Introduction to neuropsychopharmacology.

Neurotransmitter mechanisms and specific neurotransmitter systems.

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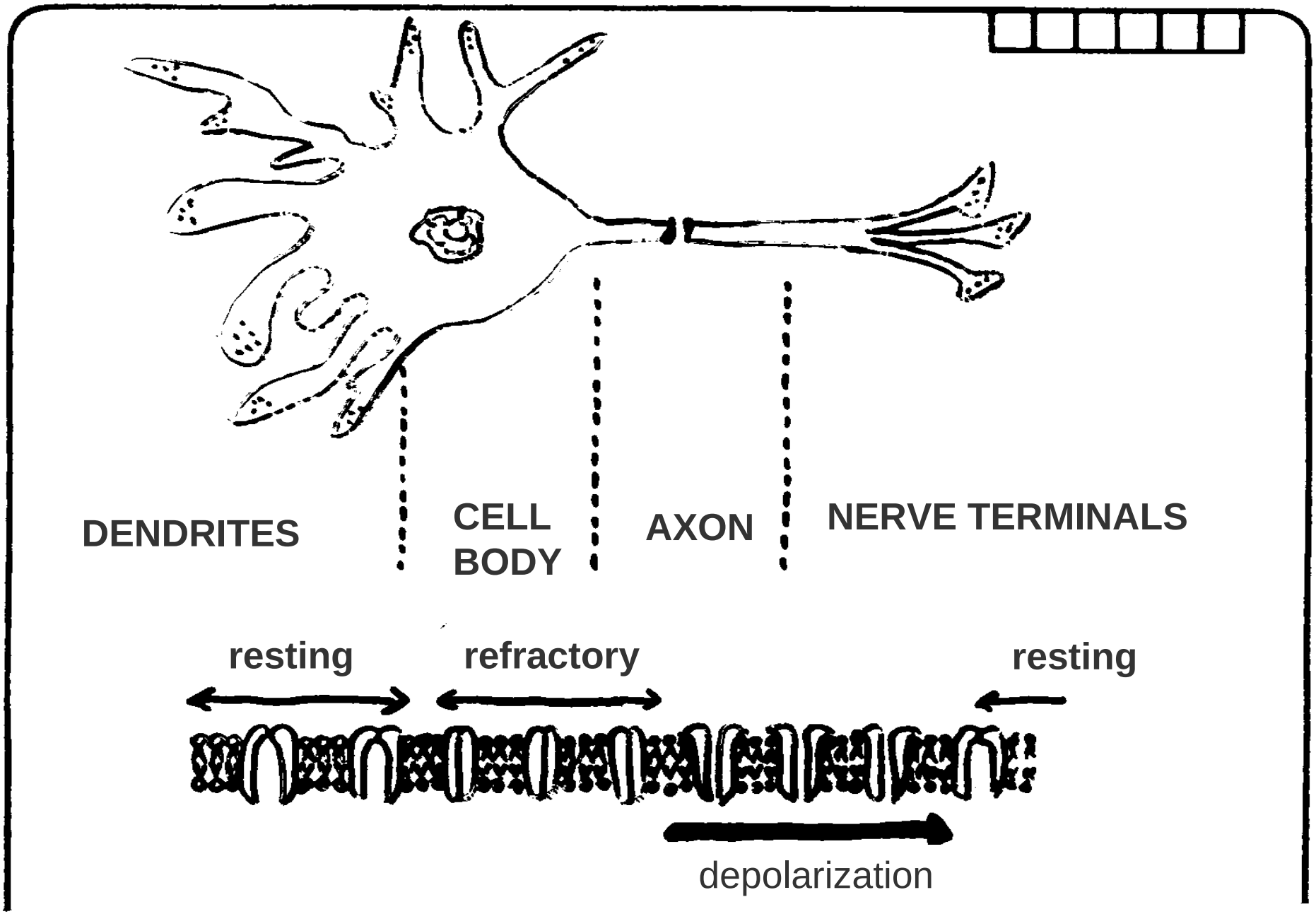
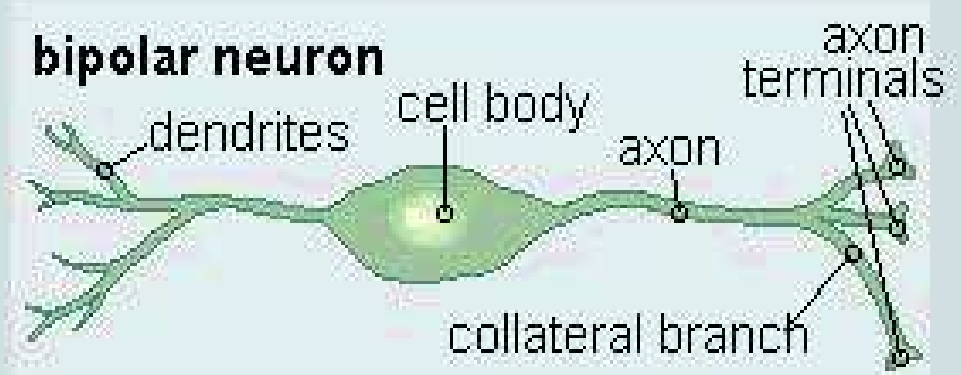
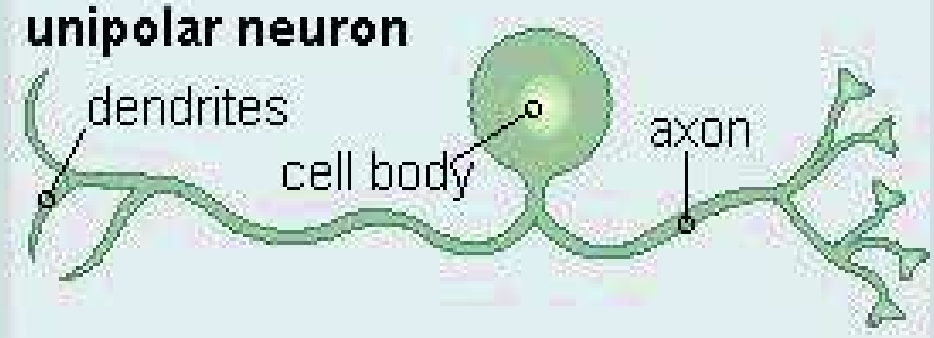
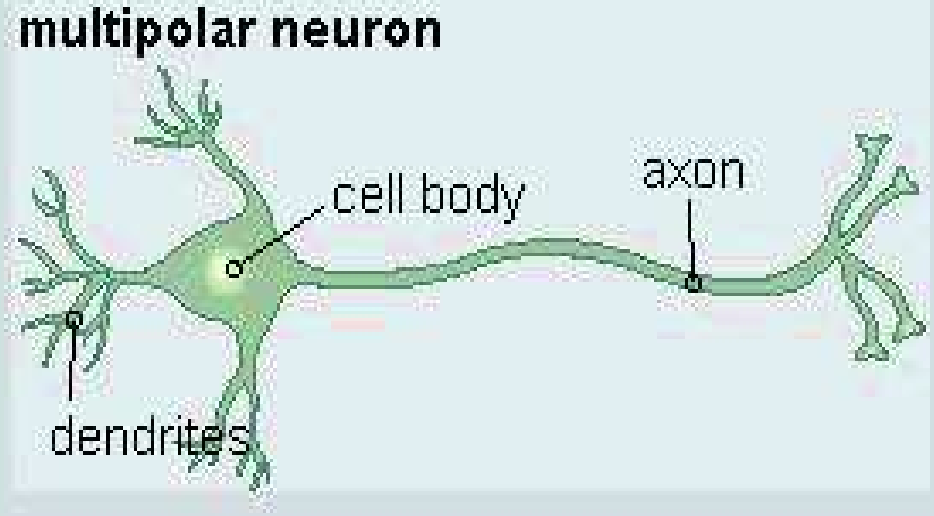
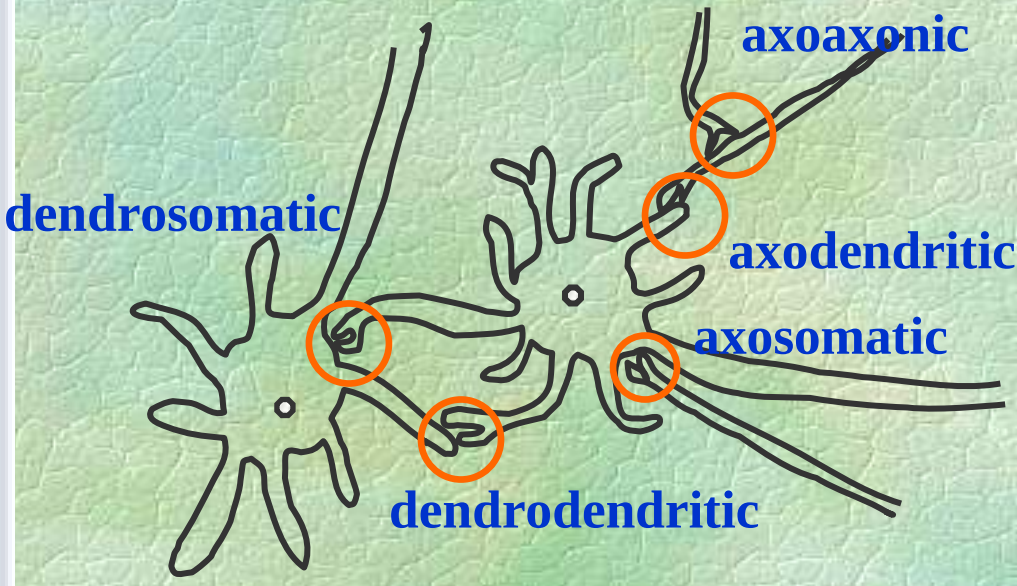

DENDRITES
CELL BODY
AXON
NERVE TERMINALS
resting
refractory
resting
depolarization

