Uvod v farmakologijo osrednjega živčevja

Prof. dr. Mojca Kržan
Prof. dr. Lovro Stanovnik

Zdravila z delovanjem na osrednje živčevje (OŽ)

- Velik delež vseh zdravil
  - UK - 1/6 bolnikov v 1 letu (podatki za l. 1977)
  - ženske 45 - 59 let $\Rightarrow$ 1/3
- Veliko odkritih " slučajno" ali kot nadaljevanje raziskav na starih empiričnih podatkih (prometazin $\Rightarrow$ klorpromazin)
- Natančen mehanizem delovanja pogosto neznan

Funkcionalno anatomske enote - KORTEKS

- vrhovna integrativna enota
- citoarhitektonika - vertikalne cilindrične enote (100 nevronov)
- abstraktno mišljenje, spomin, zavest
- vrhovna integracija avtonomnih funkcij
- hippocampus (del korteksa) $\Rightarrow$ prostorski spomin

LIMBIČNI SISTEM (visceralni možgani)

- integracija emocionalnega stanja z motoričnimi in vegetativnimi funkcijami
- amigdaloidni kompleks
- septum
- olfaktorni in piriformni lobus
- bazalni gangliji
- deli talamusa
- hipotalamus

Bazalni gangliji

- bistveni del ekstrapiramidnega sistema (komplementaren piramidnemu sistemu)
  - nucleus caudatus
  - putamen
  - nucleus lentiformis STRIATUM
  - globus pallidus

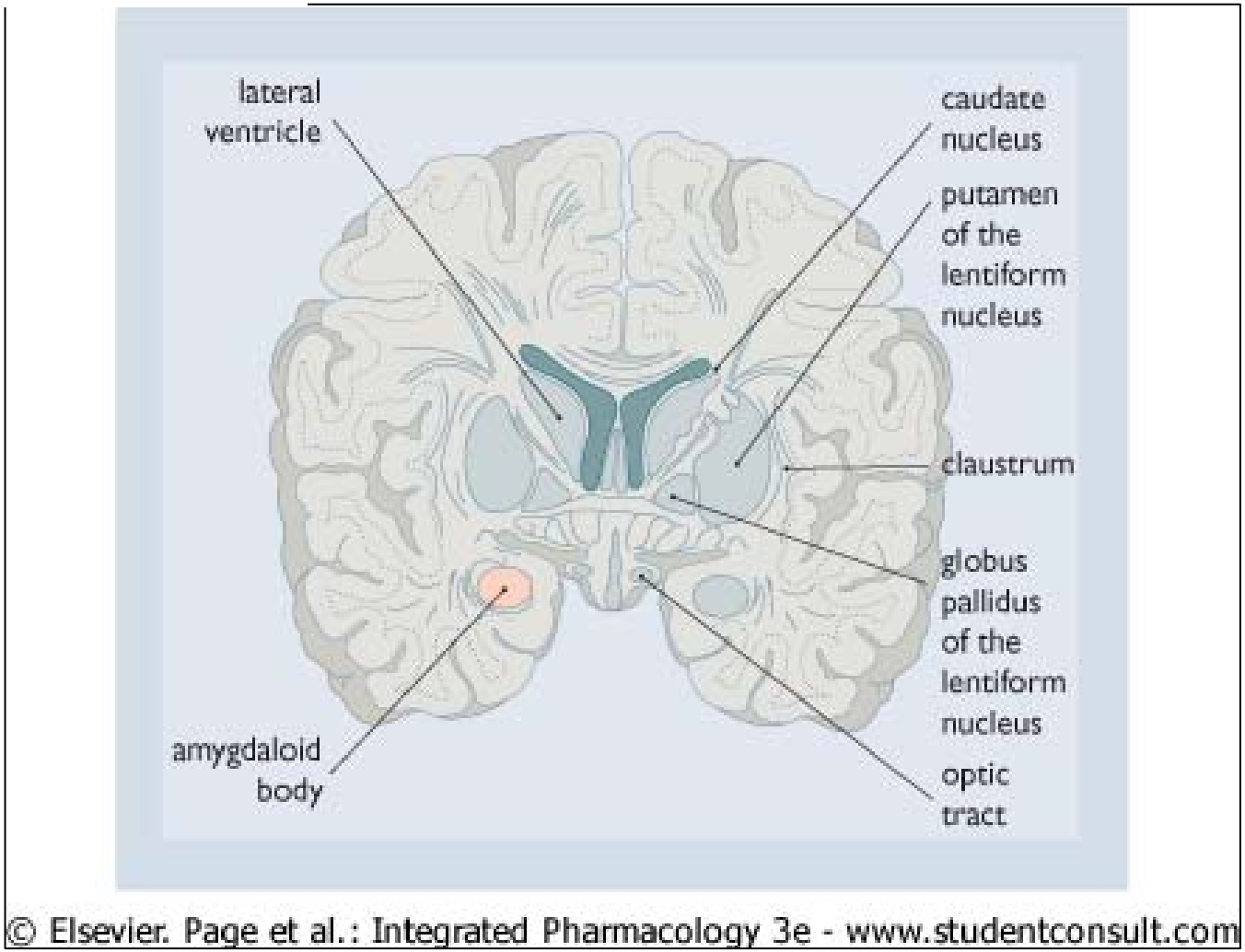
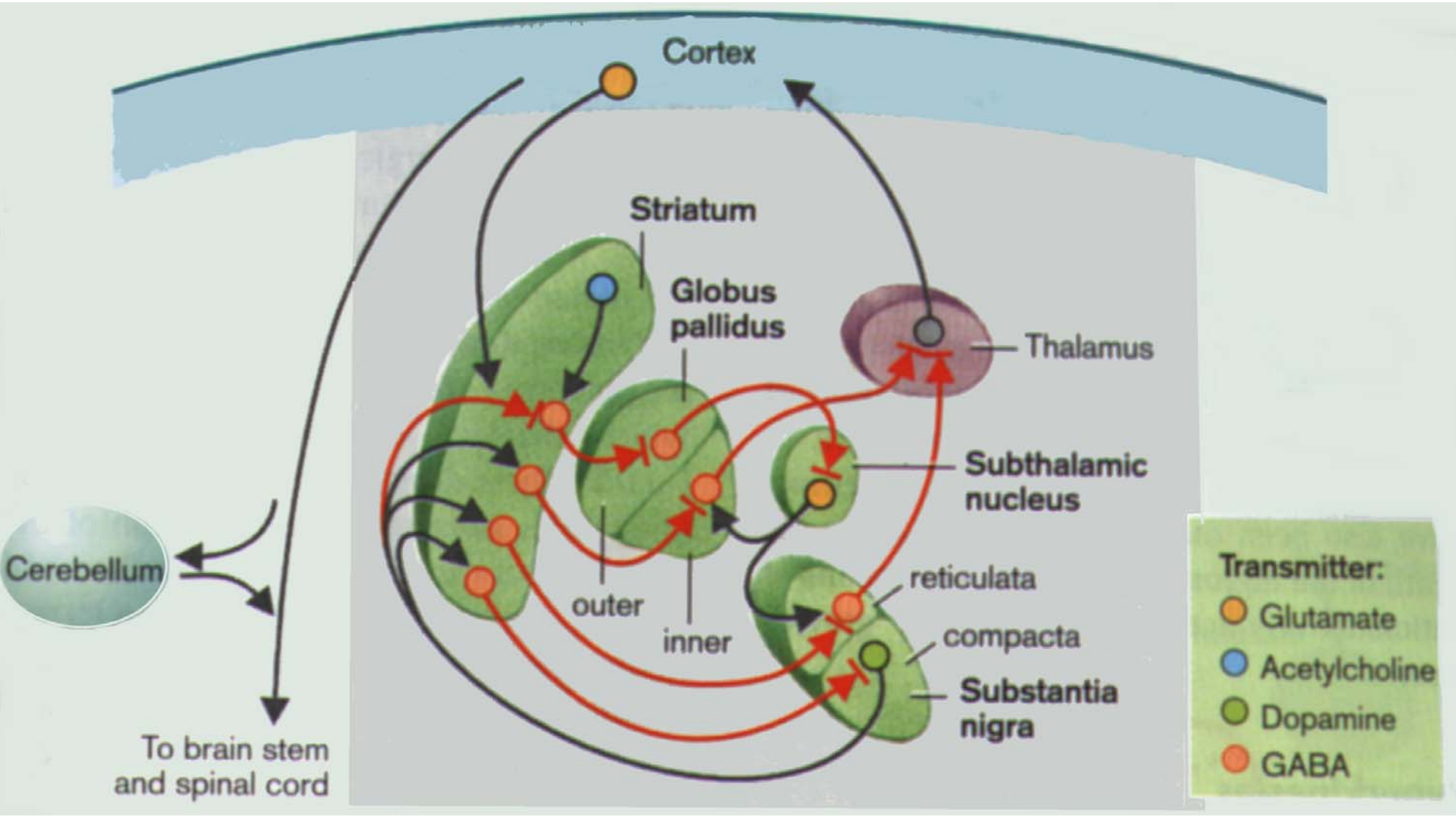


Figure 8.23 Basal ganglia. The bilaterally represented masses of gray matter form deep structures. The corpus striatum consists of the caudate nucleus and the lentiform nucleus, which are separated by the internal capsule except at the anterior-inferior aspect of the caudate nucleus where the head of the caudate is continuous with the putamen of the lentiform nucleus. The lentiform nucleus consists of the putamen and the globus pallidus.

Nigrostriatne povezave in mediatorji



Thalamus

- integracija vhoda informacij
- komunikacije s:
  - korteksom
  - malimi možgani
  - bazalnimi gangliji
  - hipotalamusom

Hypothalamus

- osnovna integracija celotnega avtonomnega živčevja

MESENCEPHALON IN MOŽGANSKO DEBLO

Povezava hemisfer korteksa, talamusa in hipotalamusa z medulo spinalis

- retikularna formacija - ascendentni aktivacijski sistem
  - regulacija: spanje, budnost, kardiovaskularni sistem, center za bruhanje, koordinacija požiranja

CEREBELLUM

- vloga v regulaciji položaja telesa
- povezave z:
  - motoričnim korteksom (preko talamusa)
  - bazalnimi gangliji

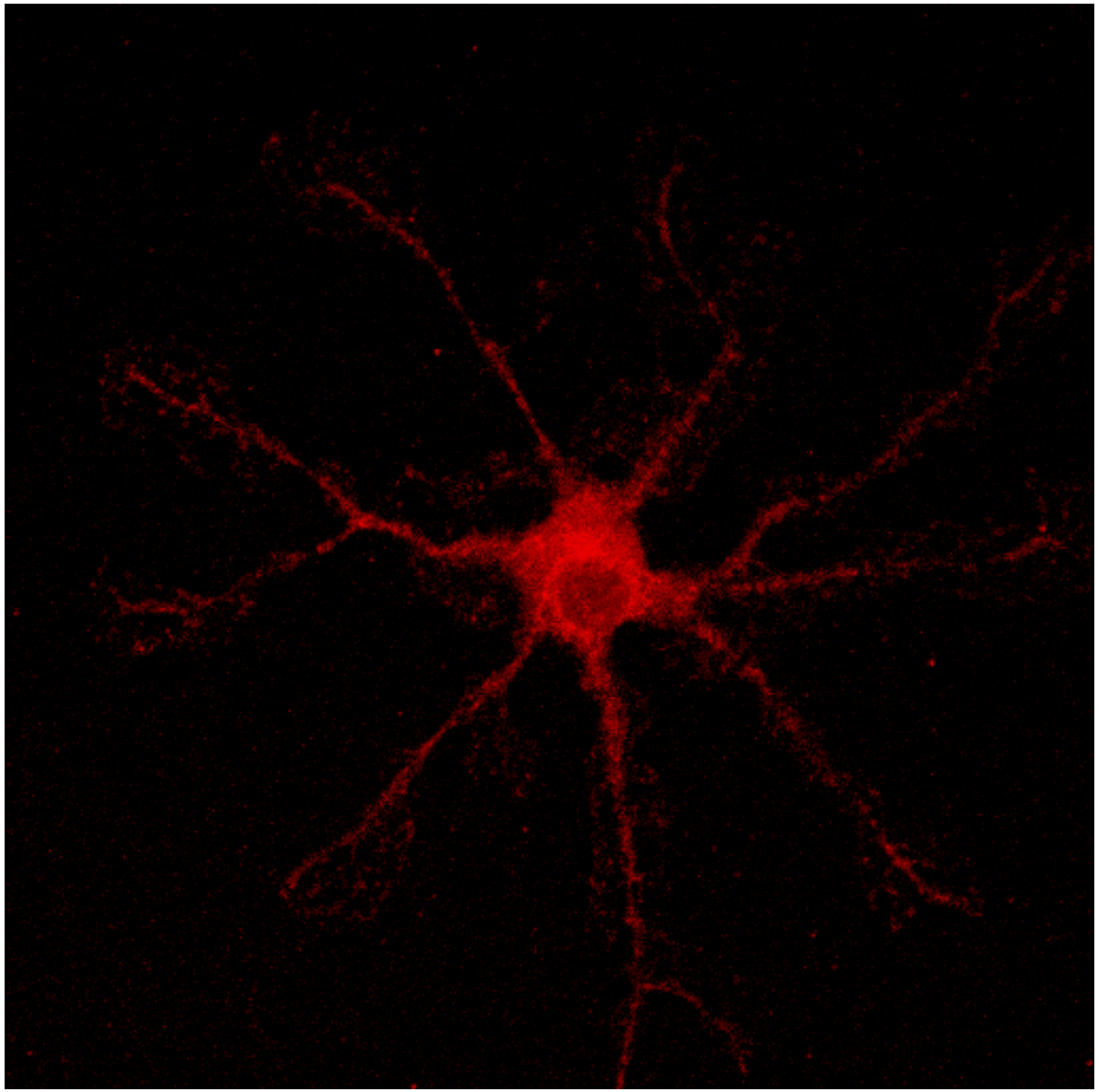
MEDULA SPINALIS

- prevajanje informacij - periferija (⇑⇓)
- določena koordinacija že na tem nivoju
- avtonomni refleksi

Celice v OŽ

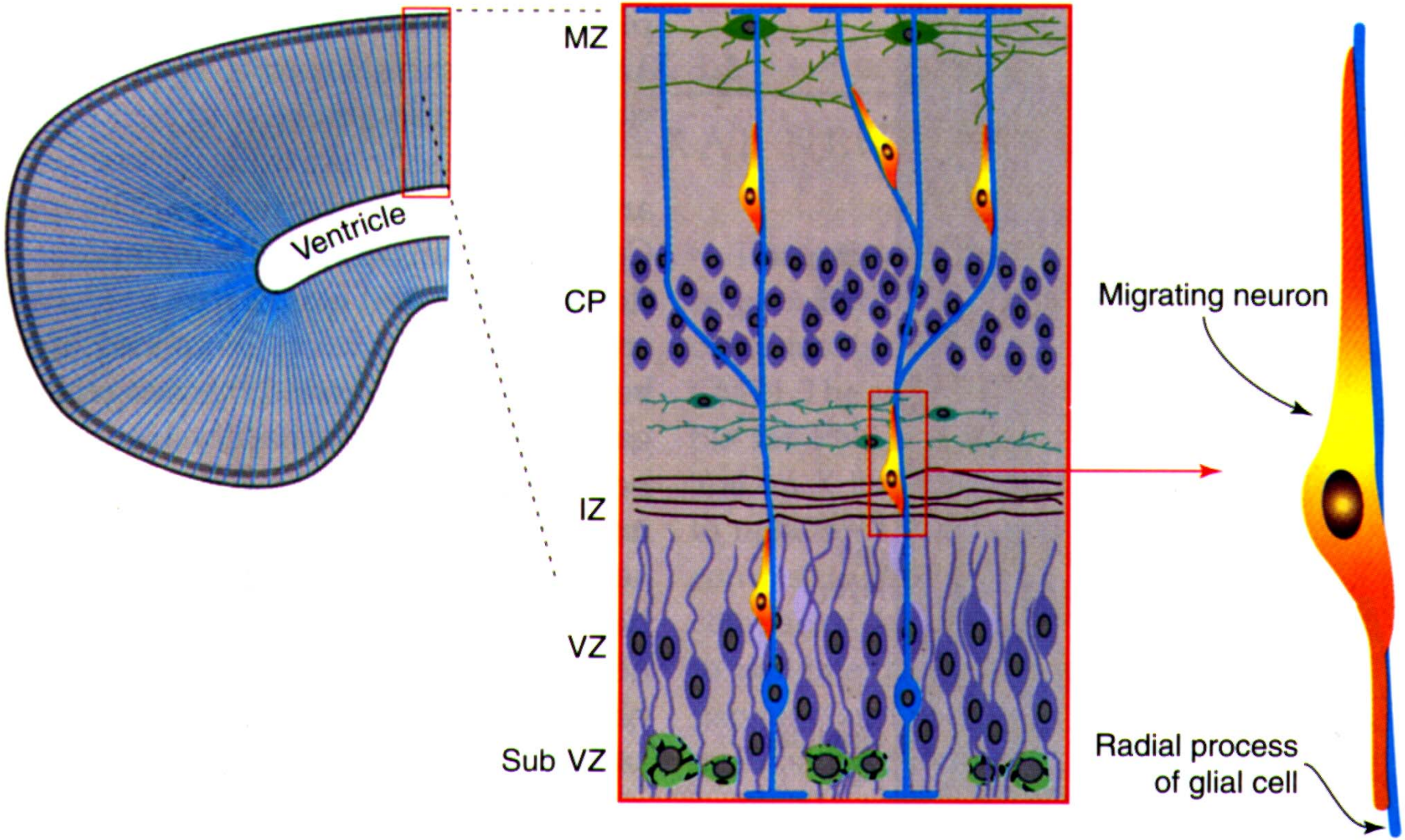
- Nevroni: 10^{11} celic
- Glia 10^{12} celic: astrociti, oligodendrociti, mikroglija
- Endotelijske celice
- Krvno-možganska pregrada
  - Transportni sistemi za zdravila: P -glikoproteini

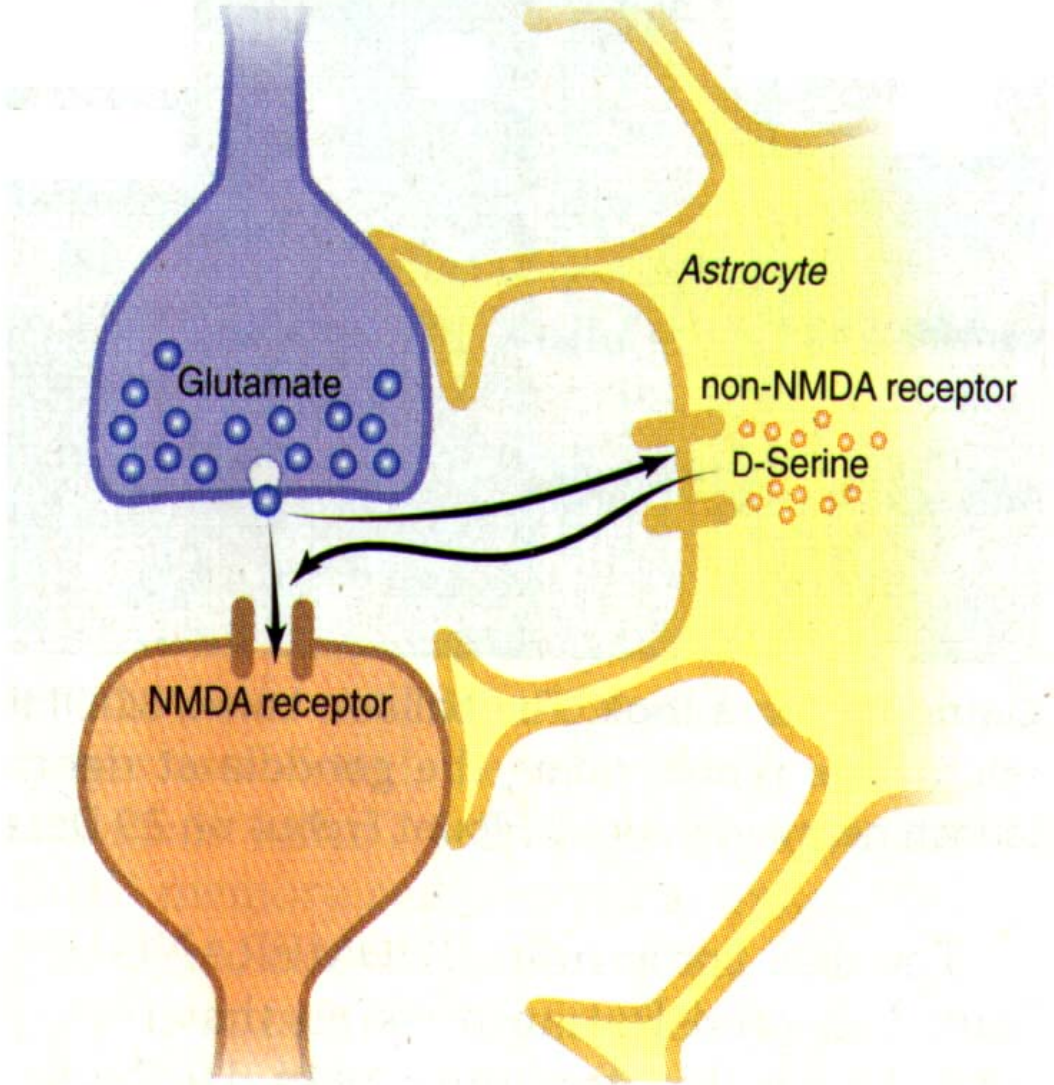
Astrocyte in culture stained with GFAP



Različne faze (obdobja) v delovanju OŽ

- Razvoj
- Normalno odraslo obdobje
- Poškodba
- Stanje po poškodbi


Ventricle
MZ
CP
IZ
VZ
Sub VZ
Migrating neuron
Radial process
of glial cell



Cross-talk. Under glutamate's influence, astrocytes release D-serine into the synapse between two neurons (left).

