Pharmacological treatment of psychosis and depression

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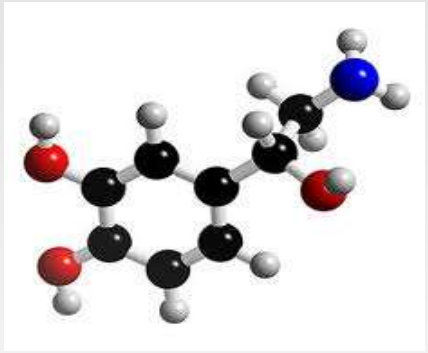
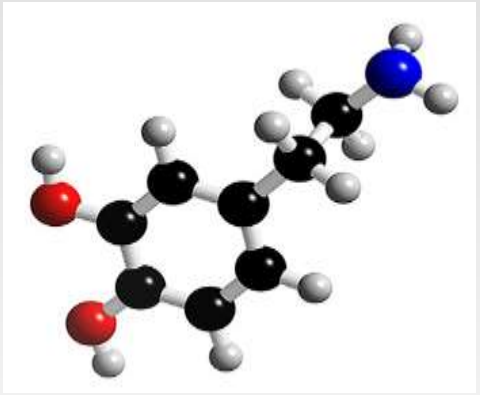
2019. 11. 08

NEUROTRANSZMITTERS in the central nervous system I

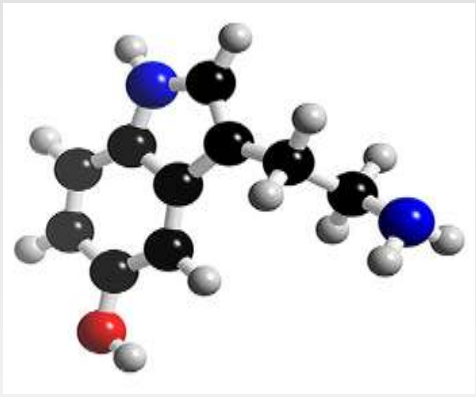
Monoamines



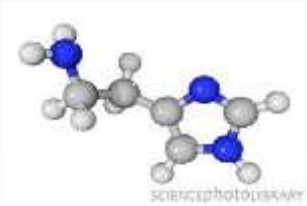
noradrenalin/adrenalin



dopamine

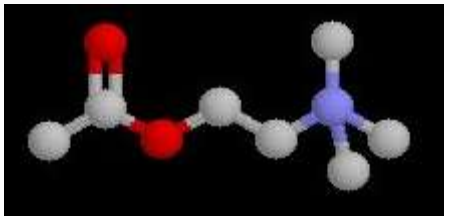


serotonin



histamine

Acetylcholine

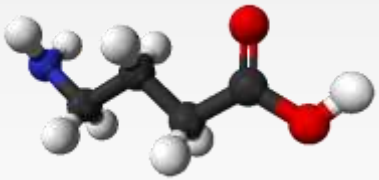


NEUROTRANSZMITTERS in the central nervous system II

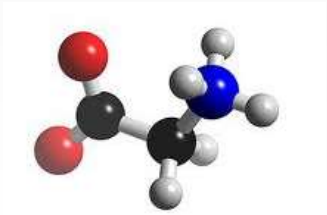
Amino acid transmitters

Neutral amino acids (inhibitory)

GABA gamma butyric acid

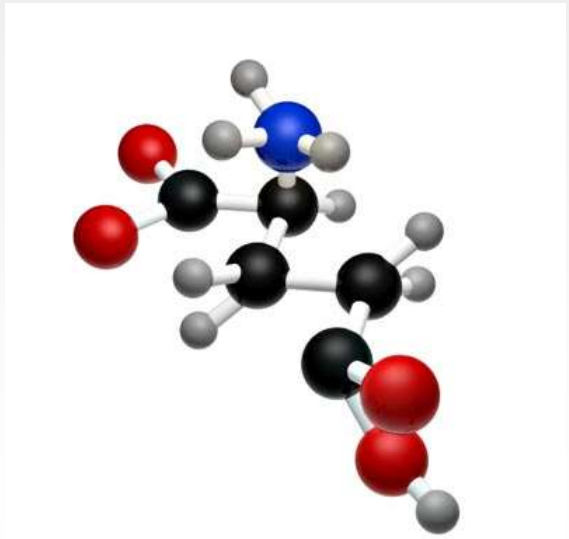


glycine

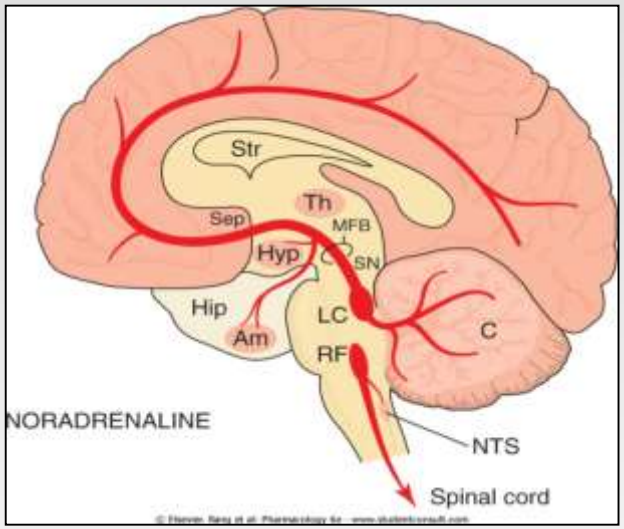


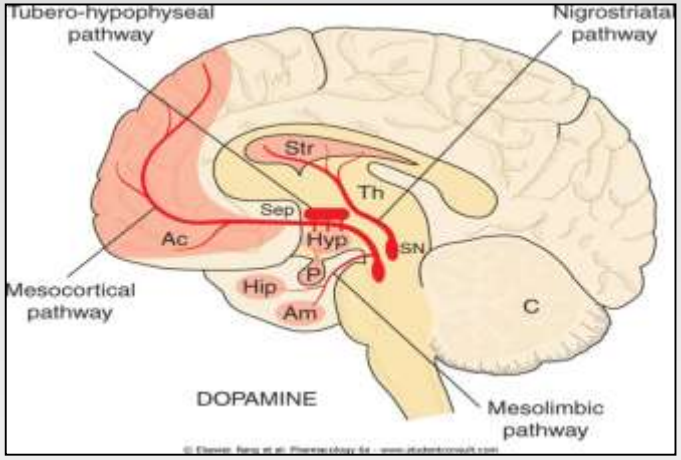
Acidic amino acids (excitatory)

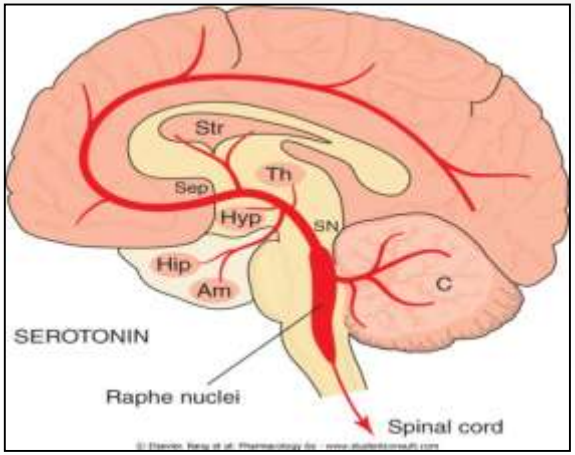
glutamate

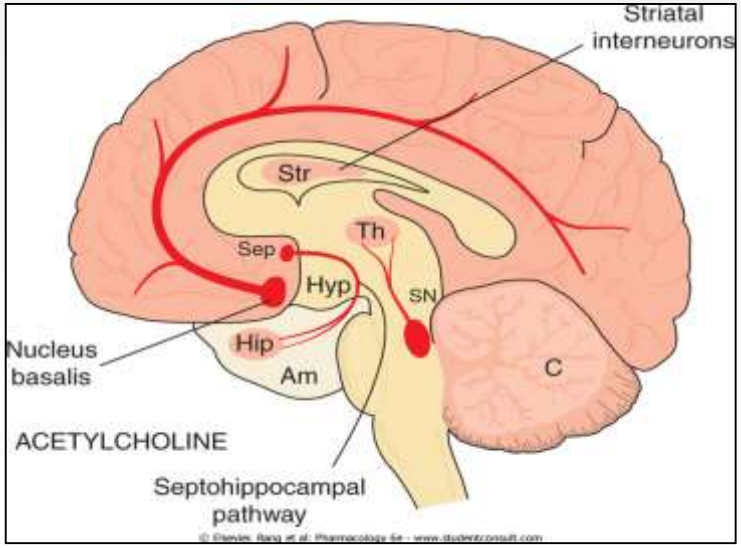


Diffuse neuronal systems



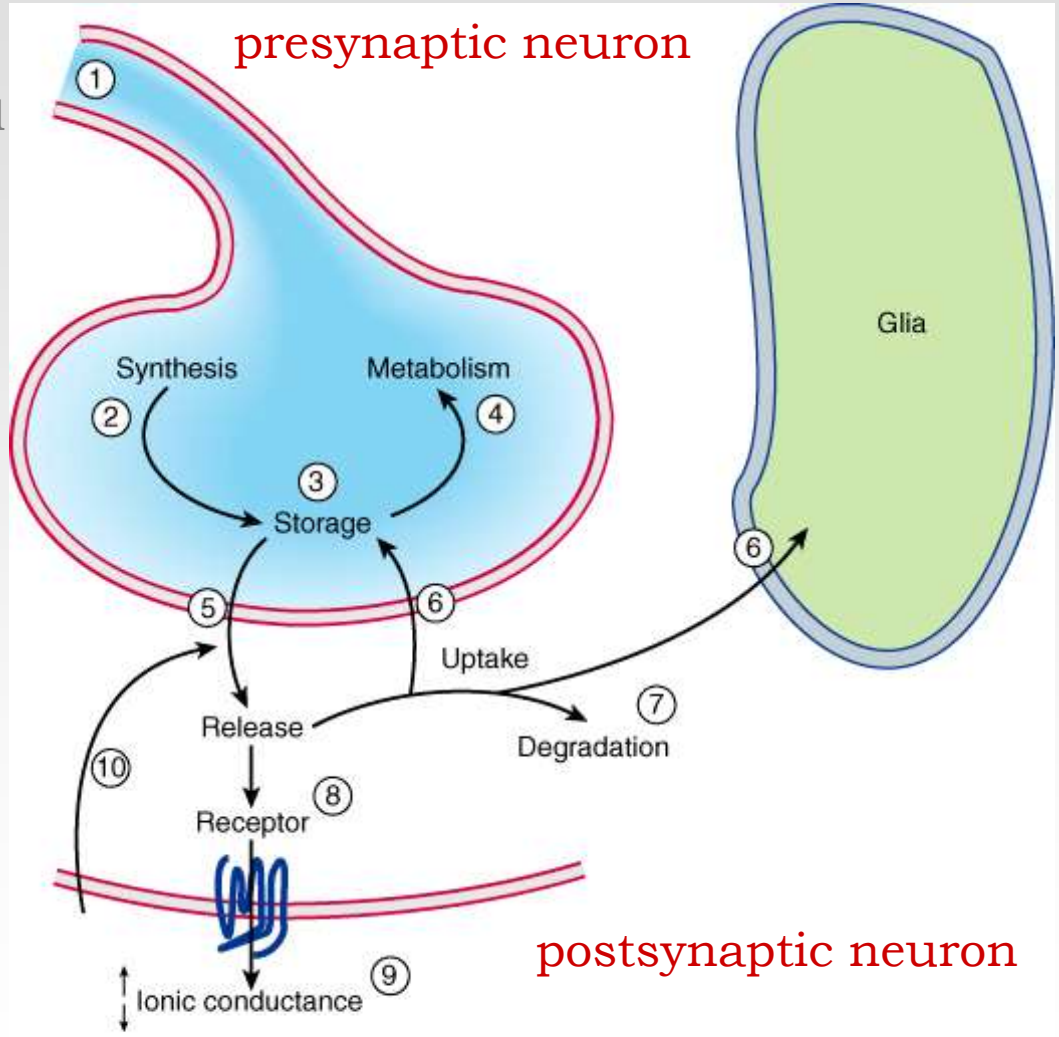






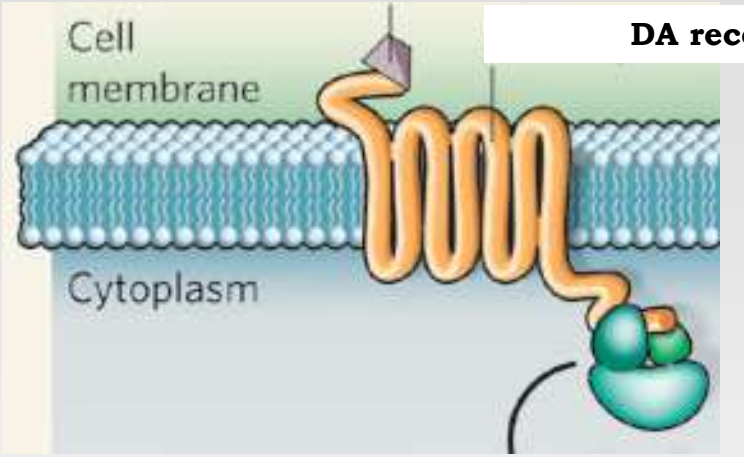
Sites of drug action in the CNS

action potential



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

DOPAMINE RECEPTORS



DA receptors

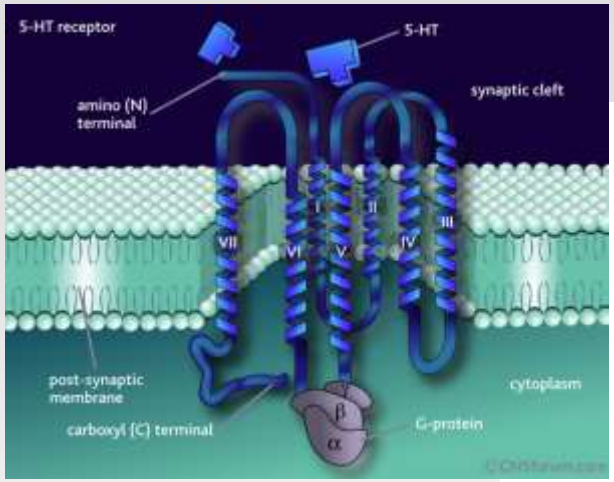
D_1 receptor family – D_1, D_5 – G_s-coupled - cAMP↑

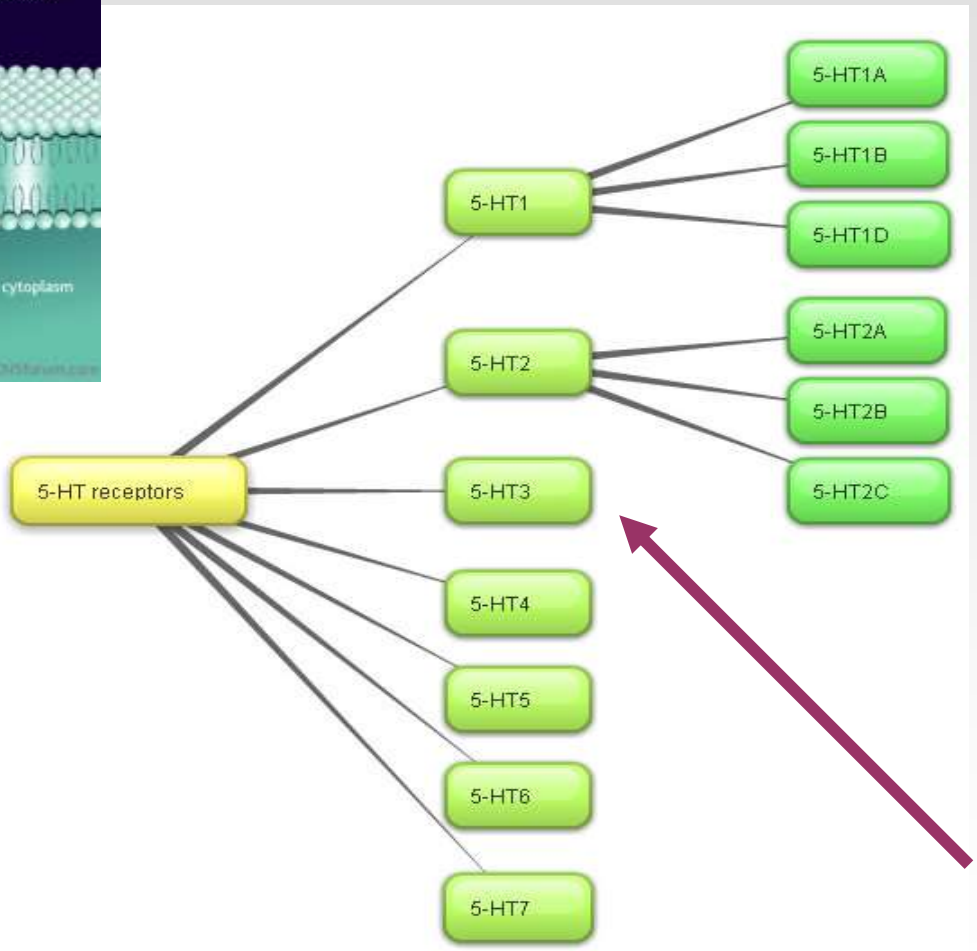
localization - postsynaptic

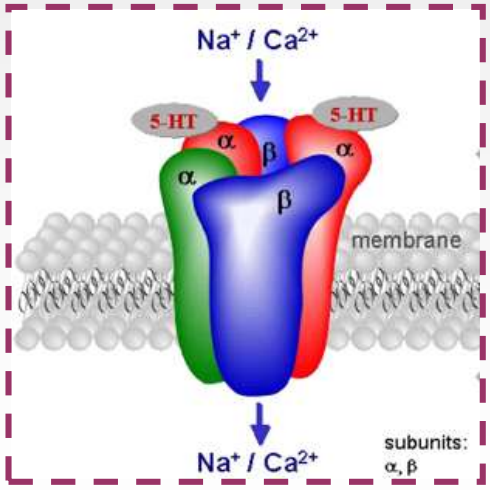
D_2 receptor család – D_2, D3, D_4 – G_i-coupled - cAMP↓

localization - pre (D_2,D_3) - and postsynaptic

Serotonin receptors







Pharmacological treatment of psychosis

SCHISOPHRENIA

A schizophrenia a neurodevelopmental, genetic disorder with high, but incomplete heritability, with a 1% prevalence. Neurodevelopmental disorder?

Positive symptoms

hallucination (acoustic), delusions (false belief), paranoia
(systematized delusions)
agitation, psychomotor excitation
conceptual disorganization,
verbal and physical aggressiveness

Negative symptoms

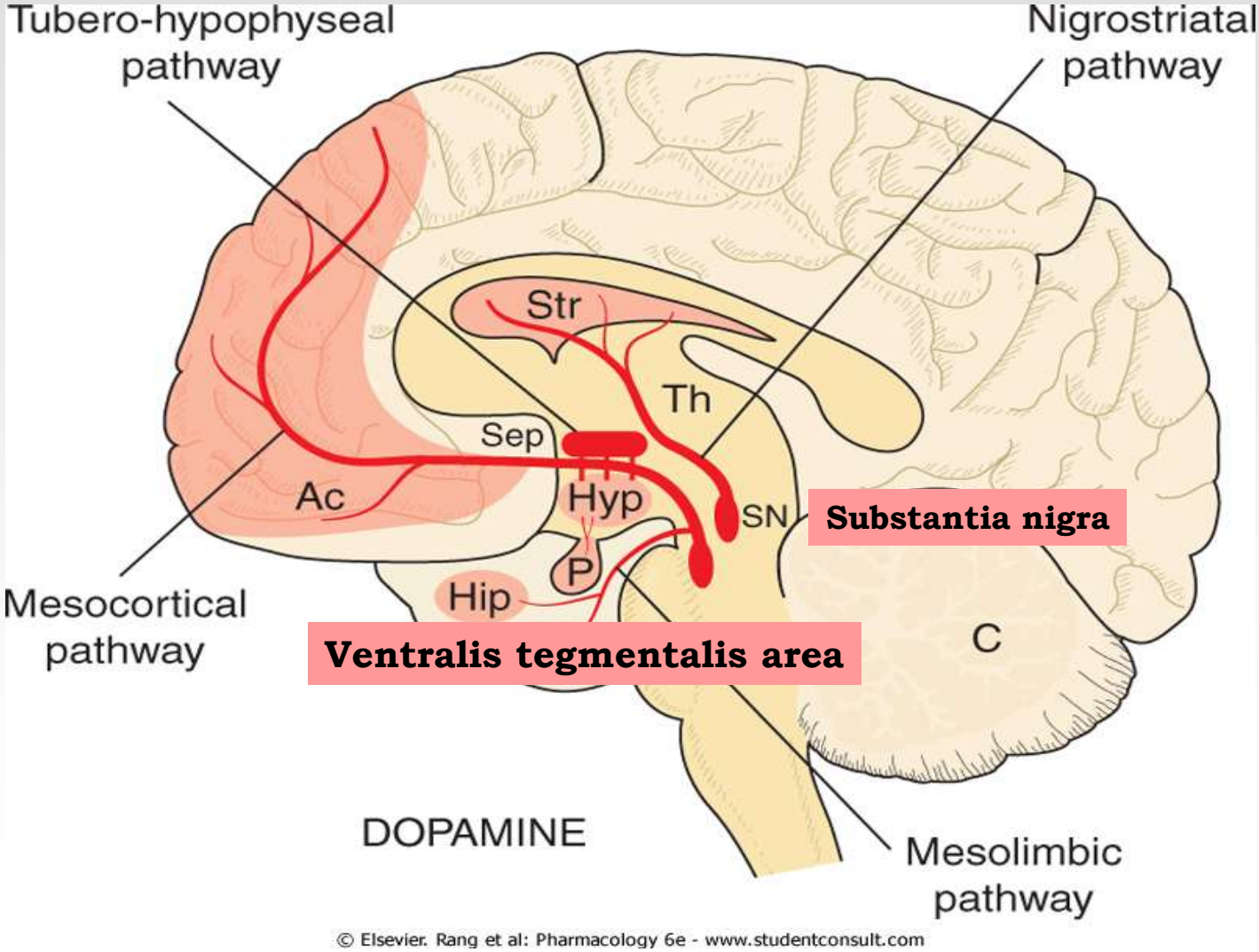
anhedonia; apathy, social and emotional withdrawal, reduced capacity

Cognitive deficit

impairment of memory and attention, reduced ability to abstract, reduced vigilance

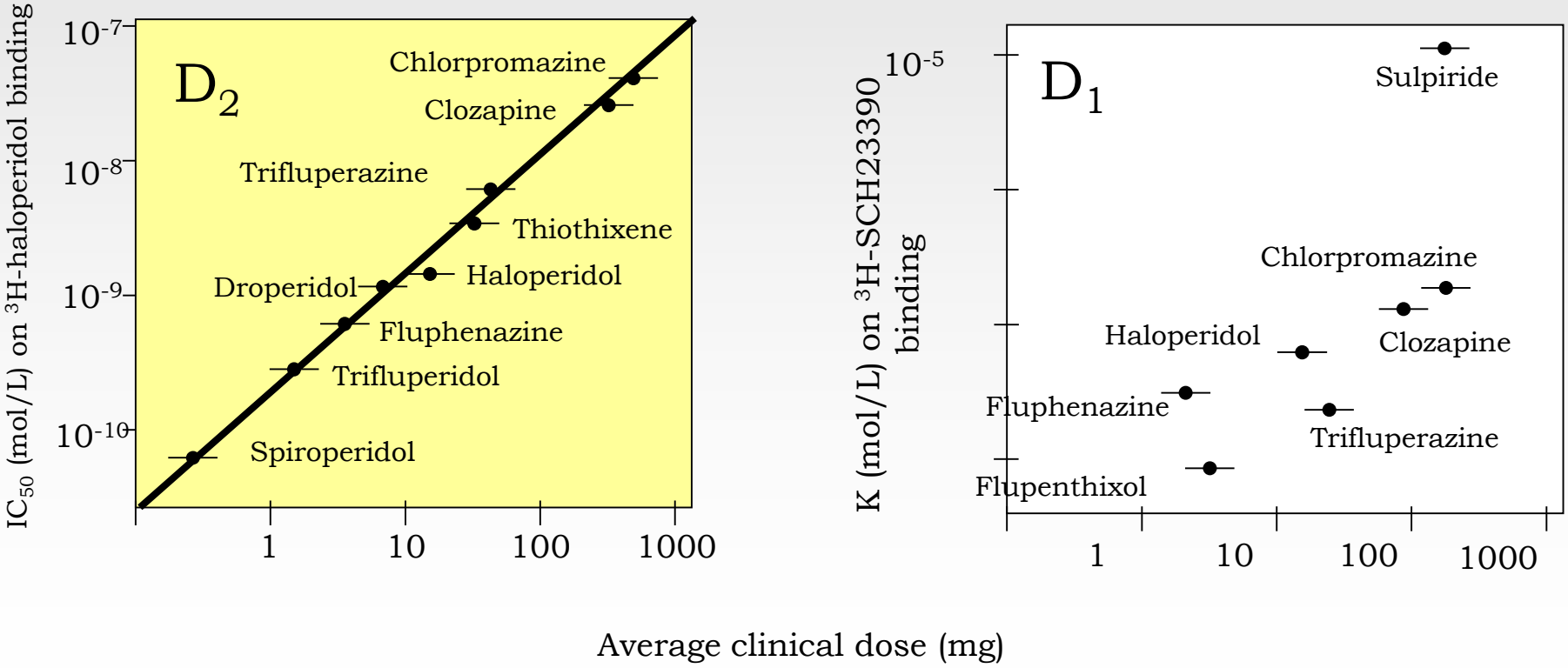
MOLECULAR BACKGROUND of SCHIZOPHRENIA I

DA – „hypothesis”



Arguments for the dopamine hypothesis:

- most (all) of the antipsychotic drugs used until now block postsynaptic D_2 receptor



Arguments for the dopamine hypothesis:

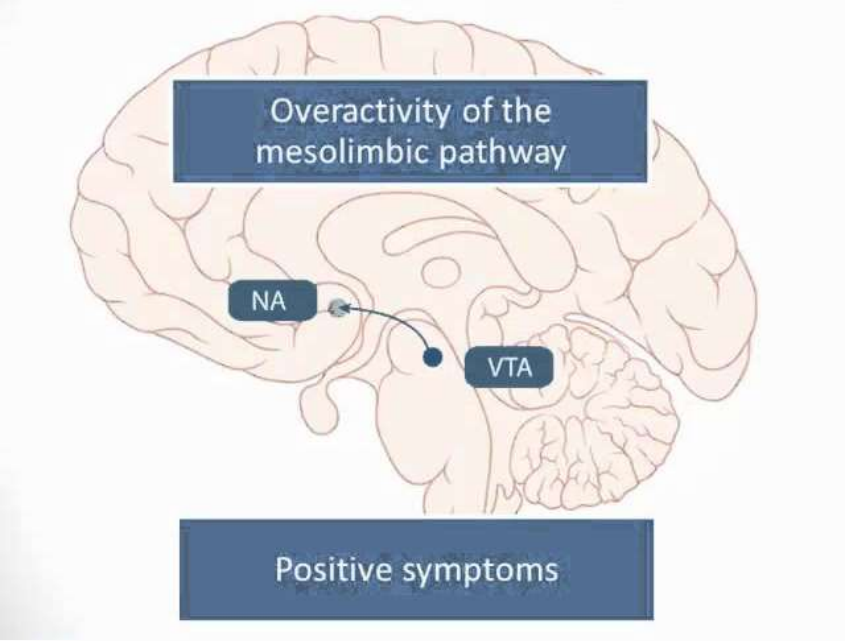
- most (all) of the antipsychotic drugs used until now block postsynaptic D_2 receptor

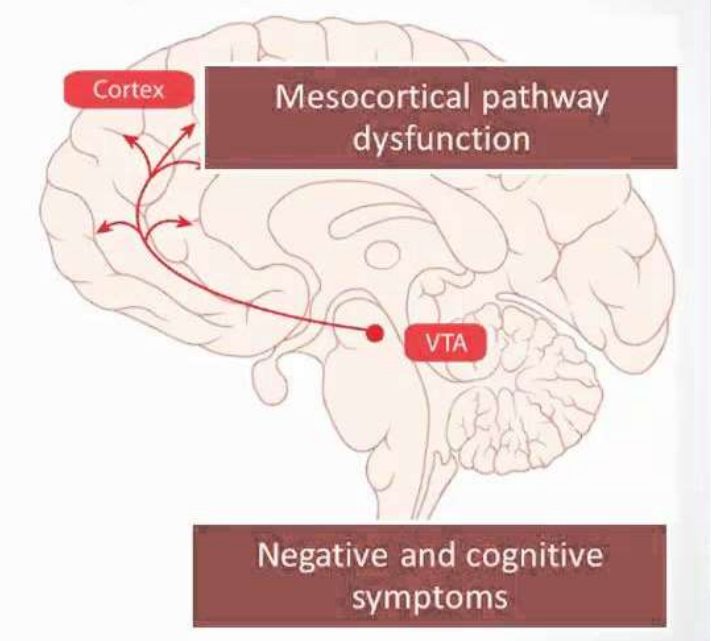
- drugs that increase dopaminergic activity (like amphetamine) aggravate schizophrenia

- density of dopamine receptors has been found to be increased in the brain of schizophrenic patients

  - A lot of contraversion in relation to DA hypothesis

Dopamine Pathways Relevant to Schizophrenia Symptoms



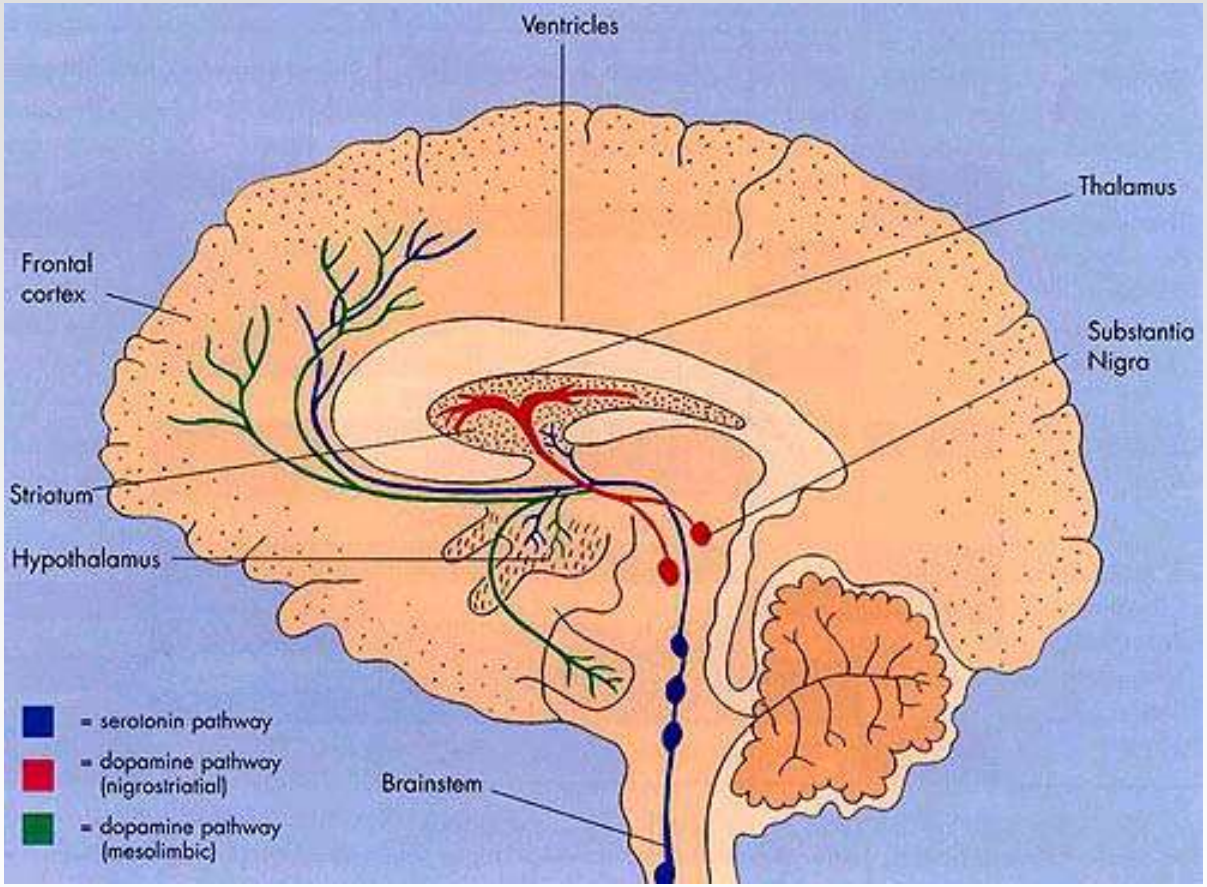


MOLECULAR BACKGROUND of SCHIZOPHRENIA II

„disturbance in regulation" hypothesis

❖ 5-HT system

5-HT-erg fibers starting from the dorsal raphe ending in the striatum, in the limbic system or in the cortex modulate the DA (and also NA, GABA, glutamate, acetylcholine) tone



MOLECULAR BACKGROUND of SCHIZOPHRENIA II

„disturbance in regulation" hypothesis

❖ 5-HT system

Arguments for serotonin hypothesis

- Hallucinogenic abused drugs (eg. LSD) acting via the system may provoke psychotic symptoms

- Majority of the new (2. generation) drugs are inverse agonists on the 5-HT_2 (mainly 5-HT_{2A} and 5-HT_{2C}) receptors

MOLECULAR BACKGROUND of SCHIZOPHRENIA III

„disturbance in regulation" hypothesis

- Glutamate system

Glutamate system

Ionotrop receptors

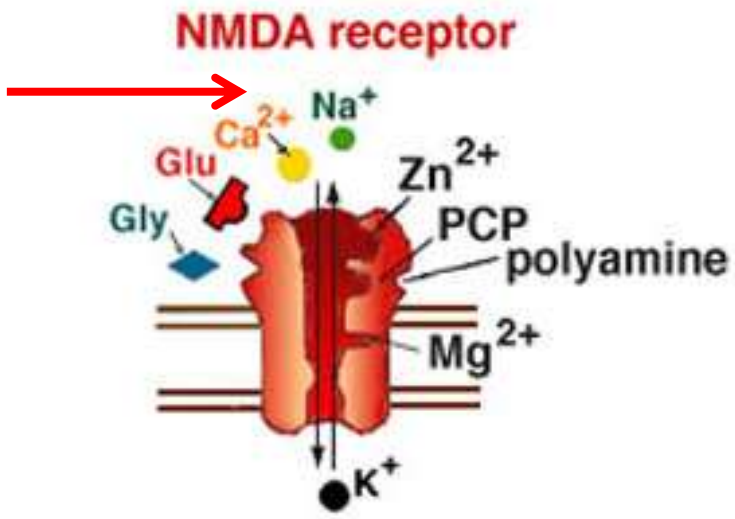


Fig. 6b. NMDA receptors are structurally complex, with separate binding sites for glutamate, glycine MG+2, Zn+2 and polyamines. NMDA-gated channels are more permeable to Ca+2 than Na+ ions (from Kandel et al., 1991).

