RAJA NARENDRALAL KHAN WOMEN'S COLLEGE (AUTONOMOUS)

HUMAN PHYSIOLOGY

PG 2ND SEMESTER

Molecular pharmacology & Chronobiology

Paper-PHY-203/UNIT-18/Module-IV

&

PHY-202/UNIT-16-Module-IV

Name of the Teacher-

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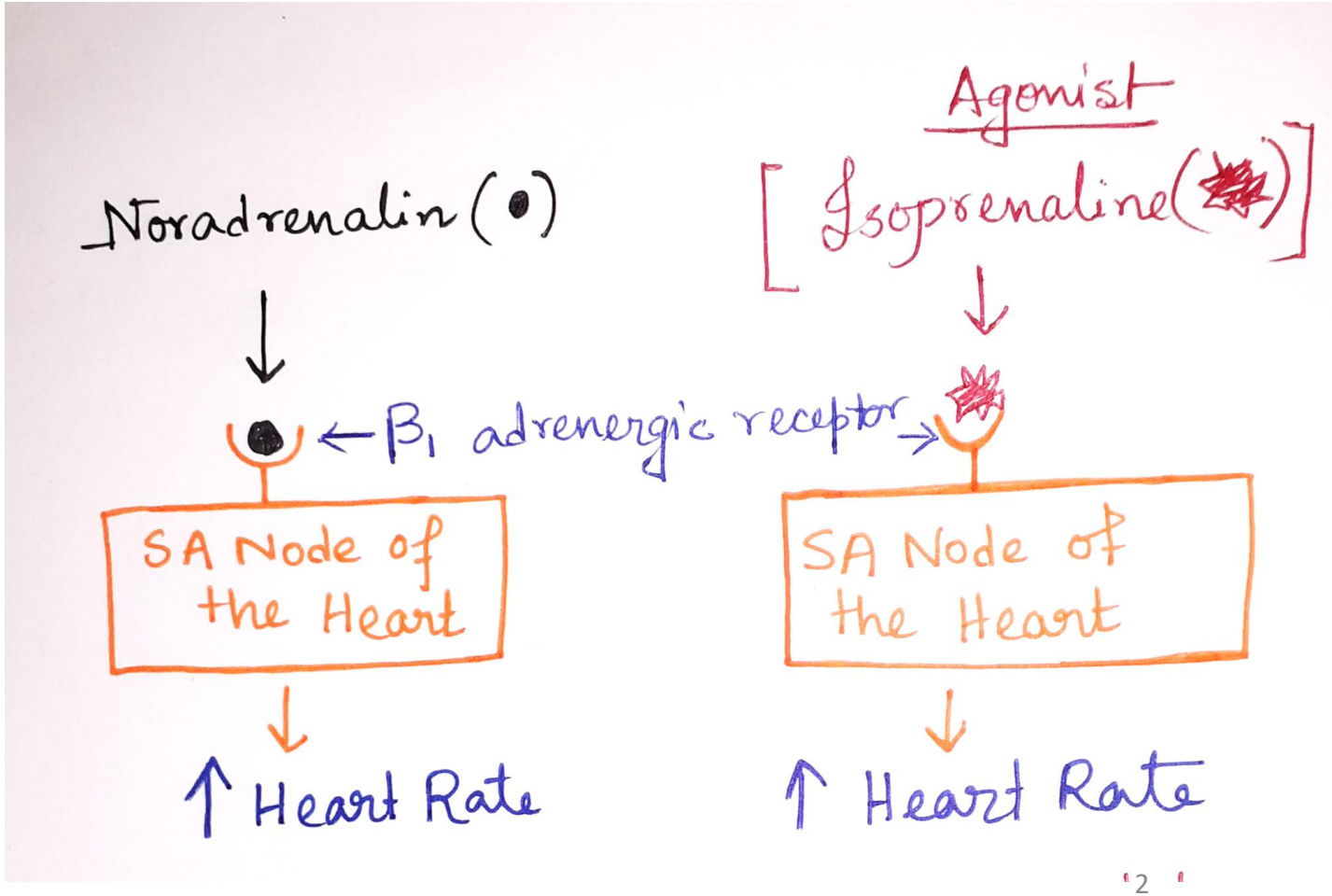
Agonist

An agent which activates a receptor to produce an effect similar to that of the physiological signal molecule.

