

Drugs react on SEROTONIN RECEPTORs



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SEROTONIN

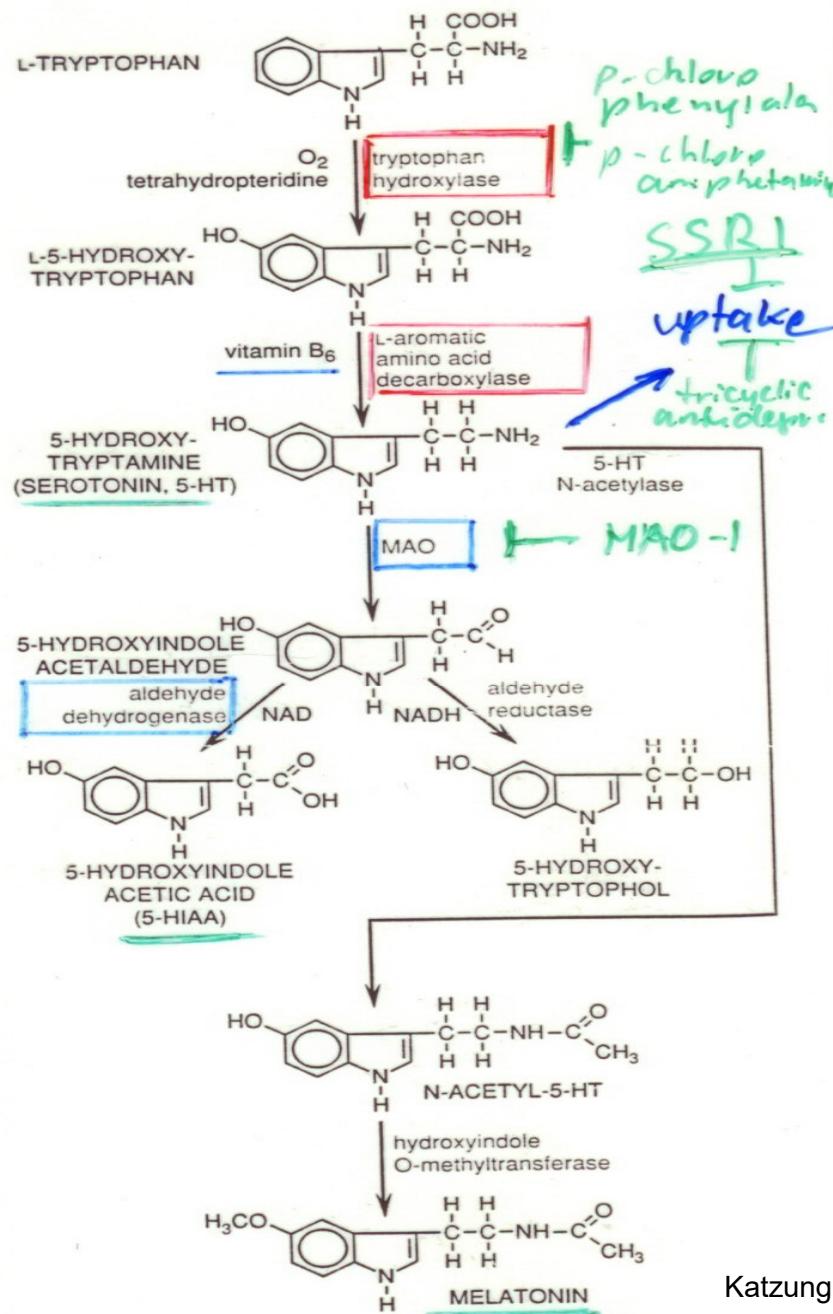
Autacoid-local hormon
Biogen amin neurotransmitter

Production and distribution in tissues

1. **enterochromaffin cells** produce 90% of serotonin content of human body

In gastrointestinal system, liver and lung capillaries \rightarrow blood \rightarrow thrombocytes

2. **CNS** raphe nuclei in midbrain



Katzung et al Basic and Clinical Pharmacology textbook

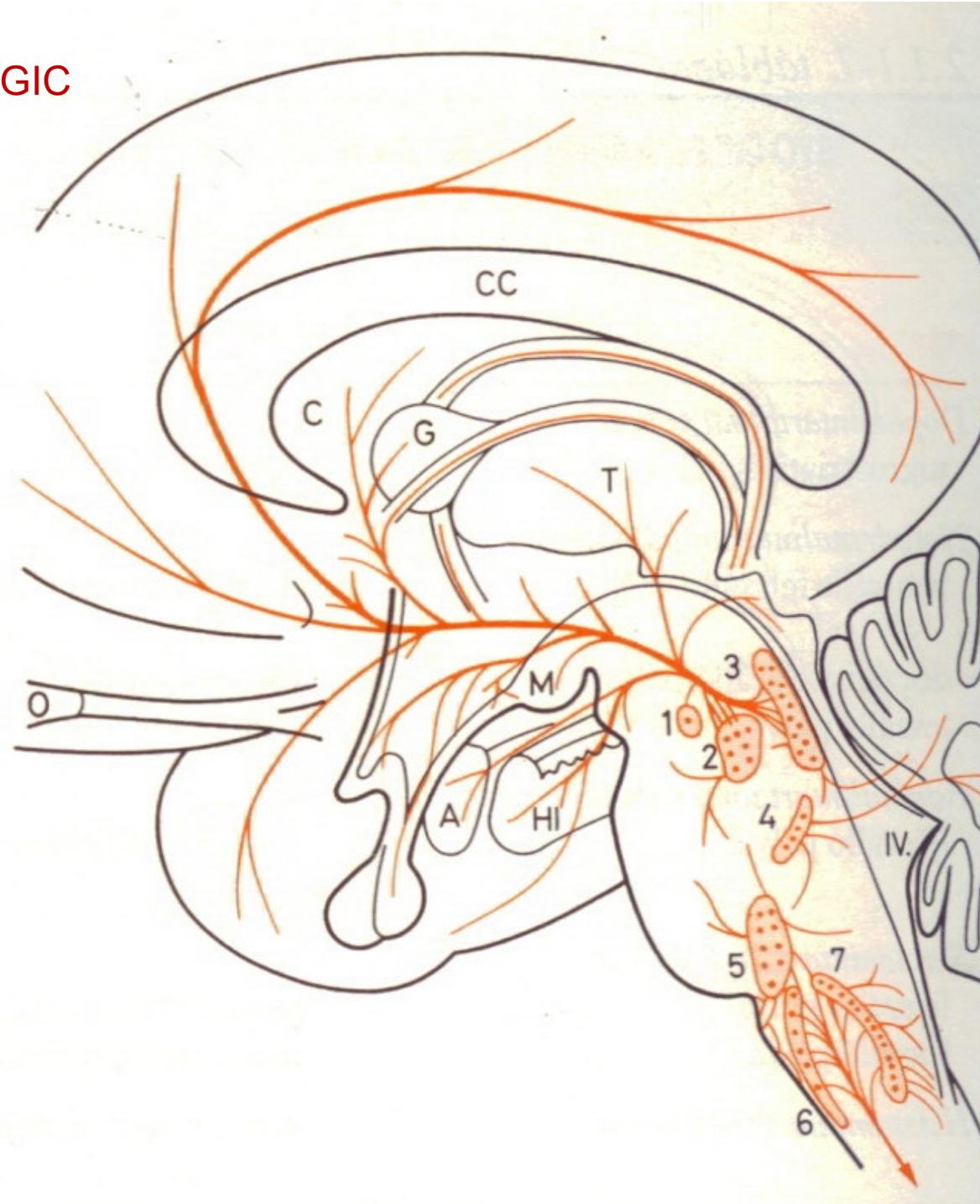
Figure 11-2. Synthesis and inactivation of serotonin.