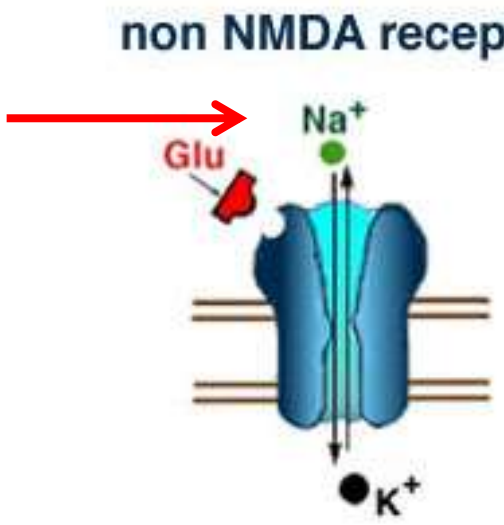
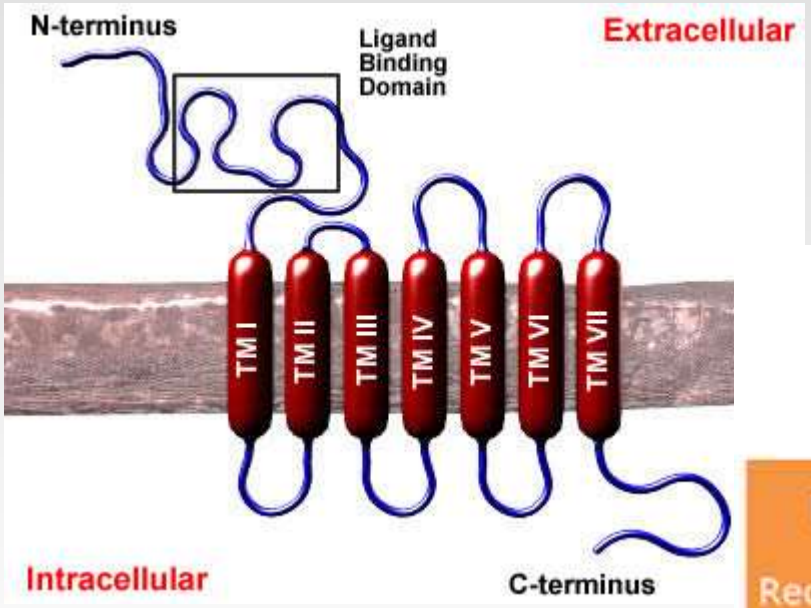
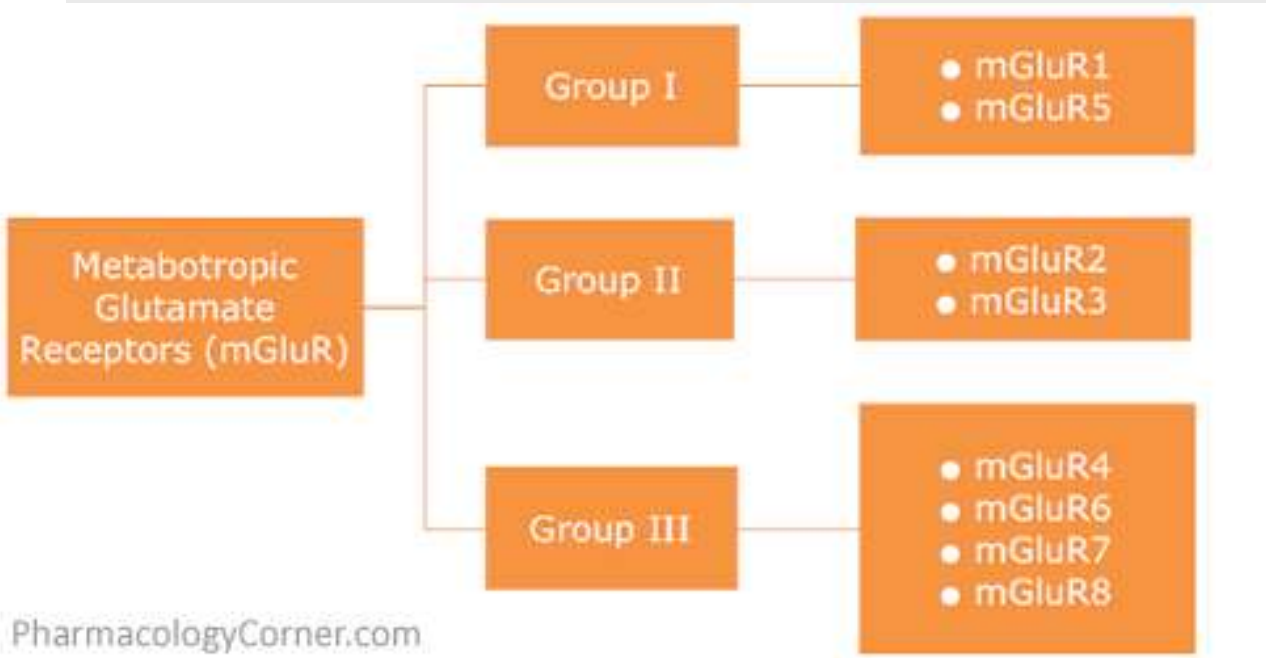


Fig. 6a. Non-NMDA receptors are selectively agonized by kainate, AMPA and quisqualate. The associated ion channels are more perm eable to Na+ and K+ ions tha Ca+2 (from Kandel et al,.1991).

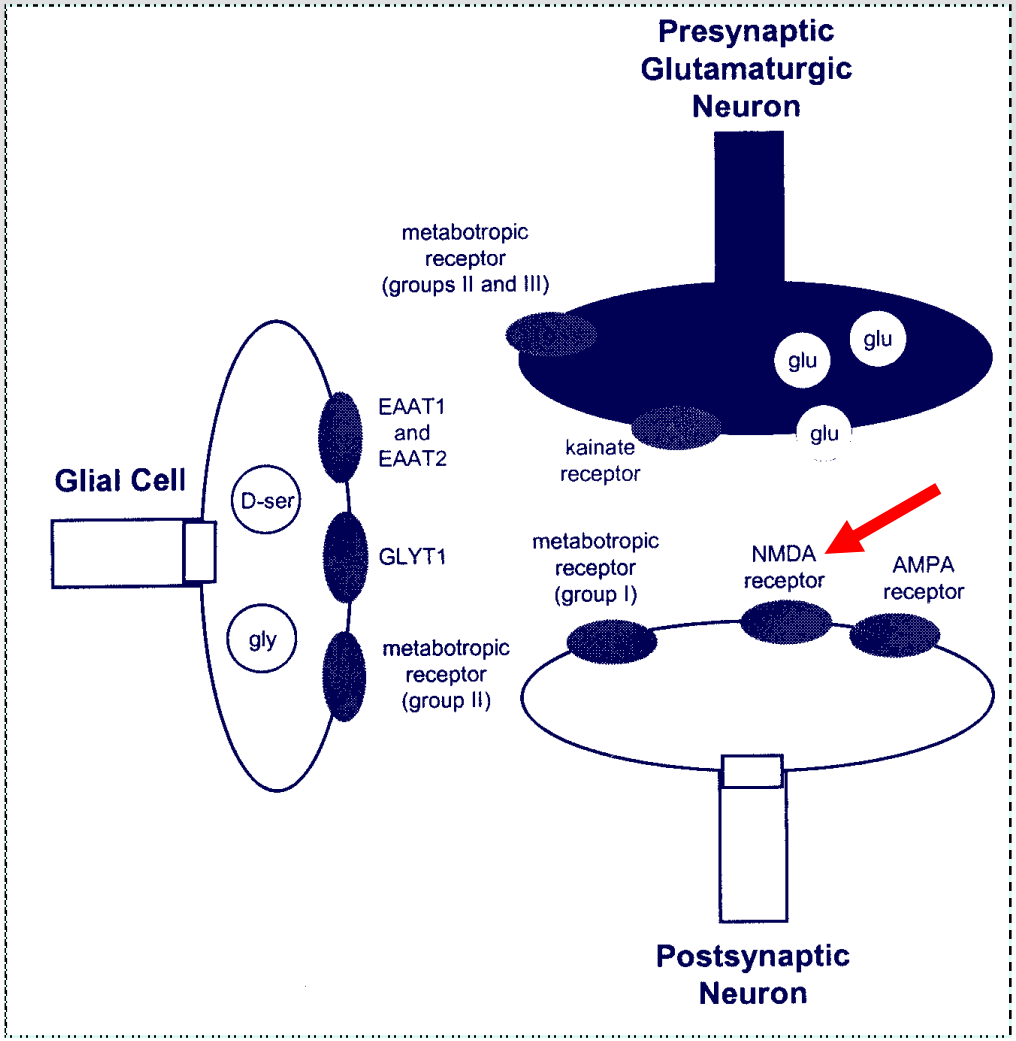
Glutamate system

Metabotrop glutamate receptors





Glutamate system



NMDA hipofunction

MOLECULAR BACKGROUND of SCHIZOPHRENIA III

„disturbance in regulation" hypothesis

- Glutamate system

Arguments for the glutamate hypothesis

- The NMDA antagonist PCP may provoke psychotic symptoms
- 3. generation pharmacons ?

Glutamate system's role in the cognitive deficit ?

CLASSIFICATION

FROM CLINICAL POINT OF VIEW

1st generation (typical, traditional)
antipsychotics/neuroleptics

2nd generation (atypical, new)
antipsychotics

1st GENERATION ANTIPSYCHOTICS

EPS (extrapyramidal symptoms)

Early symptoms

acute dystonia, acathisia (uncontrollable restlessness), Parkinson's syndrome

Late symptoms

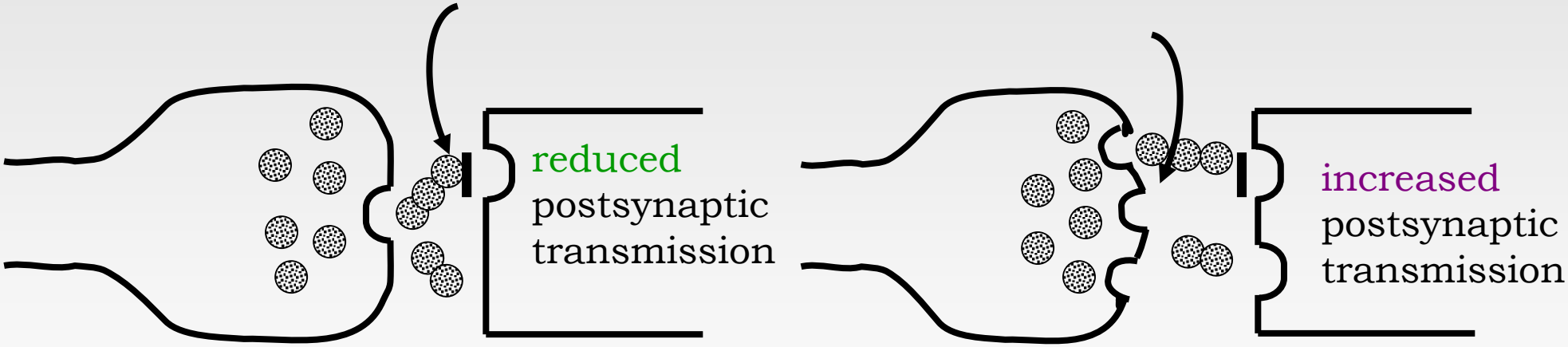
perioral tremor, responds to anticholinergic drugs

tardive dyskinesia

EXTRAPYRAMIDAL SYMPTOMS (EPS)

parkinsonian symptoms

tardive dyskinesia
(decrease of parkinsonian syndrome)



blockade of DA receptor

Supersensitivity ?

withdrawal of antipsychotic

alleviates

exacerbates

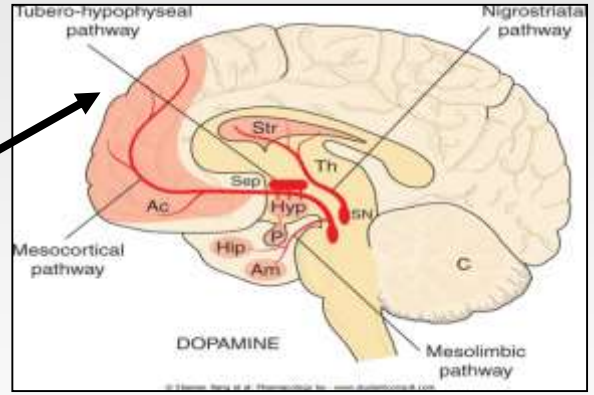
2nd GENERATION ANTIPSYCHOTICS

↓

clinical definition

- smaller risk (or lack) of EPS symptoms

- smaller effect on the prolactin level



- better action against the negative symptoms

- action in the non-responders

clozapine

1st GENERATION ANTIPSYCHOTICS

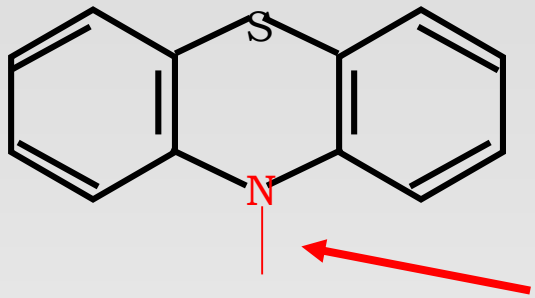
Phenothiazines

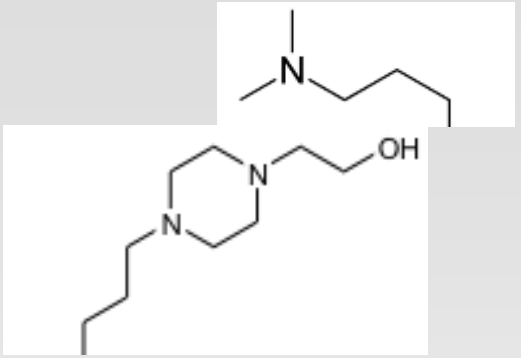
Aliphatic side chain

Chlorpromazine

Piperazine side chain

Fluphenazine





Substituting C for N in the nucleus

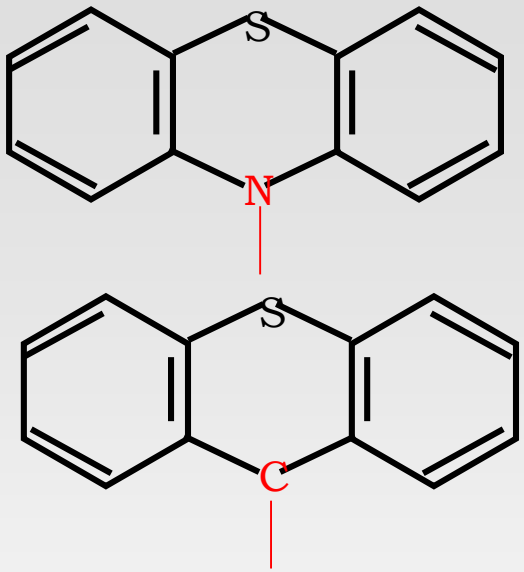
Aliphatic (dimethylamine) derivatives - H_1, α_1 and M receptor inhibition

CLINICAL CONSEQUENCES of the PHARMACOLOGICAL EFFECTS

H_1 antagonism	sedation, dizziness, confusion, weight gain
α_1 blockade	dizziness, hypotension, reflex tachycardia
anticholinergic effects	peripheral parasympatholytic symptoms (dry mouth, constipation, urinary hesitation) delirium memory impairment

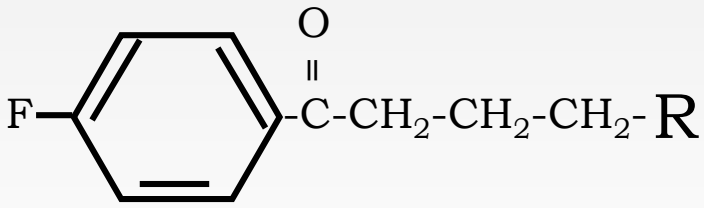
1st GENERATION ANTIPSYCHOTICS

Thioxanthenes



Thiothixene, Flupenthixol
Zuclopenthixol

Butyrophenones



Haloperidol
Droperidol

Droperidol is used mainly as antiemetic iv. (QT-time prolongation)

2nd GENERATION ANTIPSYCHOTICS

- Mixed antagonists (D_2 antagonist /5-$HT_{2A/(C)}$ inverse agonist)

  partial agonists

  D_2 partial agonist, 5-HT_2 antagonist

  D_3 /D_2 partial agonist

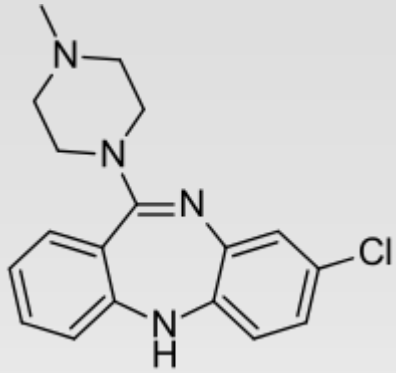
- Selective antagonists

  D_2/D_3 antagonists

2nd GENERATION ANTIPSYCHOTICS I

Mixed (DA_2/ 5-$HT_{2A/C}$) antagonists

Tricyclic compounds (dibenzepines)



clozapine

Clozapine - weak D_2 - stronger D_4 affinity

Olanzapine - good affinity to D_2/5-HT_{2AC} receptors

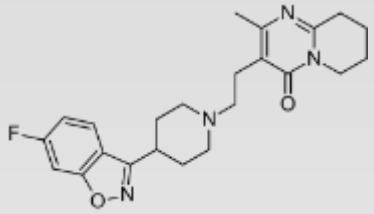
Quetiapine - good affinity to D_2/5-HT_{2AC} receptors

H_1, α_1 and M receptor blockade

2nd GENERATION ANTIPSYCHOTICS II

Mixed (DA_2/ 5-HT_{2A}) antagonists

Other heterocyclic compounds



risperidone

Risperidone – good affinity to 5-HT_2 and D_2 receptors
Paliperidone – 9-OH-risperidone metabolit
Ziprasidone – relatively higher affinity to 5-HT_2 than D_2 receptors
Iloperidone
Lurasidone – new, D_2, 5-HT_2 and $_7$ antagonist
(Sertindole) – (rarely used because of cardiotoxicity)

Smaller anticholinergic effect

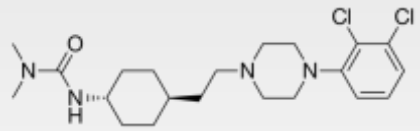
risperidone, palipredone – marked, ziprazidone, lurazidone, iloperidone **smaller H_1 binding**
risperidone, palipredone, iloperidone – marked, lurazidone **smaller α_1 binding**
ziprazidone, paliperidone, lurazidone – **binds to the 5-HT_{1A} receptors**
(partial agonists?)

2nd GENERATION ANTIPSYCHOTICS II

Partial agonists on DA receptor

Dichlorophenylpiperazines

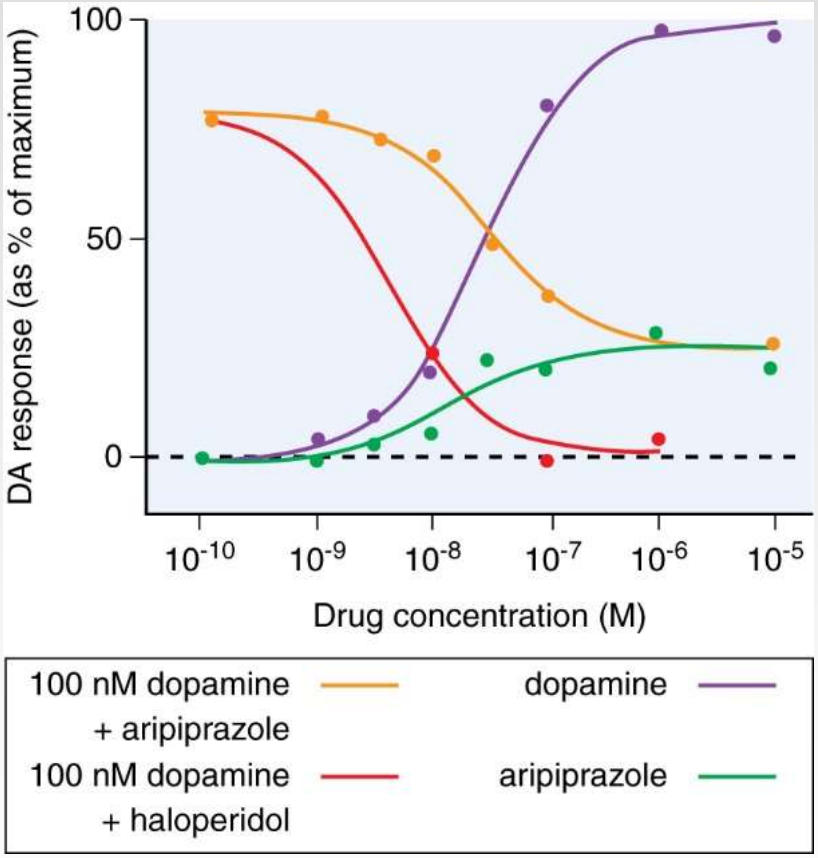
Aripiprazole - D_2 partial agonist, 5-HT_{2A} antagonist, 5-HT_{2c} and 5-HT_{1A} partial agonist



Cariprazine - D_3/D_2 partial agonist –with higher affinity to D_3 5-HT_{1A} partial agonist

Both compounds can be characterized with lower anticholinergic effect, medium strong H_1 and lower α_1 binding

Effect of the partial agonist aripiprazole on the D_2 receptor in presence of DA



Receptor activity was measured as inhibition of forskolin-induced cAMP accumulation in CHO cells transfected with human D_{2L} DNA.
(Adapted from Burris et al., 2002.)

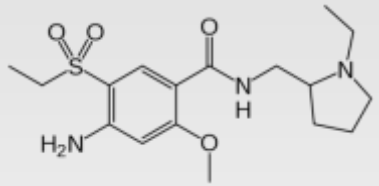
Aripiprazole may act as an antipsychotic by:

- Lowering dopaminergic neurotransmission in the mesolimbic pathway
- Enhancing dopaminergic activity in the mesocortical pathway
- It has a lower risk of EPS and hyperprolactinemia than other antipsychotics.