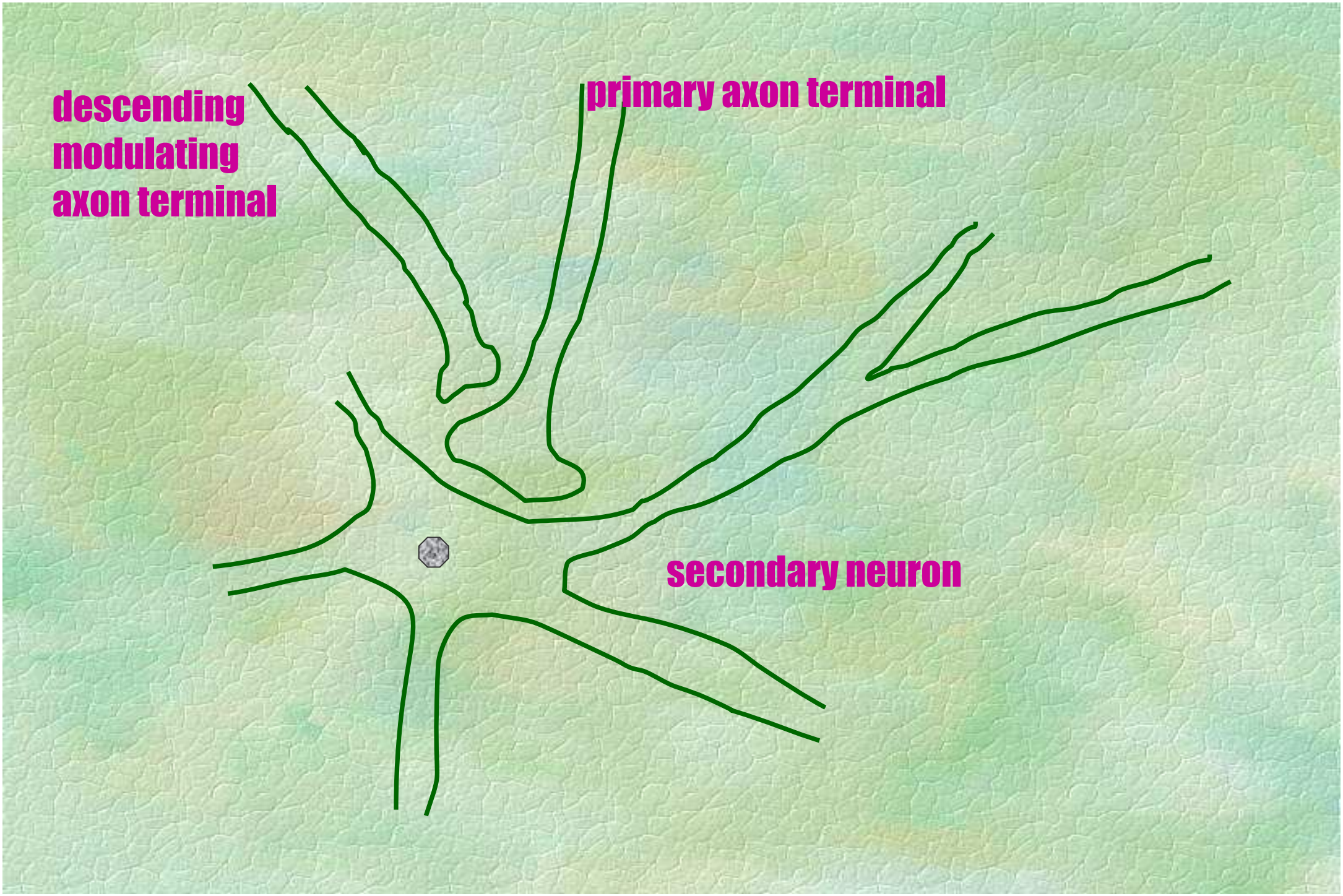




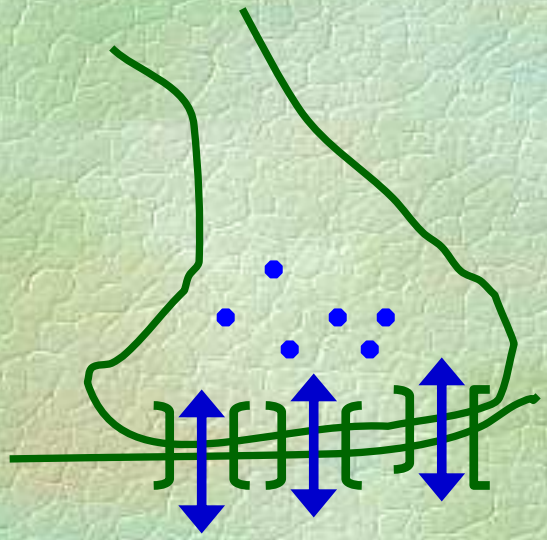


TYPES of SYNAPSES

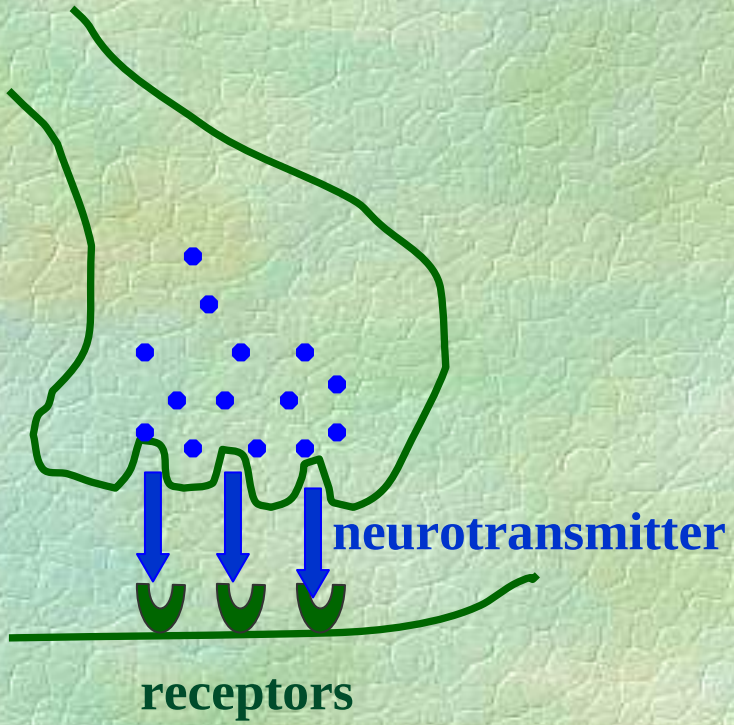



descending
modulating
axon terminal
primary axon terminal
secondary neuron

SYNAPSE



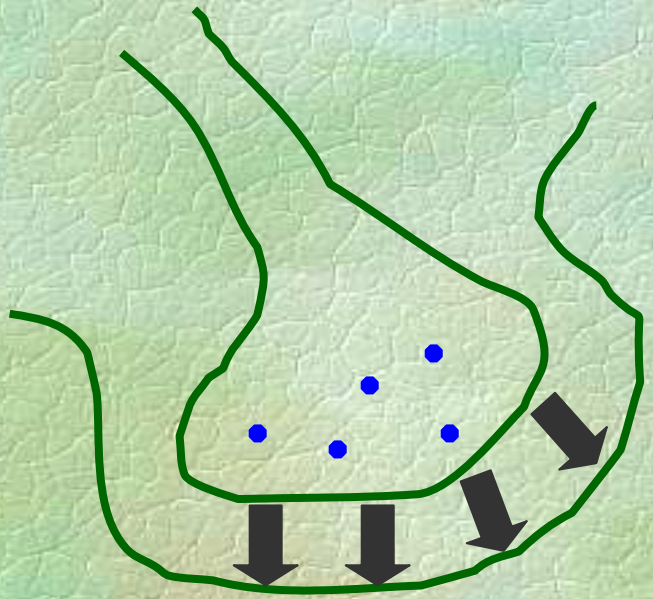
electrical
("gap junction")



chemical

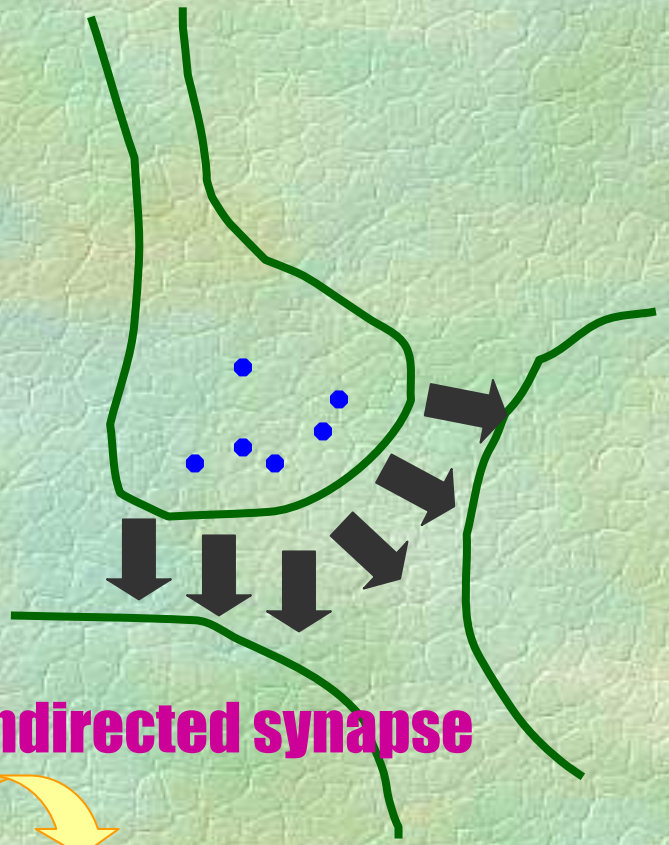
bidirectional passage of ions and
small molecules through channels