Synthetic enzymes are identified in blue text, and cofac-

SEROTONIN RECEPTORS

	$5HT_1$	$5HT_2$	$5HT_3$	$5HT_4$
distribution	cortex, subcortical nuclei	cortex subcort. nuclei trombocytes	brain enteral plexus neurons	brain enteral plexus neurons
postreceptorial mech.	↓ cAMP	↑ IP_3	Na/K channel	↑ cAMP
physiologic or pathologic effects	neurotr.	neurotr. thrombocyte aggregation	neurotr. vegetative and sensorial	neurotr. GI contr.
		GI contr. vasoconstr. bronchus-	neurotransm.	
		uterusconstr.	pain	

SEROTONINERGIC PROJECTIONS



EFFECTS OF SEROTONIN ON CENTRAL NERVOUS SYSTEM

Regulation of

SLEEP – WAKEFULNESS
MOTOR ACTIVITY

SENSATION – MAPPING OF THE OUTWORLD
ANXIETY, HALLUCINATIONS

Gatekeeper in
sensory transmission

MOOD – EMOTION
COGNITIVE FUNCTIONS

BEHAVIOUR

AGGRESSION – IMPULSIVE ACTIONS
SEXUAL BEHAVIOUR
HORMONAL SECRETIONS

APPETITE – BODY WEIGHT

BODY TEMPERATURE

CIRCADIAN RHYTHMS

In pain inhibitory descendent pathway

Antiemetic effect in vomitus centre

Table 11-3
Physiological Effects of Serotonin Receptors

SUBTYPE	RESPONSE
5-HT _{1A,B}	Increase K ⁺ conductance Hyperpolarization
5-HT _{2A}	May increase both glutamate and GABA release from different neurons Decrease K ⁺ conductance Slow depolarization
5-HT ₃	Gating of Na ⁺ , K ⁺ Fast depolarization
5-HT ₄	May facilitate Ach release presynaptically Decrease K ⁺ conductance Slow depolarization