2. GENERÁCIÓS ANTIPSZICHOTIKUMOK II

Szelektív D_2/D_3 antagonisták

Benzamidok

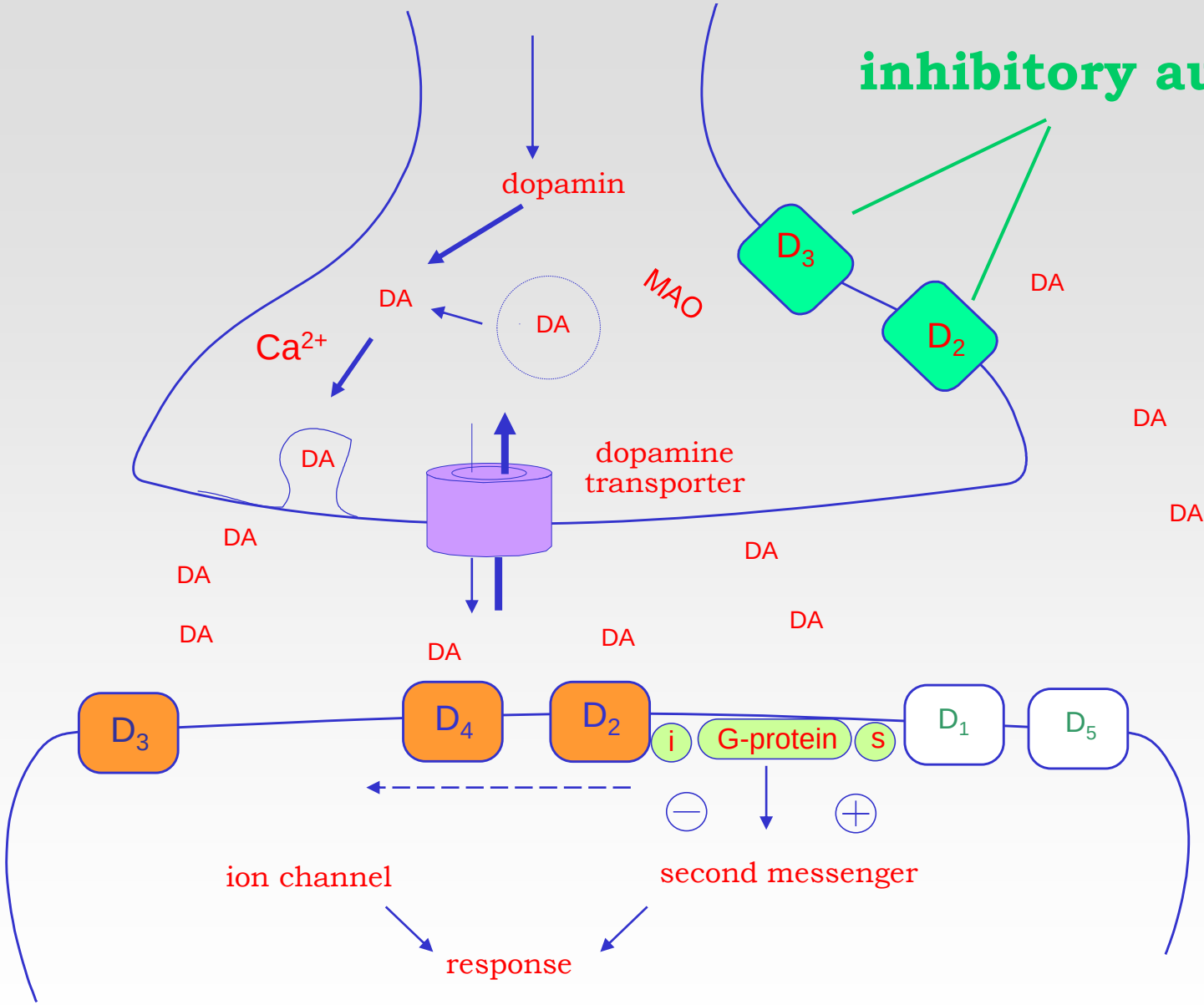


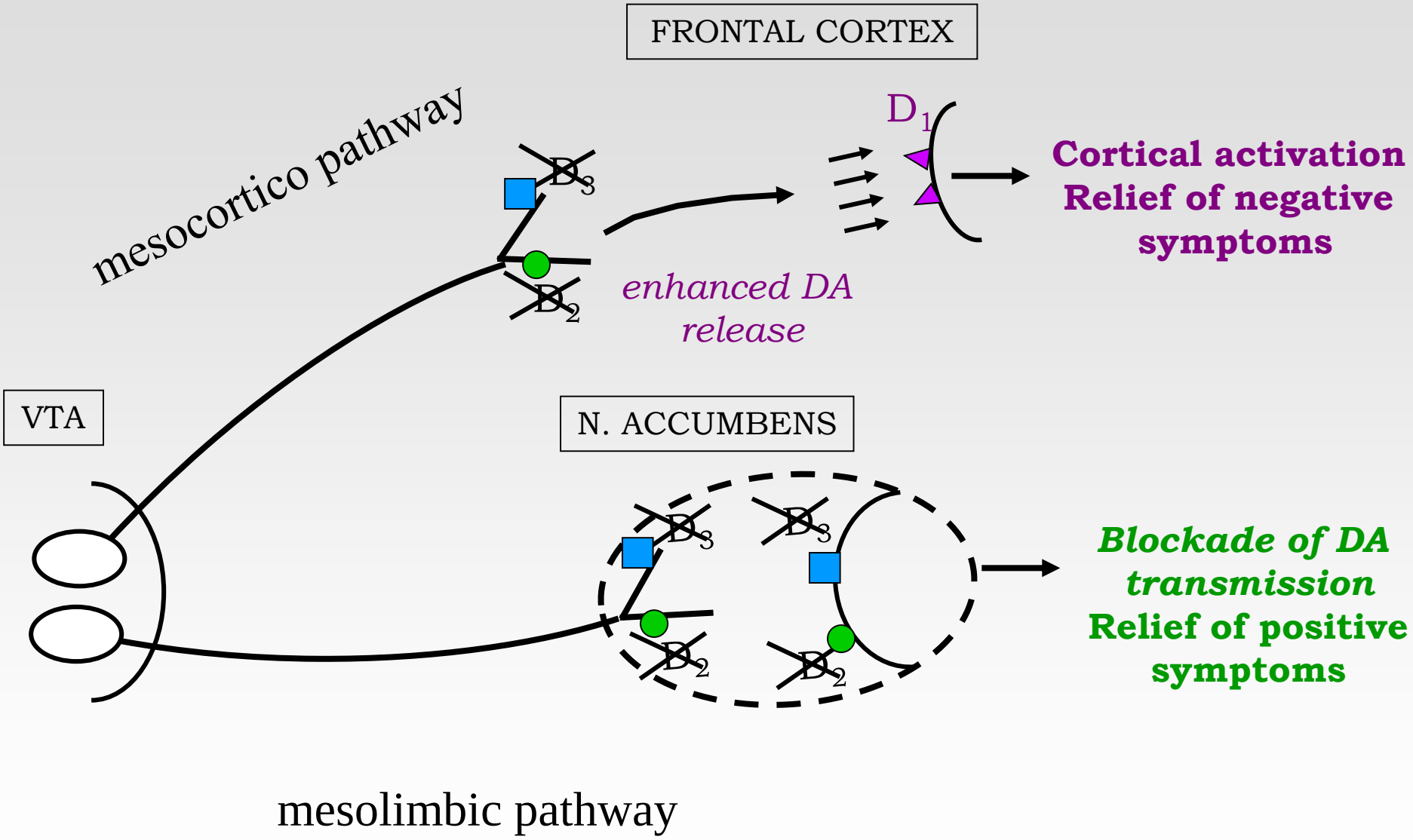
Sulpirid

Tiaprid

Amisulprid

inhibitory autoreceptors





mesolimbic pathway

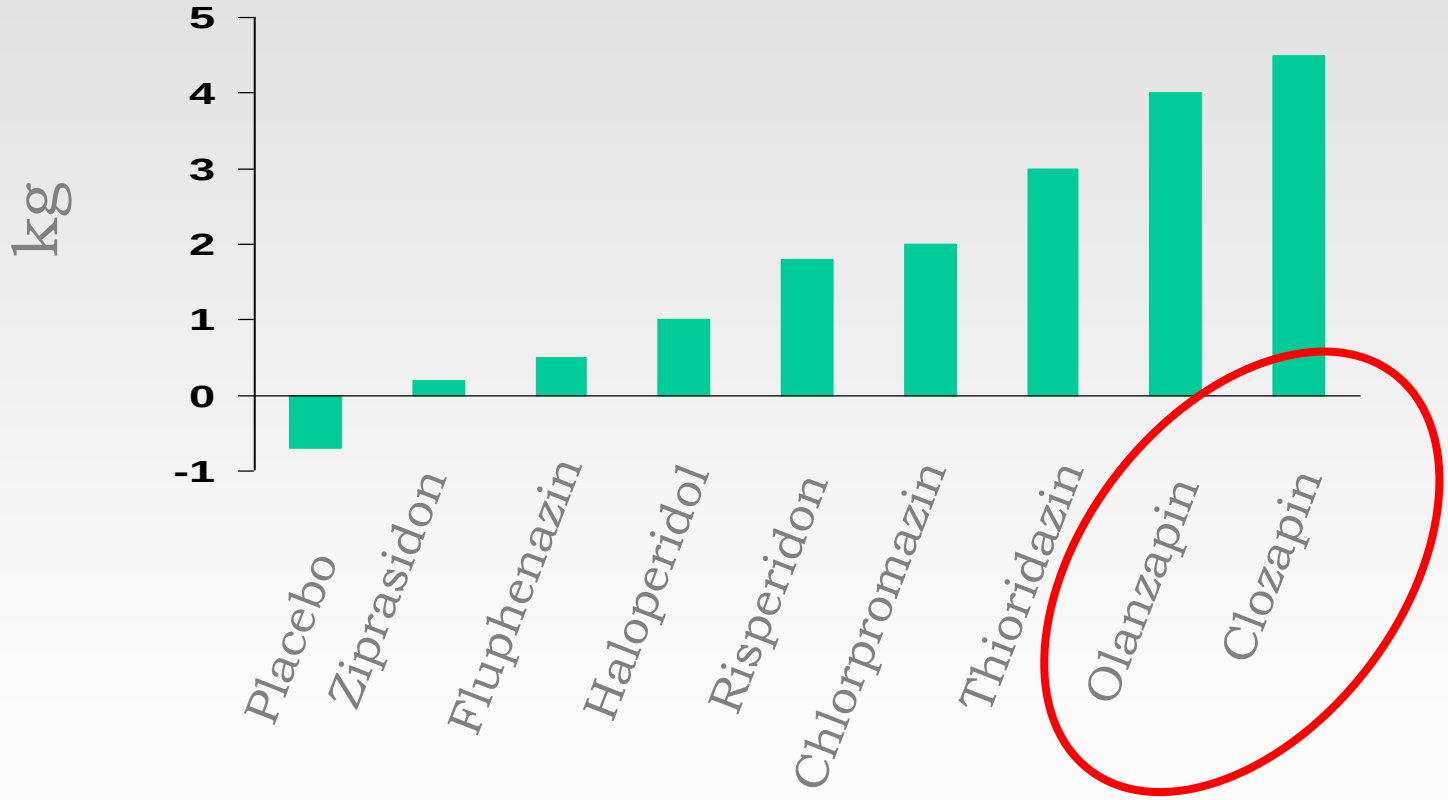
OTHER ADVERSE EFFECTS of 2nd GENERATION APs

- *hyperprolactinemia*

  amenorrhea-galactorrhea, infertility, impotence

- *obesity (H_1 and 5-HT_{2C}) – diabetes, hyperlipidemia, etc.*

Weight gain after 10 weeks treatment



Sussman N. J. Clin Psychiatry, 62, 2001

Role of $5HT_{2C}$

Consequences of obesity

- diabetes
- hypertension
- heart failure
- rheumatic diseases

OTHER ADVERSE EFFECTS

- *neuroleptic syndrome*

  symptoms: hyperthermia, muscle rigidity, cardiovascular lability, creatine-fosfokinase enhancement, tachikardia, tachipnoé, diaphoresis, leukocitózis, delirium
  recovers may last even for 2 weeks

- *hypothermia*

CLINICAL INDICATIONS

- *as ANTIPSYCHOTIC*

- manic phase in bipolar affective disorder (some of the 2nd generation even for prophylaxis)

Neuroleptics (1st generation) additional usage

- antiemetic (centrally and on CTZ) – even in terminal states

- control of intractable hiccough

- preoperative treatment (potentiation of the effect of general anesthetics)

- facilitation of induction of surgical hypothermia (chlorpromazine prevents the shivering and induces vasodilation)

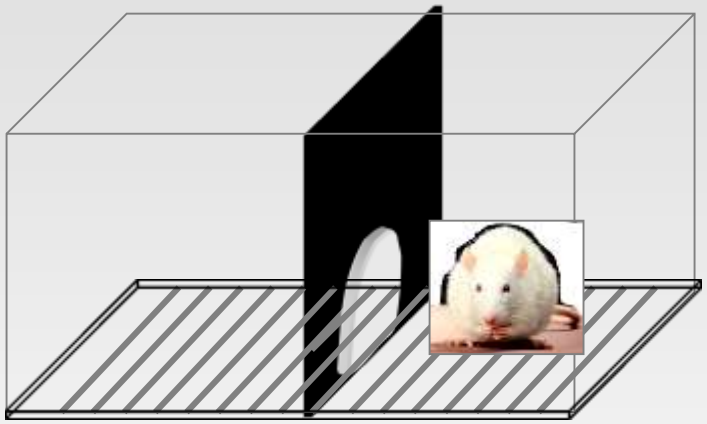
Animal models for psychosis

Inhibition of shuttle-box learning

SHUTTLE-BOX

two-way actives avoidance test

Trial 1



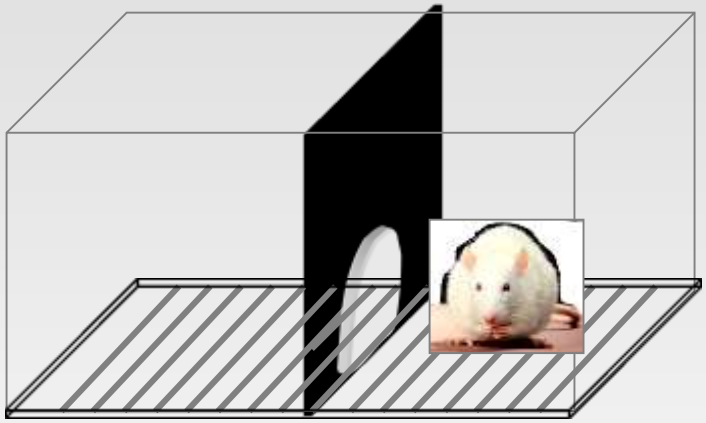
intertrial crossing

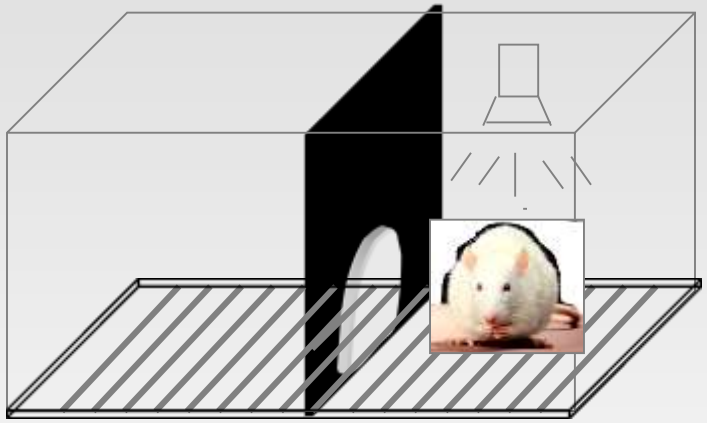
IC

SHUTTLE-BOX

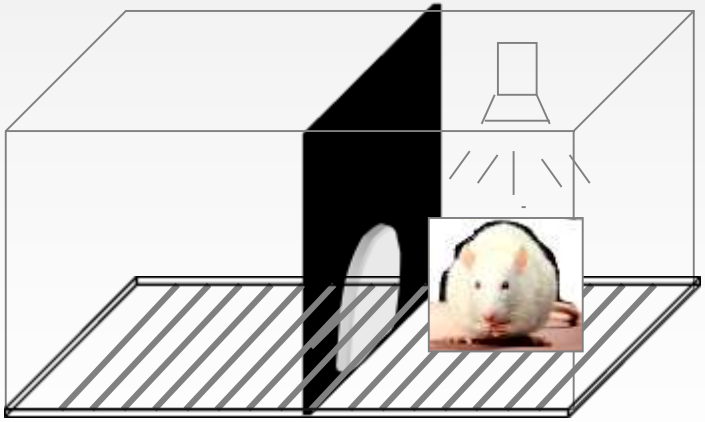
two-way actives avoidance test

Trial 1



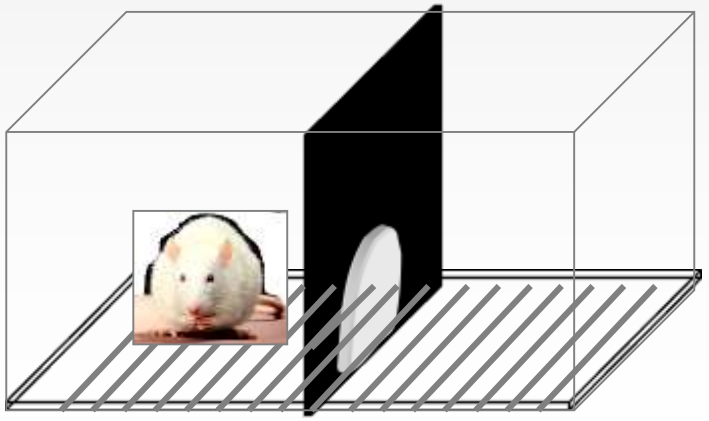


CS 10 sec



CS+US (0.8mA, 5 sec)

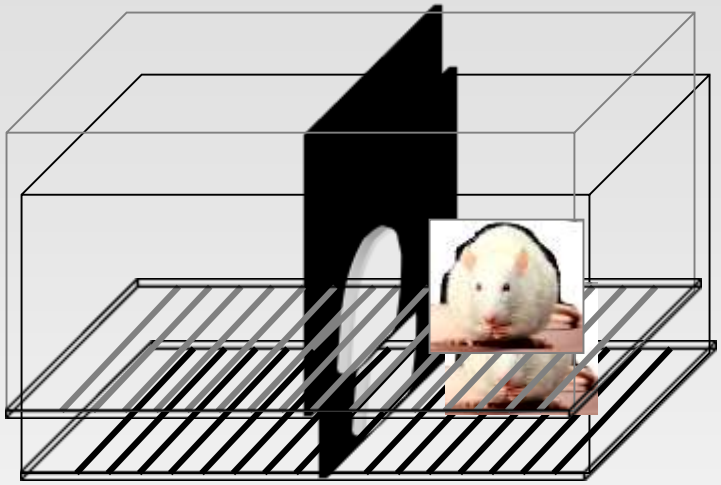
Trial 2

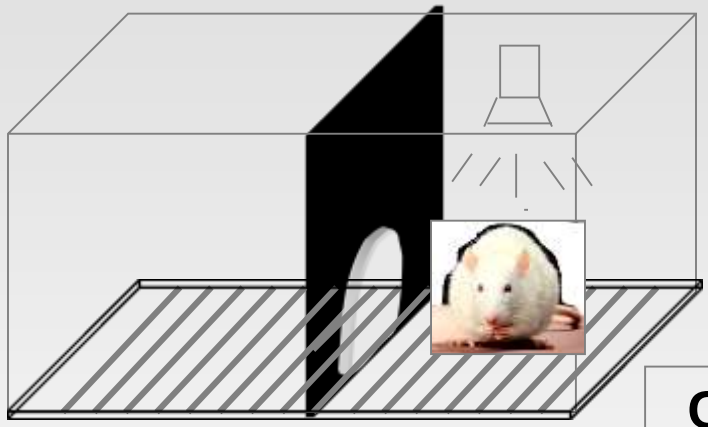


SHUTTLE-BOX

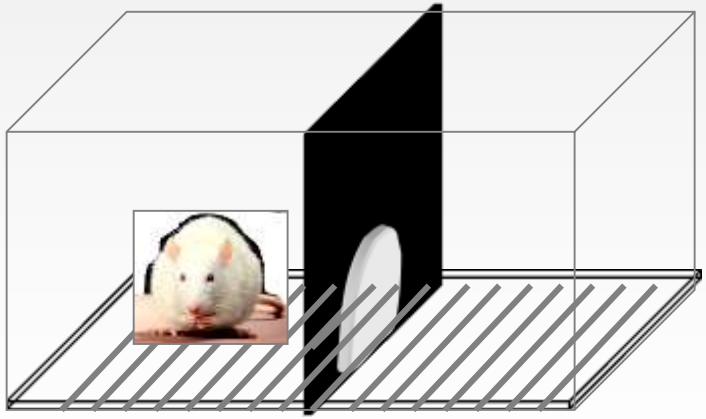
two-way actives avoidance test

Trial 1

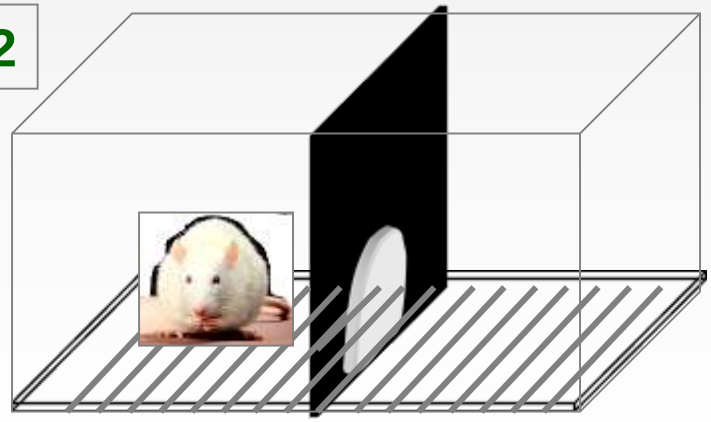




CS 10 sec



Trial 2

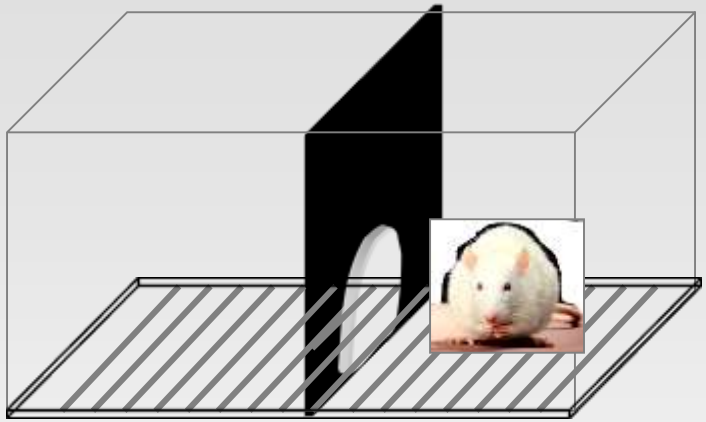


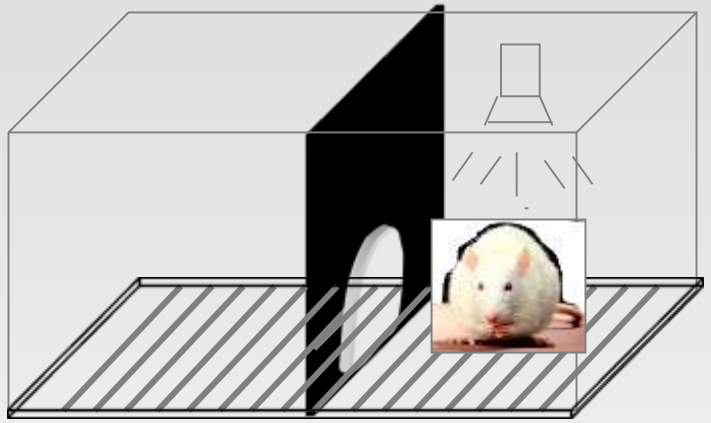
conditioned avoidance response - CAR

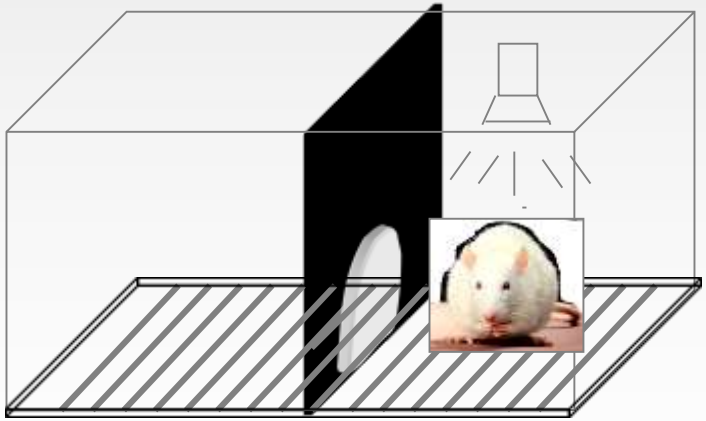
SHUTTLE-BOX

two-way actives avoidance test

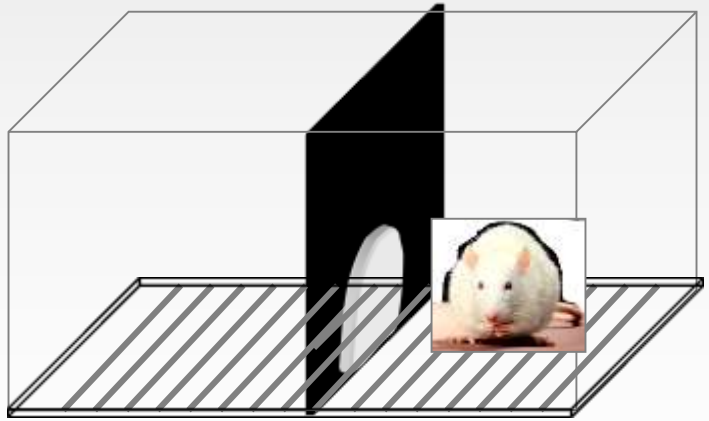
Trial 1







Trial 2



CS+US (0.8mA, 5 sec)

Escape failure – EF

PARAMETERS MEASURED

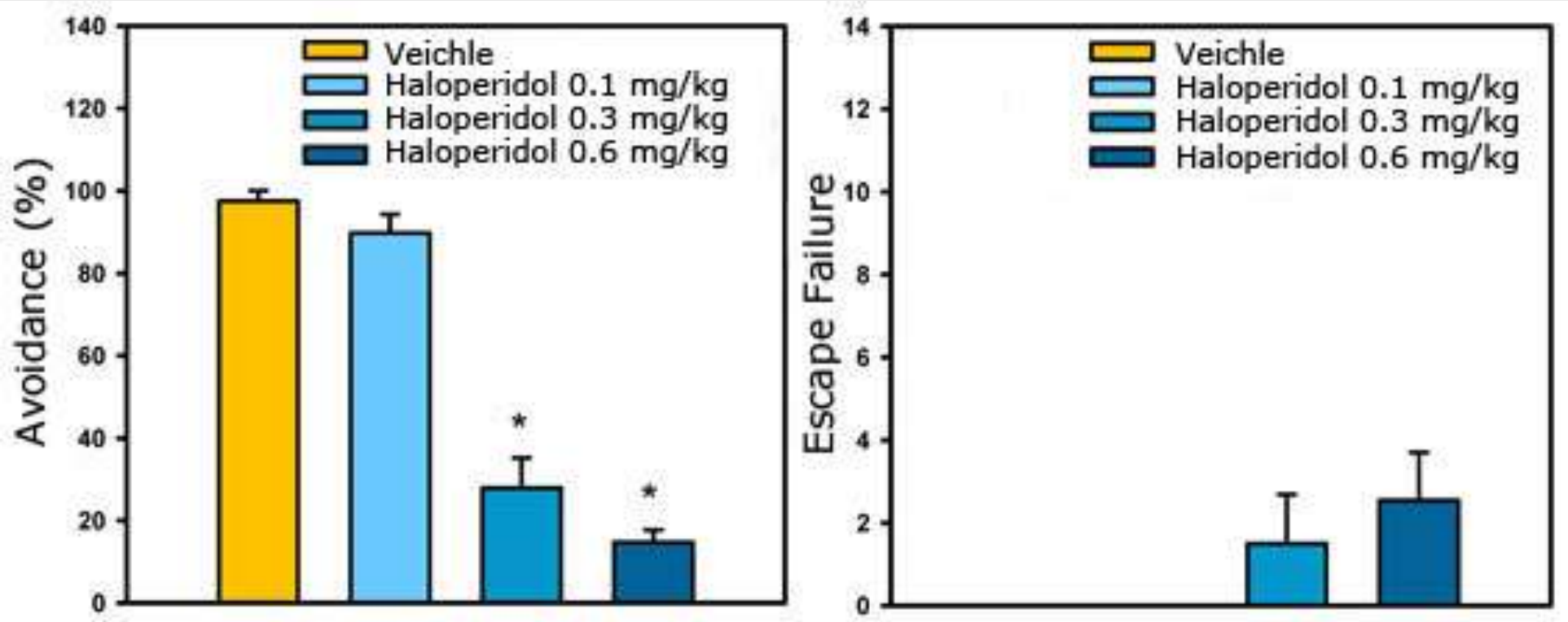
- **IC (intertrial crossing)**
  crossing recorded during the resting phase

- **CAR (conditioned avoidance response)**
  response to the conditioned stimuli

- **EF (escape failure)**
  no response to the unconditioned stimuli

Models for psychosis I

- Inhibition of the Shuttle-box learning



Models for psychosis II

- Inhibition of the Shuttle-box learning

- Actions on the DA agonist (apomorphine, amphetamine) induced behavior

DA-INDUCED STEROTYPED BEHAVIOR

rearing, sniffing

licking, biting

starting time of the observation: immediately after treatment

observation intervals: 10 min

Scores: 0 – rest; 1 - rearing, sometimes sniffing
2 – permanent sniffing; 3 – permanent sniffing, sometimes kicking/biting
4 – permanent licking/biting

Models for psychosis III

- Inhibition of the Shuttle-box learning
- Actions on the DA agonist (apomorphine, amphetamine) induced behavior

- Actions on the 5-HT agonist (fenfluramine) induced behavior

5-HT SYNDROME

- forepaw treading
- hind limb abduction
- Straub tail

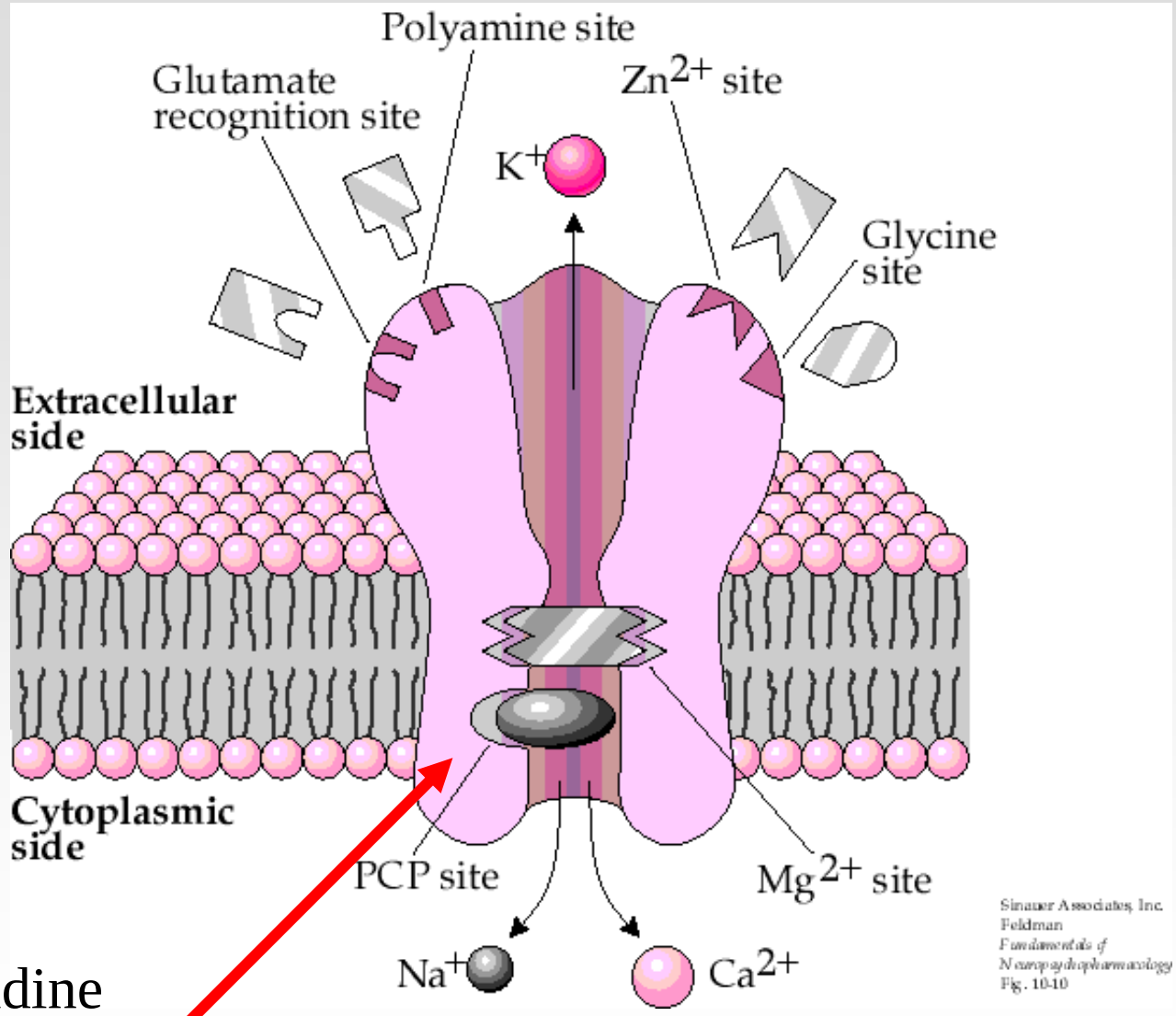
starting time of the observation: 15 min after treatment

observation intervals: 5 min

Scores: 0-4/observation/parameter max: 36

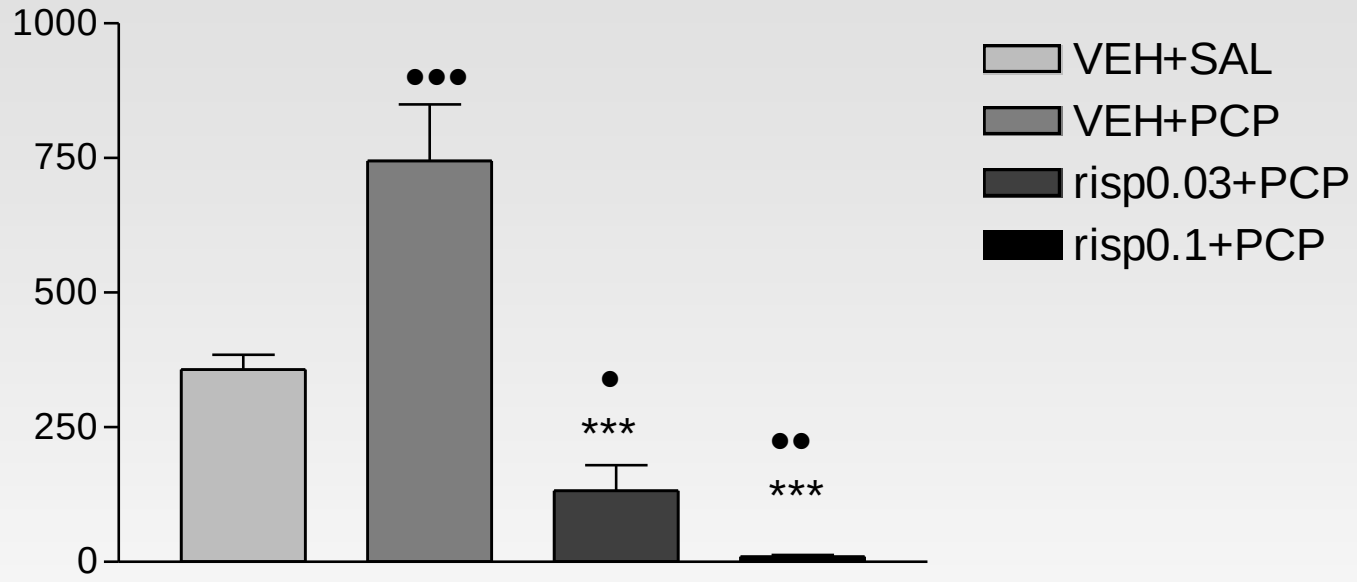
Models for psychosis IV

- Inhibition of the Shuttle-box learning
- Actions on the DA agonist (apomorphine, amphetamine) induced behavior
- Actions on the 5-HT agonist (fenfluramine) induced behavior
- Actions on the glutamate antagonist (phencyclidine) induced behavior



