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Antidepressant Drugs

- Margaret Gnegy
- Professor
- Department Pharmacology

Fall 2008

University of Michigan
Medical School

The Bottom Line

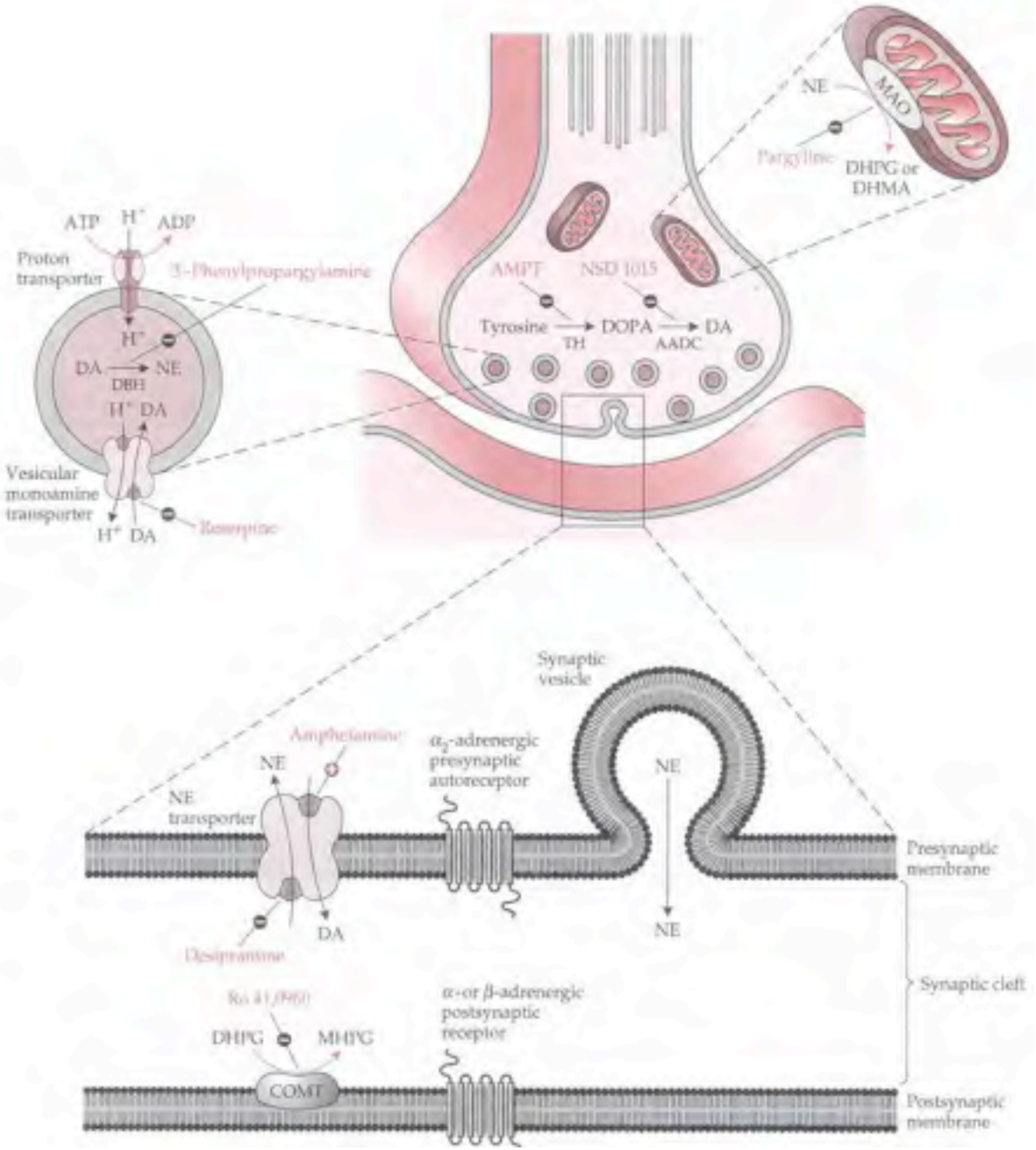
- There is a strong interrelationship between serotonergic and noradrenergic neurons and they regulate each others' activities
- Most antidepressant drugs enhance serotonergic and noradrenergic activity in the brain but they take weeks to work.
- A common mechanism of antidepressant drug action is to block monoamine reuptake.
- Each type of antidepressant has characteristic side effects which strongly influence which one is prescribed.
- Long term antidepressant treatment may lead to trophic effects on neuron remodeling and production of important growth factors.

Monoamine Theory of Depression

- Deficiency of aminergic transmission in the CNS might be causative of depression

- An excess of aminergic transmission could result in mania

The Norepinephrine Synapse

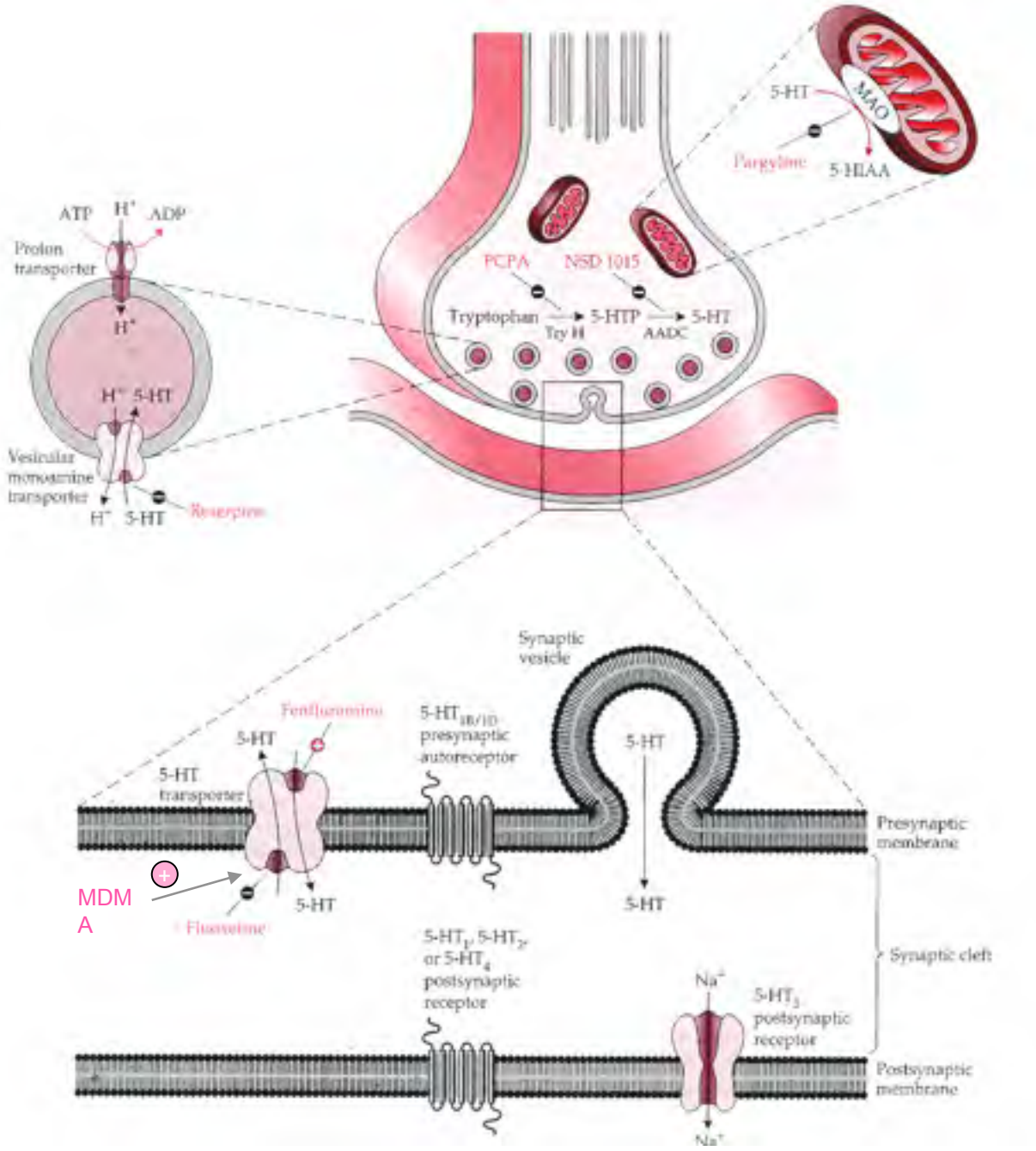


Synthesis:
Tyrosine hydroxylase
Aromatic amino acid decarboxylase
Dopamine beta hydroxylase