Types:

- *Inverse agonist* An agent which activates a receptor to produce an effect in the opposite direction to that of the agonist.

- *Partial agonist* An agent which activates a receptor to produce submaximal effect bu antagonizes the action of a full agonist.



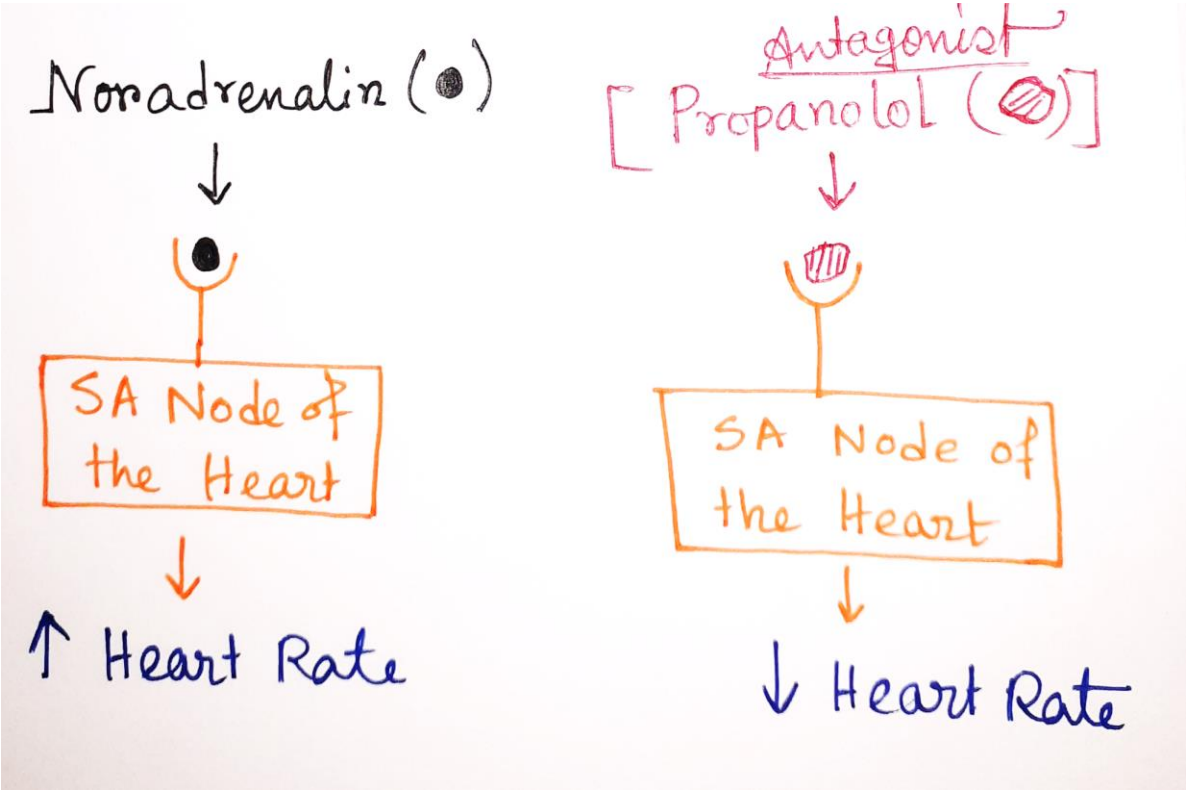
Antagonist:

- An agent which prevents the action of a n agon is t on a receptor or the subsequent response, but does not have any effect of its own.