CHEMICAL SYNAPSES



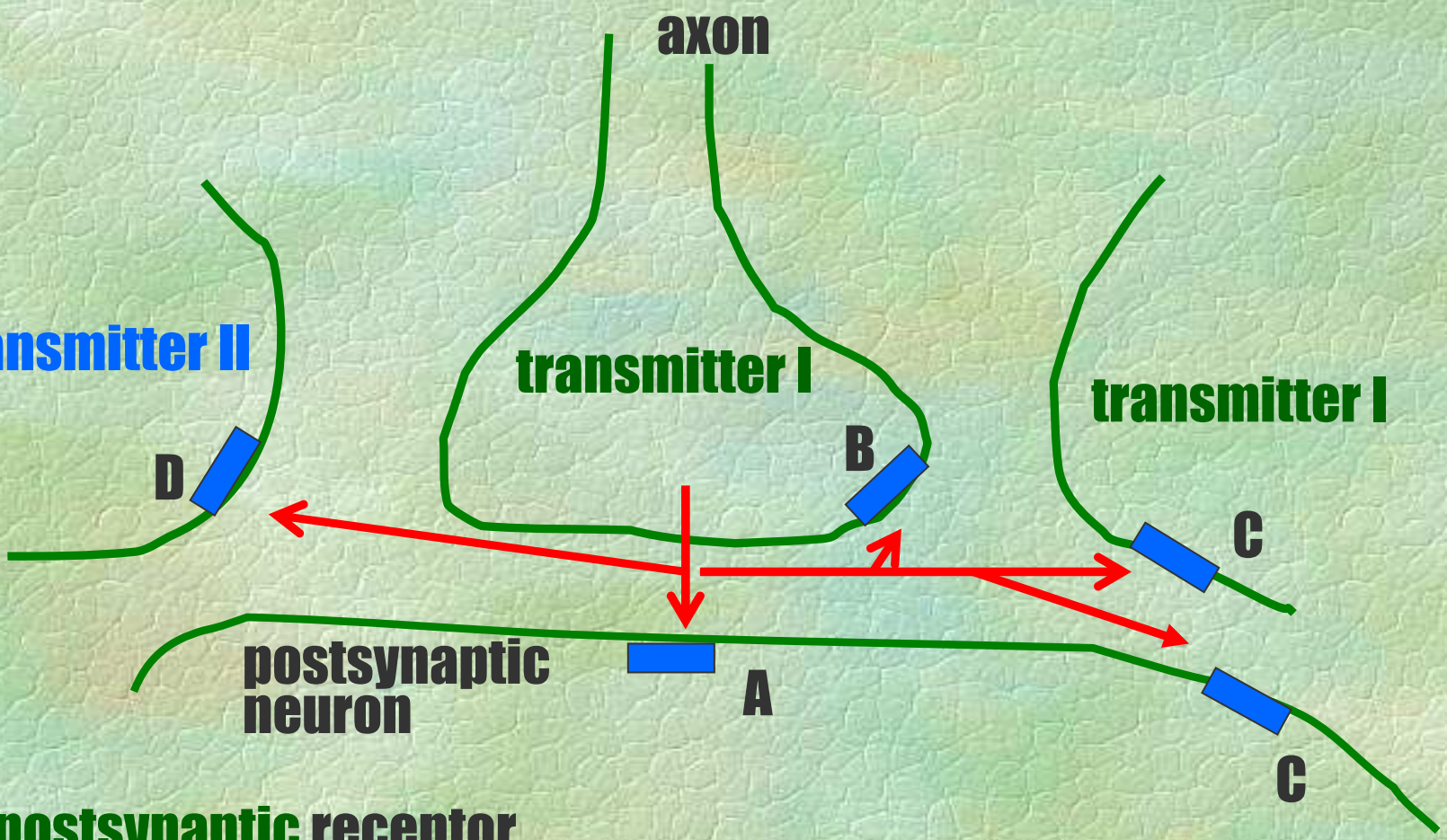
directed synapse

20 - 30 nm



nondirected synapse

till 400 nm



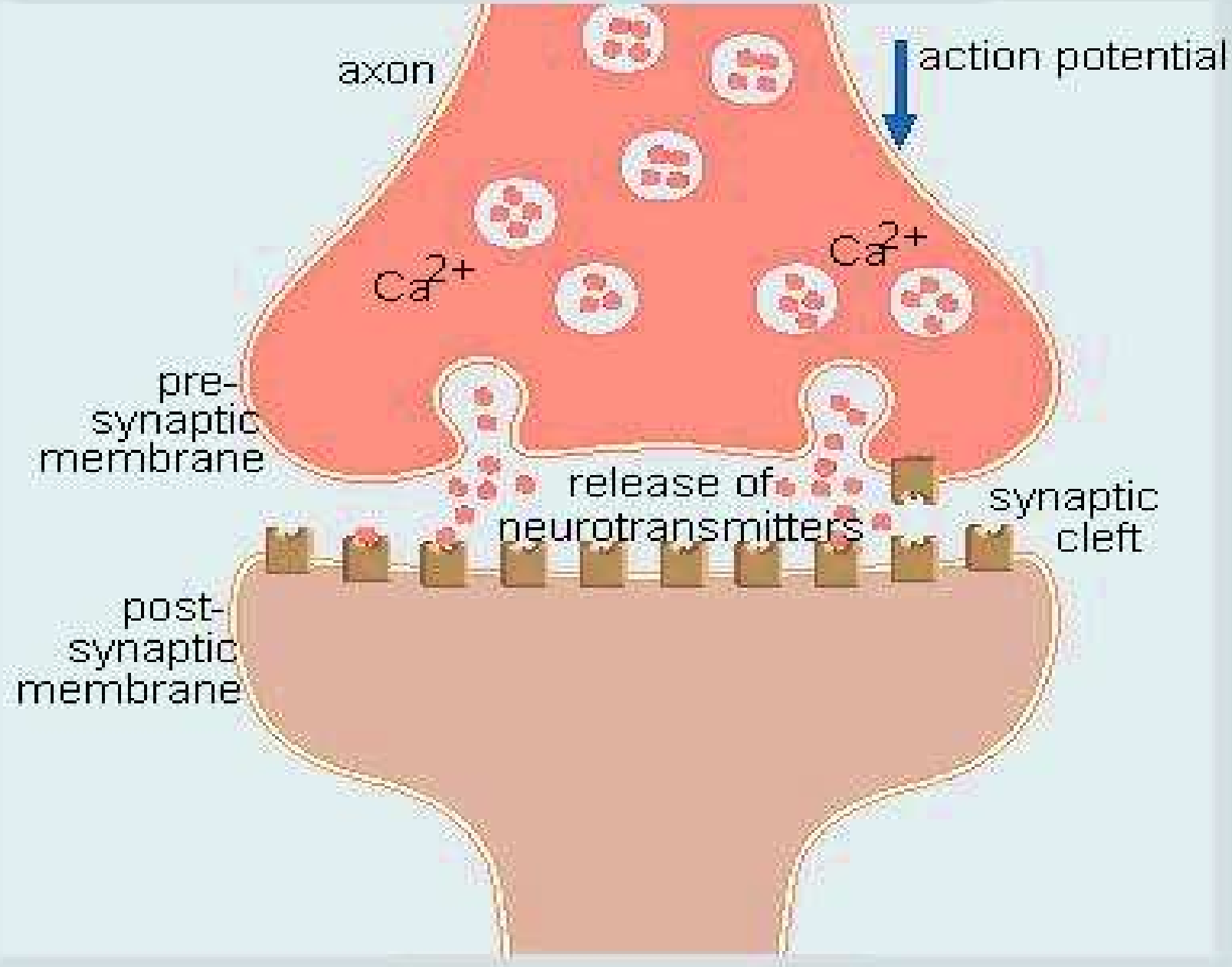
A - postsynaptic receptor

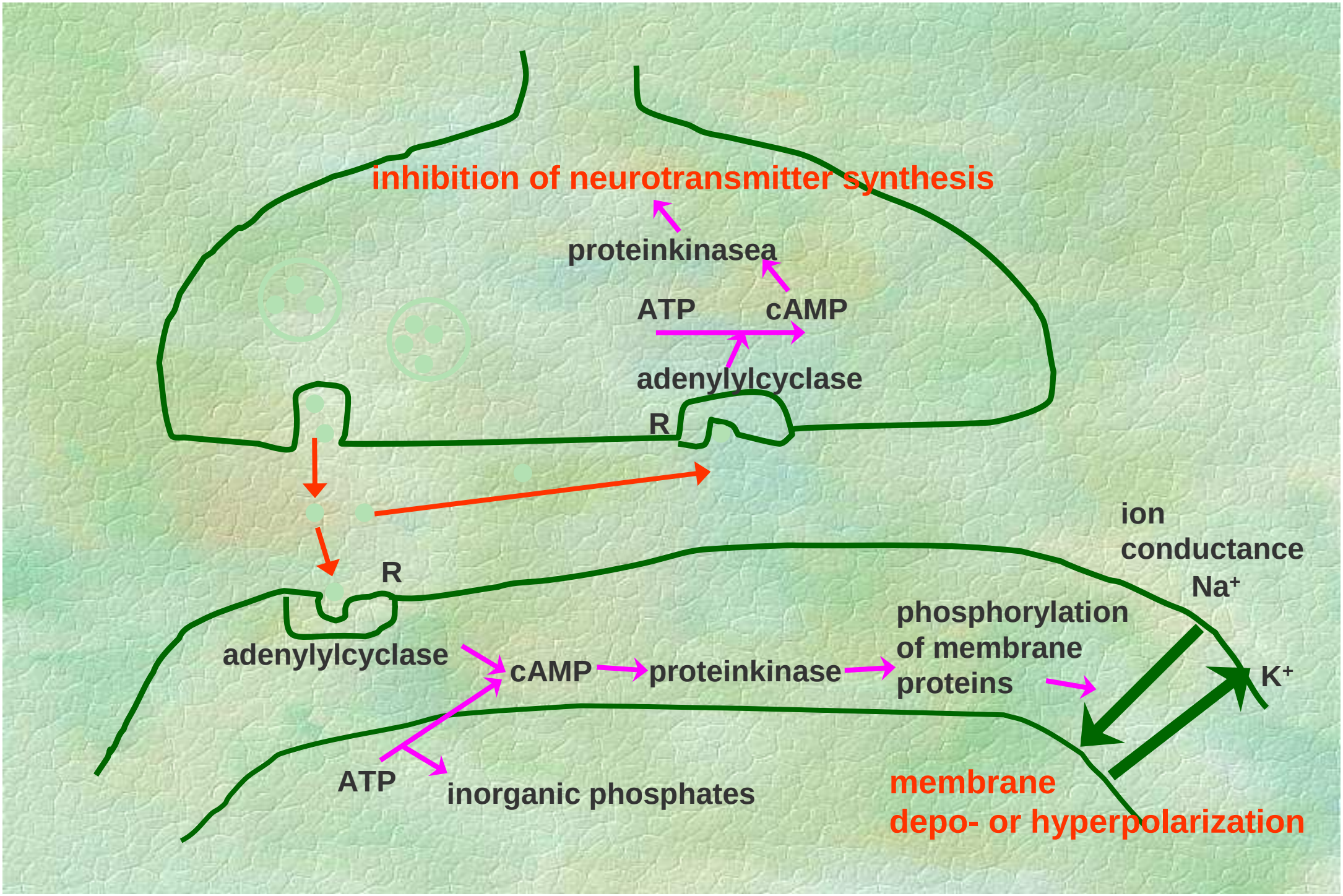
B - autoreceptor (presynaptic)