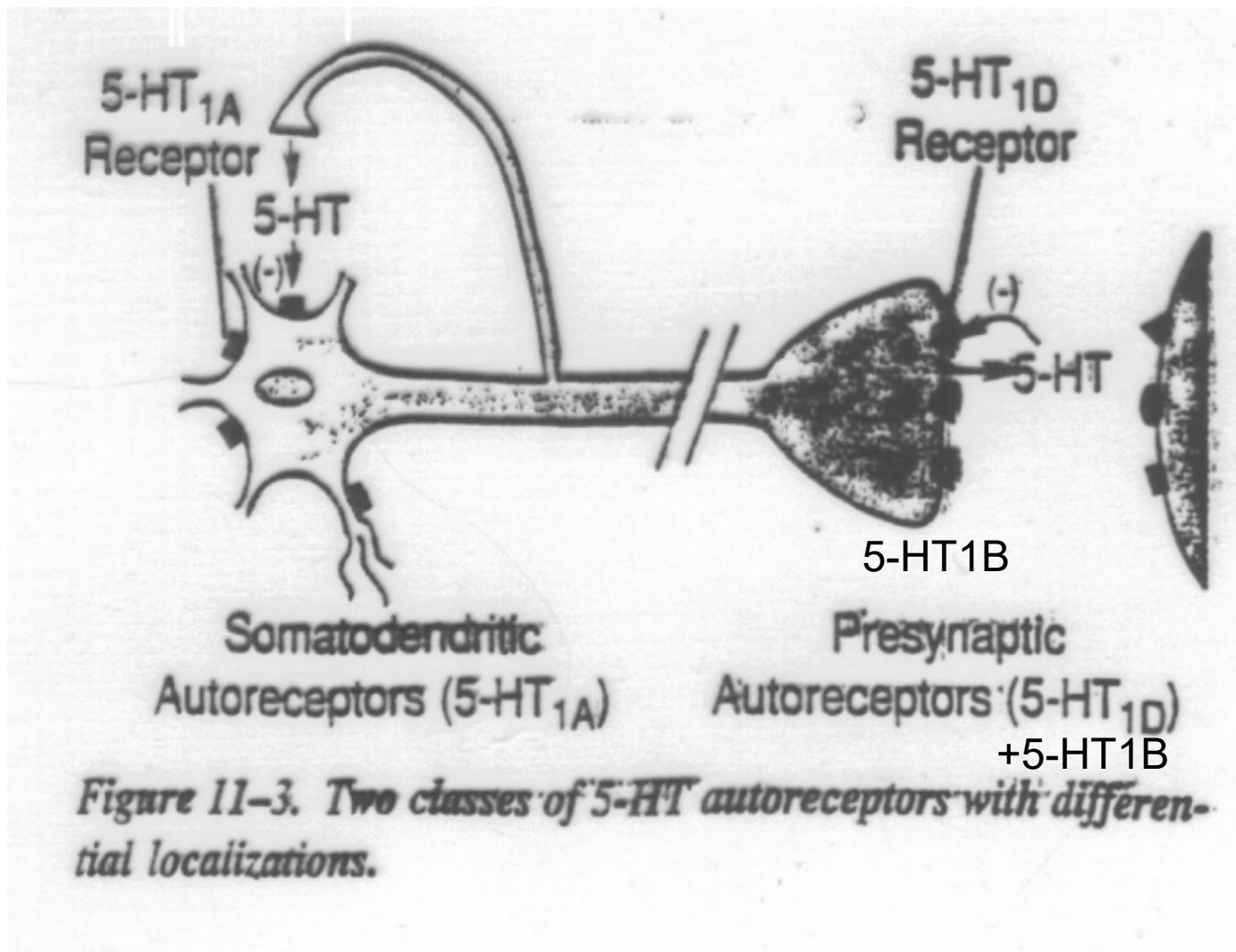
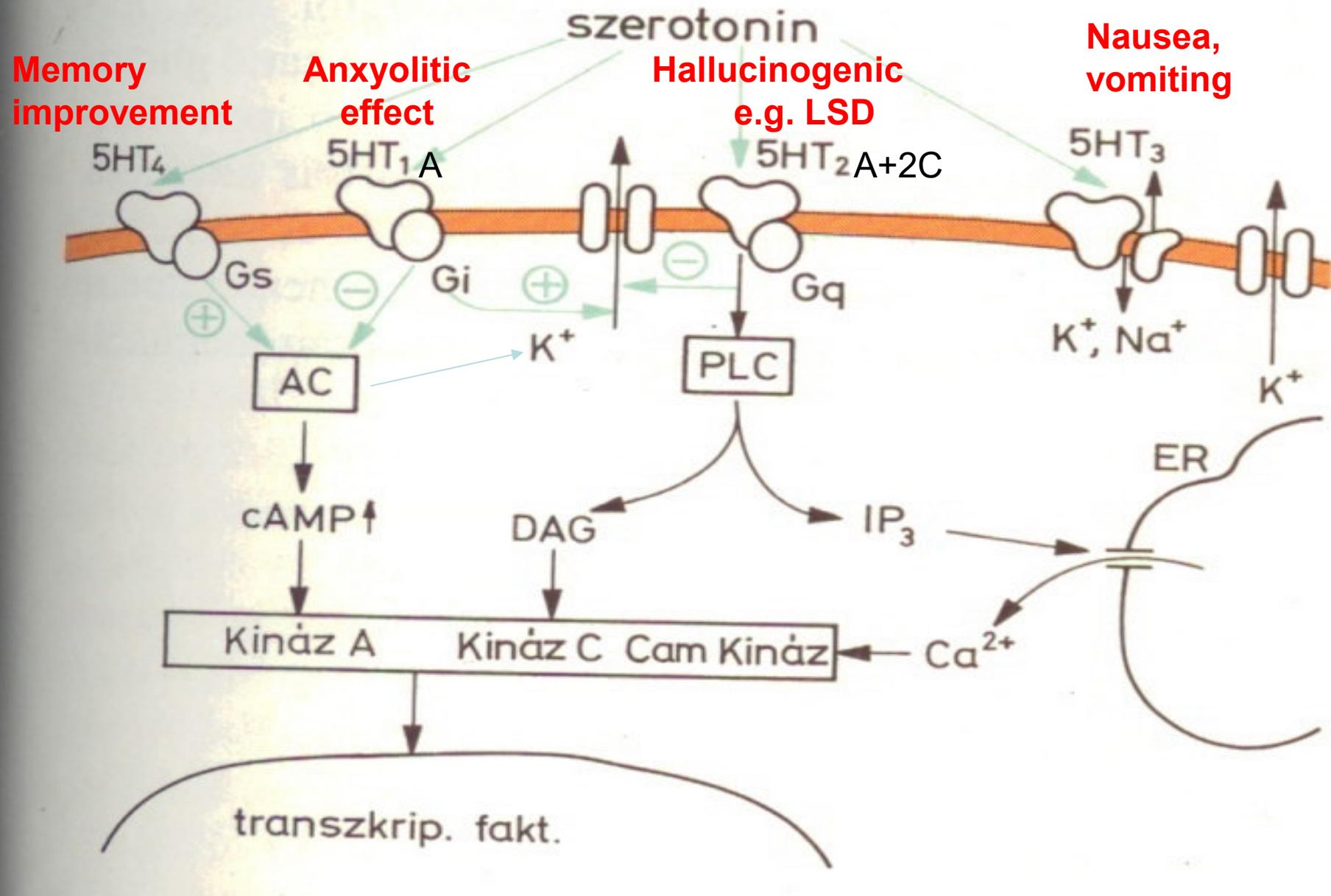


Figure 11-3. Two classes of 5-HT autoreceptors with differential localizations.

