

# Neuromodulators

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# Dopamine

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# Norepinephrine

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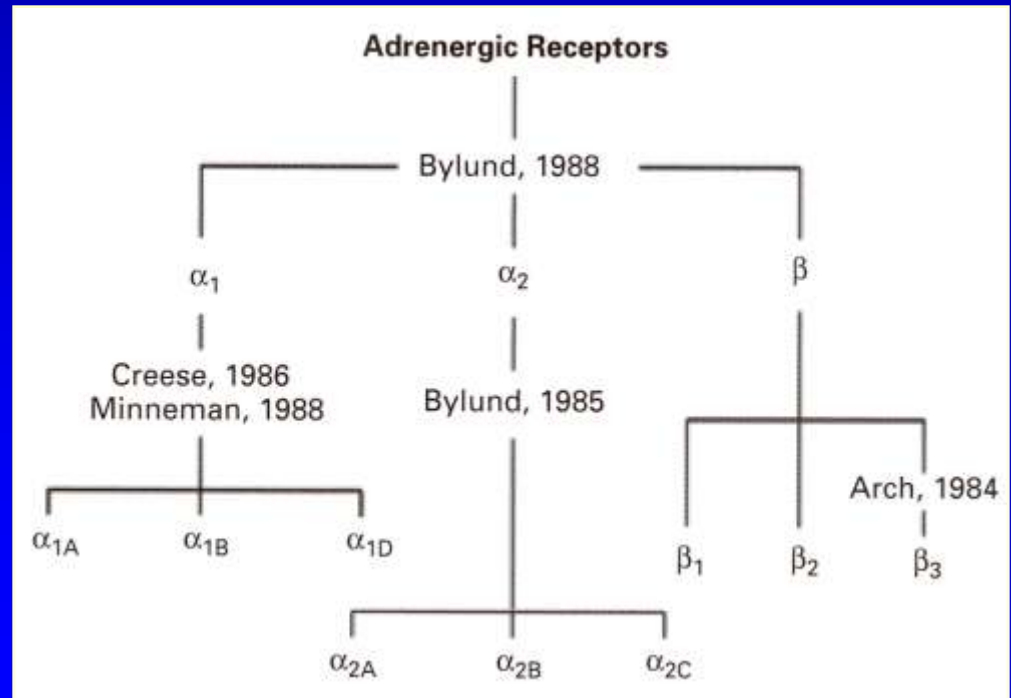
# Norepinephrine receptors

- $\alpha$  family
- B family

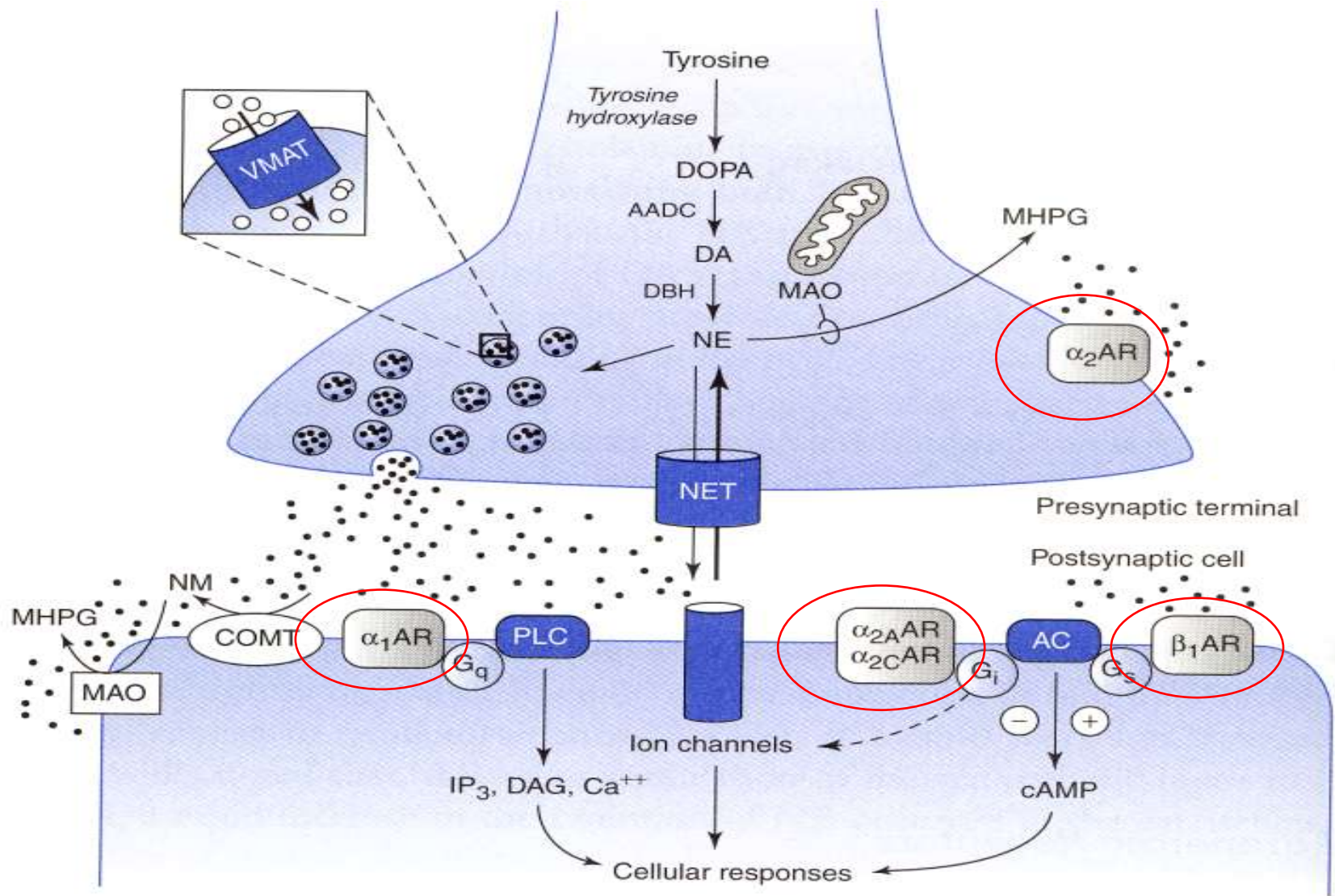
# Norepinephrine receptors

- $\alpha$  family
- $\beta$  family

## Current Nomenclature of Adrenergic Receptor Subtypes



# Subtype Differentiation

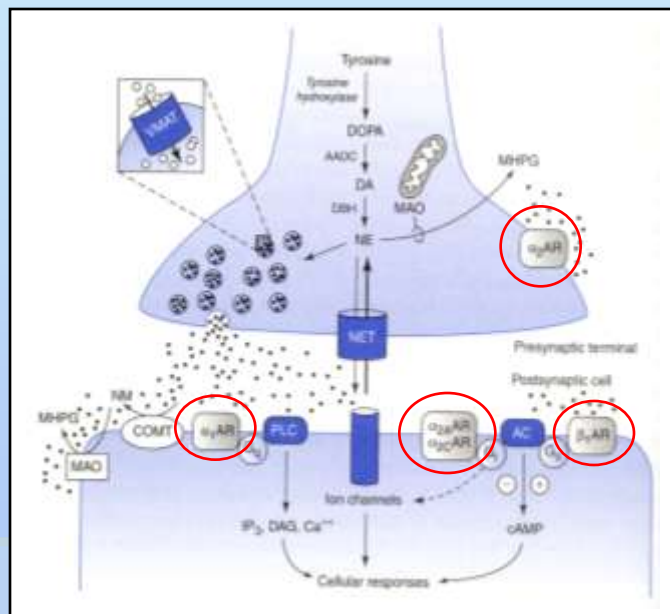


# Subtype Differentiation

**β1-** The dominant receptor in heart and adipose tissue equally sensitive to epinephrine and norepinephrine.

**β2-** Responsible for relaxation of vascular, uterine, and airway smooth muscle. Less sensitive to NE as compared to E.

**β3-** Insensitive to commonly used β-adrenergic receptor antagonists. Previously referred to as the “atypical” β-adrenergic receptor.

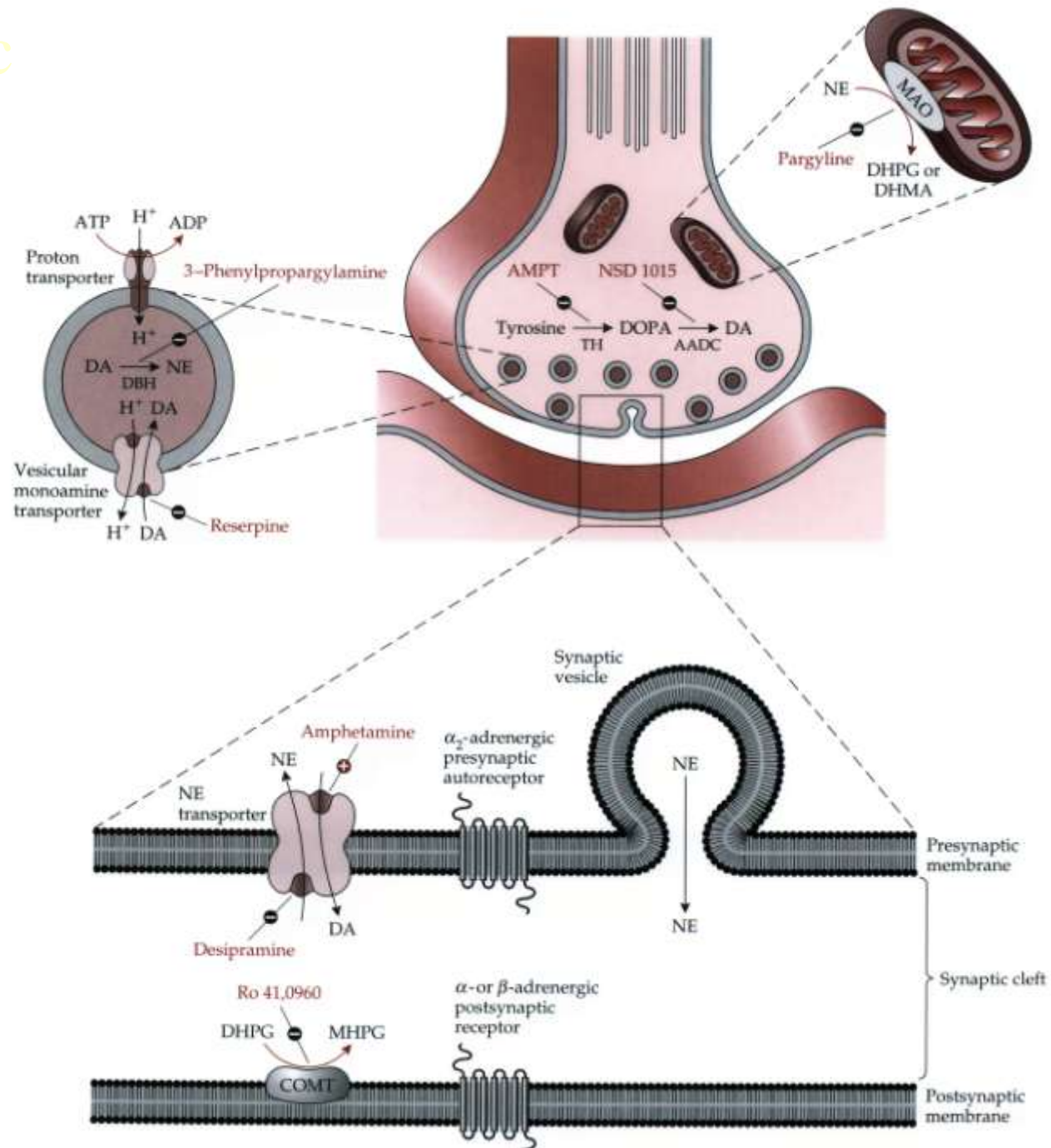


(The Biochemical Basis of Neuropharmacology, 2003)

**α1-** Postsynaptic. 1A and 1B subtypes defined by their differential affinity for agents such as WB4101 & phentolamine. No 1C subtype.

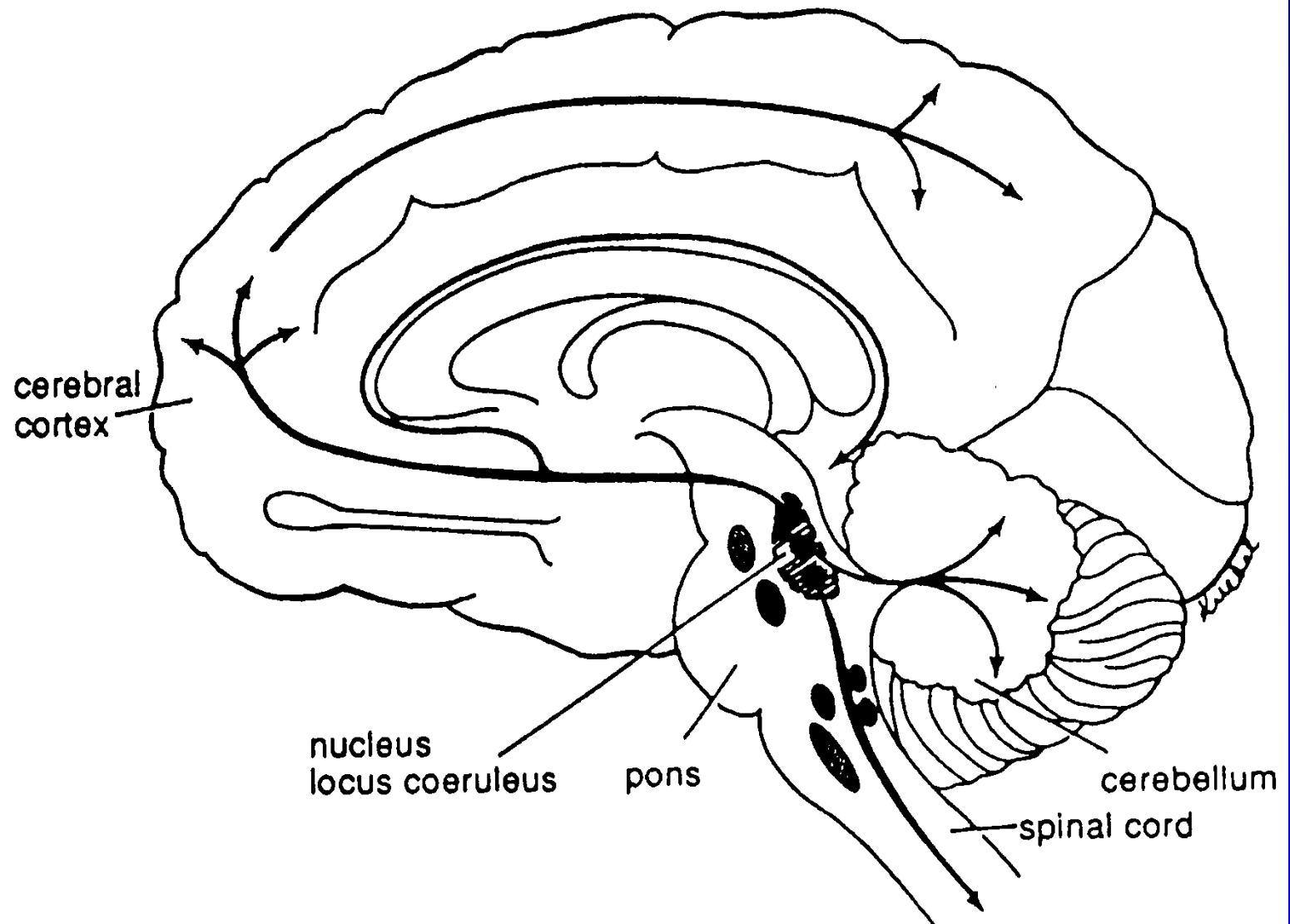
**α2-** Postsynaptic & **presynaptic**. First thought to be exclusively presynaptic. 2A & 2B subtypes differentiated by their affinity for agents such as prazosin & oxymetazoline.