Metabolism:
Monoamine oxidase
Catecholamine-O-methyltransferase

Adapted from Feldman, et al., Principles of Neuropsychopharmacology, Sinauer, 1997, p. 280

The Serotonin Synapse

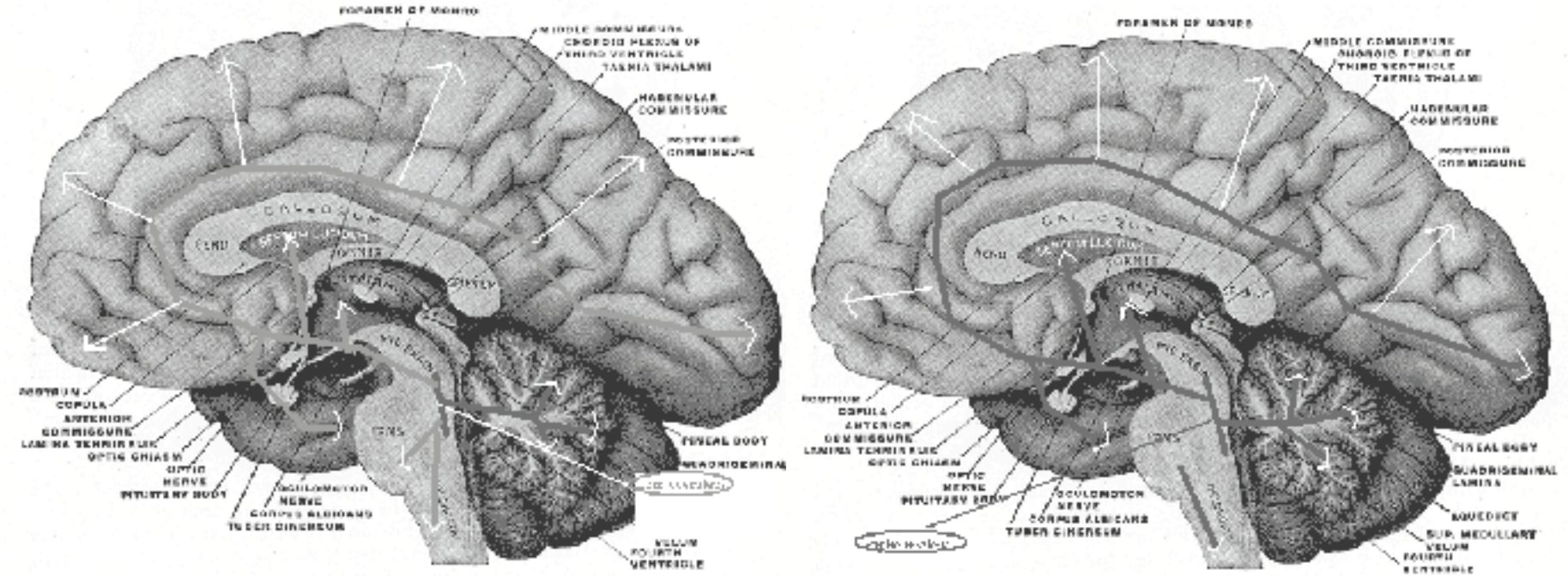


ynthesis:
ryptophan hydroxylase
romatic amino acid
ecarboxylase

letabolism:
lonoamine oxidase

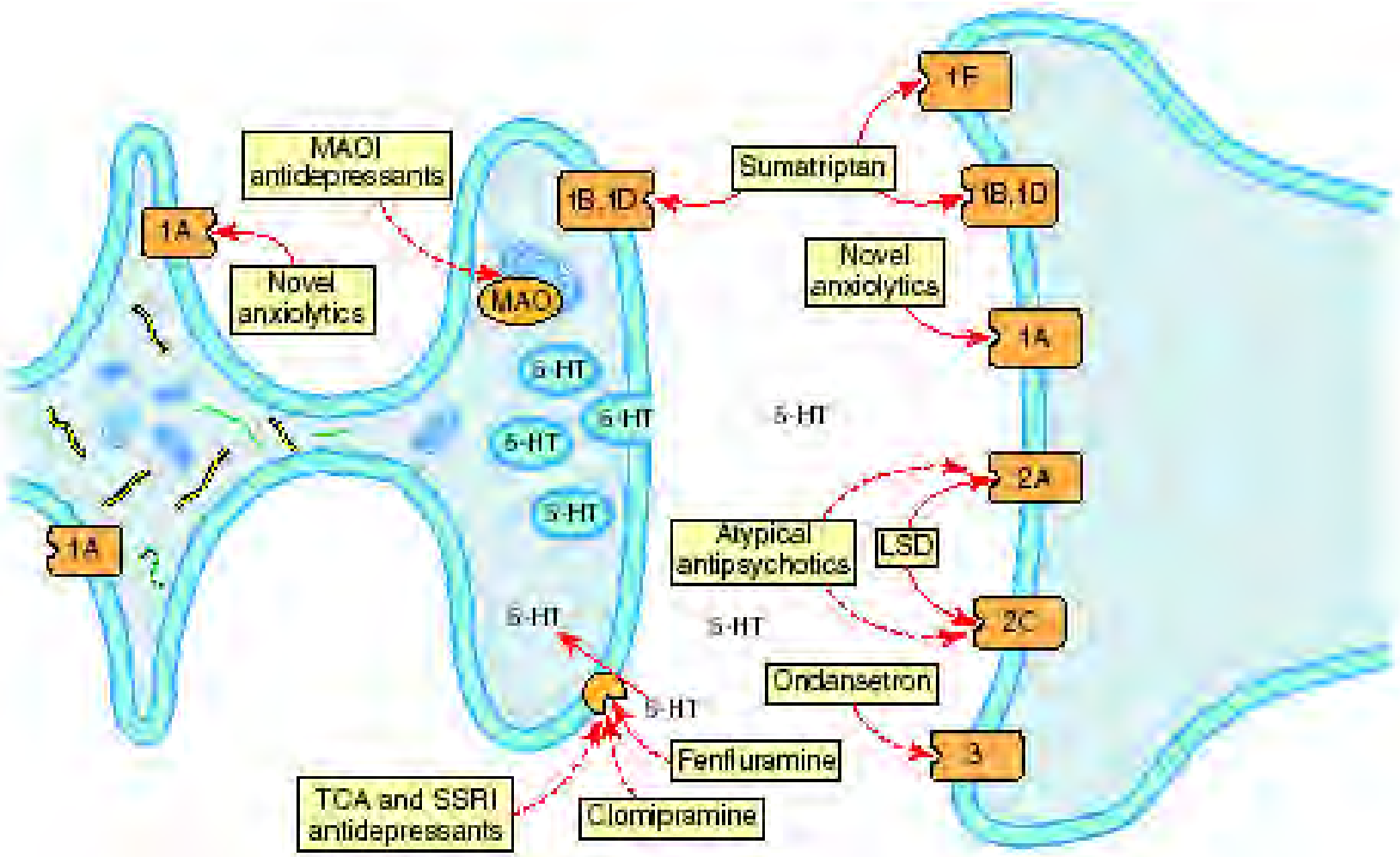
Adapted from Feldman, et al., Principles of Neuropsychopharmacology, Sinauer, 1997, p. 347

Innervation of the brain by serotonin and norepinephrine neurons involves similar pathways



