PHARMACODYNAMICS

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ABSTRACT:

The field of pharmacodynamics studies how a ligand (Hormone or a Neurotransmitter),binds to it’s receptor to produce a pharmacological response. It’s a term used to describe the effects of a drug on the body, including the biochemical and physiologic effects that influence the interaction of drug with the receptor .The integration of the molecular actions into an effect on the organism as a whole is a subject addressed in this chapter. It is important to describe the effects of a drug quantitatively in order to determine appropriate dose ranges for patients, as well as to compare the potency, efficacy and safety of one drug to that of another.

KEYWORDS: Pharmacodynamics, ligand-receptor binding ,pharmacological response, interaction

INTRODUCTION:

Successful pharmacotherapy depends on the impact of these variables as well as how effectively the body responds to drugs at specific target locations. The process of drug delivery involves three phases, namely drug administration phase, the pharmacokinetic phase and the pharmacodynamic phase. In this chapter we will be discussing about the third phase which deals with drug producing a change or an effect on a specific target. This phase involves interaction of a drug with it’s specific target , called a receptor.

**DRUG ADMINISTRATION PHASE**

**PHARMACOKINETIC PHASE**

**PHARMACODYNAMIC PHASE**

Pharmaco- is derived from the Greek word for “drug,” pharmackon, and dynamics means “of or relating to variation of intensity.” Pharmacodynamics (PD) is the study of the magnitude of drug response. In particular, it is the study of the onset, intensity, and duration of drug response and how these are related to the concentration of a drug to produce desired effect in the site of action.

Pharmacokinetics and Pharmacodynamics:

There are two phases of drug action. (Fig.1) .The pharmacokinetic phase is concerned with the relationship between the value of the dose administered and the value of the drug concentrations achieved in the body; the pharmacodynamic phase is concerned with the relationship between drug concentrations at the site of action and the onset, intensity, and duration of drug response.



 Fig.1

I.FUNDAMENTALS OF DRUG ACTION:

The alteration of biochemical or physiological process of tissues of organisms by any chemical agent which is intended for diagnostic ,preventive and therapeutic purpose is called “drug”. The term drug is derived from the French term “Drogue” which means a medicament. Sources of drugs can be plants, animals, synthetic sources, minerals and genetic means.

A drug molecule is expected to exhibit it’s mechanism of action on target site. There are principles based on which the drug elicit an action can be classified broadly into the following types,

 (a)Activation: Drug molecule stimulates the process or selectively accelerates the process by binding to the target site. Example: Caffeine causes CNS stimulation and increased alertness.

 (b)Inhibition: Drug molecule exhibiting its action by inhibiting the process or selectively deaccelerating the process by binding to the target site. Example: Aspirin inhibits cyclooxygenase, thereby inhibiting the formation of prostaglandins.

 (c)Complexation: Drug molecule exhibiting its action by making a complex,thereby making it inactive by sequesterization. Example: Deferoximine chelates ion.

 (d) Neutralization: Drug molecule binding to the target site and neutralizing the action of the existing molecule directly through a chemical reaction. Example: Antacids



Fig 2.The recognition of a drug by a receptor triggers biological response

II.FACTORS INFLUENCING THE EFFECTIVENESS OF DRUG THERAPY:

|  |
| --- |
| Concentration of administered drugMetabolic rateFrequency of doses administeredGeneticsFood-Drug interactionDrug-Drug interactionExcretion rateAbsorption rateHalf-life of administered drugMedical conditions |

III.TARGETS OF DRUG ACTION:

In most instances, drugs act by associating with specific macromolecular elements in ways that alter their biochemical or biophysical activity. The principal targets for drug action on mammalian cells can be broadly divided into the following categories.

 (a)**Receptors** are the most important targets of drug action. Ion channels, enzymes and carrier molecules can also be indirectly activated or inhibited by receptor-mediated actions.Receptors can be regarded as the sensing elements in the system of chemical communicatitons that cordinaes the functions of all the different cells in the body, the chemical messenger being hormone or transmitter substance.Some of the common receptors are of biogenic amines, acetylcholine and opiates. The receptors determine the quantitative relation between drug dosage and pharmacological action ,and are responsible for selectivity of drug action.Many drugs function by blocking receptors as antagonists although they do not alter receptor function as aganists do.