PCP - phencyclidine

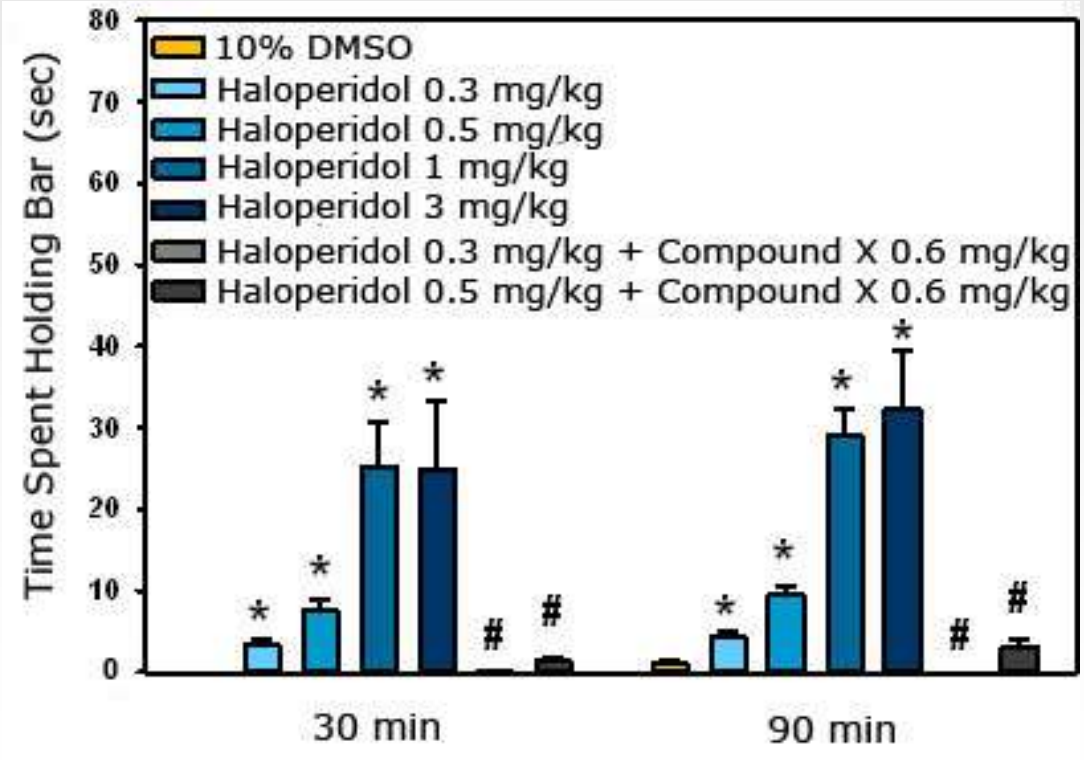
ENHNCED LOCOMOTOR ACTIVITY



One way ANOVA (F(3,32)=28,04 ***p<0.001
NK post hoc ***p<0.001 versus PCP
● p<0.05; ●● p<0.01; ●●● p<0.001 versus VEH

Models for psychosis V

Catalepsy - a state of behavioral immobility characterized by muscle rigidity and failure to correct an externally imposed posture for a prolonged period of time, **providing a measure of the extrapyramidal side-effects of antipsychotics**

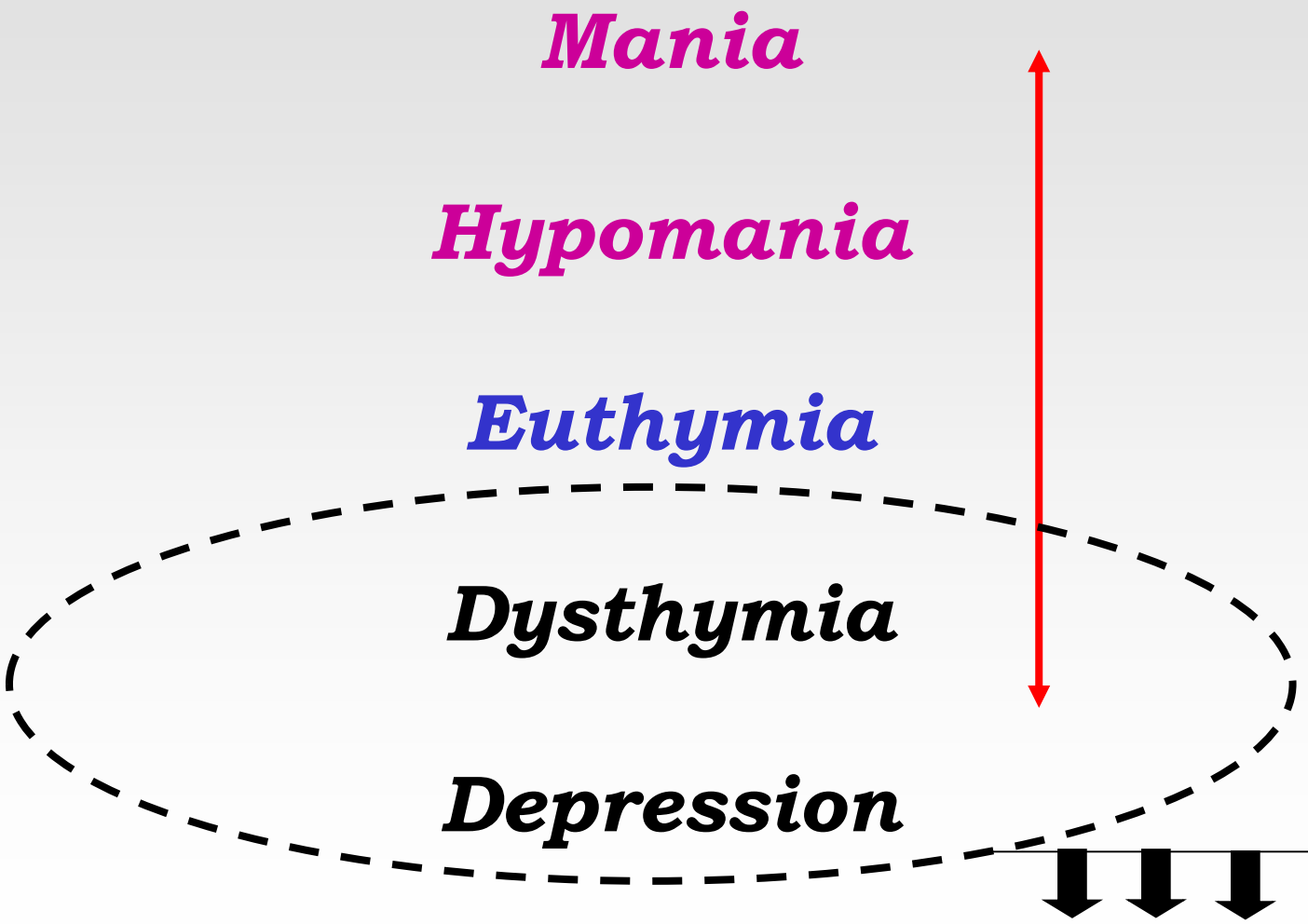


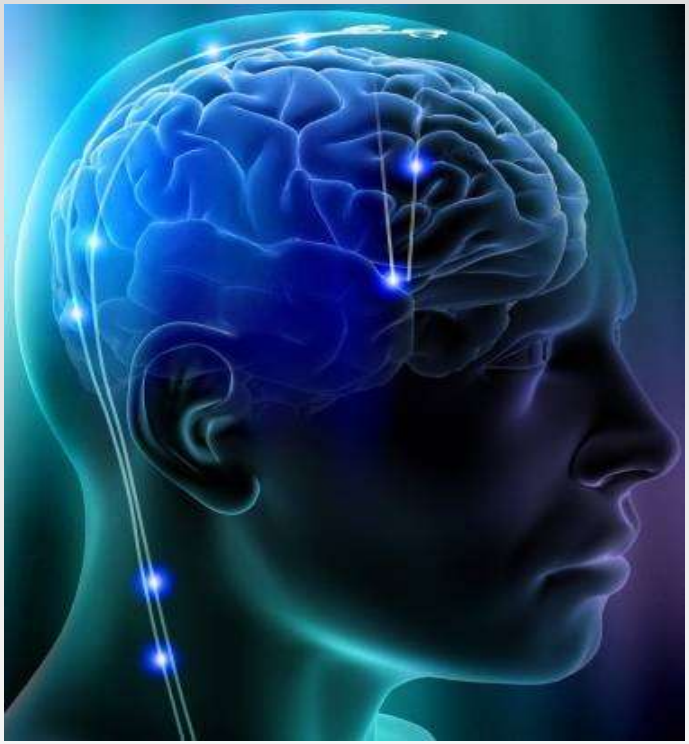
Pharmacological treatment of depression

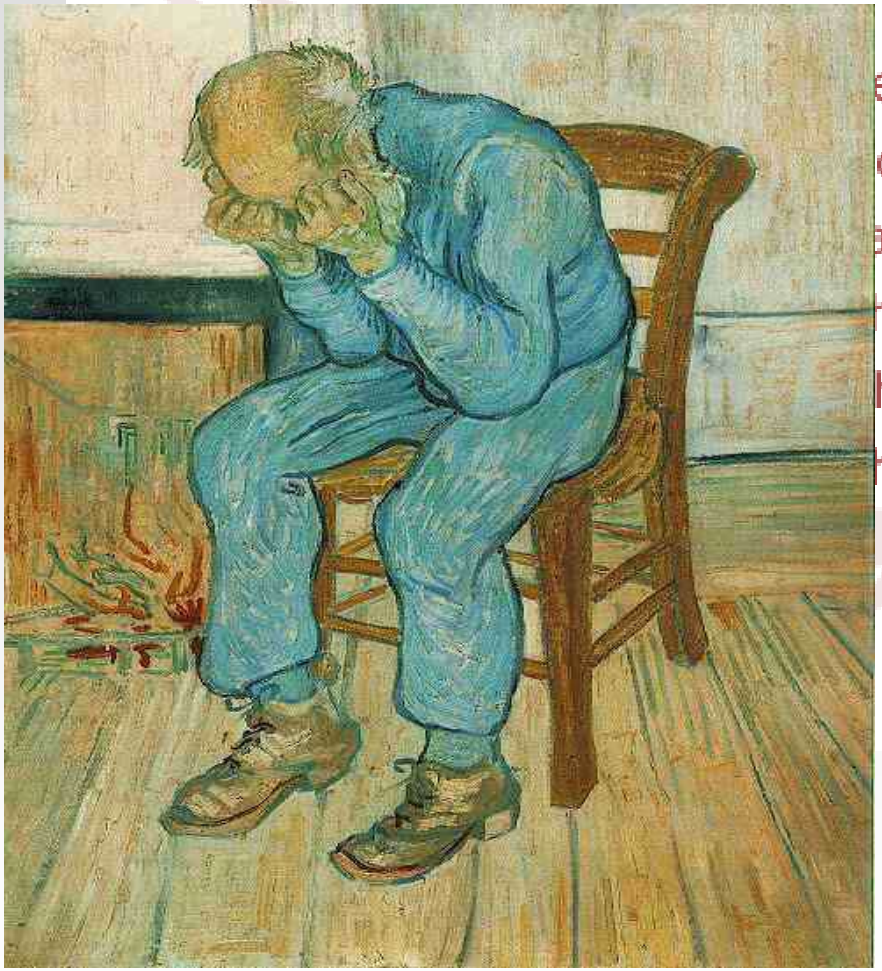
AFFECTIVE DISORDERS
(mood disorders)

- **depression (unipolar depression, major depression)**
- **bipolar disorder**
- **anxiety disorder**

MOOD VARIATIONS







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Stark

van Gogh 1890

SYMPTOMS OF DEPRESSION

- Low mood
- Marked decrease in interest
- Marked lack of feeling joy
- Significant changes in the body weight (loosing or gaining weight)
- Insomnia or sleepiness
- Psychomotor agitation or retardation
- Fatigue
- Feeling of worthlessness or exaggerated consciousness of guilt
- Decrease of ability to concentrate
- Returning thoughts in relation to death and suicide

Depression

- **major depression – MDD**

genetic back ground ?

MDD prevents a person from functioning normally, it interferes with a person's ability to work, sleep, study, eat, enjoy once-pleasurable activities

- **dysthymia** - characterized by long-term (2 years or longer) symptoms that may not be severe enough to disable a person but can prevent normal functioning or feeling well.

- **minor depression** - symptoms for 2 weeks or longer that do not meet full criteria for MDD. Without treatment, people are at high risk for developing MDD

Psychotic depression, postpartum depression, seasonal affective disorder (SAD)

AFFECTIVE DISORDERS
(mood disorders)

- **depression (unipolar depression, major depression)**
- **bipolar disorder**
- **anxiety disorder**

MOOD VARIATIONS

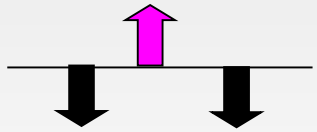
Mania

Hypomania

Euthymia

Dysthymia

Depression



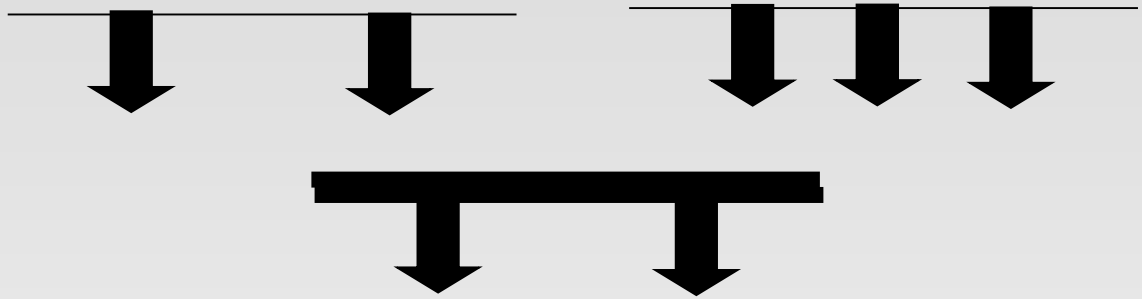
depressive and manic phases may alternate

SYMPTOMS OF MANIC EPISODES

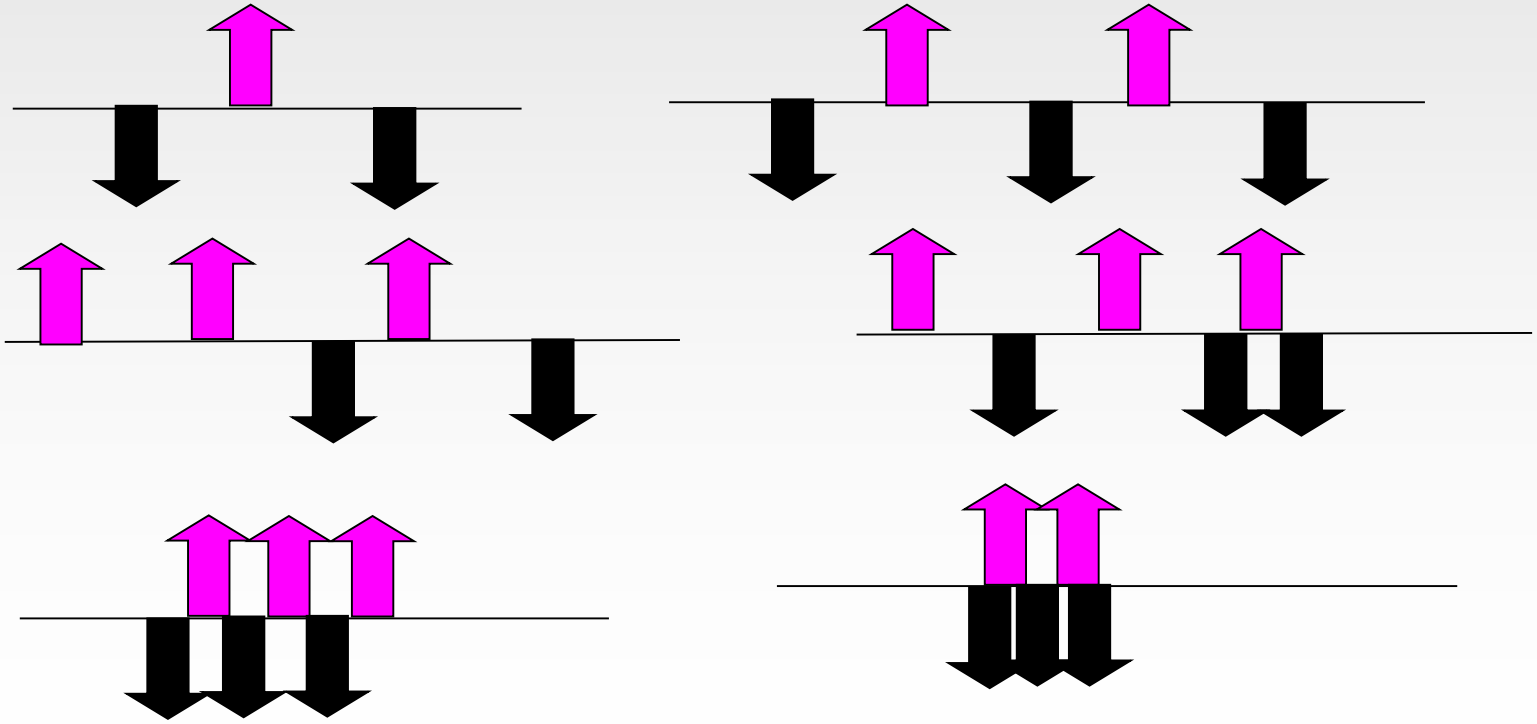
- Increased activity, energy or agitation.
- Unusual talkativeness, Racing thoughts
- Decreased need for sleep
- Marked restlessness, impulsivity
- Exaggerated sense of well-being and self-confidence (euphoria)
- Hazardous, sometimes deleterious behavior

Both include subtypes and variations in severity

Depression



Bipolar disorder



AFFECTIVE DISORDERS
(mood disorders)

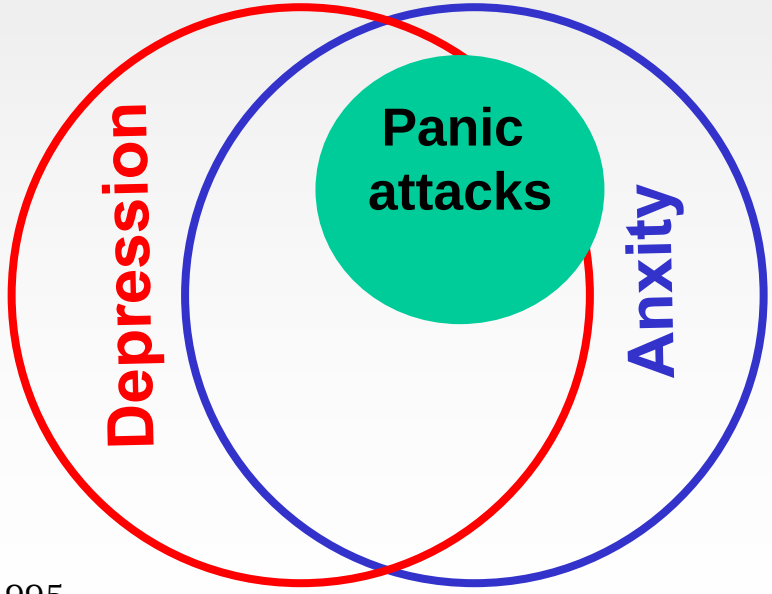
- **depression (unipolar depression, major depression)**
- **bipolar disorder**
- **anxiety disorder**

Anxiety disorders

- **Panic disorder** (dyspnoe, palpitation, tremor, sweating, nausea - gastrointestinal discomfort, depersonalizations, feeling of hot/cold, substernal pain, fear of death, general fear)
- **Obsessive-compulsive disorder (OCD)**
- **Posttraumatic stress disorder (PTSD)**
- **Generalized anxiety disorder (GAD)**
- **Premenstrual dysphoric disorder (PMDD)**

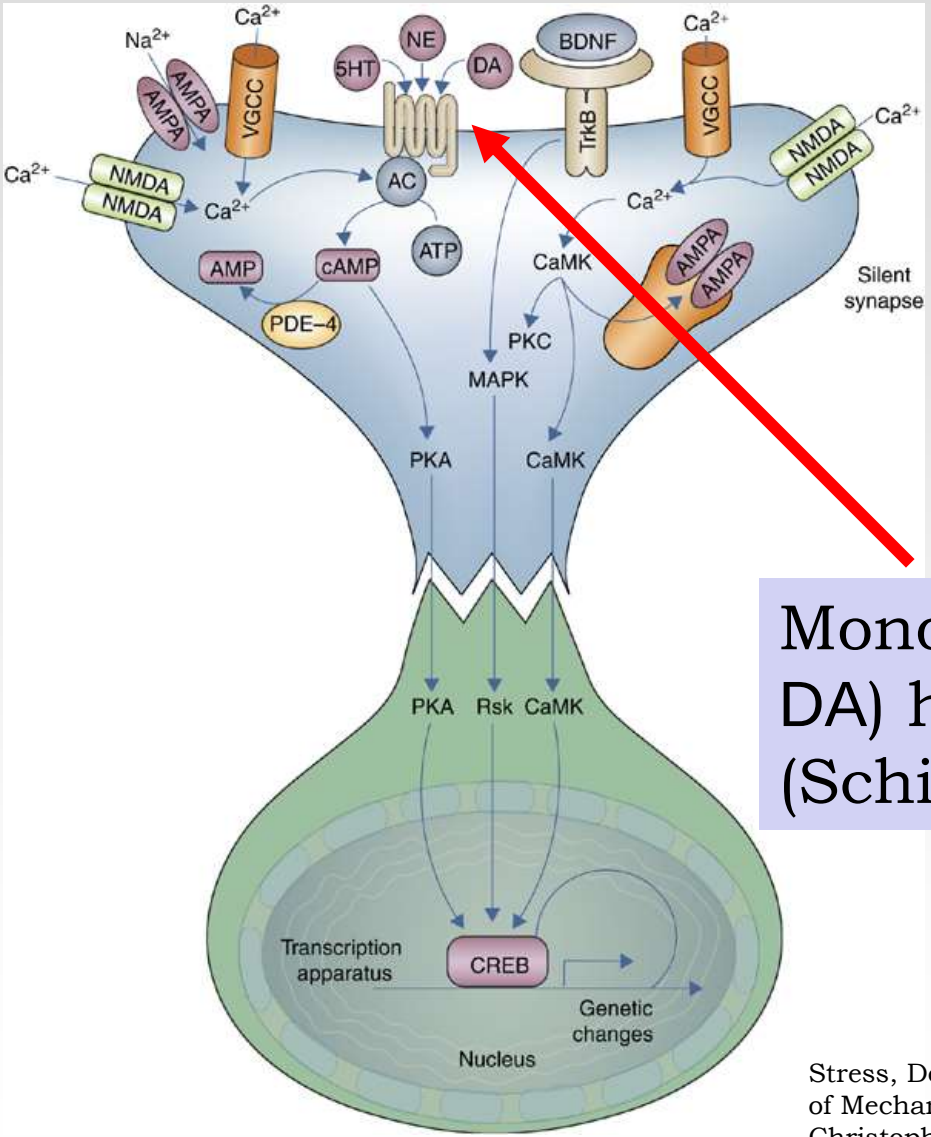
- **Drugs for treatment of depression**
- **Drugs for treatment of manic phase**
- **Drugs for treatment of anxiety disorders**

comorbidity of depression and anxiety



Schatzberg AF, J Clin Psych Monograph, 13:2, 1995

PATHOGENEZIS of MDD I



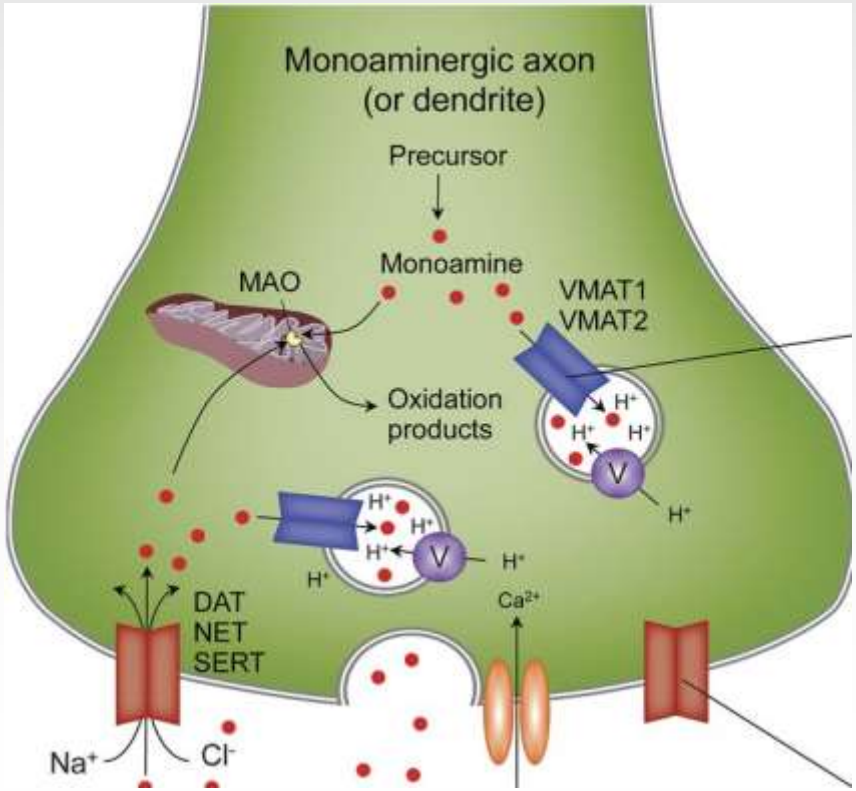
Monoamine (NE,5-HT, DA) hypothesis (Schildkraut)

Stress, Depression, and Neuroplasticity: A Convergence of Mechanisms
Christopher Pittenger and Ronald S Duman, Neuropsychopharmacology 2007, 33:88

Monoamine (NE,5-HT) hypothesis

Some argues for it:

- Monoamine depletors (reserpine) induce depression



reserpine inhibits VMAT

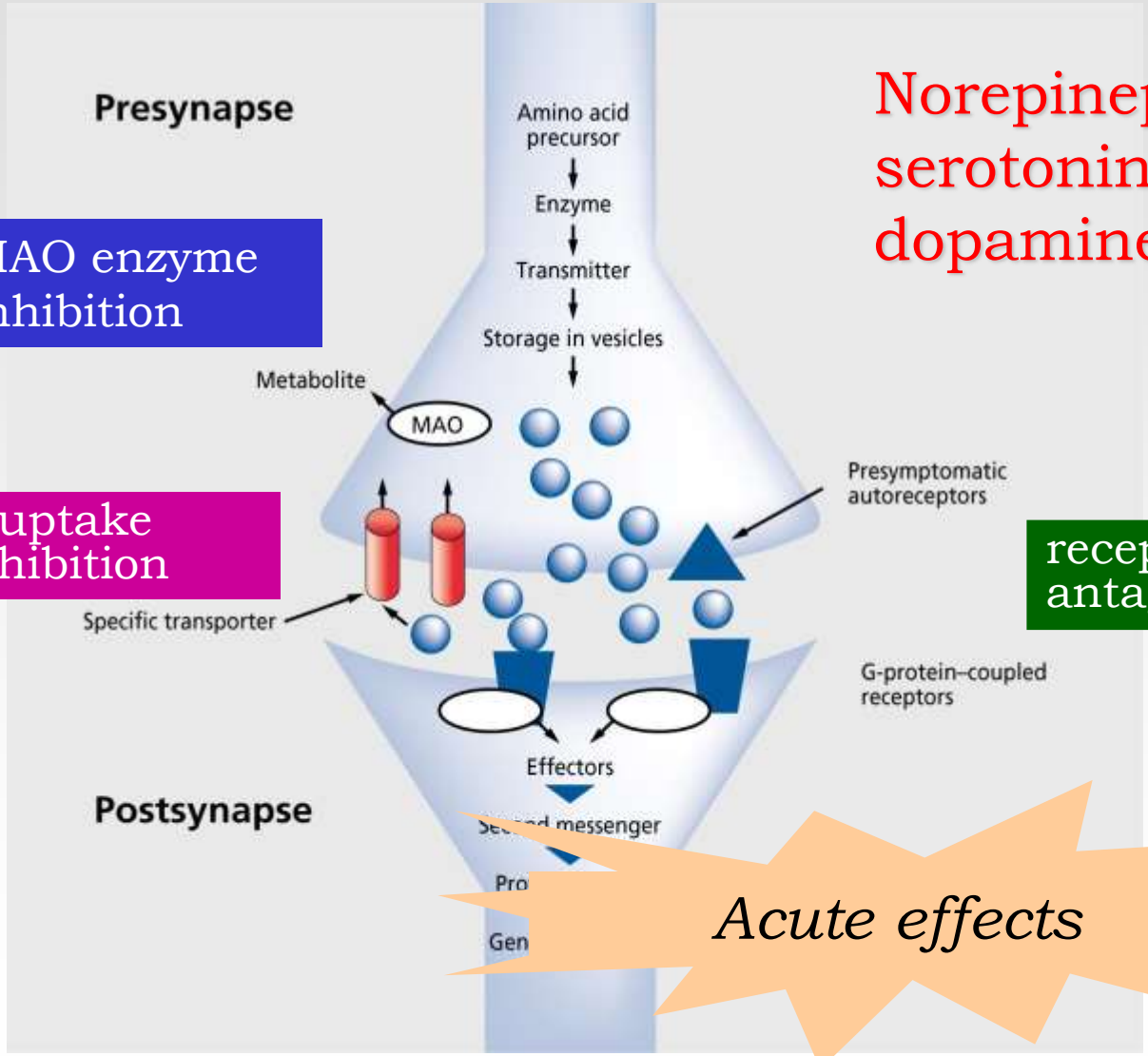
Monoamine (NE,5-HT) hypothesis

Some argues for it:

- Monoamine depletors (reserpine) induce depression
- Genetic studies – functional polymorphism exists for SERT (5-HT transporter) gen
- Reduction of 5-HIIA (5-HT metabolite) in CSF is associated with violent and impulsive behavior (not specific for depression)

- Nearly all the antidepressants enhance the availability of NE and/or 5-HT and/or DA in the synaptic cleft

Majority of the pharmacons used nowadays are based on the monoamine hypotheses



MAO enzyme inhibition

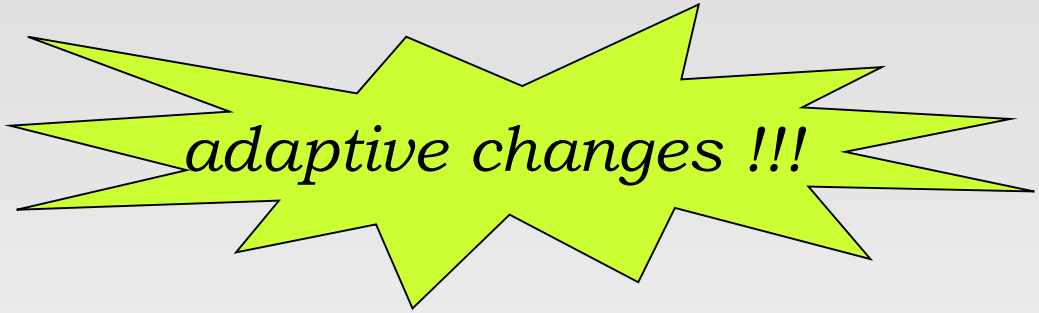
reuptake inhibition

Norepinephrine, serotonin, dopamine

receptor antagonism

Acute effects

Weeks (4-6) are needed for development of antidepressant effect



????