Gray's Anatomy

Targets for drugs affecting serotonergic system



Siegel et al. eds. Basic Neurochemistry, 7th Ed. p. 236

Drugs used in the treatment of depression

Selective serotonin reuptake inhibitors: fluoxetine, sertraline

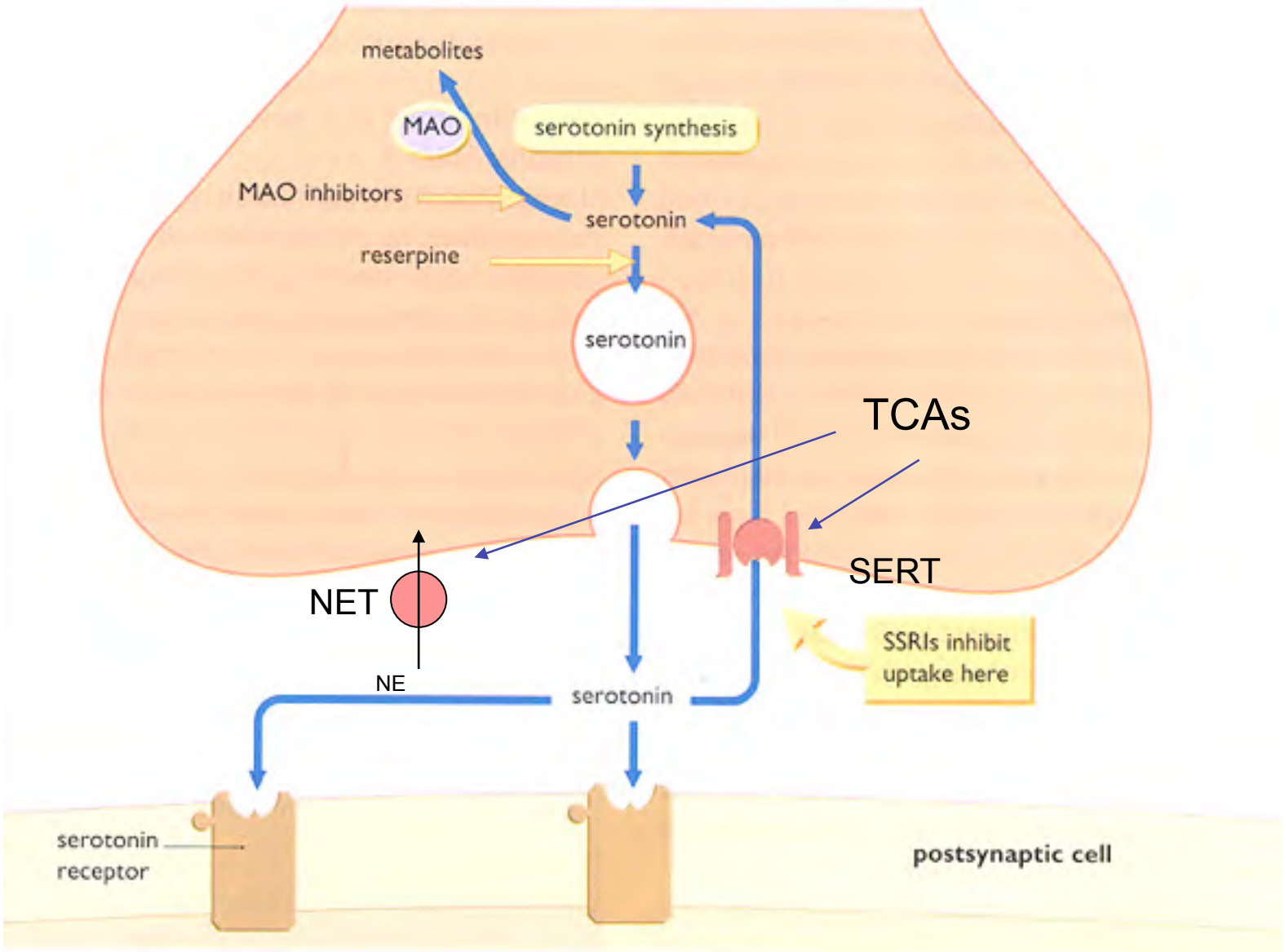
Other heterocyclic drugs: bupropion, trazodone, venlafaxine

MAO inhibitors: phenelzine, moclobemide

Tricyclic antidepressant drugs: amitriptyline, imipramine, desipramine

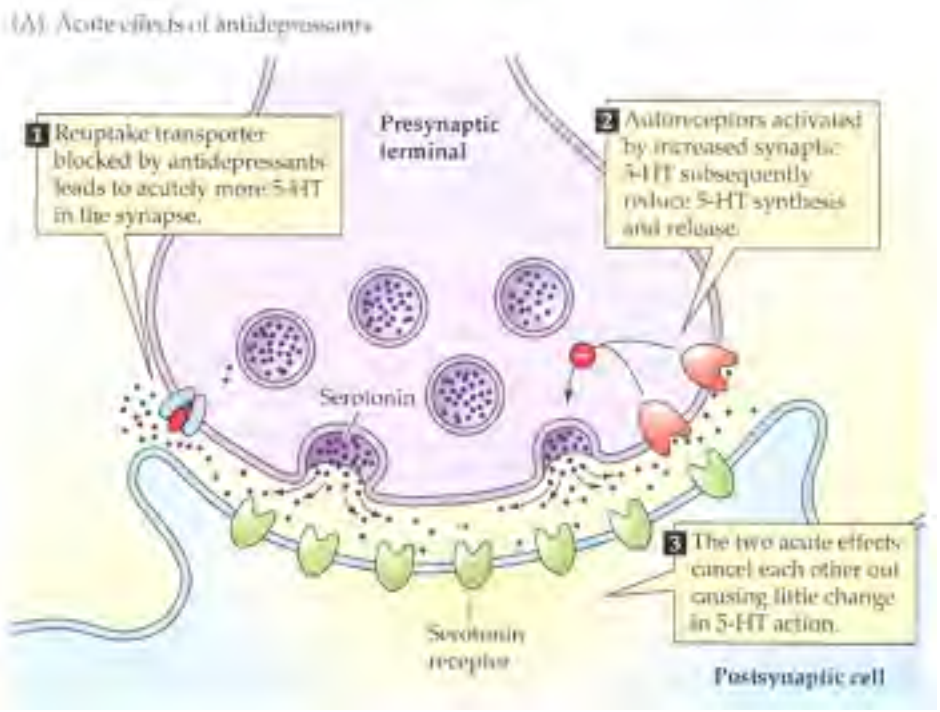
Electroconvulsive shock

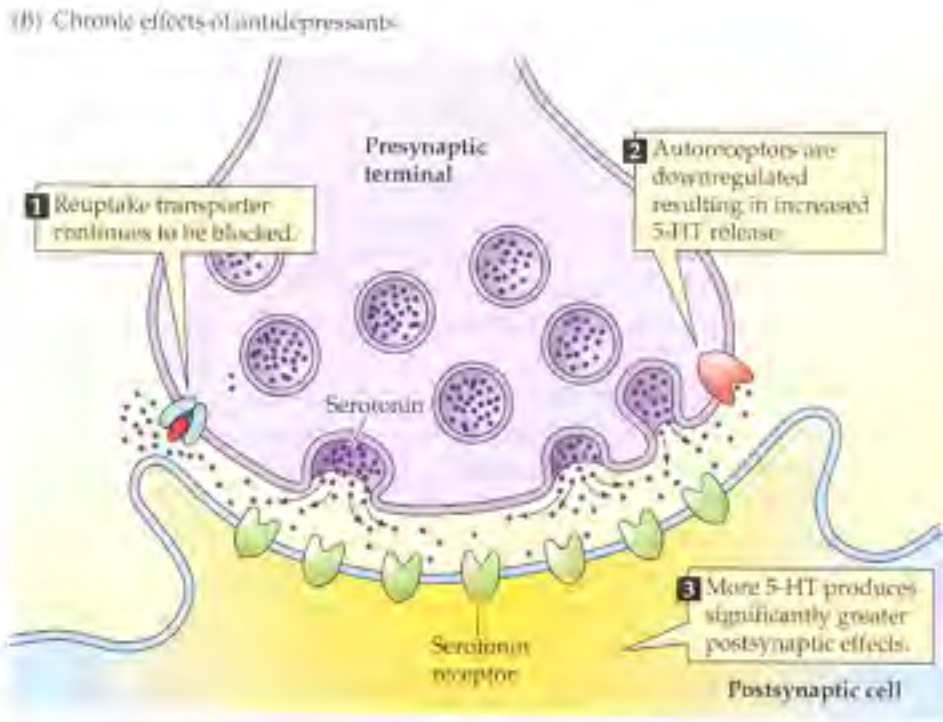
Most, but not all, antidepressants affect monoamine uptake