 (b)**Ion Channels** can be modulated by drugs in different ways. Some are ligand-gated receptor-mediated ion channels, and others are modulated indirectly involving G-proteins or other intermediaries .But most of the ion channels are modulated by binding of drugs directly to parts of the channel protein. Common ion channels are of Na⁺, K⁺ ,Cl⁻.

 ( c)**Enzymes** are targets for many drugs. Most commonly the drug molecule acts as a substrate analogue which acts as a competitive inhibitor of the enzyme. In some cases the inhibition can be irreversible, eg. organophosphorus compounds on AChE, and aspirin on platelet cyclooxygenase. Common target enzymes are cholinesterase, monoamine oxidase, cyclooxygenase and angiotensin converting enzyme.

 (d)**Carrier molecules** transport ions and small organic molecules across cell membrane. These are carrier proteins with recognition sites which can be targets for drug. A few carrier proteins are Na⁺/K⁺ pump, proton pump and noradrenaline uptake. In addition to these some drugs act on structural proteins, eg. Colchicine on tubulin.

IV.SIGNAL TRANSDUCTION:

Drugs act as signals, and receptors act as signal detectors. A drug is termed an “agonist” if it binds to a site on a receptor protein and activates it to initiate a series of reactions that ultimately result in a specific intracellular response. “Secondary messenger” or effector molecules are part of the cascade of events that translates agonist binding into a cellular response.

A.The drug-receptor complex:

Cells have many different types of receptors ,each of which is specific for a particular agonist and produces a unique response.The magnitude of cellular response is proportional to the number of drug-receptor complexes.This concept is conceptually similar to the formation of complexes between an enzyme and substrate .It is also important to know that , not all drugs exert effects by interacting with a receptor. For example, antacids chemically neutralise excess gastric acid, thereby reducing stomach upset.

B.Receptor states:

Receptors exist in atleast two states, inactive (R) and active (R\*), that are in reversible equilibrium with one another, usually favouring the inactive state. Binding of agonists causes the equilibrium to shift from R to R\* to produce a biological effect. Antagonists are drugs that bind to the receptor but do not increase the fraction of R\* ,instead stabilizing the fraction of R. Some drugs shift the equilibrium from R to R\*, but the fraction of R\* is less than that caused by an agonist. The magnitude of biological effect is directly related to the fraction of R\*. In conclusion, agonists, antagonists and partial agonists are examples of molecules or ligands that bind to the activation site on the receptor and can affect the fraction of R\*.

V.RECEPTORS AND RECEPTOR-BINDING:

 Paul Ehrlich, who initiated the concept of ‘receptor’ in the beginning of this century , described the drug-receptor interaction as a ‘lock and key system’ .Most drug receptors are macromolecular proteins which provide both the necessary diversity and specificity of shape and electrical charge.Receptors present in different cellular constituents are specific in size, shape and structure, and allow interaction with specific ligands or substrates. Therefore, specific drugs bind with specific receptors.If the forces that bind the two are weak (hydrogen bonds, vander waals’ bonds, electrostatic bonds),the binding will be reversible, but if the forces involved are strong, ie. Covalent bonds, the binding will be effectively irreversible. Drug-receptor binding is also known as receptor occupancy. Receptor occupancy of a drug is dependent on affinity of the receptor for the drug which is a function of structural relationship between the two-the drug and the receptor. The relationship between the ligand concentration and receptor occupancy *law of mass action.*

*The law of mass action states the rate of a chemical reaction is directly proportional to the product of the reactant concentration values.*

This means receptor occupancy (%) is directly related to log-concentration of ligand over a wide range.Drug-receptor interactions at different sites in the body are basically similar, but the transduction mechanisms or the signalling mechanisms by which the drug-receptor occupancy is translated into biological effects are different at different sites.Four such mechanisms have been distinguished , given below in the table.

 (i)The first three types concern membrane-bound receptors

 (ii)The fourth one concerns cystolic or nuclear protein receptors.