Effects of agonists on serotonin receptors in CNS



Drugs influencing serotonergic neurotransmission in central nervous system

1. Serotonergic effects by increasing its concentration in synapses

ANTIDEPRESSANTS

terciary amine tricyclic antidepressants

MAO inhibitors

SSRIs

SSRI drugs with 5-HT2A antagonist effect

Centrally acting indirect sympathomimetics

amfetamine, metamfetamine

2. Serotonin receptor agonists

Psychostimulants

5-HT2A, 2C

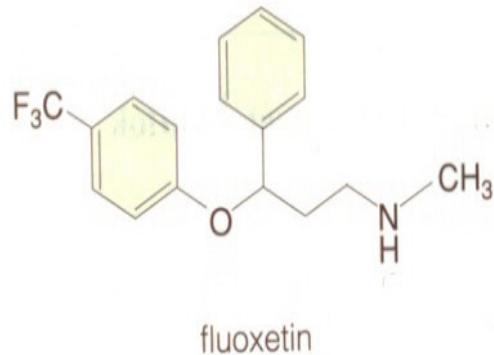
LSD, mescaline, psilocibine

Antidepressants

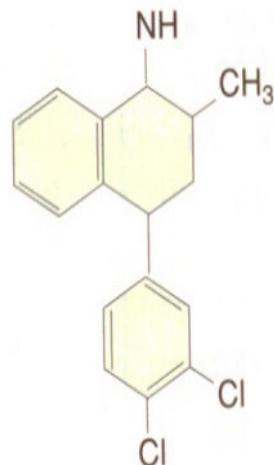
Tricyclic antidepressants	Hatásuk a biogénamin transzmisszióra	Napi dózis (mg)
Tercier aminok Tertiary amines		
amitriptylin (Teperin) clomipramin (Anafranil) doxepin (Adapin) imipramin (Melipramin) trimipramin (Surmontil) dibenzepin (Noveril)	(felvétel gátlók) NA, 5-HT NA, 5-HT NA, 5-HT NA, 5-HT NA, 5-HT NA, 5-HT	100–200 100–200 100–200 100–200 100–200 120–720
Secunder aminok		
amoxapin (Asendin) desipramin (Pertofrán) nortriptylin (Pamelor) protriptylin (Vivactil)	NA, DA NA NA NA	200–300 100–200 75–150 15–40
Selective serotonin reuptake inhibitors	SSRI	
fluoxetin (Prozac) fluvoxamin (Feverin) paroxetin (Seroxat) sertralin (Zoloft) venlafaxin (Effexor)	5-HT 5-HT 5-HT 5-HT 5-HT, NA	20–40 100–200 20–40 100–150 75–225
MAO-inhibitors		
phenelzin (Nardil) tranylcypromin (Parnat) selegiline (Jumex) moclobemid (Aurorix)	(szelektív szubsztrátorok) NA, 5-HT, DA (MAO-A, -B) NA, 5-HT, DA (MAO-A, -B) DA (MAO-B) DA, 5-HT, NA (MAO-A reverzibilis)	30–60 20–30 10 300–750
Atypic antidepressants		
bupropion (Wellbutrin) nefazodone trazodon (Desyrel) maprotilin (Ludiomil) mianserin (Tolvon) venlafaxin (Efexor)	(felvétel gátlók) DA, NA 5-HT NA NA, 5-HT* NA, 5-HT	200–300 150–200 100–150 30–150 75–375
	5-HT2A antagonists	

* α_2 - és 5-HT₂-receptor antagonist

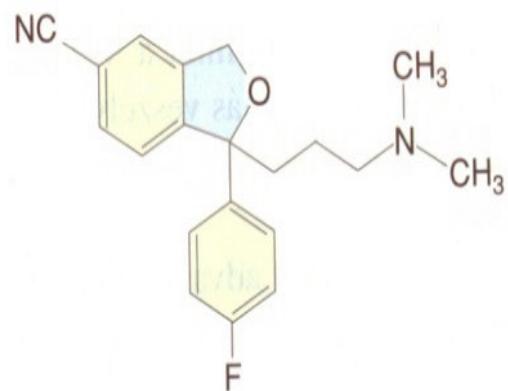
Selective serotonin reuptake inhibitors (SSRI)



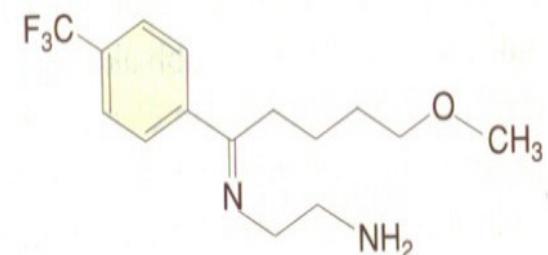
fluoxetine



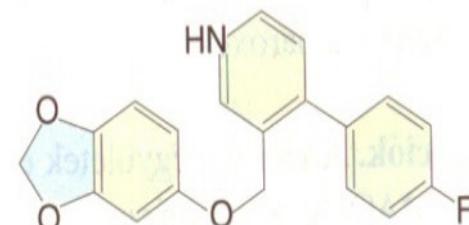
sertraline



citalopram



fluvoxamine



paroxetine

Serotonin syndrome, the life-threatening side effect

Synonyms:

Sympathetic overflow, serotonin syndrom, disco fever, amfetamin intoxication

Overstimulation of vegetative sympathetic centre in hypothalamus

Dysorder in controlling of body temperature

malignant hypertermia $> 40^{\circ}\text{C}$



DEATH

High blood pressure with wide amplitudes

Malignant hypertonia-hypertonic crisis

stroke



DEATH

Muscle rigidity

heat production

aggravates hypertermia



SERT inhibitors with 5-HT2A antagonist effect

Trazodone

+ SERT inhibitor

before SSRI group the most frequently prescribed antidepressant

Nefazodone

+ SERT and NA inhibitor

chemically related to trazodone

2001 FDA warning about hepatotoxicity

Their clinical use:

major depression

trazodone a hypnotic drug without tolerance and dependence
anxiety disorders

Pharmacokinetics:

rapid absorption with high first pass effect in liver

strong protein binding

short T1/2

active metabolites with similar effects

Side effects:

sedation, orthostatic hypotension (alpha receptor inhibitory effect)

fulminant hepatic failure 1:250000 for nefazodone

In central nervous system

3. Inhibition of serotonin storage in presynaptic vesicles

reserpine	alkaloid from Rauwolfia serpentina	antihypertensive, for sleep aid
DO NOT USE today because it results in		serious depression+parkinsonism

4. Serotonin receptor agonists on inhibitory serotonin receptors

5-HT1A agonists	anxyolitics	buspiron, gepiron
5-HT1D agonists	for migraine attack	sumatriptan, naratriptan

In central nervous system

5. Serotonin receptor nonselective antagonists

new neuroleptics	5-HT2A antagonists 5-HT2A inverz agonists + D2/D4 antagonists	olanzapin, sertindol clozapin, quetiapin
5-HT1 és 2A antagonists + H1 antagonist	improvement of appetite dumping sy	ciproheptadin

6. Serotonin receptor selective antagonists

5-HT3 selective antagonists	antiemetics	ondansetron, tropisetron
5-HT2 antagonist	for jet-lag syndrome	ritanserin

ANTAGONISTS

Dopamine release is increasing
in striatum

Table 29–1. Relative receptor blocking actions of neuroleptic drugs.

Drug	D ₂ Block	D ₄ Block	Alpha ₁ Block	5-HT ₂ Block ^A	M Block	H ₁ Block
Most phenothiazines and thioxanthenes	++	-	++	+	+	+
Thioridazine	++	-	++	+	++	+
Haloperidol	+++	-	+	-	-	-
Clozapine	-	++	++	++	++	+
Molindone	++	-	+	-	+	+
Olanzapine	+	-	+	++	+	+
Quetiapine	+	-	+	++	+	+
Risperidone	++	-	+	++	+	+
Sertindole	++	-	+	+++	-	-

¹Key: +, blockade; -, no effect. The number of plus signs indicates the intensity of receptor blockade.