Page et al. Integrated Pharmacology, Mosby, c1997, p. 111

Effects of antidepressants on serotonergic cells

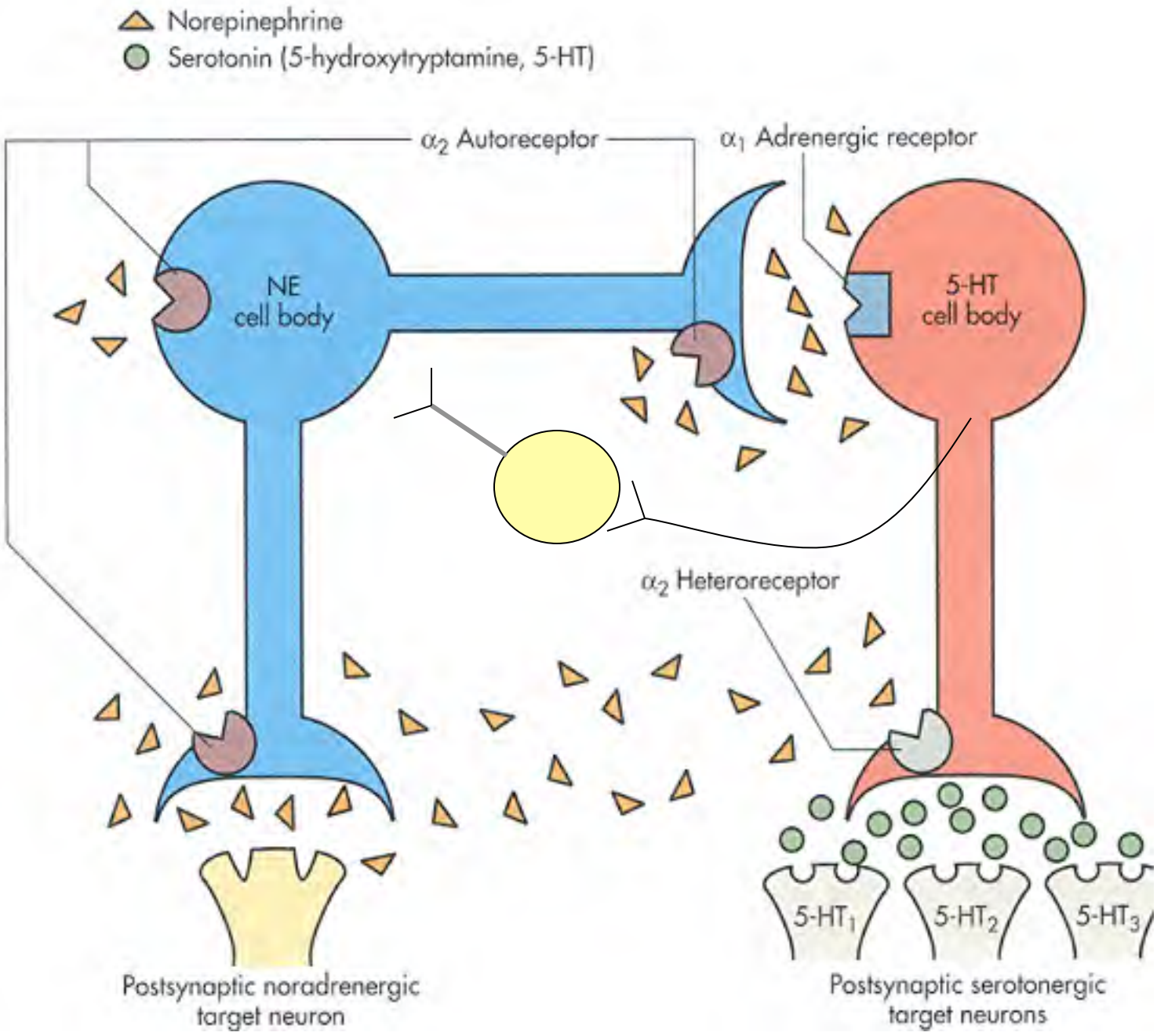




Down regulation of 5HT1A receptors may contribute to antidepressant effect

There is much the same regulation of noradrenergic cells

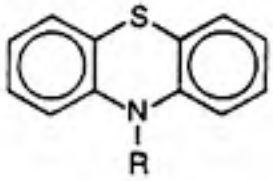
 J. Meyer, L. Quenzer, Psychopharmacology. Sinauer Associates, 2004 p. 404 (Both Images)



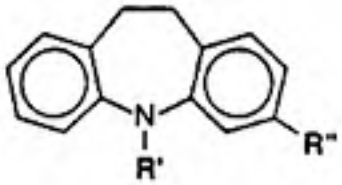
Brody, Larner & Minneman, Human Pharmacology, 3d ed. Mosby, c1998, p. 356

Tricyclic antidepressant drugs

PHENOTHIAZINE STRUCTURE



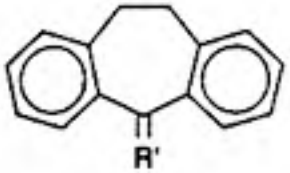
IMINODIBENZYL DERIVATIVES



R' = $(CH_2)_3 - N(CH_3)_2$ — Imipramine (Tofranil®)

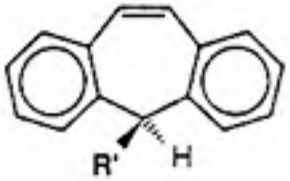
R' = $(CH_2)_3 - NH - CH_3$ — Desipramine (Norpramin®, Pertofrane®)

DIBENZOCYCLOHEPTENE DERIVATIVES



R' = $CH(CH_2)_2 - N(CH_3)_2$ — Amitriptyline (Elavil®)

R' = $CH(CH_2)_2 - NH - CH_3$ — Nortriptyline (Aventyl®)



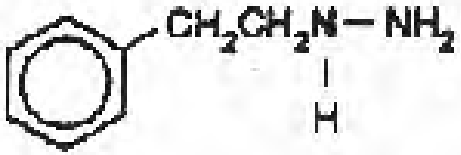
R' = $(CH_2)_3 - NH - CH_3$ — Protriptyline (Vivactil®, Triptil®)

Side effects of TCA's

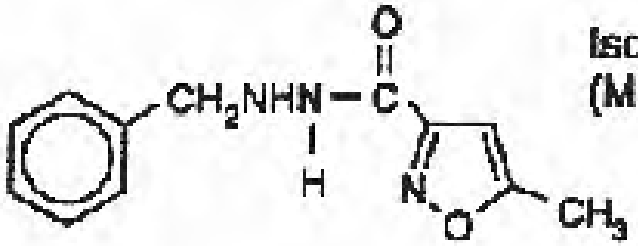
- Antimuscarinic: xerostomia, dizziness, mental clouding, constipation, blurred vision
- Cardiovascular: orthostatic hypotension, arrhythmias
- Sedation
- Weight gain
- Extreme CNS depression: suicide

Monoamine Oxidase Inhibitors

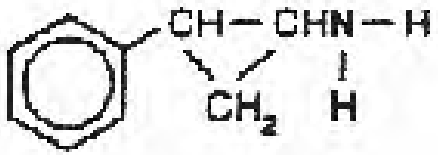
IRREVERSIBLE



Phenelzine
(Nardil®)

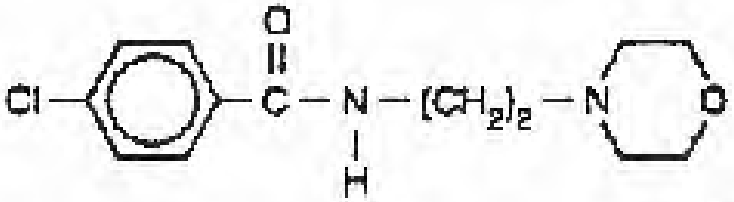


Isocarboxazid
(Marplan®)



Tranylcypromine
(Parnate®)

REVERSIBLE



Moclobemide
(Aurorix®)