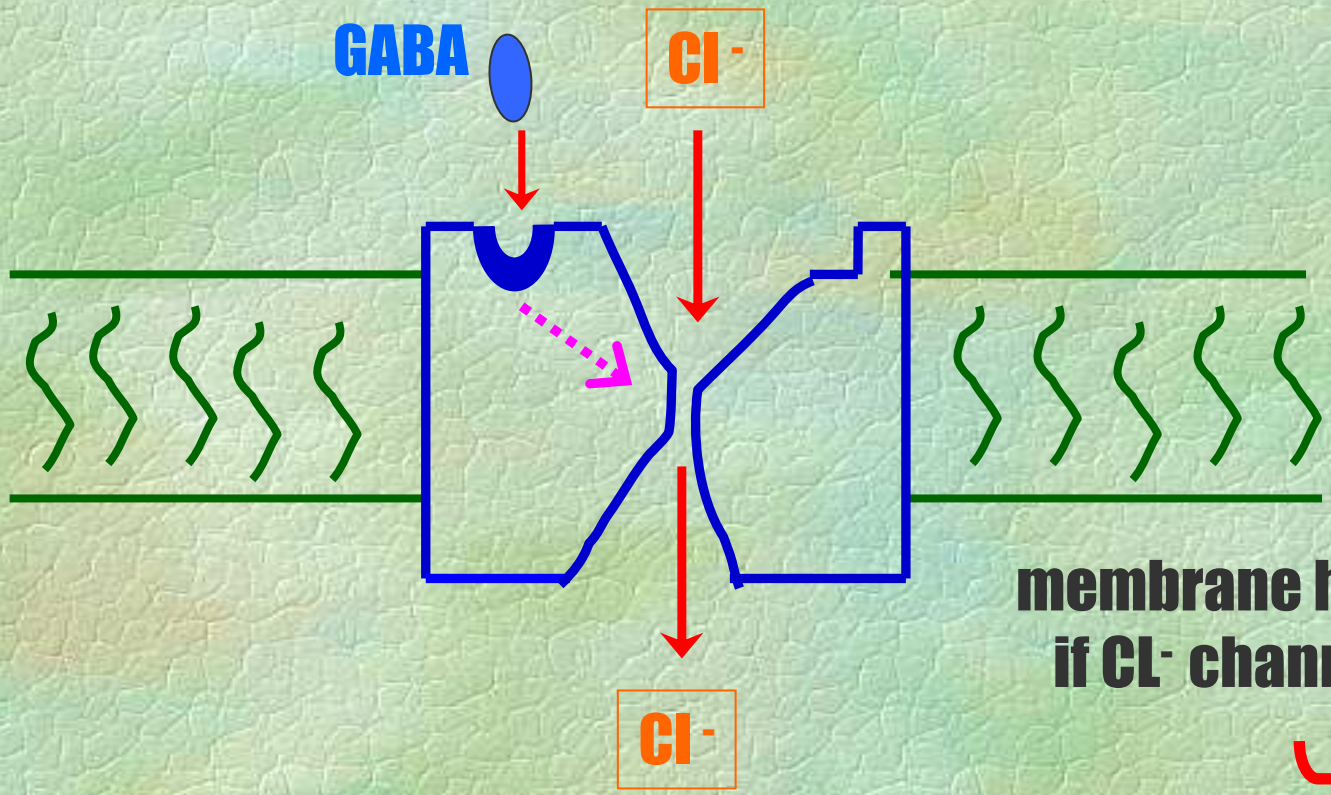
C - homoreceptor

D - heteroreceptor

Potential targets for transmitter released from nerve terminal

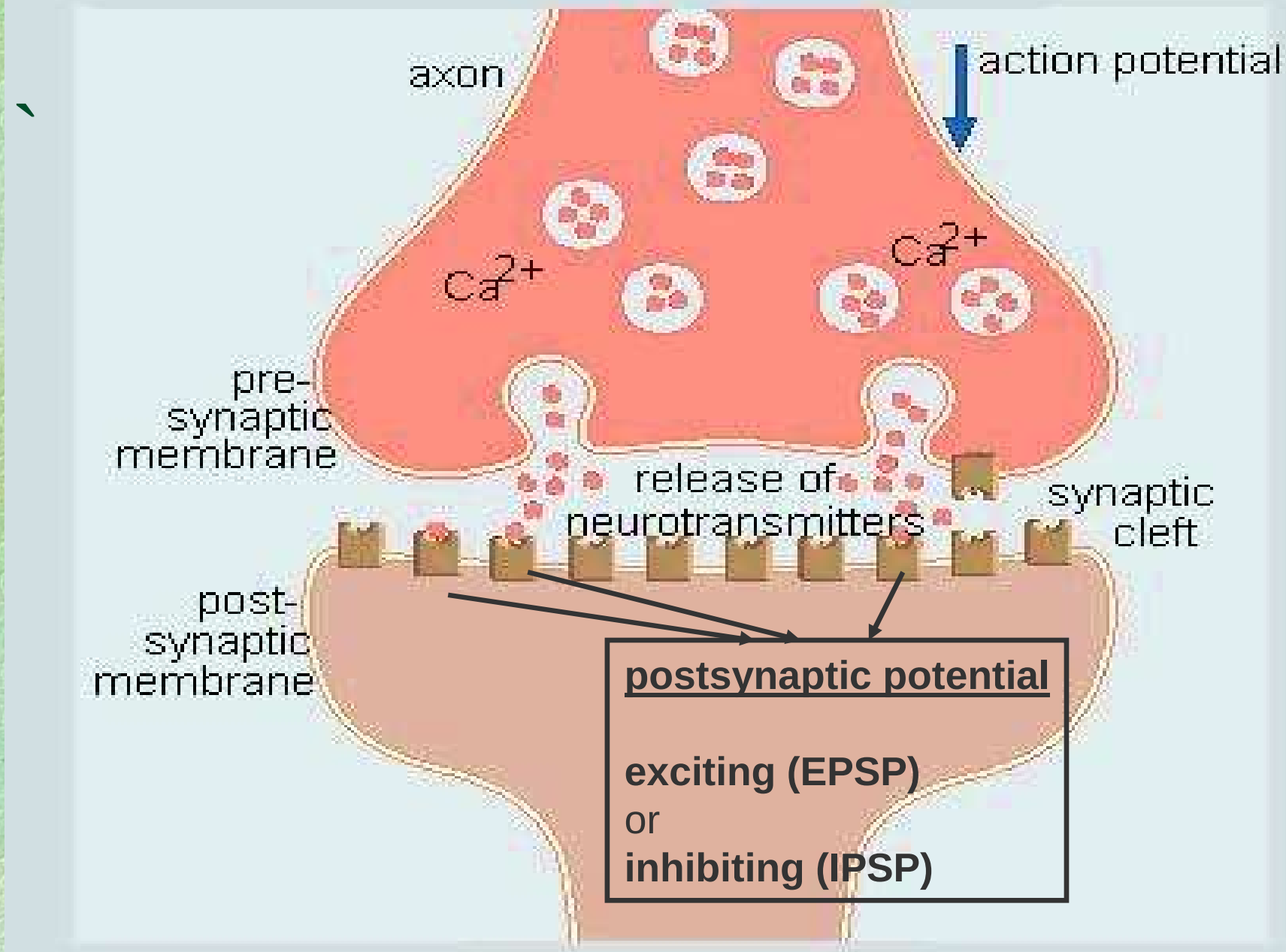

axon
action potential
Ca^{2+}
Ca^{2+}
pre-
synaptic
membrane
release of
neurotransmitters
synaptic
cleft
post-
synaptic
membrane


inhibition of neurotransmitter synthesis
proteinkinasea
ATP
cAMP
adenylylcyclase
R
R
adenylylcyclase
cAMP
proteinkinase
phosphorylation
of membrane
proteins
ion
conductance
Na+
K+
ATP
inorganic phosphates
membrane
depo- or hyperpolarization



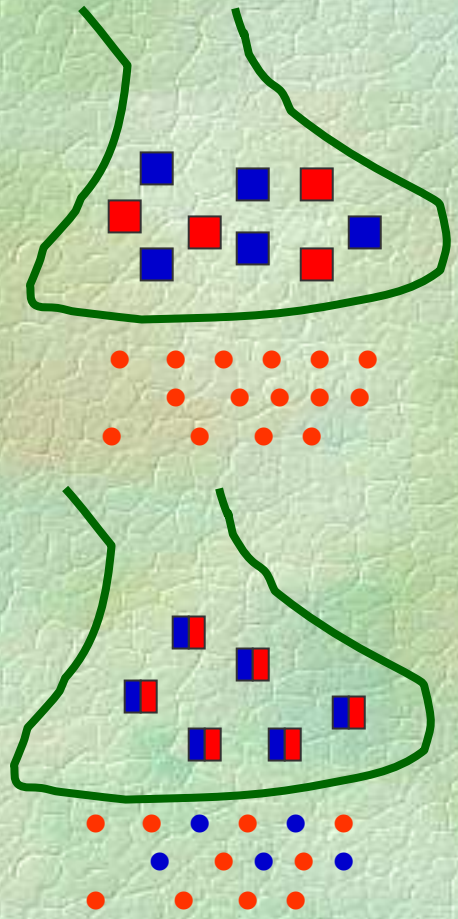
membrane hyperpolarization
if CL- channels are opened

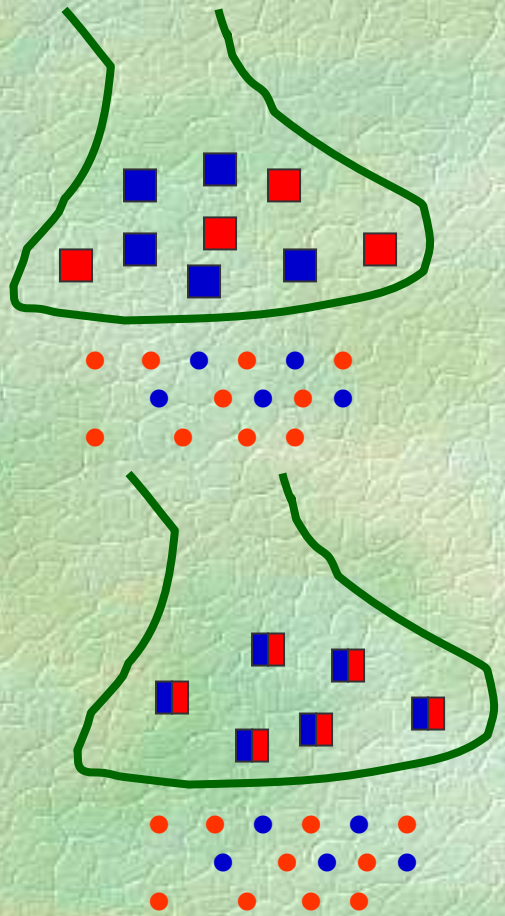
inhibiting influence
of GABA


axon
action potential
Ca^{2+}
Ca^{2+}
pre-
synaptic
membrane
release of
neurotransmitters
synaptic
cleft
post-
synaptic
membrane
postsynaptic potential
exciting (EPSP)
or
inhibiting (IPSP)