Types:

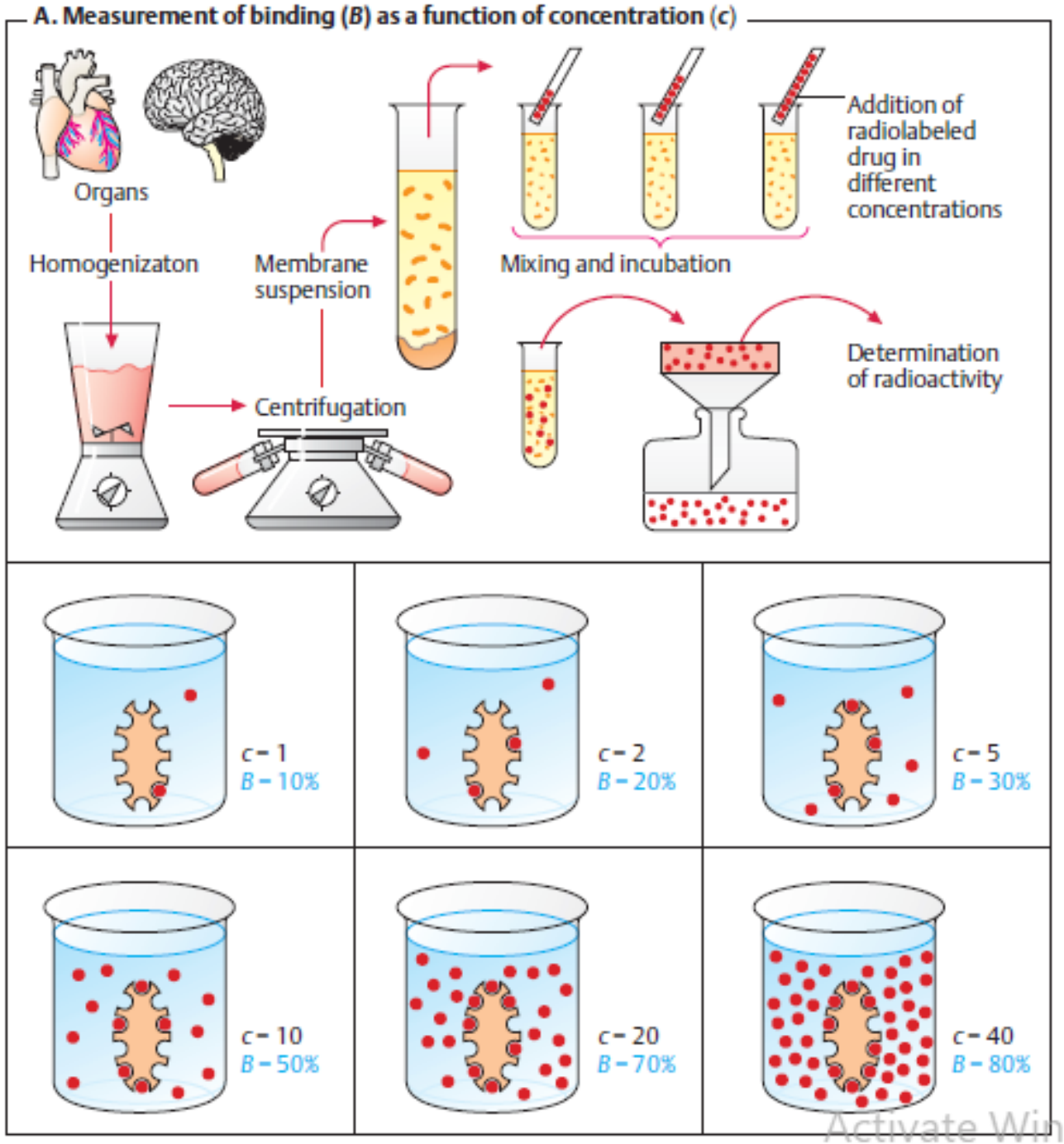
Competitive antagonist: It possesses chemical similarity to the agonist and competes with it for the binding site of the receptor and inhibit normal receptor functions.