Very efficacious in depression

2-3 times a day dosing

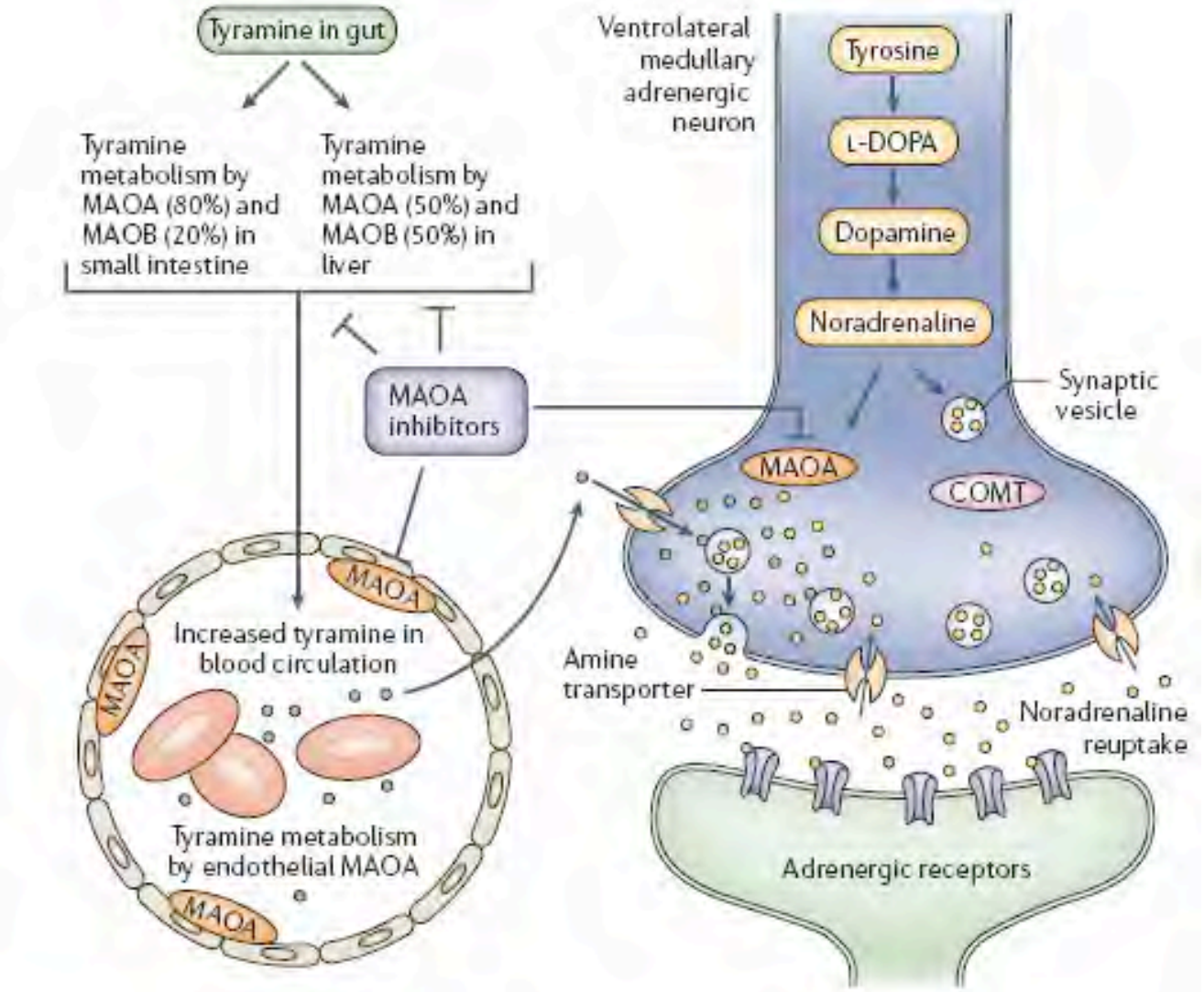
Must have tyramine free diet

Interactions with other agents that affect monoaminergic systems

Side effects and drug interactions of MAOIs

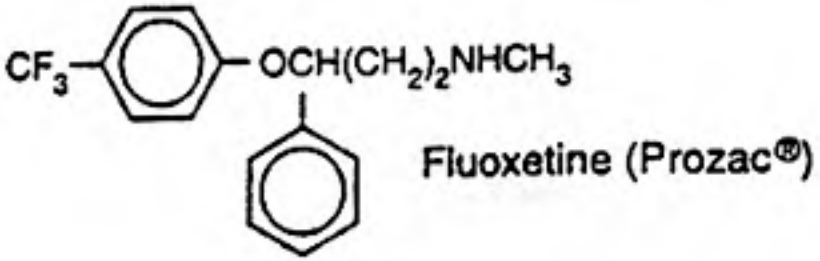
- CNS effects: hallucinations, agitation, convulsions
- Cardiovascular: orthostatic hypotension
- Sedation
- Prolongs CV effects of indirectly-acting sympathomimetic amines, food with tyramine
- Should not be given with TCAs or SSRIs
- Potentiate effect of other CNS depressants

The mechanism of potentiation of cardiovascular effects of tyramine: the cheese effect

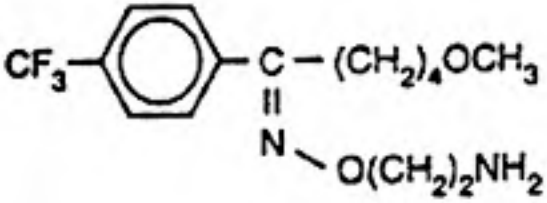


 Nature Reviews Neuroscience, 7:295, 2006

Selective serotonin reuptake inhibitors (SSRI)



Fluoxetine (Prozac®)

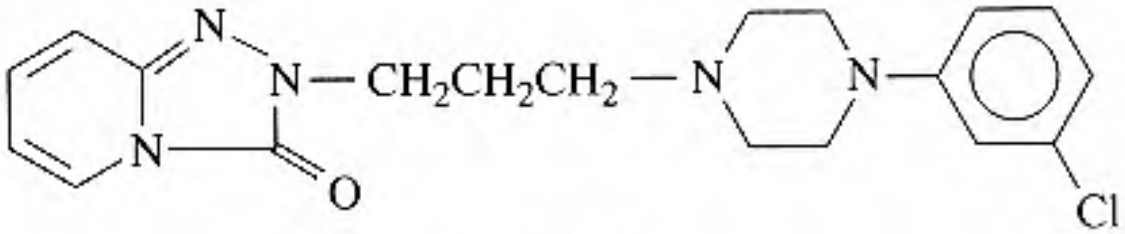


Fluvoxamine (Luvox®)

Adverse effects of SSRIs

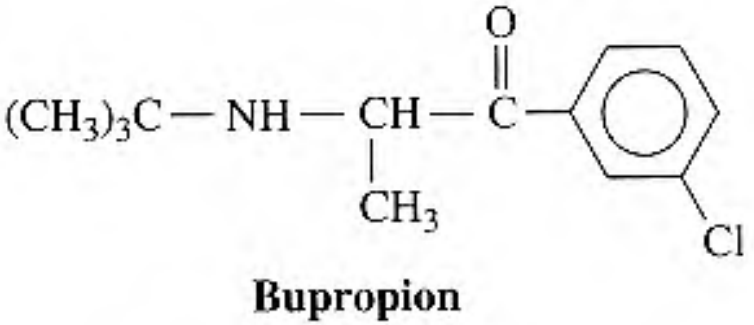
- Those due to activation of serotonin receptors
  - Nausea
  - Sexual effects
  - Agitation or restlessness

