Pharmacodynamics

OUTLINE

- Definition.
- Mechanisms of drug action.
- Receptors
  - Types
  - Locations
  - Effects
- Agonists
  - Definition
  - Types

Outlines of Pharmacodynamics

- Antagonists
  - Definition
  - Types
- Therapeutic Index
  - Definition
  - Significance
- Receptor desensitization
- Dose- Response Curve

Outlines of Pharmacodynamics

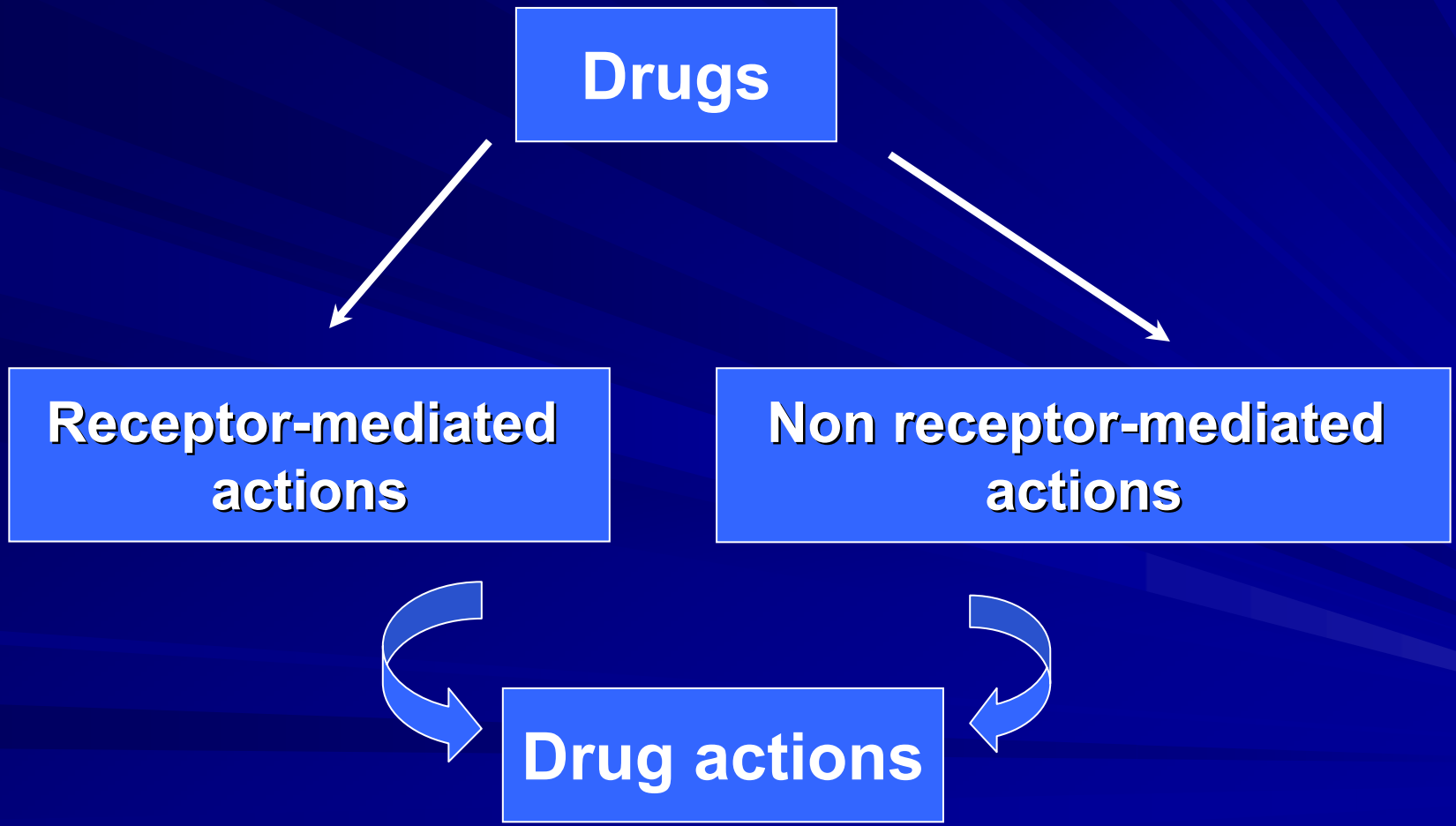
- Factors modifying drug action.
- Adverse drug reactions

Pharmacodynamics•

- a branch of pharmacology that deals with the mechanisms of action and pharmacological effects.

What are the mechanisms of drug action?

