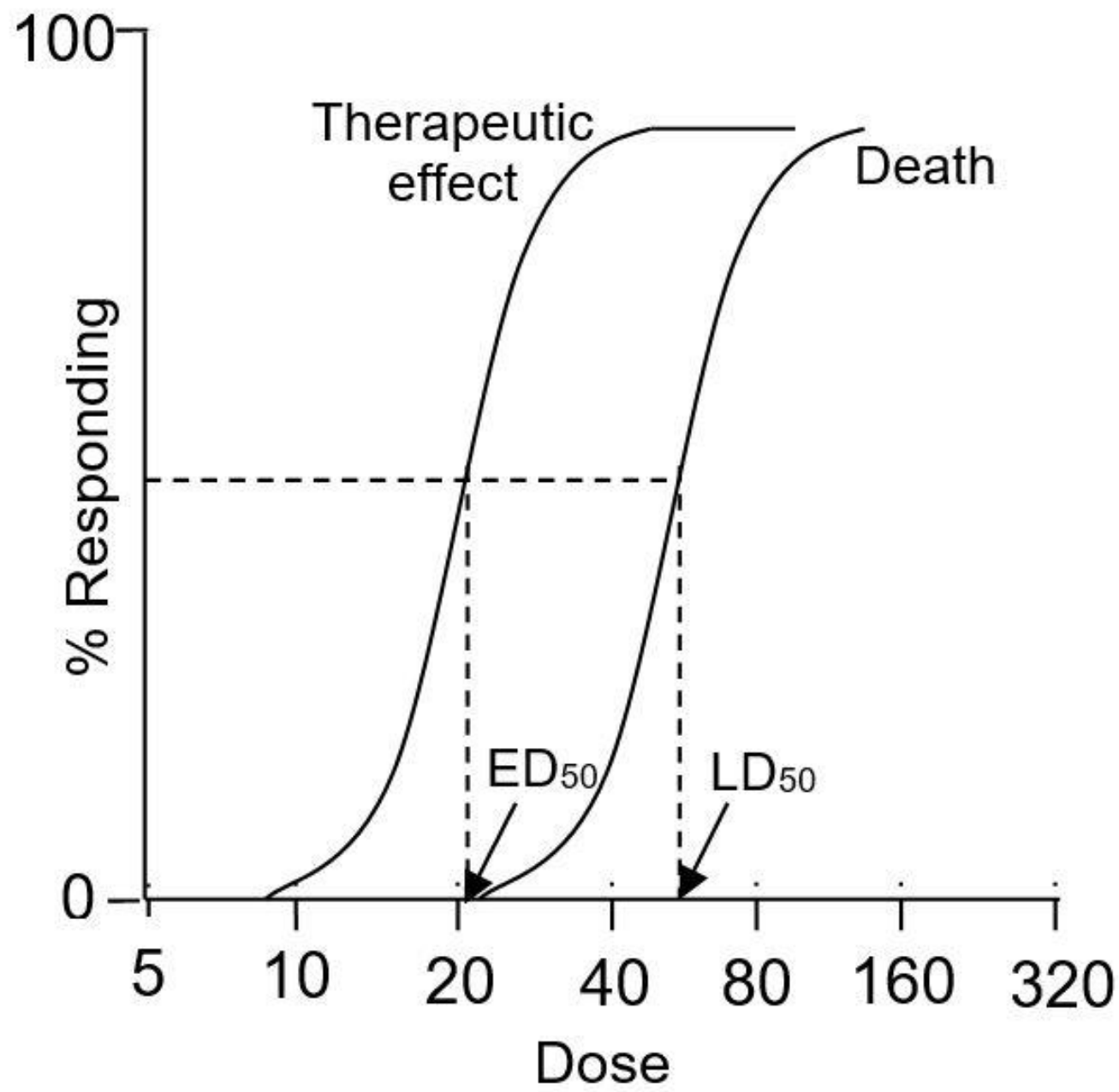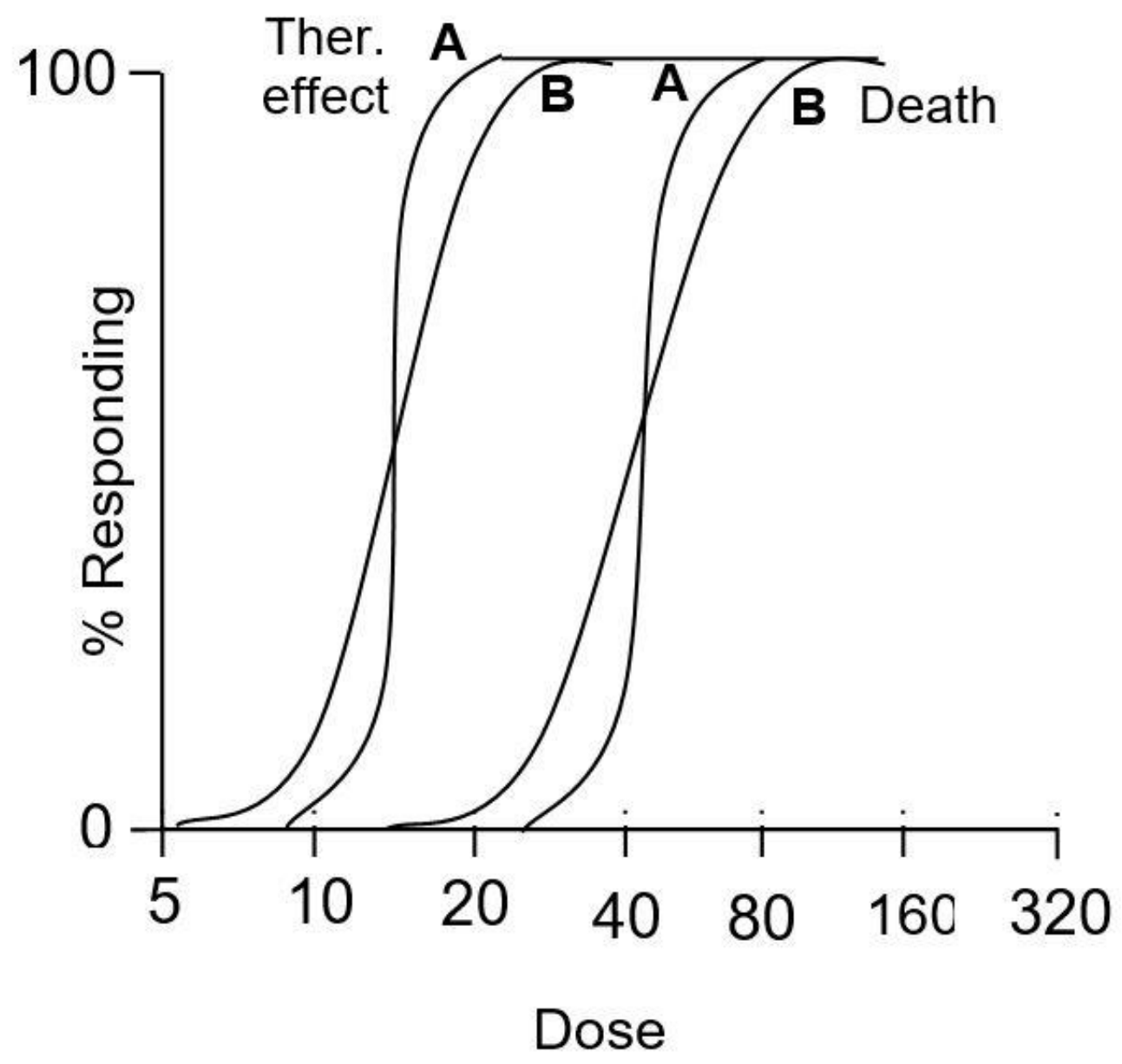
Quantal DRC contd…

LD_{50}: It is called median lethal dose, which is defined as the dose which would be expected to kill 50% of the exposed population.

ED_{50}: It is called median effective dose, which is defined as the dose which would be expected to produce a desired therapeutic response among 50% of the exposed population.

Therapeutic index = LD_{50}/ED_{50}.

Therapeutic ratio = LD_{25}/ED_{75}.

Thank You