Atypical Antidepressants



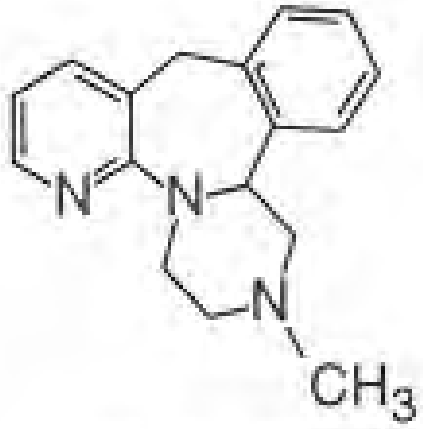
Trazodone

Desyrel



Bupropion

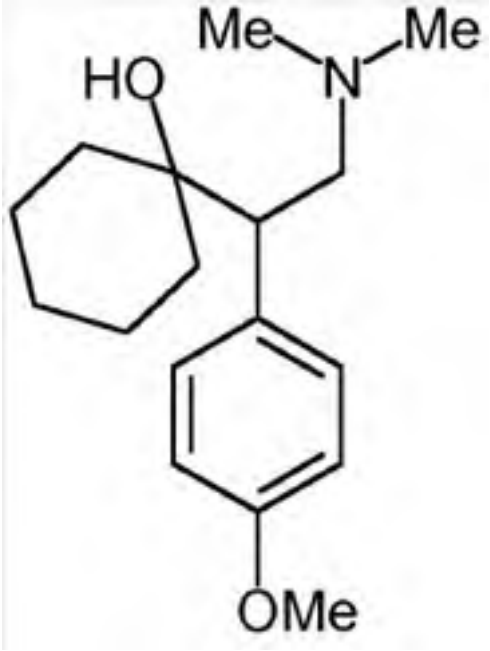
Wellbutrin
Xyban



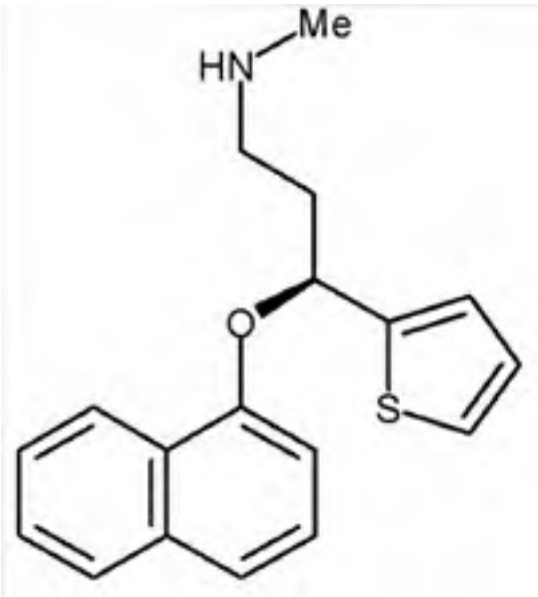
Mirtazapine

Remeron

Selective serotonin and norepinephrine uptake inhibitors

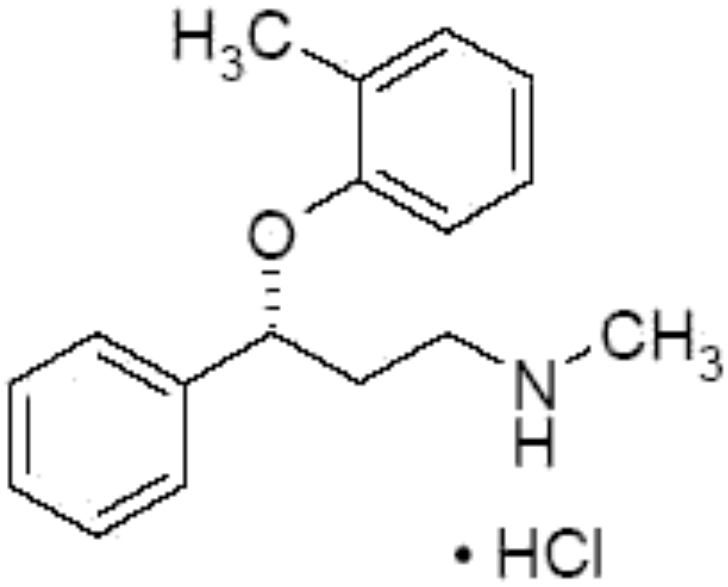


Venlafaxine (Effexor)

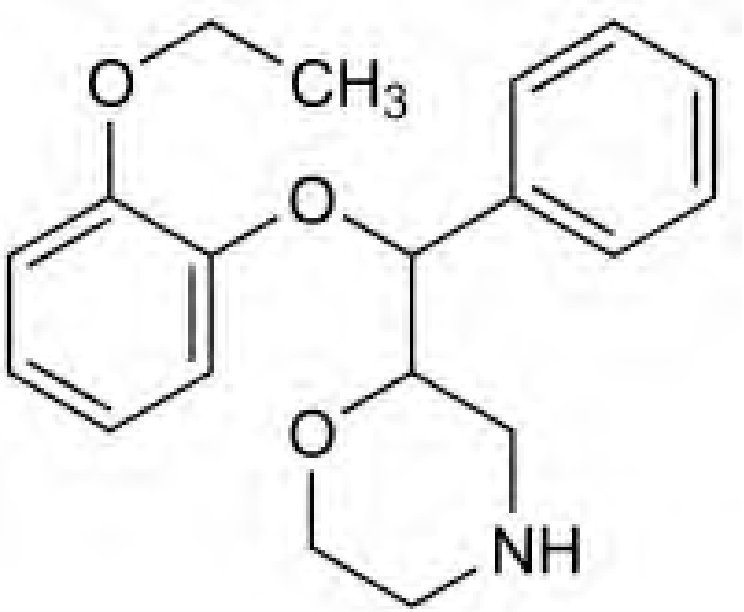


- Duloxetine (Cymbalta)

Selective Norepinephrine Uptake Inhibitors (SNRI)



Atomoxetine
Strattera



Reboxetine
Edronax

Potencies of antidepressants at Human Monoamine transporters

Drug	NET	SERT	DAT
	Ki (nM)		
Amitriptyline	34.5	**4.3**	3200
Desipramine	**0.83**	17.5	3200
Sertraline	417	**0.293**	25
Bupropion	52,600	9100	**526**
Duloxetine	**11.2**	**1.55**	-

In vitro acute receptor affinity of selected antidepressant drugs

Drug	mAChR	H1 R	α_1 R
	Ki (nM)		
Amitriptyline	**17.9**	**1.1**	**27**
Desipramine	106	110	130
Sertraline	625	24,000	370
Bupropion	40,000	6700	4550
Duloxetine	3000	2300	8300

Source Undetermined

Absorption, Distribution and Metabolism

- Most antidepressants are well absorbed
- Once absorbed they are widely distributed
- Most are metabolized by cytochrome P450 system, then glucuronidation
- A number of them have active metabolites:
  - Bupropion (to amphetamine-like compounds)
  - Fluoxetine → norfluoxetine ($t_{½}$ = 10 days)
- Most take several days to be eliminated
- Short half-lives: venlafaxine (3-6 hrs) and bupropion (14 hrs)

Interactions with Cytochrome P_{450} enzymes

- Metabolism of most ADs dependent on hepatic P_{450}s
- Some ADs inhibit metabolic clearance of other drugs, may produce clinically significant drug-drug interactions
  - Fluoxetine & fluvoxamine inhibit CYP2C9 (NSAIDS), CYP2D6 (Antidepressants, antipsychotics, β-blockers)
  - Sertraline and fluoxetine increase levels of benzodiazepines, clozapine and warfarin

Antidepressants: Dose and side effects

Drug	Dose	Side Effects						
	mg/ day	Seda- tion	Hypo- tension	Anti- musc	GI	Weight gain	Weight loss	Sexual Effects
Amitriptyline	100- 200	**+++**	**+++**	**+++**	±	**++**	0	++
Desipramine	100- 200	±	+	+	±	+	0	++
Sertraline	50-1 50	±	0	0	**+++**	0	+	**+++**
Duloxetine	80-1 00	±	±	0	±	±	±	±
Bupropion	200- 300	**0 agitation**	0	0	+	+	+	0
Trazodone	150- 200	+++	0	0	++	+	+	0

Tolerance and Physical Dependence

- Some tolerance develops to sedative and autonomic effects of TCAs
- Some tolerance develops to initial nausea from SSRIs
- Physical dependence following abrupt withdrawal

Drug-drug interactions with antidepressants

- Metabolism of most antidepressants is through hepatic CYPs
- Some antidepressants can inhibit CYPs
- SSRIs especially will compete with metabolism of other drugs
- Antidepressants potentiate the effects of alcohol and probably other sedatives

Withdrawal effects

- Occurs upon abrupt discontinuation of an antidepressant that has been taken for ≥ 6 wks
- Typical symptoms of antidepressant discontinuation syndrome: flu-like symptoms, malaise, insomnia, nausea, imbalance, sensory disturbances, and hyperarousal.
  - Can be serious with MAO inhibitors
- More likely with a longer duration of treatment and a shorter half-life of the treatment drug
- Recurrence of morbidity

Safety throughout life cycle

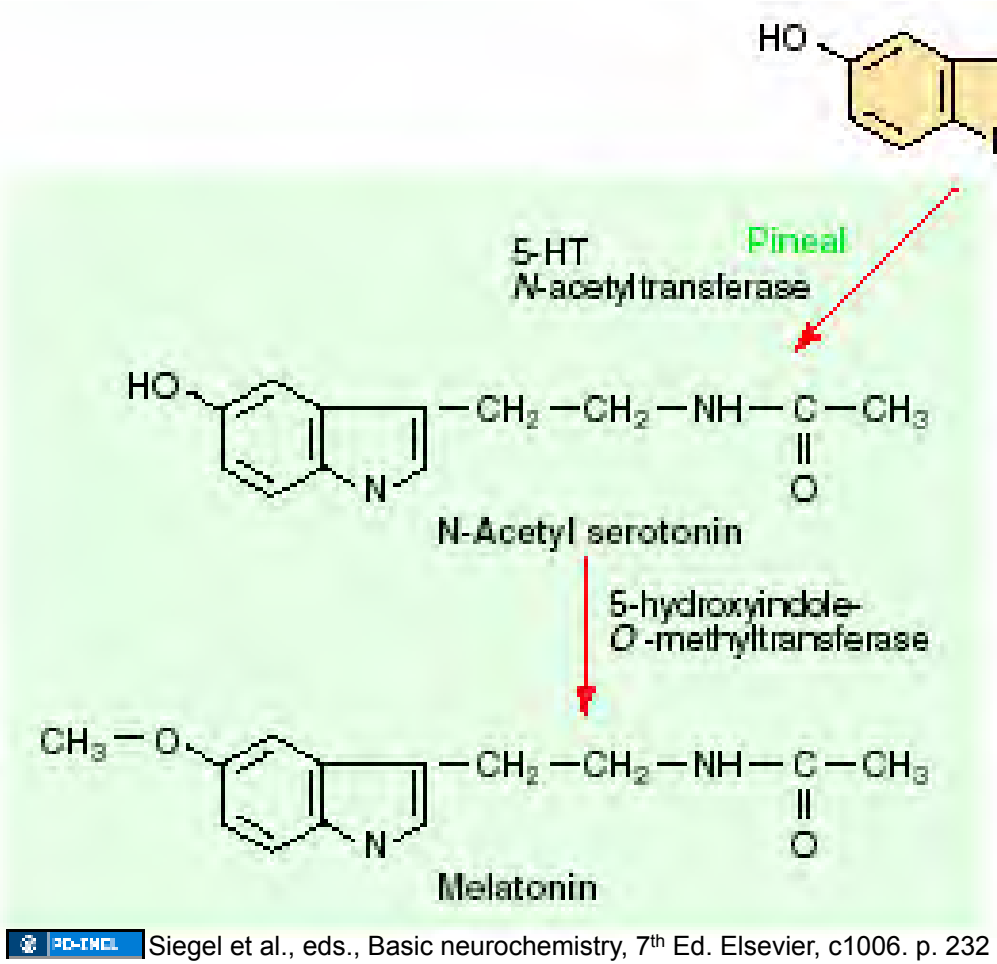
- Generally safe throughout pregnancy but will get into breast milk
- Risk-benefit ration in children uncertain
- More effective in adolescents
- Risks in geriatric patient higher due to decreased metabolic clearance

Danger of suicide

- Tricyclic antidepressants
- MAO inhibitors
- SSRIs???