CO-TRANSMISSION

stimulation frequency

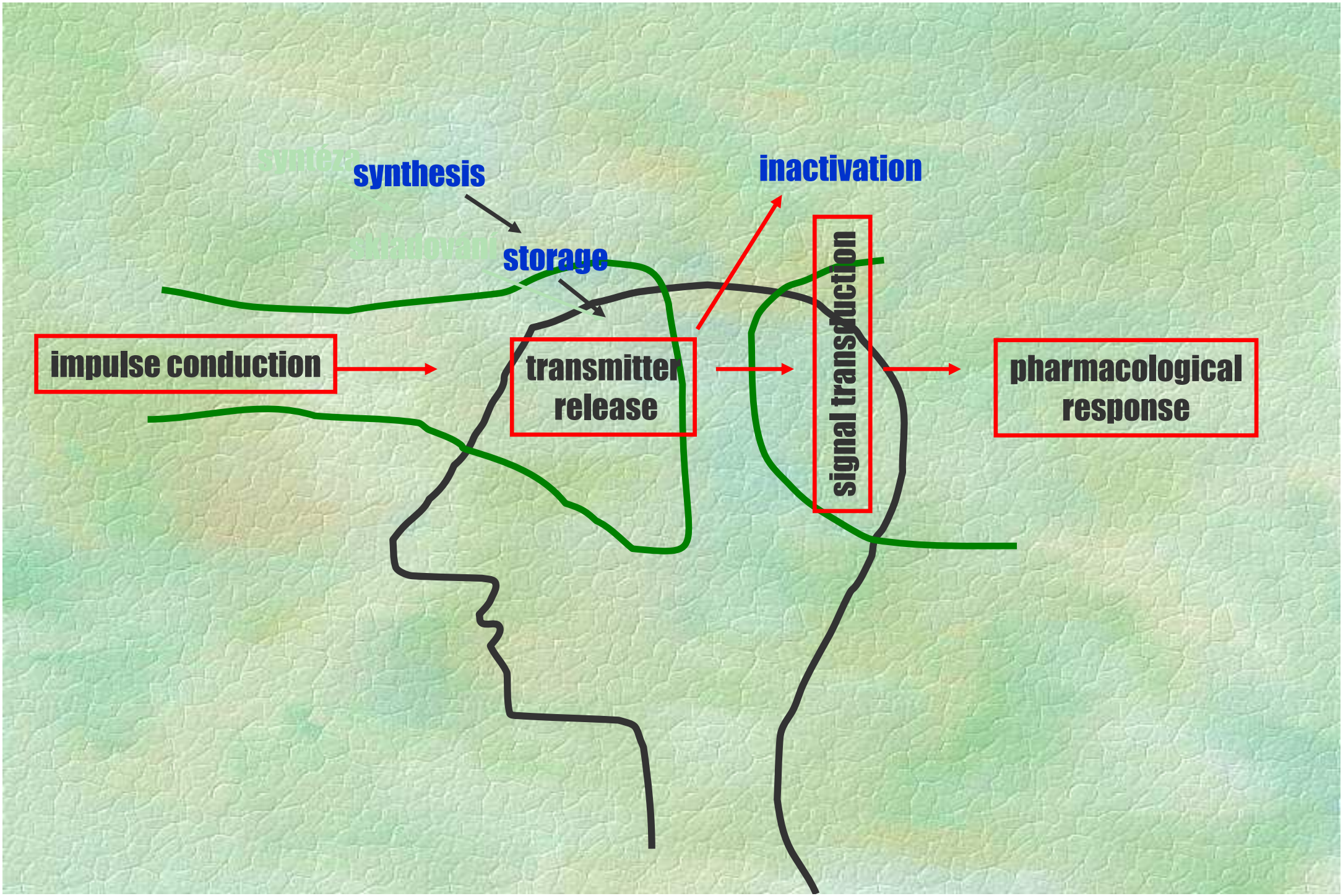




Co-transmission

- co-transmitters stored in the same vesicles; convey different messages to different receptors at the same time
- co-transmitters stored in the differential vesicles; released preferentially in response to different frequency nerve impulses

Exogenic influences affecting just one transmitter cannot simulate the physiological synaptic effects


synthesis
storage
inactivation
impulse conduction
transmitter release
signal transduction
pharmacological response

CNS SPECIFIC NEUROTRANSMITTERS

1. physiologically active substance; can be identified in appropriate regions together with enzymes needed for its synthesis and breakdown
2. can be identified in the perfusate of a region when stimulated but not when it is inactive
3. applied locally is capable of mimicking the effects of nerve stimulation
4. effects of the putative neurotransmitter and of nerve stimulation can be modified, enhanced, or attenuated in the same manner by appropriate drugs
5. on nerve stimulation is released selectively in dependence on intracellular calcium ion concentration
6. it is possible to increase/decrease its effects by administration of agonists/antagonists of relevant specific receptors
7. after release is rapidly inactivated by specific enzymes or re-uptake

CNS SPECIFIC NEUROTRANSMITTERS

1. physiologically active substance; can be identified in appropriate regions together with enzymes needed for its synthesis and breakdown

2. can be identified in the perfusate of a region when stimulated but not when it is

3

4

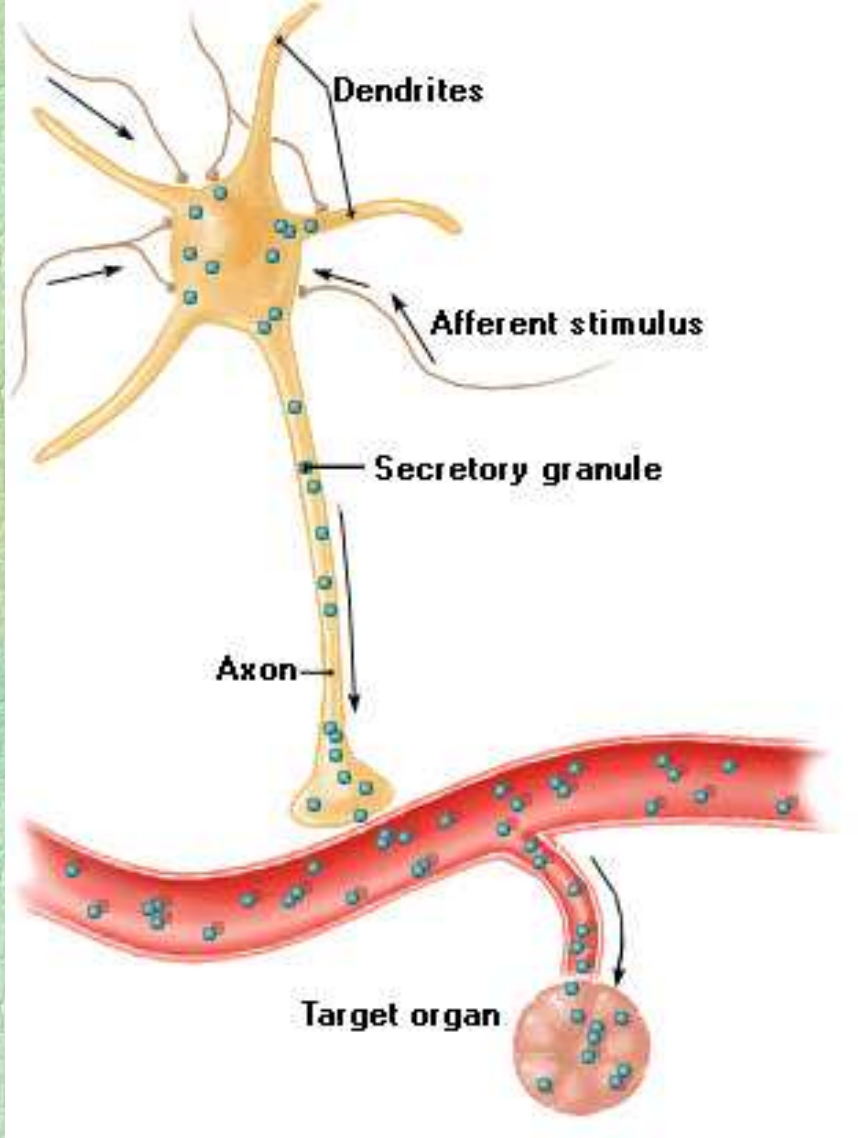
5

TO BE ABLE TO CONSIDER DRUG INTERACTIONS
WITH EACH NEUROTRANSMITTER
we study
synthesis, storage, release, breakdown, regulation,
specific receptors (and their subtypes)
for each neurotransmitter

6. it is possible to increase/decrease its effects by administration of agonists/antagonists of relevant specific receptors

7. after release is rapidly inactivated by specific enzymes or re-uptake

neurotransmitters released by nerve cells into blood circulation



NEUROHORMONES

e.g.:
oxytocine vasopressin,
gonadotropin, corticotropin . . .

NEUROMODULATORS (e.g. opioids, anandamide, NO ...)

biologically active in small amounts,

released on synapses, however, also by e.g. glial cells,

have impact on receptor activity either directly
or through interaction with neurotransmitter

Acetylcholine

synthesis choline → cholinacetyltransferase (acetyl ko-enzym A)
⇒ Ach → acetylcholinesterase ⇒ choline + acetate

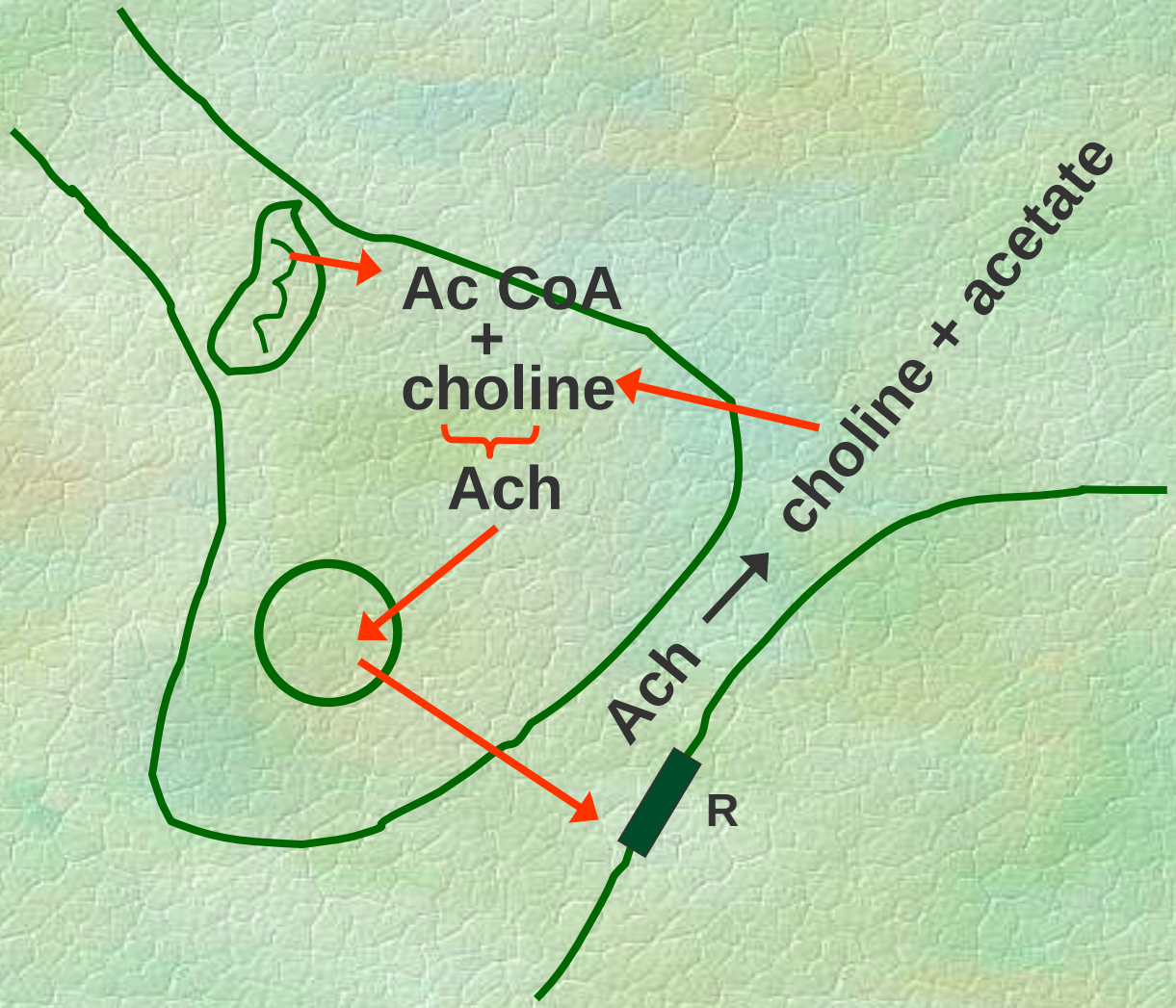
storage in synaptic vesicles

breakdown (very fast)
specific cholinesterase – in neurones and neuroeffector junction

pseudocholinesterase(butyrylcholinesterase) – throughout the body, including body fluids

re-uptake choline

Cholinergic synapse - acetylcholin (Ach)