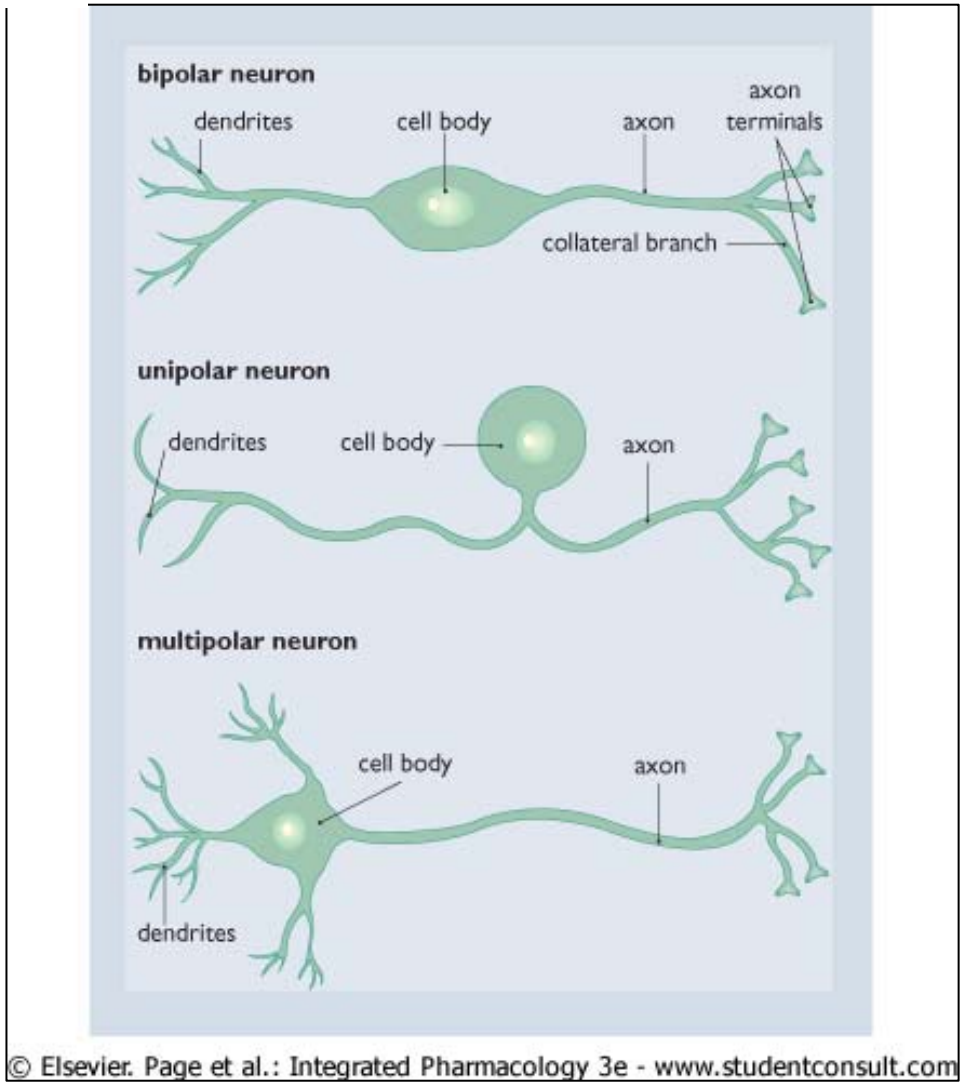
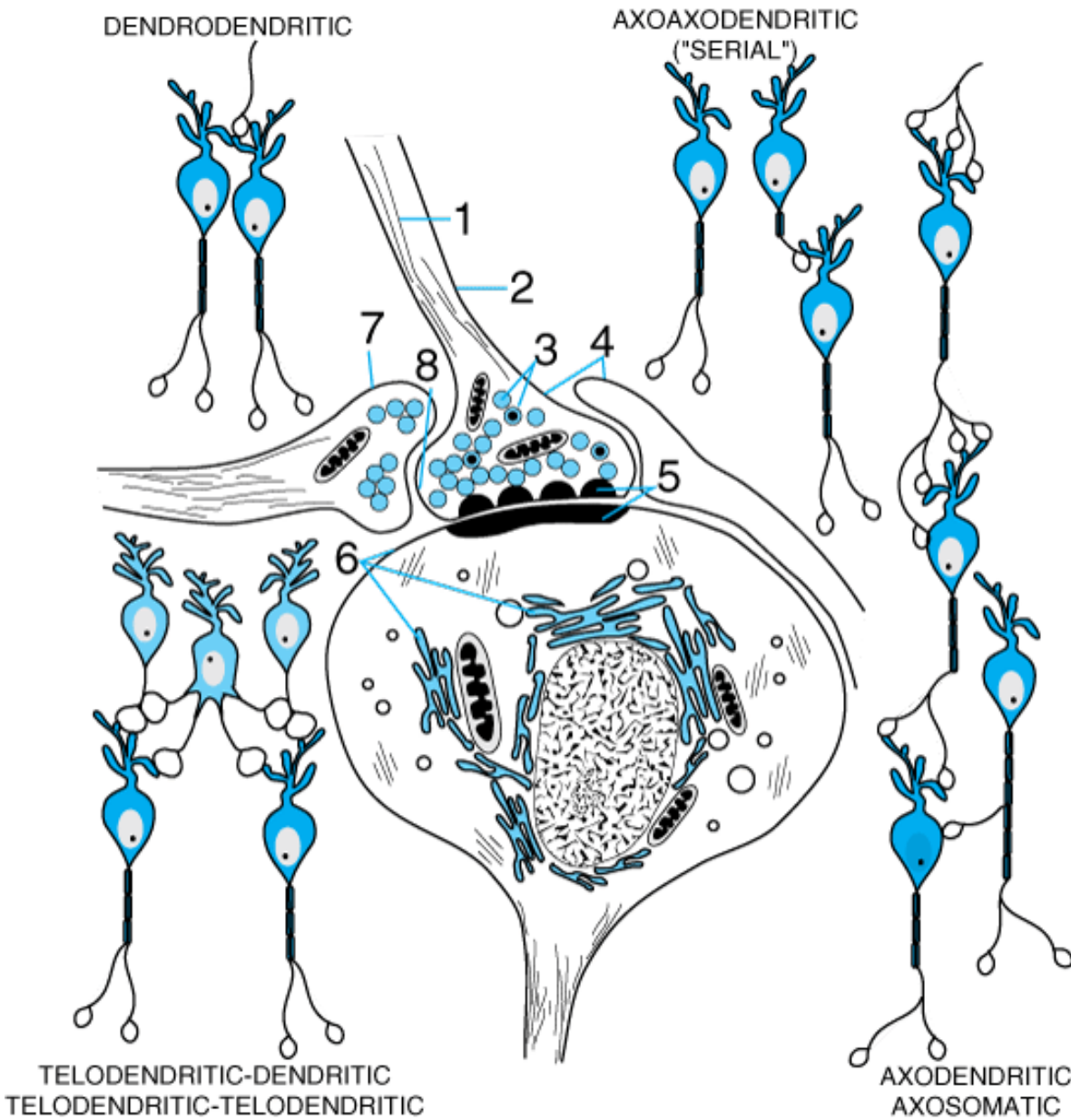


Figure 8.2 Types of neuron. There are many different types of neuron, which are shaped according to function. Bipolar cells are commonly interneurons, while unipolar cells tend to be sensory neurons, and multipolar cells are often motor neurons.

Sinapse v OŽ



Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

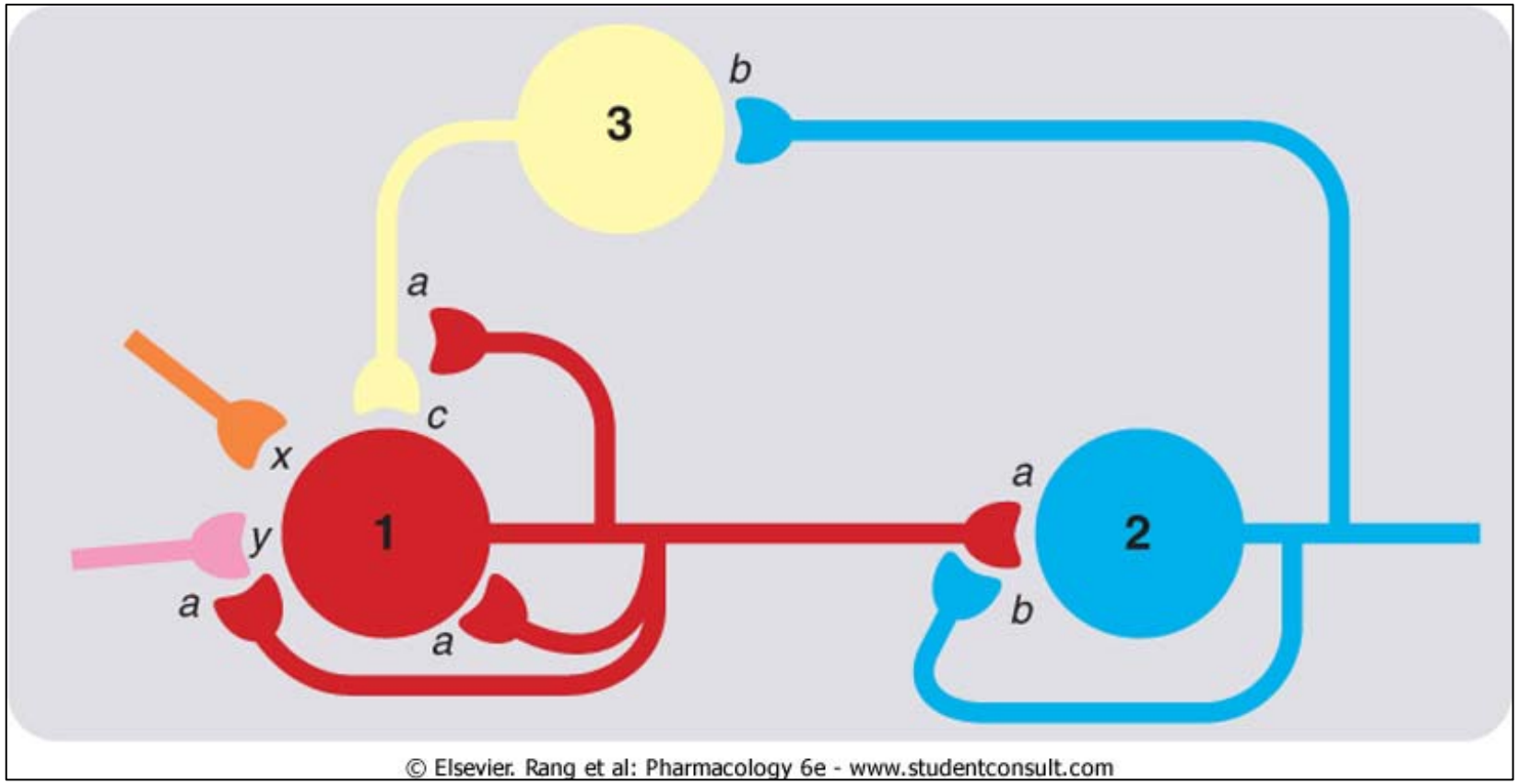


Figure 32-2 Simplified scheme of neuronal interconnections in the central nervous system. Neurons 1, 2 and 3 are shown releasing transmitters a, b and c, respectively, which may be excitatory or inhibitory. Boutons of neuron 1 terminate on neuron 2, but also on neuron 1 itself, and on presynaptic terminals of other neurons that make synaptic connections with neuron 1. Neuron 2 also feeds back on neuron 1 via interneuron 3. Transmitters (x and y) released by other neurons are also shown impinging on neuron 1. Even with such a simple network, the effects of drug-induced interference with specific transmitter systems can be difficult to predict.

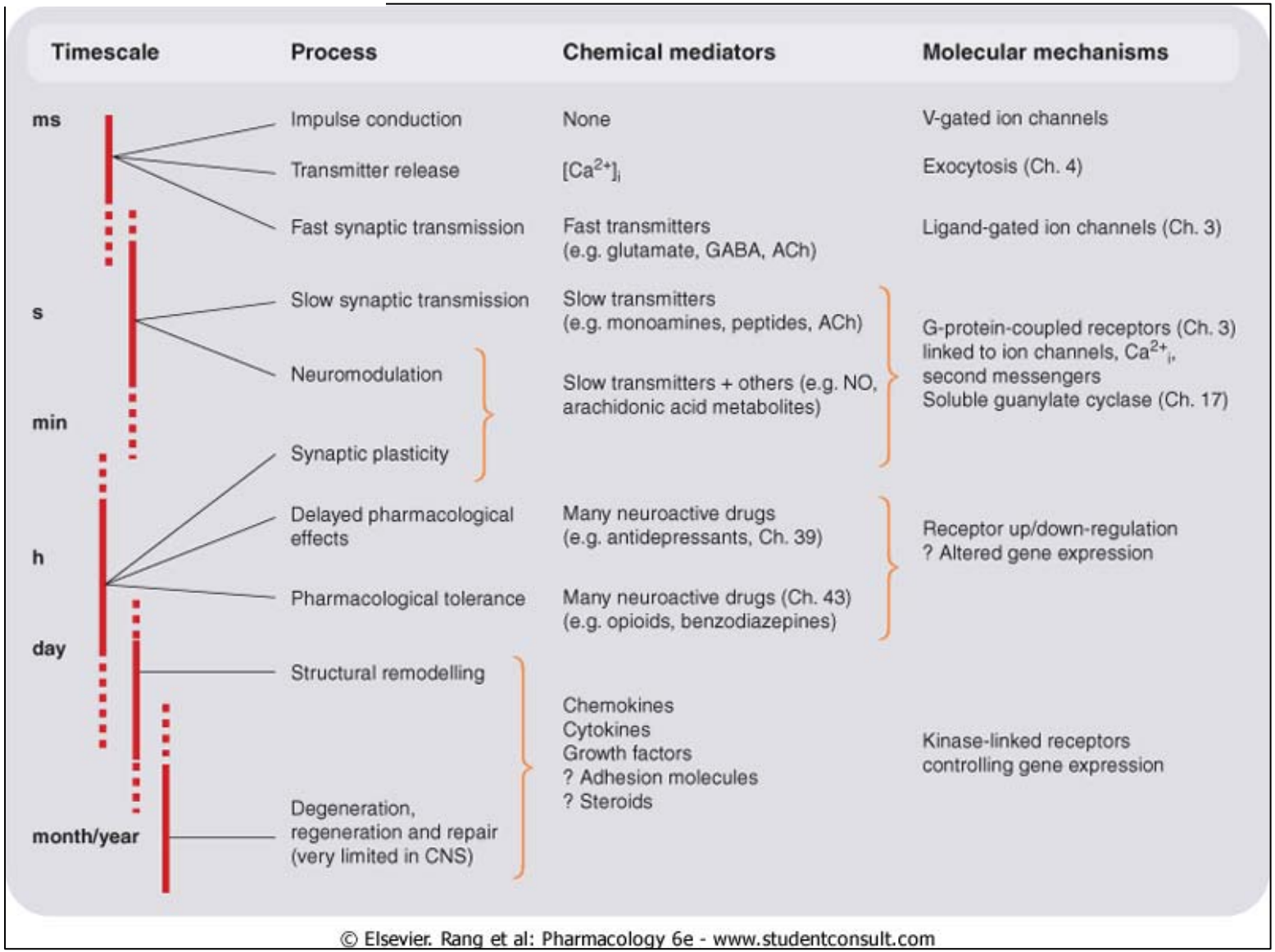
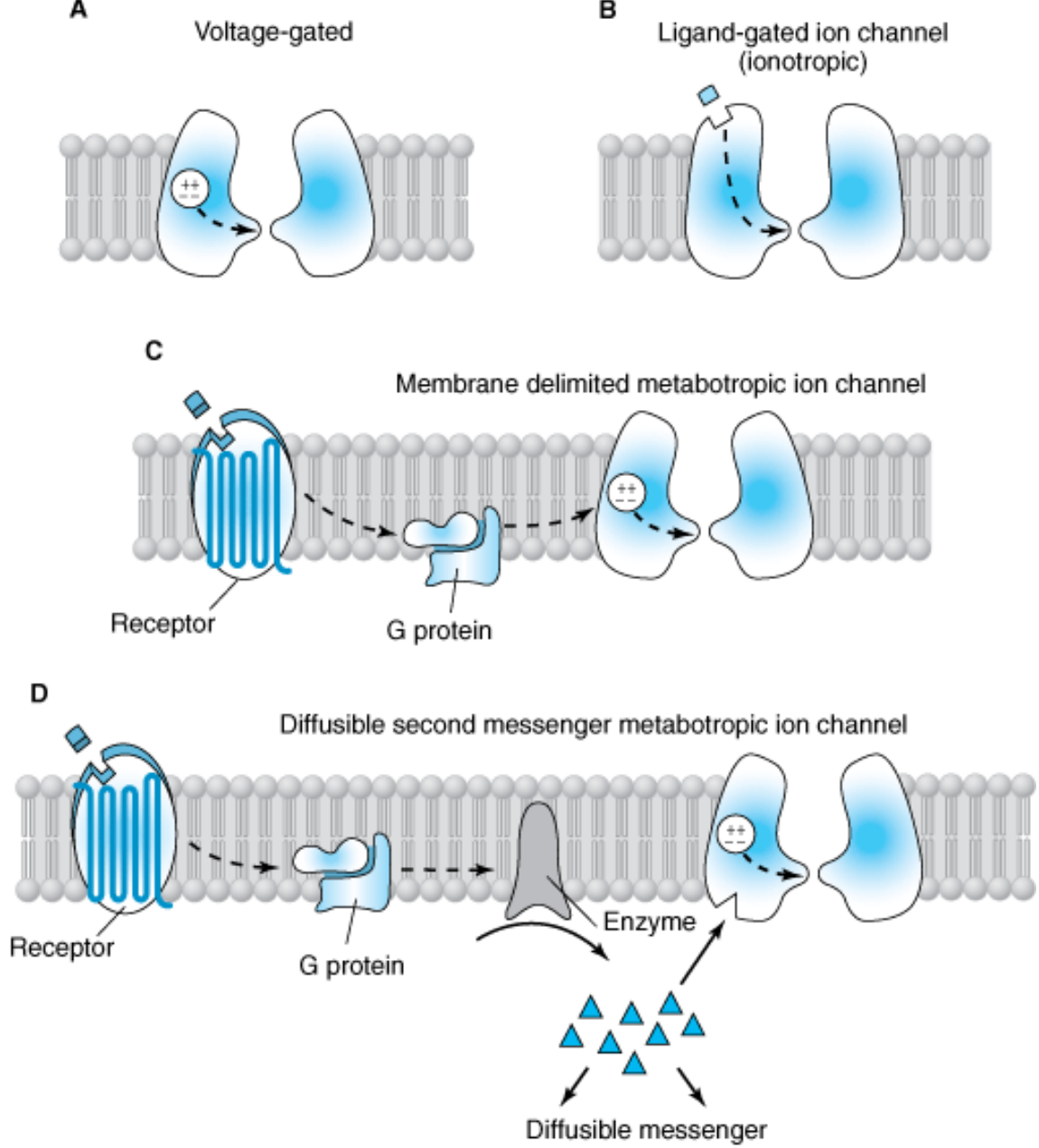


Figure 32-1 Chemical signalling in the nervous system. Knowledge of the mediators and mechanisms becomes sparser as we move from the rapid events of synaptic transmission to the slower ones involving remodelling and alterations of gene expression. ACh, acetylcholine; CNS, central nervous system; NO, nitric oxide.

Načini komunikacij v OŽ

Oblika	Fazičen	Toničen
Razdalja	2-50 nm	μm - mm
Čas	μsek - msek	msek - min
Prenašalci	Ioni, hitri prenašalci	Nevromodulatorji, hormoni
Konc. prenašalca	μM - mM	nM
Afiniteta receptorja	nM - μM	pM - nM
Zamik odgovora	msek	min

Povezave receptorjev z ionskimi kanali



Source: Katzung BG: *Basic & Clinical Pharmacology*, 10th Edition:
http://www.accessmedicine.com

Mediatorji v OŽ

Kriteriji za določitev mediatorja:

- Prisotnost v presinaptičnih končičih in v nevronu, iz katerega izhajajo
- Sproščanje mediatorja ob živčni aktivnosti
- Učinek dodanega mediatorskega kandidata $\Rightarrow$ enak učinku stimulacije presinaptične poti
- Antagonisti
- Težave pri aplikaciji teh kriterijev v OŽ:
  - številne sinapse v neposredni bližini in zapletene povezave
  - veliko število različnih mediatorjev

Metode za študij mediatorjev in njihove vloge v OŽ

- Klasična: vplivi destrukcije dol. predelov na delovanje transmitorskih kandidatov / vedenjski modeli/ (denervation supersensitivity)
- Histo-, citokemija (dokaz encimov za sint. in razgr.) fluoresc. $\Rightarrow$ kateholamini
- Mikroiontoforeza
- IC, EC registracija sprememb potencialov
- Merjenje prevodnosti za določene ione
- Metode molekularne biologije:
  - in situ hibridizacija: R, E za sintezo
  - transfekcija različnih nevronov
  - transgene poskusne živali (brez določenih R ali E)
- ESR, PET
- Modeli patoloških stanj na poskusnih živalih
- Problemi – akutni poskusi – realnost ?