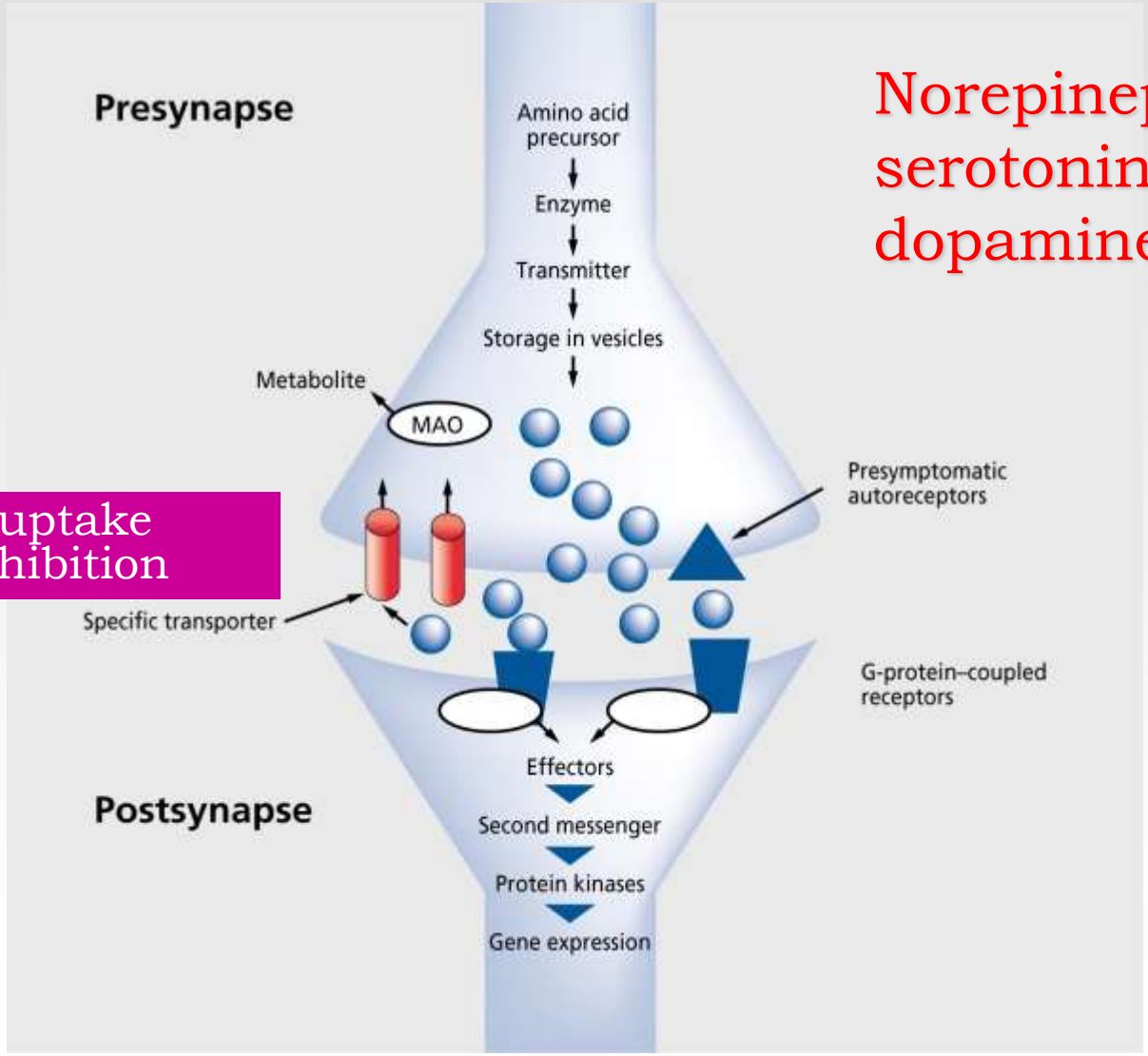
α_2 receptor desensitization (presynaptic)

5-HT_2 receptor desensitization

enhanced sensitivity of 5-HT_{1A} receptors

β receptor desensitization and down regulation

Majority of the pharmacons used nowadays are based on the monoamine hypotheses

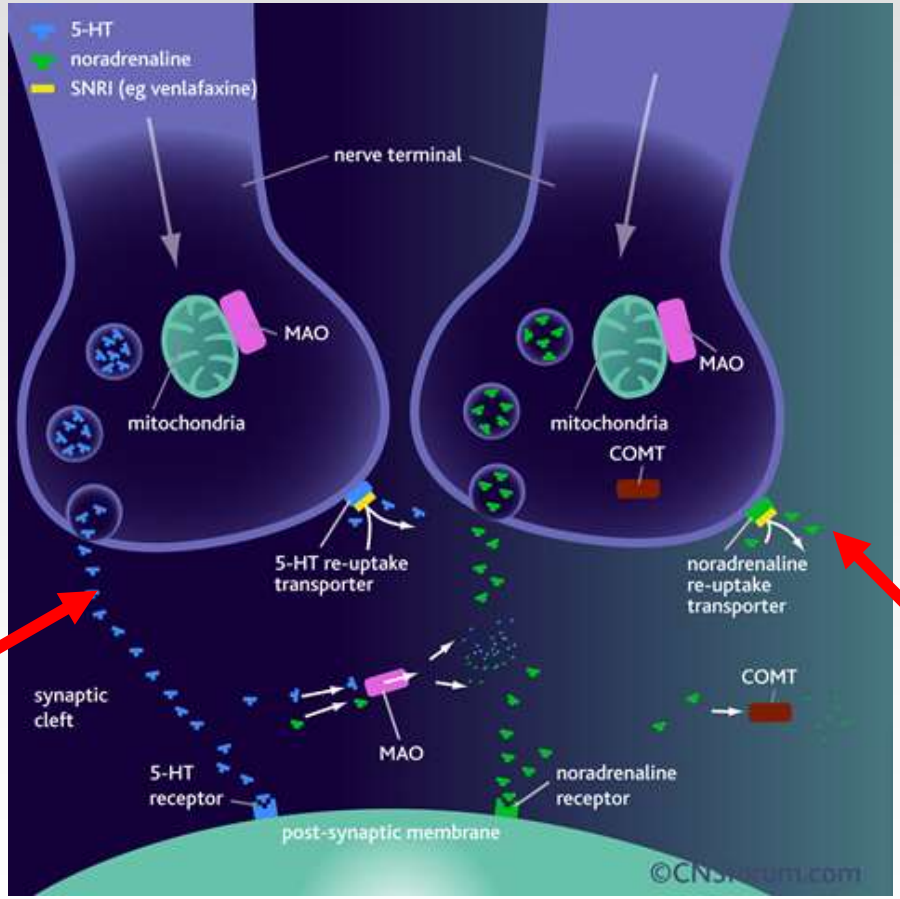


Norepinephrine, serotonin, dopamine

reuptake inhibition

Reuptake inhibitors I

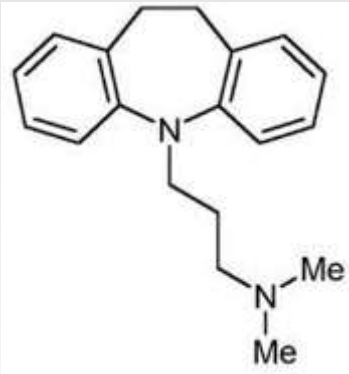
5-HT



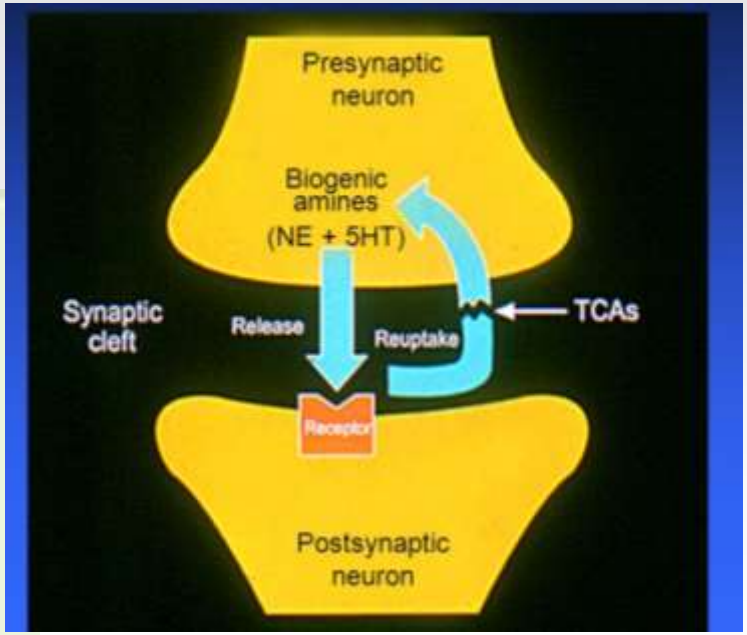
NE

Reuptake inhibitors

TCAs (tricyclic antidepressants)



amitriptyline
nortriptyline
desipramine
clomipramine
amoxapine
doxepin
protriptyline
trimipramine
imipramine

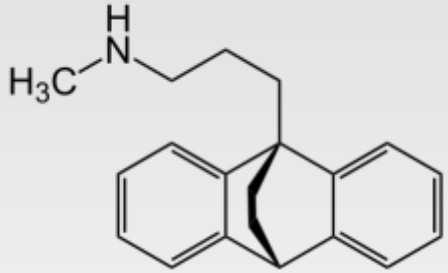


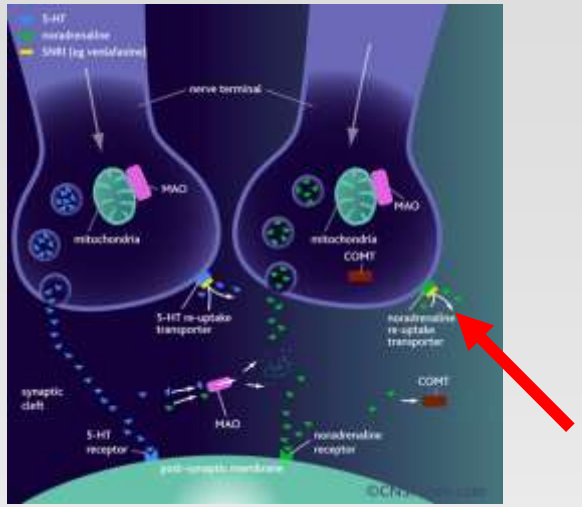
http://slideplayer.com/8377657/26/images/14/MECHANISMS+OF+ACTION+OF+TRICYCLIC+ANTIDEPRESSANTS.jpg

Tetracyclic antidepressants

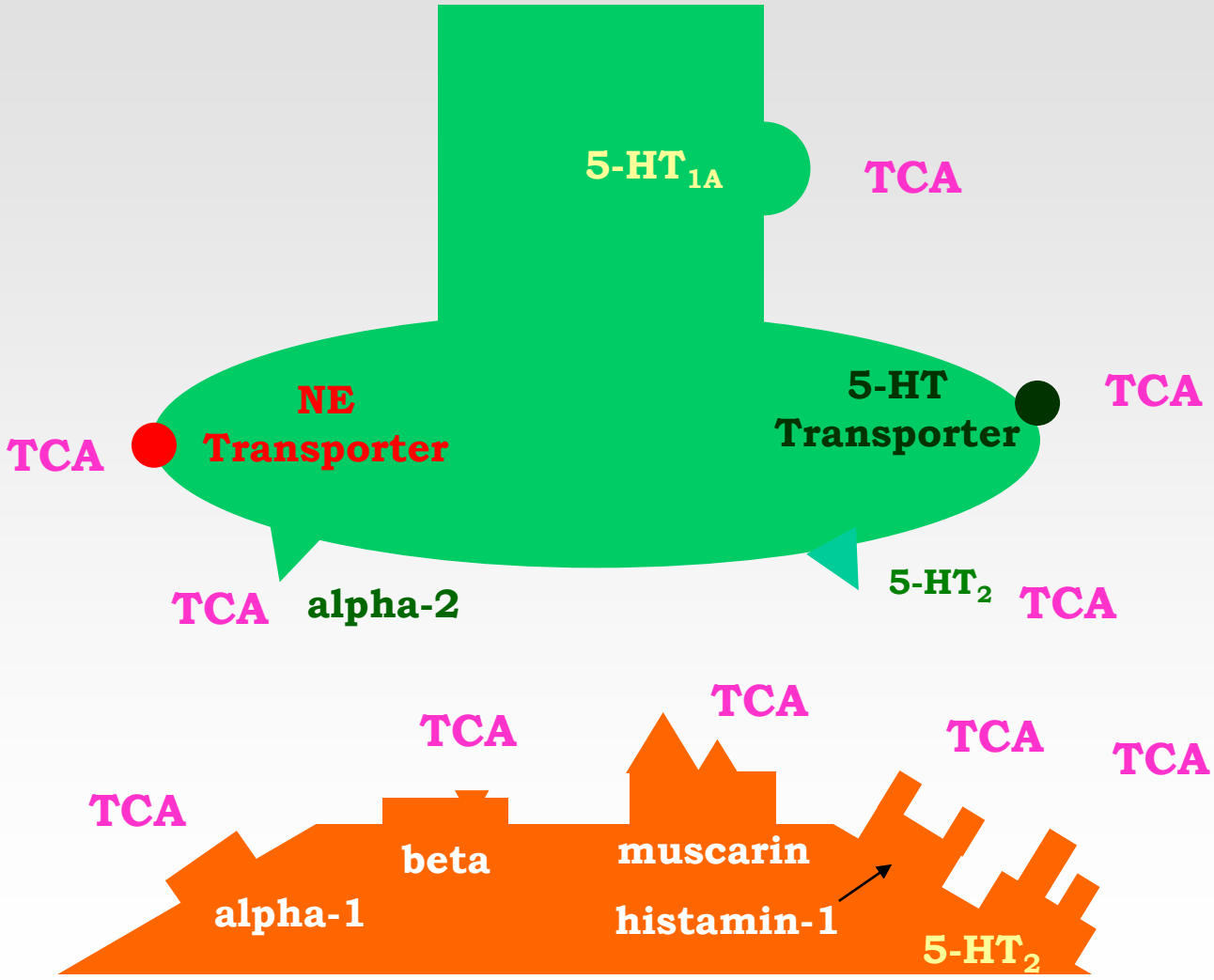
maprotiline

high affinity to NERT

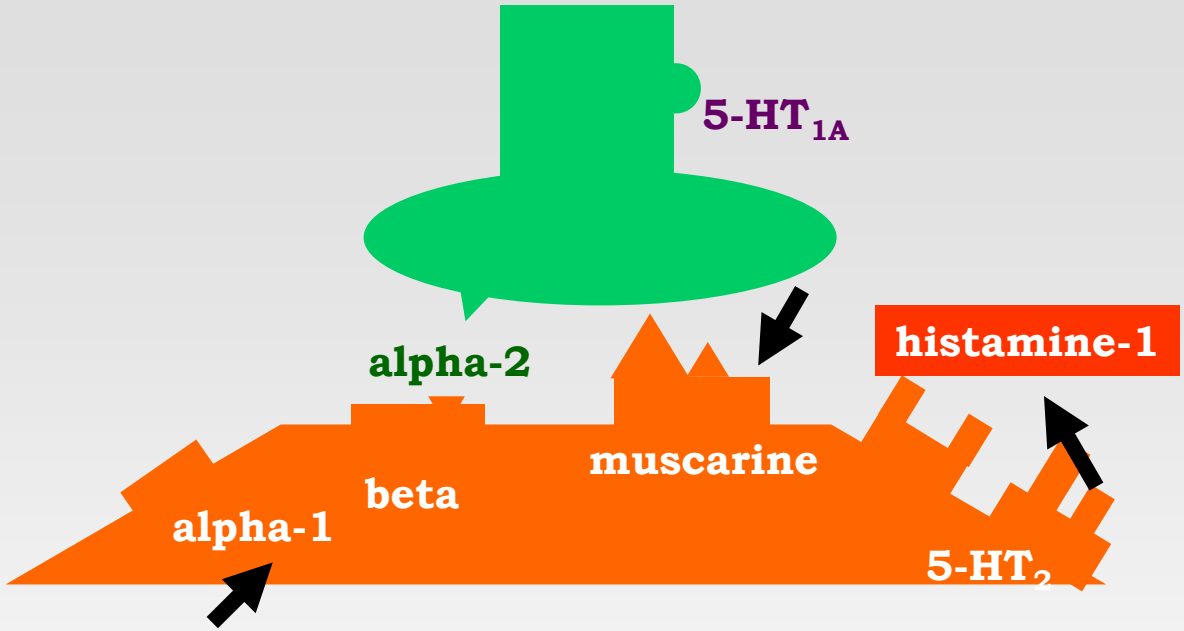




Binding profile of TCAs



Adverse effects of TCAs I



H_1 blockade - sedation, dizziness, confusion, weight gain

α_1 blockade - dizziness, hypotension, reflex tachycardia

M blockade - peripheral parasympatholytic symptoms
delirium, memory impairment

Adverse effects of TCAs II

- ***Cardiovascular***

  tachycardia, orthostatic hypotension, conduction defects, arrhythmias)

- ***Psychiatric/Neurological***

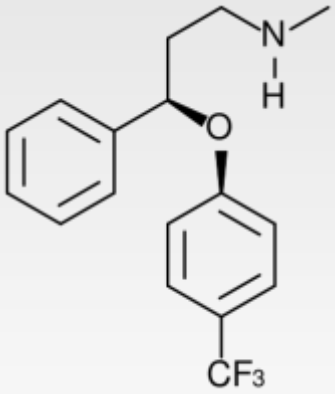
  sedation, sleepiness, aggravation of psychosis, tremor, additive effects with other sedative drugs, **seizures !!!**

- ***Metabolic-endocrine***

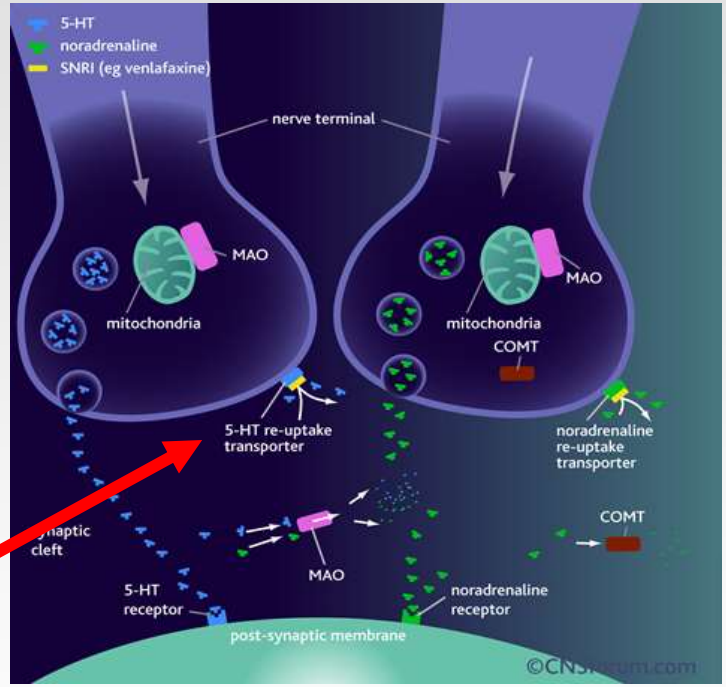
  weight gain/loss, sexual disturbances)

Reuptake inhibitors II

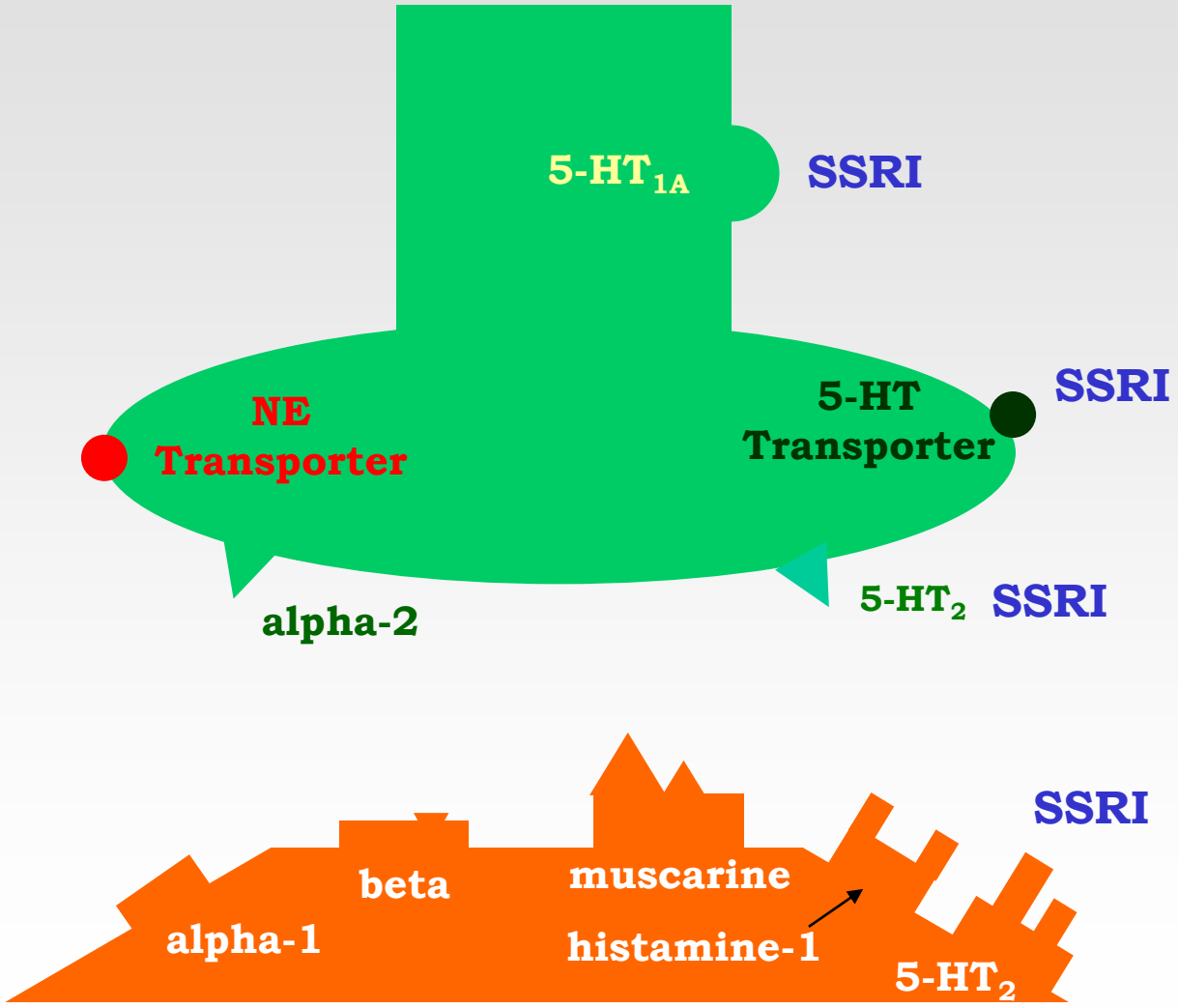
Selective Serotonin Reuptake Inhibitors (SSRIs)



fluoxetine
paroxetine
sertraline
fluvoxamine
citalopram
escitalopram

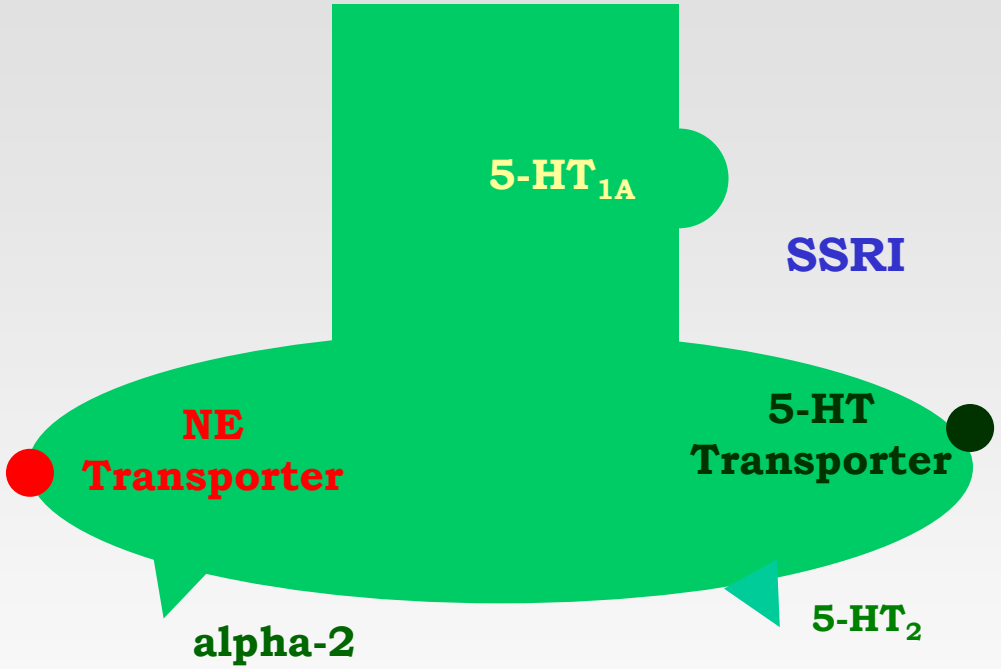


Comparative receptor specificity for SSRIs and TCAs



Comparative receptor specificity for SSRIs and TCAs

➢ **stimulation of 5-HT2 receptors** - agitation, akathisia, anxiety (temporary), panic attacks (temporary), hallucination, psychosis, insomnia, sexual dysfunction



➢ **stimulation of the 5-HT3 receptors (central and peripheral effects** -nausea, vomiting, GI discomfort, diarrhea, headache

Adverse effects of SSRI/SSNRIs

Central: **headache, anxiety, insomnia/hypersomnia, tremor, hallucination, psychosis, decrease of libido and sexual function**

GI: nausea and vomiting, GI discomfort, diarrhea

weight gain

seizures

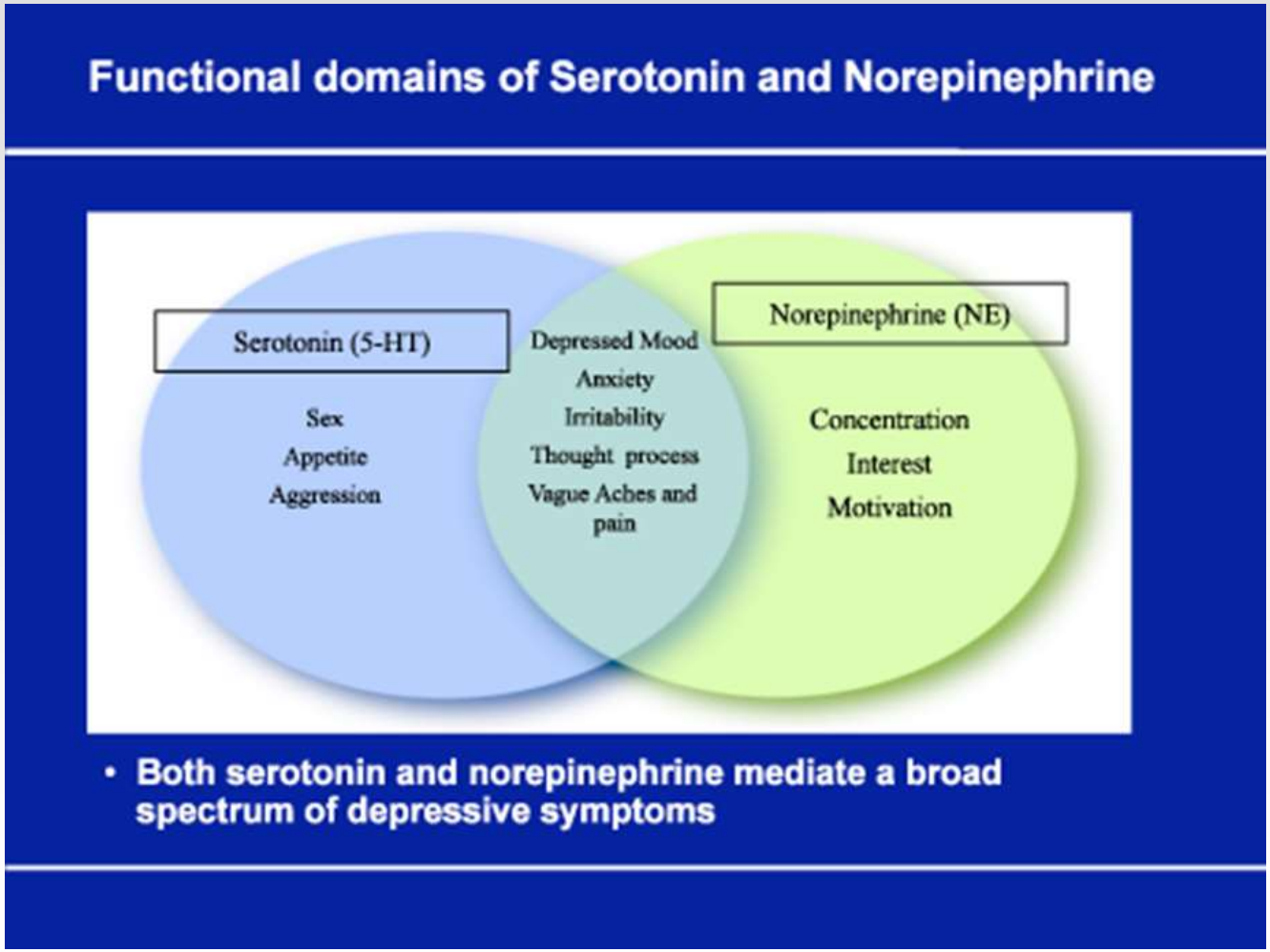
Discontinuation syndrome: dizziness, paresthesia (with short acting like paroxitene, sertraline)

serotonin syndrome

hyperthermia, hypertension, hyperactive bowel, agitation, coma (onset – hours)

th: BZs, symptomatic treatment, 5-HT antagonists (cyproheptadine)

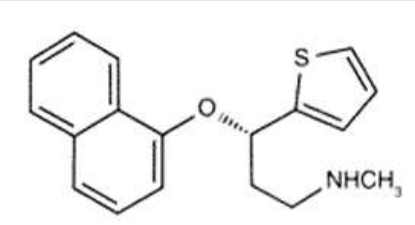
In depression serotonin and norepinephrine appear to be out of balance



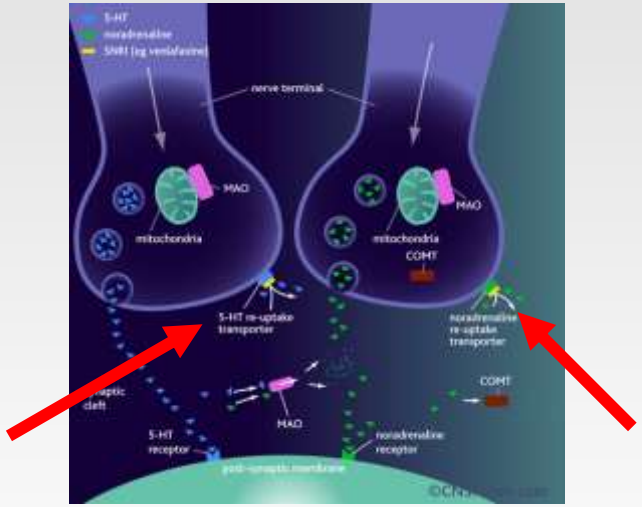
http://www.namcp.org/md_resource_centers/depression/practicingdocs/images/functional.domains.png

Reuptake inhibitors III

Selective Serotonin and Noradrenaline Reuptake Inhibitors (SSNRIs)



venlafaxine
desvenlafaxine
duloxetine

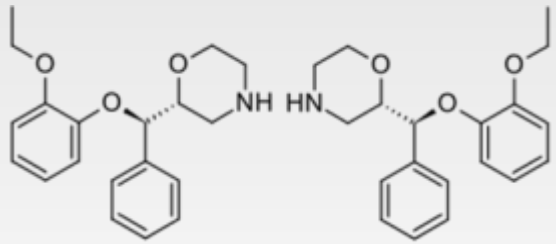


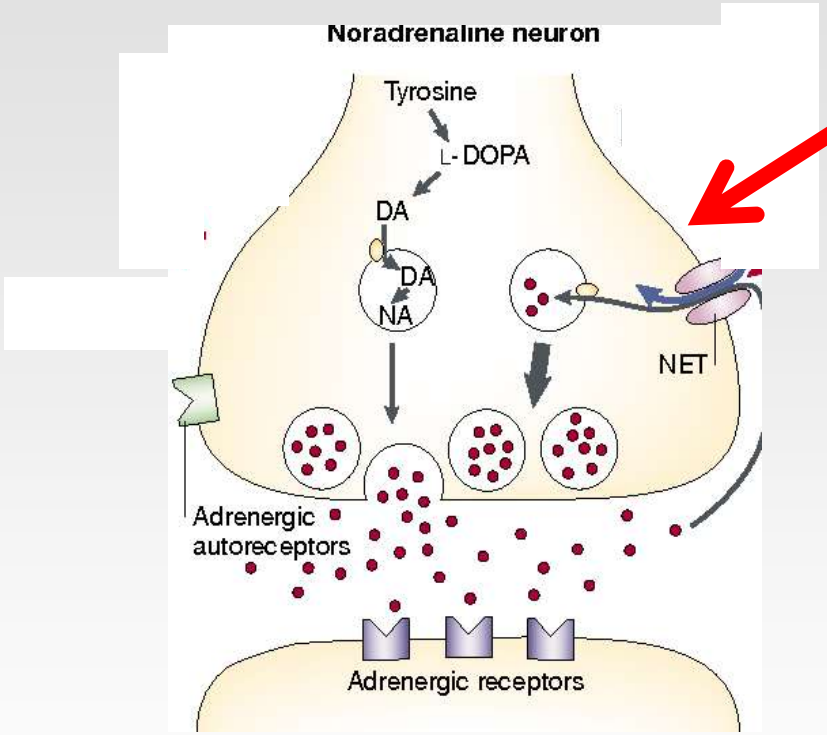
Selective – binding profile is similar to SSRIs