# Noradrenergic (NE) synapse





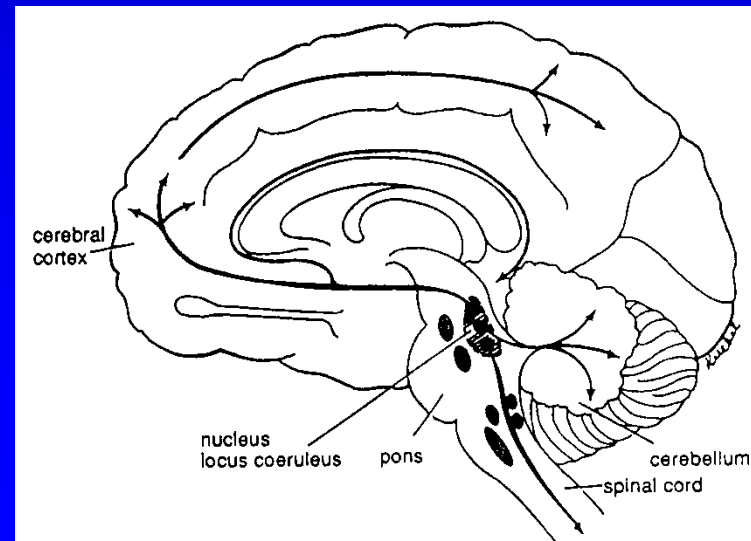
# Norepinephrine Pathway



# Norepinephrine Pathway

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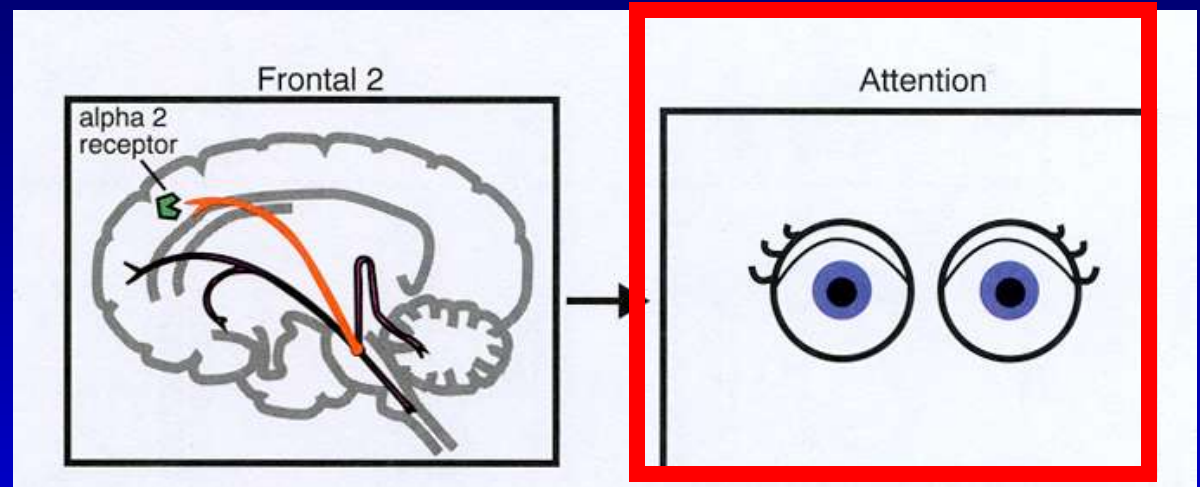
- LC noradrenergic system is highly responsive external stimuli → attention
- Learning/memory and sleep/wake cycle
- Anxiety and stress response
- In FRONTAL CORTEX:
  - Mood regulation → Hypofunction of pathway → Depression



# NE: Locus Ceruleus → FRONTAL CTX

$\alpha 2$  postsynaptic receptor  
In FRONTAL CORTEX:

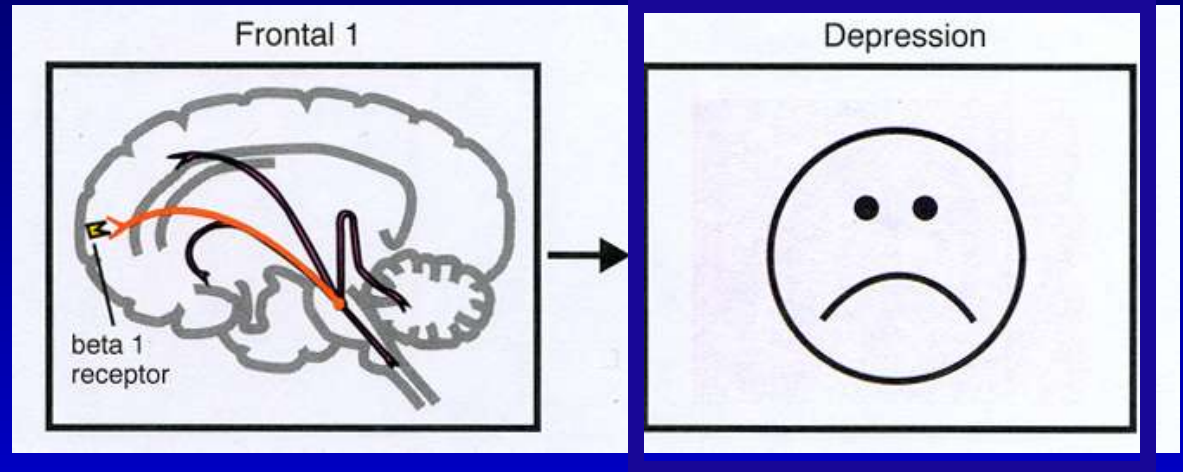
- **Attention**, working memory, information processing.





# NE: Locus Ceruleus → FRONTAL CTX

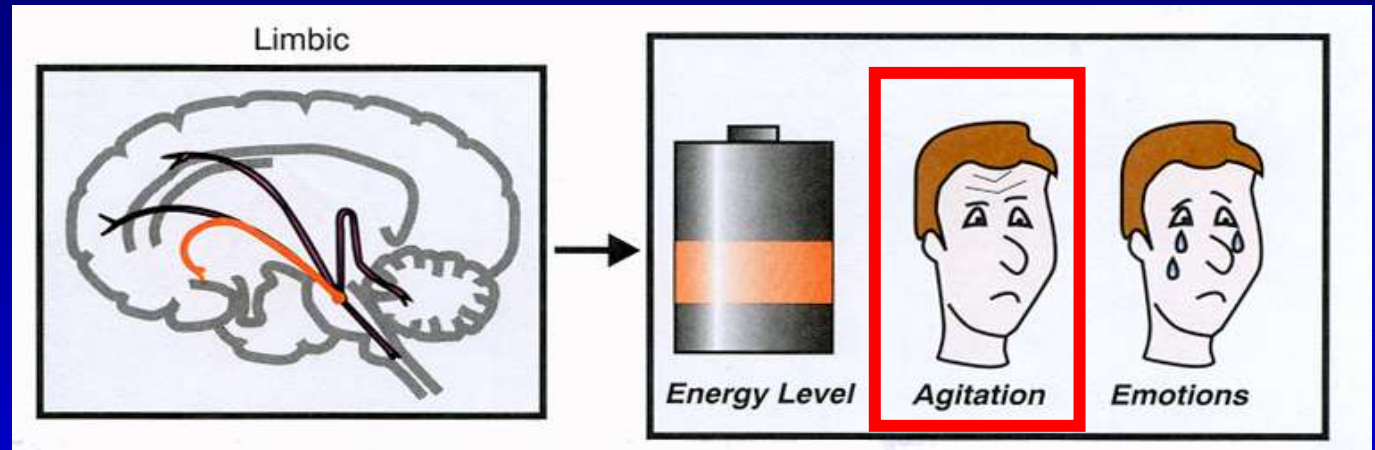
$\beta 1$  postsynaptic receptor  
In FRONTAL CORTEX:

- Mood regulation.
- **Hypofunction** of pathway:
  - Depression



# NE: Locus Ceruleus → LIMBIC CTX

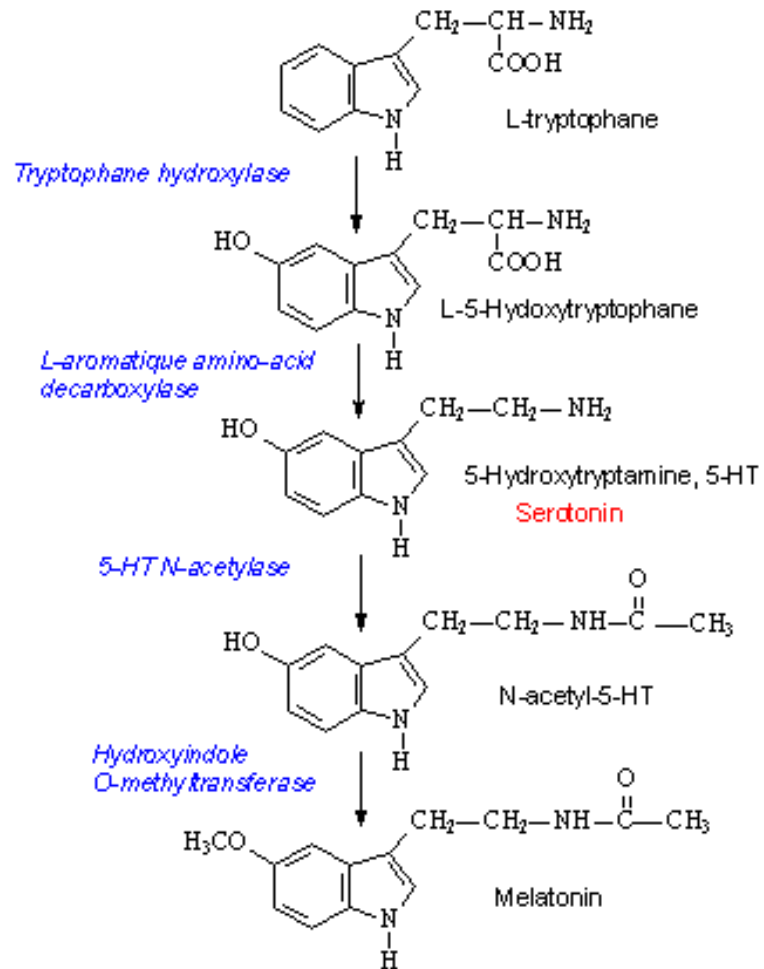
- Emotions
- Energy level
-  **Psychomotor agitation**
-  **Psychomotor retardation**