Non-Competitive antagonist: It possesses no chemical similarity to the agonist and binds with another binding site of the receptor and inhibit normal receptor functions.



Receptor family	Endogenous agonist(s)	Subtypes	G-protein coupling
5-HT	5-hydroxytryptamine	5-HT_{1A}, 5-HT_{1B},	G_i/G_o
		5-HT_{1D} 5-HT_{1F}	G_i/G_o
		5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}	G_q
		5-HT_4, 5-HT_5, 5-HT_7	G_s
Adenos	Adenosine	A_1, A_3	G_i/G_o
		A_{2A}, A_{2B}	G_s
Adreno	Adrenaline	α_{1A}, α_{1B}, α_{1C}	G_q
	Noradrenaline	α_{2A}, α_{2B}, α_{2C}	G_i/G_q
		β_1, β_2, β_3	G_s
Angiote	Angiotensin II	AT_1	G_q
		AT_2	Unknown[a]
Cannabinoid	Anandamide[b]	CB_1, CB_2	G_i/G_o
Dopam	Dopamine	D1, D5	G_s
		D2, D3, D4	G_i/G_o
$GABA_B$	γ-aminobutyric acid	$GABA_{B1}$, $GABA_{B2}$	G_i/G_o
Glutam	L-glutamate	$mGlu_1$, $mGlu_5$	G_q
(metabotropic)	L-aspartate	$mGlu_2$, $mGlu_3$, $mGlu_4$	G_i/G_o
		$mGlu_6$, $mGlu_7$, $mGlu_8$	G_i/G_o
Histam	Histamine	H_1	G_q
		H_2	G_s
		H_3, H_4	G_i/G_o
Muscar	Acetylcholine	m1, m3, m5	G_q
		m2, m4	G_i/G_o
Opioid	Enkephalins	Delta (δ; DOR)	
	β-endorphin	Kappa (κ; KOP)	All G_i/G_o
	Dynorphins	Mu (μ; MOR)	
Somatostatin	Somatostatin-14	sst_1, sst_2, sst_3,	All G_i/G_o
	Somatostatin-28	sst_4, sst_5	