Reuptake inhibitors IV

SNRIs (selective **NE** *reuptake inhibitors)*

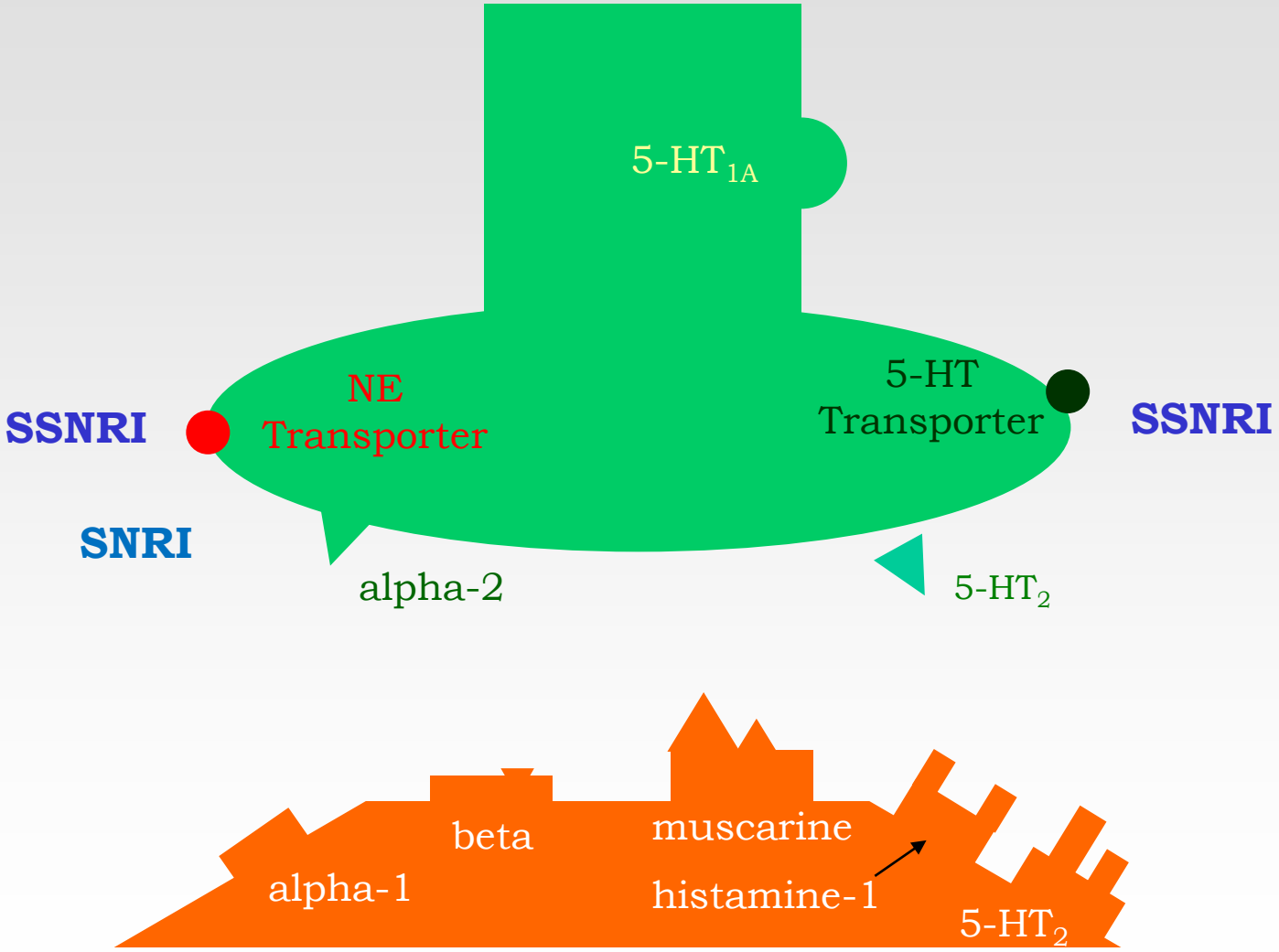
reboxetine

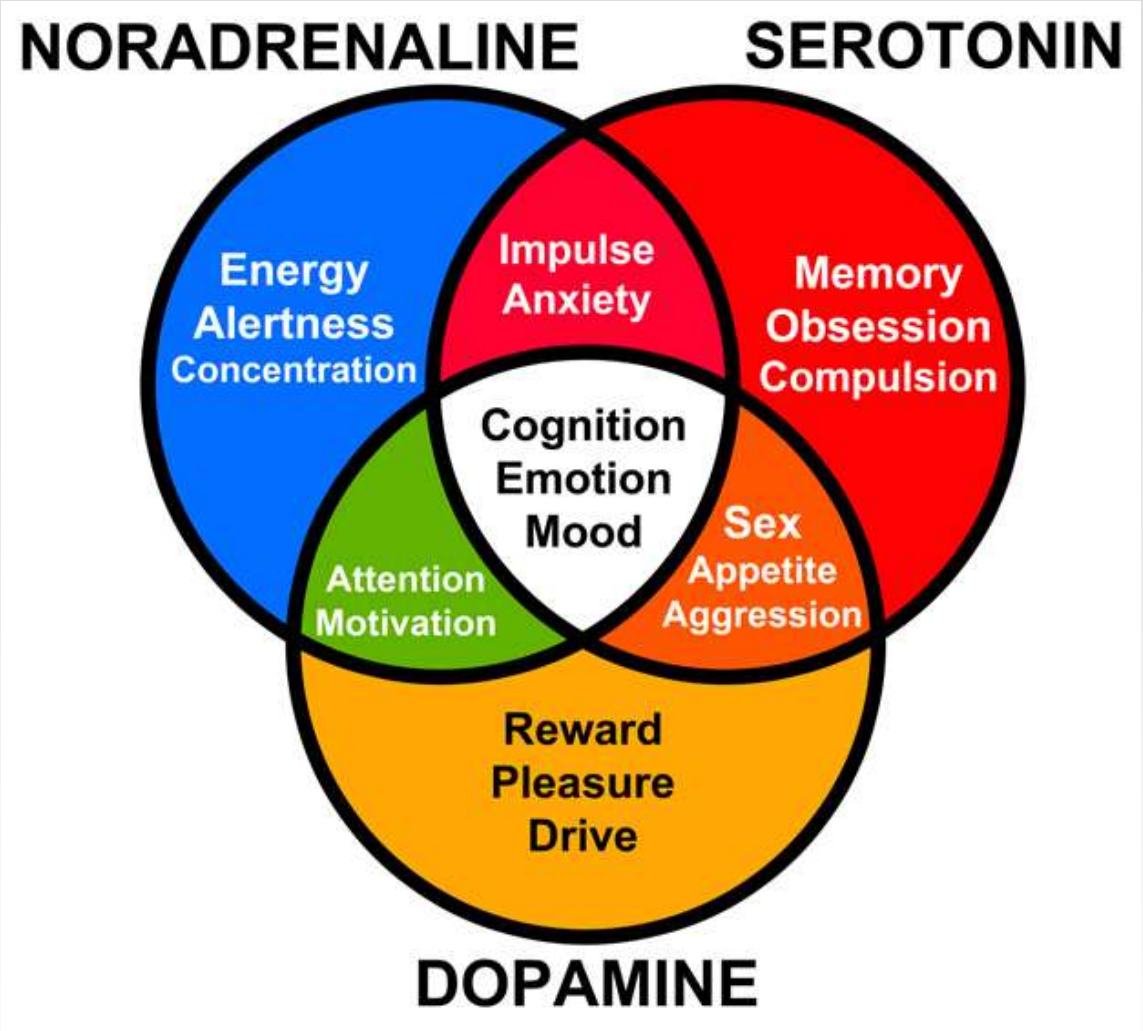




no antiadrenergic, antimuscarinergic, antihistaminergic effect

Comparative receptor specificity for SSNRIs and TCAs

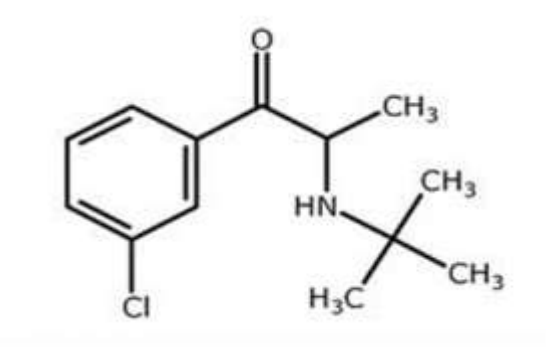




https://universityhealthnews.com/media/brain_chemistry-neurotransmitters.jpg

Reuptake inhibitors V

bupropion



Inhibits DA and NA reuptake
(not 5-HT)

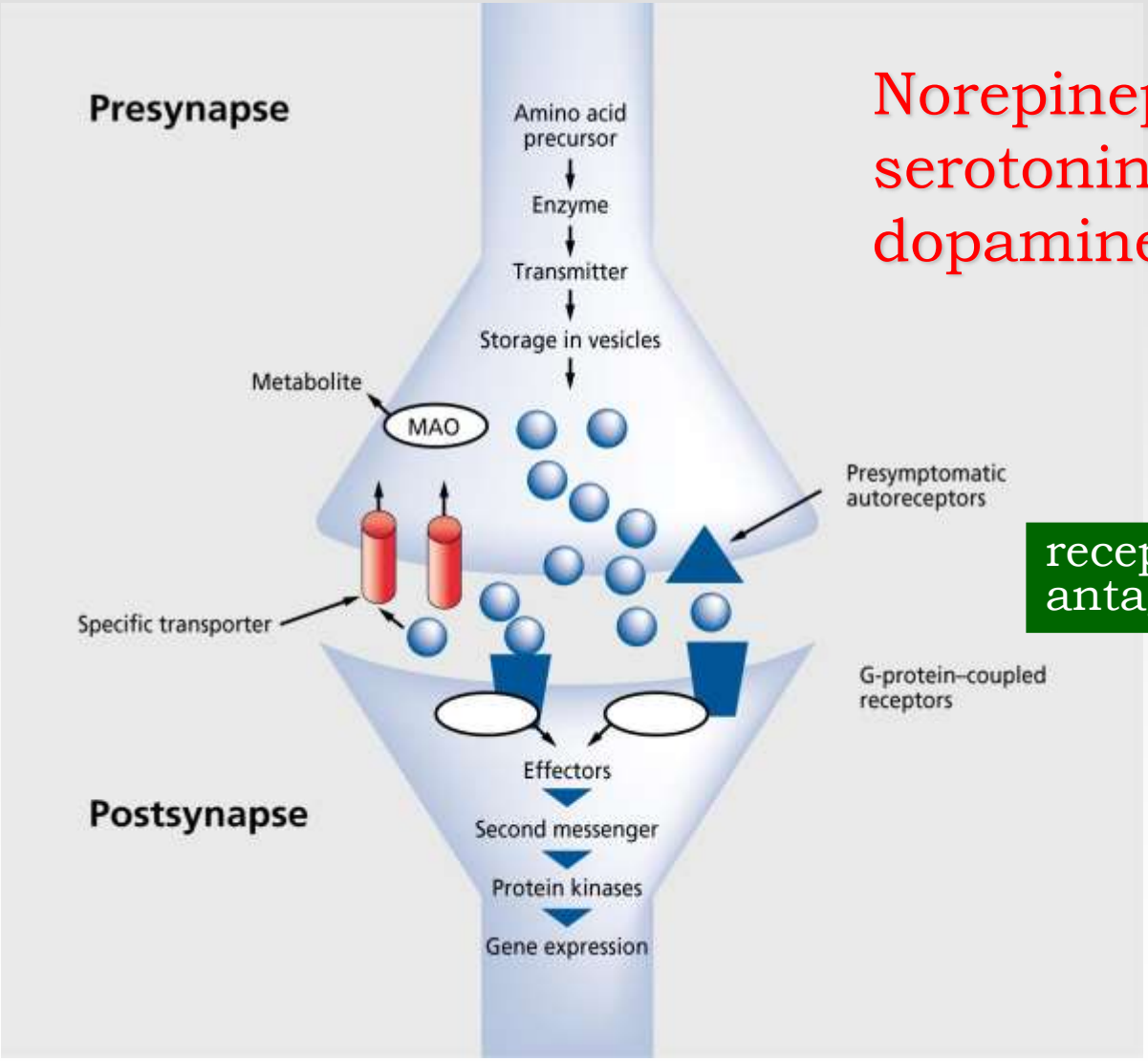
Inhibits nicotine receptor

Besides MD used:

for helping smoking cessation

together with naloxone as
anorectic

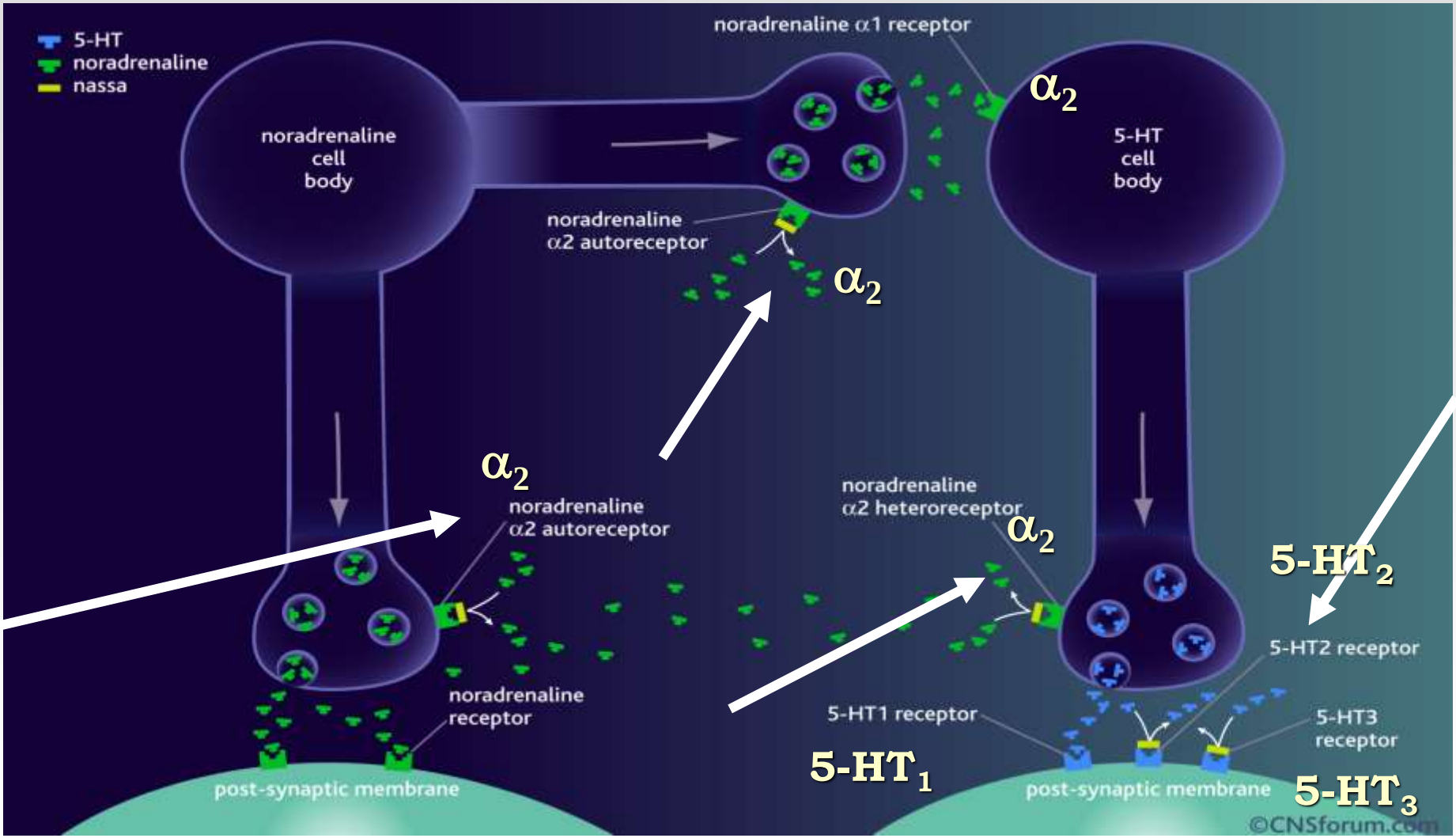
Majority of the pharmacons used nowadays are based on the monoamine hypotheses



Norepinephrine, serotonin, dopamine

receptor antagonism

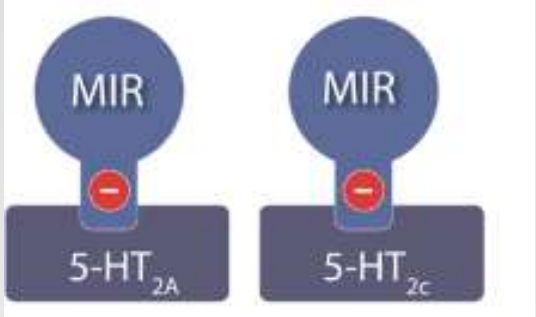
receptor antagonism

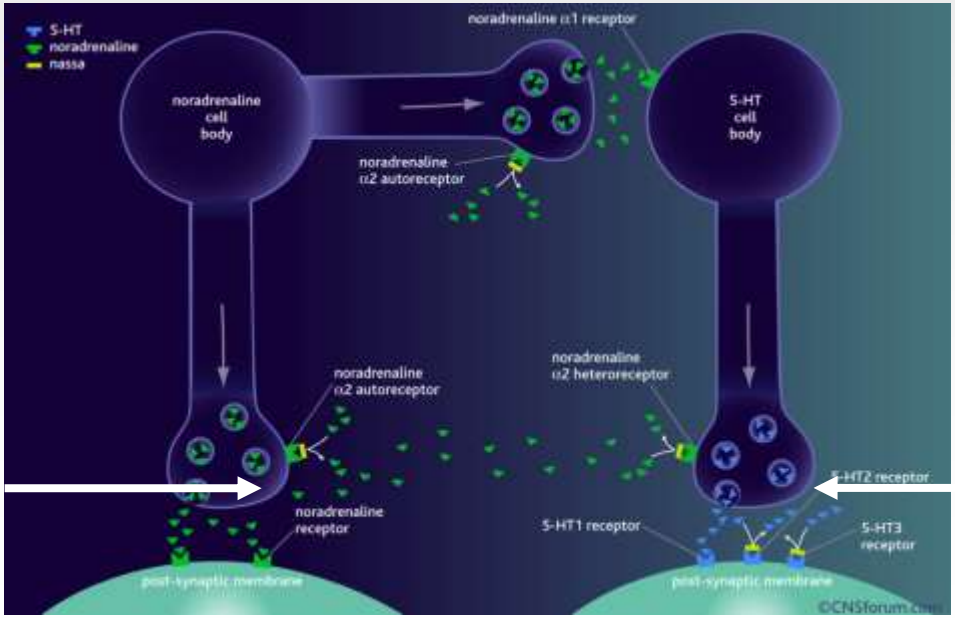


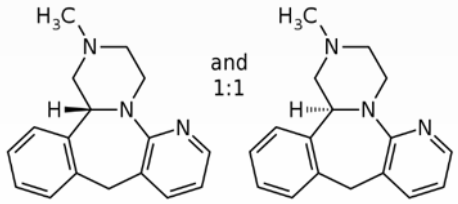
Receptor antagonists I

receptor blockers

mirtazapine







Receptor antagonists II

Reuptake inhibitors and receptor blockers

nefazodone

Inhibitor of NE and 5-HT reuptake + 5-HT2 blocker

trazodone

Weak inhibitor of 5-HT reuptake + 5-HT2 blocker

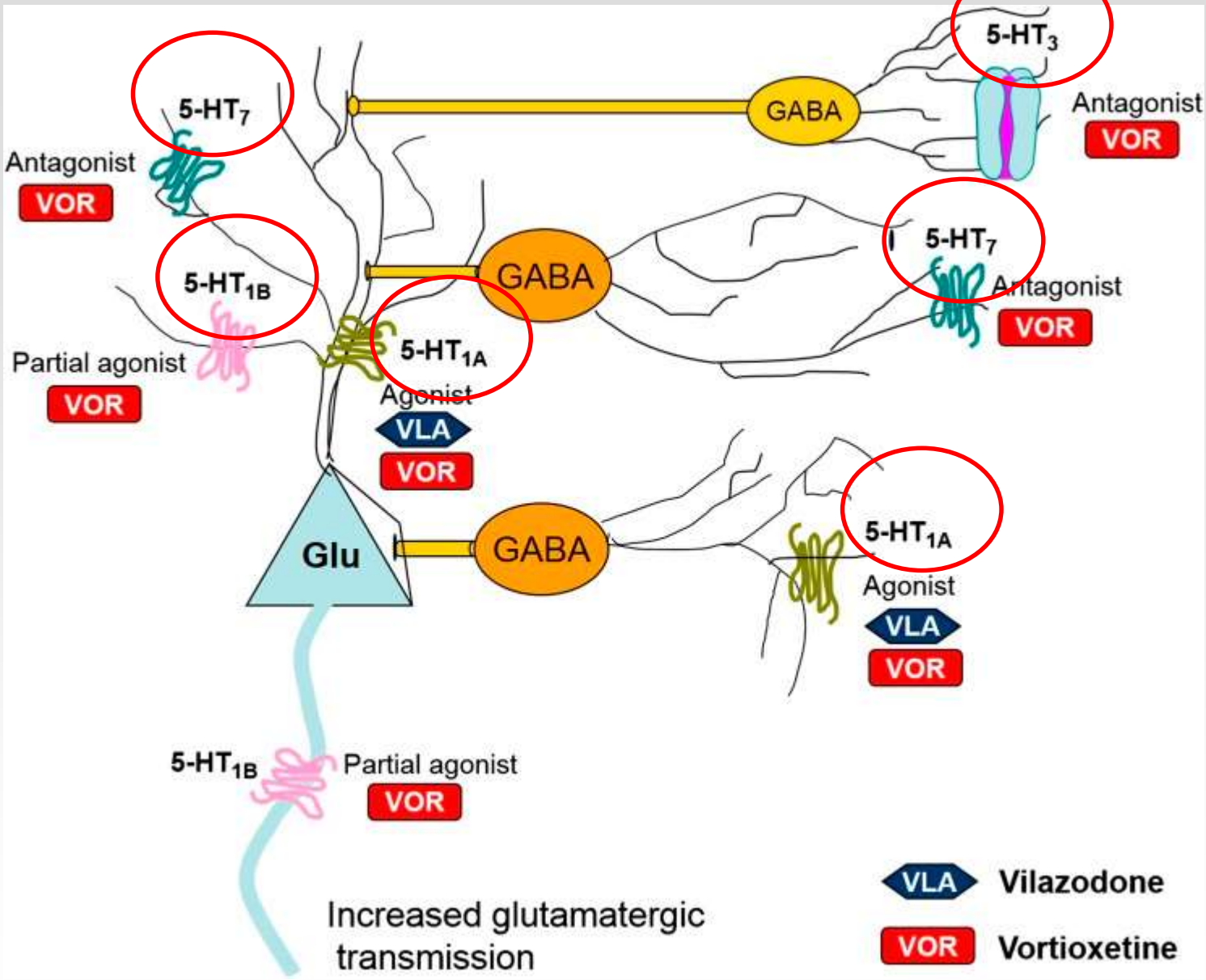
Receptor antagonists III

Newly developed compounds affecting the serotonergic system

The central serotonergic system works as a rhythmic homeostat

Enhanced activity of the serotonergic neurons are partly reduced by

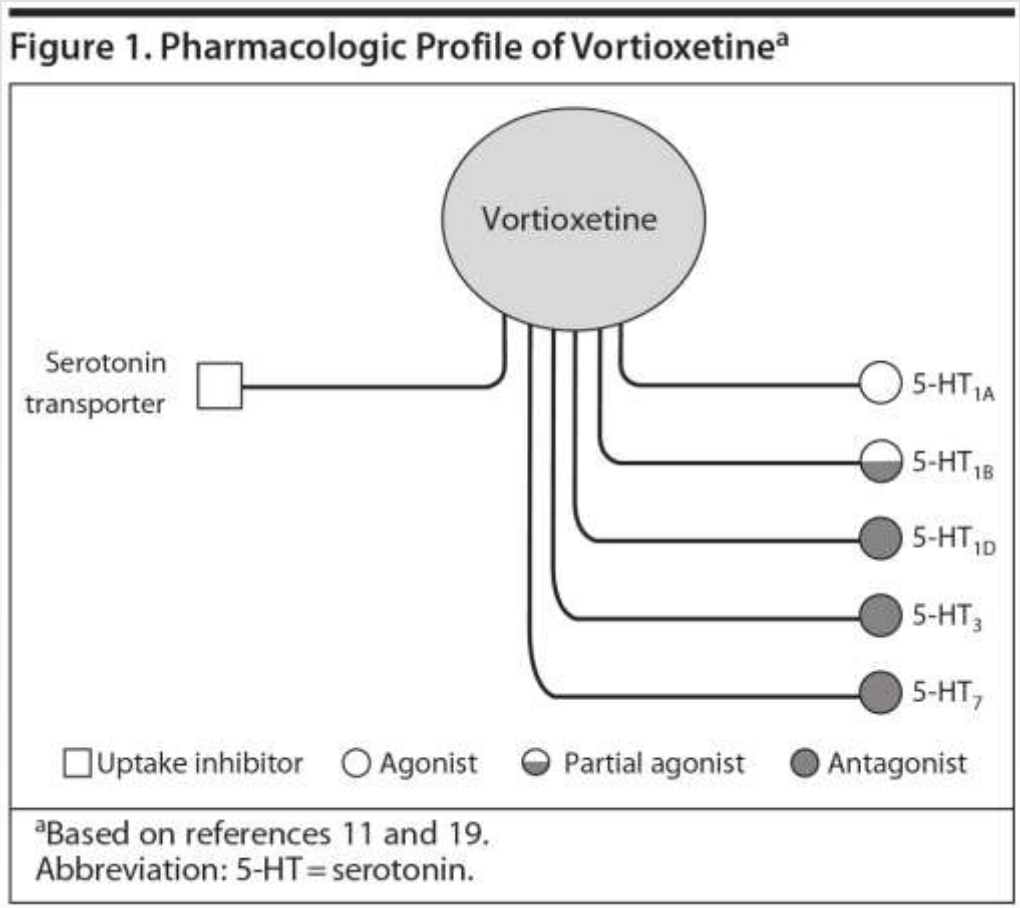
- **5HT1B/1D** receptors in the synapse
- **5HT1A** receptors on the dendrites
- **5HT3/7** receptors via the GABA-erg interneurons



https://www.researchgate.net/profile/Connie_Sanchez/publication/254260702/figure/fig1/AS:202630321184768@1425322241168/A-schematic-diagram-of-the-hypothesized-modulatory-role-of-5-HT-receptors-on.png

Receptor antagonists III

Vortioxetin - a new AD with ”multimodal” serotonergic mechanism of action



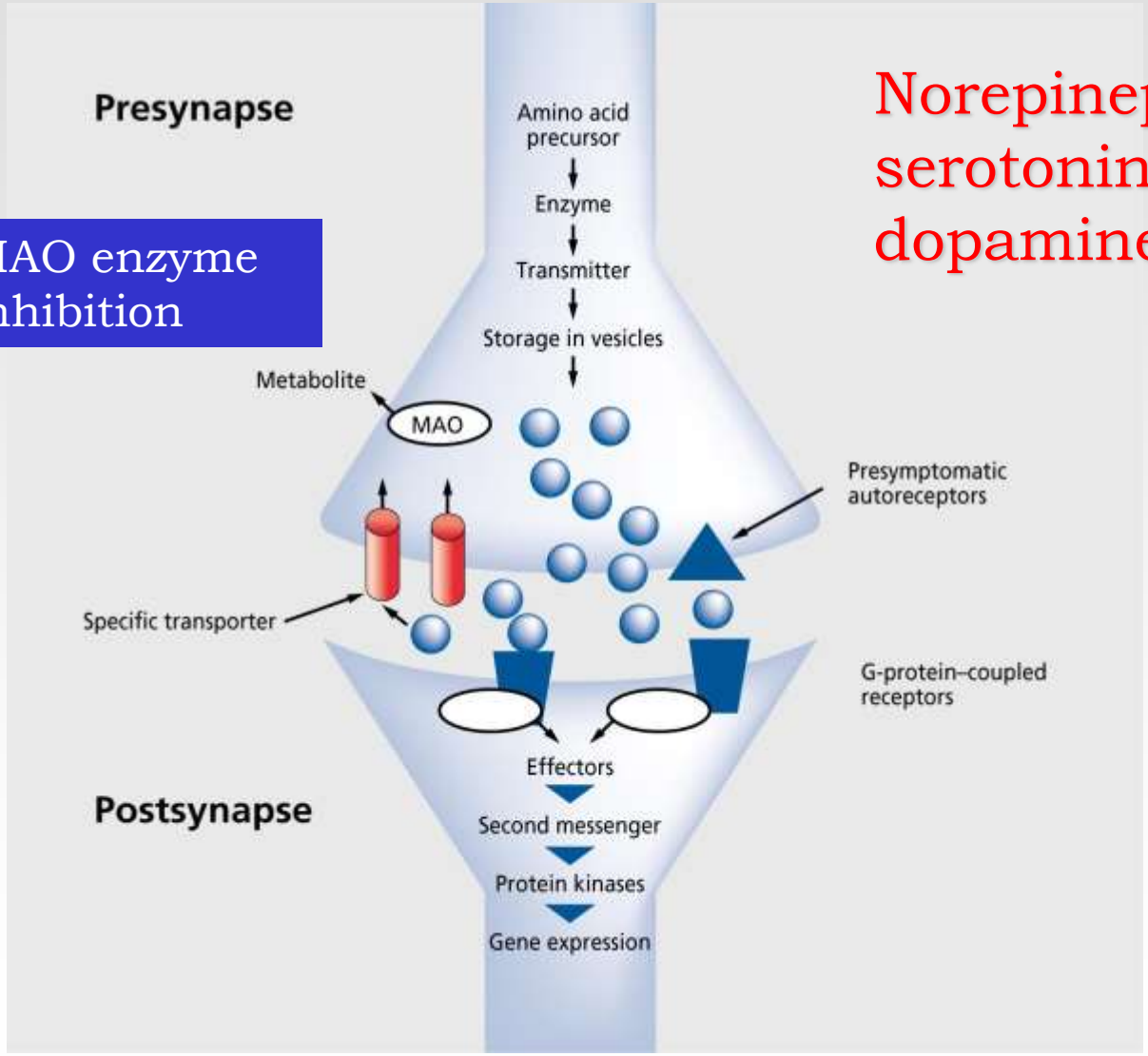
The result of this complex receptorial effect is - beside enhancement of the serotonerg activity - the noradrenergic, dopaminergic, cholinergic, histaminergic, glutamatergic neuronal activity will also increased (via by blockade of the 5HT3/7 receptors on the GABA-neurons)

http://leonardopalmeira.com.br/website/wp-content/uploads/2016/03/news_001.gif

Majority of the pharmacons used nowadays are based on the monoamine hypotheses

MAO enzyme inhibition

Norepinephrine, serotonin, dopamine

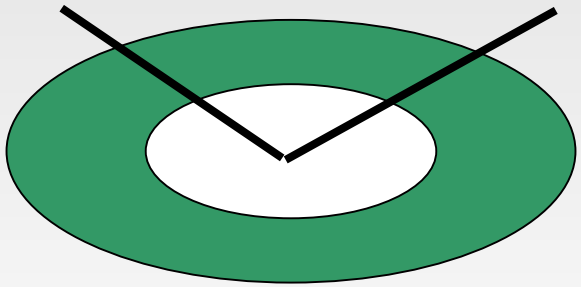


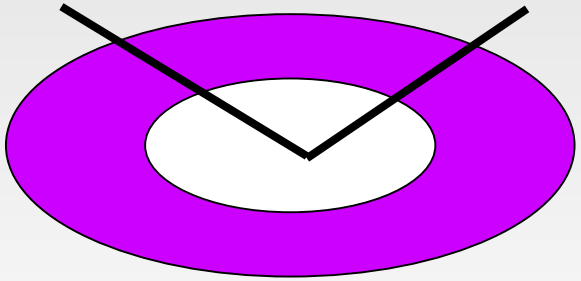
Monoamino-oxidase enzyme

norepinephrine
serotonin

dopamine
tyramine

phenylethylamine
benzilamine





MAO-A

GI
neuronal end-terminals

MAO-B

platelets
glia

Classification of MAO inhibitors (MAOIs)

non selective irreversible MAO inhibitors

in extremely severe depression

phenelzine, tranylcypromine

selective reversible MAO-A inhibitors (RIMA)

moclobemide

depression

selective irreversible MAO-B inhibitors

selegiline

Parkinsonian disease

depression

Alzheimer disease

Adverse effects of MAOIs

- ”cheese effect" - dietary restriction (first of all for irreversible MAOIs)