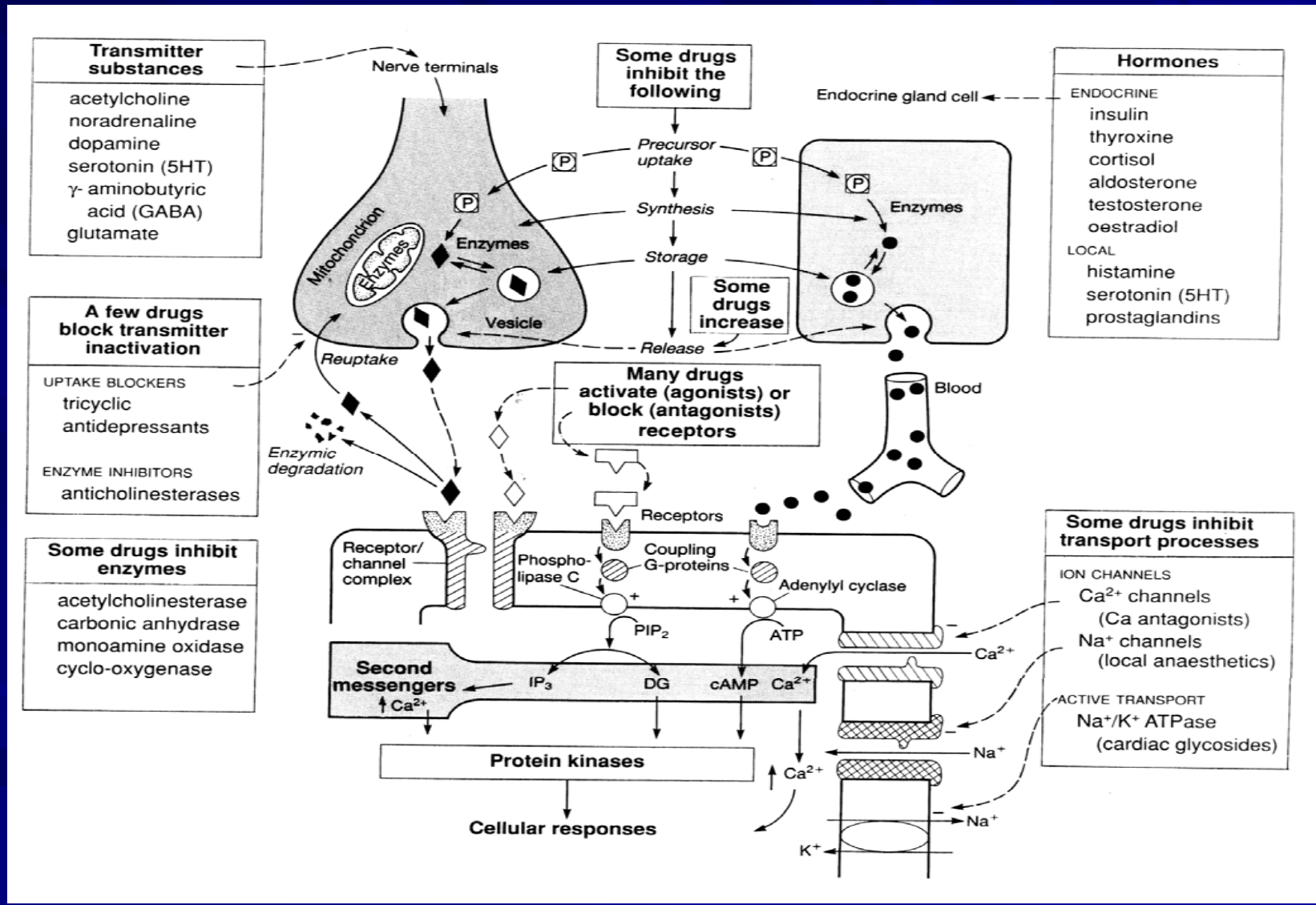
What are target protein sites for drug binding ?



Non receptor –mediated mechanisms

- **Direct chemical interaction**
  - Antacids.
  - Laxatives
  - osmotic diuretics.
- **Enzymes**
  - carbonic anhydrase inhibitors (diuretics).
  - Monoamine oxidase inhibitors.
  - ACE inhibitors

- **Ion channels**
  - Na-channel blockers (local anesthetics).
  - Ca-channel blockers (antiarrythmics).
- **Chemical transmitters**
- **Carrier molecules (Transport process)**
  - Probenecid
- **Incorporation into large molecules**
  - Anticancer (5-fluorouracil)


Transmitter substances
acetylcholine
noradrenaline
dopamine
serotonin (5HT)
γ- aminobutyric acid (GABA)
glutamate
Nerve terminals
Some drugs inhibit the following
Hormones
Endocrine gland cell
ENDOCRINE
insulin
thyroxine
cortisol
aldosterone
testosterone
oestradiol
LOCAL
histamine
serotonin (5HT)
prostaglandins
Precursor uptake
Synthesis
Storage
Release
Mitochondrion
Enzymes
Vesicle
Some drugs increase
A few drugs block transmitter inactivation
UPTAKE BLOCKERS
tricyclic antidepressants
ENZYME INHIBITORS
anticholinesterases
Reuptake
Enzymic degradation
Many drugs activate (agonists) or block (antagonists) receptors
Blood
Receptors
Receptor/ channel complex
Phospho-lipase C
Coupling G-proteins
Adenylyl cyclase
PIP2
ATP
Second messengers
IP3
DG
cAMP
Ca2+
Protein kinases
Cellular responses
Some drugs inhibit enzymes
acetylcholinesterase
carbonic anhydrase
monoamine oxidase
cyclo-oxygenase
Some drugs inhibit transport processes
ION CHANNELS
Ca2+ channels (Ca antagonists)
Na+ channels (local anaesthetics)
ACTIVE TRANSPORT
Na+/K+ ATPase (cardiac glycosides)
Na+
K+

Receptors

Is a special constituent of the cell that binds with the drug and mediates its pharmacological actions.

Examples

Adrenergic , cholinergic receptors

Where?

- Cell membrane.
- Cytoplasm
- Nucleus

Types of receptors ?

Type I (Ion Channel-Linked receptors)

Nicotinic receptors

Type II (G-Protein coupled receptors)

Muscarinic receptors

Type III

(Kinase-Linked receptors)