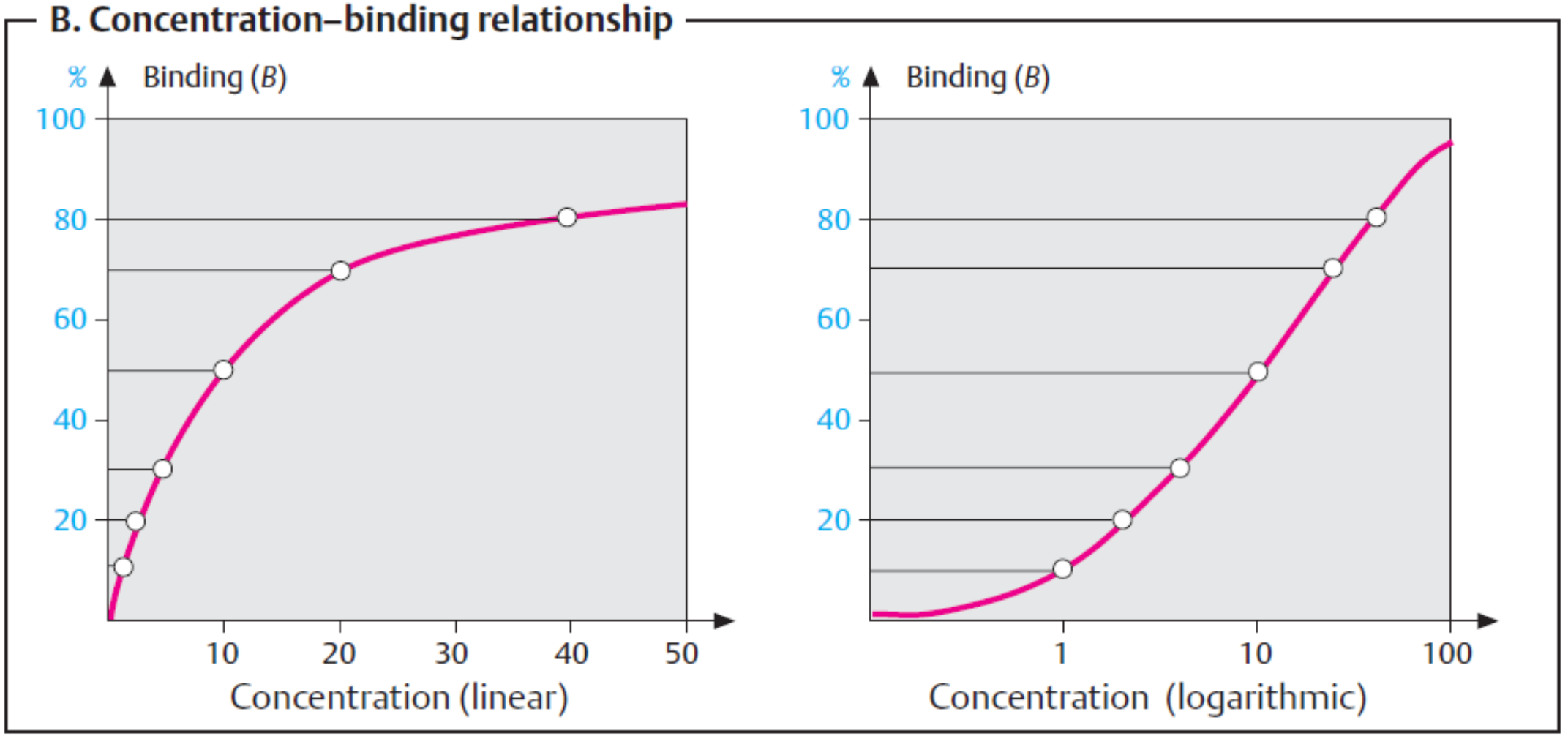
[a]Activates several G-protein independent signalling pathways.
[b]Several other endogenous agonists have also been identified.



In studying the affnity and number of such binding sites, use is made of membrane suspensions of different tissues. This approach is based on the expectation that binding sites will retain their characteristic properties during cell homogenization.

The **law of mass action** describes the hyperbolic relationship between binding (*B*) and ligand concentration (*c*). This relationship is characterized by the drug's af nity ($1/K_D$) and the maximum binding (*B*max), i. e., the total number of binding sites per unit of weight.