Use of antidepressant drugs in outpatients

Generic name	Other indication
Amitryptyline	Chronic pain, delusions, insomnia, migraine, postherpetic neuralgia
Desipramine	Attention deficit disorder, bulimia, diabetic neuropathy, postherpetic neuralgia
Sertraline	Obsessive compulsive disorder, panic disorder, post-traumatic stress disorder, anxiety
Mirtazapine	Anxiety, insomnia
Bupropion	Attention-deficit disorder, smoking cessation, post-traumatic stress disorder
Trazodone	Insomnia



Siegel et al., eds., Basic neurochemistry, 7th Ed. Elsevier, c1006. p. 232

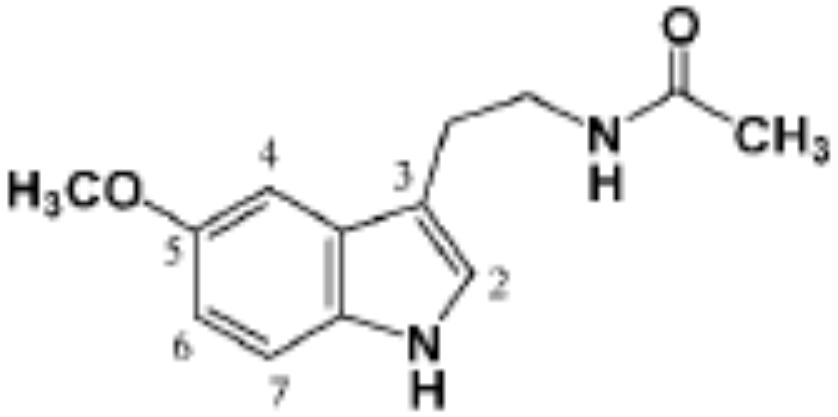
Melatonin is synthesized and released from the pineal at night in response to stimulus from the suprachiasmatic nucleus (SCN) of the hypothalamus, the major circadian pacemaker in the brain.

SCN → Superior cervical ganglion —Night, NE→ **β-Adr R in pineal gland → ↑cAMP → pCREB → ↑ melatonin**

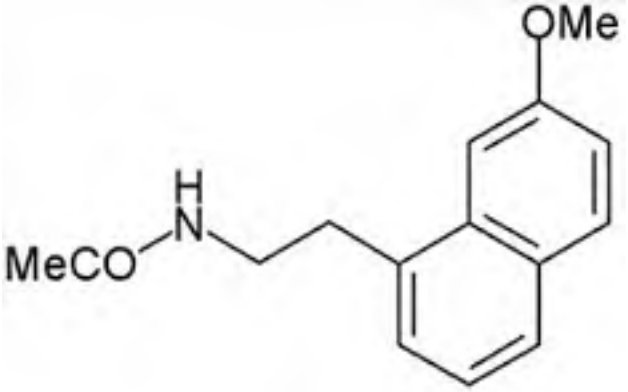
↑cAMP → ICER —Day→ **↓ melatonin**

Inducible cAMP early repressor

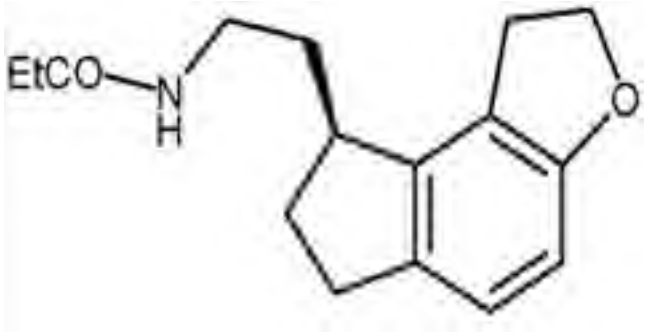
Melatonin receptor agonists



Melatonin



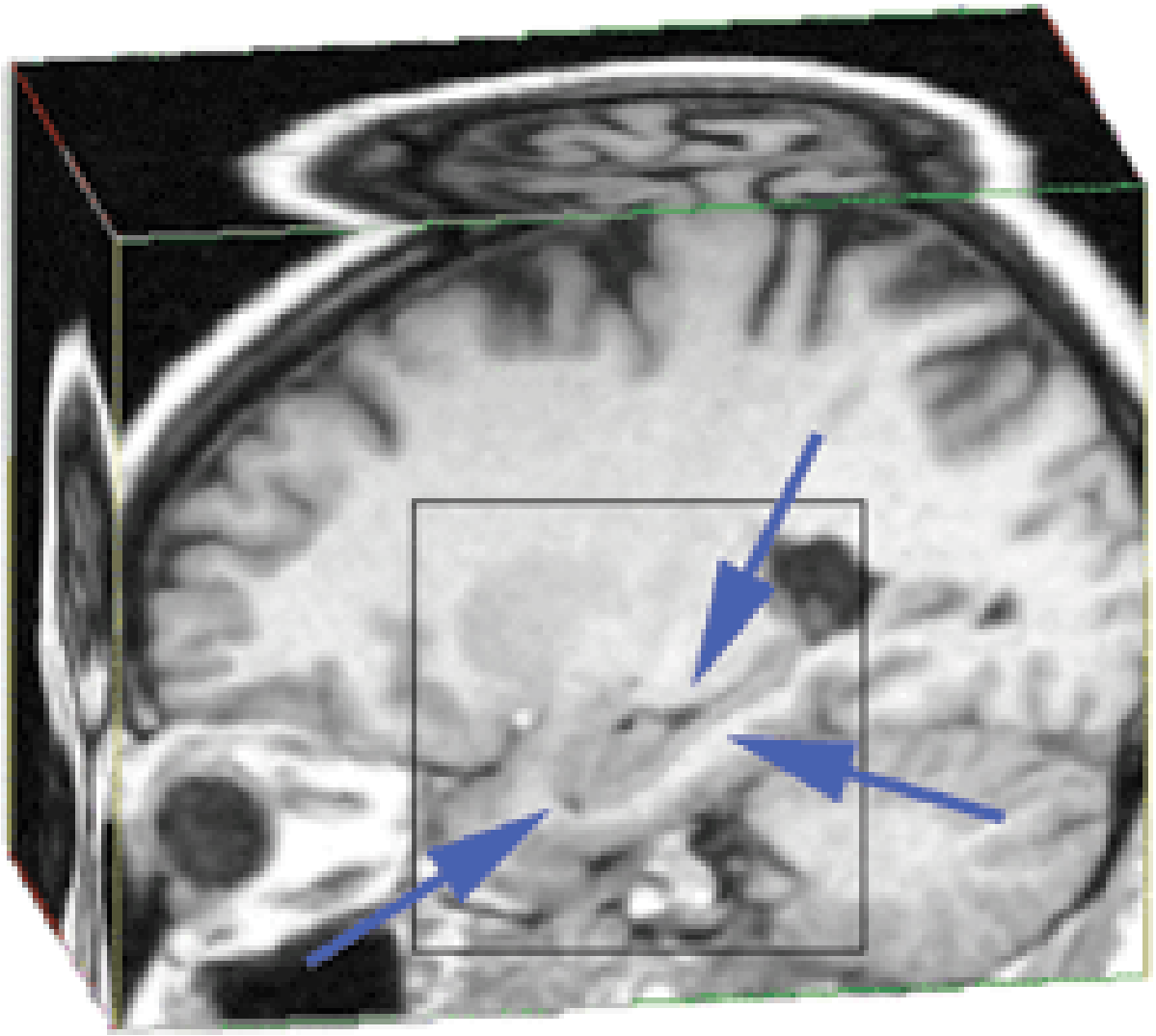
Agomelatine (Valdoxan)