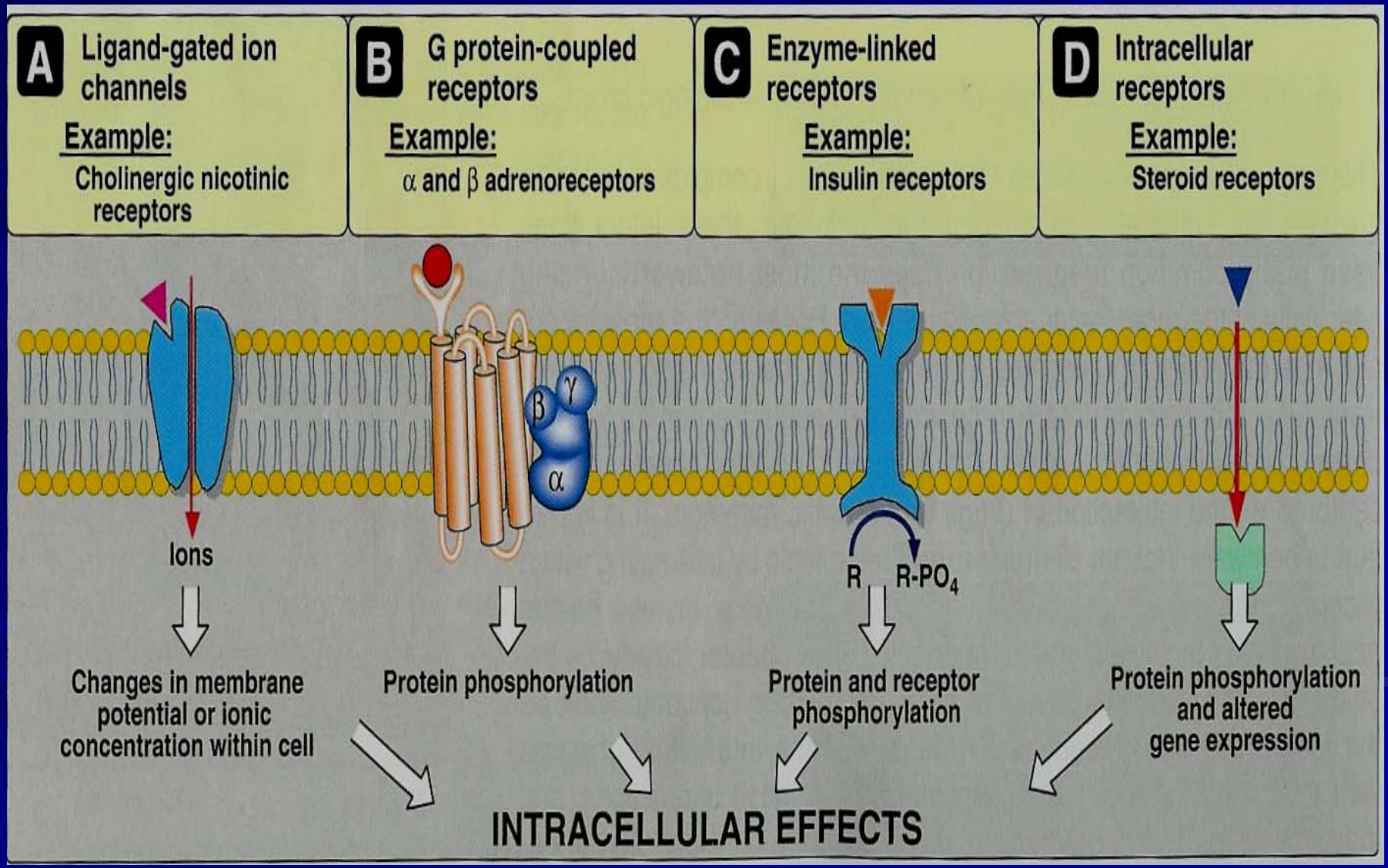
Insulin receptors

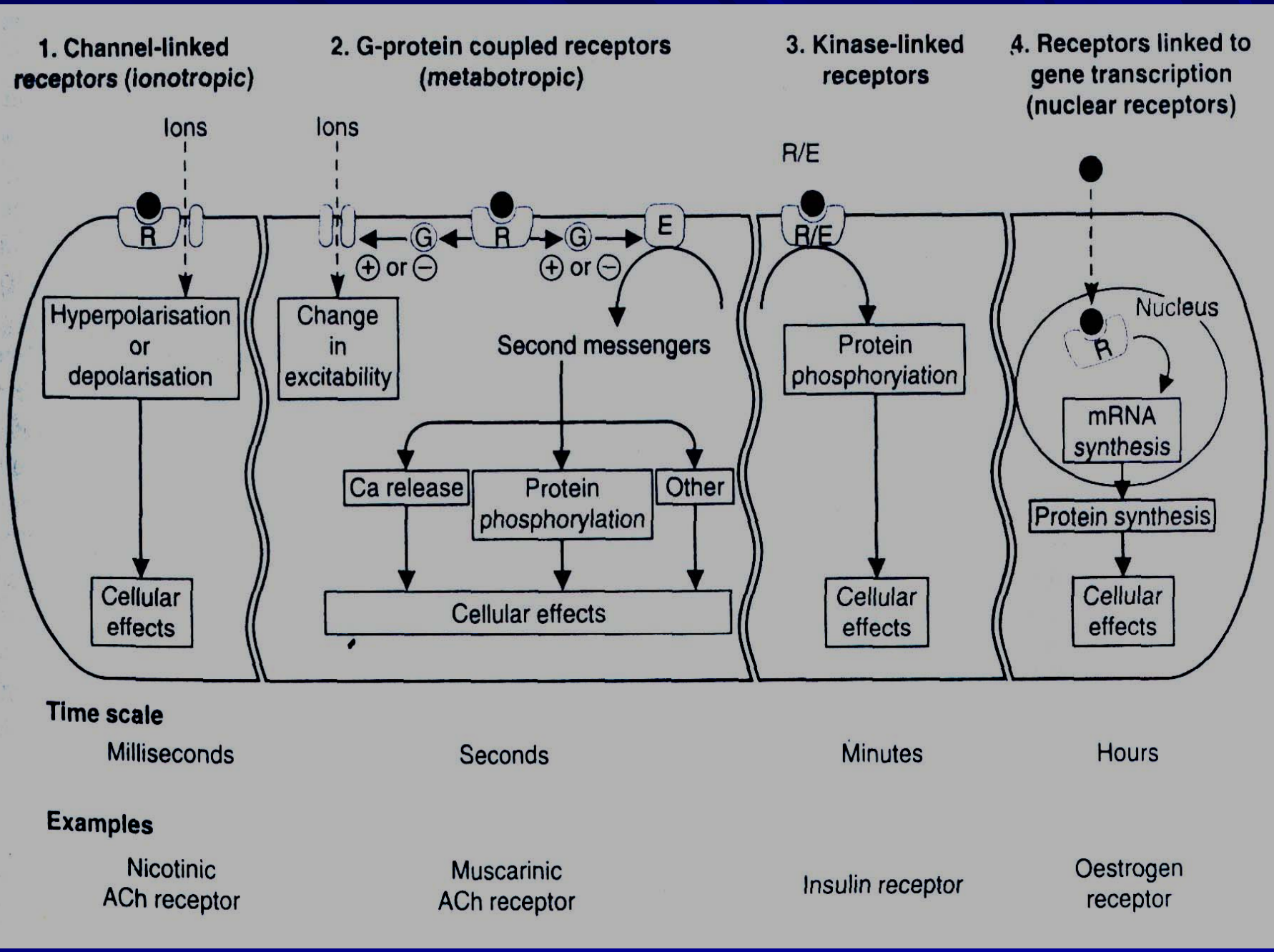
Type IV

(Receptors linked to gene transcription)