Acetylcholin

continuation

receptors $M_{1\text{-}5}$ (muscarinic) - stimulation has slower and more sustained action, G-protein coupled

N (nicotinic) - stimulation has rapid and short action, part of receptor mediated Cl^- channels , often occurring as heteroreceptors (increase of neurotransmitter release)

Ach ↑ IQ (learning, memory, attention, emotions, nociception, sleep . . .)

Ach ↓ demention, delirium

Catecholamines

dopamine (basal ganglia, limbic system . . .)

noradrenaline (hypothalamus, cortex, cerebellum)

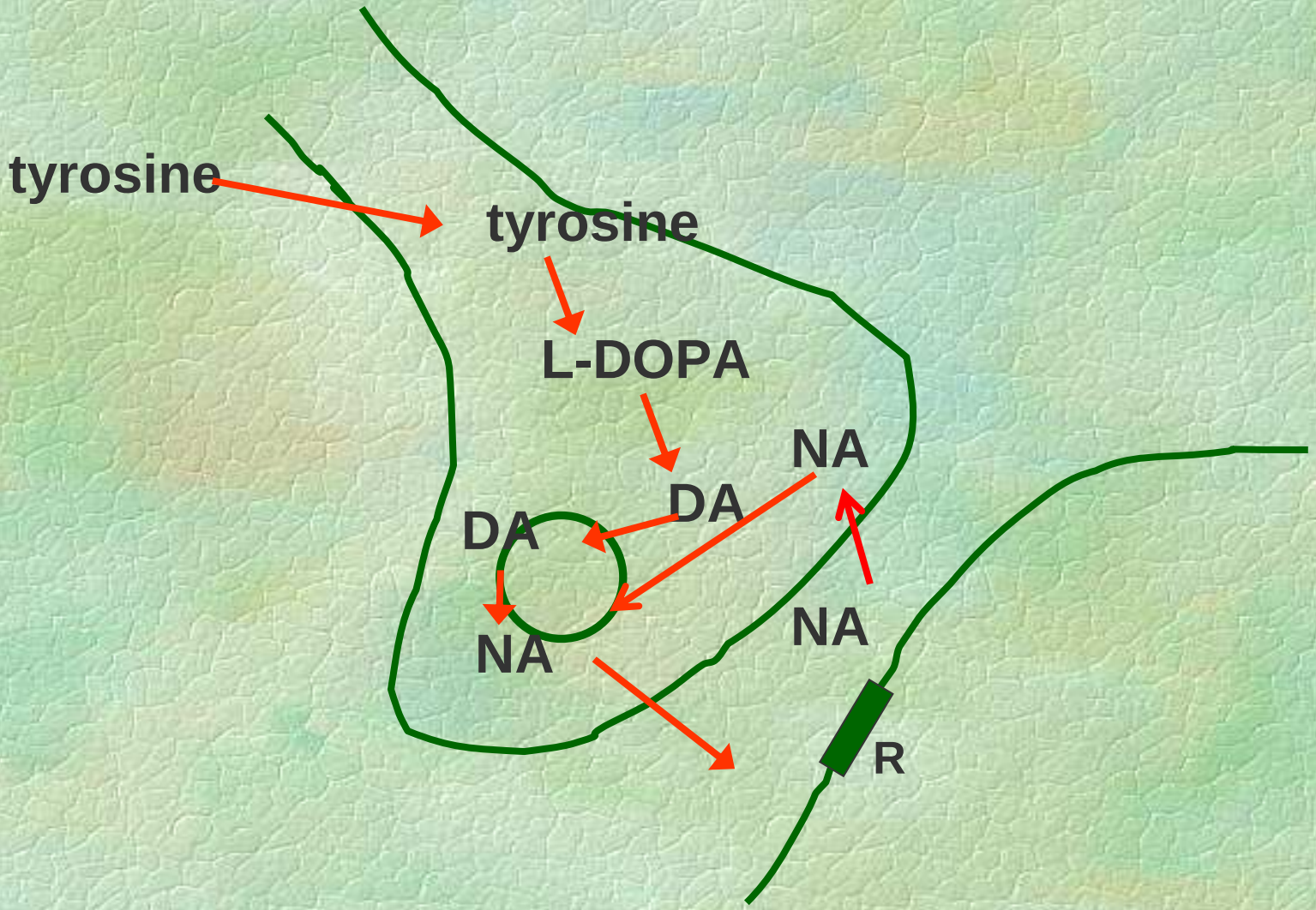
adrenaline

synthesis tyrosine → tyrosine hydroxylase ⇒ DOPA → decarboxylase ⇒ dopamine → hydroxylasea ⇒ noradrenaline → N-methyltransferase ⇒ adrenaline

storage - in vesicles (with ATP - 4 : 1)
- free in cytoplasmic fluid

breakdowb - re-uptake !!
- diffusion
- intracellularly - MAO_A (A a Na) + MAO_B (DA)
  extracellularly - MAO_B + COMT

Adrenergic synapse - noradrenaline (NA) (norepinephine)



Catecholamines

continuation

receptors

DA r. - partly sensitive to A a Na, too

$D_{1, 5}$ - coupled to adenylylcyclase → ↑ cAMP – excitation

$D_{2, 3, 4}$ - coupled to phosphodiesterase (cAMP degradation) - ↓cAMP - inhibition

adrenergic r. (in the CNS in neurons; on vessels)

- α

  α_1 - stimulation of phosphatidylinositol metabolism

  α_2 - ↓cAMP
  ↑ K^+ channel
  ↓ Ca^{2+} channel
  } regulated by G-protein

- $\beta_{1, 2, 3}$ - ↑ cAMP

Katecholaminy

continuation

Na (A) ↑ unrest

Na (A) ↓ sedation, depression

DA ↑ aggressivity

DA ↓ apathy

Serotonin (5-HT)

synthesis tryptophan → hydroxylase ⇒ 5-hydroxytryptophan →
decarboxylase ⇒ 5-hydroxytryptamine (5-HT)

storage - in vesicles (with ATP) in presynaptic terminals
- in a mobile extravesicular cytoplasmic pool

breakdown - re-uptake ! !
- MAO_A (cytoplasmic)

receptors $5\text{-}HT_{1A, B, C, D}$ - ↓ cAMP
$5\text{-}HT_{2A, B, C}$ - stimulation of phosphoinositol metabolism
$5\text{-}HT_{4}$ - ↑ cAMP
$5\text{-}HT_{5A, B}$
$5\text{-}HT_{6, 7}$

= metabotropic receptors

$5\text{-}HT_3$ - stimulation of ion channels (= ionotropic receptor)

Serotonin (5-HT)

continuation

5-HT ↑ anxiety, aggressivity

5-HT ↓ sedation, depression

GABA (gama-aminobutyric acid)

synthesis glutamic acid $\rightarrow\rightarrow\rightarrow$ decarboxylase $\Rightarrow$ GABA

storage in neurones, in glial cells

beakdown - re-uptake
- GABA-transaminase (in neurones, in glial cells]

receptors $GABA_A$, $GABA_C$ - part of Cl^- channel structure, (postsynaptic)

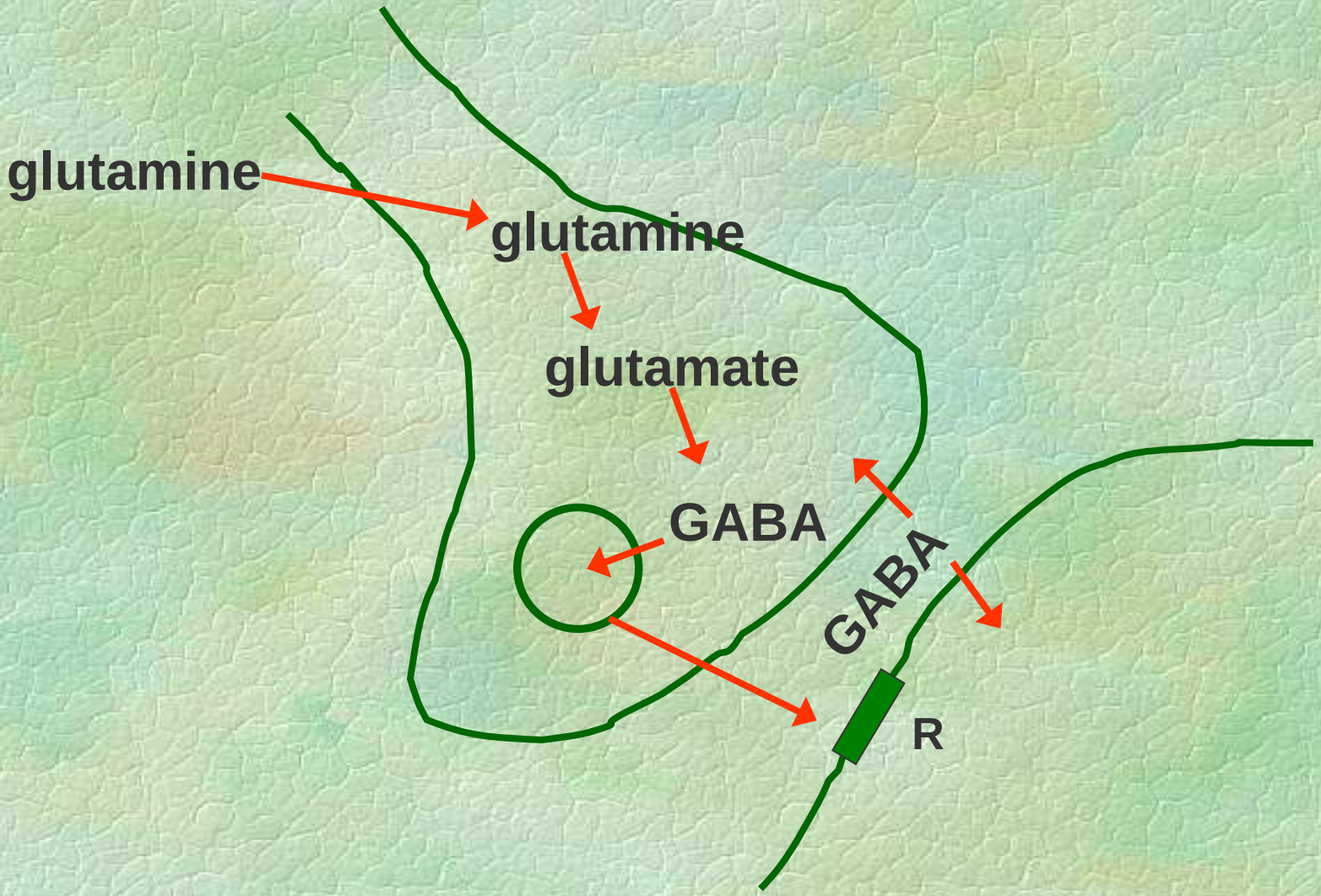
$GABA_B$ - ↓ cAMP
↑ K^+ kanálu
↓ Ca^{2+} kanálu,
(presynaptic)