VRSTE MEDIATORJEV

Kriteriji: efekt na postsinaptični membrani, način in mesto sproščanja in način prenosa

- NEVROTRANSMITORJI (nevromediatorji) izrazita sprememba v potencialu postsinaptične membrane
- NEVROMODULATORJI - snovi, ki same ne spremene (ali le malo) prevodnosti ali potenciala membrane
- (NEVRO)HORMONI (lokalni krvni obtok)
- NEVROTROFIČNI FAKTORJI – vpliv na metabolizem nevronov

NEVROMODULATORJI

Zmanjšanje ali povečanje odgovora na klasične nevrotransmitorje

- polipeptidi (konkomitantno sproščanje s klasičnimi mediatorji)
  - Snov P - SP
  - Vazoaktivni intestinalni polipeptid - VIP
  - Holecistokinin - CCK
  - Nevropeptid Y - NPY
  - Polipeptid, povezan z genom za kalcitonin (Calcitonin gene related polypeptide – CGRP)
- Adenosin
- Prostaglandini
- NH_4
- NO, CO
- CO_2

Številni delujejo kot samostojni nevrotransmitorji

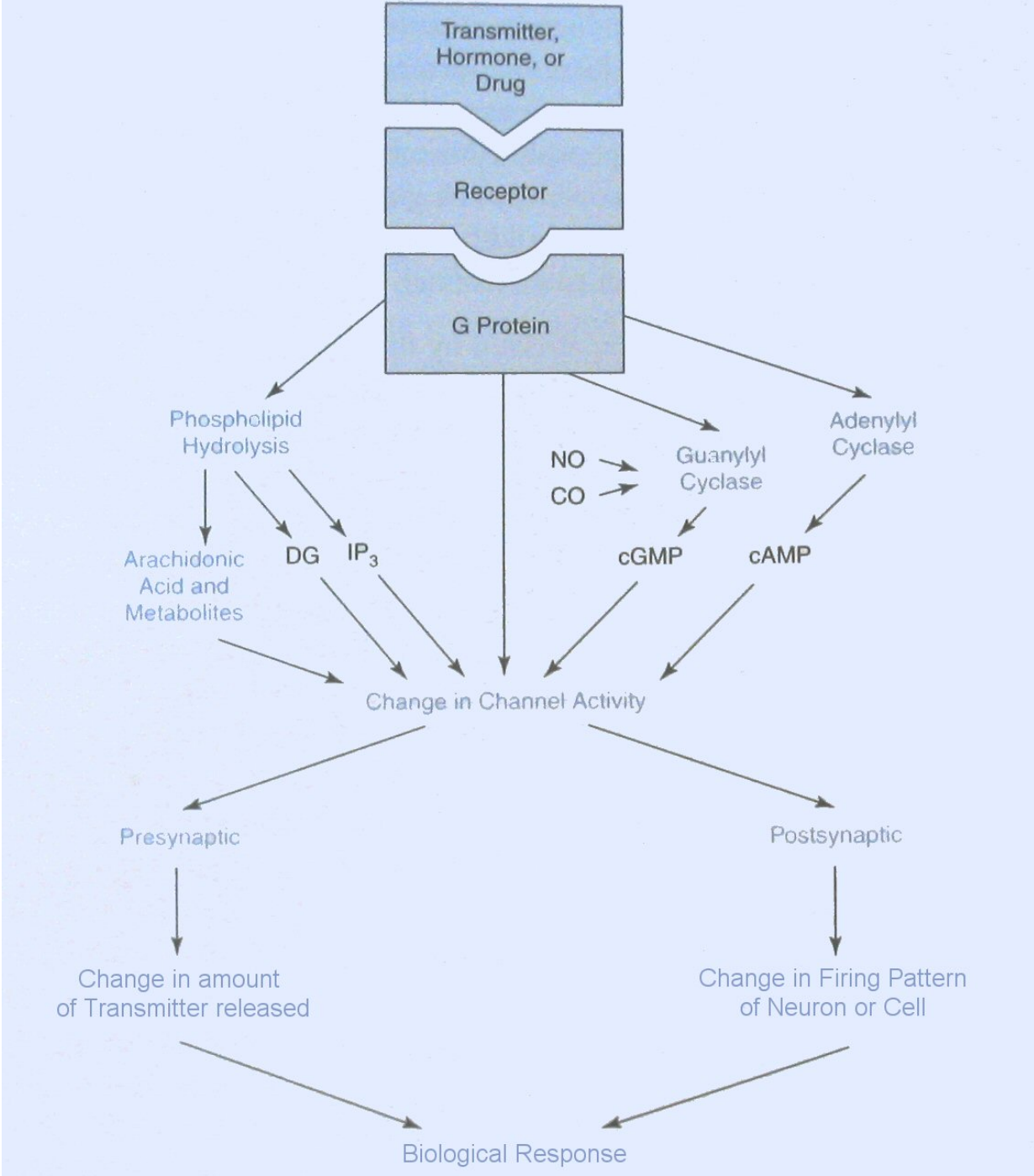
Prenašalci v OŽ

- **Dale-ov princip:** En nevron, en prenašalec
- **Hoeckfeldov princip:** En nevron, več prenašalcev

Primeri hkratnega prenosa (kotransmisije) v OŽ

Glavni tranmitor	Kotransmitor	Lokalizacija
GABA	somatostatin	skorja, hipokampus
	holecistokinin	skorja
Acetilholin	VIP	skorja
	snov P	pons
Noradrenalin	nevropeptid Y	med. oblongata, pons
	nevrotenzin	locus coeruleus
Dopamin	holecistokinin nevrotenzin	ventrotegmentalno jedro
Serotonin	snov P, TRH enkefalini	jedra raphe

Modulacija sinaptičnega prenosa



Mediatorji v OŽ

Transmitter	Anatomy	Receptor Subtypes and Preferred Agonists	Receptor Antagonists	Mechanisms
Acetylcholine	Cell bodies at all levels; long and short connections	Muscarinic (M_1): muscarine	Pirenzepine, atropine	Excitatory: ↓ in K^+ conductance; ↑ IP_3, DAG
		Muscarinic (M_2): muscarine, bethanechol	Atropine, methoctramine	Inhibitory: ↑ K^+ conductance; ↓ cAMP
	Motoneuron-Renshaw cell synapse	Nicotinic: nicotine	Dihydro-β-erythroidine, α-bungarotoxin	Excitatory: ↑ cation conductance
Dopamine	Cell bodies at all levels; short, medium, and long connections	D_1	Phenothiazines	Inhibitory (?): ↑ cAMP
		D_2: bromocriptine	Phenothiazines, butyrophenones	Inhibitory (presynaptic): ↓ Ca^{2+}; Inhibitory (postsynaptic): ↑ in K^+ conductance, ↓ cAMP
GABA	Supraspinal and spinal interneurons involved in pre- and postsynaptic inhibition	$GABA_A$: muscimol	Bicuculline, picrotoxin	Inhibitory: ↑ Cl^- conductance
		$GABA_B$: baclofen	2-OH saclofen	Inhibitory (presynaptic): ↓ Ca^{2+} conductance Inhibitory (postsynaptic): ↑ K^+ conductance

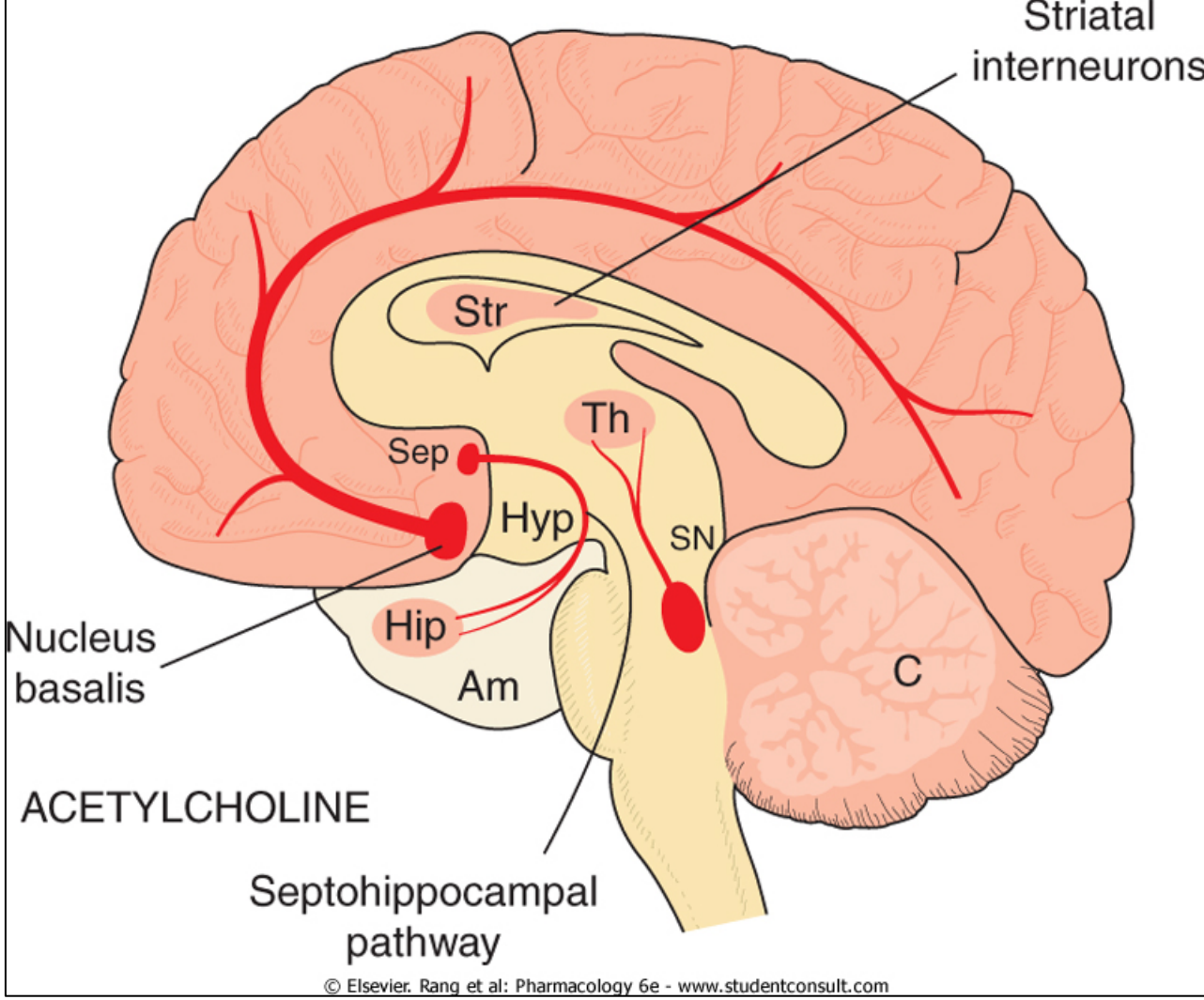


Figure 34-7 Acetylcholine pathways in the brain. Am, amygdaloid nucleus; C, cerebellum; Hip, hippocampus; Hyp, hypothalamus; LC, locus coeruleus; MFB, medial forebrain bundle; NTS, nucleus of the tractus solitarius (vagal sensory nucleus); RF, brain stem reticular formation; Sep, septum; SN, substantia nigra; Str, corpus striatum; Th, thalamus.

Acetilholin - 1

- Sinteza: iz holina in AcCoA (holinacetiltransferaza)
- Holin se v nevron privzema. Inhibitorja privzema: hemiholinium in vezamikol
- Skladiščenje: vezikli inhibitor: vezamikol
- Sproščanje:
  - Stimulacija: α-latrotoksin
  - Inhibicija: Botulinus toksin, tetanus toksin
  - Razgradnja: z AChE (holin in acetat)

Acetilholin - 2

- **Receptorji:**
- **Nikotinski (ionski kanali) – avtonomni gangliji**
- **Muskarinski M1, M2, M3, M4, M5 (sklopljeni z G-proteini)**
- **M1, M3, M5 – G_q**
- **M2, M4 – G_i**

- **M1,M2,M4 skorja, hipokampus**
- **M1, M4 striatum**
- **M2 sprednji del možganske baze**
- **M5 difuzno po CŽS, vendar jih je zelo malo**

Zdravila, ki učinkujejo v holinergični sinapsi

- **Sproščanje: botulinus toksin**
- **Inaktivacija: zaviralci acetiholinesteraze**
- **Mb. Parkinson (muskarinski antagonisti), Mb. Alzheimer (↑ tonus Ach: M1 agonisti – ksanomelin) inh. AChE: takrin, donepezil, galantamin)**

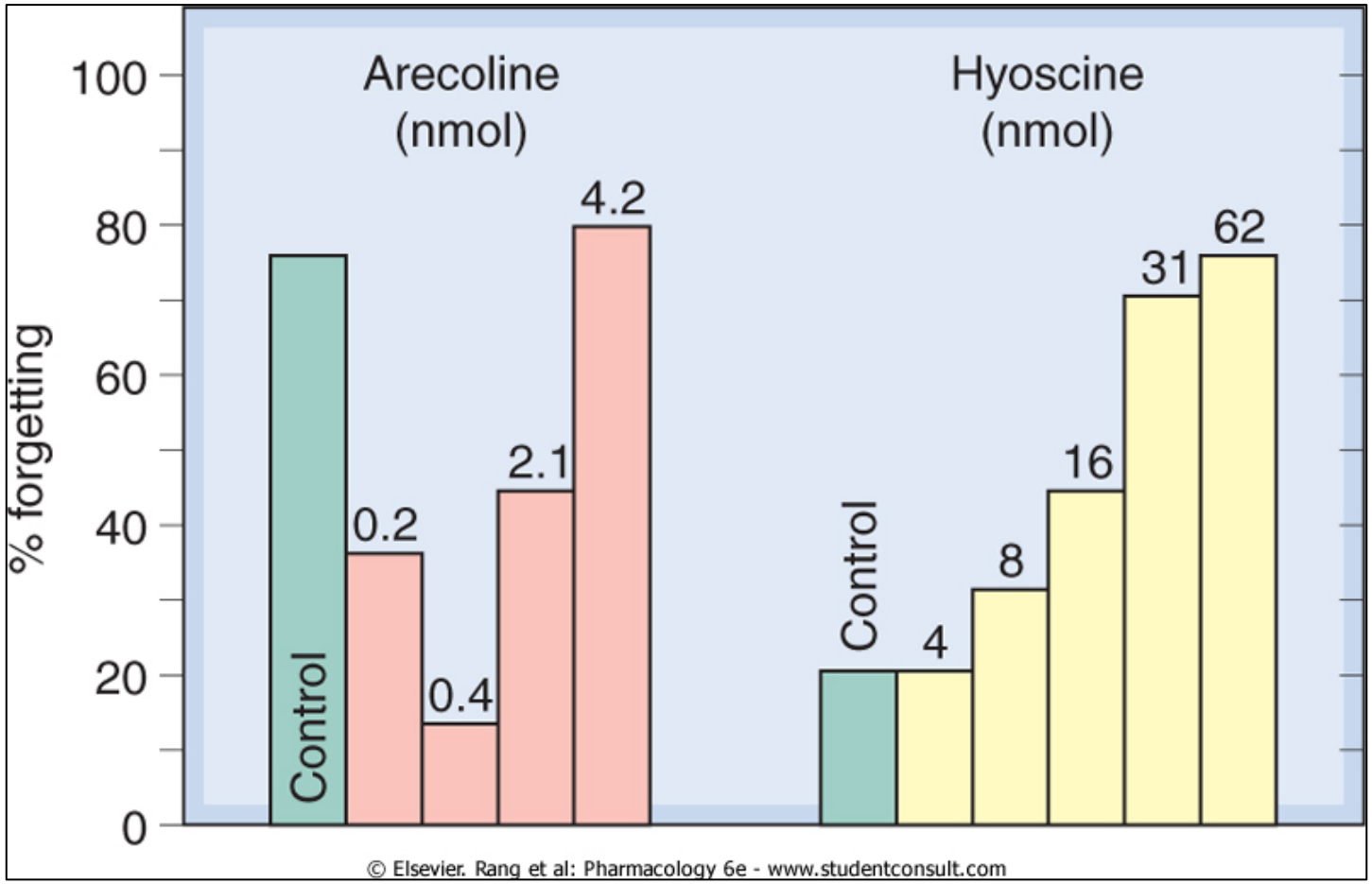


Figure 34-8 Effect of arecoline and hyoscine on learning. Mice were trained to perform a behavioural feat in order to avoid an electric shock, and tested for their ability to remember it 7 days later. Mice in the group that performed least well (left) were given the cholinergic agonist arecoline by intracerebroventricular injection; at low doses, their performance improved markedly, but at higher doses their performance declined. Animals in the group that performed best in the initial test were given the muscarinic receptor antagonist hyoscine, which caused a deterioration of their performance. (From Flood J F, Landry D W, Jarvik M E et al, 1981 Brain Res 215: 177-185.)

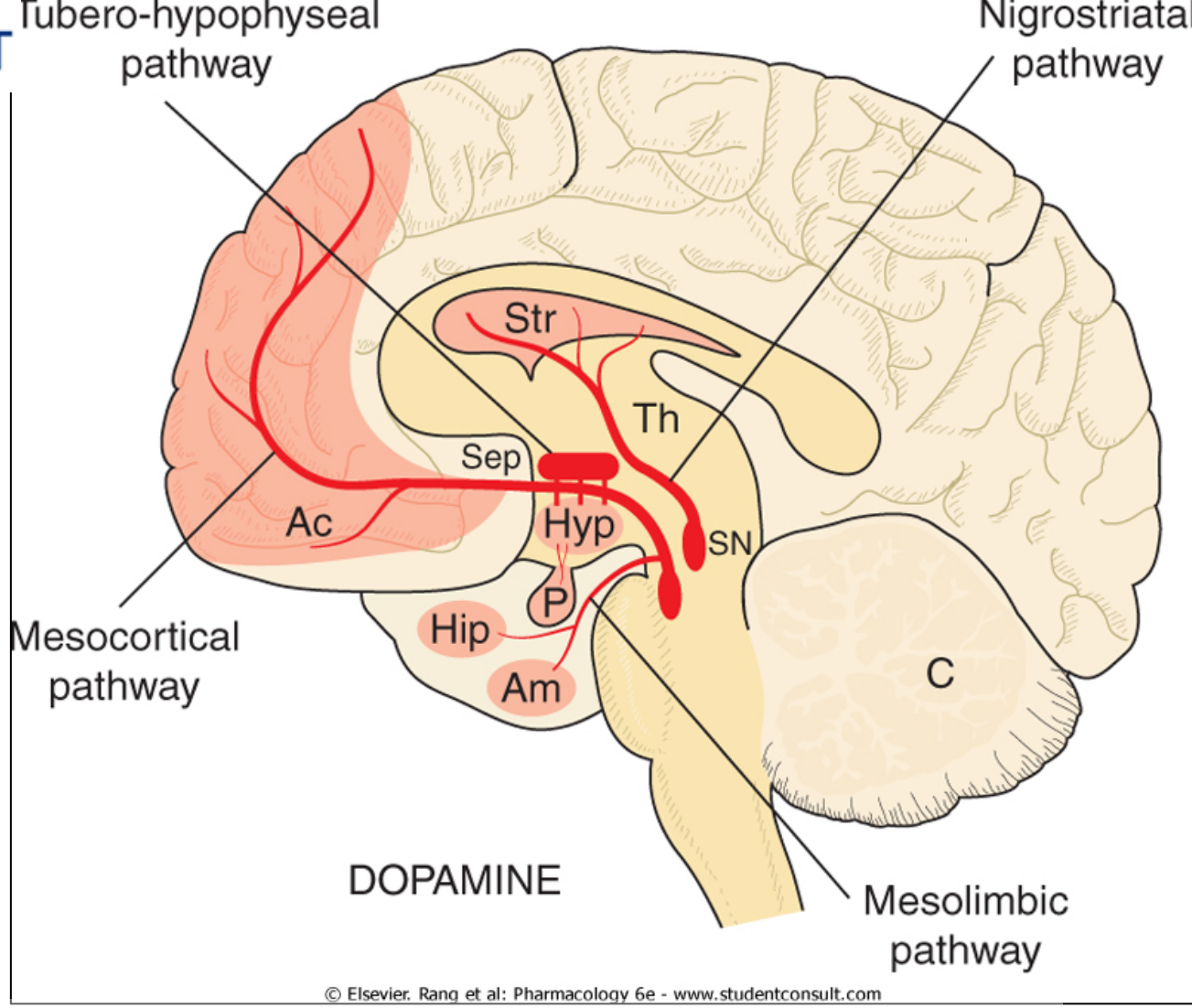


Figure 34-3 Dopamine pathways in the brain. The pituitary gland (P) is shown, innervated with dopaminergic fibres from the hypothalamus. Ac, nucleus accumbens; Am, amygdaloid nucleus; C, cerebellum; Hip, hippocampus; Hyp, hypothalamus; LC, locus coeruleus; MFB, medial forebrain bundle; NTS, nucleus of the tractus solitarius (vagal sensory nucleus); RF, brain stem reticular formation; Sep, septum; SN, substantia nigra; Str, corpus striatum; Th, thalamus.