Estrogen receptors

Signaling Mechanisms




1. Channel-linked receptors (ionotropic)
2. G-protein coupled receptors (metabotropic)
3. Kinase-linked receptors
4. Receptors linked to gene transcription (nuclear receptors)
Ions
Ions
R/E
R
G
R
G
E
⊕ or ⊖
⊕ or ⊖
R/E
Hyperpolarisation or depolarisation
Change in excitability
Second messengers
Protein phosphoryiation
Nucleus
R
mRNA synthesis
Ca release
Protein phosphorylation
Other
Protein synthesis
Cellular effects
Cellular effects
Cellular effects
Cellular effects
Time scale
Milliseconds
Seconds
Minutes
Hours
Examples
Nicotinic ACh receptor
Muscarinic ACh receptor
Insulin receptor
Oestrogen receptor

The four main types of receptor

	Type 1	Type 2	Type 3	Type 4
Location	Membrane	Membrane	Membrane	Nucleus
Effector	Channel	Enzyme or channel	Enzyme	Gene transcription
Coupling	Direct	G-protein	Direct	Via DNA
Examples	nAChR	mAChR	Insulin receptor	Steroid/thyroid receptor
	$GABA_A$ receptor	Adrenoceptors	ANF receptor	

Type I : Ion Channel-Linked receptors

Located at cell membrane

Directly related to channels.

Involved in fast synaptic transmission.

Response occurs in milliseconds.

Nicotinic receptors

Type II (G-Protein coupled receptors)

Located at cell membrane

The largest family

Coupled to G-protein

Response through ion channels or enzymes.

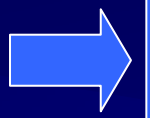
Involved in rapid transduction

Response occurs in seconds.

Muscarinic, adrenergic, serotonin, others

Coupled to G-protein ???

- Interaction with guanine nucleotides GDP, GTP.
- Comprise of three subunits (αβγ), α subunits possess GTPase activity
- Drug makes conformational change of receptor



Increase affinity for trimer,
Dissociation of α-subunit GTP complex (Active),
Activation of channel or enzymes

EFFECT

Targets for G-proteins

1. Ion channels

Muscarinic receptors in heart (K-channel), decrease heart rate.