- drug interaction
- orthostatic hypotension
- insomnia, irritability
- sexual disturbances

seizures

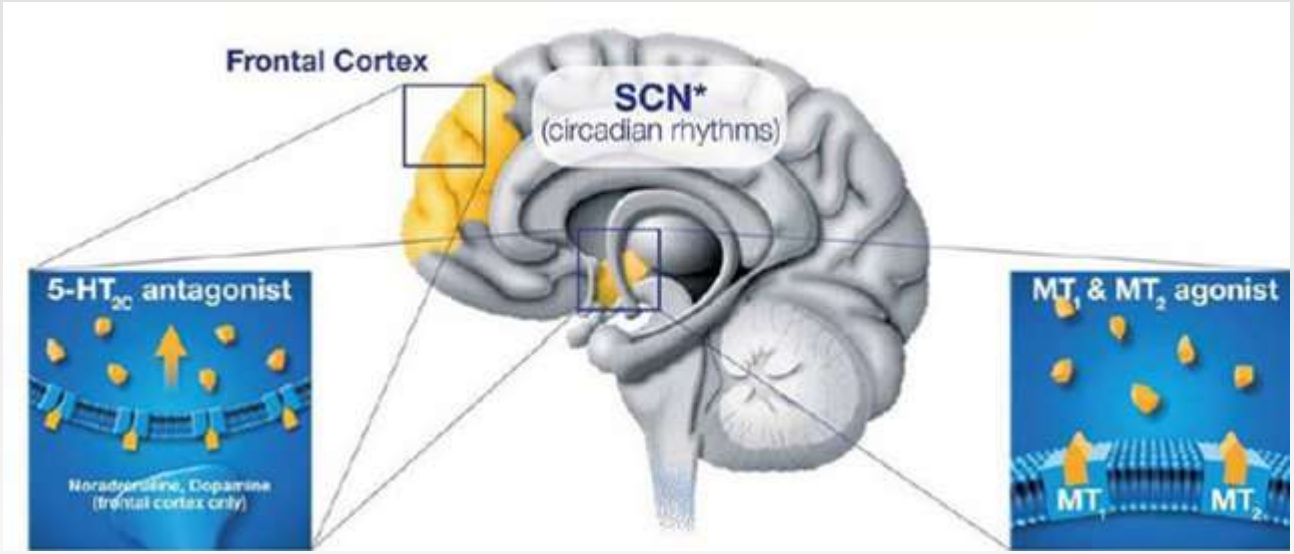
In case of RIMA the symptoms are less marked and shorter

In case of selegiline minimal risk of cheese effect

Other possibilities

Melatonin (MT1 and MT2) agonist and 5-HT_{2c} receptor antagonists

agomelatine



No effect on the monoamine uptake, no influence on the extracellular 5-HT level

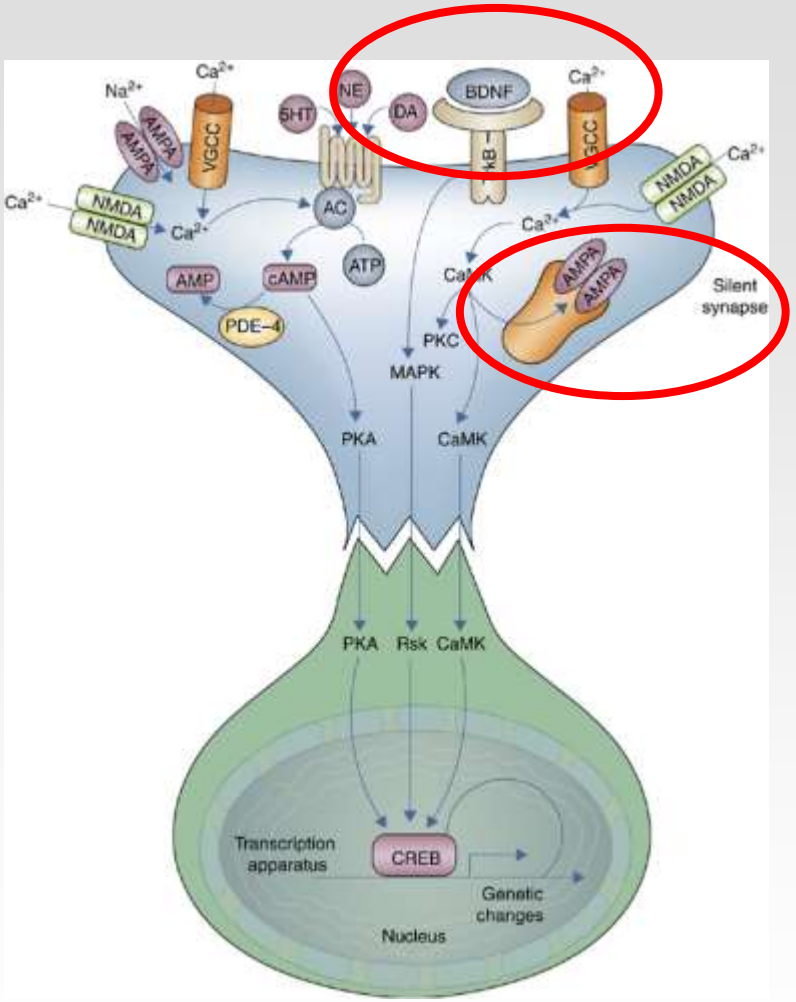
Main adverse effects – obesity, risk of hepatotoxicity

Other possibilities

tianeptine

enhancer of 5-HT reuptake

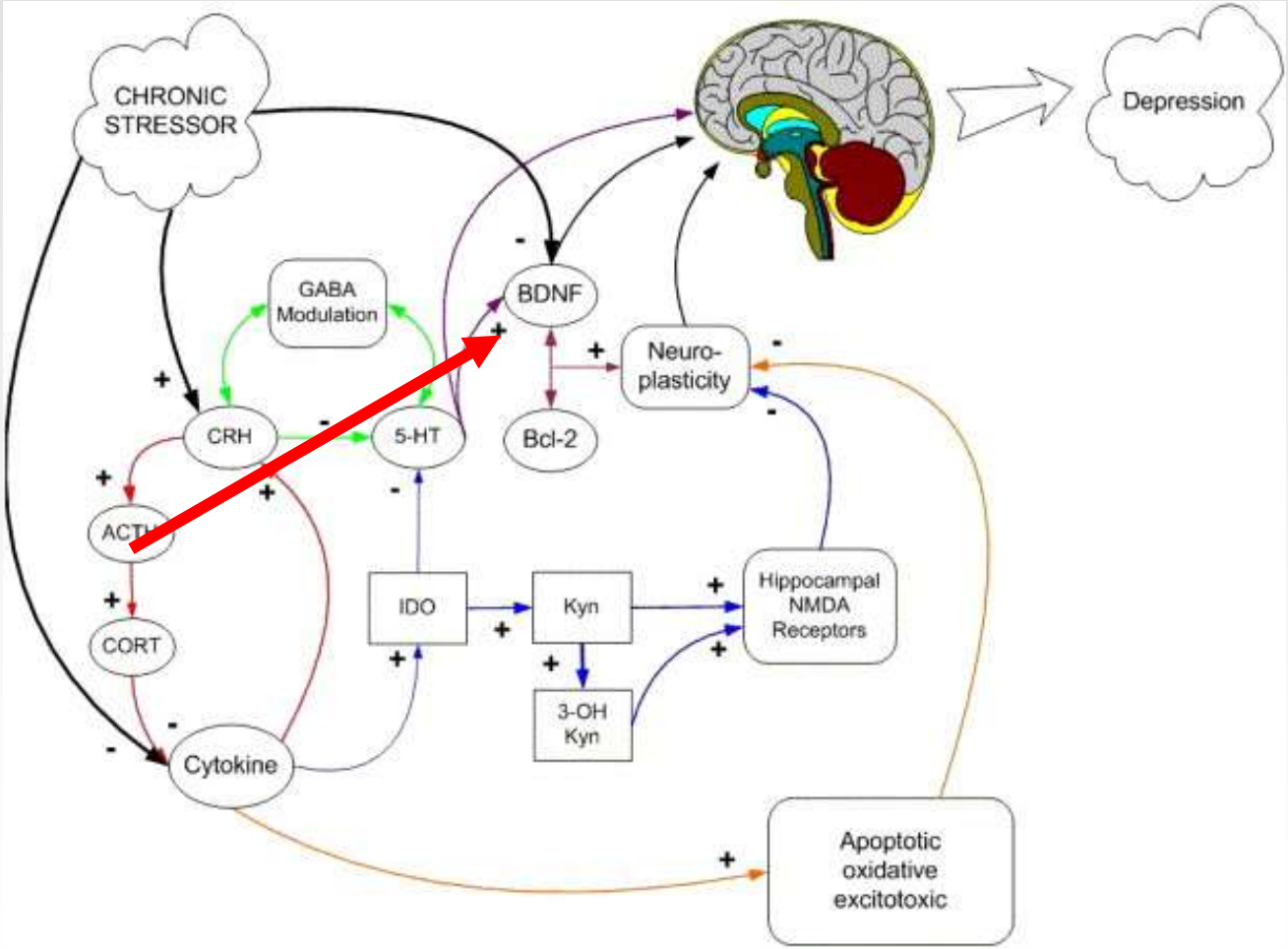
- ✓ Decrease of the stress induced activation of the hypothalamic-pituitary-adrenal axis ?
- ✓ Enhancement of AMPA receptor function; enhancement of the BNFD release ??



Advantages:
Therapeutical effects develops within 1-2 weeks,
not anticholinergic effect

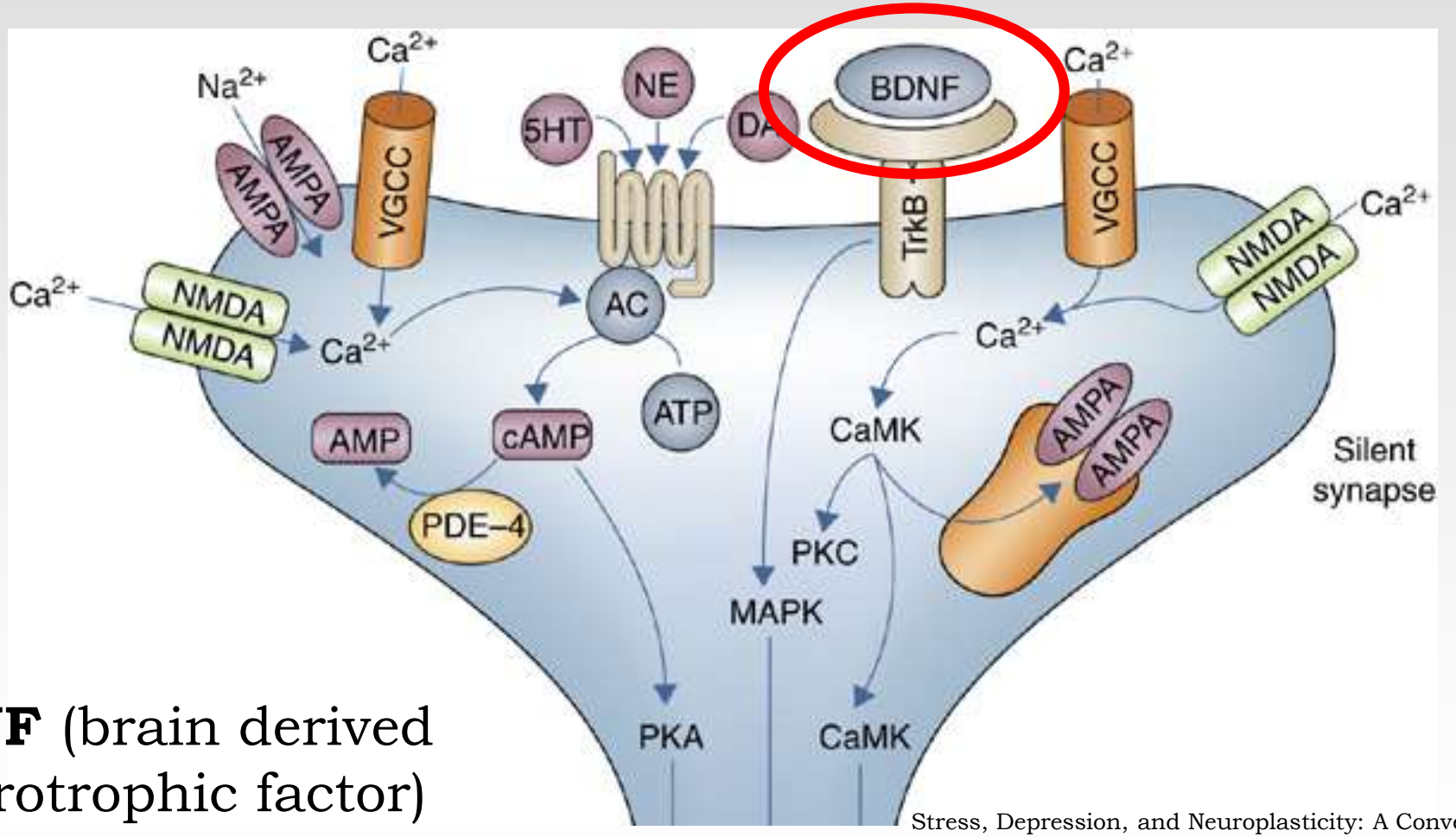
Other possibilities

Electro Convulsion Therapy



PATHOGENEZIS of MDD II

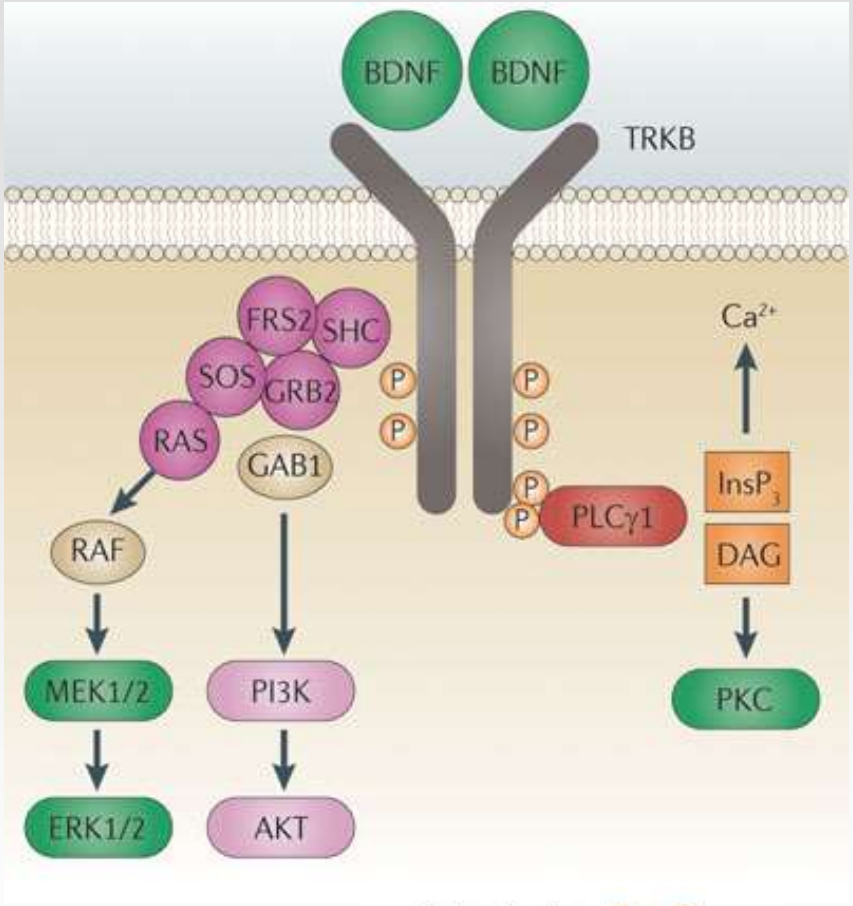
Neurotrophic (BFNF) hypothesis

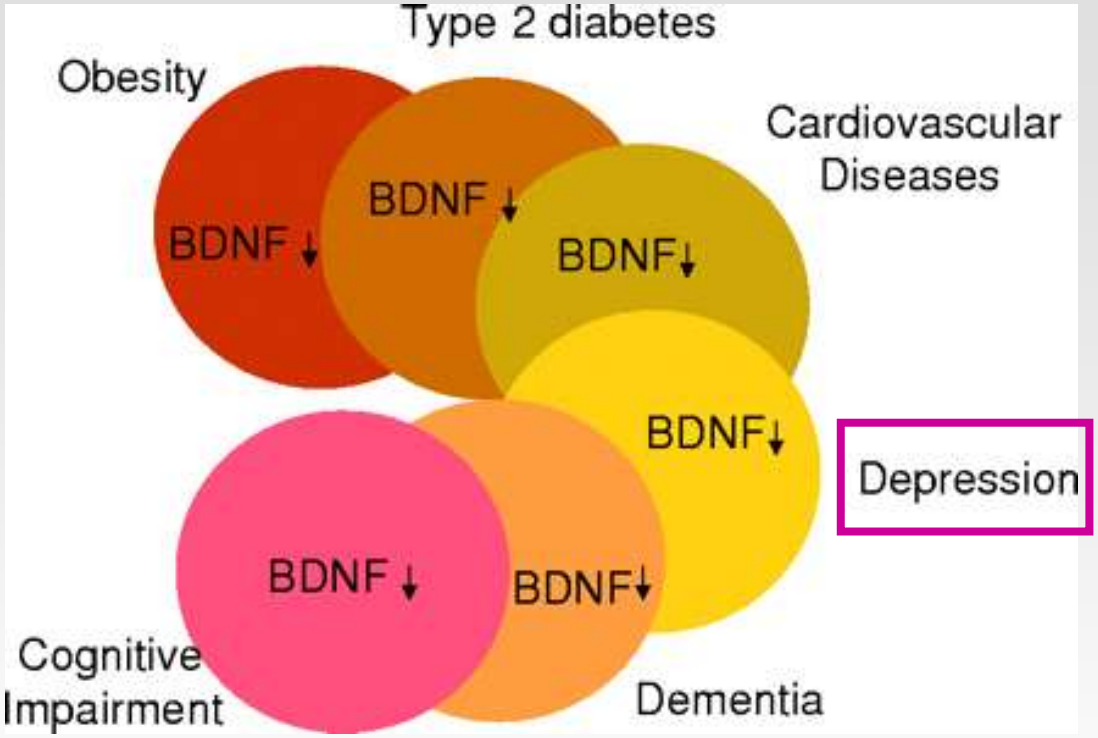


BDNF (brain derived neurotrophic factor)

Stress, Depression, and Neuroplasticity: A Convergence of Mechanisms
Christopher Pittenger and Ronald S Duman,
Neuropsychopharmacology 2007, 33:88

BDNF

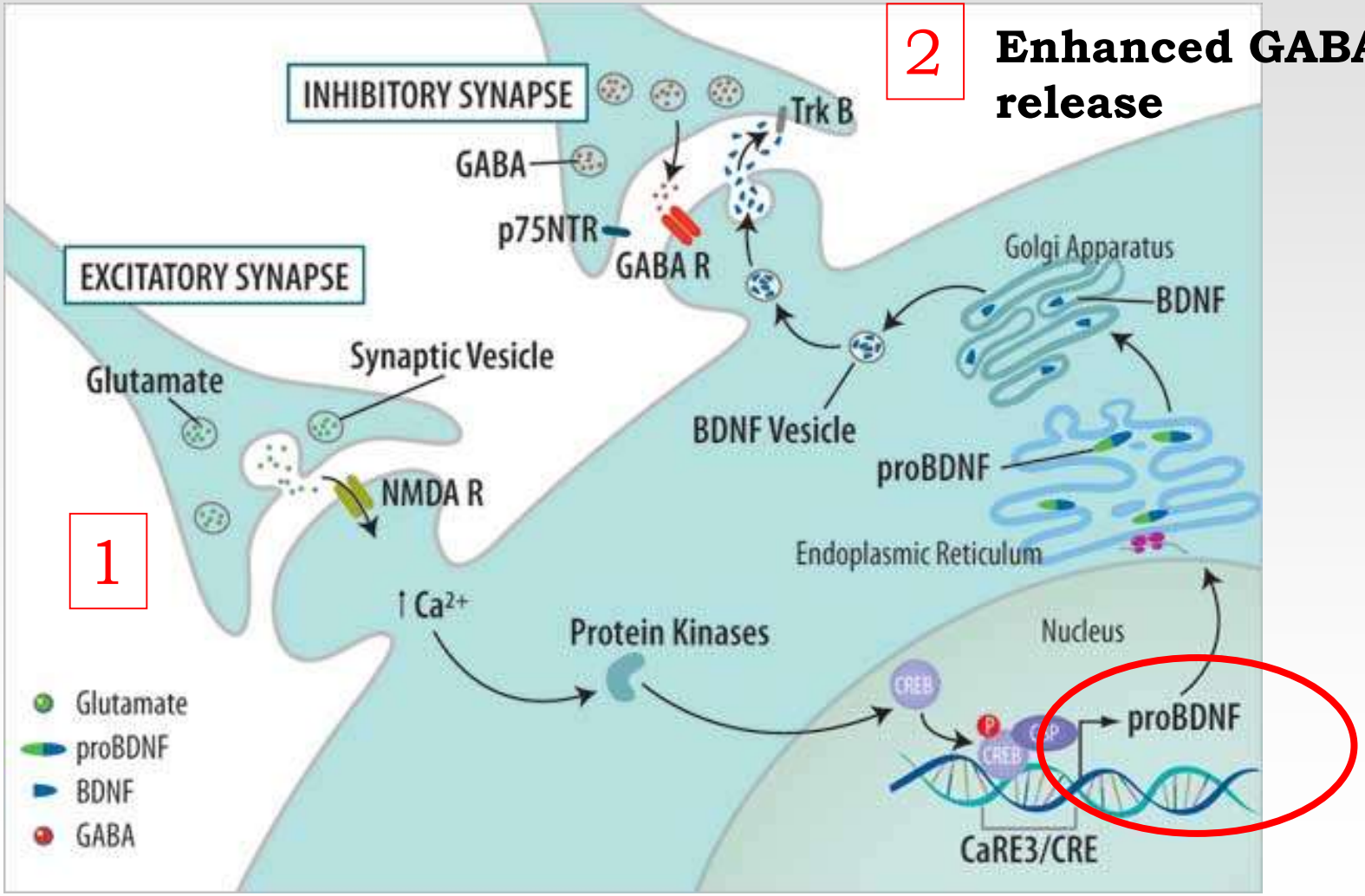




BDNF plays critical role in regulation of neural plasticity, neurogenesis, neuronal survival, etc.

BDNF

Role of BDNF expression on the activity homeostats



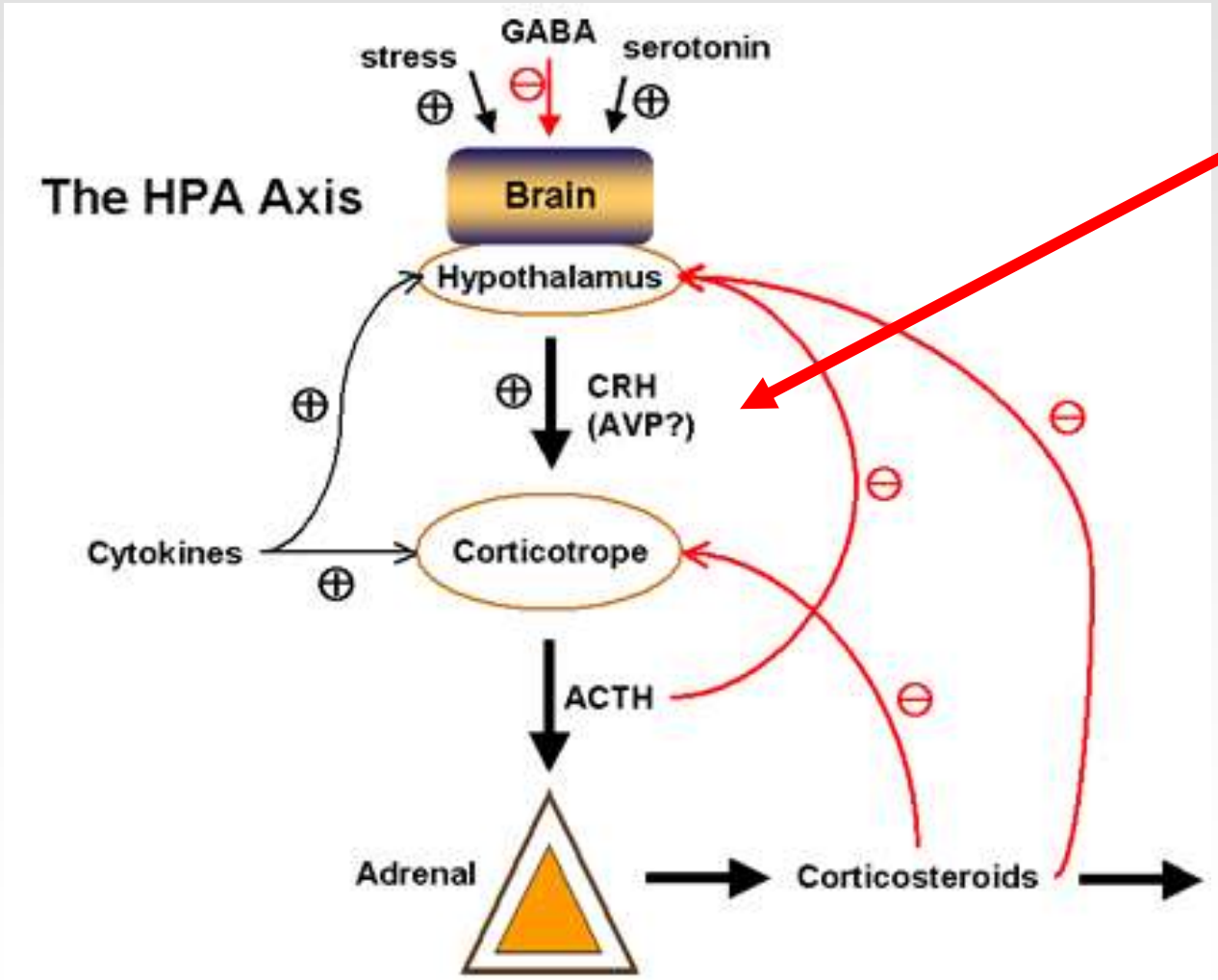
Some argues for BDNF hypothesis:

- During stress the BNDF level decreases in the a hippocampus

- In animal experiments all the antidepressants (and even electroshock) enhance the BDNF level (following chronic administration !!)