From the table below it is evident that the time lag between ligand-receptor coupling and response is widely variable depending on the mechanism. The lag period may be in milliseconds, seconds, minutes or even in hours or days.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | ***Ligand-gated channel*** | ***G-protein coupled receptors*** | ***Tyrosine kinase-linked receptors*** | ***Intracellular receptors*** |
| ***RECEPTOR SITE*** | Membrane | Membrane | Membrane | Intracellular |
| ***RECEPTOR-EFFECTOR COUPLING*** | Direct | G-protein | Direct | via DNA |
| ***EFFECTOR*** | Channel | Enzyme/Channel | Tyrosine Kinase | Gene Transcription |
| ***COULPING-RESPONSE TIME LAG*** | Milliseconds | Seconds | Minutes | Hours/days |
| ***CELLULAR EFFECTS*** | Hyperpolarization/Depolarization | Second messenger/Channel modulation | Protein Phosphorylation | Protein synthesis |
| ***EXAMPLES*** | n-ACh recep.GABA recep.Glutamate recep.Aspartate recep. | m-Ach recep.Adrenergic recep.5-HT recep.Polypeptide Hormones | InsulinGrowth factors | CorticosteroidsSex hormonesVitamin DThyroid Hormones |

Table.1. Receptor and receptor binding

VI.MAJOR RECEPTOR FAMILIES:

A receptor is defined as any biological molecule to which a drug binds and produces a measurable response. Thus ,enzymes nucleic acids and structural proteins can act as receptors for drugs or endogenous agonists. However, the richest sources of receptors are membrane-bound proteins that transduce extracellular signals into intracellular responses. These receptors may be divided into four families (Fig.3)

1. Ligand-gated ion channels
2. G protein-coupled receptors
3. Enzyme-linked receptors
4. Intracellular receptors



 Fig.3.Transmembrane signalling mechanisms

1. TRANSMEMBRANE LIGAND-GATED ION CHANNELS:The extracellular portion of ligand-gated ion channels contains the drug-binding site.This site regulates the opening of the pore through which ions can flow across cell membranes.The channel is usually closed until the receptor is activated by an agonist, which opens the channel for a few milliseconds.

 Depending on the ion conducted to through these channels , these receptors mediate diverse functions ,including neurotransmission and muscle contraction.

1. TRANSMEMBRANE G PROTEIN COUPLED RECEPTORS: The extracellular portion of this receptor contains the ligand-binding site, and the intracellular portion interacts (when activated) with a G protein. There are many kinds of G proteins ,but all types are composed of three protein sub-units. The α subunit binds guanosine triphosphate (GTP), and the β and γ subunits anchor the G protein in the cell membrane. Binding of an agonist to the receptor increases GTP binding to the α subunit, causing dissociation of the α-GTP complex from the βγ complex. The α and βγ subunits are then free to interact with specific cellular effectors, usually an enzyme or an ion channel, that cause further actions within the cell. These responses usually last several seconds to minutes. Often, the activated effectors produce “second messenger” molecules that further activate other effectors in the cell, causing a signal cascade effect.
2. ENZYME-LINKED RECEPTORS: This family of receptors undergoes conformational changes when activated by a ligand, resulting in increased intracellular enzyme activity. This response lasts for minutes to hours. The most common enzyme-linked receptors(for example, growth factors and insulin) possess tyrosine residues on itself and other specific proteins. Phosphorylation can substantially modify the structure of the target protein, thereby acting as a molecular switch. For example, the phosphorylated insulin receptor in turn phosphorylates other proteins that now become active. This, enzyme linked receptors often cause a signal cascade effect similar to that caused by G protein-coupled receptors.
3. INTRACELLULAR RECEPTORS: The fourth family of receptors differs considerably from the other three in that the receptor is entirely intracellular, and ,therefore, the ligand (for example, steroid hormones) must have sufficient lipid solubility to diffuse into the cell to interact with the receptor. The primary targets of activated intracellular receptors are transcription factors in the cell nucleus that regulate gene expression. The activation or inactivation of transcription factors alters the transcription of DNA into RNA and subsequently translation of RNA into proteins. The effect of drugs or endogenous ligands that activate intracellular receptors takes hours to days to occur. Other targets of intracellular ligands are structural proteins , enzymes , RNA , and ribosomes.

VII.CHARACTERISTICS OF SIGNAL TRANSDUCTION:

Signal transduction has two important features:

 1)the ability to amplify small signals

 2)mechanisms to protect the cell from excessive stimulation

1)Signal amplification: A characteristic of G protein-linked and enzyme-linked receptors is the ability to amplify signal intensity and duration via the signal cascade effect. Activated G-protein persist for a longer duration than does the original agonist-receptor complex. Prolongation and amplification of the initial signal are mediated by the interaction between G proteins and their respective intracellular targets. Because of this amplification , only a fraction of the total receptors for a specific ligand may need to be occupied to elicit a maximal response. Systems that exhibit this behaviour are said to have spare receptors. About 99% of insulin receptors are “spare” , providing an immense functional reserve that ensures the adequate amounts of glucose entering into the cell. On the other hand, only about 5% to 10% of the total β-adrenoceptors in the heart are spare, only a little functional reserve exists in the failing heart, because the receptors must be occupied to obtain maximum contractility.