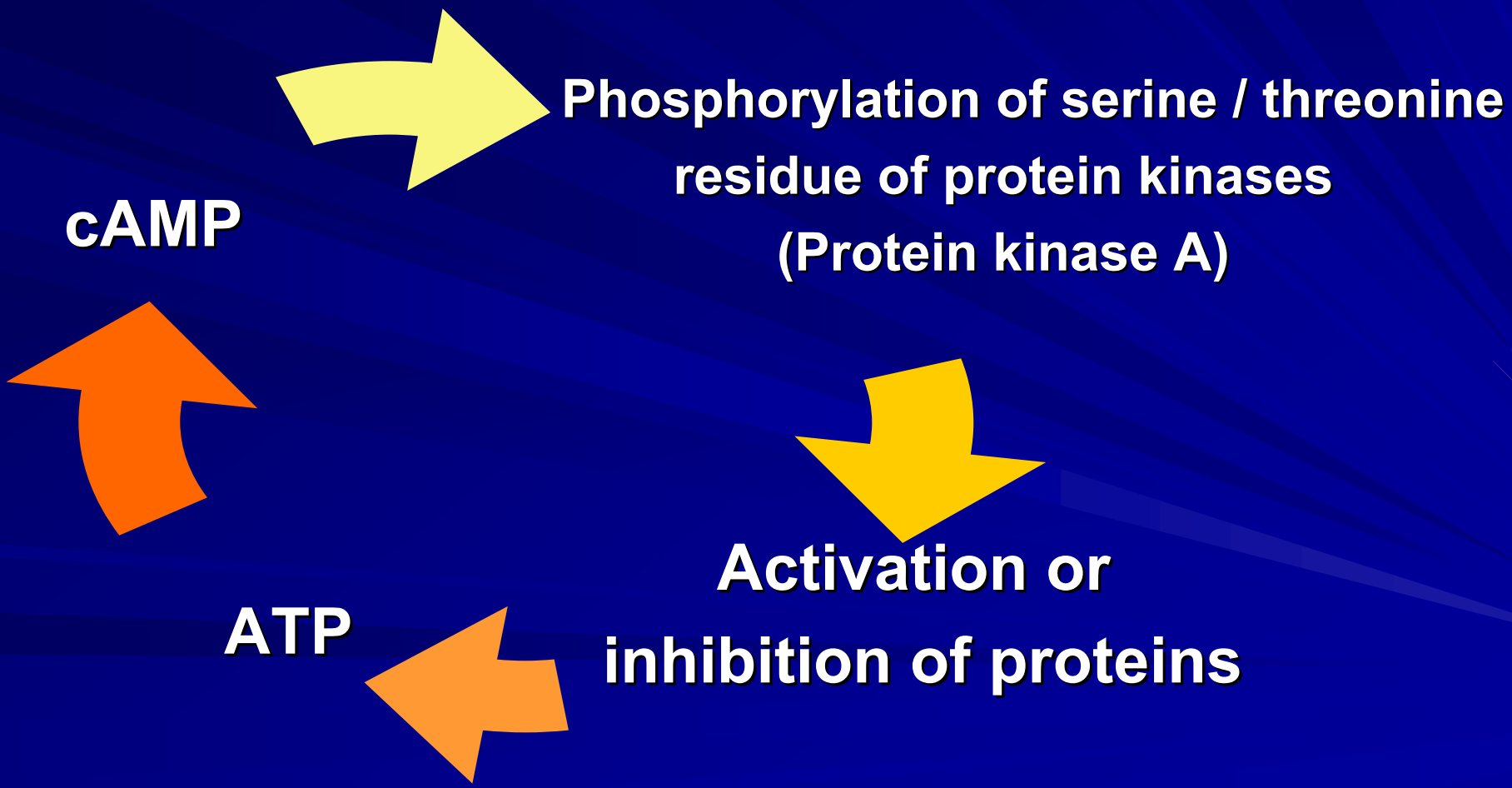
2. second messengers

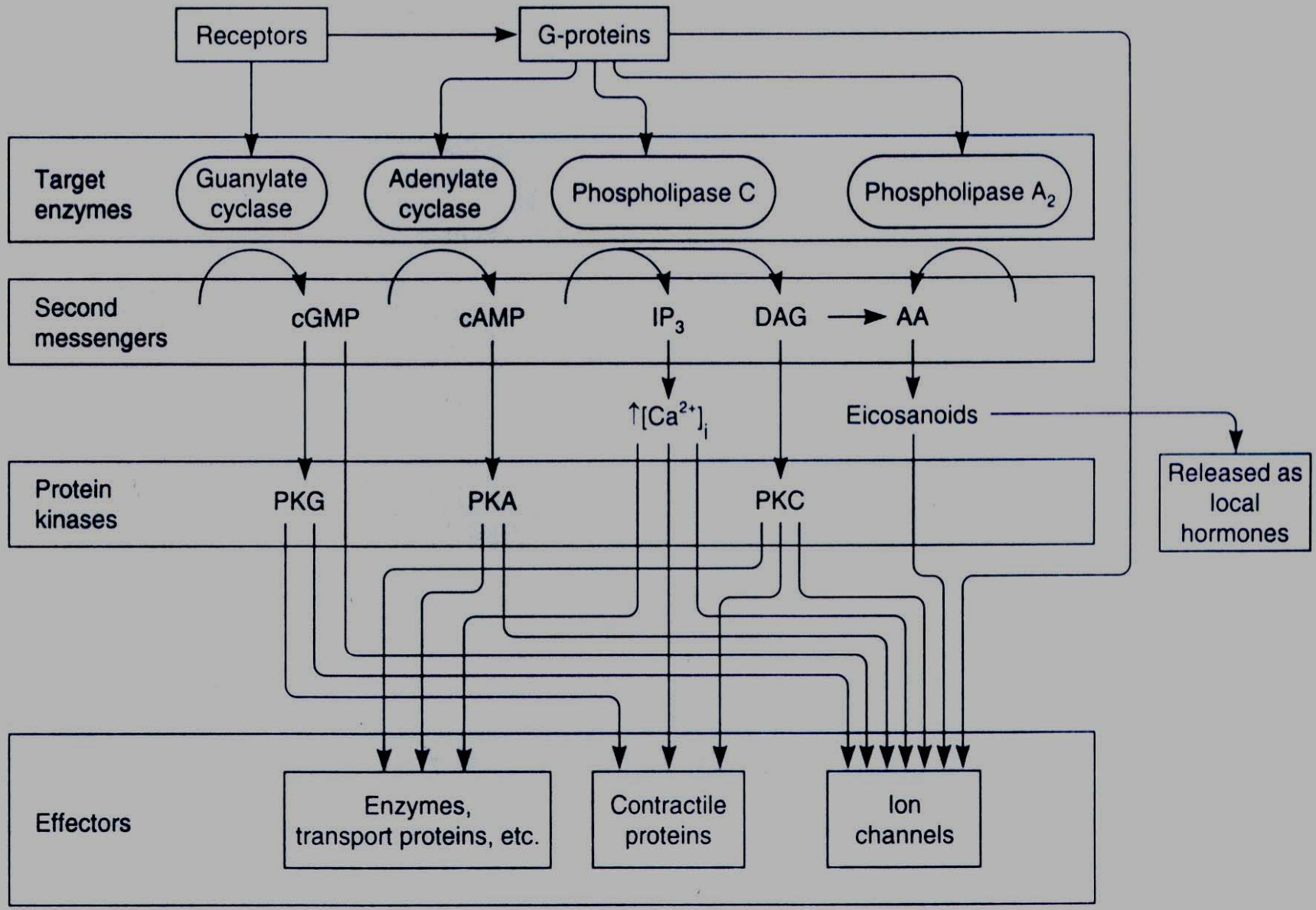
Three second messengers

- Cyclic AMP system (cAMP)
- Cyclic GMP system (cGMP)
- Inositol phosphate system

Cyclic AMP system (cAMP)