Inhibitory effect in mesolimbic
system on hallucinations

	efficacy in schizophrenia			untoward effects		
	positive symptoms	negative symptoms	depression	extrapyramidal	hyperprolactinemia	agranulocytosis
HALOPERIDOL <i>Haloperidol</i>	+	-	-	++	++	
CLOZAPINE <i>Leponex</i>	+	-	-	-	-	+
RISPERIDON <i>Risperdal</i>	+	+	-	+	+	
OLANZAPINE <i>Zyprexa</i>	+	+	+	-	-	

selective ANTAGONISTS on SEROTONIN RECEPTORS			
ritanserin For jet-lag symptoms	selective 5HT ₂ antagonist	decreases formation of thromboxan → influences bleeding time	
metoclopramide = Cerucal ondansetron = Zofran tropisetron = Navoban granisetron KYTRIL	5HT ₃ /dopamine receptors selective 5HT ₃ antagonists	antiemeticum for relaxing of pylorus vomiting caused by cytostatic agents	diarrhea headache

Therapeutical effects on serotonin receptors peripherally

1. In gastrointestinal system

Prokinetic drugs

Drugs for treatment of Irritabil bowel syndrome

2. In cardiovascular system

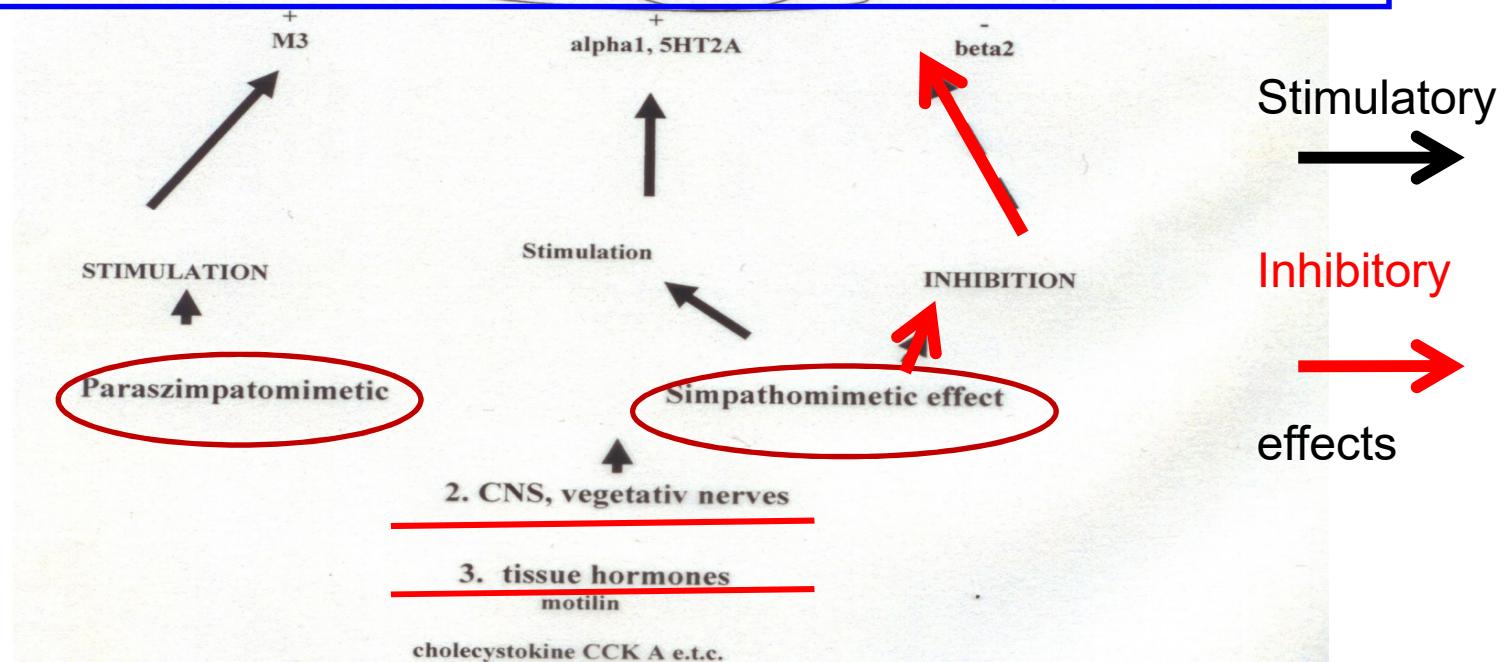
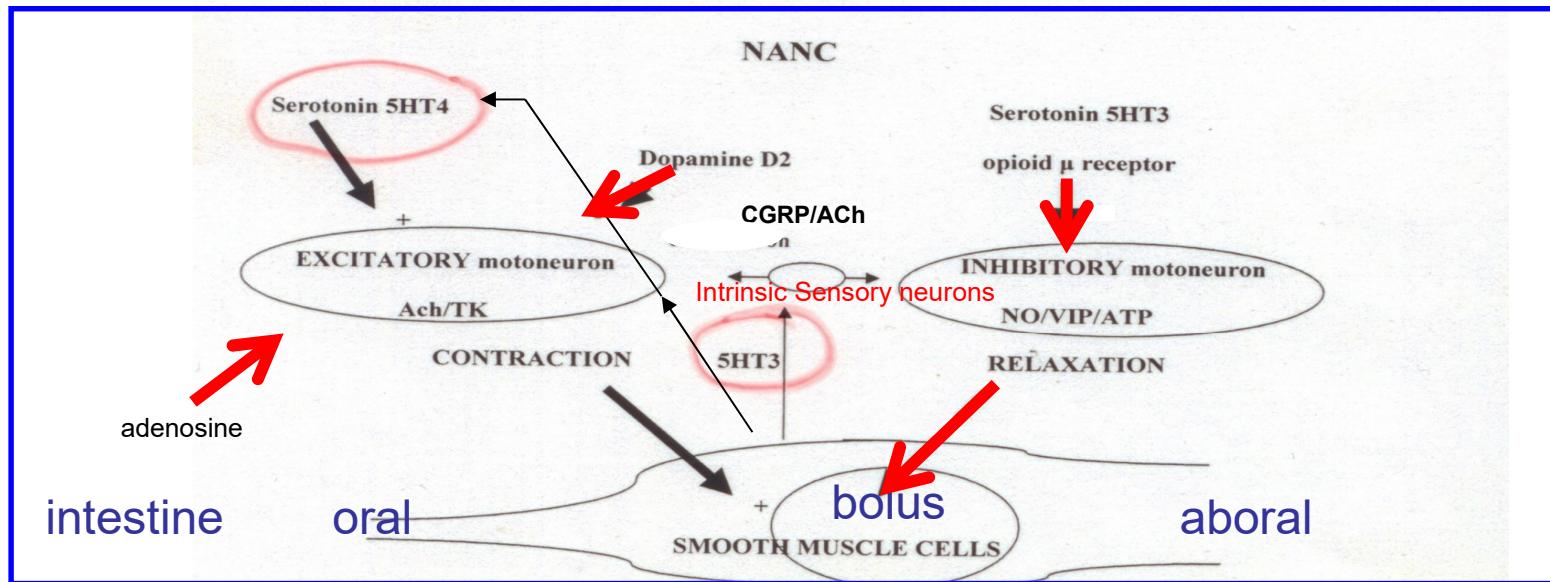
Inhibition of trombocyte aggregation