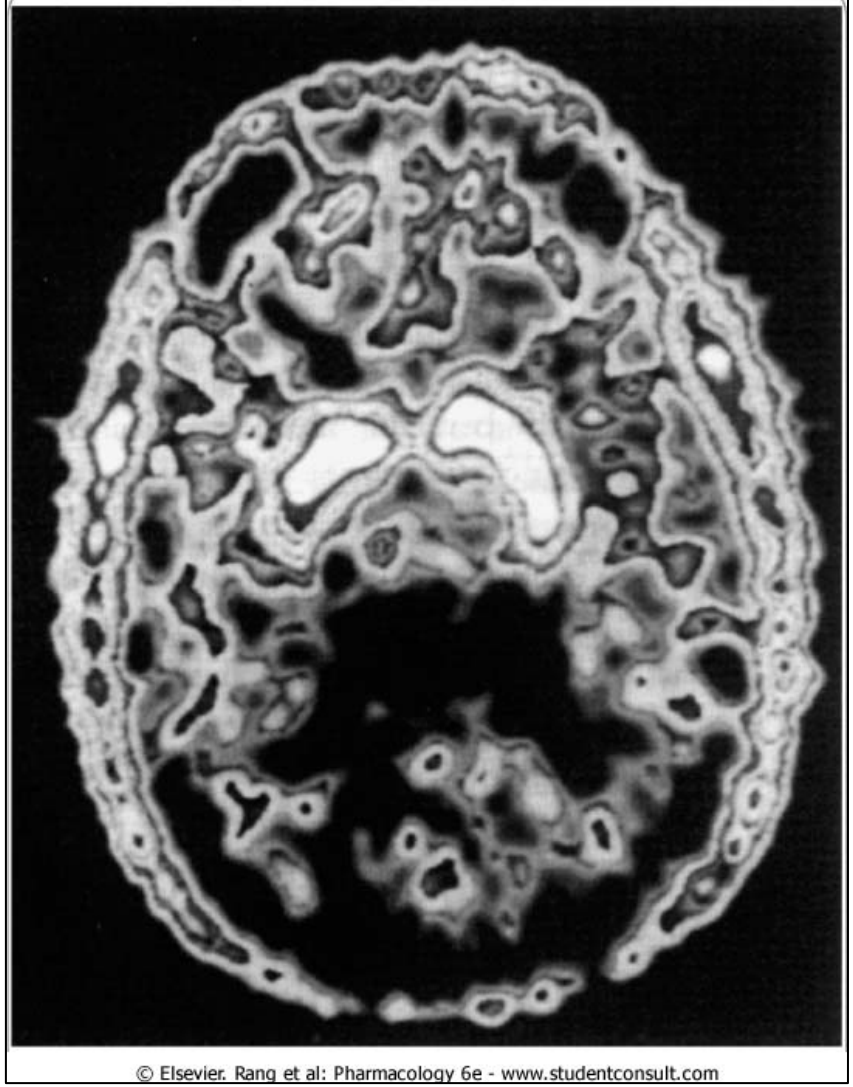


Figure 34-4 Dopamine in the basal ganglia of a human subject. The subject was injected with 5-fluoro-dopa labelled with the positron-emitting isotope 18F, which was localised 3 hours later by the technique of positron emission tomography. The isotope is accumulated (white areas) by the dopa uptake system of the neurons of the basal ganglia, and to a smaller extent in the frontal cortex. It is also seen in the scalp and temporalis muscles. (From Garnett E S et al. Nature 305: 137.)

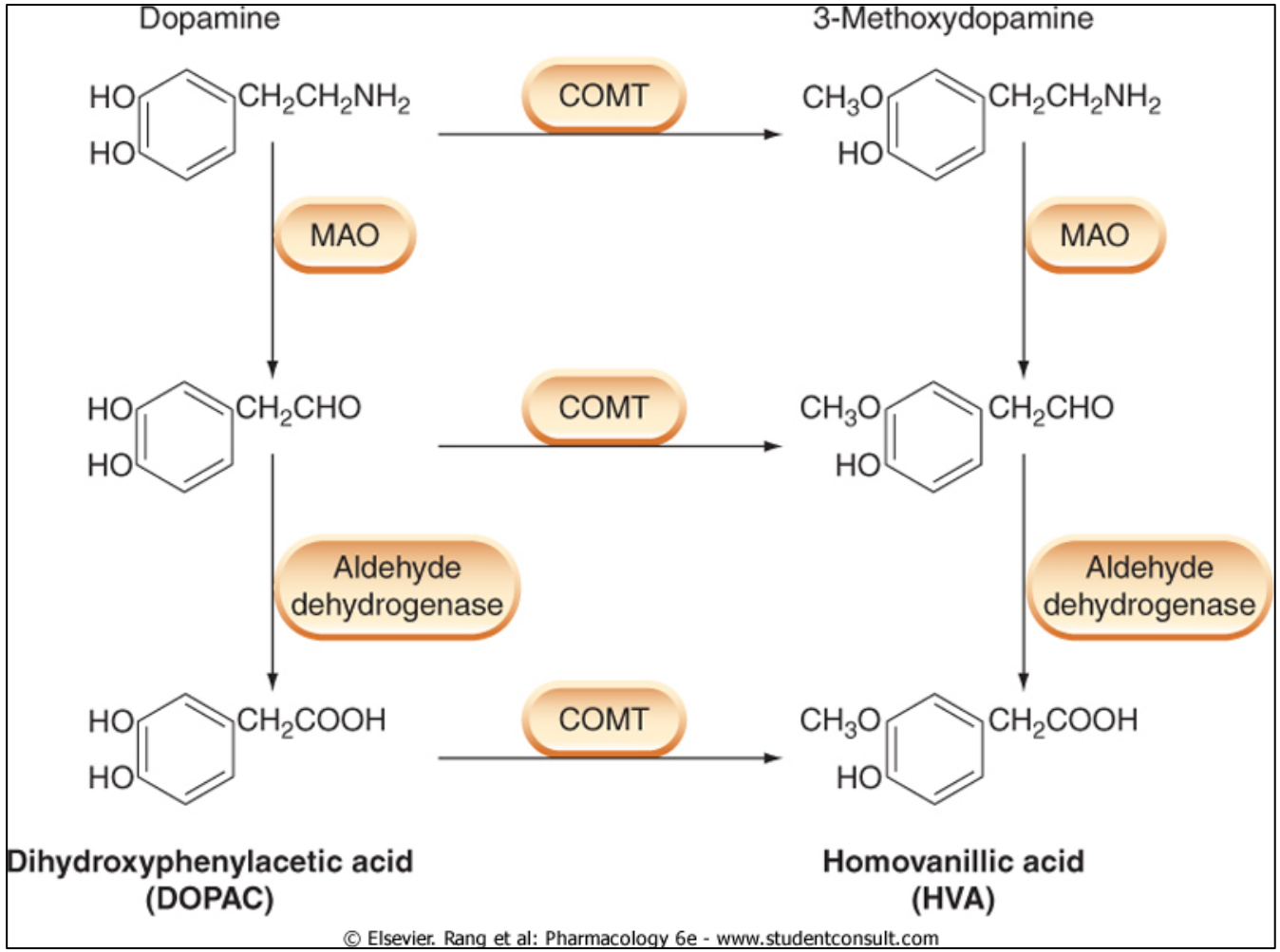


Figure 34-2 The main pathways for dopamine metabolism in the brain. COMT, catechol-O-methyl transferase; MAO, monoamine oxidase.

Dopamin- 1

- **Skladiščenje: vezikli VMAT**
  inhibitor: rezerpin

- **Sproščanje:**
  - **Ca, receptorji (D2, D3, D4)**
  - **Zdravila: amfetamin, amantadin**

- **Razgradnja: MAO- B, COMT**
- **Zdravila: inhibitorji MAO-B (selegilin), inhibitorji COMT (entokapon, tokapon)**

Dopamin - 2

- **Receptorji:**
- **D1,D2, D3, D4, D5**
- **D1, D5: ↑cAMP**
- **D2, D3, D4: ↓ cAMP**

- **DA agonisti: apomorfin, bromokriptin, miraplexin**

- **DA antagonisti: nevroleptiki**

- **Privzem – DAT**

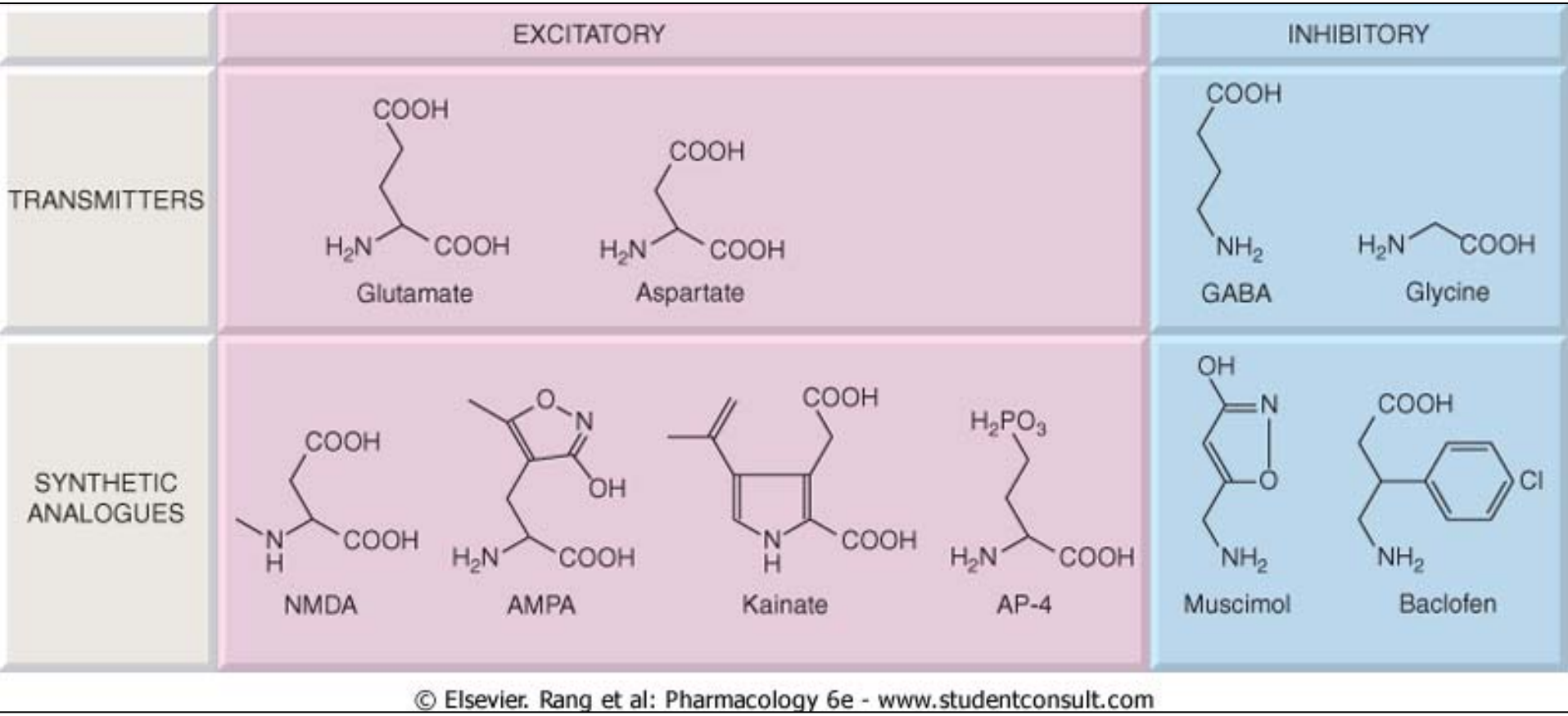


Figure 33-3 Structures of agonists acting on glutamate, GABA and glycine receptors. The receptor specificity of these compounds is shown in Tables 33.1 and 33.2. AP-4, 3-amino-4-phosphonopentanoic acid. AMPA, α amino-3-hydroxy-5-methylisoxazole-4-propianic acid; NMDA, N-methyl-D-asparatic acid.

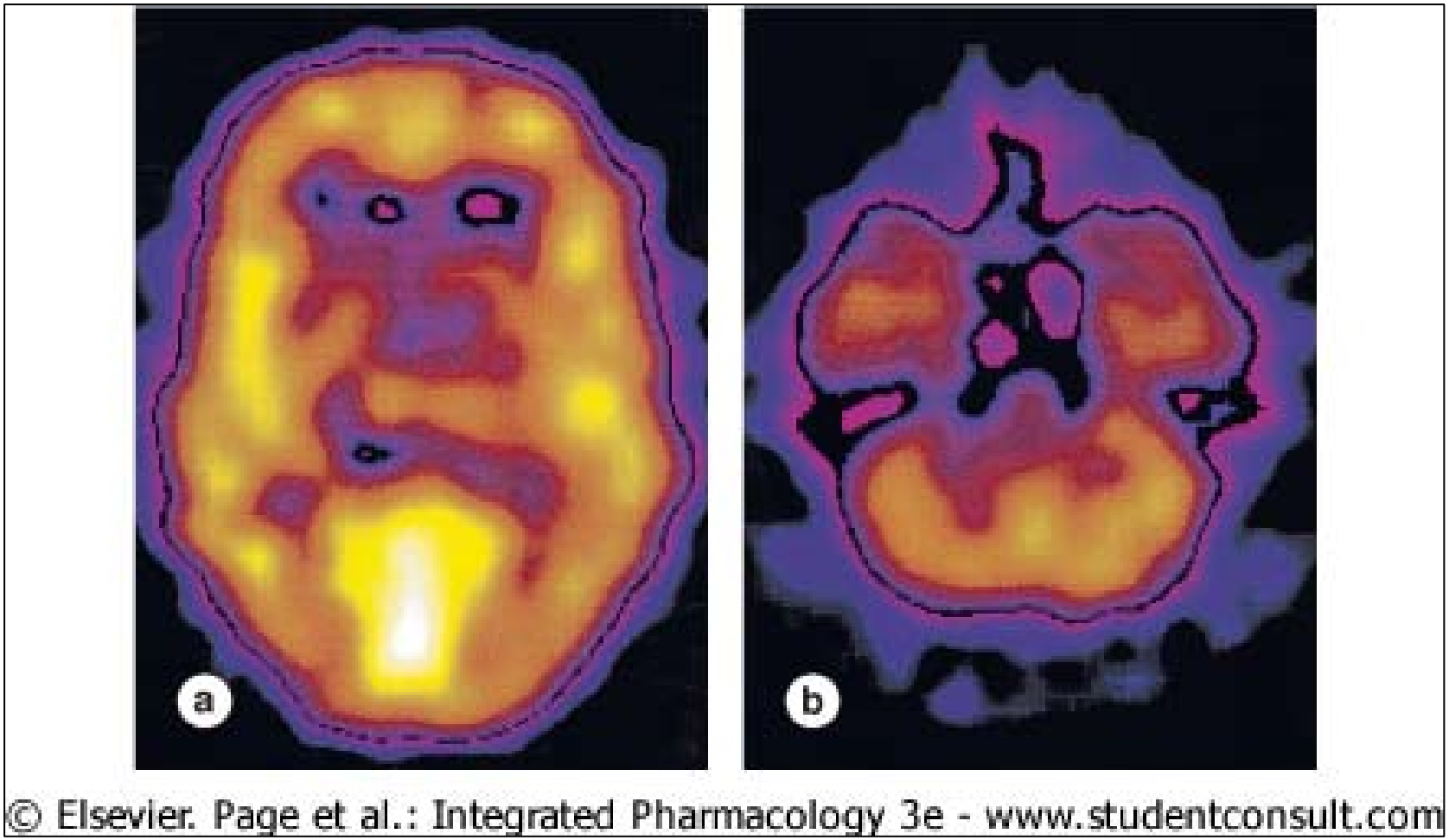
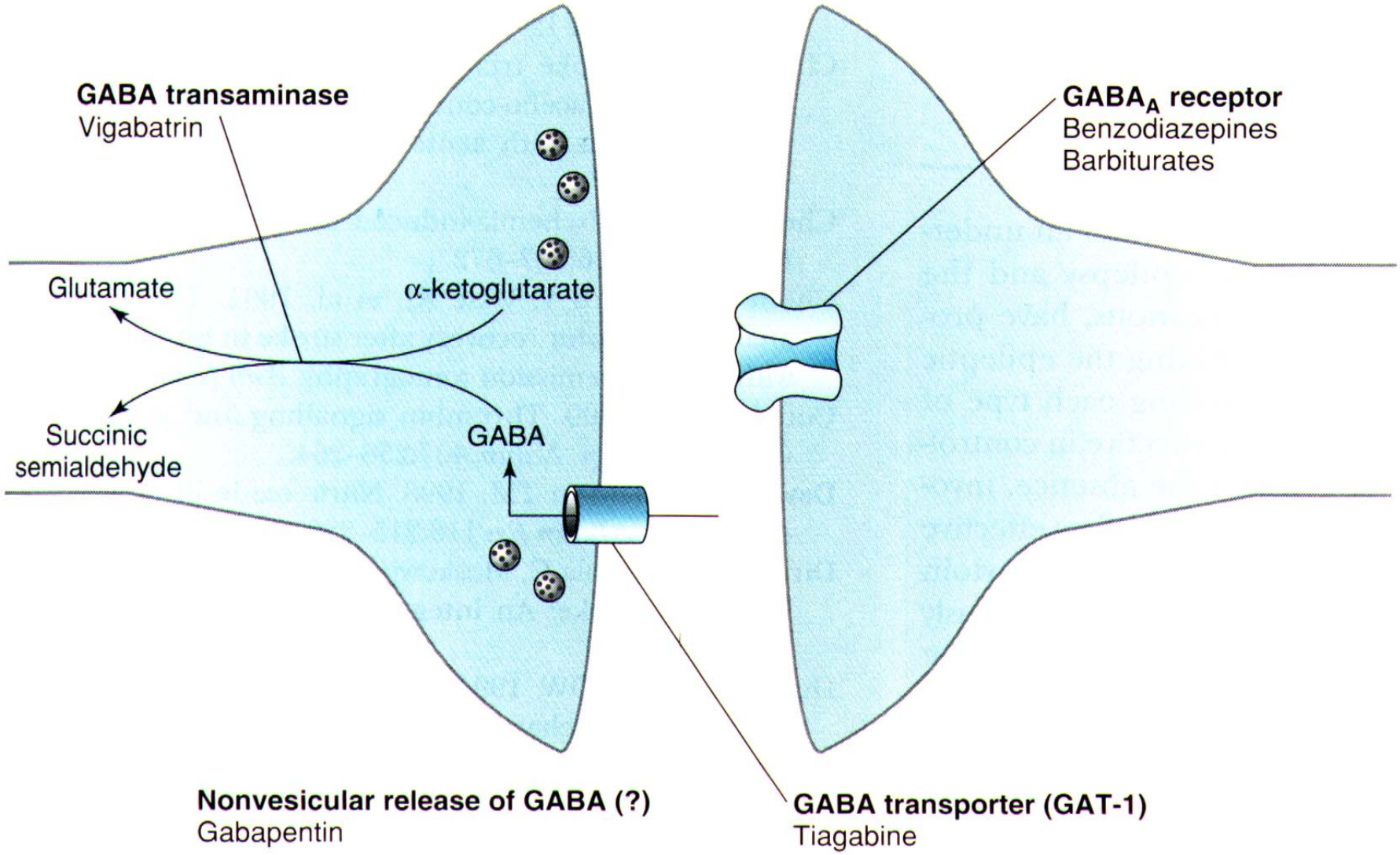


Figure 8.25 The cortical distribution of $GABA_A$ receptor complexes. This is shown using a radioactively labeled benzodiazepine analog lomazenil and single-photon emission tomography (SPET). The brightest areas have the highest density of receptors. (a) An image at the level of the midoccipital cortex. (b) The image at the level of the cerebellum.