GABA ↑
(sleep)

GABA ↓
(anxiety)

GABAergic synapse

gama-aminobutyric acid (GABA)



Excitatory amino acids - glutamate, aspartate

receptors

ionotropic:

- **NMDA r (NR_{1-3}) -** **(N-methyl-D-aspartate, glutamate)**
- **AMPA r. ($GluR_{1-4}$) – (alfa-amino-3-hydroxy-5- methyl-4-isoxazolepropionic acid)**
- **kainate-ergic r. ($GluR_{5-7}$, KA_1, K_2)**

metabotropic, G-protein coupled:

$mGluR_{1-8}$ inhibition of glutamate release from presynaptic terminal or Increase of phosphatidylinositol turnover

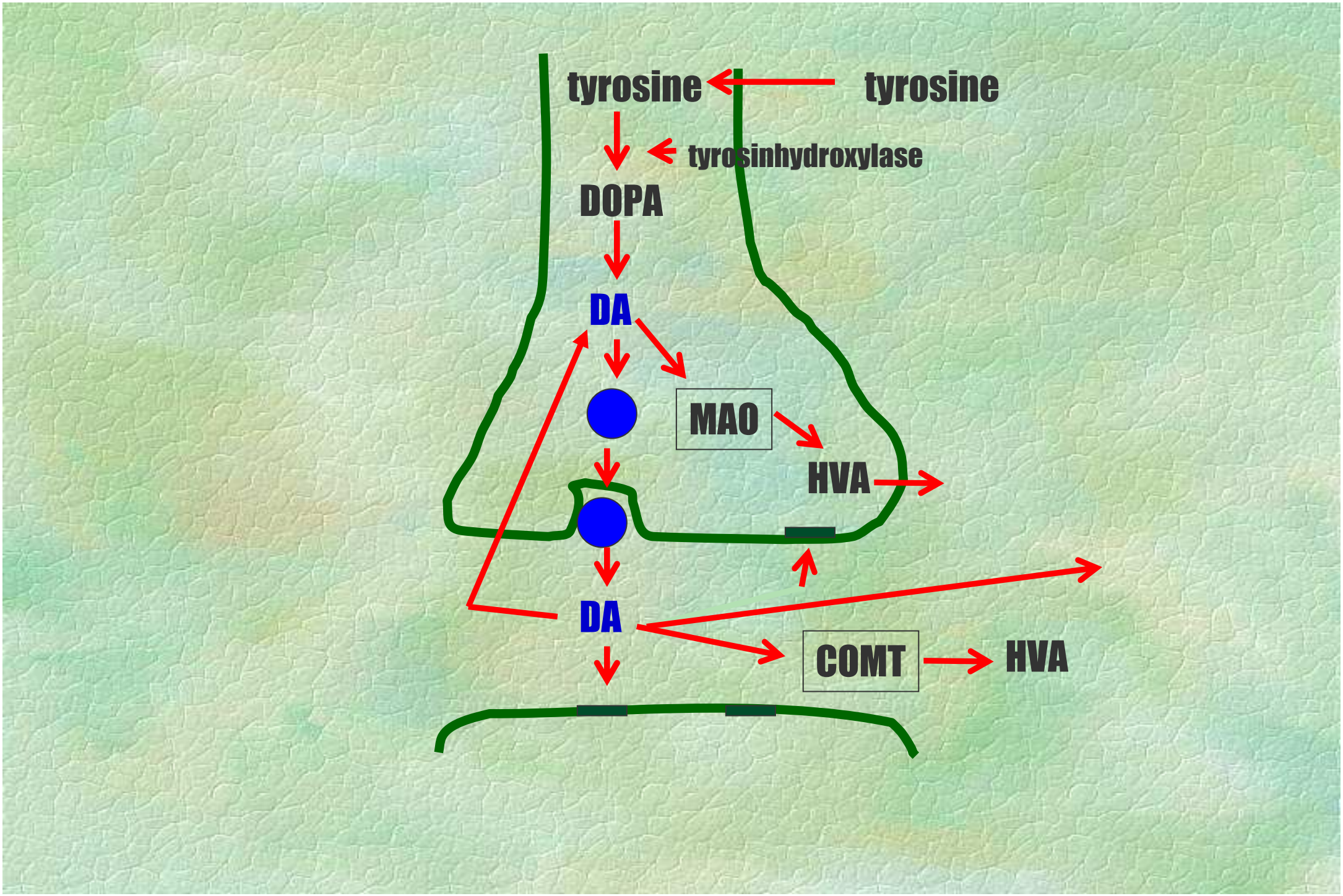
memory functions, learning processes

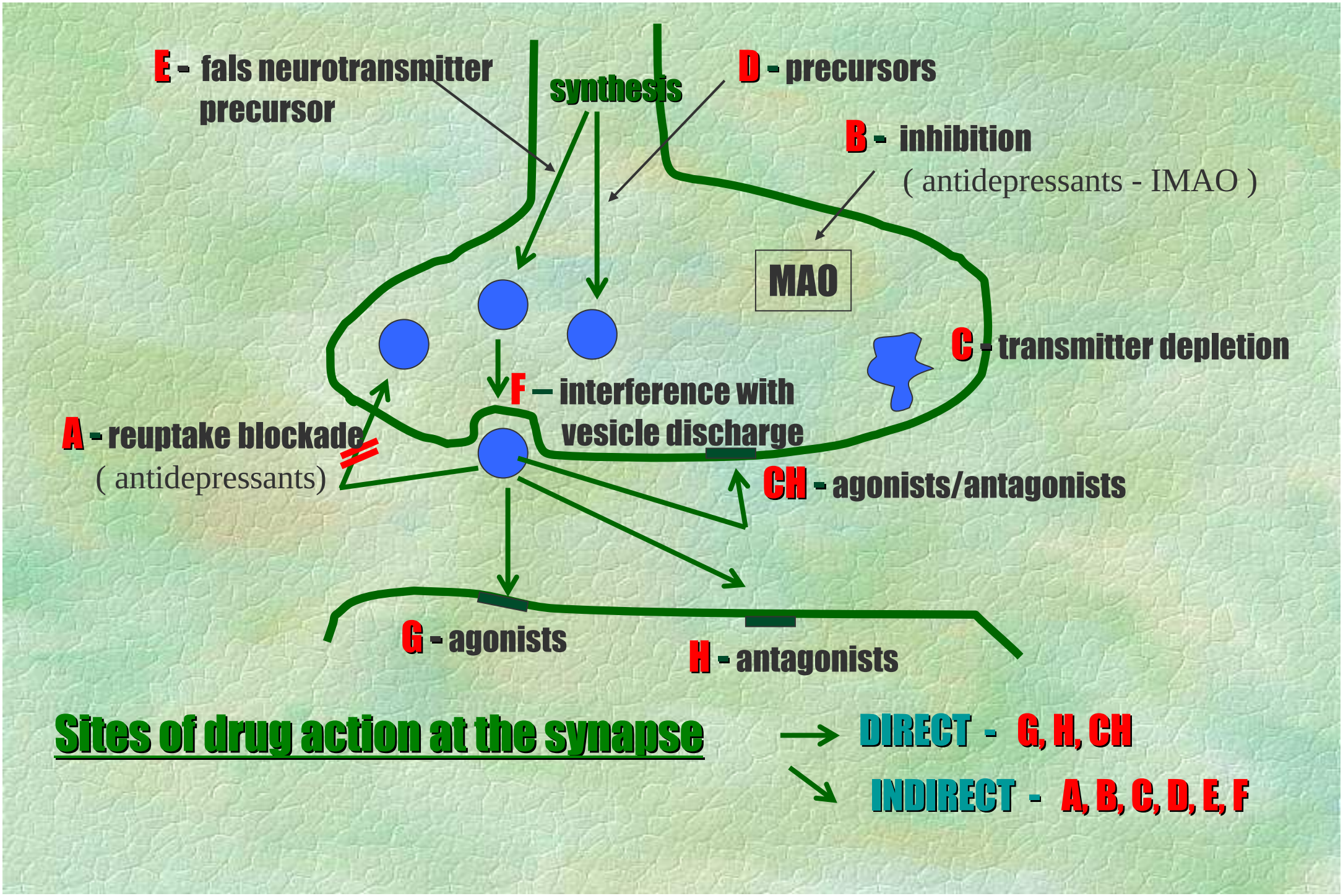
Other neurotransmitters, co-transmitters, neurohormones

endogenic opioids (enkefaline, endorphine, dynorphine) ↑ euforia
↓ anhedonia

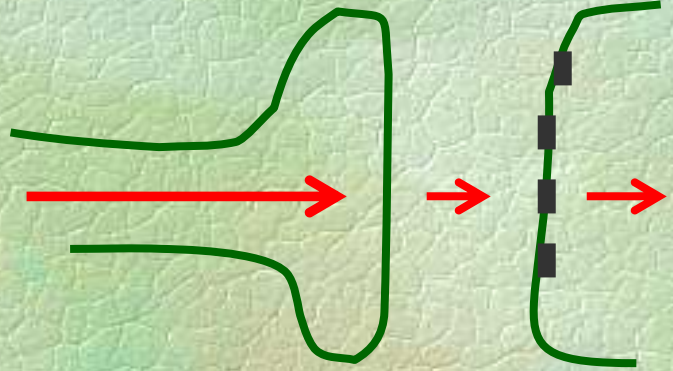
cholecystokinine (CCK) ↑ satiety, panic disorder
↓ hunger

angiotensine
gastrine
neurokinines
neuropeptide Y
neurotensin
substance P
bradykinine
somatostatin
.....
.....