3. In uterus

Drugs for hemorrhage in postpartum period

1. Enteric nervous system (ENS)

automacy



CONTROLING OF INTESTINAL PERISTALSIS

Serotonin 5-HT4 receptor agonists are very good prokinetic drugs but only for limited use

because of their cardiototoxicity:

cisapride inhibits hERG (human ether-to-go-go-related gene) K⁺channels, which results in prolonged QTc in some patients

harmful arrhythmias, cardiovascular death

better TI in the case of tegaserod, which inhibits 5-HT1P receptors in the heart

prucalopride is under development with great hope

TREATMENT OF IRRITABLE BOWEL SYNDROME

with diarrhoe

5-HT3 antagonists

alosetron

Highly potent and selective

Absorption: 50-60%

T1/2: 1.5 hours

Extensive hepatic CYP450 metabolism

Long duration of action because of high affinity
and slow dissociation from the receptors

GI toxicity: constipation 30%

Rare but serious some fatal: Ischaemic colitis

**Alosetron is restricted to women
with severe diarrhea-predominant IBS**

with constipation

5-HT4 agonists

**tegaserod and
prucalopride**

**tegaserod was approved for the short-term
treatment of women with IBS who had
predominant constipation**

2. THROMBOCYTES, CARDIOVASCULAR EFFECTS

vasoconstriction: splanchnic, renal, pulmonar, brain vessels

vasodilatation: local effects

cardial effects: + inotrop, + chronothrop
Bezold-Jarish reflex , extrem bradycardia, hypotension

DRUGS:

ketanserine SUFREXAL inhibites thr aggregation, antihypertensive effects
ritanserine inhibites thr aggregation

5HT-1B inhibits voltage gated K⁺ channels

on **vascular smooth muscle cells**

vasoconstriction



Pulmonary hypertension

5HT1A increases PGI2 deliberation from endothel

vasodilation



3. Smooth muscles

Uterus contraction 5-HT_{2A} , 5-HT_{1F}

Drugs for therapy: ergot alkaloids

ergonovin
ergotamin

Post partum: for ameliorating bleeding

CARCINOID tumor

The malignancy of enterochromaffine cells in GI

Carcinoid tumor = Serotonin release peripherally

Symptoms: flush, diarrhoe

endocardial fibrosis in the right half of the heart
Retroperitoneal fibrosis

dexfenfluramine

anorexigen by serotonin release

After using it by millions of people it was withdrawn because of cardiomyopathy

with endocardial fibrosis with high mortality



Ergot intoxication

St. Anthony fever

- 1. Hallucination**
- 2. Gangraine**
- 3. abortion**

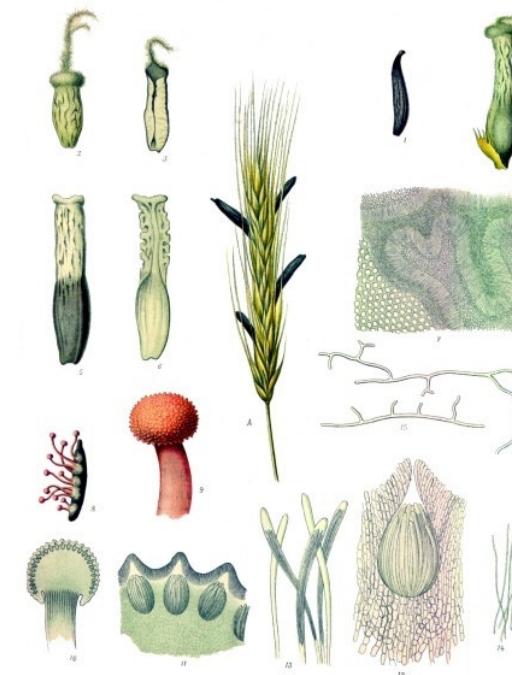


Table 16-4. Major ergoline derivatives (ergot alkaloids).

Amine alkaloids		Peptide alkaloids	
<p>INDOLE CORE</p>			
6-Methylergoline	-H	-H	Ergotamine ERGAM, <i>Cat ergot = SECADOL</i>
Lysergic acid	-H	-COOH	α -Ergocryptine Bromocriptine <i>BROMOCRIPTINE - RICHTER, PARLODEL</i>
Lysergic acid diethylamide (LSD)	-H	$\begin{matrix} \text{O} \\ \parallel \\ -\text{C}-\text{N}(\text{CH}_2-\text{CH}_3)_2 \end{matrix}$	dihydroergotamine = Dihydroergot [~ REDERGAM]
Ergonovine (ergometrine)	-H	$\begin{matrix} \text{O} \\ \parallel \\ -\text{C}-\text{NH}-\text{CH}-\text{CH}_3 \\ \\ \text{CH}_2\text{OH} \end{matrix}$	
Neo-Gynofort			
Methysergide	-CH ₃	$\begin{matrix} \text{O} \\ \parallel \\ -\text{C}-\text{NH}-\text{CH}-\text{CH}_2-\text{CH}_3 \\ \\ \text{CH}_2\text{OH} \end{matrix}$	

ERGOT ALKALOIDS

TABLE 16-2. EFFECTS OF ERGOT ALKALOIDS AT SEVERAL RECEPTORS.

Ergot Alkaloid	Alpha Adrenoceptor	Dopamine Receptor (D_2)	Serotonin Receptor ($5-HT_2$)	Uterine Smooth Muscle Stimulation
Bromocriptine	-	+++	-	0
Ergonovine	+	+	-(PA)	+++
Ergotamine	-(PA)	0	+(PA)	+++
Lysergic acid diethylamide (LSD)	0	+++	+++	+
Methysergide	+/0	+/0	--(PA)	+/0

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Agonist effects are indicated by +, antagonist by -, no effect by 0. Relative affinity for the receptor is indicated by the number of + or - signs. PA, partial agonist.