GABA transaminase
Vigabatrin
GABA$_A$ receptor
Benzodiazepines
Barbiturates
Glutamate
α-ketoglutarate
Succinic semialdehyde
GABA
Nonvesicular release of GABA (?)
Gabapentin
GABA transporter (GAT-1)
Tiagabine

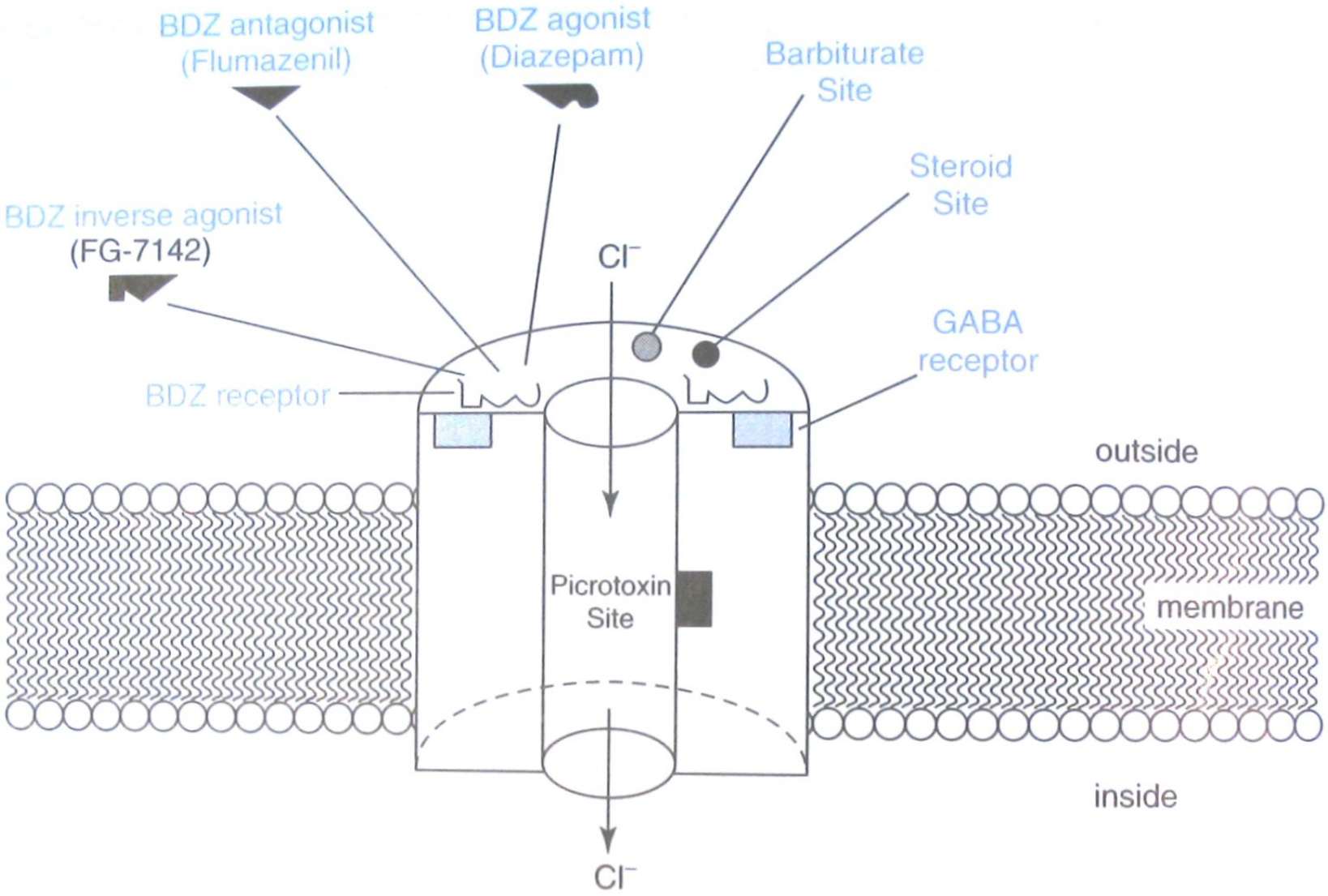


FIGURE 6–3. Schematic illustration of the $GABA_A$ receptor complex and the sites of action of different agents on the receptor. BDZ, benzodiazepine.

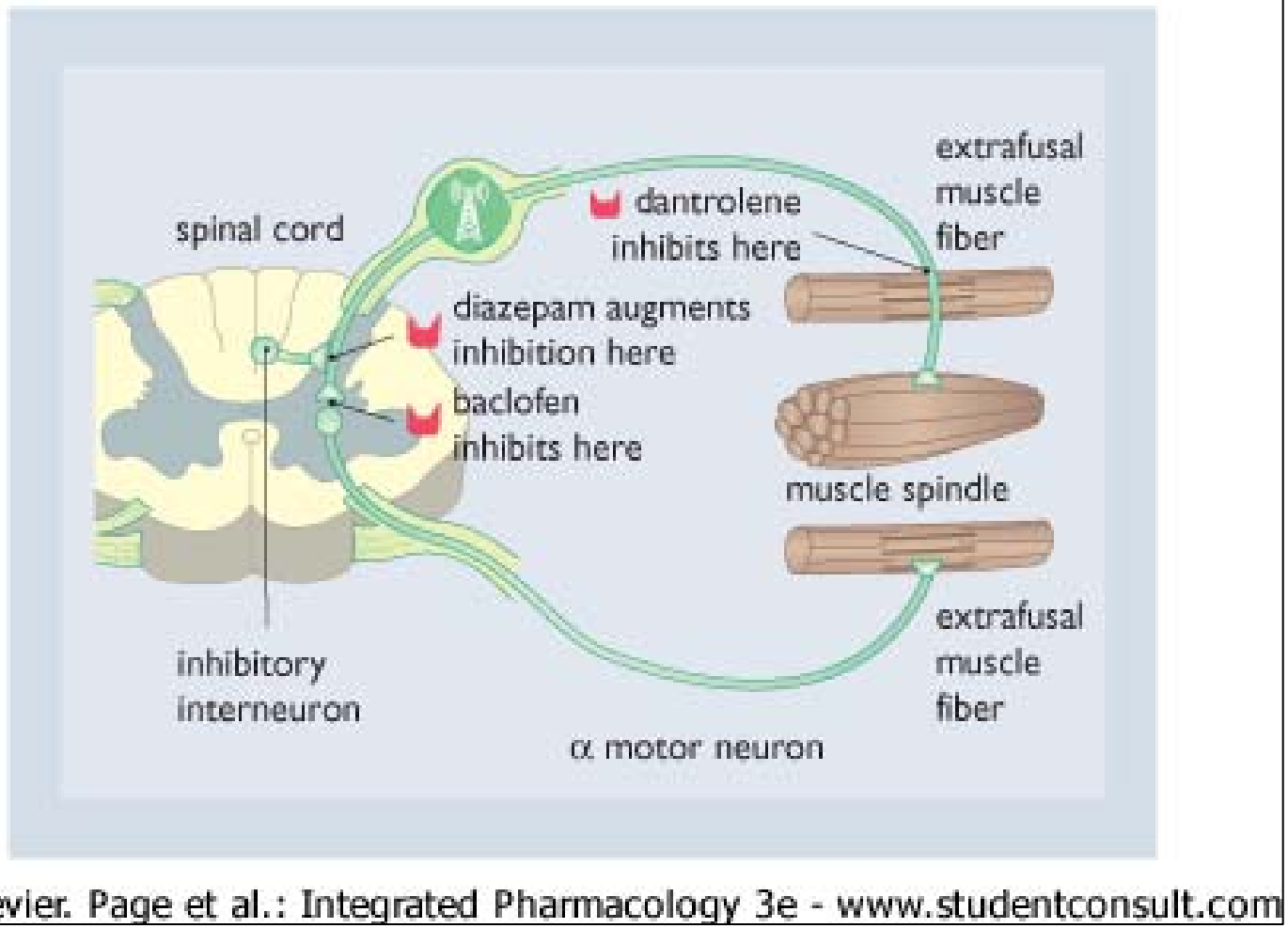


Figure 8.17 The neuronal pathway that contributes to the development of clonus in spasticity is inhibited by diazepam and baclofen. Stretching the muscle activates the IA afferents from the muscle spindle and sends a flood of impulses to the α motor neuron, triggering contraction of the muscle. This relieves the tension on the spindle and terminates activity in the afferents. However, when the muscle relaxes, the tension on the spindle returns because the sensitivity of the reflex is increased in spasticity and the cycle of events is repeated, giving rise to clonus.

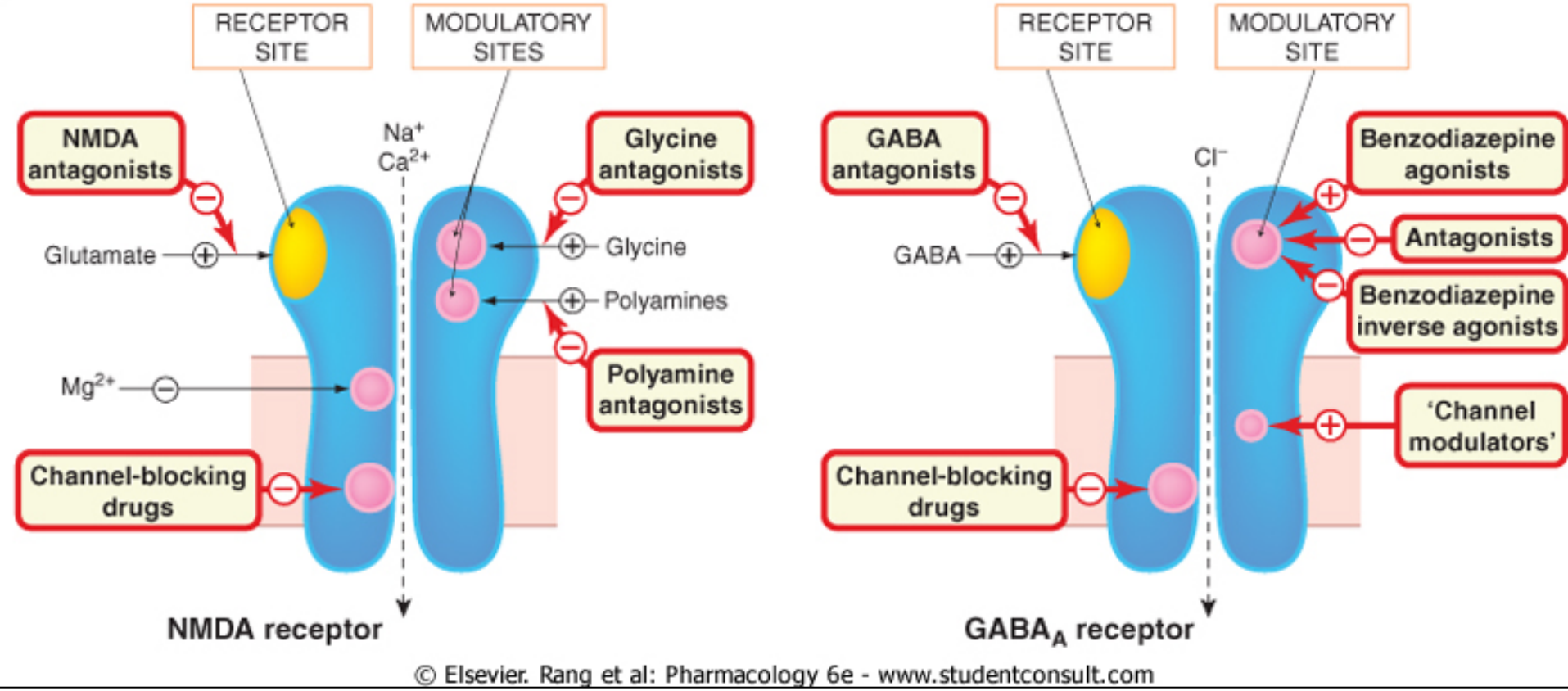
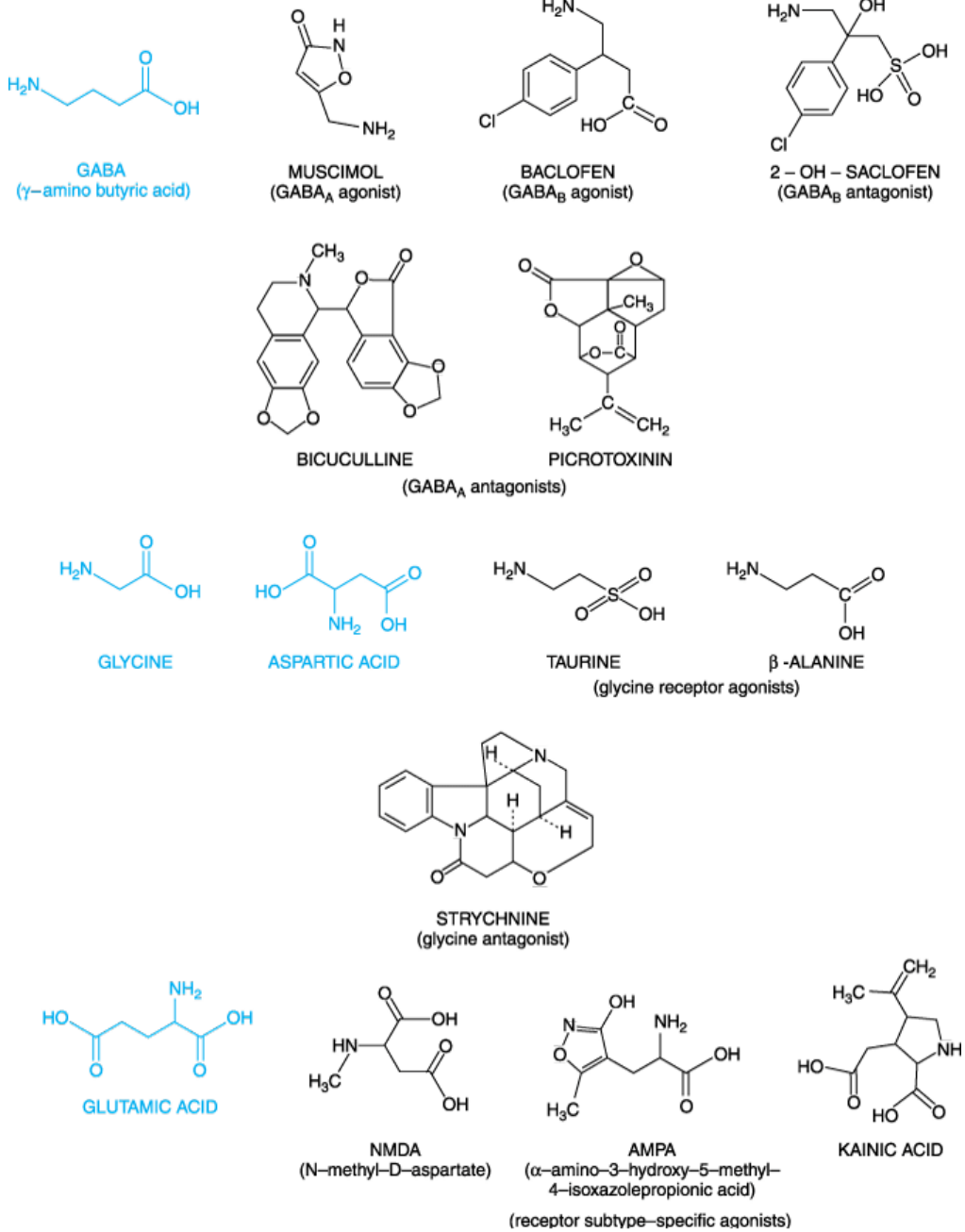


Figure 33-4 Main sites of drug action on NMDA and GABAA receptors. Both receptors are multimeric ligand-gated ion channels. Drugs can act as agonists or antagonists at the neurotransmitter receptor site or at modulatory sites associated with the receptor. They can also act to block the ion channel at one or more distinct sites. In the case of the GABAA receptor, the mechanism by which 'channel modulators' (e.g. ethanol, anaesthetic agents) facilitate channel opening is uncertain; they may affect both ligand binding and channel sites. The location of the different binding sites shown in the figure is largely imaginary, although study of mutated receptors is beginning to reveal where they actually reside. Examples of the different drug classes are given in Tables 33.1 and 33.2.

Transmitter	Anatomy	Receptor Subtypes and Preferred Agonists	Receptor Antagonists	Mechanisms
Glutamate	Relay neurons at all levels and some interneurons	*N*-Methyl-D-aspartate (NMDA): NMDA	2-Amino-5-phosphonovalerate, dizocilpine	Excitatory: ↑ cation conductance, particularly Ca^{2+}
		AMPA: AMPA	CNQX	Excitatory: ↑ cation conductance
		Kainate: kainic acid, domoic acid		
		Metabotropic: ACPD, quisqualate	MCPG	Inhibitory:(presynaptic) ↓Ca^{++} conductance ↓cAMP Excitatory: ↓K^{+} conductance, ↑IP_3 , DAG

Struktura različnih agonistov v OŽ



Glutamat - 1

- **Sinteza: iz glutamina ali aspartata**
- **Skladiščenje: vezikli VGLU1**
- **Sproščanje:**
  - **Ca, receptorji (mGluR2 ali mGluR3)**
- **Razgradnja: difuzija, privzem: GLAST, GLT-1, EAAT1, EAAT2, EAAT3, EAAT4, EAAT5**

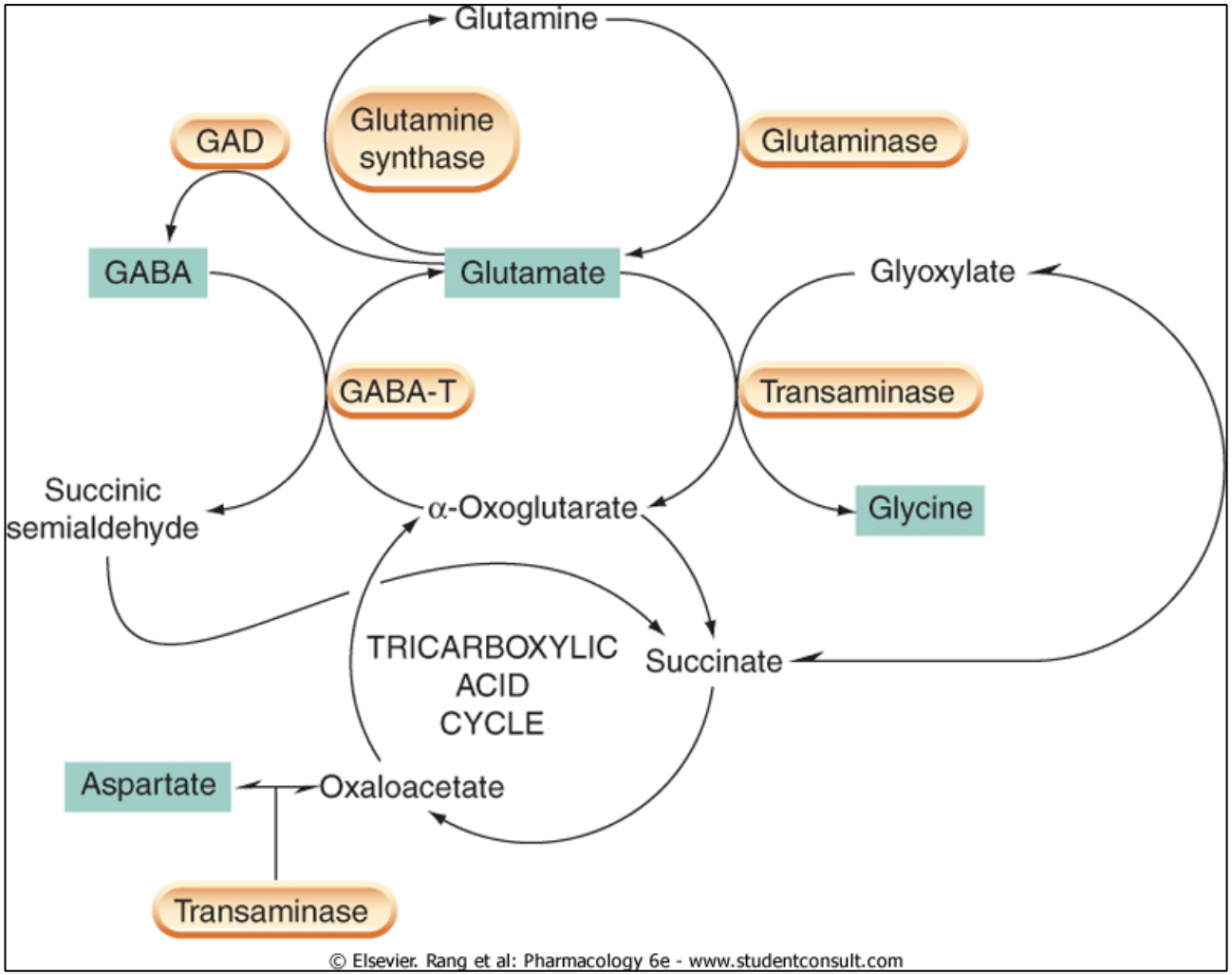
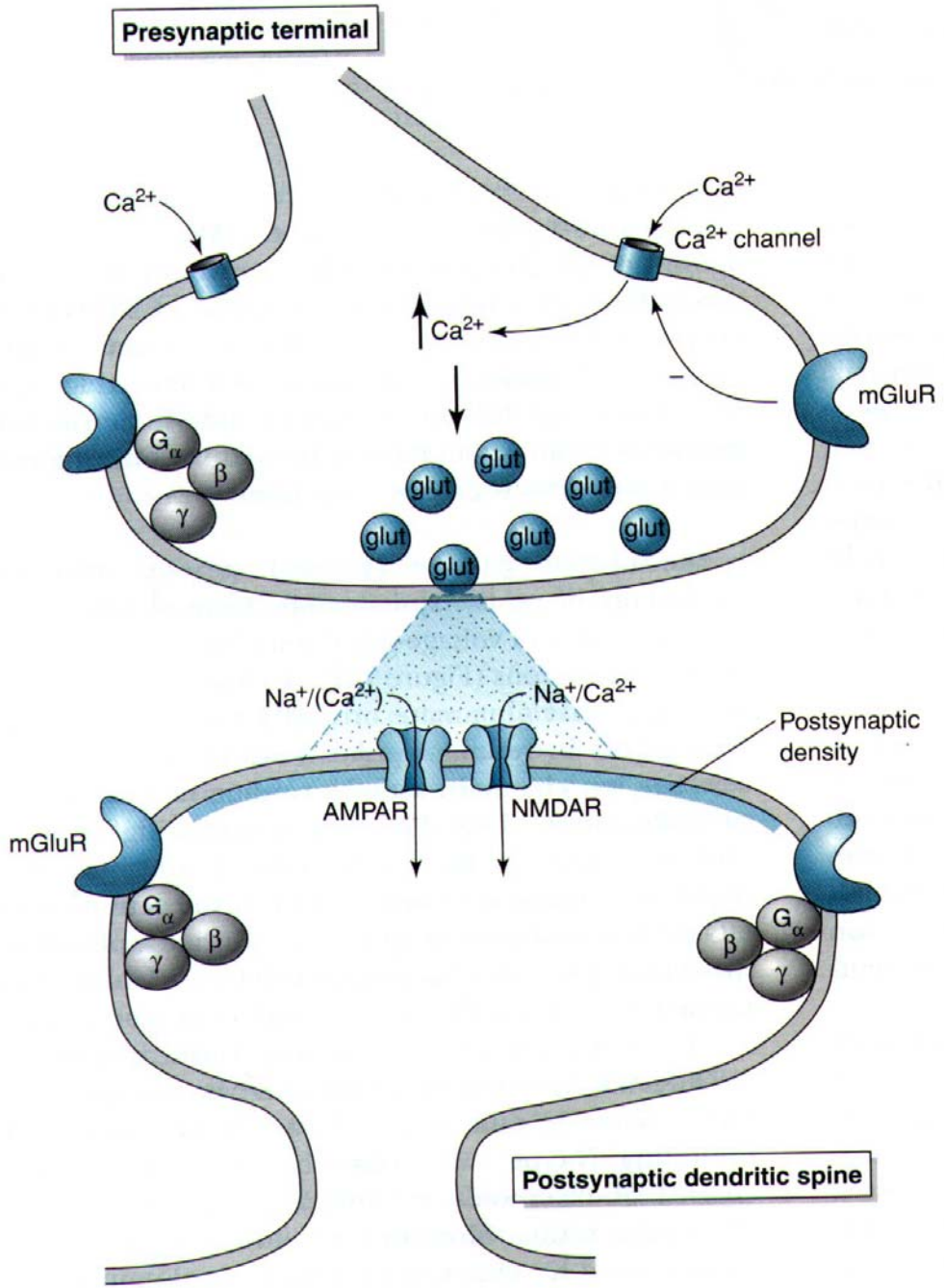


Figure 33-1 Metabolism of transmitter amino acids in the brain. Transmitter substances are marked with green boxes. GABA-T, GABA transaminase; GAD, glutamic acid decarboxylase.