2)Desensitization and down-regulation of receptors: Repeated or continuous administration of an agonist or antagonist often leads to changes in the responsiveness of the receptor. The receptor may become desensitized due to too much agonist stimulation ,resulting in a diminished response. This phenomenon , called tachyphylaxis, is often due to phosphorylation that renders receptors unresponsive to the agonist. In addition, receptors may be internalized within the cell, asking them unavailable for further agonist interaction. Some receptors, particularly ion channels ,require a finite time following stimulation before they can be activated again. During this recovery phase, unresponsive receptors are said to be ‘refractory’. Repeated exposure of a receptor to an antagonist, on the other hand, results in up-regulation of receptors, in which receptors reserves are inserted into the membrane, increasing the number of receptors available. Up-regulation of receptors can make cells more sensitive to agonists or more resistant to effects to the antagonist.



Fig.4.Desensitization of doses

VIII.RESPONSE OF DRUG-RECEPTOR INTERACTION:

If a drug has affinity for the receptor, and if it is in close proximity to the receptor site, receptor-occupancy takes place. This drug-receptor coupling leads to a variety of responses depending upon the nature of the drug molecule.

1. Agonists: Drugs resemble the natural transmitter or hormone, may activate the concerned receptor, and result in response. The capacity of a drug to interact with a receptor is due to it’s ‘affinity’ ,and the capability to produce a response is called it’s “intrinsic efficacy” or “intrinsic activity”. Thus an agonist has affinity as well as an intrinsic activity. Noradrenaline, acetylcholine, histamine, 5-HT and their chemical analogues are all examples of agonists.
2. Antagonists: Some drugs because of their structural similarity with the natural ligand of a receptor have affinity for the receptor and so bind with receptor. They are however incapable of activating the receptor due to lack of intrinsic activity (efficacy), and hence there is no response . These drugs compete with the endogenous ligand or exogenous agonists and prevent their receptor occupancy and response. Drugs with affinity without any intrinsic activity and which competitively antagonize the effects of agonists are called pure antagonists. A large number of antagonists are in clinical use, eg. Antiadrenergic, anticholinergics and antihistaminic.

Antagonists can be categorized based on whether they bind to a site on the receptor for agonist or interrupt agonist-receptor signalling by other means.

 ANTAGONISTS

 Receptor Nonreceptor

Antagonists antagonists

 Active Allosteric Chemical Physiologic

Site binding binding Antagonist Antagonist

Reversible Irreversible Reversible Irreversible

Competitive Noncompetitive Noncompetitive

Antagonist active site allosteric

 Antagonist antagonist

1. Partial agonists: Some drugs have both agonist and antagonist actions. They have affinity but very low intrinsic efficacy. They competitively antagonize the effects of a full agonist, but by themselves produce a response much lower than that of a full agonist even at a full receptor-occupancy. A classical example of partial agonist is saralasin acting on angiotensin II receptors. It has antihypertensive effect in patients with increased angiotensin II production, but raises blood pressure in patients who produce low amounts of angiotensin.
2. Inverse agonists: Some drugs produce actions that are paradoxical in nature, and are specifically opposite to those of the agonists. These are called inverse agonists. β -Carbolines are examples of inverse agonists. These agents, by acting on benzodiazepine receptors produce anxiety, increased muscle tone and convulsions, while the agonist benzodiazepines by binding with the same receptors produce sedation, anxiolysis , muscle relaxation and control of convulsions. Both these types of drugs act by modulating the effects of the neurotransmitter GABA.



 Fig.5.Drug receptor interaction

IX. RELATIONSHIP BETWEEN DOSE-RESPONSE:

Agonist drugs mimic the action of the endogenous ligand for the receptor .The magnitude of the drug effect depends on receptor sensitivity to the drug and the drug concentration at the receptor site, which , in turn, is determined by both the dose of drug administered and by the drug’s pharmacokinetic profile, such as rate of absorption, distribution ,metabolism ,and elimination.

1. Graded dose-response relations: As the concentration of a drug increases, it’s pharmacologic effect also gradually increases until all the receptors are occupied. Plotting the magnitude of response against increasing doses of a drug produces a graded dose-response curve that has the general shape. Two important drug characteristics, potency and efficacy , can be determined by graded dose-response curves.