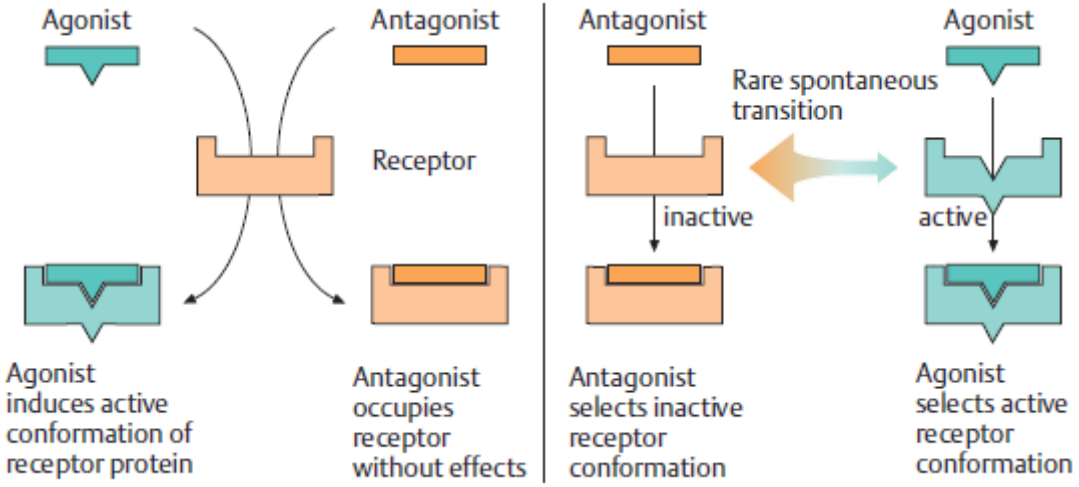
$$B = B_{max} \frac{c}{c + K_D}$$



Models of the Molecular Mechanism of Agonist/Antagonist Action

Agonist induces an active conformation. The *agonist* binds to the inactive receptor and thereby causes the resting conformation to change into the active state. The *antagonist* attaches to the inactive receptor without altering its conformation.

Agonist stabilizes spontaneously occurring active conformation. The receptor may spontaneously "flip" into the active conformation. Usually, however, the statistical probability of such an event is so small that a spontaneous excitation of the cells remains undetectable. Selective binding of the *agonist* can occur only to the active conformation and thus favors the existence of this state. The *antagonist* shows affnity only for the inactive state, promoting existence of the latter. If the system has little spontaneous activity, no measurable effect will result from adding an antagonist. However, if the system displays high spontaneous activity, the antagonist is liable to produce an effect opposite to that of an agonist: *inverse agonist*. A "true" antagonist without intrinsic activity ("neutral antagonist") displays equal af nity for the active and inactive conformations of the receptor and does not interfere with the basal activity of the cell. According to this model, a *partial agonist* has less selectivity for the active state; however, to a certain extent it binds also to the inactive state.



CHRONOBIOLOGY

THE SUPRACHIASMATIC NUCLEI ARE THE SITE OF THE PRIMARY CIRCADIAN PACEMAKER IN MAMMALS:

The mammalian circadian timing system is considerably more complicated than this simple linear scheme, because it is composed of a hierarchy of circadian oscillators (Fig).

At the pinnacle of this oscillatory system is a small brain area, the **suprachiasmatic nuclei (SCN)** of the anterior hypothalamus. The SCN often are called the master circadian clock, because these nuclei (one on each side of the brain) play a key role in coordinating oscillations in other tissues, and in regulating behavior.