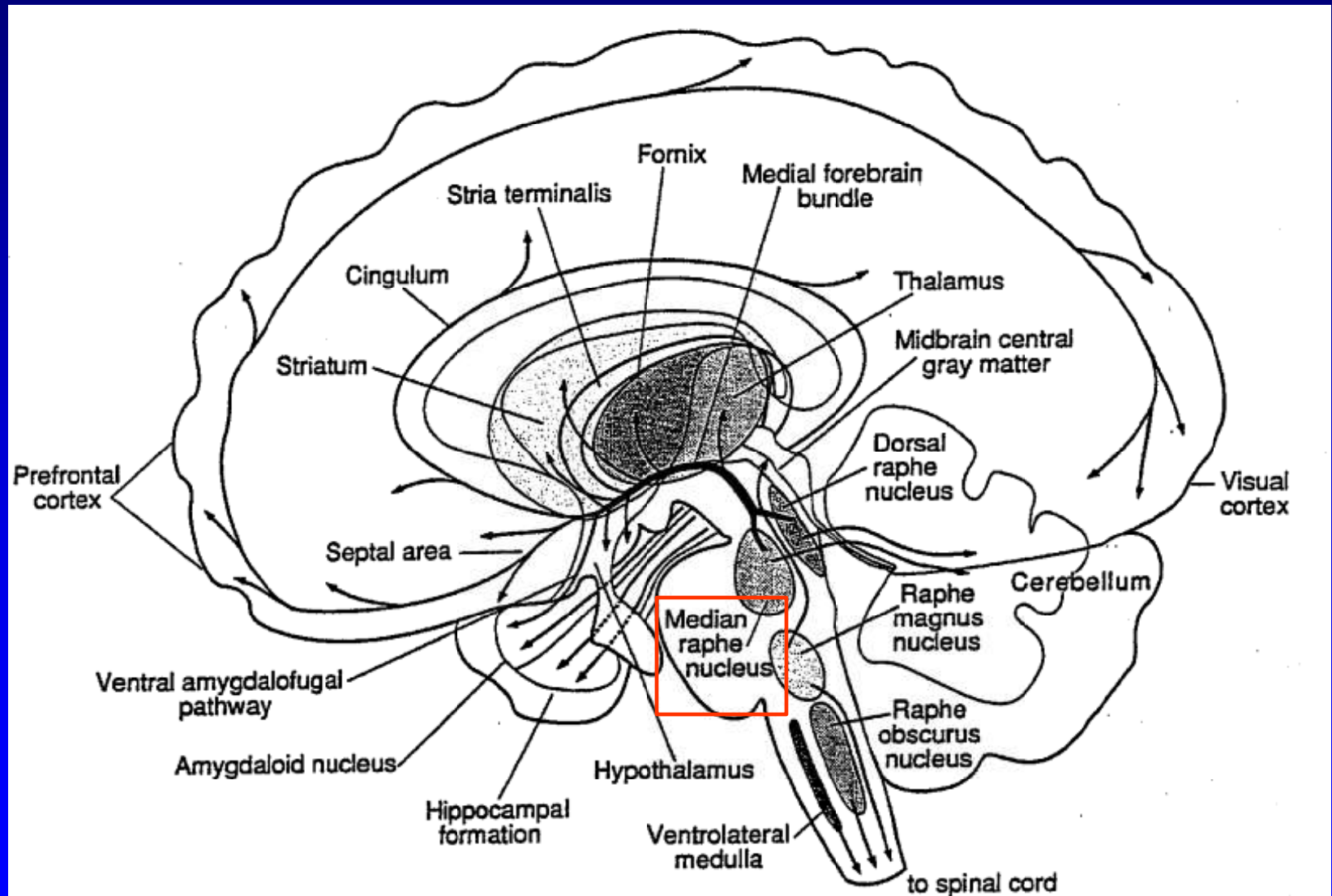
# Serotonin

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# Serotonin synthesis

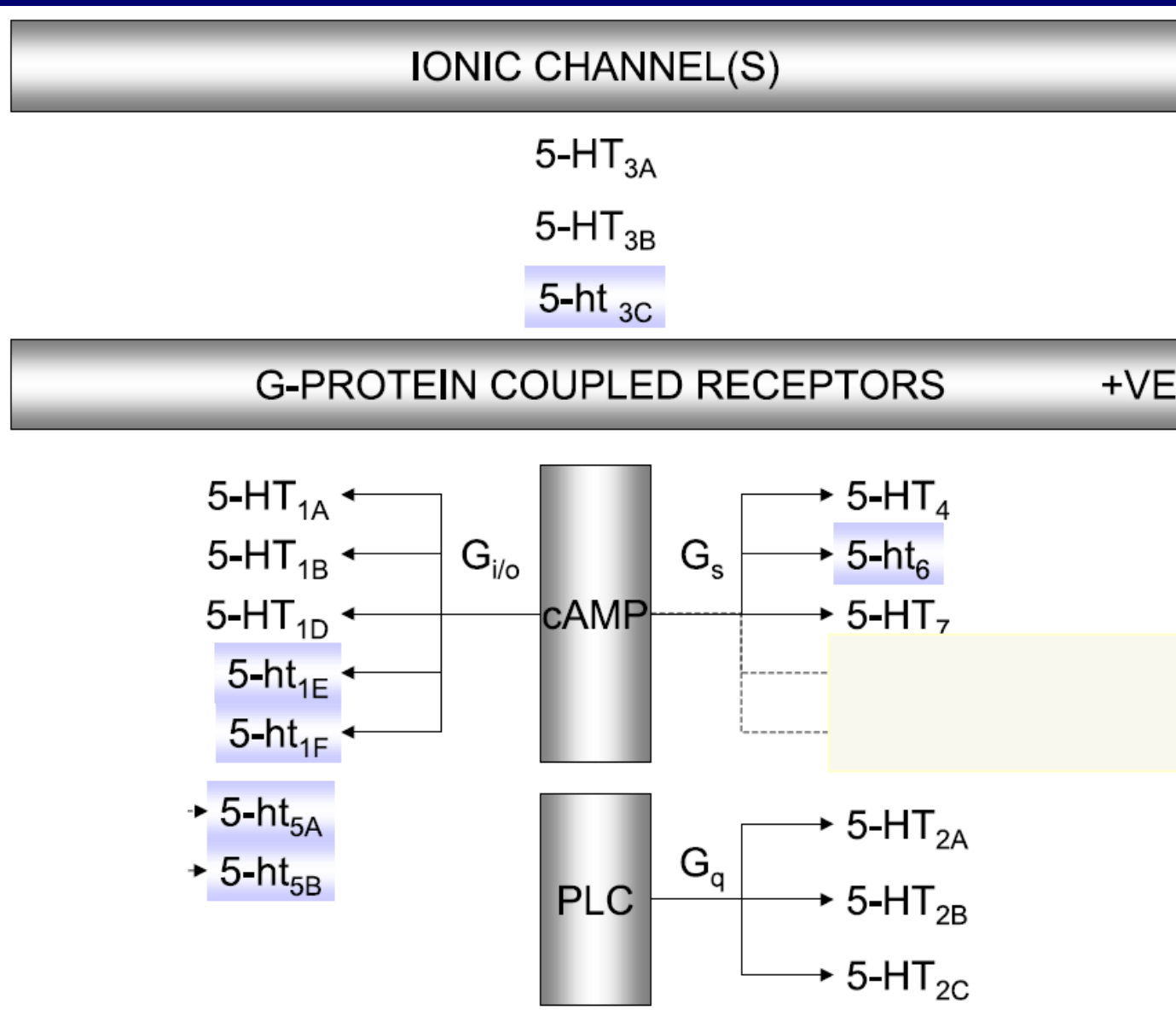


# Serotonin Pathway

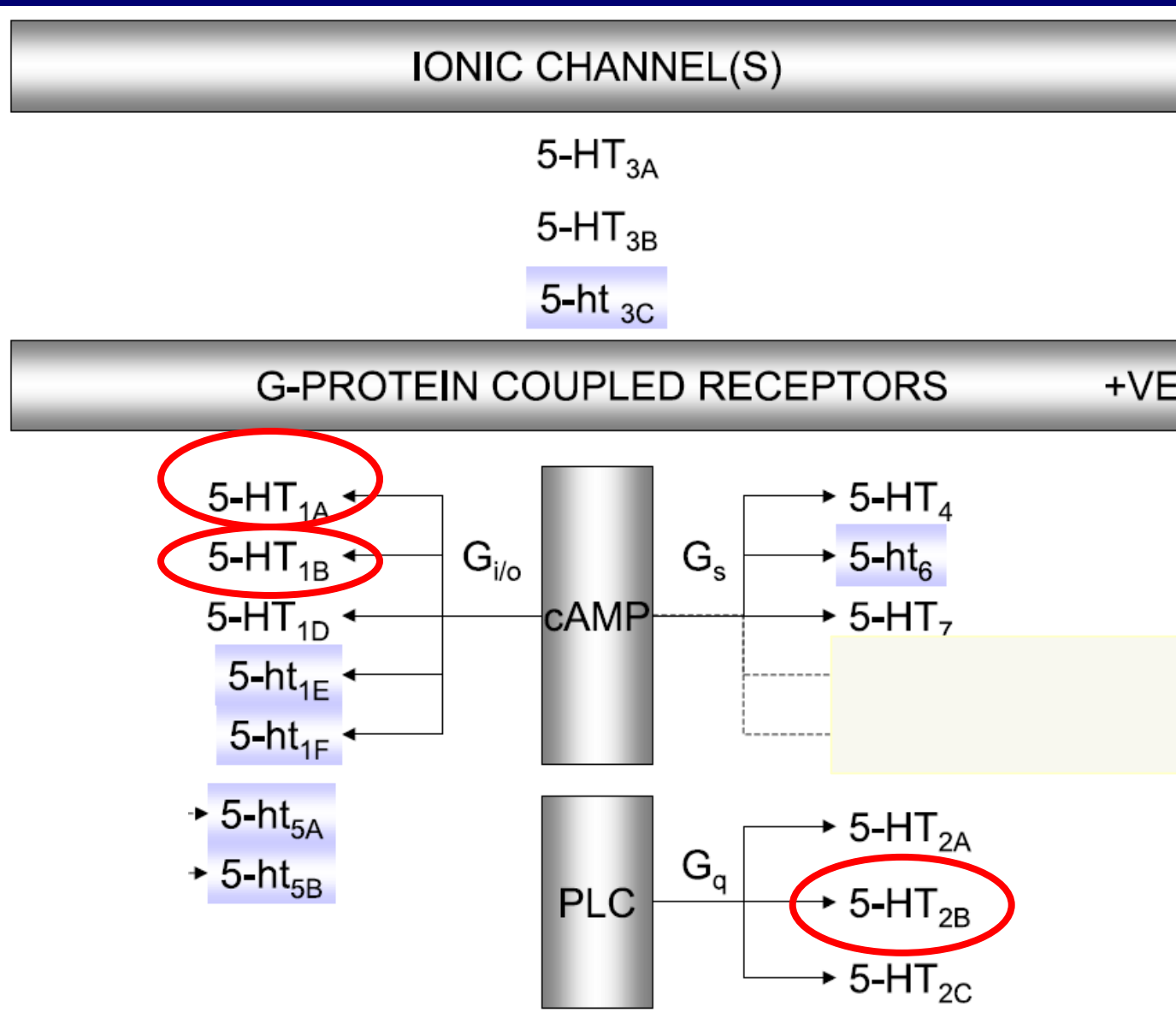




# Serotonin Receptors



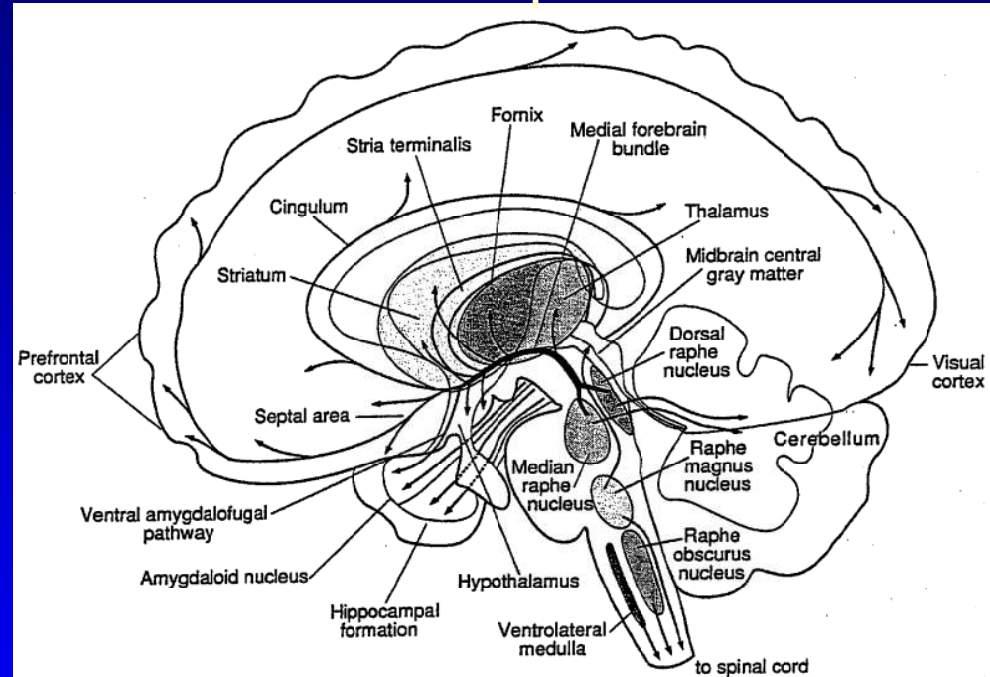
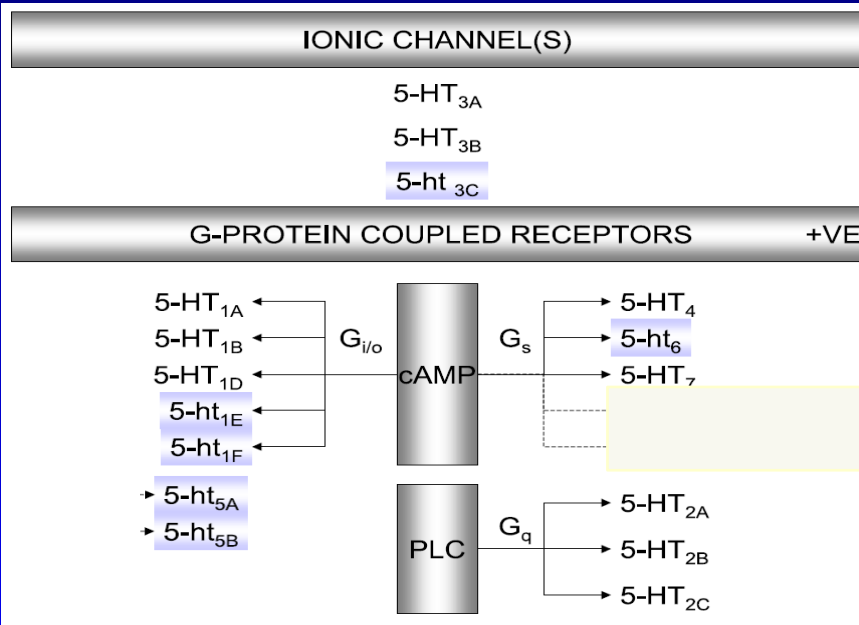
# Serotonin Receptors



# Serotonin Pathway

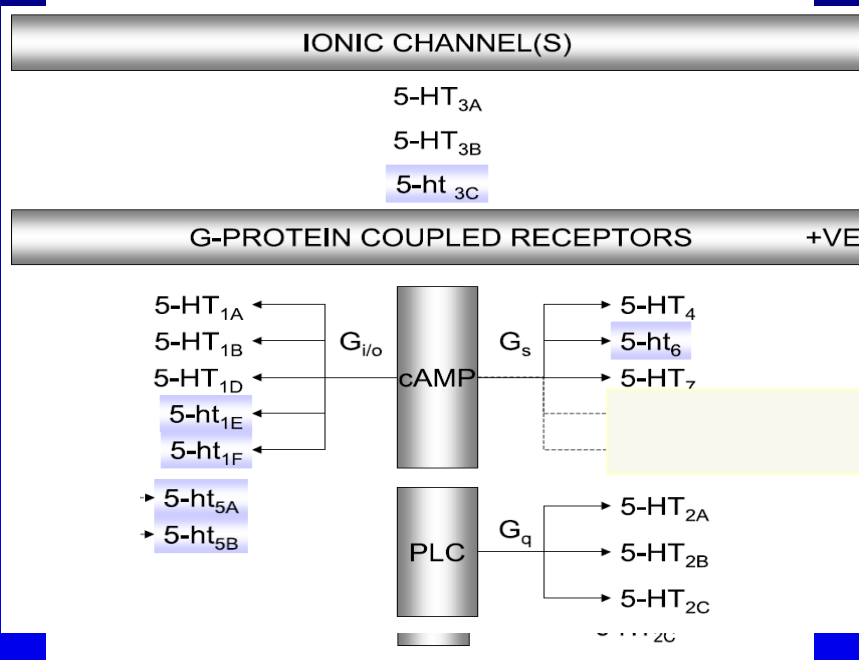
Almost 17 type of receptor

Wide spread

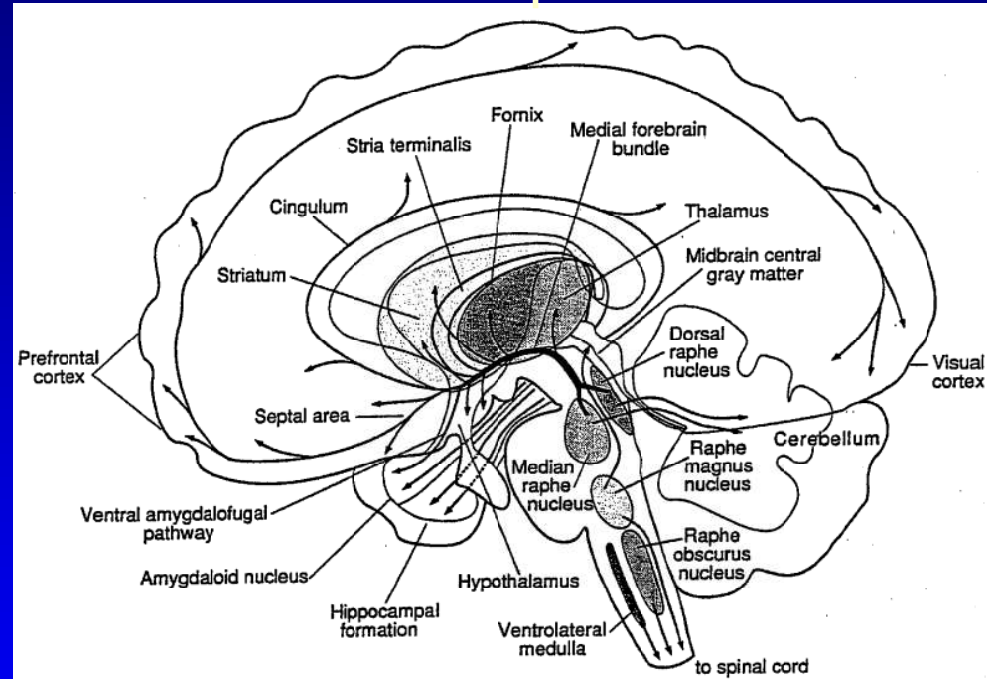


# Serotonin Pathway

Almost 17 type of receptor



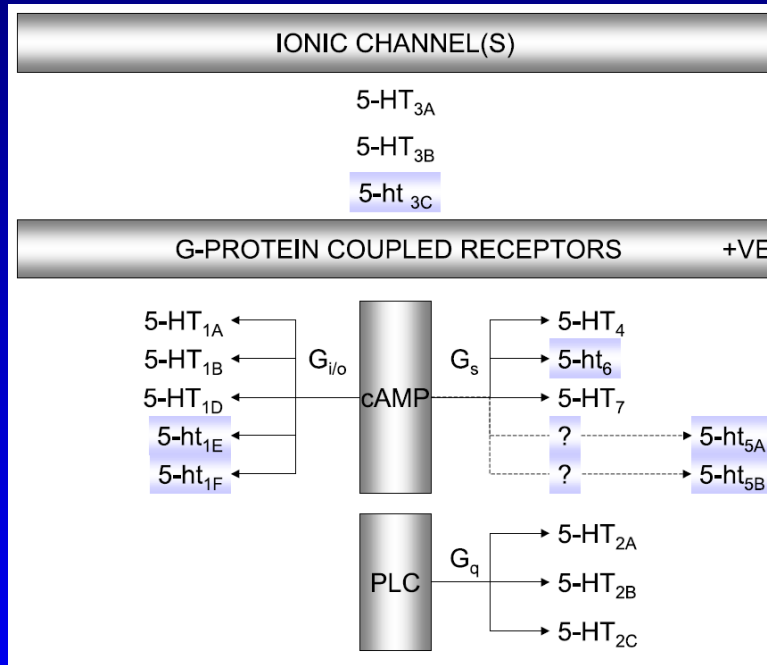
Wide spread



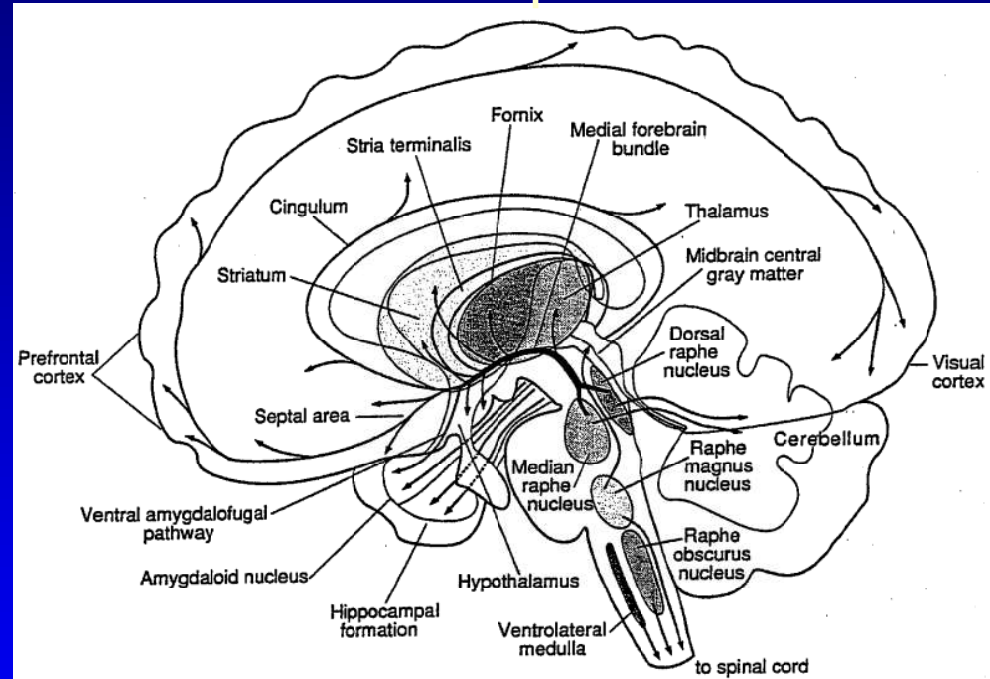
mood, sleep, sexuality, impulsivity, aggression, stress, drug abuse