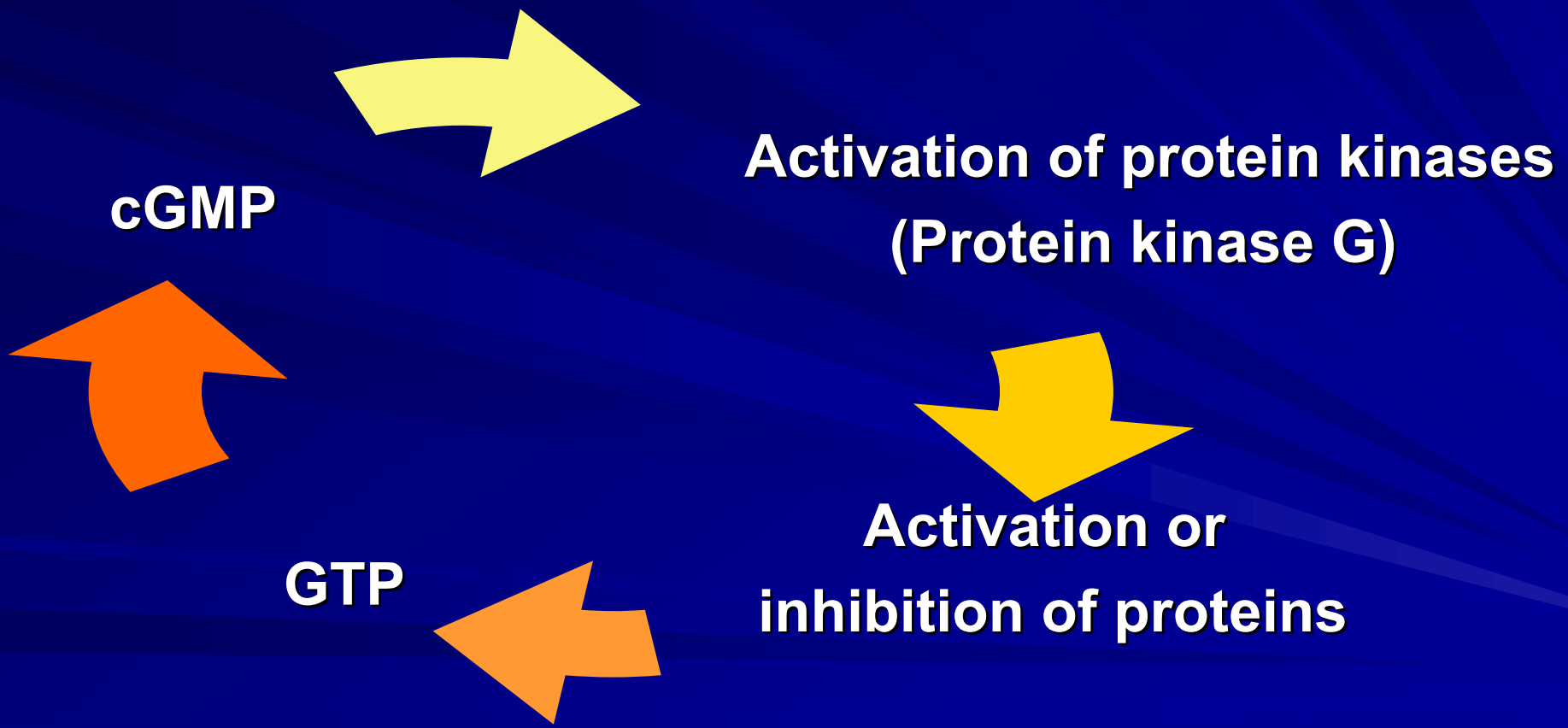
cAMP, Adenyl cyclase enzyme , ATP




Receptors
G-proteins
Target enzymes
Guanylate cyclase
Adenylate cyclase
Phospholipase C
Phospholipase A2
Second messengers
cGMP
cAMP
IP3
DAG
AA
↑[Ca2+]i
Eicosanoids
Released as local hormones
Protein kinases
PKG
PKA
PKC
Effectors
Enzymes, transport proteins, etc.
Contractile proteins
Ion channels

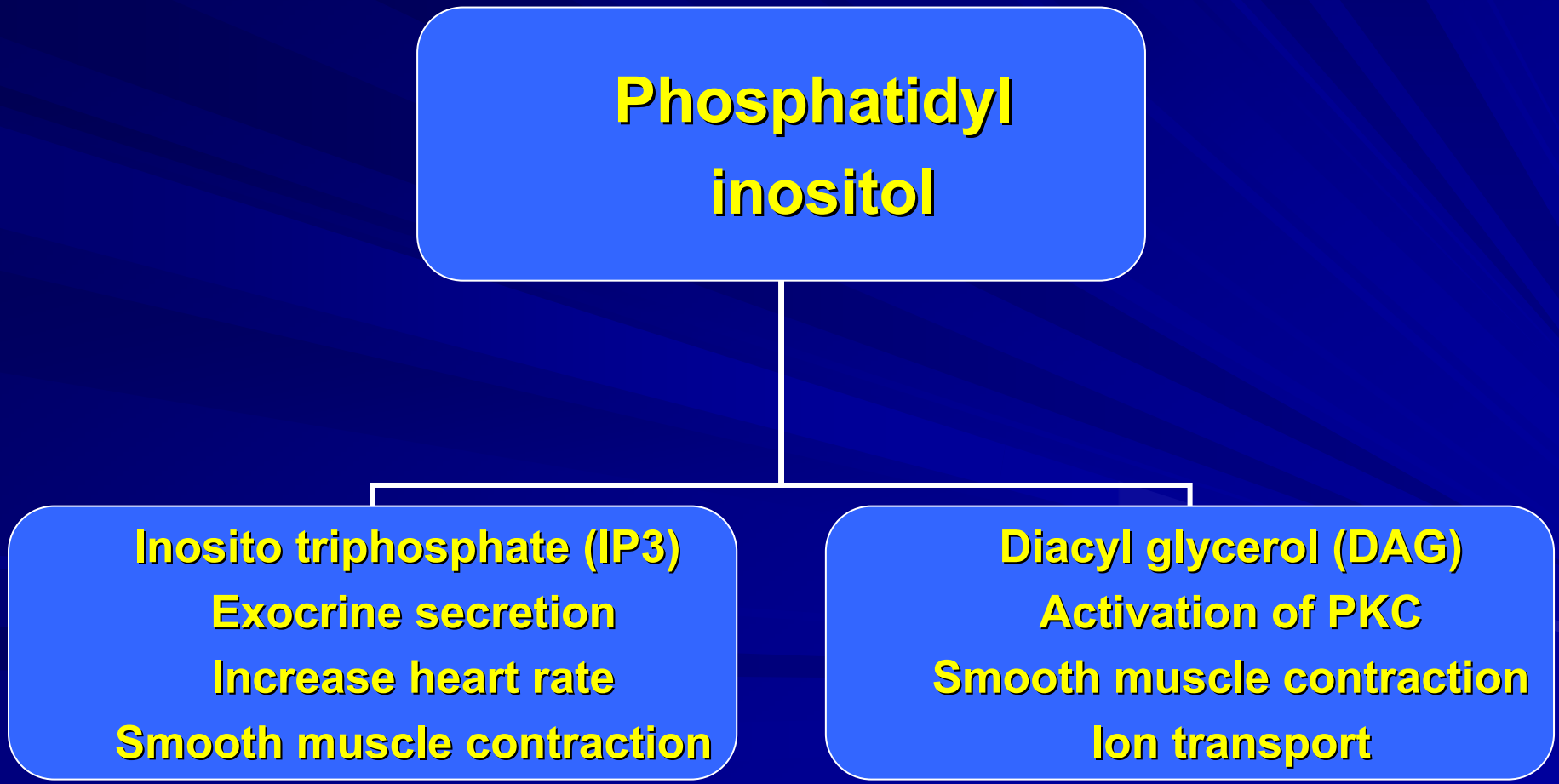
Cyclic GMP system (cGMP)