* Potency : It is the amount of drug necessary to produce an effect. The concentration of drug producing 50% of the maximum effect (EC-50) is often used to determine potency. In the given graph, the EC-50 indicate the potency of the drug. (Fig.6) The therapeutic preparations of drugs reflect their potency. We can take for example, candesartan and irbesartan are angiotensin receptor blockers used to treat hypertension. The therapeutic dose range for candesartan is 4 to 32 mg, as compared to 75 to 300 mg for irbesartan. Therefore ,candesartan is more potent than irbesartan . Since the range of drug concentrations that cause from 1% to 99% of maximal response usually spans several orders of magnitude ,semilogarithmic plots used to graph the complete range of doses .



Fig.6.Potency-Drug concentration graph

* Efficacy: It is the magnitude of response a drug causes when it interacts with a receptor. Efficacy is dependent on the number of drug-receptor complexes formed and the intrinsic activity of the drug . Efficacy is a more clinically useful characteristic than potency, since a drug with greater efficacy is more therapeutically beneficial than one that is more potent.

 (b)Drug concentration on receptor binding: This applies the law of mass action to the kinetics of the binding of drug and receptor molecules.

DRUG + RECEPTOR DRUG-RECEPTOR COMPLEX BIOLOGICAL EFFECT

It is assumed that the binding of one drug molecule does not alter the binding of subsequent molecules and by applying the mass action, mathematically it is expressed as

 [DR] = [D]

 [Rt] Kd + [D]

Where,

 [D]= the concentration of free drug

 [DR]= the concentration of bound drug

 [Rt]= the total number of receptors

 Kd= the equilibrium dissociation constant for the drug from the receptor

Affinity means the strength of the interaction between a ligand and it’s receptor. The Kd value may be used to determine the affinity of a drug for it’s receptor. The higher the Kd value , the weaker the interaction and lower the affinity , also vice versa. The above equation defines the curve that has the shapes in the given figure, when it is plotted against drug concentration or log drug concentration. A the concentration of free drug increases , the ratio of concentrations of bound receptors to total bound receptors approaches unity, thereby producing maximal effect.



Fig.7.Drug concentration on binding receptor

(c) Drug binding to pharmacologic effect:

The law of mass action can be applied ,

 [E] = [D]

 [Emax] Kd + [D]

Where,

 [E] = the effect of the drug concentration [D]

 [Emax] = the maximal effect of the drug

Law of mass action can be applied to drug concentration response when the following conditions are met,

1. Magnitude of response is proportional to the amount of receptors occupied by drug
2. Emax occurs when all receptors are bound
3. One molecule of drug binds to only one molecule of receptor

This follows if a specific population of receptors is vital for mediating a physiological effect, the affinity of an agonist for binding to those receptors should be related to the potency of that drug for causing that physiological effect. Many drugs and most neurotransmitters can bind to more than one type of receptor, thereby causing both desired therapeutic effects and undesired adverse effects. In order to establish a relationship between drug occupation of a particular receptor subtype and the corresponding biological response to that drug, correlation curves of receptor affinity and drug potency are often constructed.

X. THERAPEUTIC INDEX AND SAFETY TERM:

In the beginning of the last century Ehrlich introduced the concept of therapeutic index. Since the development of clinical pharmacology and scientific analysis of clinical data the implications have undergone radical changes . Back then, therapeutic index (TI) was derived from animal experiments, and was defined as the ratio of TD₅ₒ to ED₅ₒ for some therapeutically relevant effect. Therefore, the therapeutic index of a drug is the ratio of the dose that produces toxicity in half the population to the dose that produces a clinically desired or effective response in half the population.

 TI = TD₅ₒ

 ED₅ₒ

The TI is a measure of a drug’s safety, because a larger value indicates a wide margin between doses that are effective and doses that are toxic.

From the above derivative, TI is a number and an indicative of ‘margin of safety’. But in a clinical situation TI has limitations.

*Limitations of therapeutic index:*

1. Clinical situations with Extrapolation of animal data.
2. Toxic symptom is more relevant than lethality in humans.
3. Drugs may have more than one ED₅ₒ which depends on the measure of effectiveness.
4. Some significant toxic symptoms are seen in some individuals only.