# Serotonin Pathway

Almost 17 type of receptor



Wide spread



Serotonin system *dysfunction* involve in :  
Depression, Schizophrenia,  
OCD, Eating Disorders, Autism

## Antipsychotics

Clozapine  
Risperidone  
Olanzapine



Potent antagonist actions at  
5-HT<sub>2A</sub> receptors, in addition  
to D<sub>2</sub> antagonism

## Anxiolytics

Buspirone  
Gepirone



Partial 5-HT<sub>1A</sub> agonists  
Effective for treating GAD, OCD

## Antiemetics

Ondansetron  
Granisetron



5-HT<sub>3</sub> antagonist used for  
Minimizing chemotherapy-  
induce nausea

## Anti-migraine

Sumatriptan



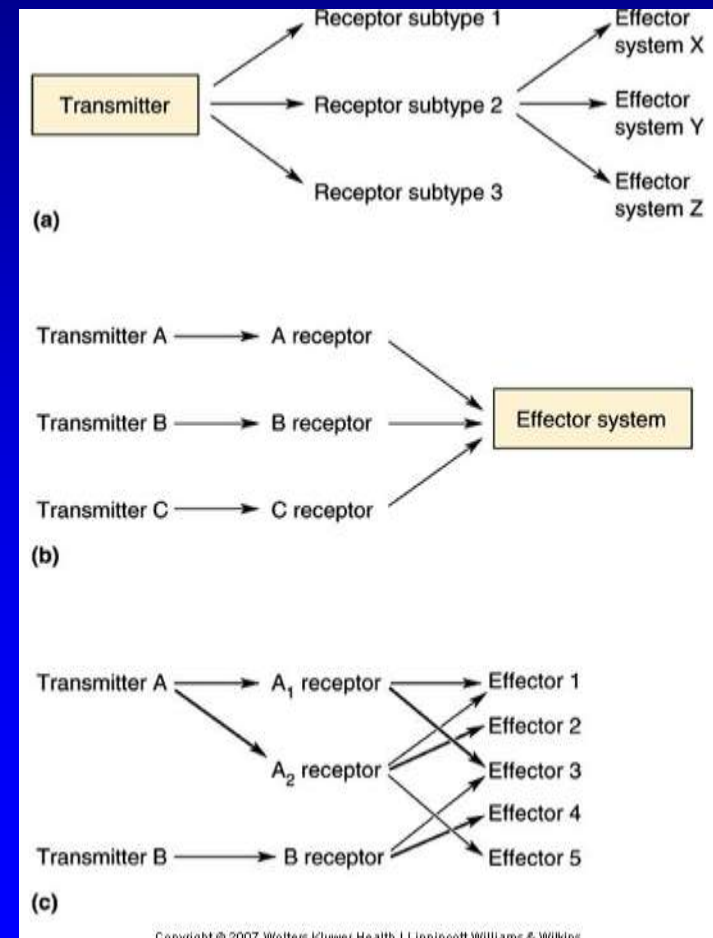
5-HT<sub>1</sub> agonist, exerts some  
Selectivity on 5-HT<sub>1D</sub> receptors

# Selective Serotonin Reuptake Inhibitors

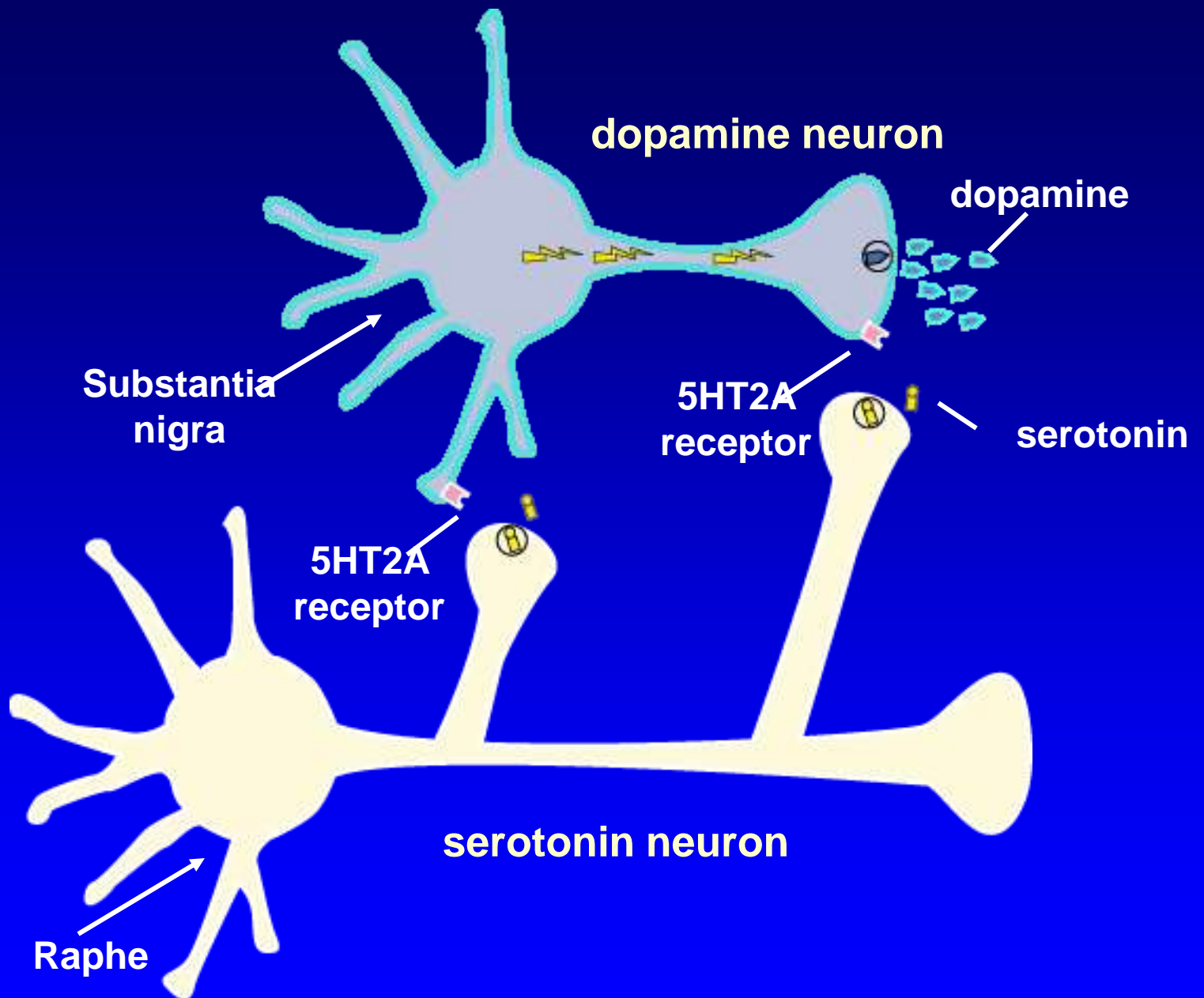


# Divergence and Convergence in Neurotransmitter Systems

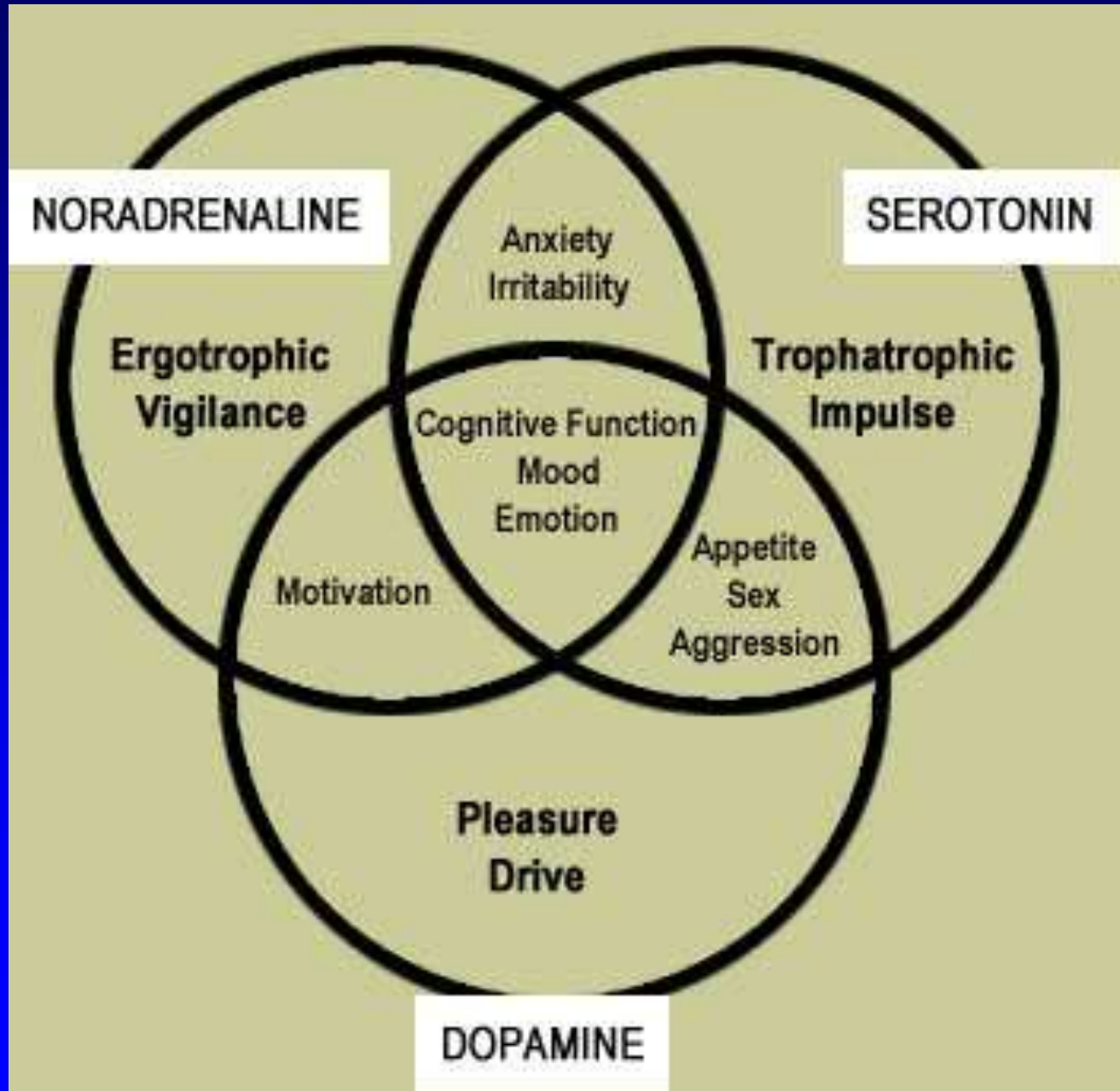
- Divergence
  - One transmitter activates more than one receptor subtype → greater postsynaptic response
- Convergence
  - Different transmitters converge to affect same effector system





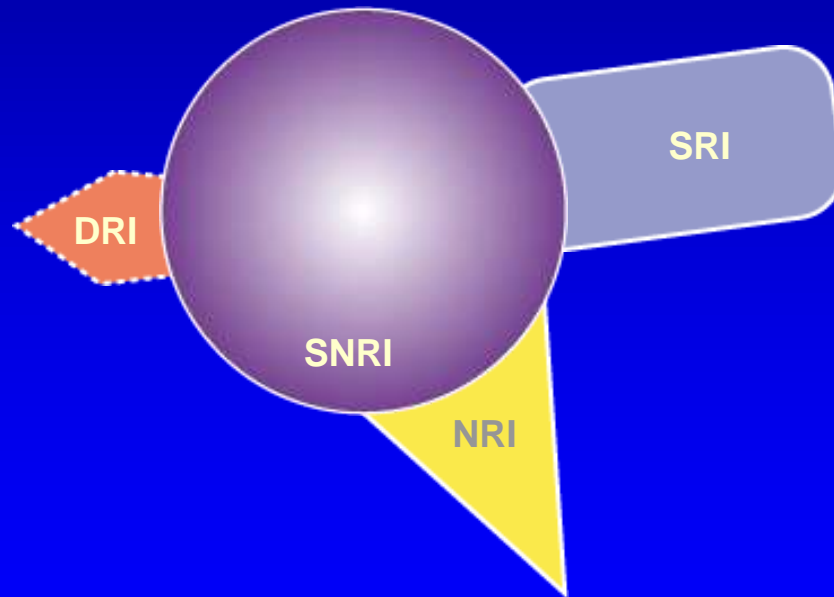


# Monoamines & Behavior



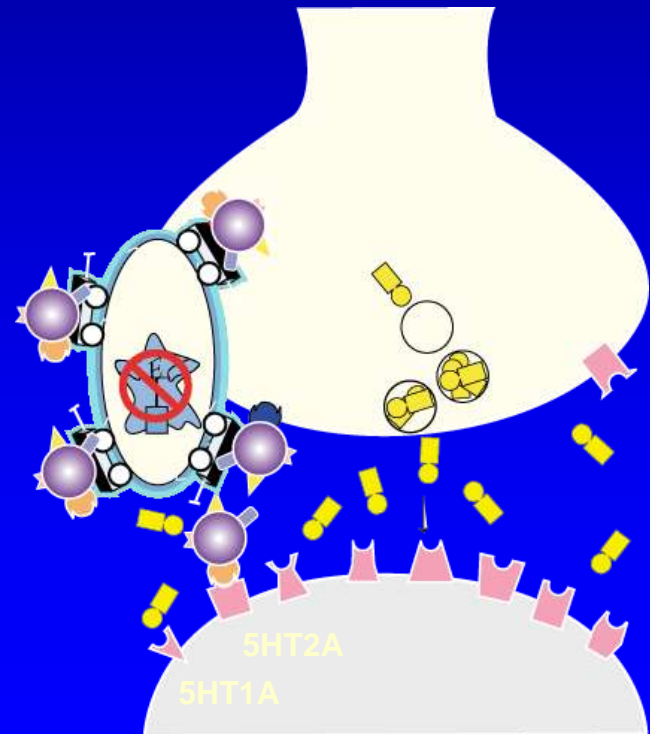
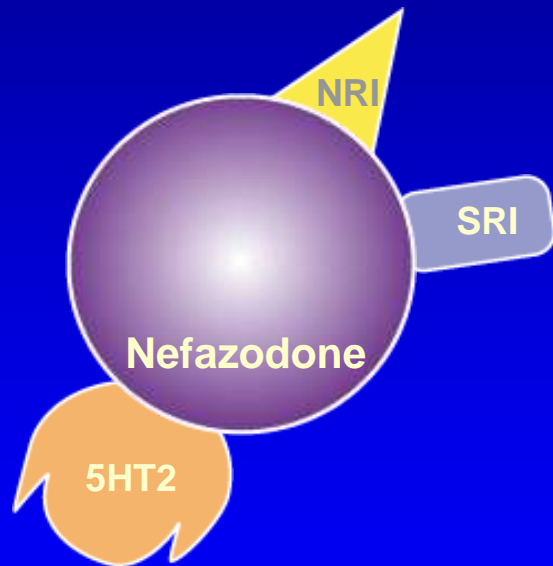
# Newer Antidepressants and Mood Stabilizers