PATHOGENEZIS of MDD III

Neuroendocrine hypothesis - role of HPA axis

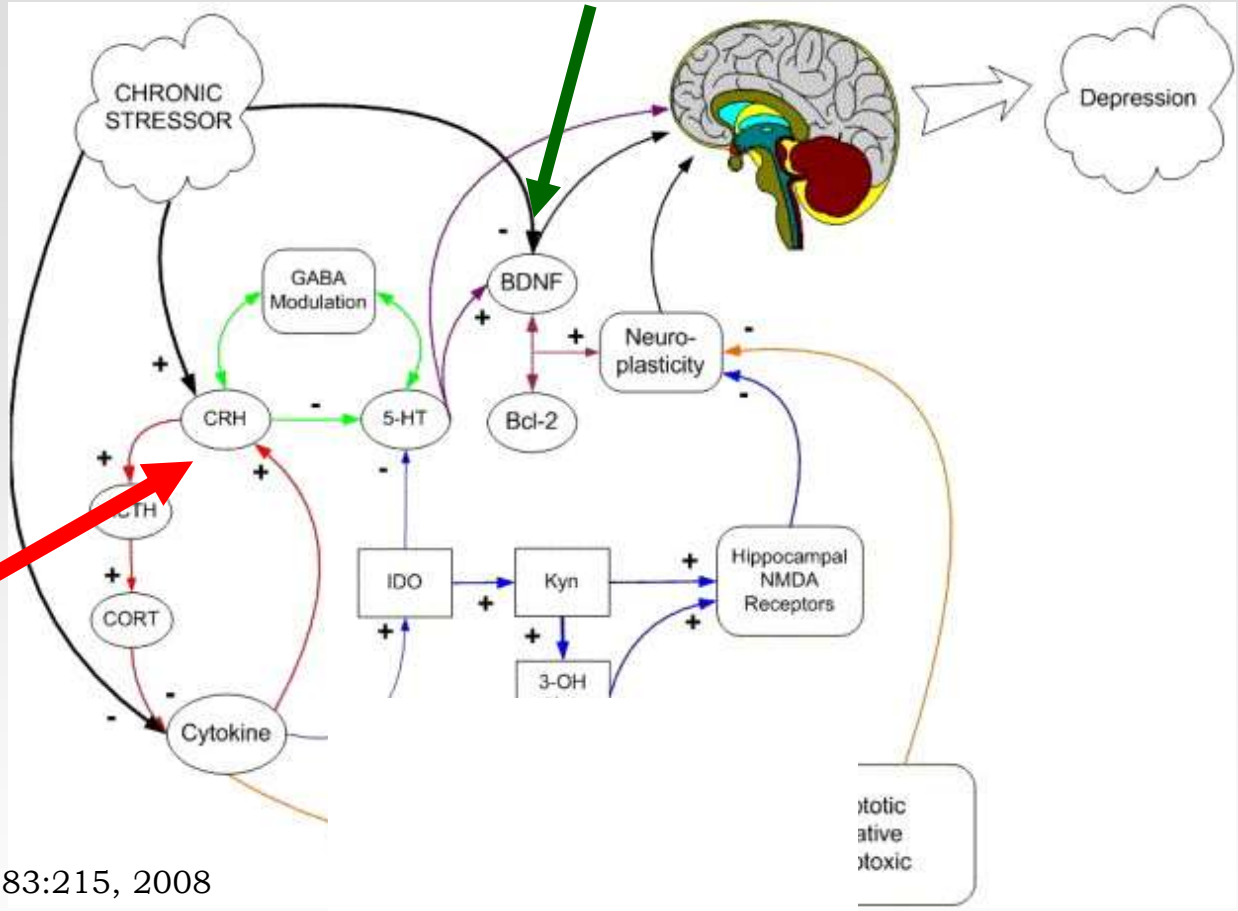


CRH- corticotrope releasing hormone

argue for neuroendocrine hypothesis:

- In MDD regulation of HPA axis is disturbed (higher cortisol and CRH level, ACTH does not act correctly in dexamethasone test)

Neuroendocrine (CRH) hypothesis

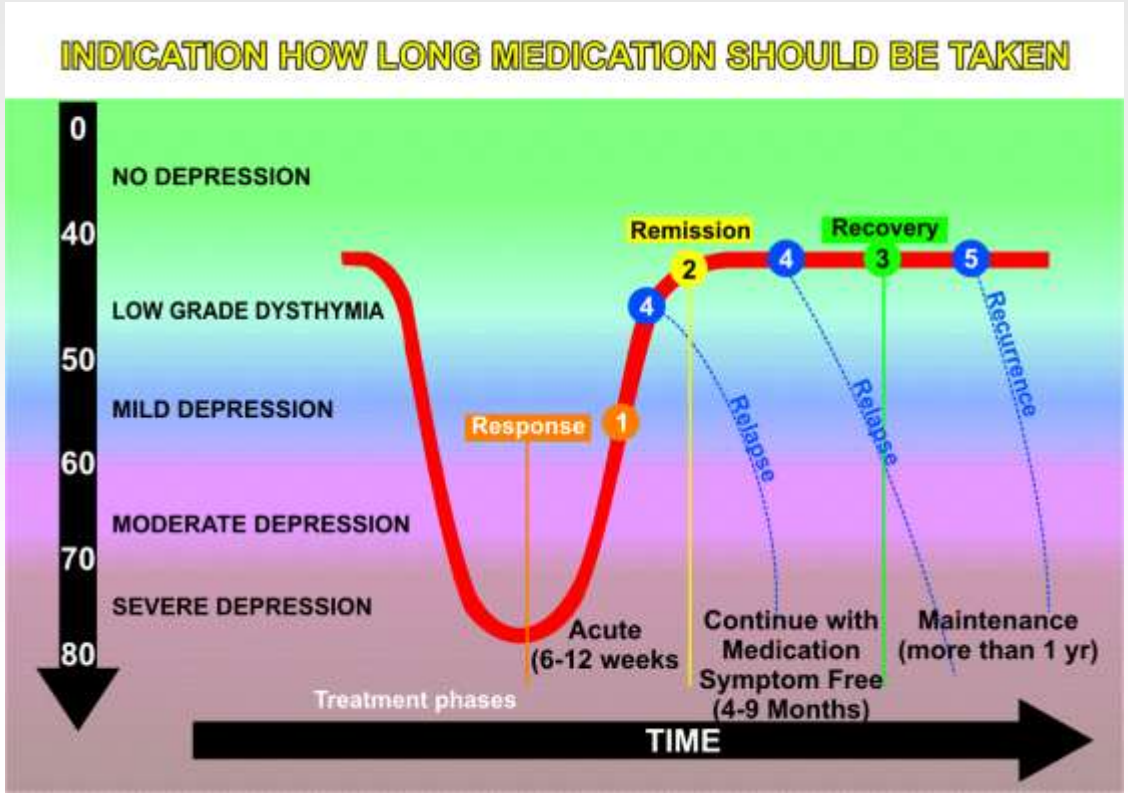


Eur J. Pharmacology 583:215, 2008

CRH reciprocally modulate $GABA_A$ receptor and inhibit 5-HT neuronal functioning, hence (via negatively affecting BDNF) may involved in depression

AIM OF ANTIDEPRESSANT/ANTIMANIC TREATMENT

- **Relief of acute symptoms weeks**
- **Prevention of relapse (maintenance therapy) months**
- **Prevention of repeated episodes (prophylactic treatment) years**



Other indicatios of ADS

- anxiety disorders - **SSRIs, SNRIs**
- chronic pain - **TCAs, SSNRIs**
- premenstrual dysphoric disorder **SSRIs**
- bulimia nervosa **SSRIs** (no real value in anorexia)
- nocturnal enuresis **TCA**
- smoking cessation **bupropion**
- urinary stress incontinence **duloxetine**
- migraine prophylaxis
- ADHD **atomoxetine**

Agents for treatment of manic (hypomanic) episodes (mood stabilizers) I

- ***Lithium carbonate***

  Prophylactic dose may prevent mood swings

- **Anticonvulsive agents**

  carbamazepine
  valproate
  clonazepam
  lamotrigine

  acute treatment
  prophylactic treatment for preventing mood swings

Agents for treatment of manic (hypomanic) episodes (mood stabilizers) II

- **Antipsychotics**

for treatment – ***risperidone, ziprasidone***
also for prophylaxis – ***aripiprazole, quetiapine, olanzapine***

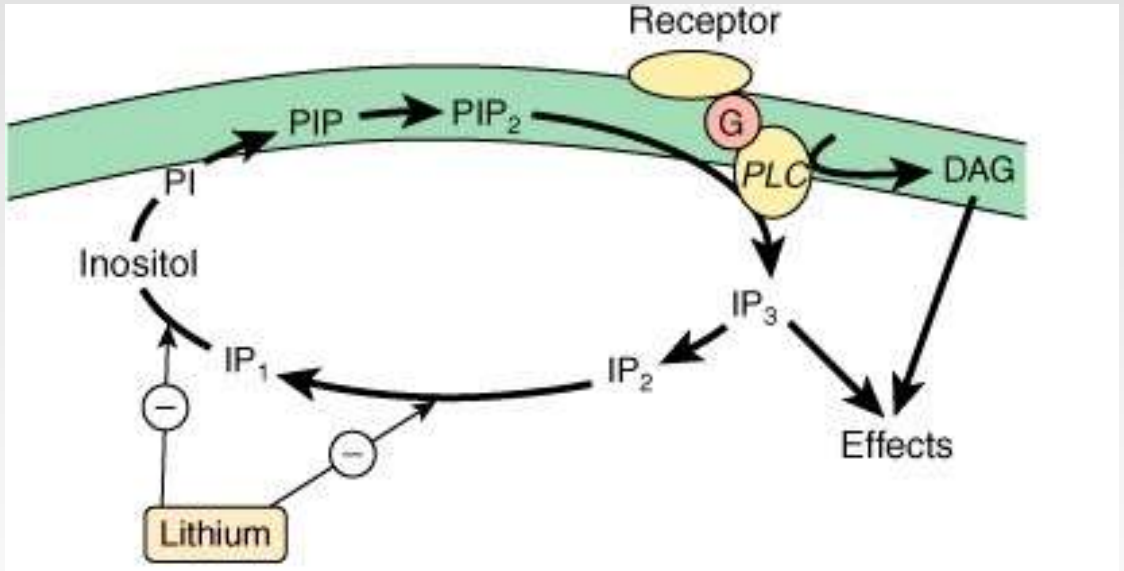
in acute phase, if absolutely needed
haloperidol

Lithium

Mechanism of action

Inhibition of two signal transduction pathway

1

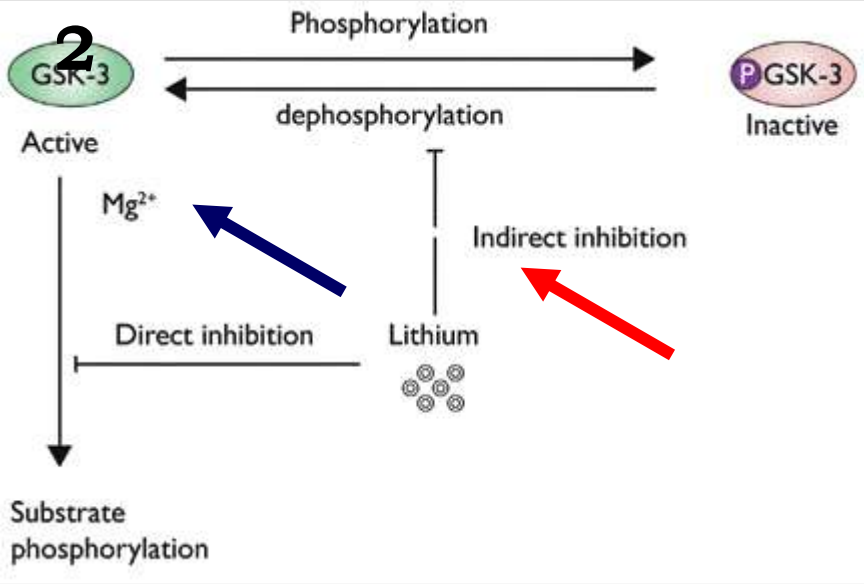


Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

Lithium

Mechanism of action

Inhibition of two signal transduction pathway



GSK3 (glycogen synthase kinase 3) is a protein kinase, phosphorylation of a protein by GSK-3 usually inhibits the activity of its downstream target

- Lithium inhibits the dephosphorylation, and consequently GSK-3 is less active
- By competing with Mg2+, lithium ions block the function of activated GSK-3.

http://www.historyofnimr.org.uk/mill-hill-essays/essays-yearly-volumes/2010-2/lithium-manic-depression-and-beyond/

Adverse effects of lithium

- Tremor, motor hyperactivity, mental confusion
- Decrease of thyroid function
- Polyuria, polydipsia, edema
- Decrease of cardiac function

Therapeutic plasma levels	**prophylactic**	**0.6-1 mol/l**
	acute manic phase	**1.0-1.2 mol/l**
toxic plasma level		**1.5-1.7 mol/l**

Agents for treatment of anxiety disorders

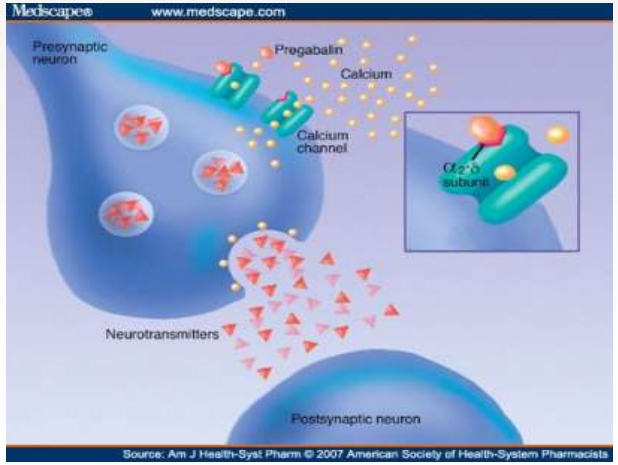
- ***SSRIs, SSRNIs, RIMA***

- ***benzodiazepines –*** ***alprazolam***
  clonazepam **(panic disorder)**
  clobazam **(severe anxiety)**

- **non-*GABA-ergic anxiolytics* –** ***buspirone*** **(GAD)**

  $5\text{-}HT_{1A}$ partial agonist

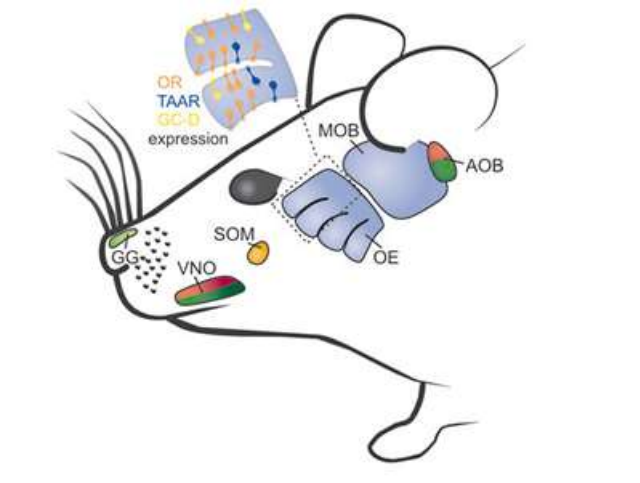
- ***pregabalin*** **(GAD)**

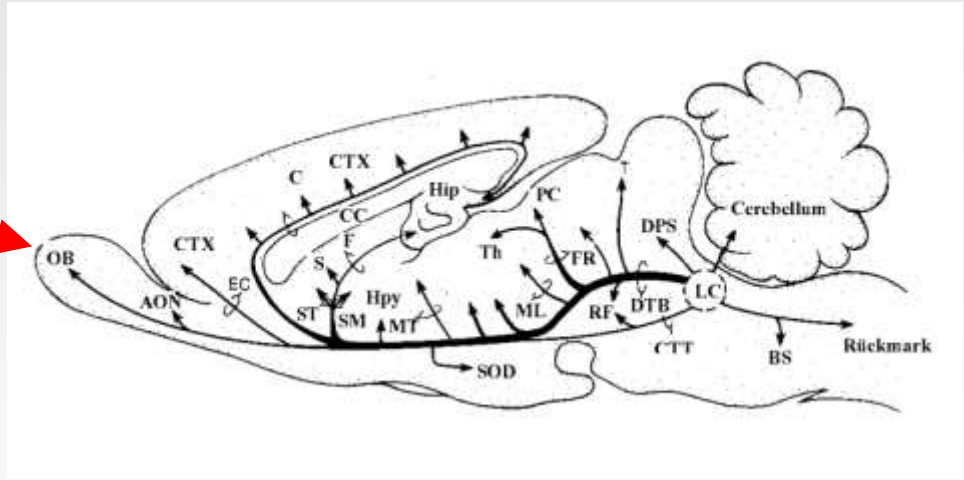


Animal models for depression

BILATERAL BULBECTOMY (OBX)

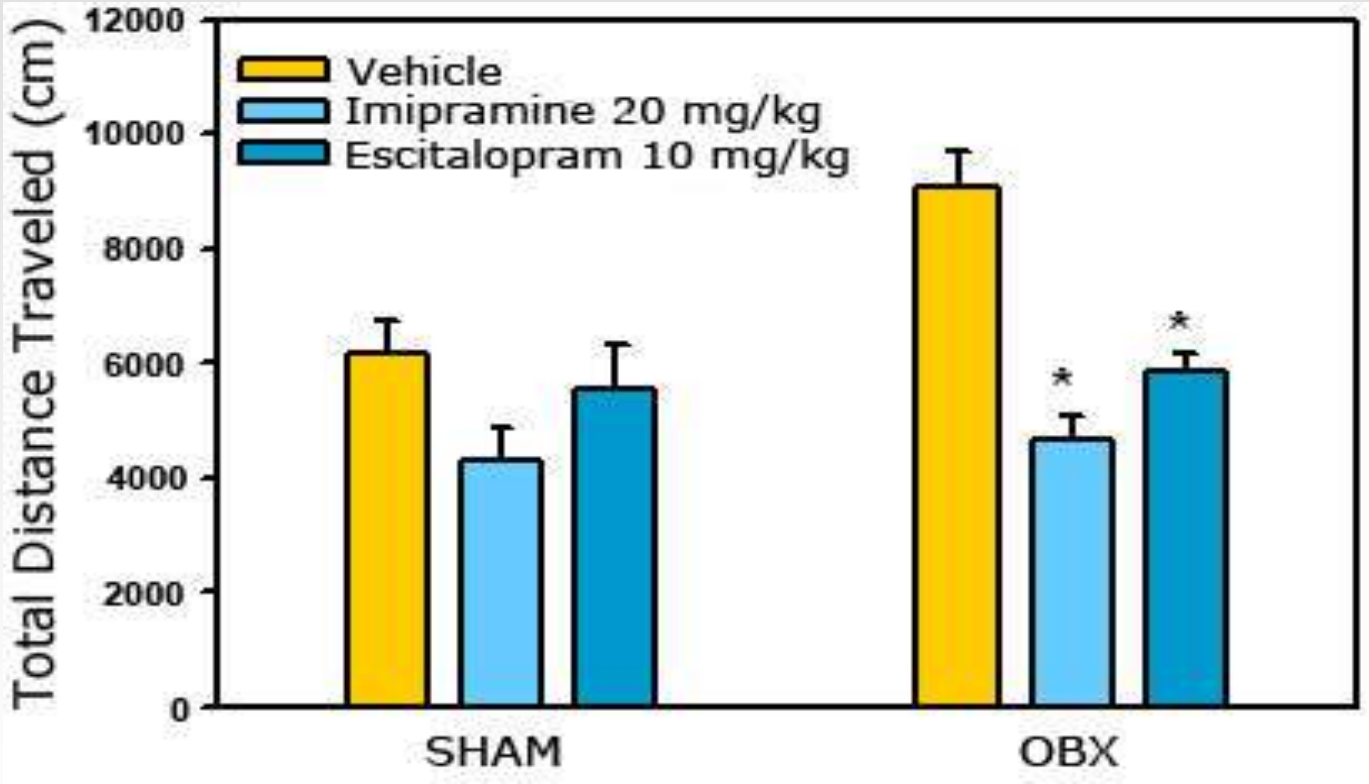
Studying the behavioral changes developing after removal of both *bulbus olfactorius*





(changes in the locomotor activity, escape failure, loss of memory, aggressiveness, etc.)

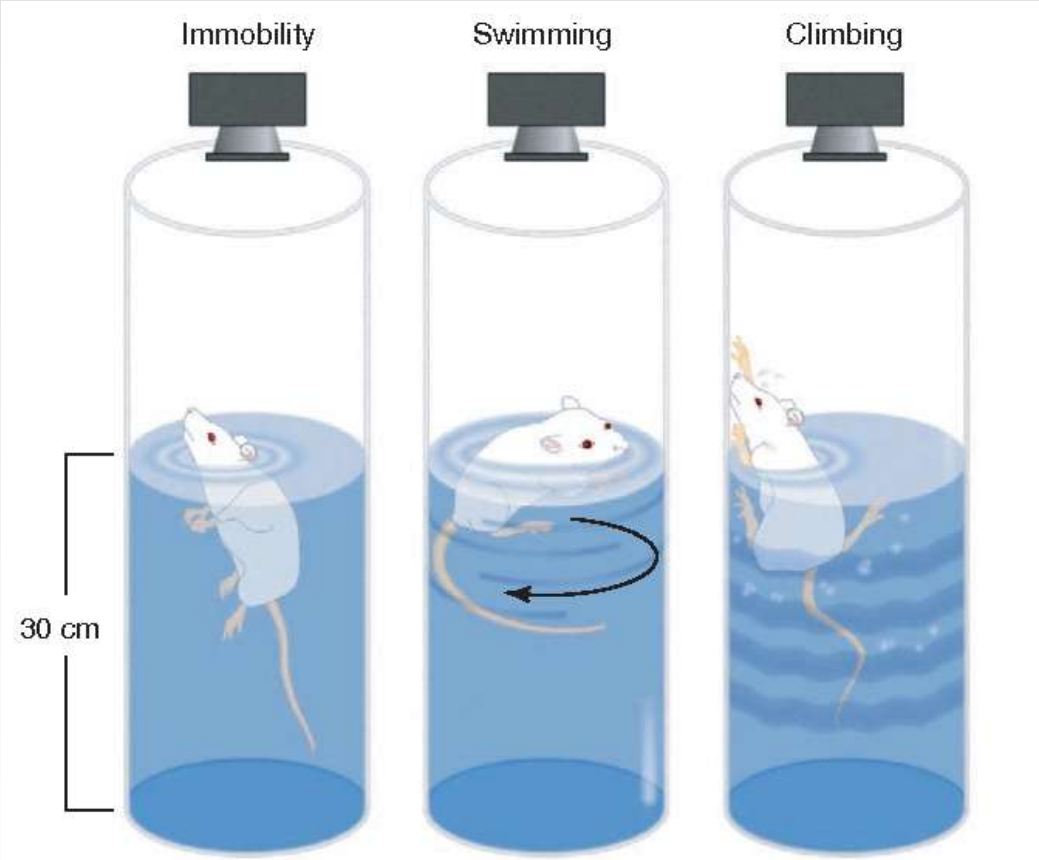
changes in the locomotor activity



Sensitive only for chronic treatment

PsychoGenics
Redefining Drug Discovery Through Innovation

FORCED SWIMMING TEST (PORSHOLT TEST)

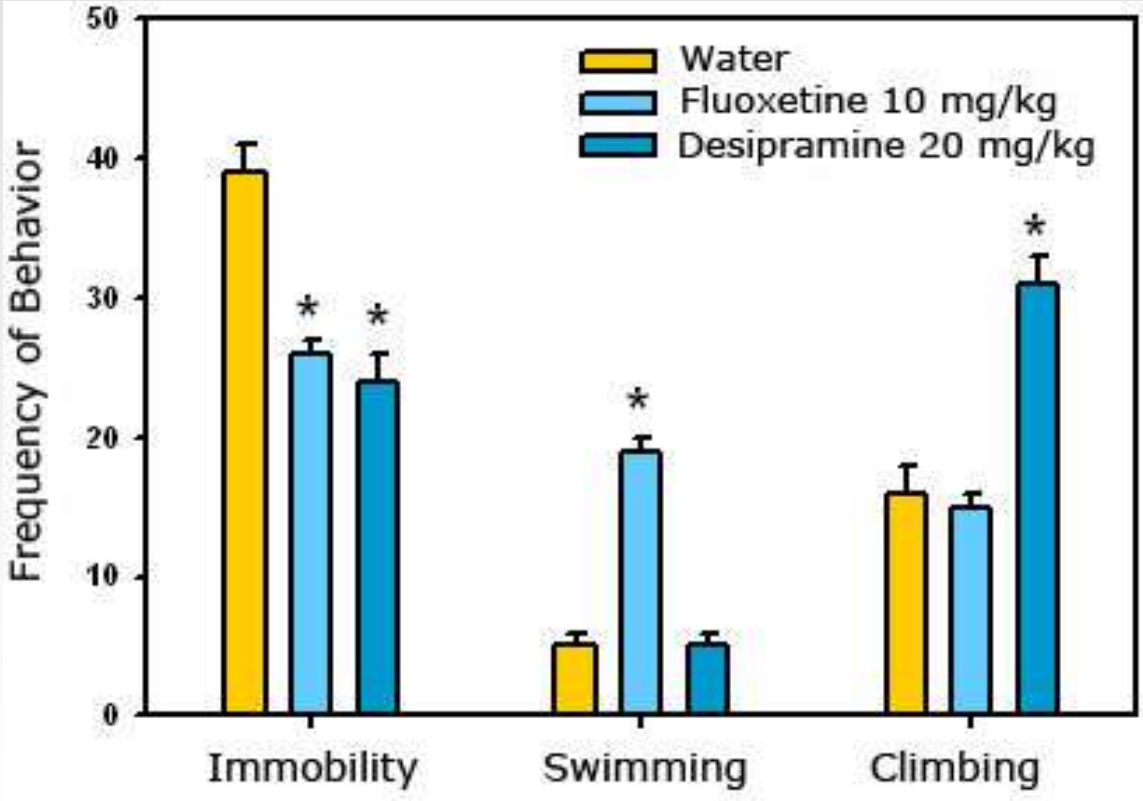


Sensitive only for acute treatment

https://ai2-s2-public.s3.amazonaws.com/figures/2017-08-08/b1b3964654f353834730289442564b4a293c9960/3-Figure2-1.png

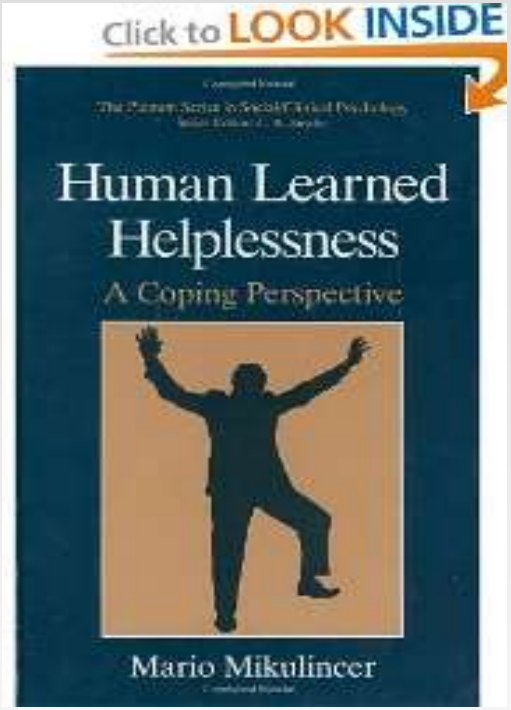
FORCED SWIMMING TEST (PORSHOLT TEST)

Sprague Dawley



http://www.psychogenics.com/forcedswim.html

LEARNED HELPLESSNESS TEST
(stress model)

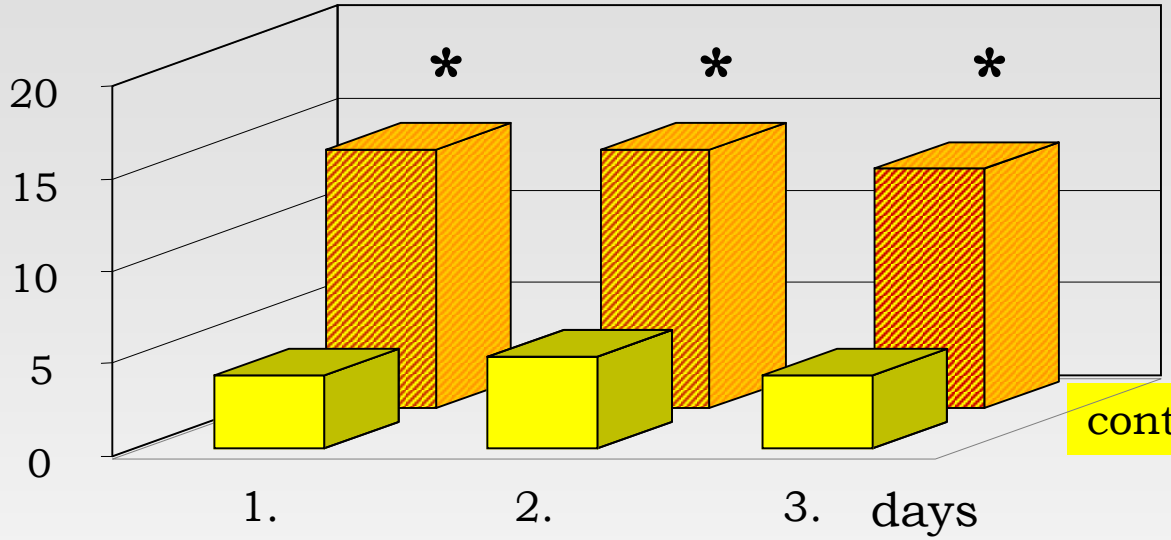


repeated unavoidable and uncontrollable moderate electric shocks are given in randomized way

response measured in shuttle box

LEARNED HELPLESSNESS TEST

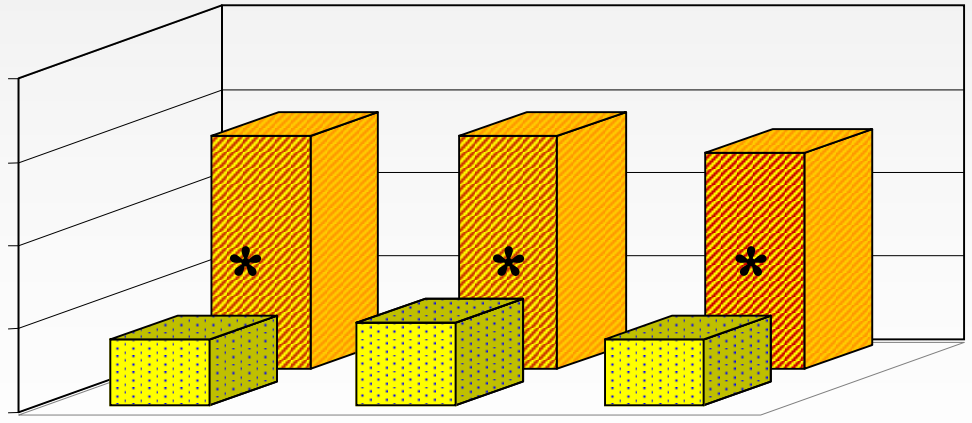
(negative escape response)



repeated unavoidable and uncontrollable electric shocks

control

Generally 5 days treatment



repeated unavoidable and uncontrollable electric shocks

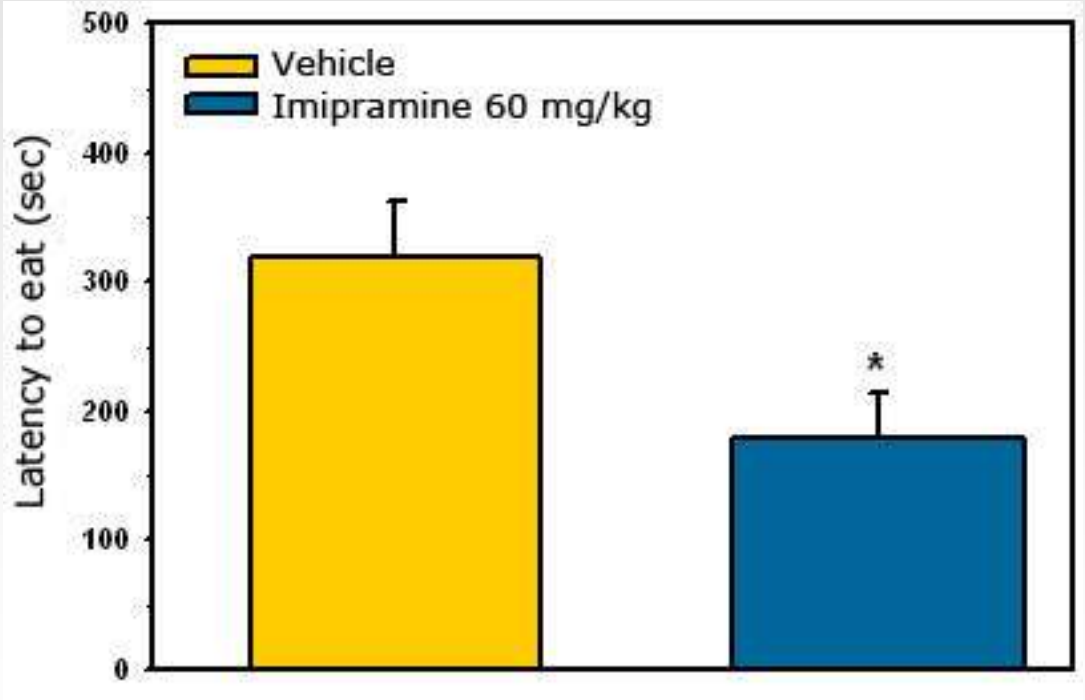
repeated unavoidable and uncontrollable electric shocks
+
imipramine

* p <0.05 ANOVA

ANXIETY BASED TESTS I

- Novelty induced hypophagia (NIH)
- Novelty suppressed feeding (NSF)

Effect of **chronic** (28 days) imipramine (60 mg/kg; po) treatment (C57Bl/6J mice)



Sensitive to acute anxiolytic and chronic antidepressant treatment

Chronic mild stress (CMS)

Presently CMS is considered to ben the most reliable depression model
During a minimum 2 weeks period animals are exposed mild but unexpected, randomize stress – this results in long-term behavioral, neurochemical and neuroendocrinological changes

Week	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1	17:00 to next day: damp bedding	4 h white noise	8 h cage tilt	Continuous light 24 h	Removal of nesting 24 h	Food and water deprivation 8 h	Swimming at 4°C for 5 min
2	Continuous light 24 h	17:00 to next day: damp bedding	Food and water deprivation 8 h	Swimming at 4°C for 5 min	8 h cage tilt	4 h white noise	Removal of nesting 24 h
3	Swimming at 4°C for 5 min	Continuous light 24 h	8 h cage tilt	Removal of nesting 24 h	4 h white noise	Food and water deprivation 8 h	17:00 to next day: damp bedding

Ream Al-Hassani et al, Front. Pharmacol, 2013 doi: 10.3389/fphar.2013.00096

Sensitive for chronic treatment