Glutamat - 2

- **Receptorji:**
- **mGluR 1-8 (**metabotropni R)
- **KA1-2,**
- **NMDA, AMPA**

- **Zdravila: amantadin, topiramat, memantin**


Presynaptic terminal
Ca2+
Ca2+
Ca2+ channel
Ca2+
mGluR
Gα
β
γ
glut
glut
glut
glut
glut
glut
glut
Na+/(Ca2+)
Na+/Ca2+
Postsynaptic density
AMPAR
NMDAR
mGluR
Gα
β
γ
Gα
β
γ
Postsynaptic dendritic spine

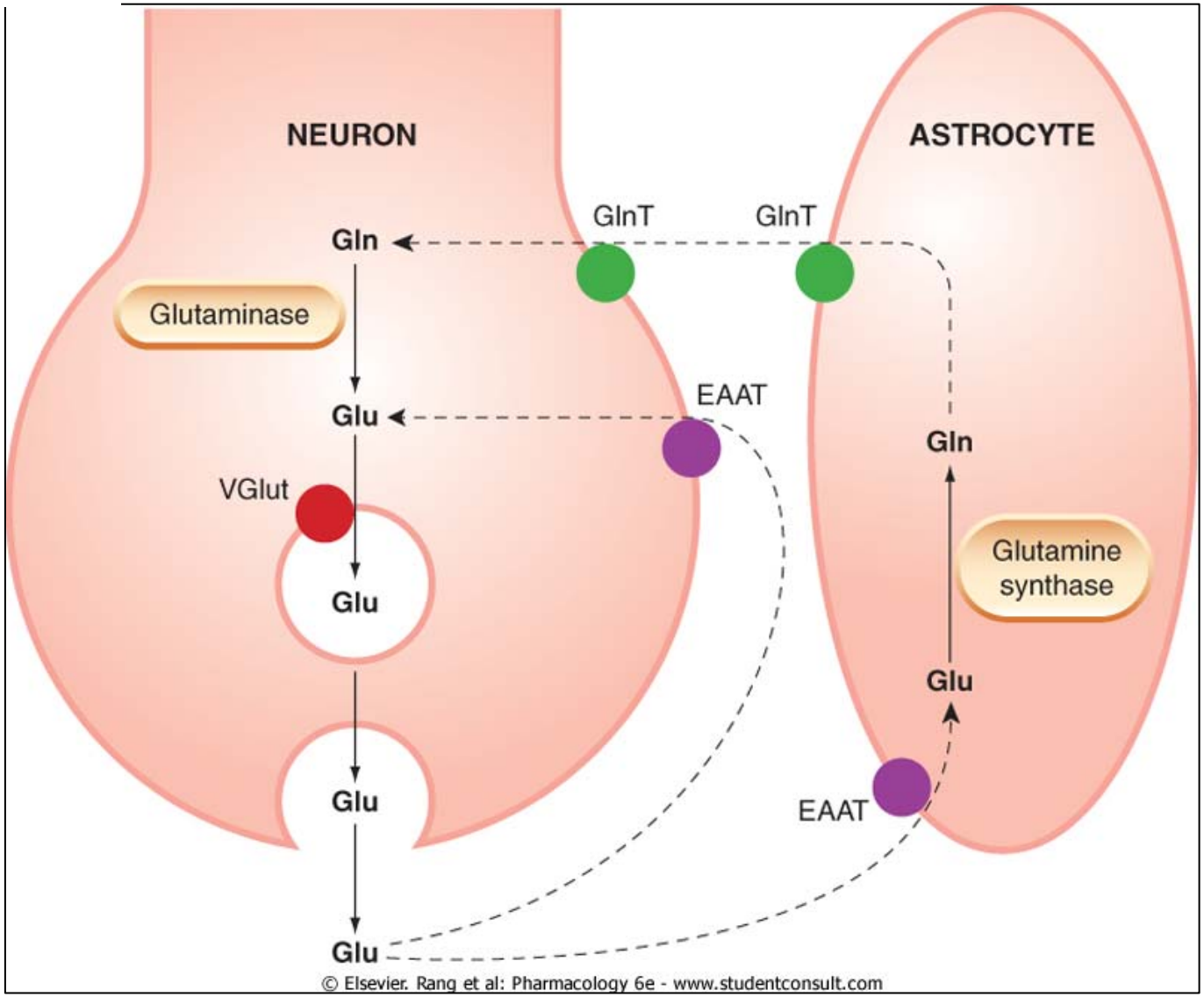
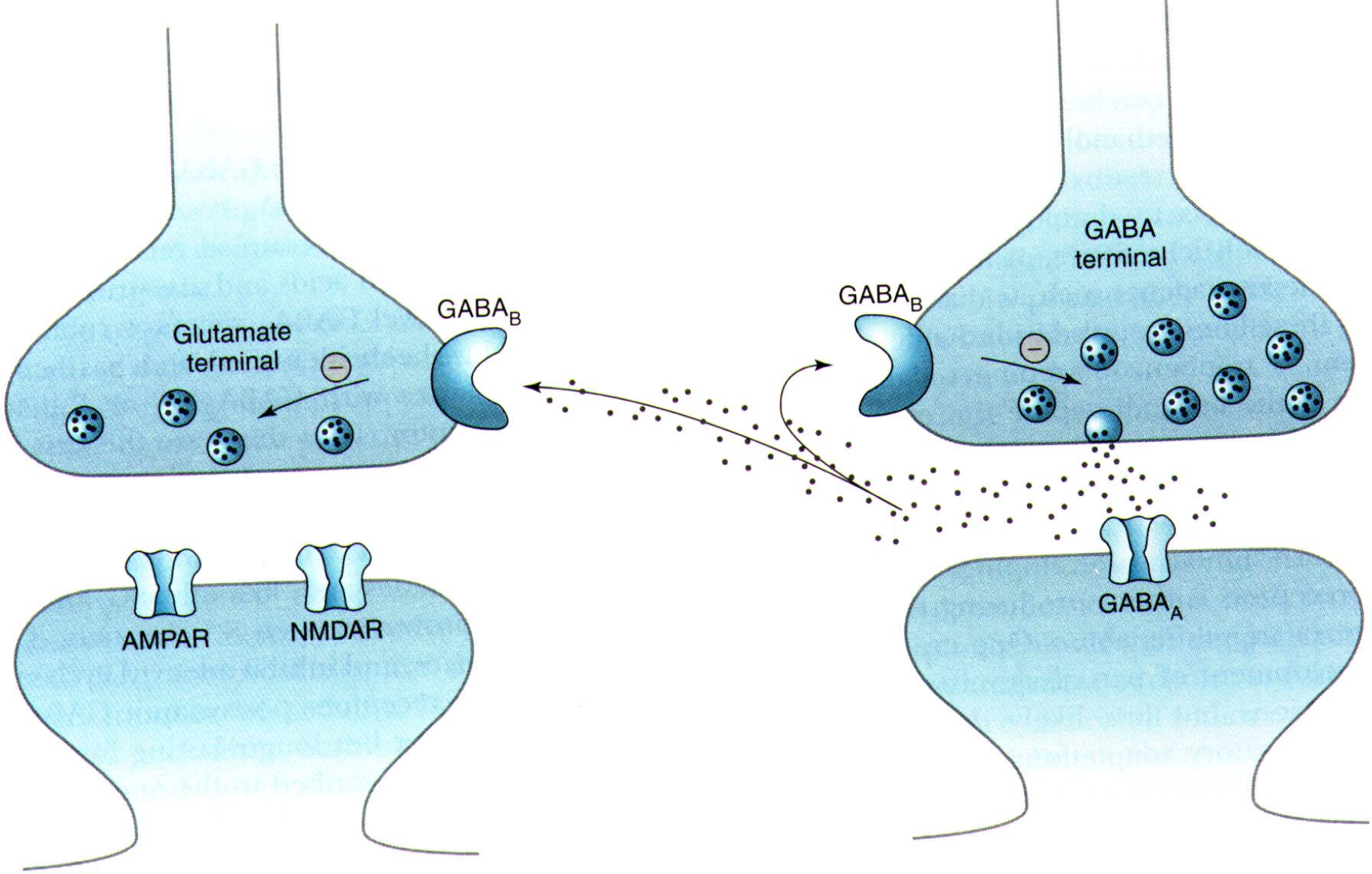


Figure 33-2 Transport of glutamate (Glu) and glutamine (Gln) by neurons and astrocytes. Released glutamate is captured partly by neurons and partly by astrocytes, which convert most of it to glutamine. EAAT, excitatory amino acid transporter; GlnT, glutamine transporter, VGluT, vesicular glutamate transporter.



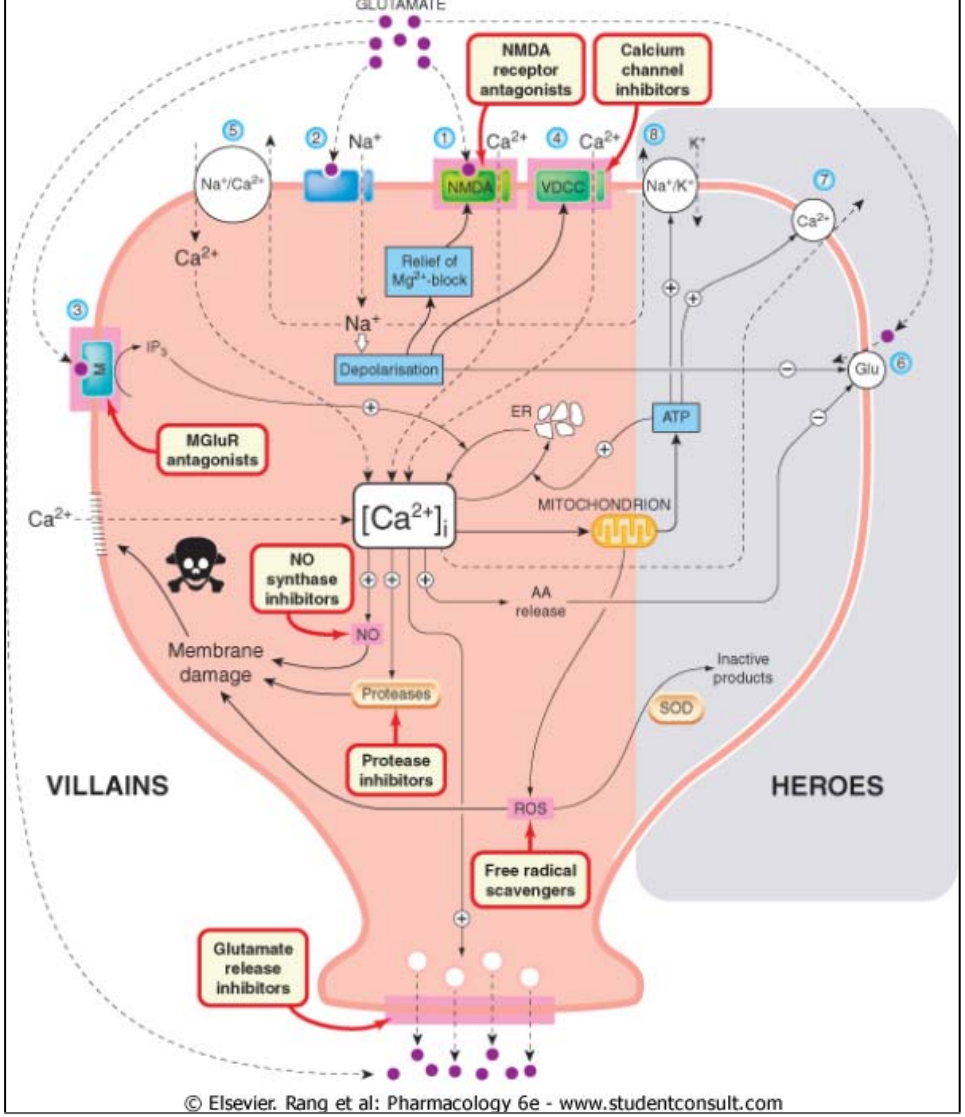
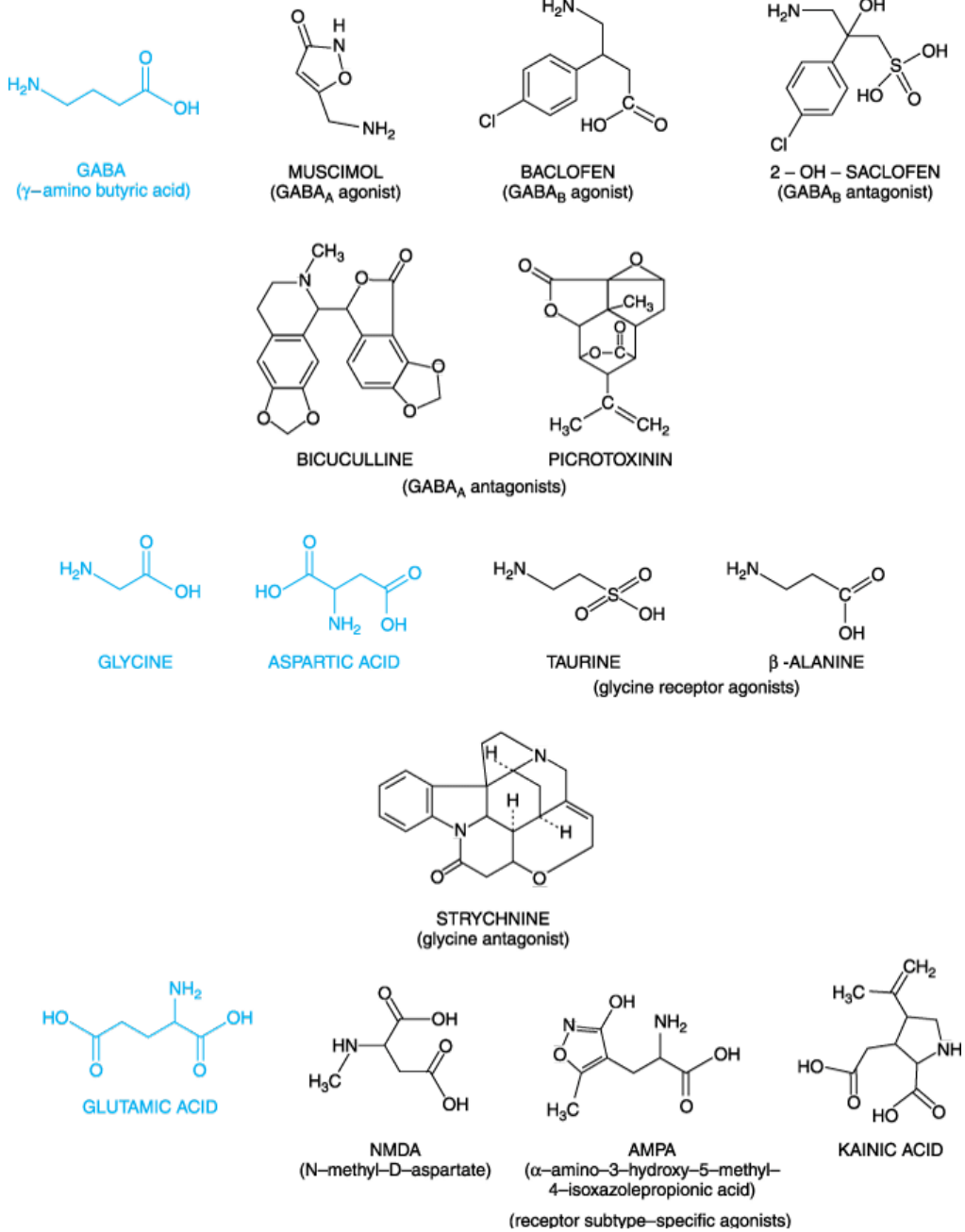


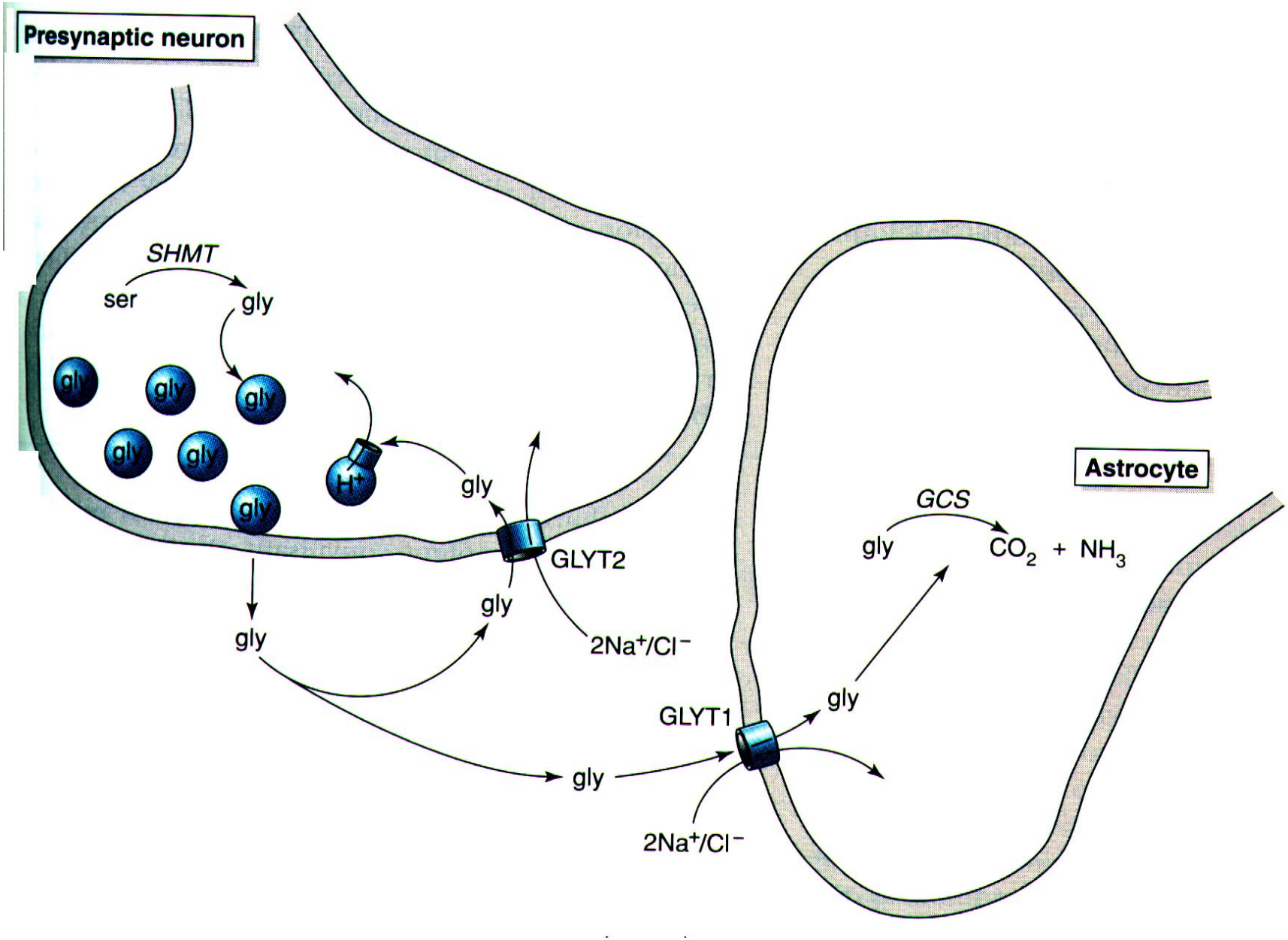
Figure 35-2 Mechanisms of excitotoxicity. Membrane receptors, ion channels and transporters, identified by numbers 1-8, are discussed in the text. Possible sites of action of neuroprotective drugs (not yet of proven clinical value) are highlighted. Mechanisms on the left (villains) are those that favour cell death, while those on the right (heroes) are protective. See text for details. AA, arachidonic acid; ER, endoplasmic reticulum; Glu, glutamate uptake; IP3, inositol trisphosphate; M, MGluR, metabotropic glutamate receptor; NO, nitric oxide; ROS, reactive oxygen species; SOD, superoxide dismutase; VDCC, voltage-dependent calcium channel.