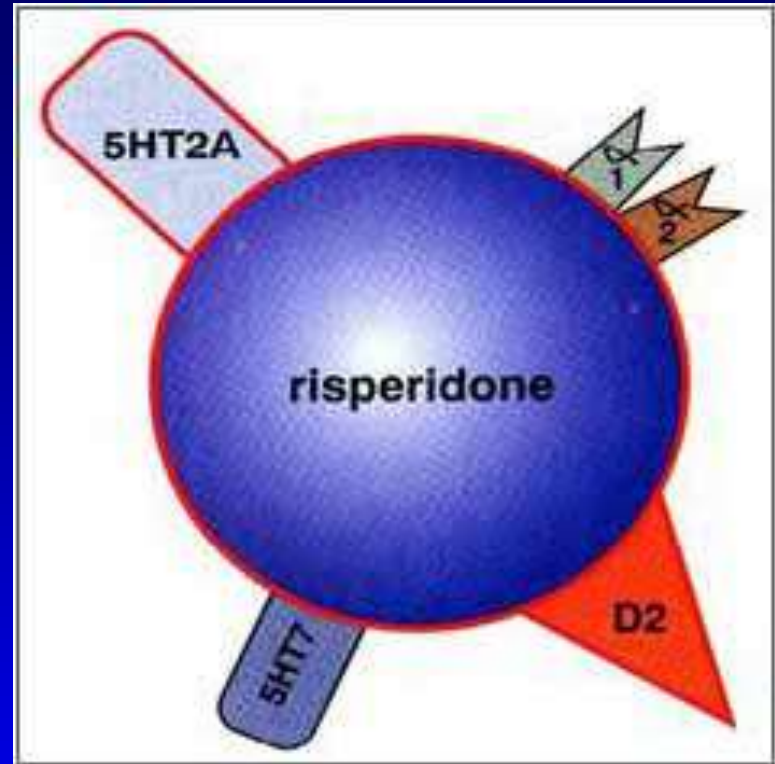
I. Serotonin-Norepinephrine reuptake inhibitor  
Venlafaxine, Milnacipran, Duloxetine

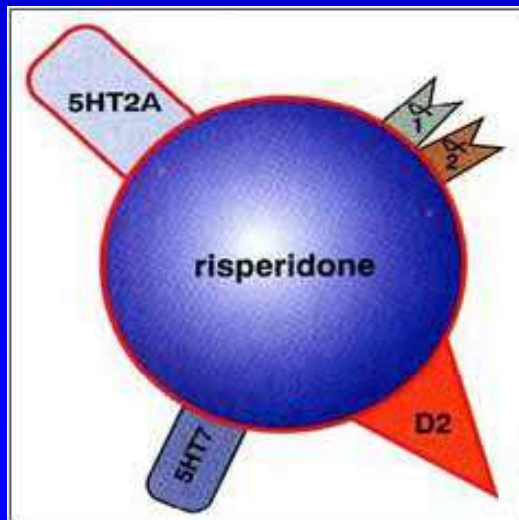


## II. Serotonin Receptor Antagonist/Reuptake Inhibitor (SARIs) Nefazodone, Trazodone

**SARI (nefazodone) actions at 5HT  
synapses**







Receptor	Action
5-HT1A	Antagonist
5-HT1B	Antagonist
5-HT1D	Antagonist
5-HT2A	Inverse agonist
5-HT2B	Inverse agonist
5-HT2C	Inverse agonist
5-HT5A	Antagonist
5-HT6	Antagonist
5-HT7	Irreversible antagonist[2]
D1	Antagonist
D2	Antagonist
D2S	Antagonist
D2L	Antagonist
D3	Inverse agonist
D4	Antagonist
D5	Antagonist
$\alpha$ 1A	Antagonist
$\alpha$ 1B	Antagonist
$\alpha$ 2A	Antagonist
$\alpha$ 2B	Antagonist
$\alpha$ 2C	Antagonist

# Neuropeptides

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- **Neuropeptides are peptides released by neurons as intercellular messengers.**
- **May co-localize with other classical transmitters in same neuron**
- **All neuropeptide receptors are G-protein linked receptors**
- **Function of Neuropeptides:**
  - **-- They can do just about everything**



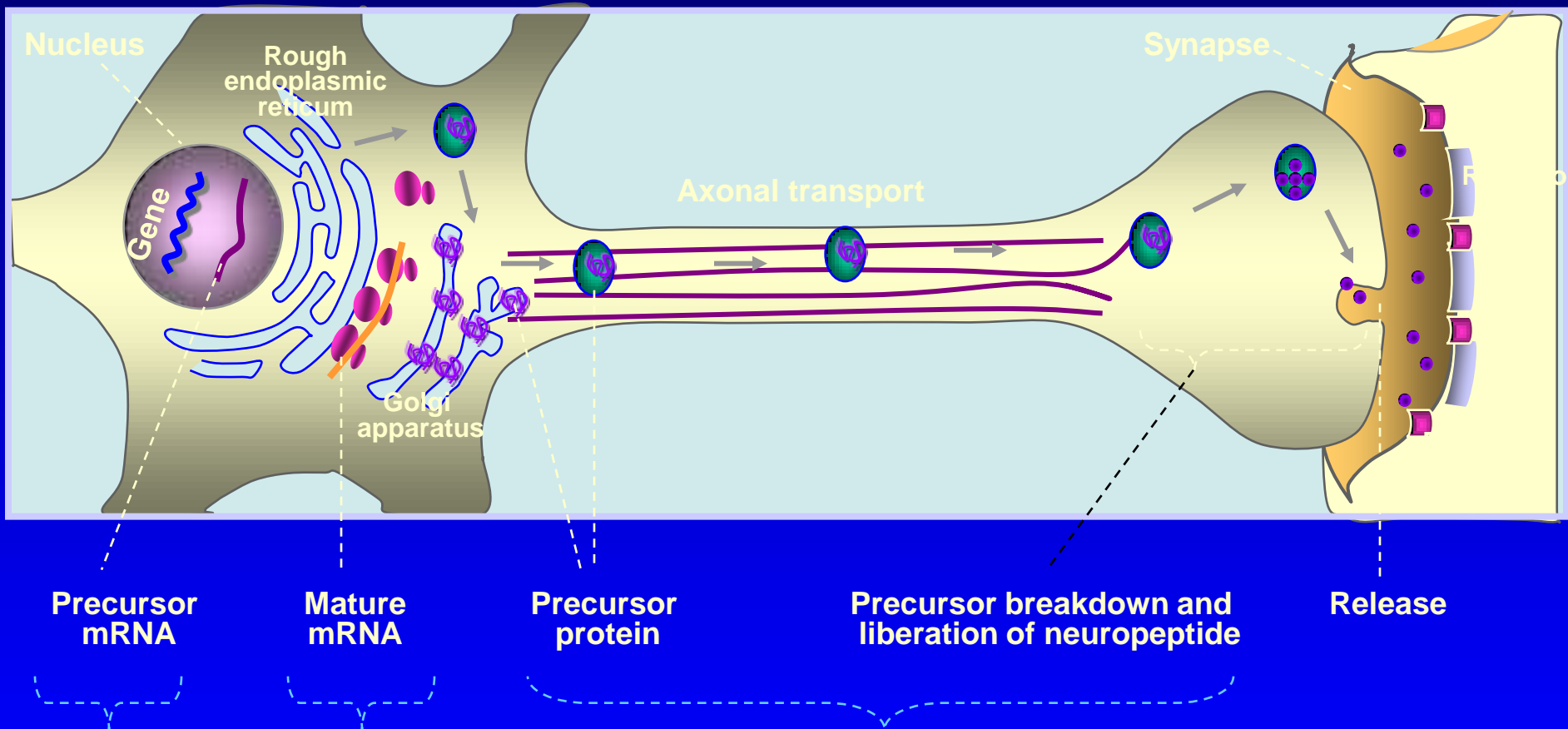
# Neuropeptides

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- **All neuropeptide receptors are G-protein linked receptors**
- **Function of Neuropeptides:**
  - **-- They can do just about everything**



# Neuropeptides synthesis



Usually are more potent than classical neurotransmitter : lower concentration and longer effect

# Example of Neuropeptides

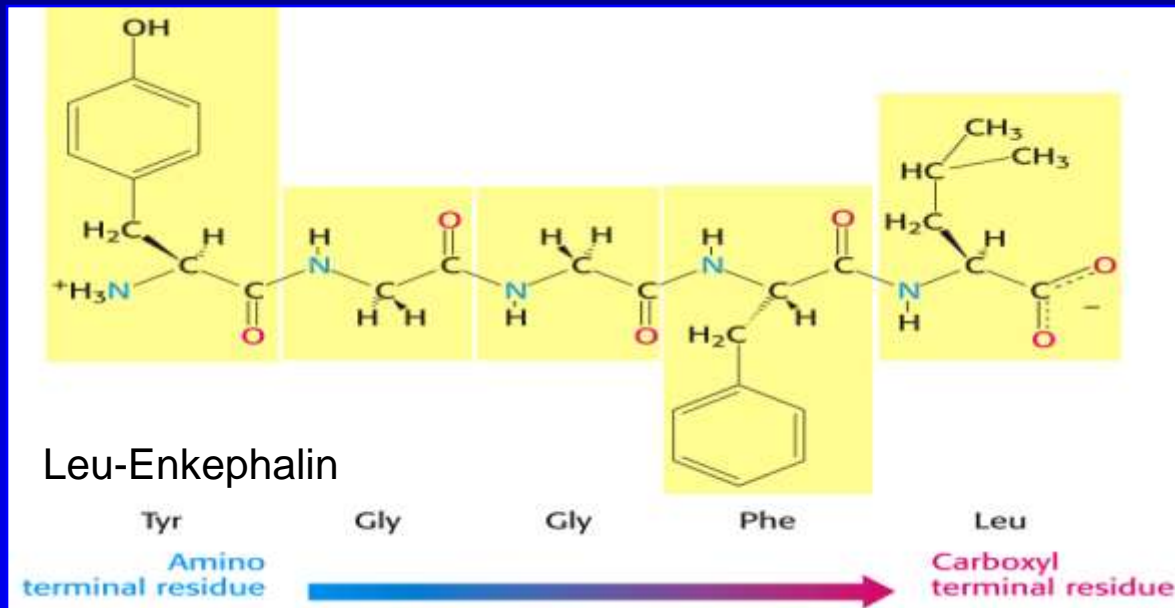
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## Opioids

- 1) Enkephalin delta ( $\delta$ )
- 2) Endorphins mu ( $\mu$ )
- 3) Dynorphin kappa ( $\kappa$ )