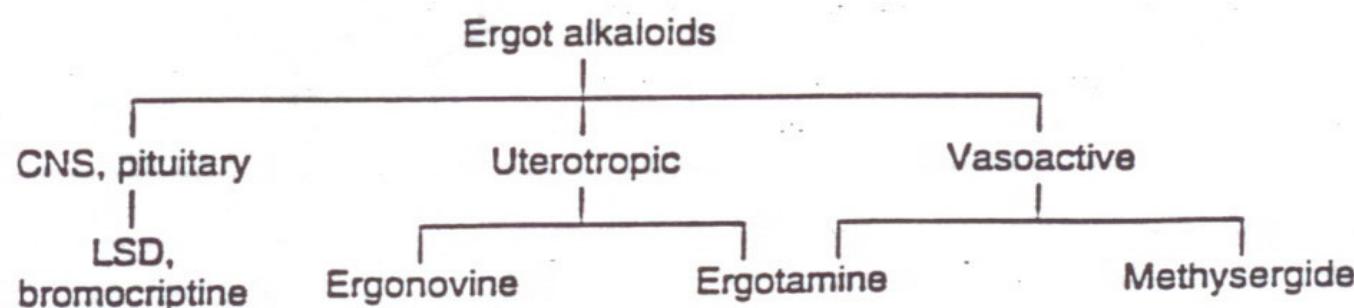


Figure 16–3. Subgroups of ergot alkaloids.

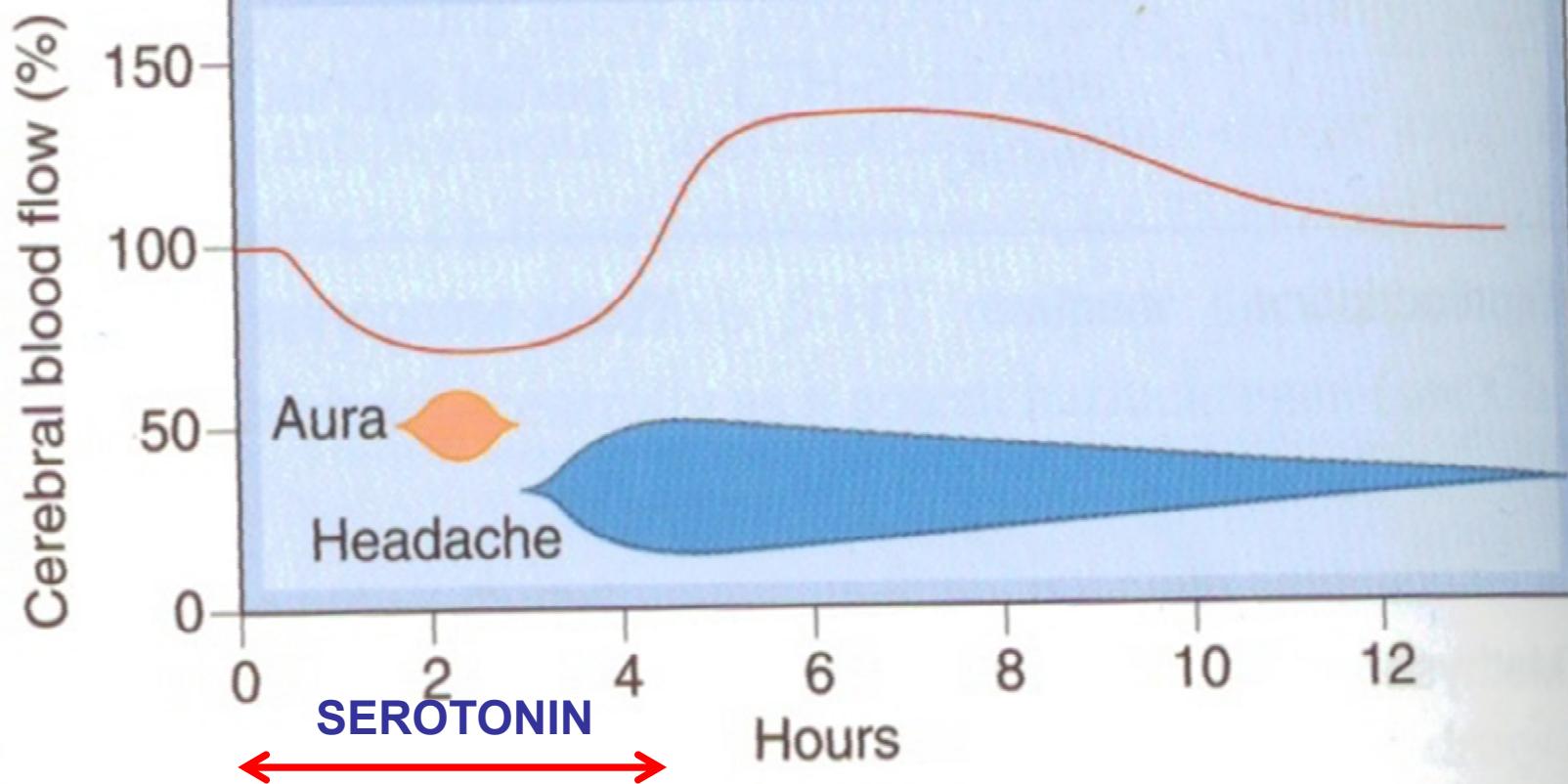
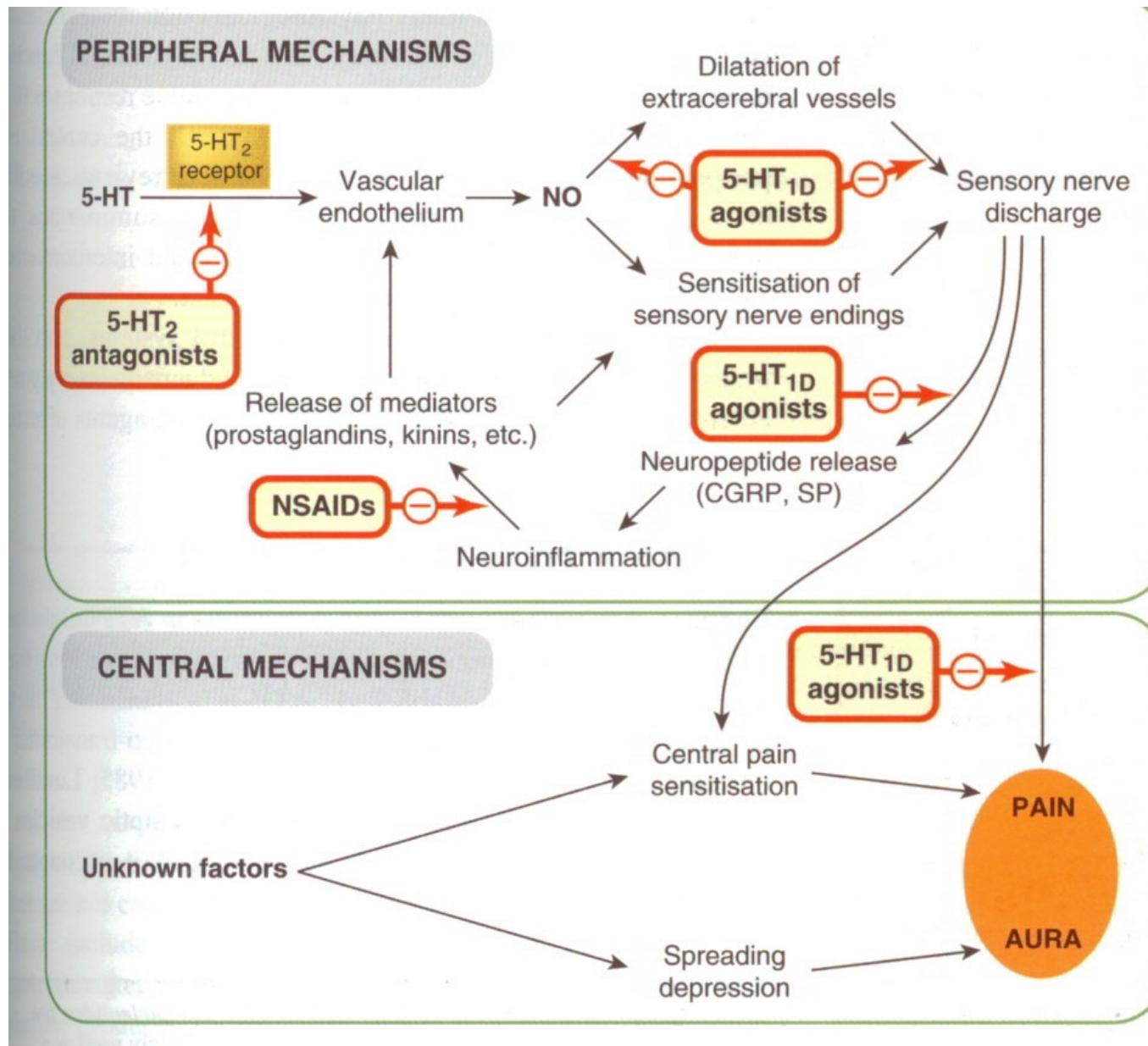