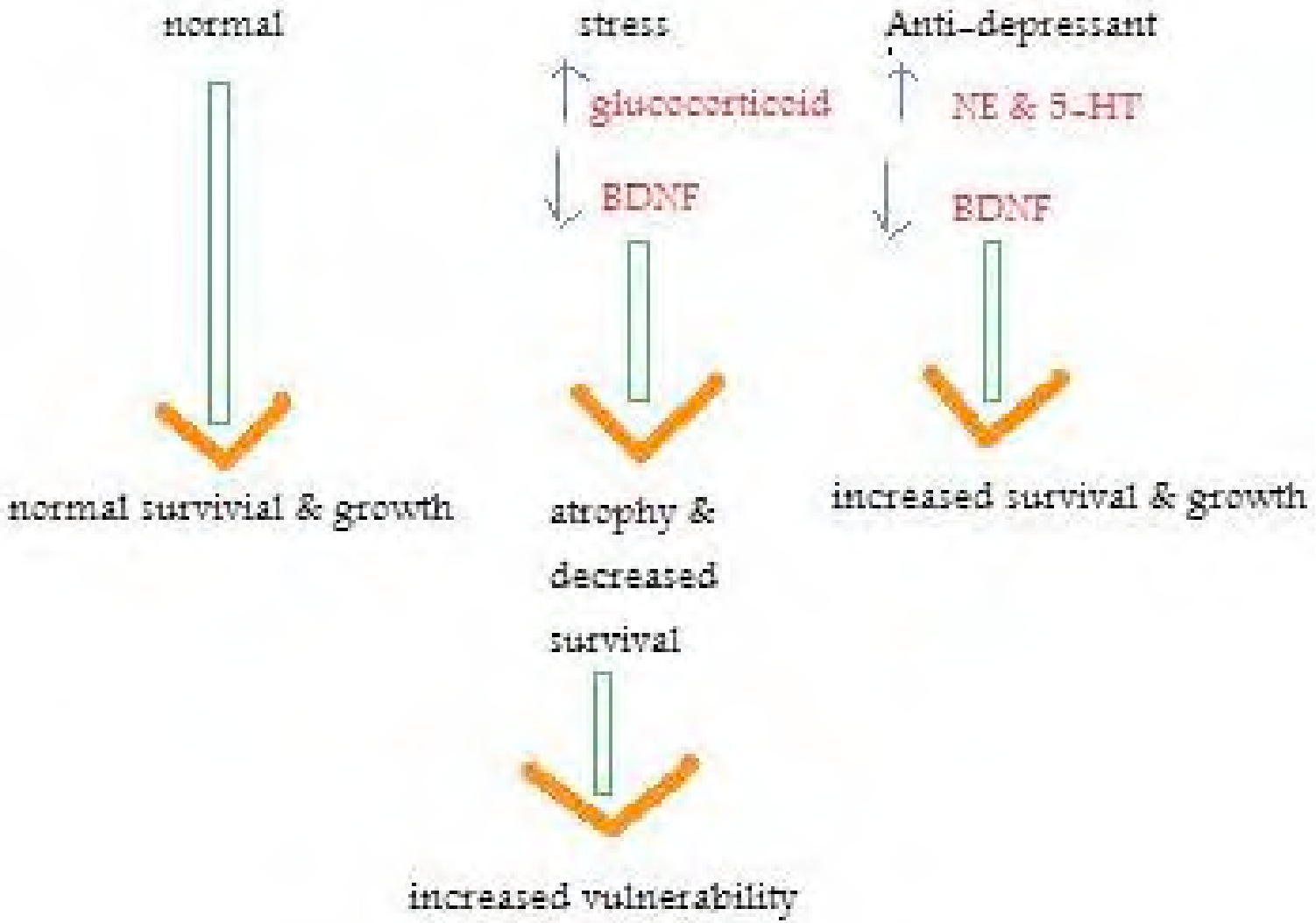
Ramelteon (Rozerem)

Both drugs are agonists at MT1 and MT2 receptors
MT1 Rs are GPCRs that inhibit adenylyl cyclase, predominant receptor in brain
MT2 Rs inhibit soluble guanylate cyclase

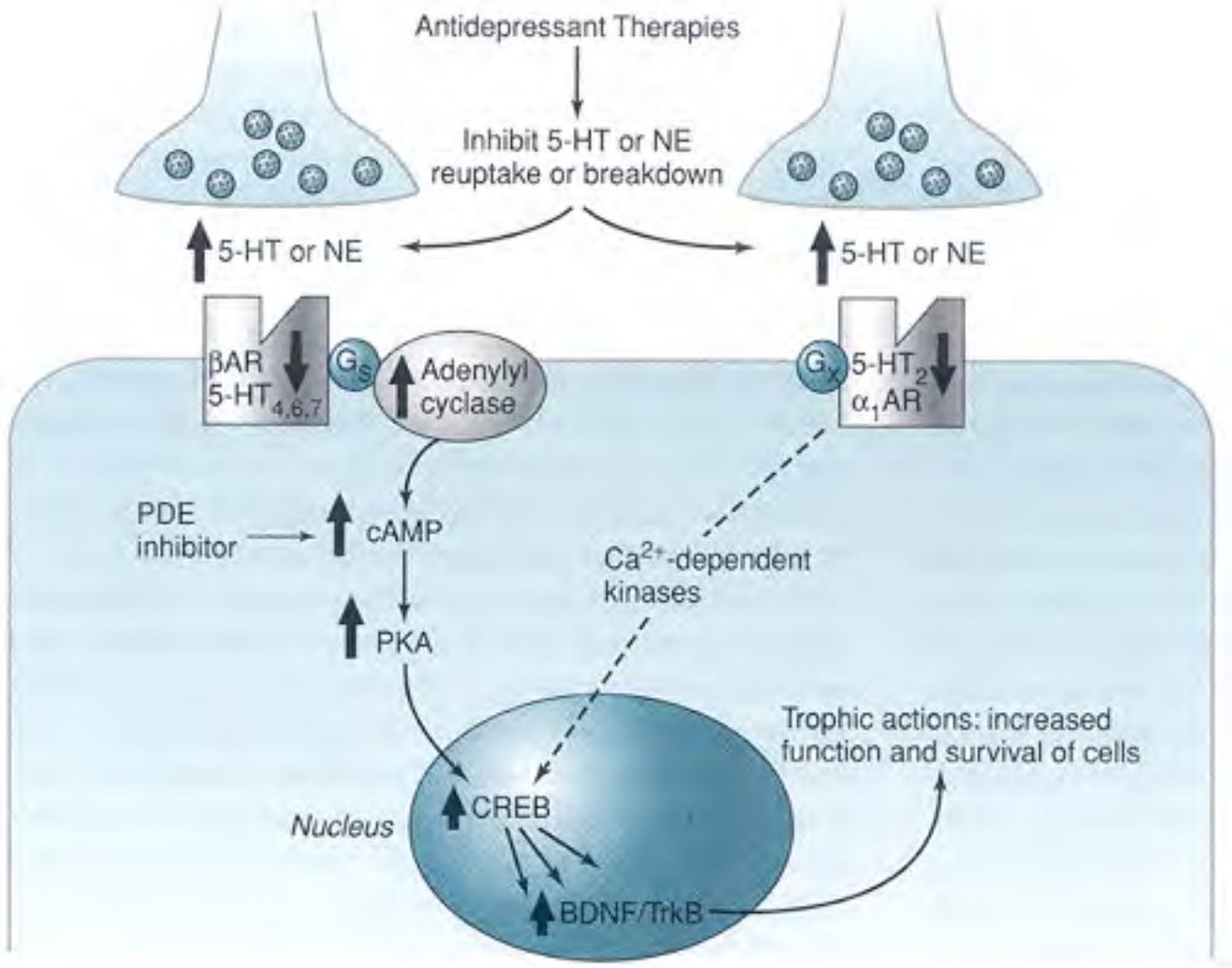
3D brain image shows hippocampus (arrows), which is about 10% smaller in people with a history of depression



Hippocampus of depressed patients has lower levels of brain derived neurotrophin (BDNF) than controls



Antidepressant therapies can lead to production of proteins including BDNF



Nestler, Hyman & Malenka, Molecular Neuropharmacology, McGraw Hill, c2001, p. 348

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Slide 37: Source Undetermined

Slide 38: Regents of the University of Michigan

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