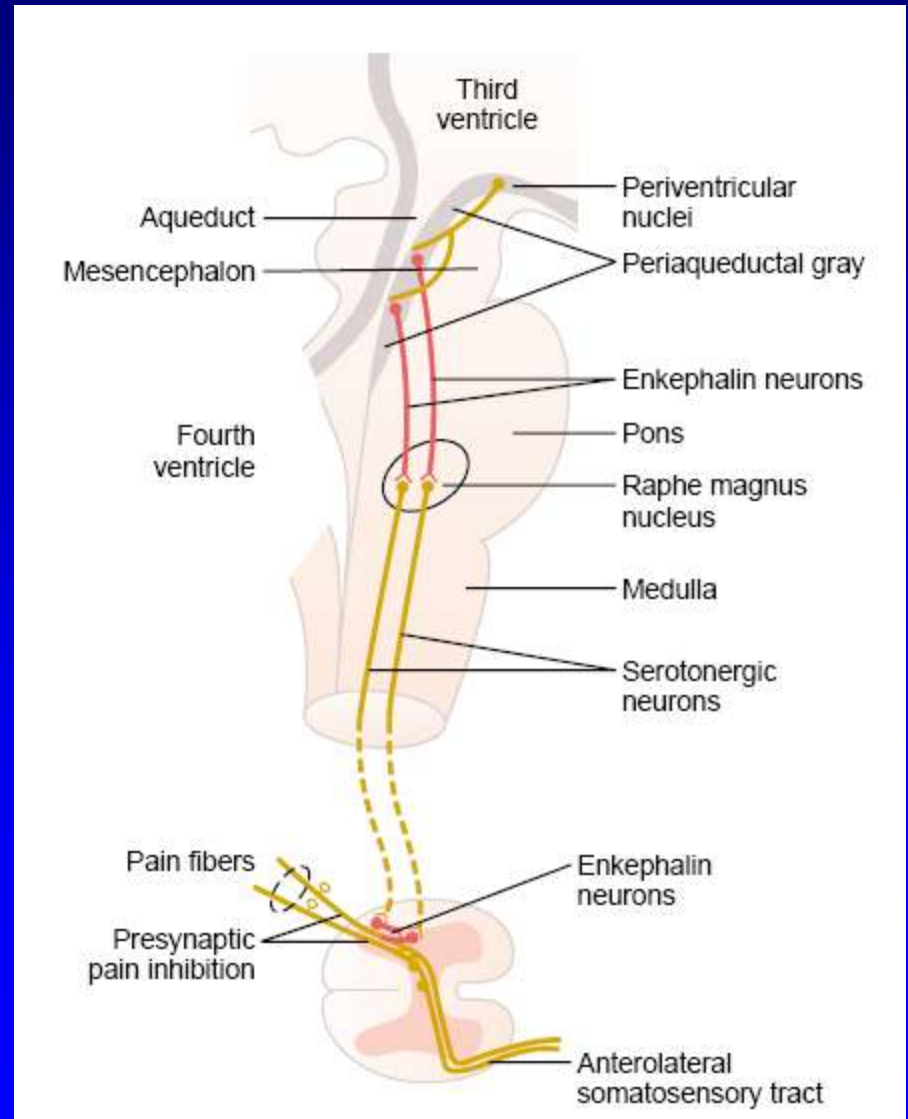
# Example of Neuropeptides

## 1) enkephalin



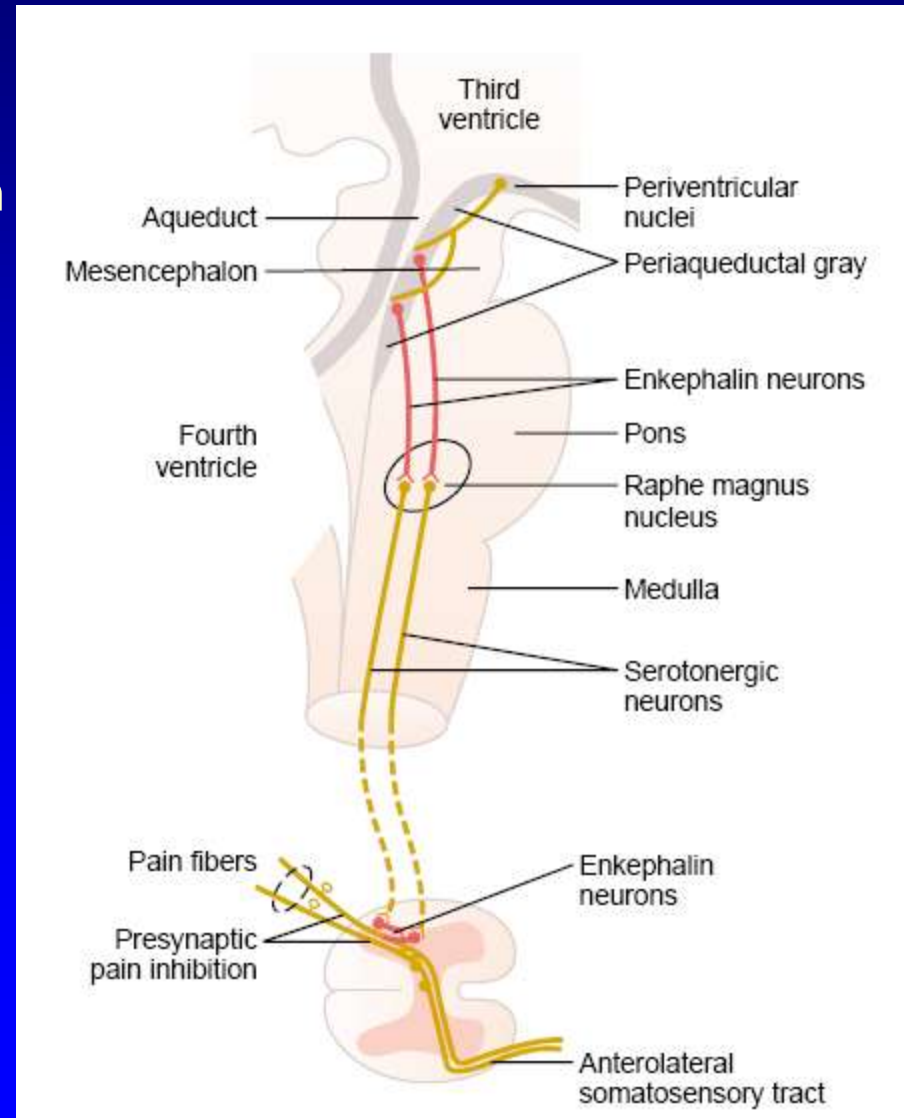
Opioid receptor :  $\delta$  receptor

# Enkephalin pathway



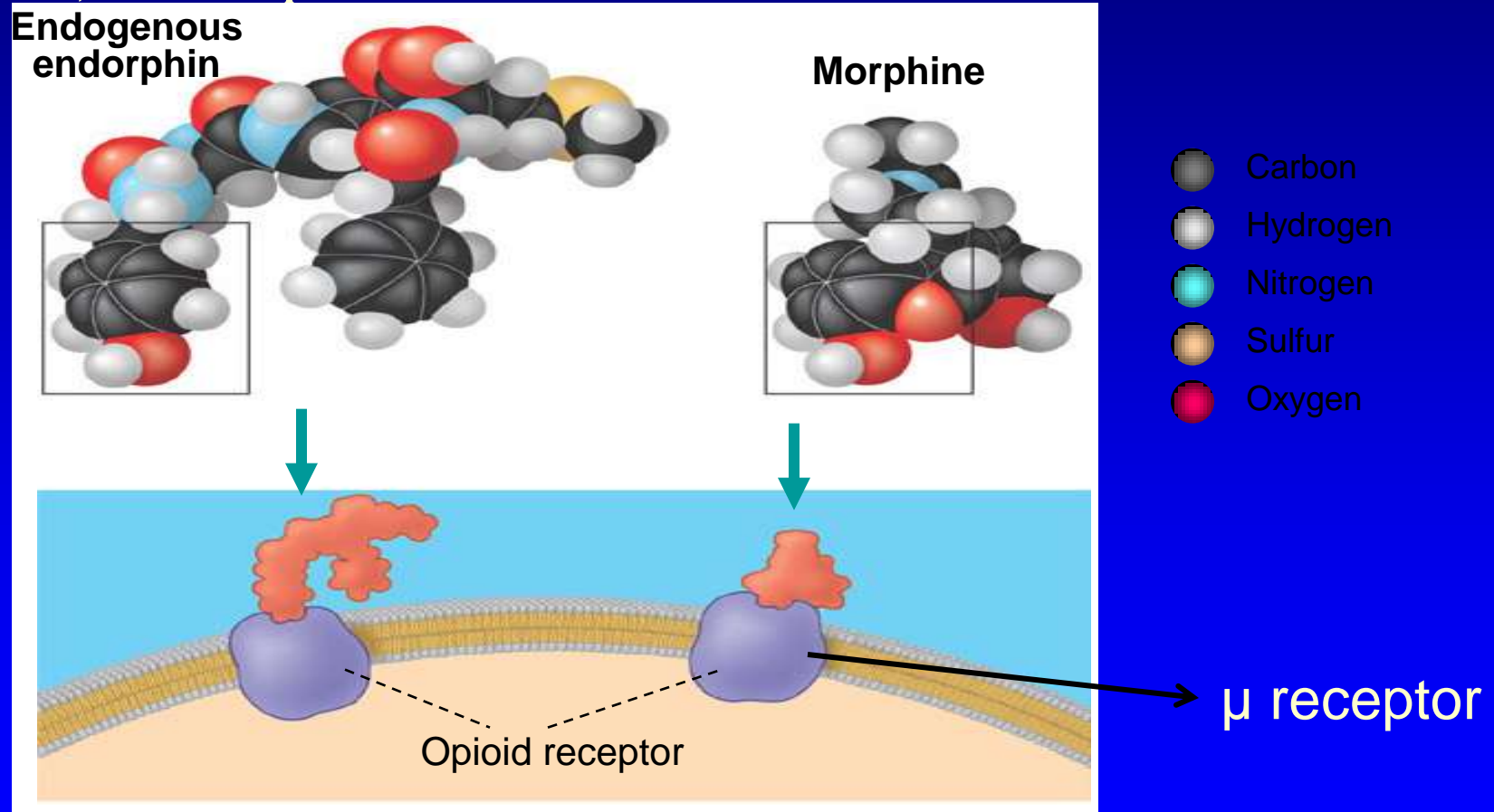
# Enkephalin pathway

Function : analgesia by block the pain before it is relayed to the brain



# Example of Neuropeptides

## 2) Endorphins



# Endorphin location and function

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**Cerebral cortex** - influence **mood, euphoria** and **emotional** aspect of pain

**Thalamus** – influence **poorly localized deep** pain

**Midbrain** (periaqueductal grey matter) - **modulation** of pain

**Brain stem** - **respiratory control, cough reflex, nausea/vomiting** etc.

**Hypothalamus** - **temperature** and **neuro-endocrine** function

# Non-traditional Neurotransmitters

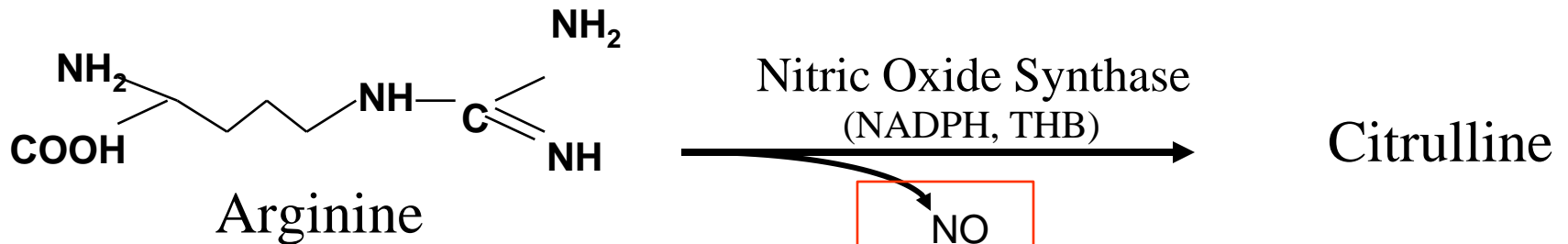
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# Nitric Oxide

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# Nitric Oxide



- NO is a diffusible bioactive gas produced from arginine by nitric oxide synthase

## NOS-1 (nNOS)

Constitutive  
Neuronal  
 $\text{Ca}^{++}$ -dependent

## NOS-2 (iNOS)

Inducible  
Mostly Glial  
 $\text{Ca}^{++}$ -independent  
Pro-inflammatory

## NOS-3 (eNOS)

Constitutive/Inducible  
Vascular endothelium  
 $\text{Ca}^{++}$ -dependent

# Nitric Oxide (NO)

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- NO is a diffusible bioactive gas produced from arginine by nitric oxide synthase
- NO is widely distributed in brain and peripheral tissues
- NO is not stored and synthesis is regulated by the enzyme activity

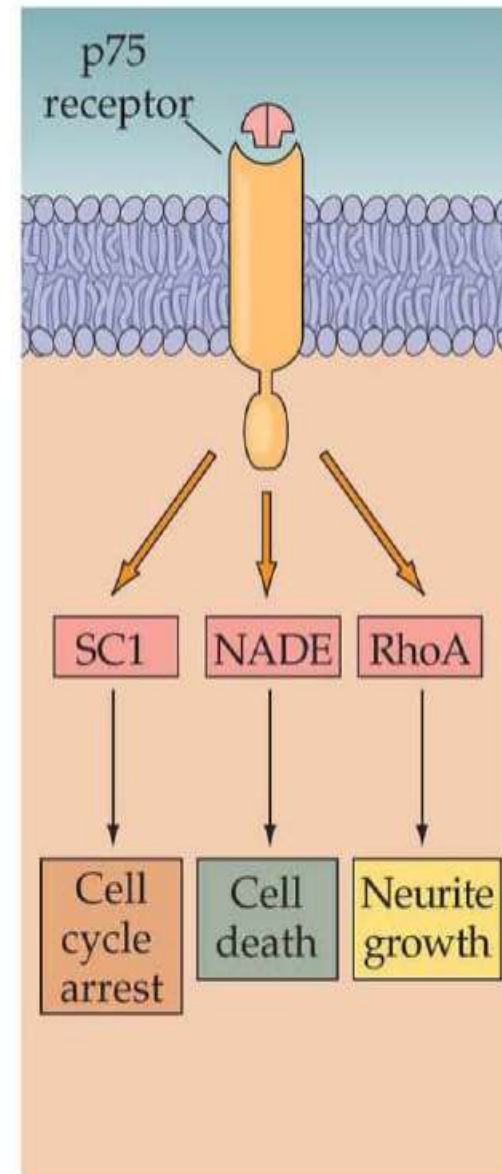
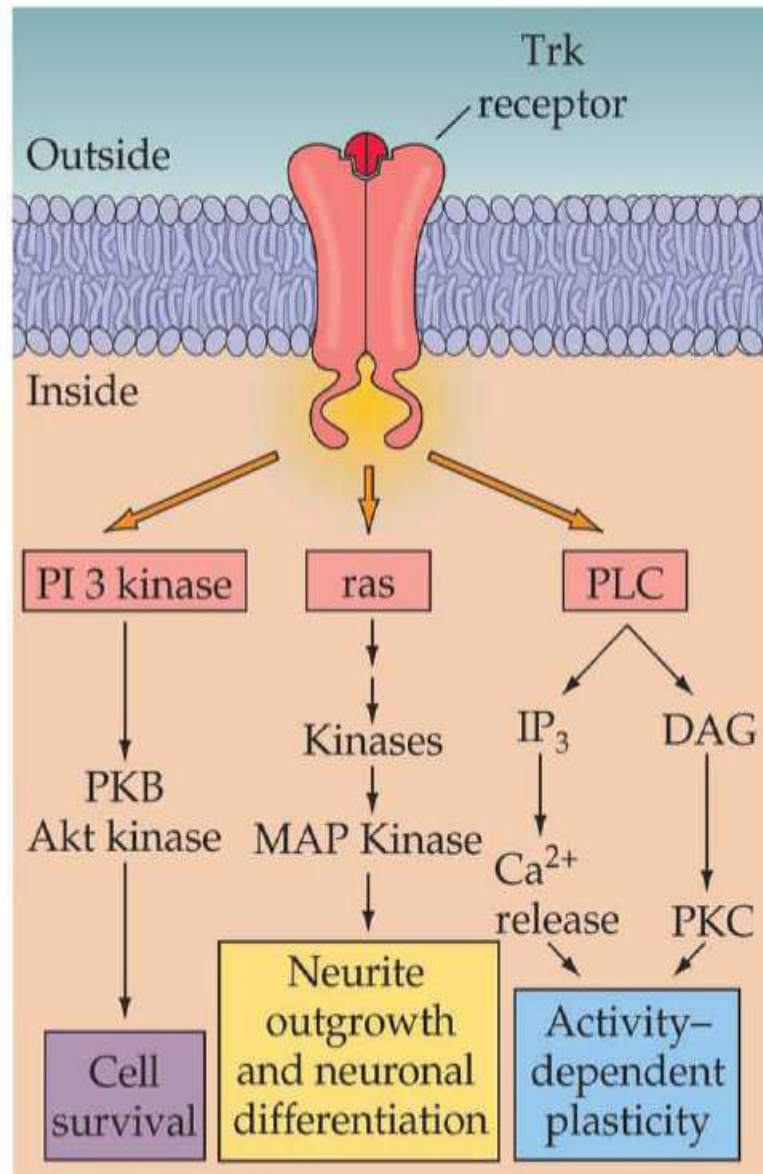
# Nitric Oxide

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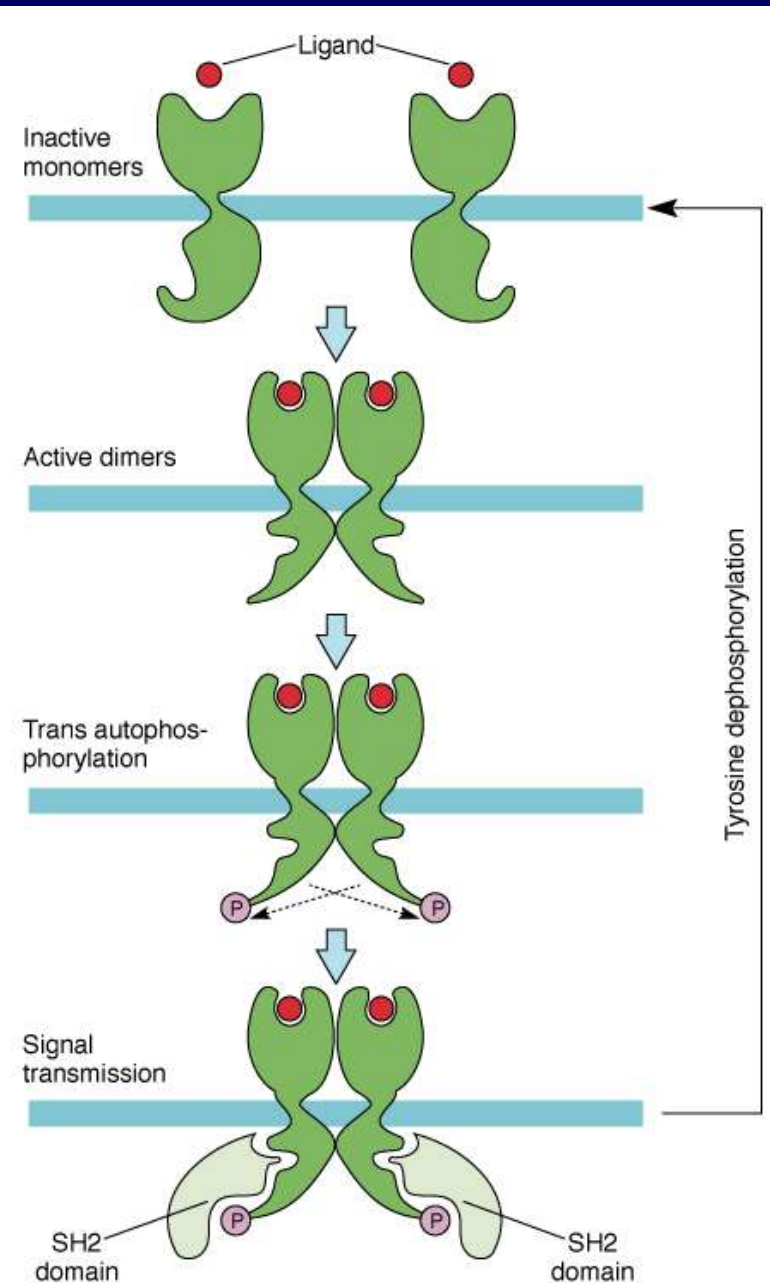
- Regulation of blood flow - Neuron-derived NO plays a major role in the regulation of blood flow, vasodilation and increased blood flow
- At the cellular level, NO can changes intracellular metabolic functions that modify neuronal excitability and influence neurotransmitter release
- In the brain, NO acts as a neuromodulator to control behavioral activity, influence memory formation, and intensify responses to painful stimuli
- May be responsible for glutamate induced neurotoxicity