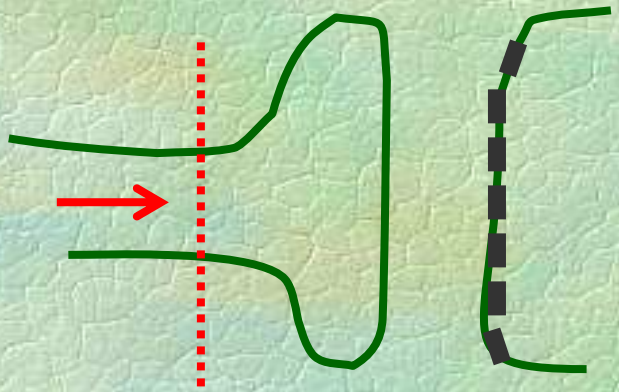

tyrosine
tyrosine
tyrosinhydroxylase
DOPA
DA
MAO
HVA
DA
COMT
HVA


E - fals neurotransmitter precursor
synthesis
D - precursors
B - inhibition
(antidepressants - IMAO)
MAO
C - transmitter depletion
F – interference with vesicle discharge
A - reuptake blockade
(antidepressants)
CH - agonists/antagonists
G - agonists
H - antagonists
Sites of drug action at the synapse
DIRECT - G, H, CH
INDIRECT - A, B, C, D, E, F

RECEPTOR SENSITIVITY

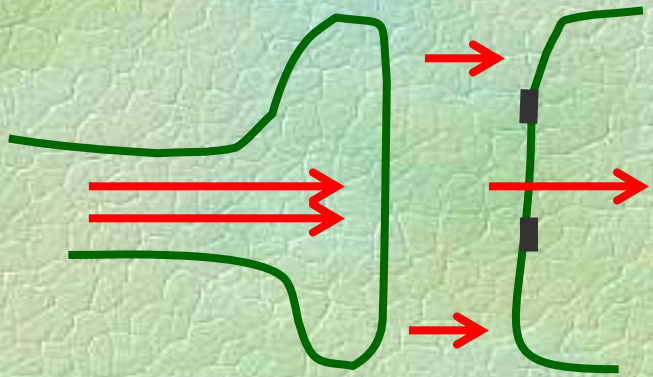


denervation supersensitivity
and chronic influence of antagonists

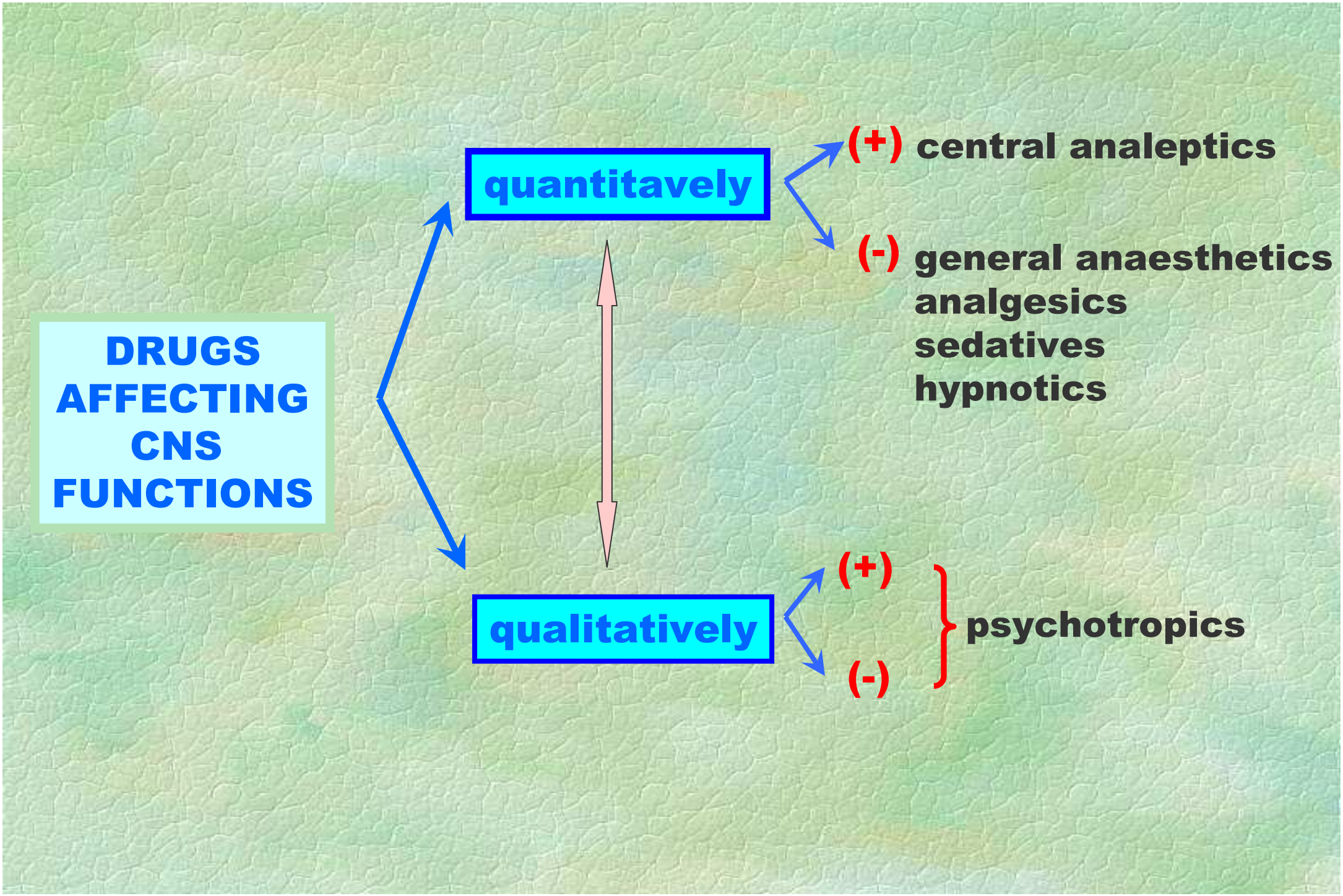


receptor system "up-regulation"

chronic influence of agonists

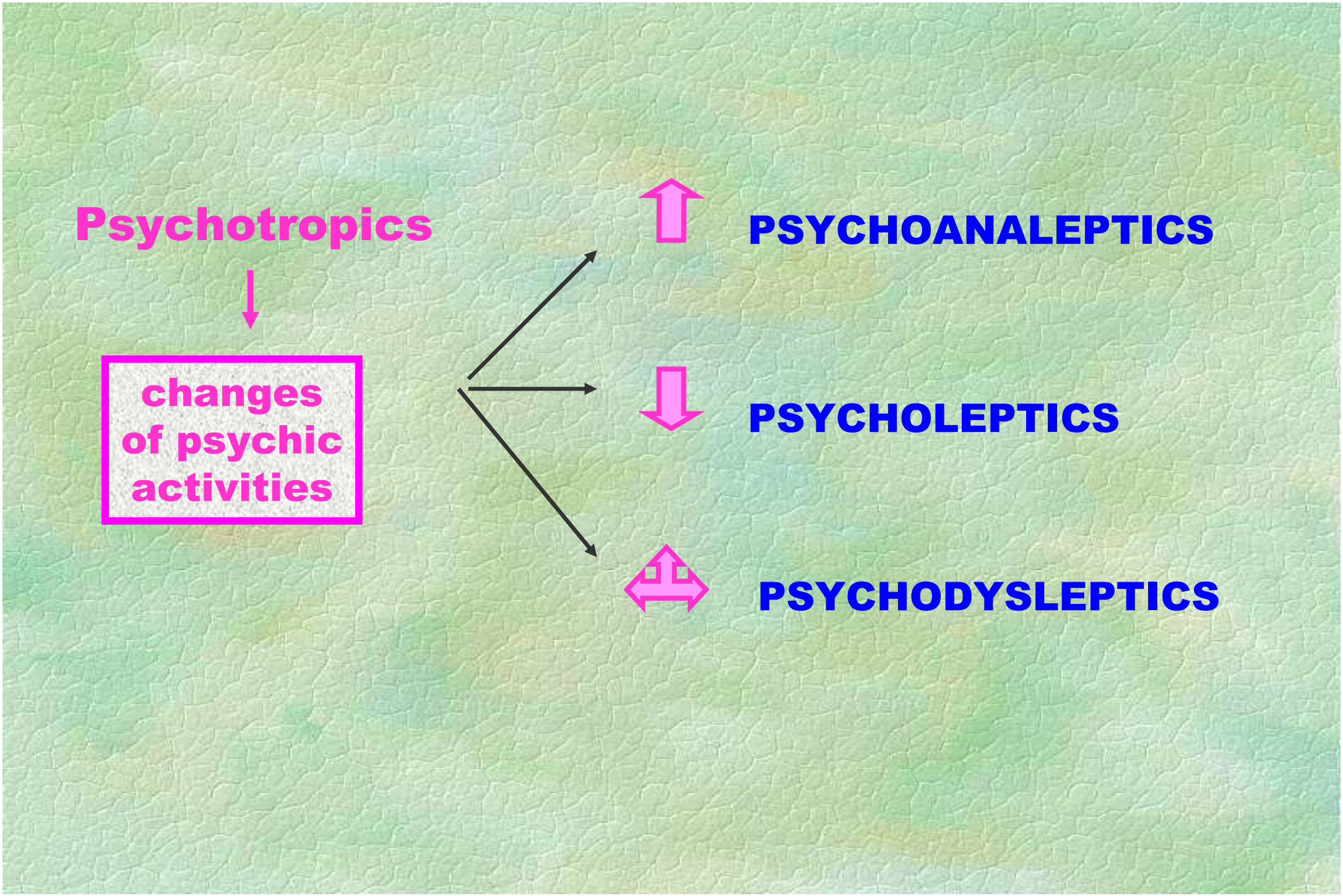


receptor system "down-regulation"


DRUGS AFFECTING CNS FUNCTIONS
quantitavely
(+) central analeptics
(-) general anaesthetics
analgesics
sedatives
hypnotics
qualitatively
(+)
(-)
psychotropics

PSYCHOTROPICS → **treatment of psychic disorders**

= inducing behavioural changes


Psychotropics
changes of psychic activities
PSYCHOANALEPTICS
PSYCHOLEPTICS
PSYCHODYSLEPTICS

neurotransmitters

inhibitory a excitatory

imbalanced functions = PATHOLOGICAL CONDITION

depression, anxiety, sleeping disorders, epilepsy, parkinsonism . . . .

" Neurotransmitter diseases "

↑ activity
of the neurotransmitter
system

↓ activity
of the neurotransmitter
system

Differential neuronal pathways use the same neurotransmitter

↓

it is difficult to target exogenous modulation on just one of them

↓

origin of adverse effects of drug acting in the CNS