Due to these limitations, the term safety margin is more in vogue. Based on this criterion, benzodiazepines, barbiturates and digoxin have high, moderate and low therapeutic index. Two parameters are needed to calculate safety margin in humans,

 (i)Effective dose: To calculate the specific effect in most of the humans, viz. EDmax

 (ii)Maximum tolerated dose, which does not produce any ADR, viz. TDₒ

 TI = TDₒ

 EDmax

*Care is needed while using drugs with low margin of safety.*

XI.DRUG-DRUG INTERACTIONS:

A drug interaction occurs when one drug is administered with or shortly after another drug and alters the effect of one drug or both the drugs. This increases or decreases the effect of drug or might cause unexpected effects. Consequences of drug-drug interactions are given below,

|  |  |  |  |
| --- | --- | --- | --- |
| DRUG-DRUG INTERACTION | DEFINITON | EXAMPLE | REPRESENTATION |
| SYNERGISM | The interaction of two or more drugs when their combined effect is greater than the sum of the effects seen when each drug is given alone. | Barbiturate drugs when taken with general anaesthetics, alcohols and other sedative hypnotic drugs can lead to greater adverse effects on the central nervous system |  + = |
| ADDITIVE EFFECT | The combining effects of two drugs equal the sum of the effects of the two drugs acting independently. | Taking aspirin and acetaminophen which is the active ingredient in drugs like Tylenol. |   + = |
| THERAPEUTIC ANTAGONISM | One drug reduces or blocks the effect of another. This can happen through many ways, for example, drugs can interfere with each other in absorption or uptake by cells in the body | Verapamil a blocker of L-type Ca channels, but which blocks Na channels at high concentrations | * = 0

  |
| POTENTIATION | The effect of one drug is increased by the intake of another drug without causing a notable effect. Although, the toxicities of drug B can also be potentiated leading to increased adverse effects. | Diazepam may potentiate the effect of alcohol. |  + =  0 |

Table.2.Drug-drug interaction

XII.FACTORS AFFECTING DRUG RESPONSE:

Drug responses can vary due to pharmacokinetic , pharmacodynamic variabilities and genetic differences. Pharmacodynamic variables can be because of genetic factors, tolerance, concurrent diseases affecting the patient, drug interactions and dependence.

1. Sex: Females have a smaller body size and require doses on the lower side range. They should not be given purgatives or uterine stimulants during menstruation, quinine during pregnancy and sedatives during lactation. Some drugs interfere with the sexual function of males exclusively and should be avoided, if possible, for example antidepressants, statins and fibrates.
2. Body weight : The concept of varying the dose with body weight of children is widely followed, adult doses have also been assumed to be the same irrespective of size and shape although adult weights may vary.

1. Age:

 Children: Children particularly neonates ,differ from adults in their response to drugs. There are some drugs that can cause problems in neonates but are tolerated by children. Examples of drugs associated with problems are chloramphenicol (grey baby syndrome).

 Elderly: Drug use generally requires significant reductions in drug dose reflecting the decline in body function with age. More attention should be given to toxicity and failure of treatment. Patients react differently to medications than young adults, as they age. In the elderly, sometimes distinguishing subtle adverse drug effects from the effects of disease is often difficult which may lead to prescribing cascade. *Prescribing cascade occurs when the adverse effect of a drug is misinterpreted as a symptom.* For example, antipsychotics can cause symptoms that is similar to Parkinson’s disease and the patients may be put on antiparkinson drugs, this causes adverse drug reactions

1. Food:

Presence of food, like fatty acids delays gastric emptying and also delays the absorption of certain drugs like rifampicin. Protein malnutrition causes many changes which may affect drug action. Alcohol induces drug metabolizing enzymes. Calcium in milk interferes with absorption of tetracyclines.

1. Biorhythm:

It is the recurring cycle in the physiology or functioning of an organism, such as the daily cycle of sleep and waking. For example, Hypnotics taken at night produce sleep more easily at a lower dose than in the day time.

1. Psychological state:

In some patients , inert drugs (*Placebo- refers to any therapeutic procedure without any specific activity, given deliberately to have an effect on patient that can be explained by drugs pharmacological and therapeutic properties)* may introduce beneficial effects equivalent to the drug.

1. Cumulation:

When a drug is excreted slowly from the body and too frequent doses are administered ,there may be a build up of high concentration of drug in the body which produces toxicity. For example, digitalis.

1. Tolerance:

A higher dose of drug is required to produce an effect, which can be ordinarily produced by the normal therapeutic dose of the drug. Natural tolerance may

also be present in some cases.

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