Transmitter	Anatomy	Receptor Subtypes and Preferred Agonists	Receptor Antagonists	Mechanisms
Glycine	Spinal interneurons and some brain stem interneurons	Taurine, β-alanine	Strychnine	Inhibitory: ↑ Cl^- conductance
5-Hydroxytryptamine (serotonin)	Cell bodies in midbrain and pons project to all levels	$5\text{-}HT_{1A}$: LSD	Metergoline, spiperone	Inhibitory: ↑ K^+ conductance, ↓ cAMP
		$5\text{-}HT_{2A}$: LSD	Ketanserin	Excitatory: ↓ K^+ conductance, ↑IP_3, DAG
		$5\text{-}HT_3$: 2-methyl-5-HT	Ondansetron	Excitatory: ↑ cation conductance
		$5\text{-}HT_4$		Excitatory: ↓ K^+ conductance
Norepinephrine	Cell bodies in pons and brain stem project to all levels	α_1: phenylephrine	Prazosin	Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG
		α_2: clonidine	Yohimbine	Inhibitory (presynaptic): ↓ Ca^{2+} conductance Inhibitory: ↑ K^+ conductance, ↓ cAMP
		β_1: isoproterenol, dobutamine	Atenolol, practolol	Excitatory: ↓ K^+ conductance, ↑ cAMP
		β_2: albuterol	Butoxamine	Inhibitory: may involve ↑ in electrogenic sodium pump; ↑ cAMP

Struktura različnih agonistov v OŽ



Glicin kot nevrotransmitor



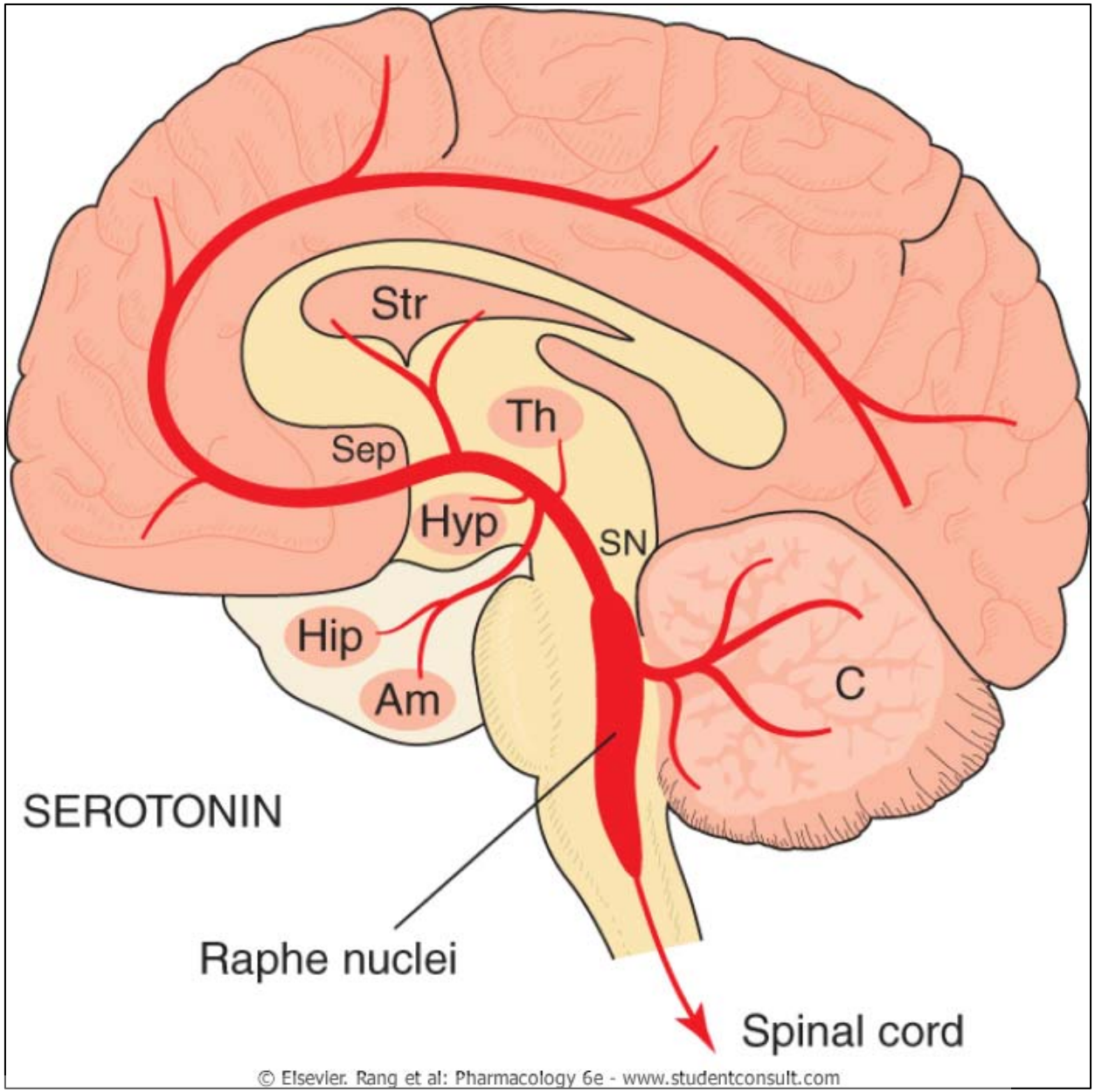
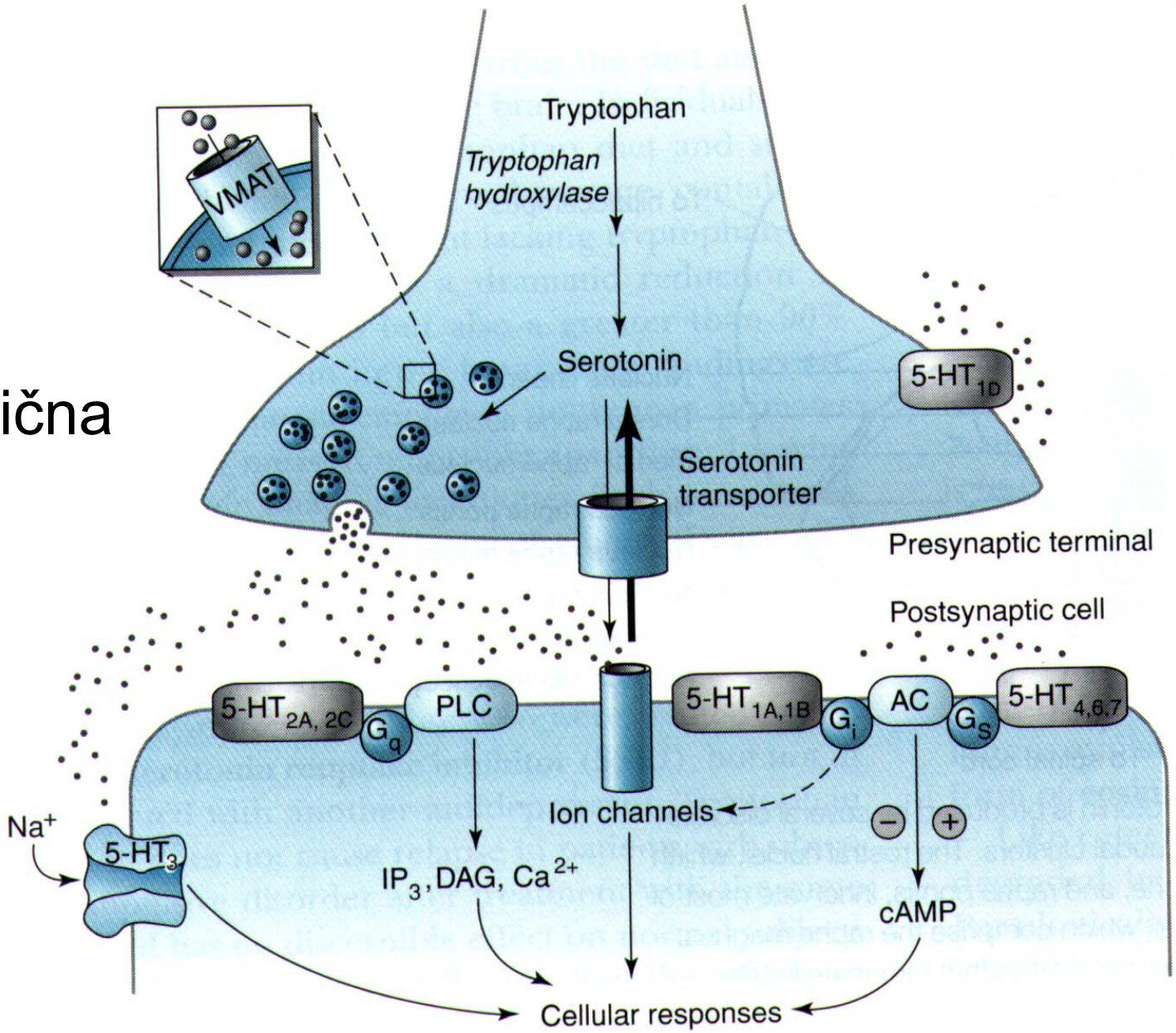


Figure 34-6 5-Hydroxytryptamine pathways in the brain. Am, amygdaloid nucleus; C, cerebellum; Hip, hippocampus; Hyp, hypothalamus; LC, locus coeruleus; MFB, medial forebrain bundle; NTS, nucleus of the tractus solitarius (vagal sensory nucleus); RF, brain stem reticular formation; Sep, septum; SN, substantia nigra; Str, corpus striatum; Th, thalamus.

Serotonergična sinapsa



Serotonin

- **Receptorji: 5-HT_{1-7}**
- **Agonisti 5-HT_{1D} sumatriptan, 5-HT_{5-7} LSD**
- **Antagonisti: 5-HT_{1A} buspiron, 5-HT_3 ondansetron**

- **Privzem –SERT**
- **Zdravila: inhibitorji SERT: paroksetin, citalopram, fluoksetin**

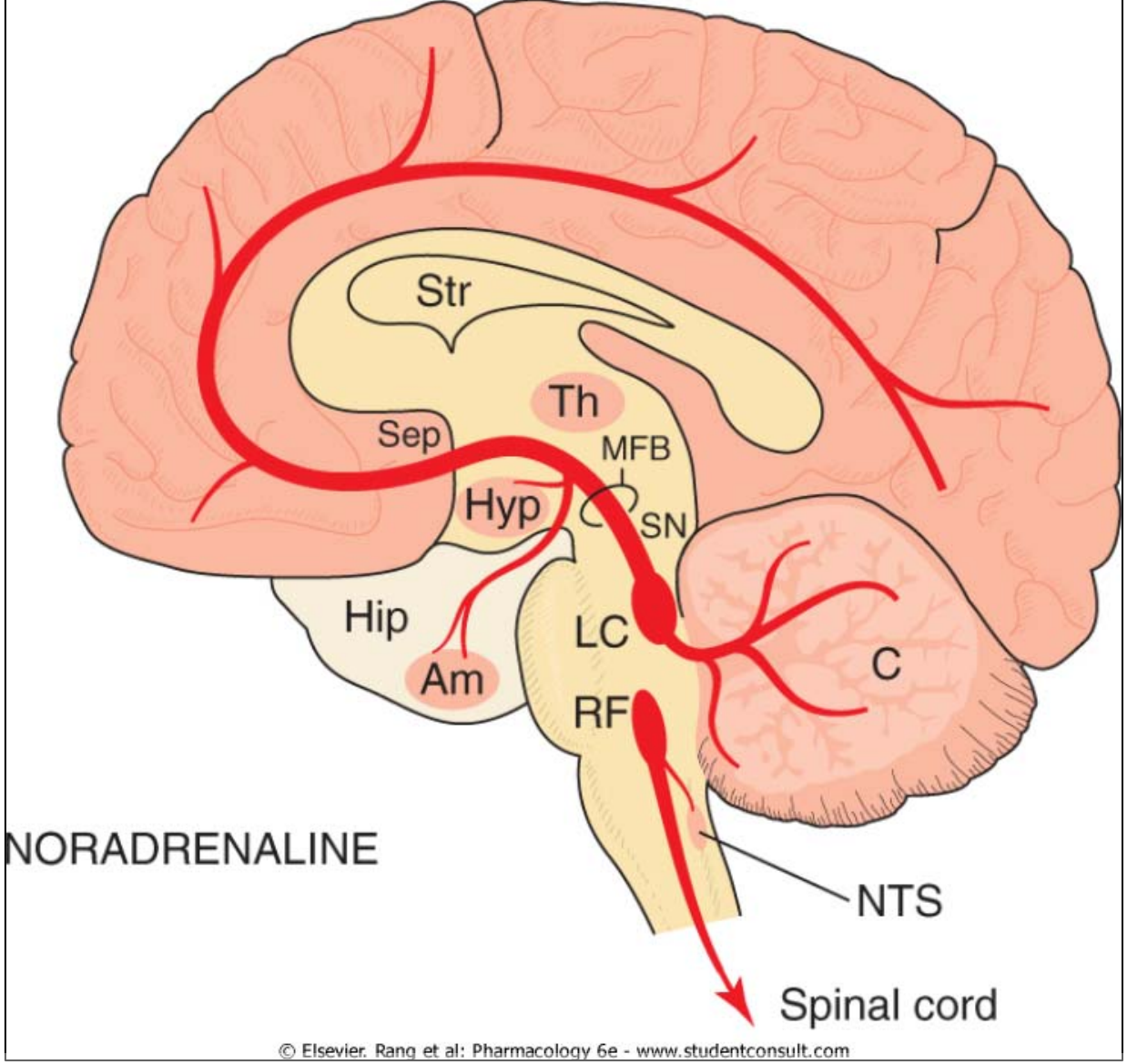


Figure 34-1 Noradrenaline pathways in the brain. The location of the main groups of cell bodies and fibre tracts is in solid colour. Light-shaded areas show the location of noradrenergic terminals. Am, amygdaloid nucleus; C, cerebellum; Hip, hippocampus; Hyp, hypothalamus; LC, locus coeruleus; MFB, medial forebrain bundle; NTS, nucleus of the tractus solitarius (vagal sensory nucleus); RF, brain stem reticular formation; Sep, septum; SN, substantia nigra; Str, corpus striatum; Th, thalamus.

Noradrenalin- 1

- **Sinteza: iz fenilalanina in tirozina – encimi**
- **Skladiščenje: vezikli VMAT, transporter inhibitor: rezerpin**
- **Sproščanje:**
  - **Ca, receptorji (α2, β2)**
  - **Zdravila: amfetamini**
- **Razgradnja: MAO, COMT**
- **Zdravila: inhibitorji MAO**

Vloga noradrenalina v OŽ

- Hranjenje
- Spanje
- Spomin
- Pozornost
- Regulacija arterijskega pritiska

Noradrenalin - 2

- **Receptorji:**
- **α1, α2, β1, β2, β3**
- **α2- agonisti: klonidin, metildopa (hipertenzija)**

- **Privzem – NET**
- **Inhibitorji NET: imipramin, desimipramin, (depresije), amfetamini**

Transmitter	Anatomy	Receptor Subtypes and Preferred Agonists	Receptor Antagonists	Mechanisms
Histamine	Cells in ventral posterior hypothalamus	H_1: 2(*m*-fluorophenyl)-histamine	Mepyramine	Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG
		H_2: dimaprit	Ranitidine	Excitatory: ↓ K^+ conductance, ↑ cAMP
		H_3: *R*-α-methyl-histamine	Thioperamide	Inhibitory autoreceptors
Opioid peptides	Cell bodies at all levels; long and short connections	Mu: bendorphin	Naloxone	Inhibitory (presynaptic): ↓ Ca^{2+} conductance, ↓ cAMP
		Delta: enkephalin	Naloxone	Inhibitory (postsynaptic): ↑ K^+ conductance, ↓ cAMP
		Kappa: dynorphin	Naloxone	
Tachykinins	Primary sensory neurons, cell bodies at all levels; long and short connections	NK1: Substance P methylester		Excitatory: ↓ K^+ conductance, ↑ IP_3, DAG
		NK2		
		NK3		
Endocannabinoids	Widely distributed	CB1: Anandamide, 2-arachidonylglyerol	Rimonabant	Inhibitory (presynaptic): ↓ Ca^{2+} conductance, ↓ cAMP

ACPD, *trans*-1-amino-cyclopentyl-1,3-dicarboxylate; AMPA, DL-α-amino-3-hydroxy-5-methylisoxazole-4-propionate; cAMP, cyclic adenosine monophosphate; CQNX, 6-cyano-7-nitroquinoxaline-2,3-dione; DAG, diacylglycerol; IP_3, inositol trisphosphate; LSD, lysergic acid diethylamide; MCPG, α-methyl-4-carboxyphenylglycine.

Histaminergične poti

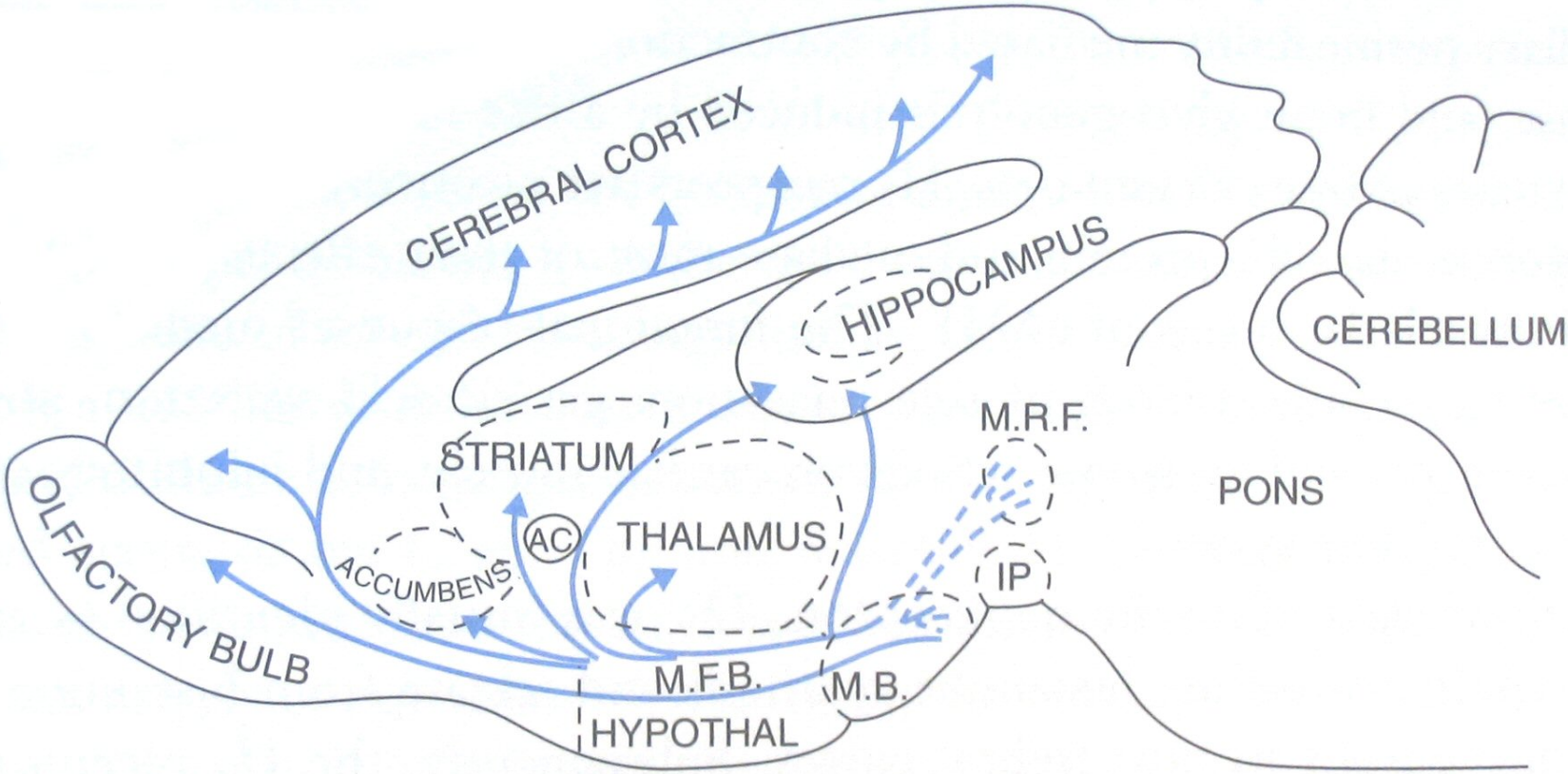


FIGURE 10–11. Schematic illustration of the distribution of histamine-containing neurons in brain. M.R.F., mesencephalic reticular formation; M.B., mammillary bodies; M.F.B., medial forebrain bundle. (Modified from Schwartz and Arrang, 2002.)