cGMP, Guanyl cyclase enzyme , ATP



Inositol phosphate system

phospholipase C, phosphatidyl inositol, IP3 , diacyl glycerol (DAG)



Type III (Tyrosine Kinase-Linked receptors)

1. Located at cell membrane
2. Involved in response to metabolic signals and growth regulation.
3. Response occurs in minutes.
4. Activation of receptors result in phosphorylation of tyrosine residue and activation of many pathways in cell.
5. Insulin receptors

Type IV (Receptors linked to gene transcription or Nuclear receptors)

1. Located at nucleus (Intracellularly)
2. Directly related to DNA.
3. Response occurs in hours or days and persist longer.
4. Activation of receptors either increase or decrease protein synthesis
5. Corticosteroids, Estrogen receptors

How drugs combine with their targets?

Binding Forces

Non Covalent bonds (reversible, weak)

1) Ionic bond (electrostatic attraction)
2) Hydrogen bond (between two electronegative groups)
3) Van-Dar-Waal (attractive forces between two neutral atoms) weakest

Covalent bonds (irreversible, strong)

Sharing of pairs of electrons between two bonded atoms (C=C)

Drug –receptor interaction

Drug binds to receptor and activates the receptor so produce a response (agonist)

or

binds to receptor but produces no action (antagonist).

- **Affinity**

  Ability of a drug to combine with the receptor.

- **Efficacy (Intrinsic Activity)**
  - Capacity of a drug to activate receptor and produce action.
  - is the ability of the drug to produce maximum response **(E max).**

- **Agonist**

  is a drug that combines with receptor and produce a response (has affinity and efficacy).

- **Antagonist**

  is a drug that combines with a receptor without producing responses. It blocks the action of the agonist (Has affinity but no or zero efficacy). It has structural similarity to agonist.

Types of agonists

- Full agonist.
- Partial agonist.
- Inverse agonist

Full Agonist

- A drug that combines with its specific receptor to produce maximal effect .
- It Has both high affinity & full efficacy.

Partial Agonist

- A drug that combines with its specific receptor to produce submaximal effect regardless of concentration (Full receptor occupancy).

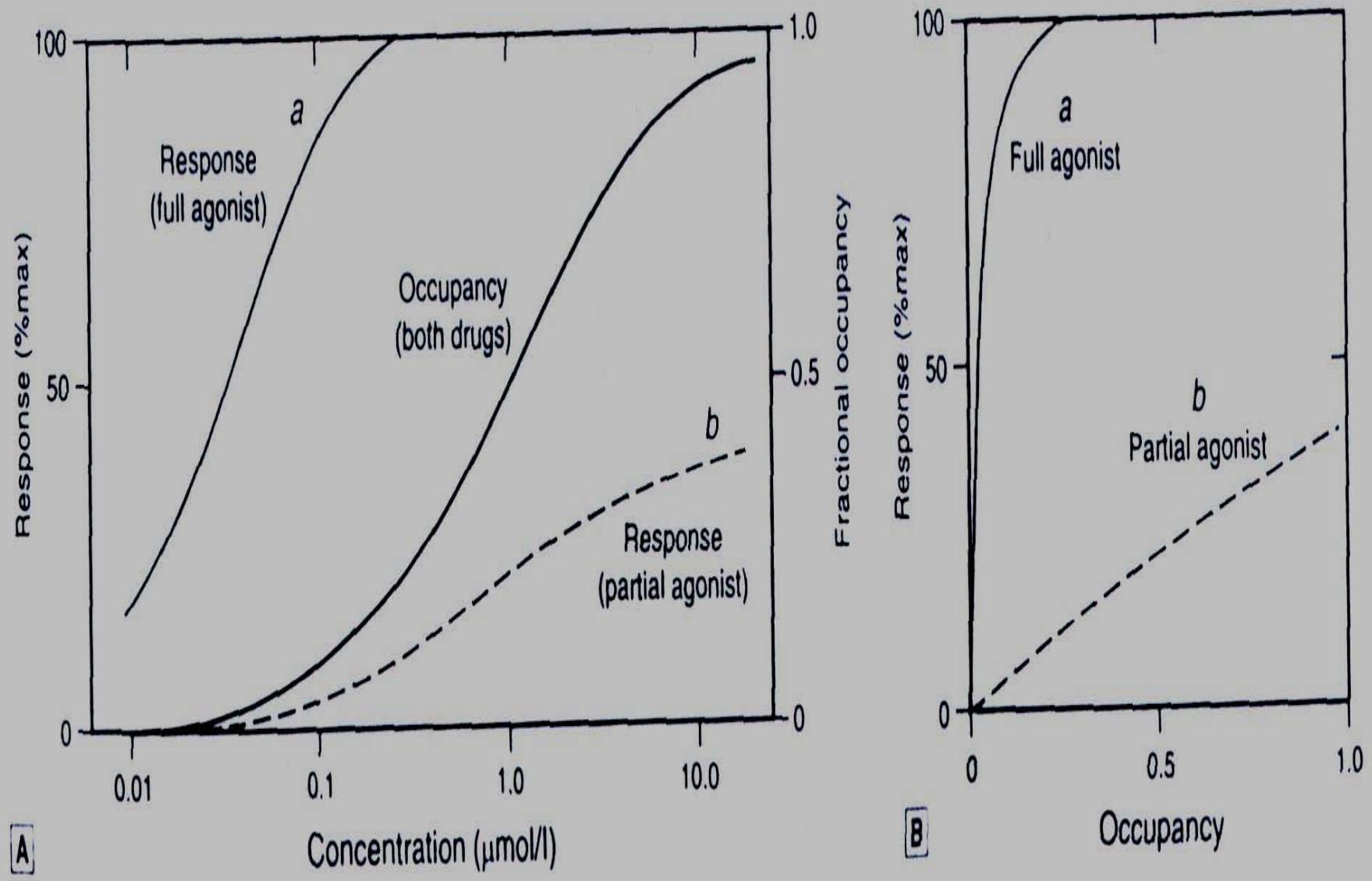
- It has high affinity & partial efficacy.