# Brain-derived neurotrophic factor “BDNF”

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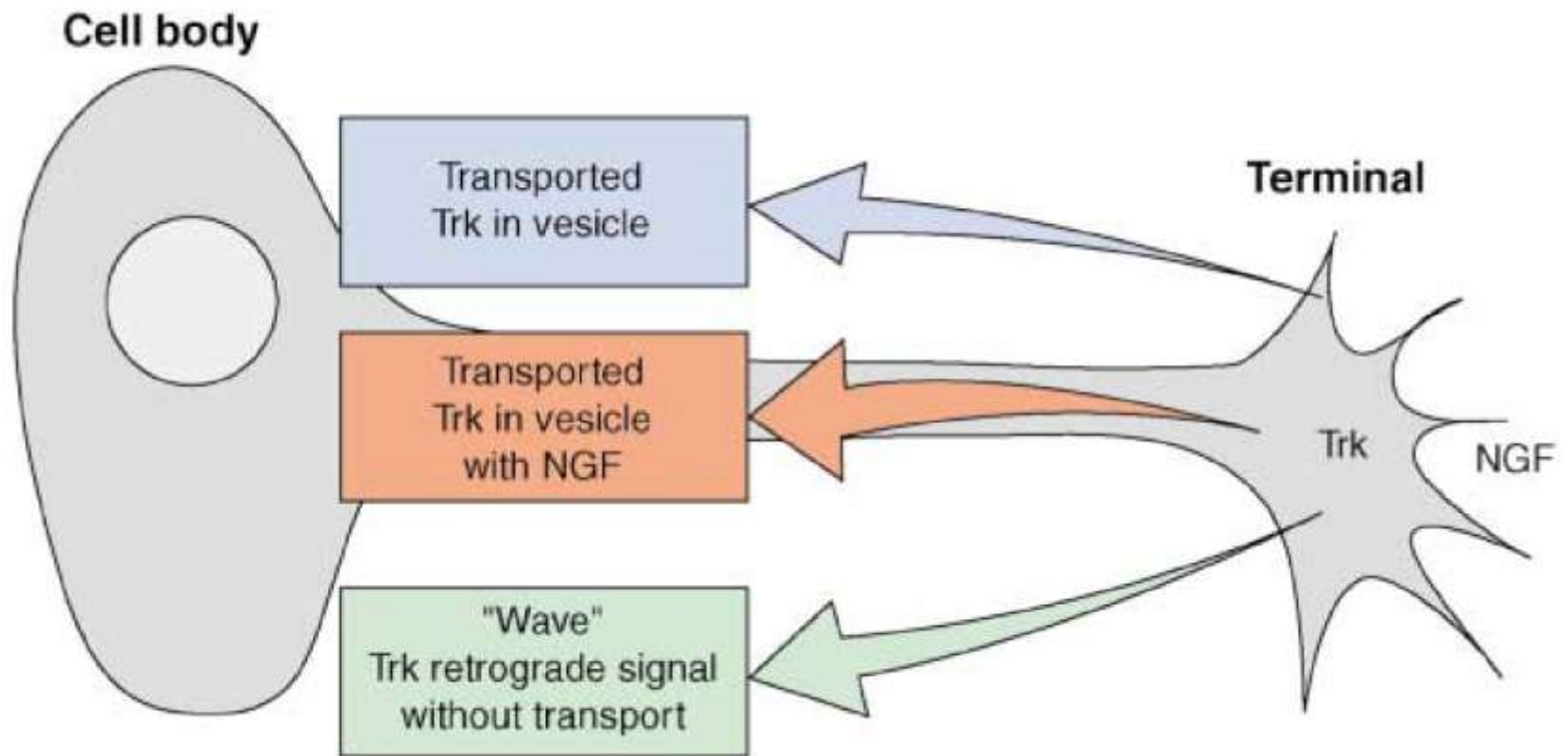


# Tyrosine kinase Receptor activation:



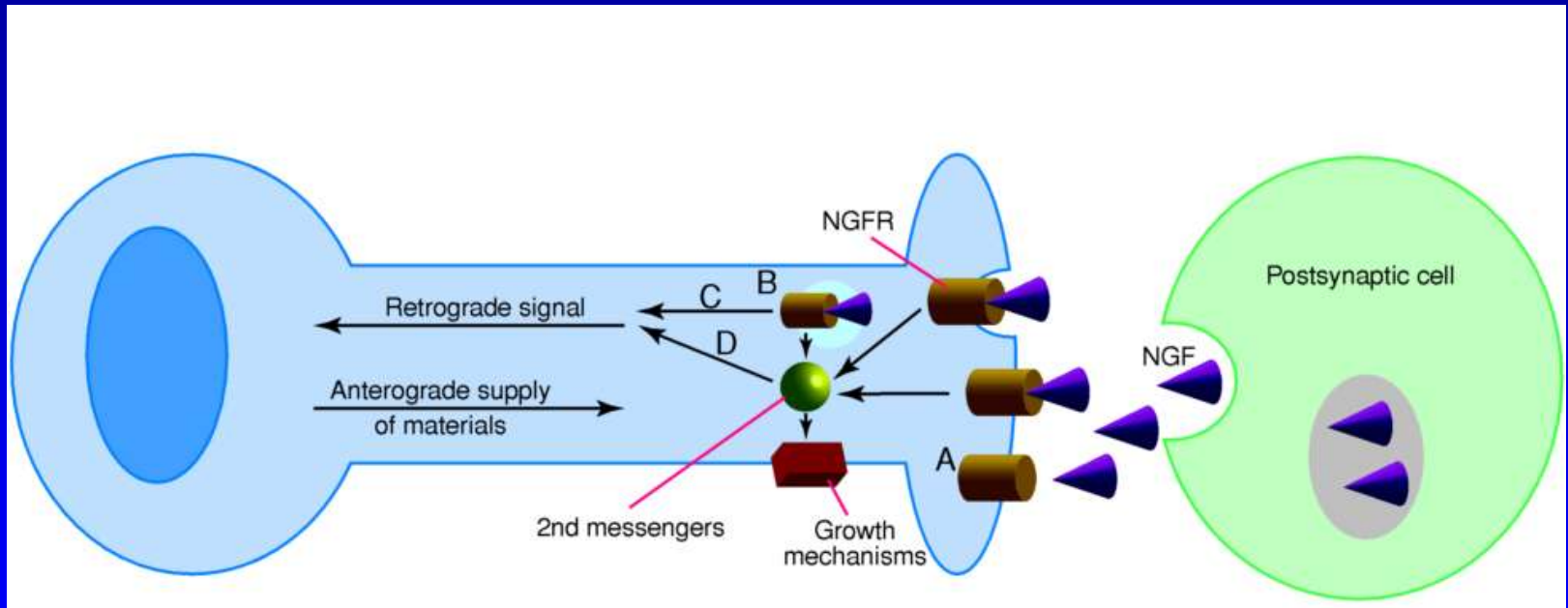
After J. Schlessinger and A. Ullrich, *Neuron* 9:384, 1992; by permission of Cell Press.  
Copyright 1999 John Wiley and Sons, Inc. All rights reserved.

Our axons can be  $>1$  m in length---how does the neurotrophin/receptor complex signal to the neuronal cell body?





# Transport of NGF



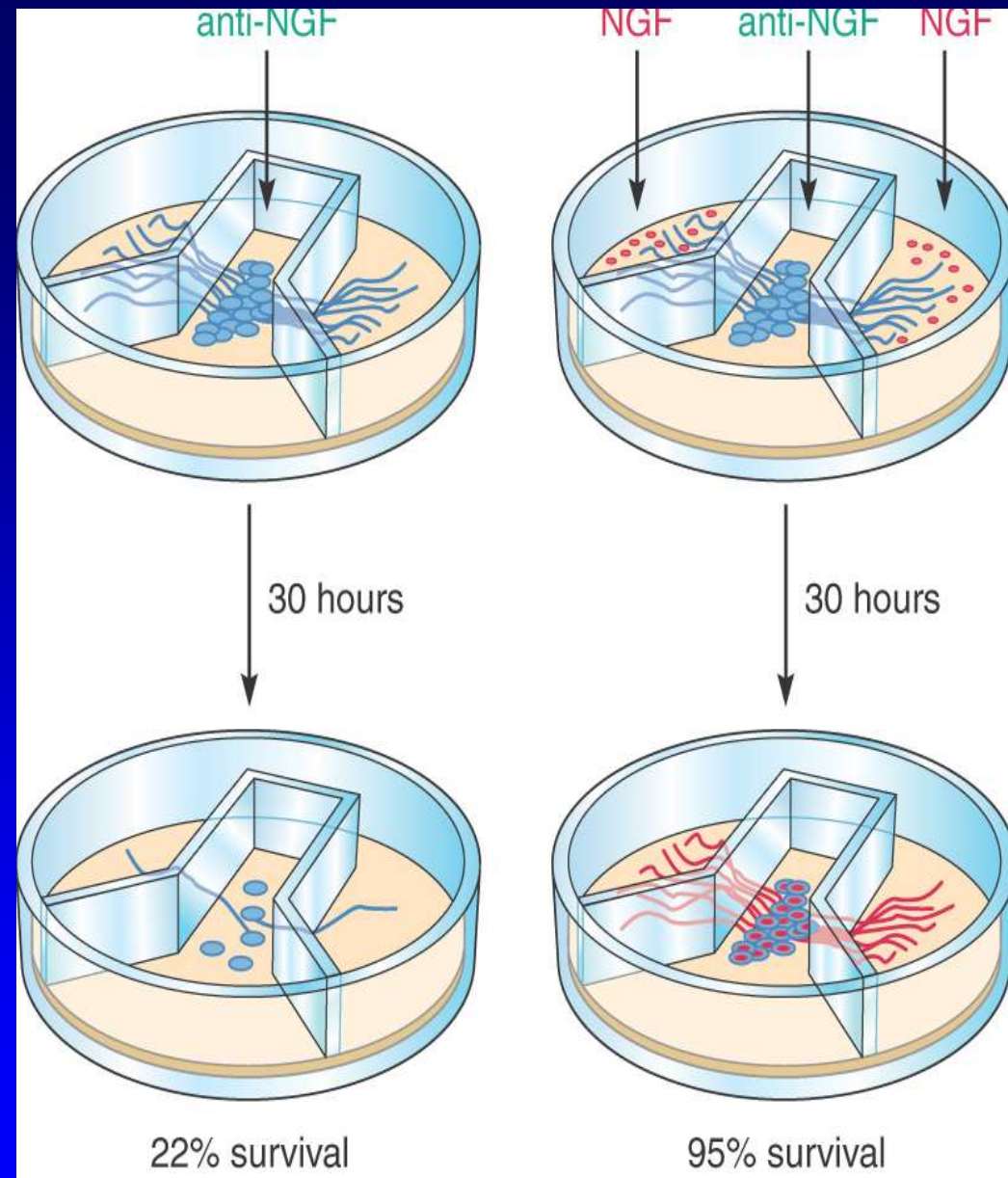
## NGF signal can be transduced at the tips of growing neuronal processes

Sympathetic neurons were placed in a TC system that allowed the somas and neurites to be bathed in different media.

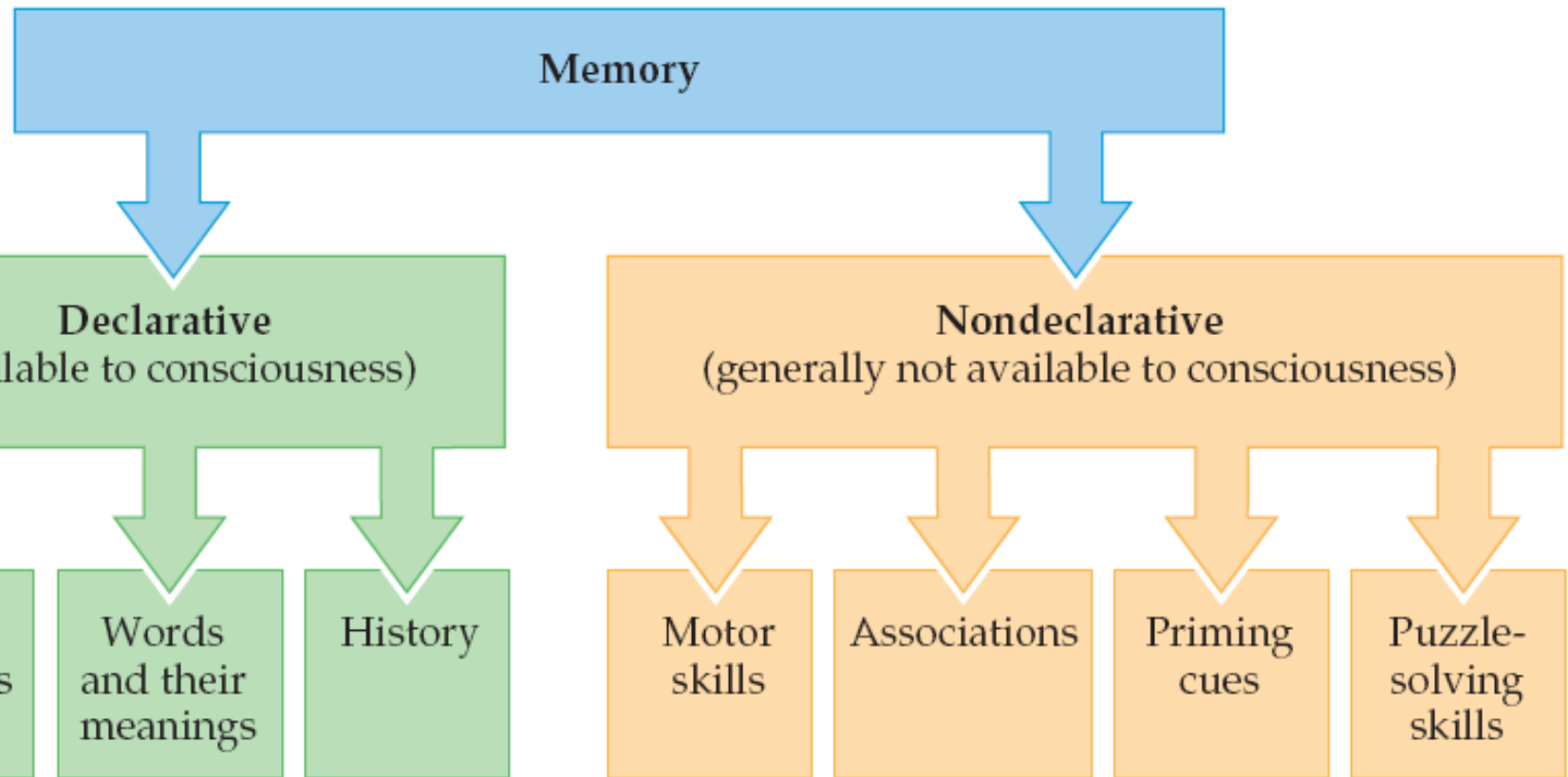
L: Most neurons die when grown without NGF for 30 hr.