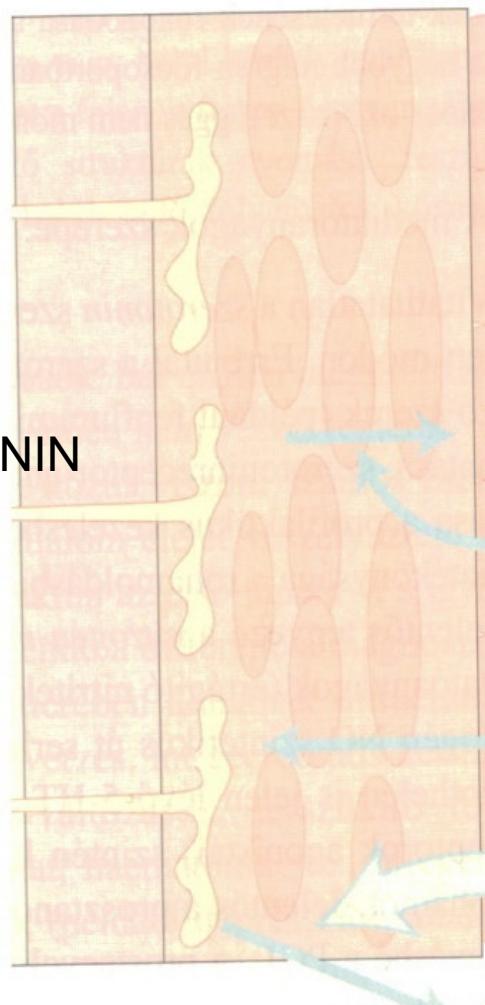
Fig. 12.2 Cerebral blood flow changes during migraine.
(After Olesen et al. 1990.)



érfal

A M E

SEROTONIN



$5-HT_{2B/C}$

(antagonisták: profilaktikumok)

antagonists

$5-HT_{1D}$

agonisták:
érszűkítés
szenzoros
neuropeptid
felszabadulásának
gátlása

agonists

5-HT_{1F} also strongly
binds sumatriptan
(antagonist)

DRUGS	effects	clinical uses	side effects
<u>bromocriptine</u> =Bromocriptin Richter, Parlodol	marked dopamine rec.effect	Parkinson sy. hyperprolactinemia	
<u>ergonovine</u> =ergometrine Neo-Gynofort	marked on uterus , partial agonist on 5HT ₂	postpartum hemorrhage migraine during coronary angiography angina provocative test	the least toxic CORONARY SPASM !!
<u>methysergide</u>	marked 5HT ₂ antagonist	migraine dumping sy. carcinoid sy.	fibrosis ! careful therapy with periodic drug holidays in every 3 weeks ! hallucination withdrawal symptom: headache
<u>ergotamine</u> = ERGAM cafergot = Secadol combined with	marked on uterus, part.agonist on 5HT ₂ and alpha adr.rec.! Pharm.kin:	migraine postpartum hemorrhage drug formulas: ERGAM: .	durable vasospasmus ! Raynaud sy. do not use for long-term therapy !!
+amino-phenazone, caff etc. KEFALGIN	mg/weak(cumulation!) low bioavailability	inj., sublingual tabl., aerosol	hallucination CORONARY SPASM !!
<u>dihydroergotamine</u> = Dihyderygot	marked on uterus,	migraine	vasospasmus less than in the case of ergotamine

THERAPY of migraine

ACUTE ATTACK in early period:

1. aspirin , paracetamol in large doses (1000 mg)

2. ergot alkaloids

Very specific effect

They have therapeutical value only at the early period !

3. sumatriptan (Imigran), only as inj.

in refracted cases:

4. migraine cocktail: Demalgonil+Seduxen+Pipolphen 1-1 amp. im.

5. Rivotril sol.(clonazepam)

6. codeine sulfate, meperidine

7. corticosteroid

for antiemetic effect:

domperidone (Motilium), promethazine (Pipolphen)

PROPHYLAXIS

Influencing serotonin metabolism:

1. amitriptyline (Teperin) + propranolol

2. methysergide (Deseril)

pizotifene (Sandomigran)

Antiepileptics:

3. carbazepine (Stazepin, Tegretol)

clonazepam (Rivotril)

Ca channel blockers:

4. [nifedipine]
verapamil

flunarizine mainly