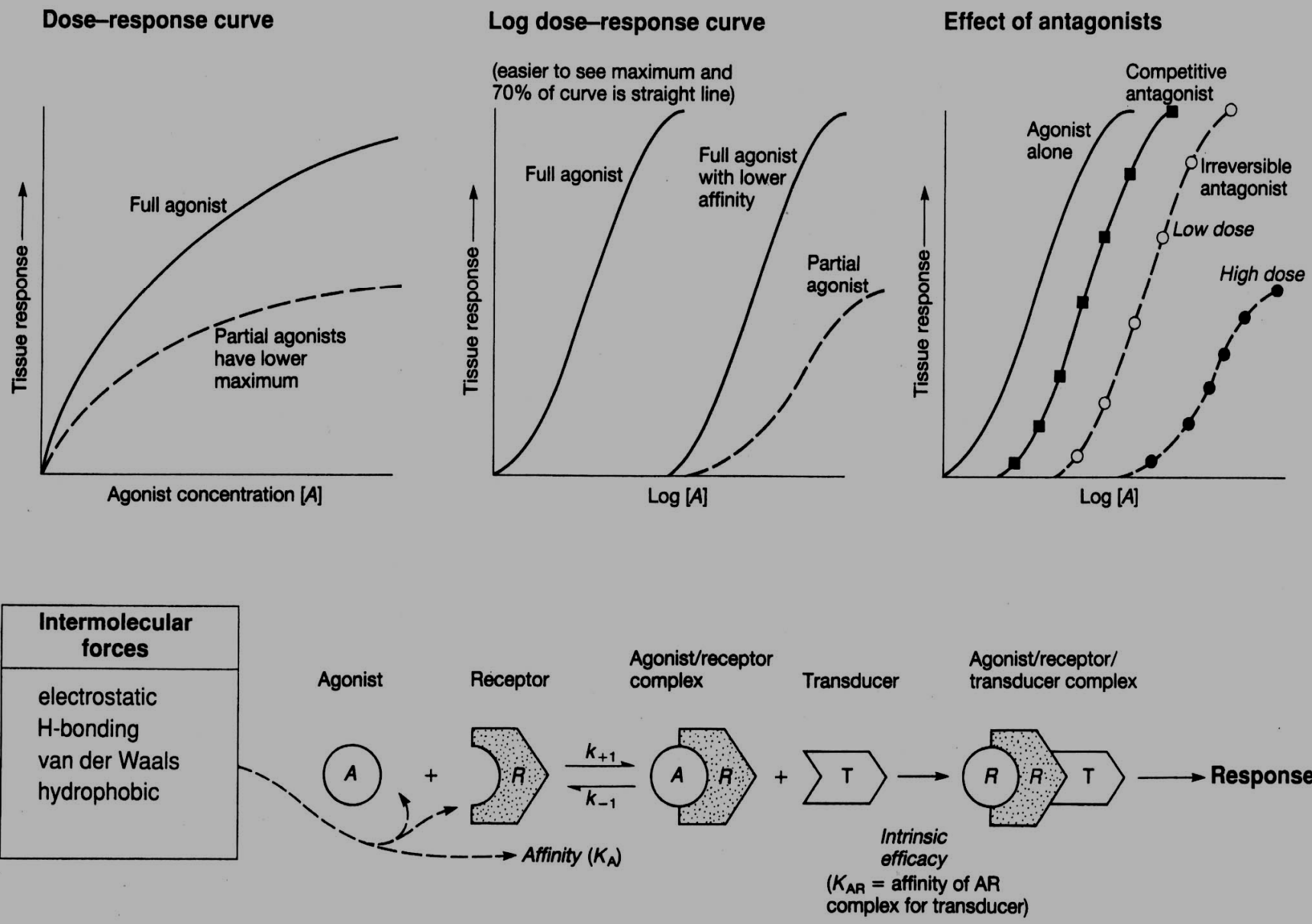
Inverse Agonist

- combines with its receptor & produce response opposite to those of the agonist
- It has high affinity & negative efficacy.

Example: B-carboline

(benzodiazepine receptor).


100
50
0
1.0
0.5
0
Response (%max)
Fractional occupancy
a
Response
(full agonist)
Occupancy
(both drugs)
b
Response
(partial agonist)
0.01
0.1
1.0
10.0
Concentration (μmol/l)
A
100
50
0
a
Full agonist
b
Partial agonist
Response (%max)
0
0.5
1.0
Occupancy
B


Dose–response curve
Tissue response
Full agonist
Partial agonists have lower maximum
Agonist concentration [A]
Log dose–response curve
(easier to see maximum and 70% of curve is straight line)
Tissue response
Full agonist
Full agonist with lower affinity
Partial agonist
Log [A]
Effect of antagonists
Tissue response
Competitive antagonist
Agonist alone
Irreversible antagonist
Low dose
High dose
Log [A]
Intermolecular forces
electrostatic
H-bonding
van der Waals
hydrophobic
Agonist
Receptor
Agonist/receptor complex
Transducer
Agonist/receptor/ transducer complex
A
+
R
k+1
k−1
A R
+
T
R R T
Response
Affinity (KA)
Intrinsic efficacy
(KAR = affinity of AR complex for transducer)