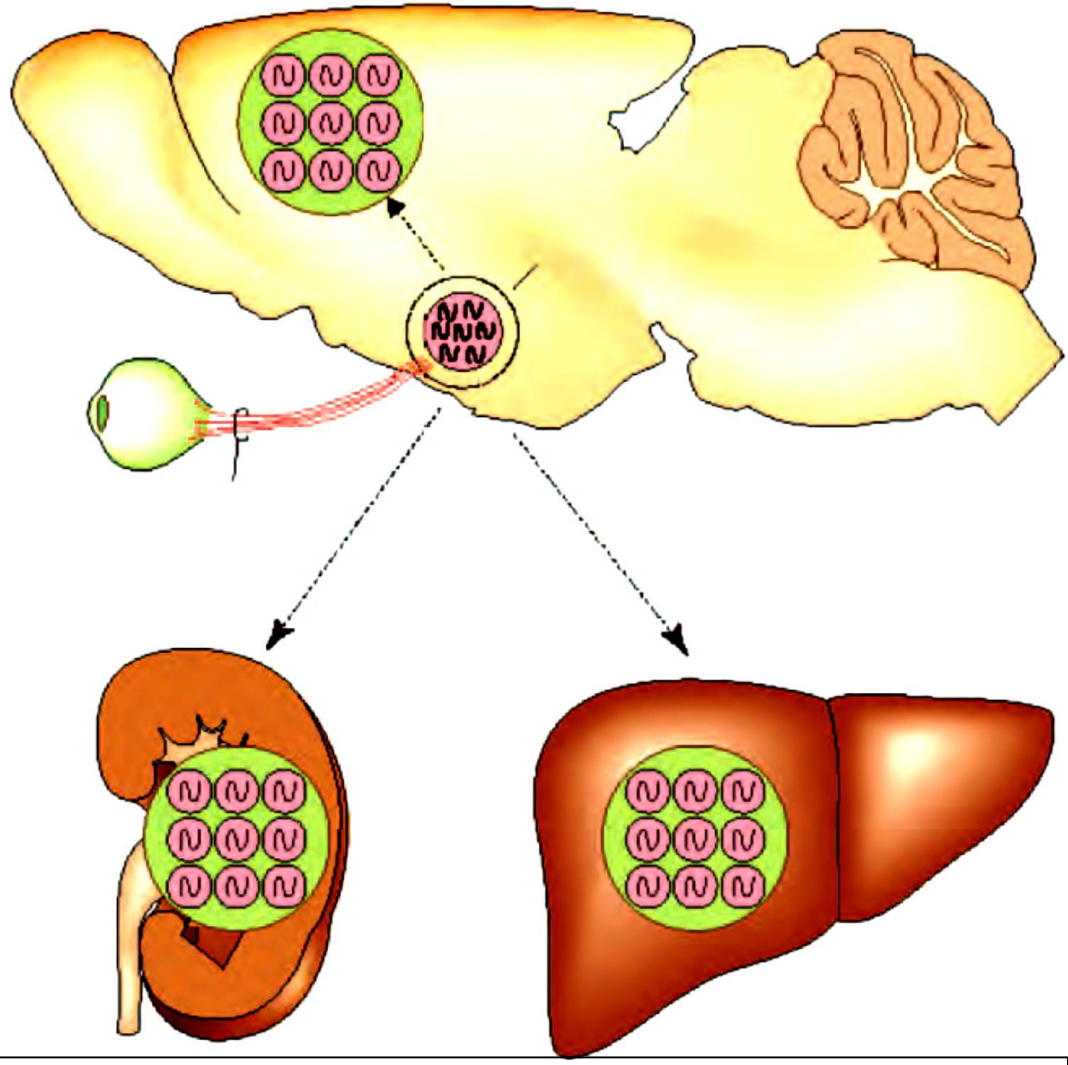


Fig: The mammalian circadian timing system consists of a hierarchy of oscillators. Oscillatory neurons in the SCN interact with each other to produce a set of coherent outputs. These outputs, which include behavioral and physiological rhythms, synchronize cellautonomous oscillations in other brain regions and in peripheral tissues. (From Reppert and Weaver, 2002.)

SCN: Oscillator and Pacemaker

- Lesion studies leading to loss of rhythmicity do not necessarily show that the SCN function as the primary circadian pacemaker. An alternative possibility is that the SCN could be a necessary element on a key output pathway leading to physiological rhythmicity, rather than a pacemaker.

- The presence of rhythms in SCN metabolic activity, electrical activity, and gene expression profiles *in vivo* do not distinguish between these possibilities. Studies demonstrating rhythms in neuropeptide secretion, metabolic activity, and electrical firing rate in SCN tissue maintained *in vitro* do show that the SCN contain a functional oscillator. The SCN do not simply oscillate, however; through their outputs, the SCN regulate rhythms in physiology and behaviour, and thus serve as a circadian pacemaker.

- This pacemaker role of the SCN is revealed most clearly by studies showing that locomotor activity rhythms can be restored in hamsters by transplanting foetal SCN tissue into the hypothalamus of animals previously made arrhythmic by SCN lesion. Furthermore, transplants between hamsters with different circadian periods reveal that the cycle length (period) of restored rhythmicity is dictated by the genotype of the SCN tissue donor and not by the recipient.

- Thus, the SCN serve as a pacemaker that communicates rhythmicity to tissues regulating behavioural rhythms.

PROBABLE QUESTIONS:

1. How SCN act as a pacemaker to regulate behavioural rhythm?

2. Differentiate agonism and antagonism.

3. Schematically describe the cell membrane fragmentation experiment used to study affinity and concentration relation of drug receptor.