NO

- **Se ne shranjuje v veziklih, se ne sprošča z eksocitozo, se ne privzema.**
- **Sinteza: pretvorba L-arginina v NO in citrulin**
- **Encimi: eNOS, iNOS, nNOS**
- **Sproščanje: fazično**
- **Veže se na gvanilil ciklazo, pasivna inaktivacija**

NO
⇓⇑
Glu

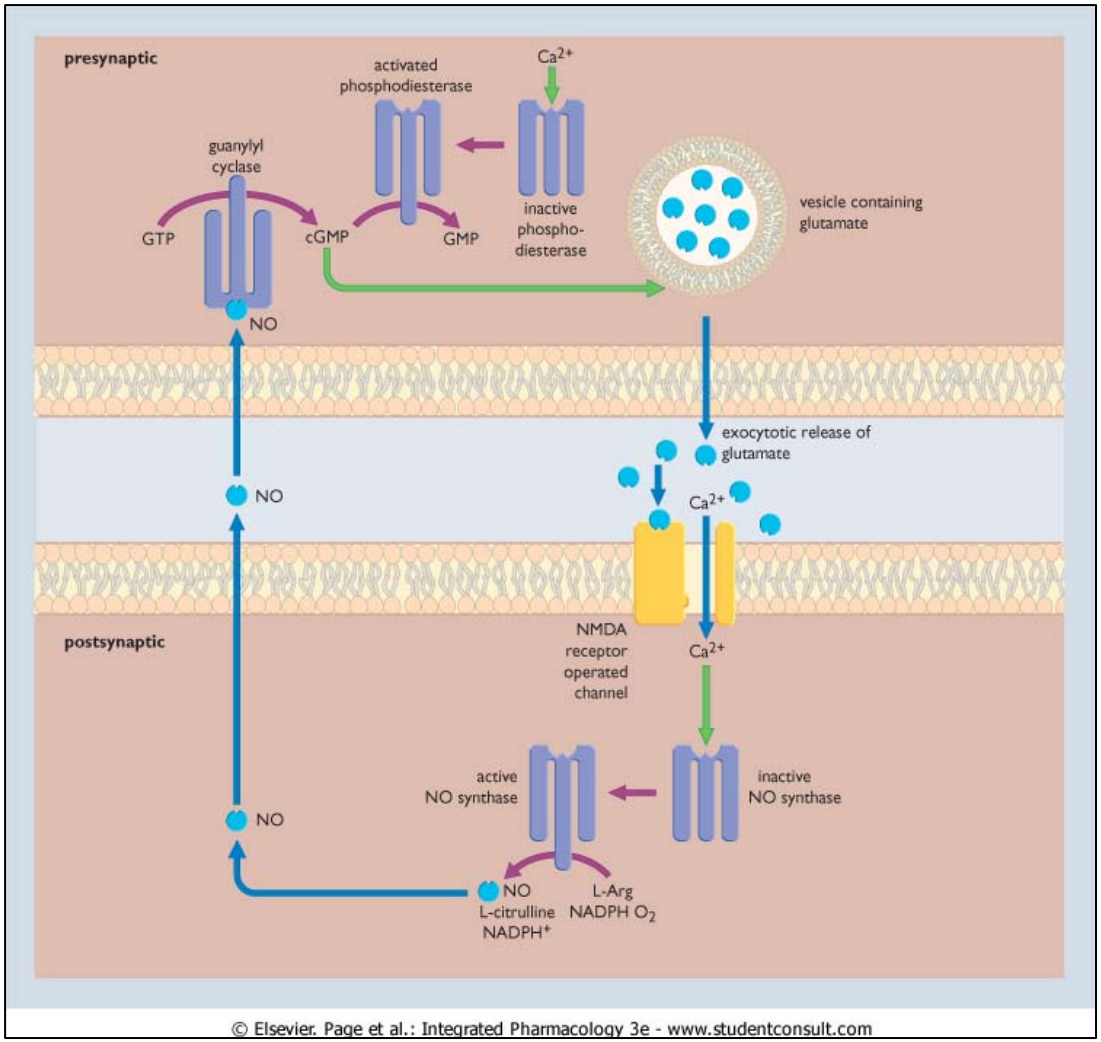


Figure 8.12 Nitric oxide and glutaminergic neural transmission. In this model, glutamate released from a presynaptic terminal binds to postsynaptic NMDA receptors causing an influx of calcium ions (Ca2+). Alternatively, calcium influx may occur through voltage-gated calcium channels. The increased Ca2+ concentration leads to activation of NO synthase, which results in production of nitric oxide (NO). Nitric oxide then diffuses to surrounding tissue, including the presynaptic release terminal, where it binds to and activates guanylate cyclase. This sets into motion a biochemical cascade that results in increased glutamate release from the presynaptic terminal. (Adapted from Holscher C. Nitric oxide, the enigmatic neuronal messenger: its role in synaptic plasticity. Trends Neurosci 1997; 20: 298-303.)

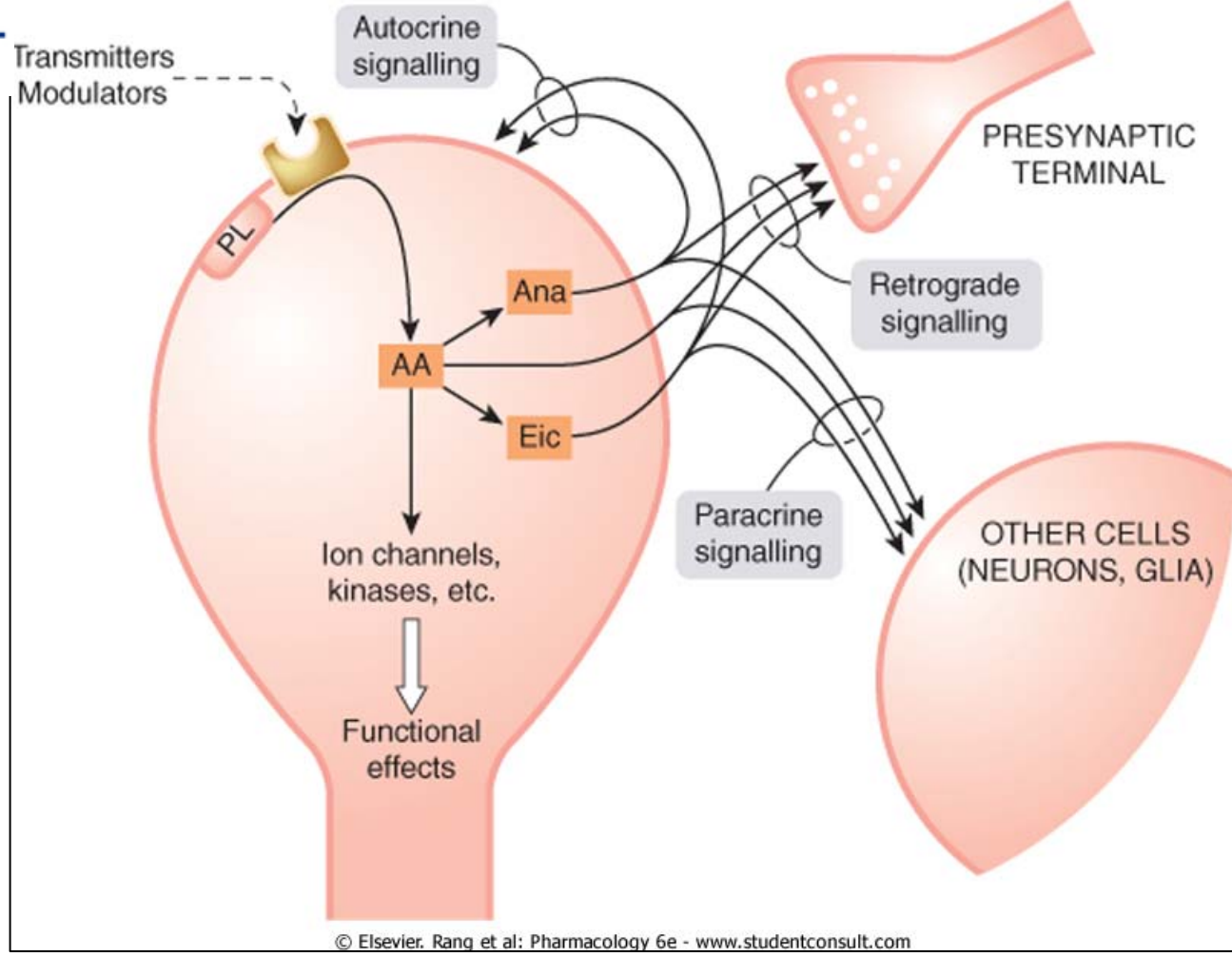


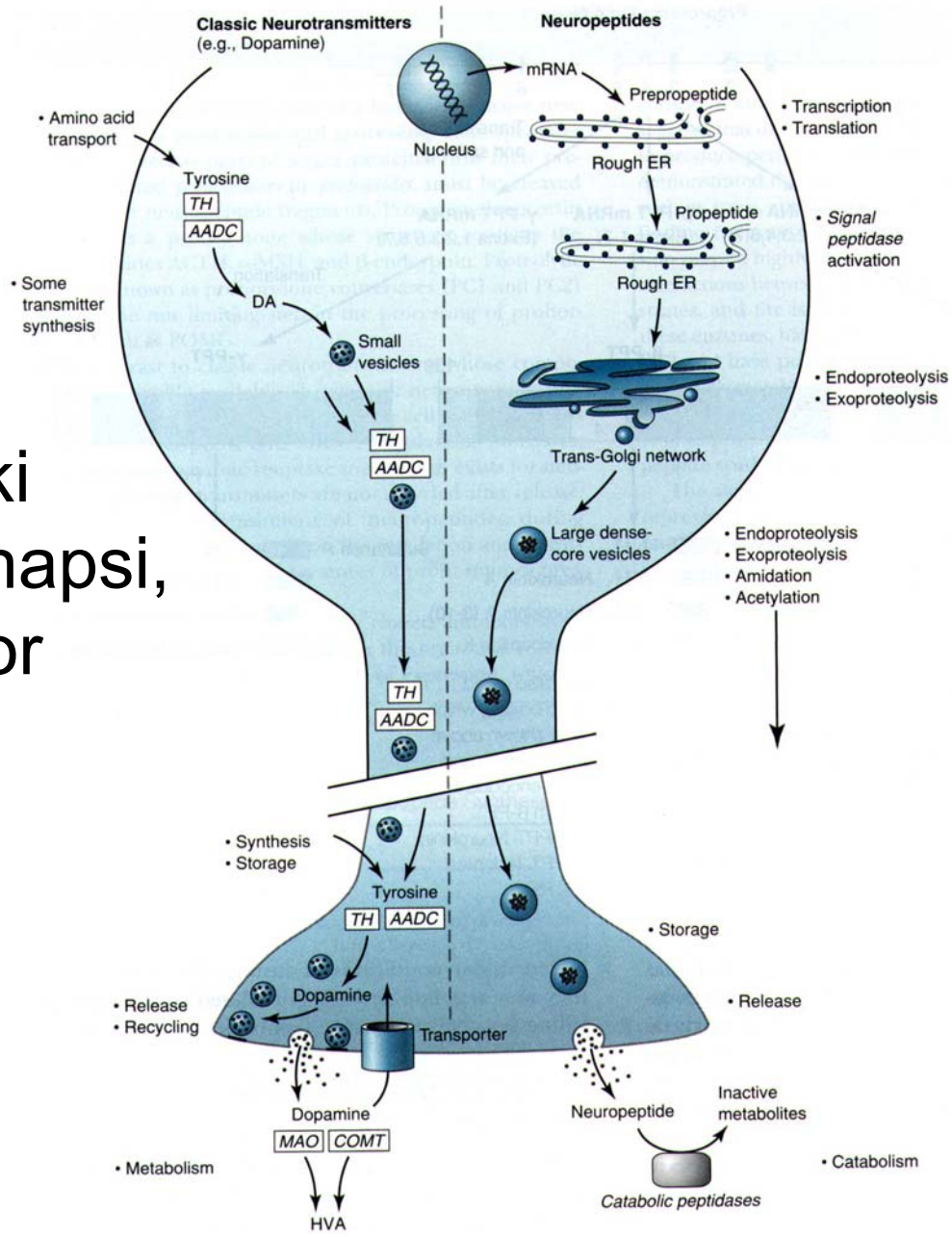
Figure 34-9 Postulated modes of signalling by lipid mediators. Arachidonic acid (AA) is formed by receptor-mediated cleavage of membrane phospholipid. It can act directly as an intracellular messenger on ion channels or components of different kinase cascades, producing various long- and short-term effects. It can also be converted to eicosanoids (prostaglandins, leukotrienes or hydroxyeicosatetraenoic acids [HETEs]) or to anandamide (Ana). HETEs can also act directly as intracellular messengers. All these mediators diffuse out of the cell, and exert effects on presynaptic terminals and neighbouring cells, acting either on extracellular receptors or intracellularly. There are examples of most of these modes of signalling but only limited information about their functional significance in the nervous system. Eic, eicosanoids; PL, membrane phospholipid.

Nevropeptidi kot nevrotransmiterji

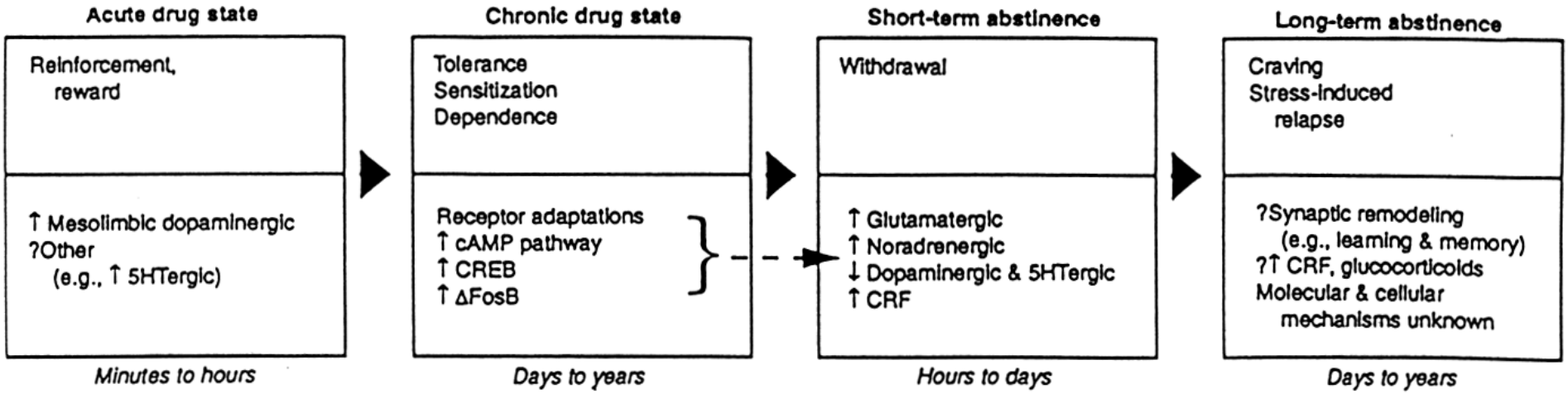
Primeri:

- **opioidni peptidi,**
- **nevrotenzin,**
- **VIP in sorodni peptidi,**
- **somatostatin**

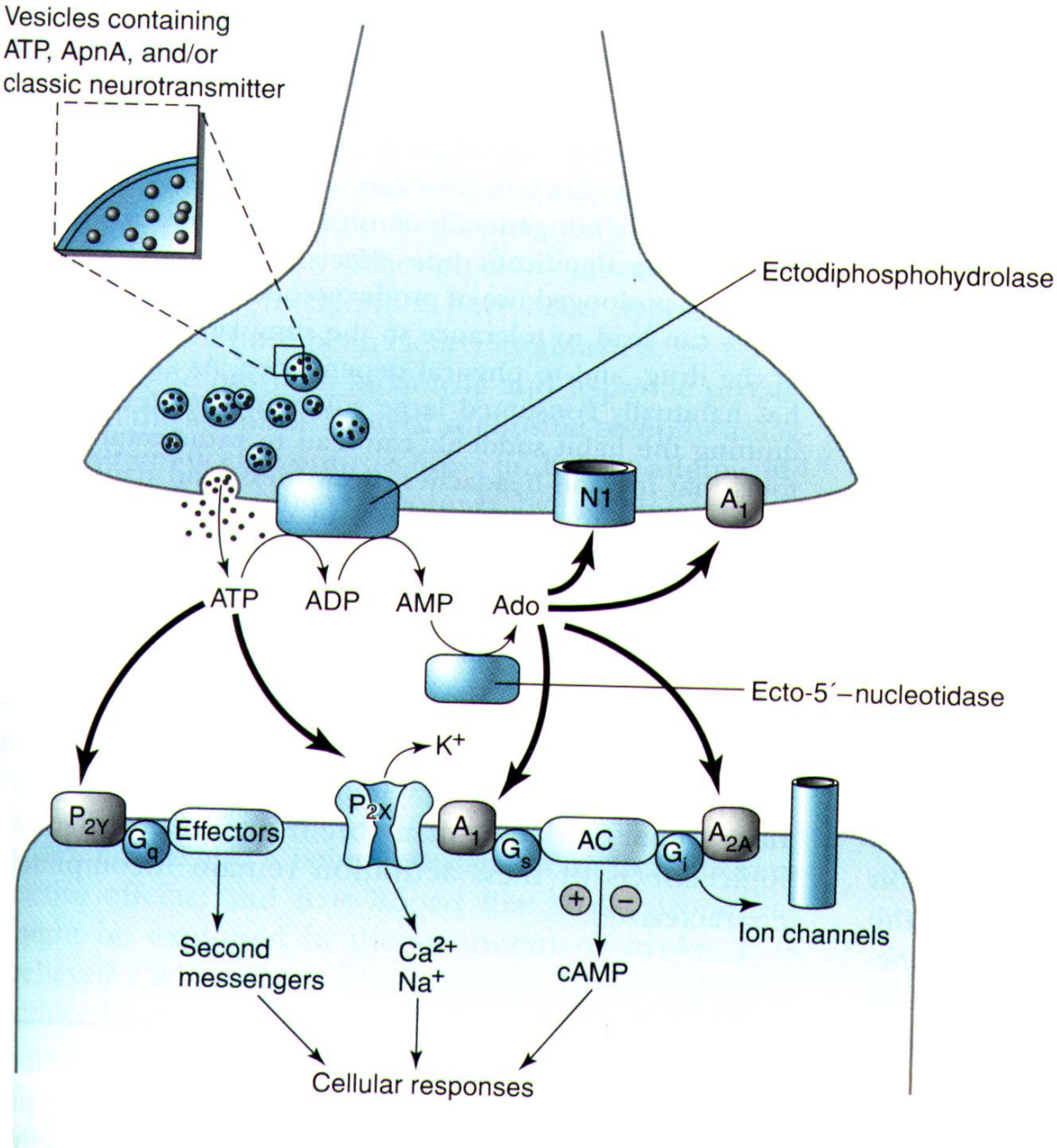
Primerjava dogajanj v monoaminski sinapsi in v sinapsi, kjer je mediator polipeptid



Vpliv dolgotrajne rabe opioidov na dogajanja v OŽ



Purini kot mediatorji



Nevrosteroidi

- **Derivati pregnenolona in deoksikortikosterona**
- **Delovanje: modulacija $GABA_A$, nikotinskih, 5-HT_3 in NMDA receptorjev**
- **Učinki: nevroprotektivni, sedativni, anestetični, modulacija spanja, antikonvulzivni**
- **Zdravila: ganaksolon – zdravilo proti migreni (faza II)**
- **CCD3693 – proti nespečnosti**
- **Co26749 - anksiolitik**

FAKTORJI, KI VPLIVAJO NA JAKOST IN TRAJANJE UČINKA ZDRAVIL V CNS

- Omejen dostop snovi iz plazme v CNS
- Hematoencefalna bariera (HEB)
  - stena kapilar
  - celice glije ZAKASNITEV UČINKA
  - omejena difuzija
  - transportni mehanizmi (prekurzorji transmitorjev)
  - transportni sistem za kisline v horioidnem pleksusu
  - HEB manj izrazita v:
    - Hipotalamusu
    - strukturah ob 4. in 3. ventriklu

Čas do nastopa učinka in njegovo trajanje

- odvisno od mehanizma:
  - agonisti, antagonisti
  - vpliv na zaloge
  - vpliv na metabolizem
  - posredni vpliv na R (⇑⇓ regulacija)

Prenos v OŽ

Čas	Proces	Mediator	Molekularni mehanizem
msek	Prevajanje impulzov Sproščanje prenašalcev Hitri sinaptični prenos	Noben Ca^{2+} Glu, GABA, ACh	V-kanali Eksocitoza Ionski kanali
Sek/min	Počasni sinaptični prenos Nevromodulacija	ACh, NA, DA, 5-HT, peptidi, NO	Receptorji, sklopljeni s proteinom G
Ure/ dnevi	Sinaptična plastičnost Farmakološka toleranca Zakasnel farmakološki odgovor	Opioidi, benzod. antidepresivi	Regulatorno spreminjanje števila receptorjev