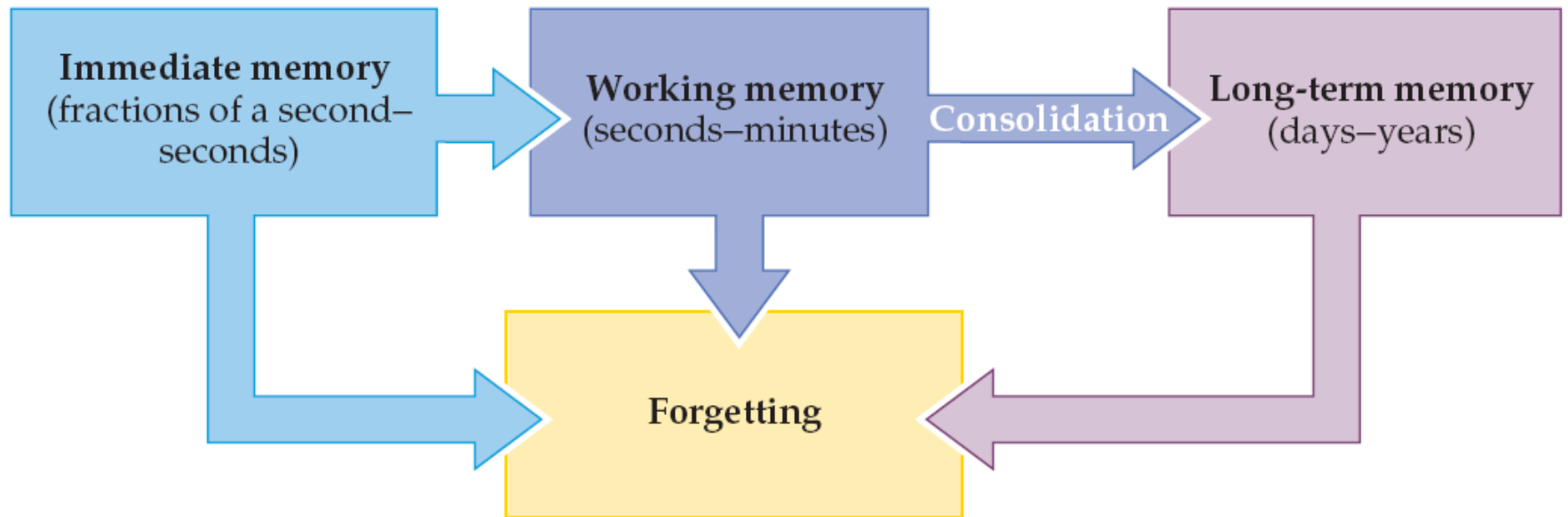
R: Neurons can be kept alive by adding NGF only to the compartments with growing neurites.

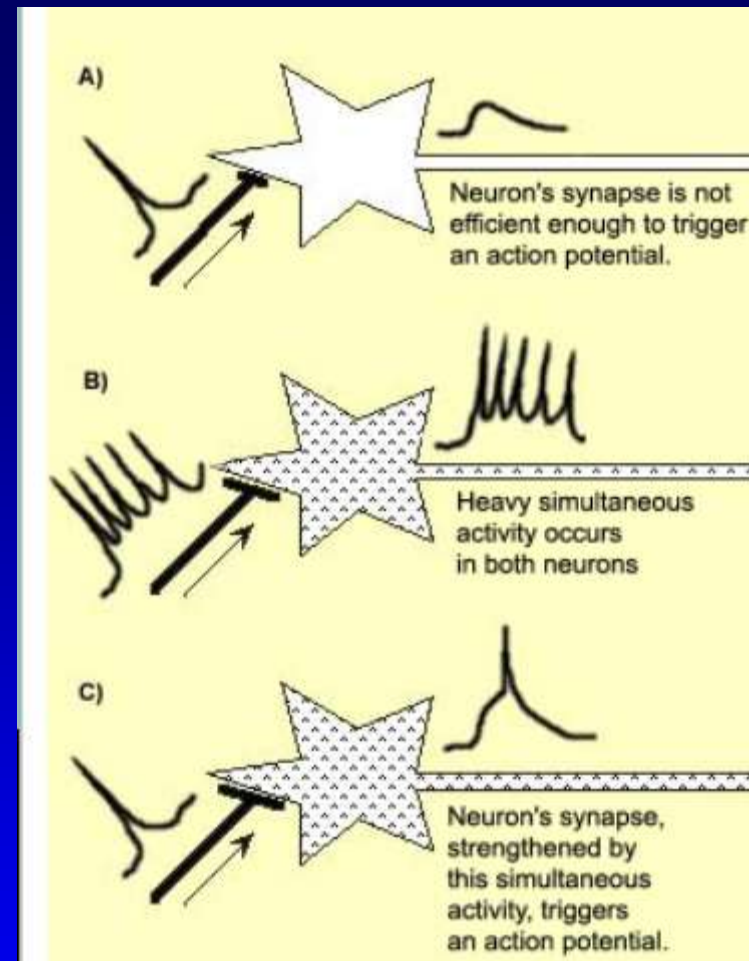
In both cases, anti-NGF prevented TrkA activation in the central compartment.



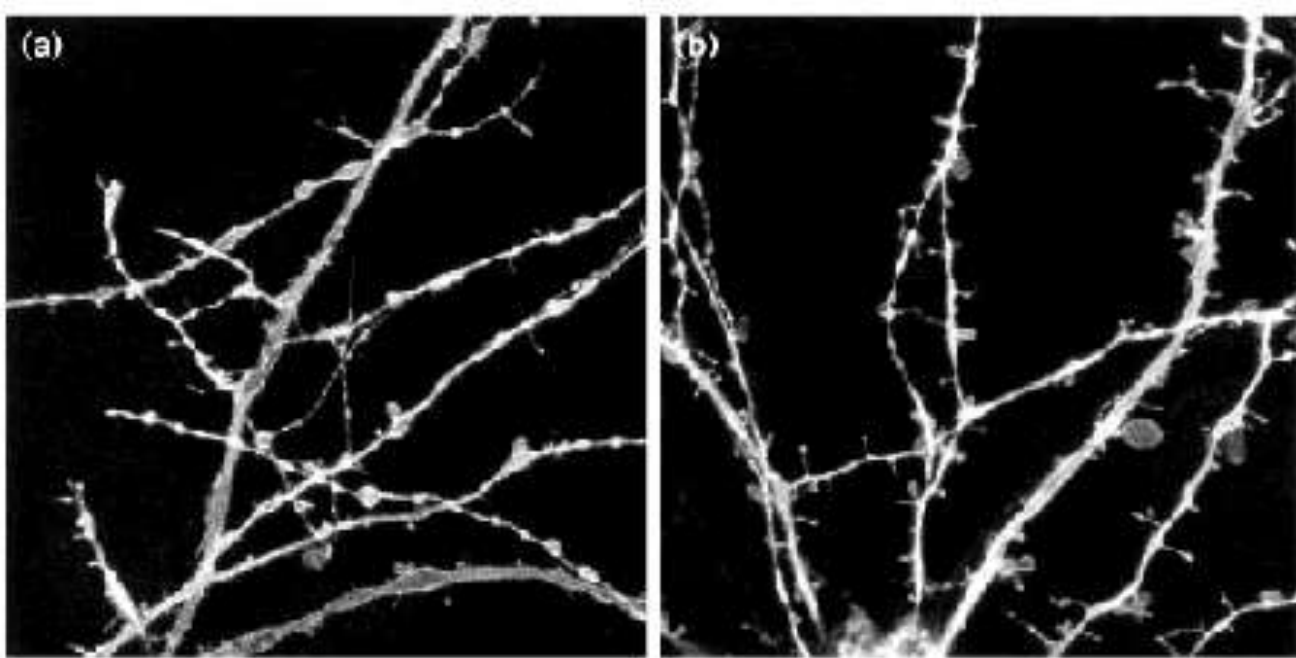
# Memory



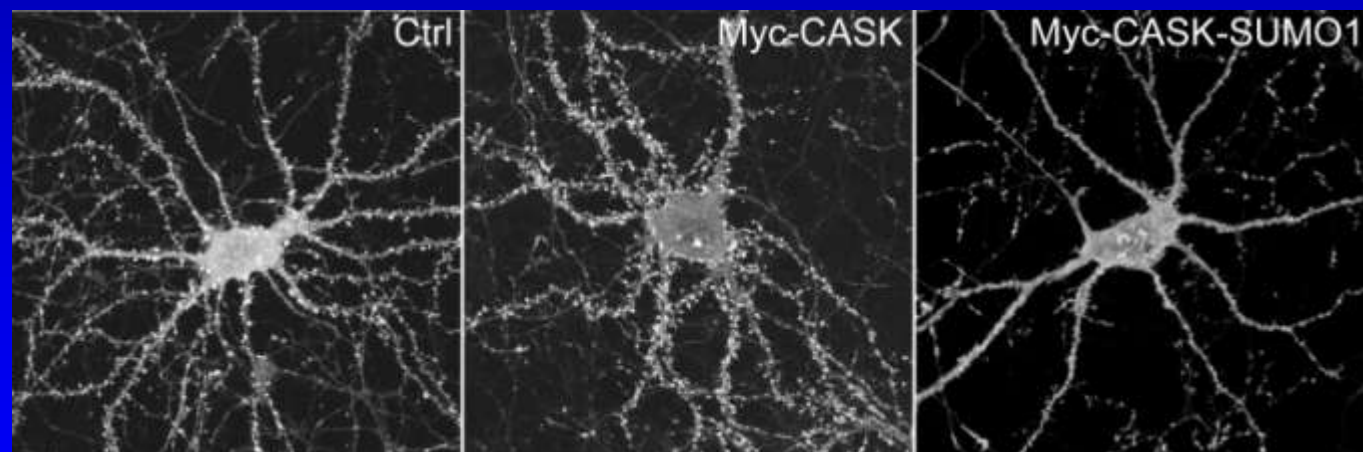


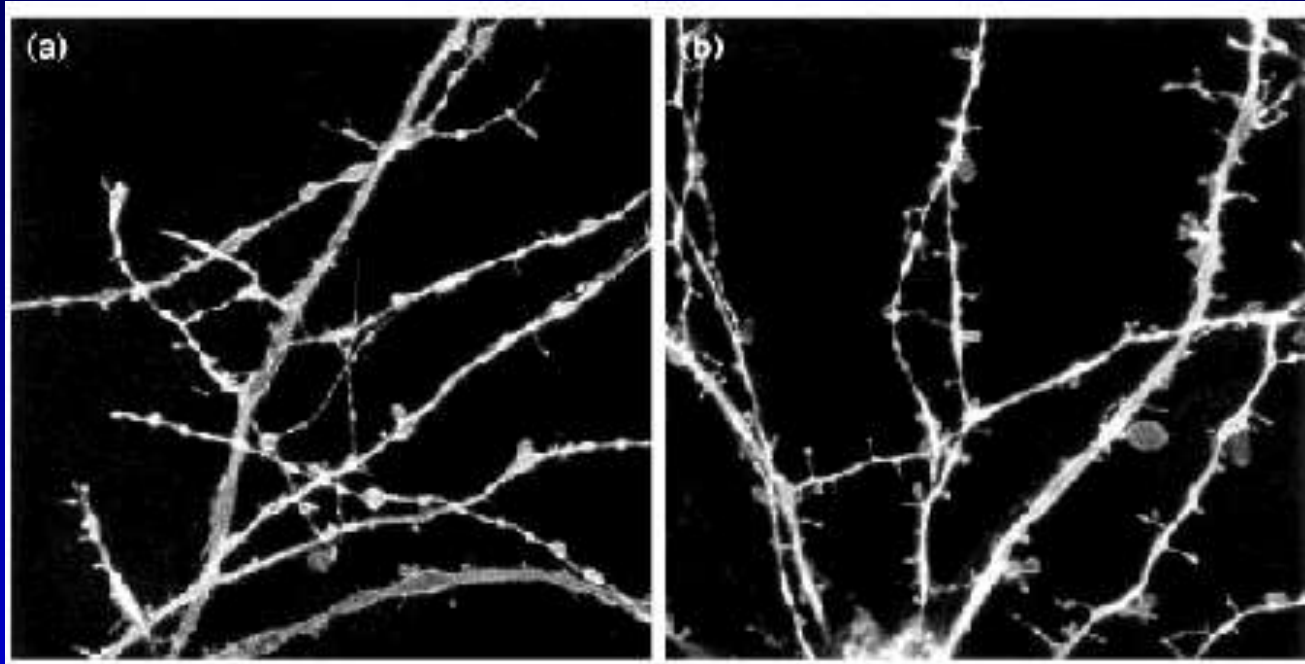


- Long term potentiation LTP , and LTD



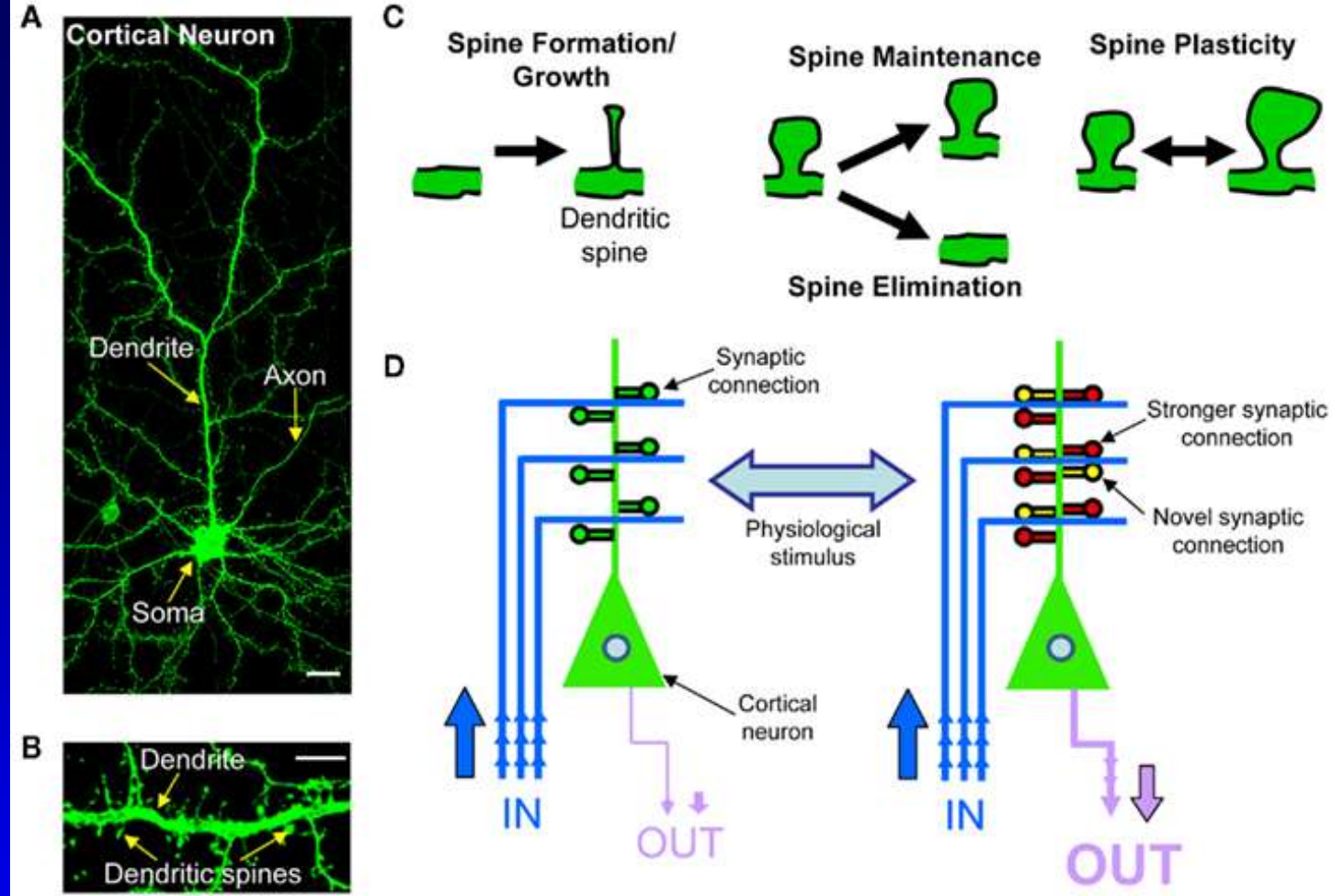
- Spines





- Spines
- Long term potentiation LTP and LTD
- The glutamate receptor (NMDA)





- Spines
- Long term potentiation LTP and LTD
- The glutamate receptor (NMDA)
- neuromodulators “NO, 5HT, norepinephrine”