University of Idaho

Receptors and Neurotransmitters Continued

Psychology 472: Pharmacology of Psychoactive Drugs

1

TABLE 3.1 Selected neurotransmitters in the CNS

Neurotransmitter	Receptors	Function[a]
Acetylcholine (ACh)	Muscarinic (M_1 through M_5) Nicotinic (N_N and N_M)	Memory function, sensory processing, motor coordination, neuromuscular junction neurotransmission, and ANS and PANS function
Norepinephrine (NE)	Alpha$_1$ and alpha$_2$; beta$_1$, beta$_2$, and beta$_3$	CNS sensory processing, cerebellar function, sleep, mood, learning, memory, anxiety, and SANS
Dopamine (DA)	D_1 through D_5 in two families designated D_1 and D_2	Motor regulation, reinforcement, olfaction, mood, concentration, hormone control, and hypoxic drive
Serotonin (5-HT)	Currently 18 receptors have been identified and broken into 8 families designated 5-HT$_1$ through 5-HT$_8$	Emotional processing, mood, appetite, sleep, pain processing, hallucinations, and reflex regulation
Glutamate (Glu)	NMDA, quisqualate, and kainate	Long-term potentiation, memory, major excitatory function within the CNS and PNS
Gamma amino-butyric acid (GABA)	$GABA_A$ and $GABA_B$	Major inhibitory neurotransmitter in the CNS
Histamine (H)	H_1 and H_2	Sleep, sedation, and temperature regulation
Glycine (Gly)		Major inhibitory function

2

- Neurotransmitter Classes
  - Acetylcholine (ACh)
  - Catecholamines
    - Dopamine (DA)
    - Norepinephrine (NE)
  - Serotonin (5-HT)
  - Amino Acids
    - Glutamate = Excitatory
    - GABA = Inhibitory
  - Peptide Neurotransmitters
    - e.g., Endorphins, Enkephalins

Acetylcholine

- Acetylcholine (ACh) is the primary NT secreted by efferent CNS cells
- In the periphery: ACh neurons are found in:
  - Autonomic ganglia (e.g. the heart)
  - The neuromuscular junction (activation of muscle movement)
- In Brain: ACh neurons are found in:
  - Dorsolateral pons
  - Medial septum
  - Basal forebrain
  - ACh release in brain results in facilitatory effects

Functions

- Role in awakening systems in the brain
- Has a role in memory
- Decrease of ACh neurons is correlated with Alzheimer's and other diseases

5

ACh Pathways

- *Septal nucleus* and *nucleus basalis*
  - Projects to forebrain.
- Midbrain
  - Projects to reticular formation, pons, cerebellum, and cranial nerve nuclei.

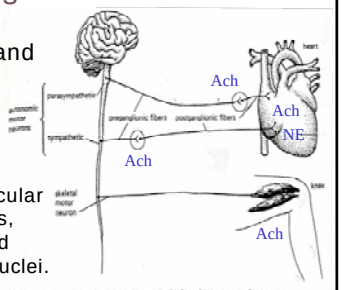
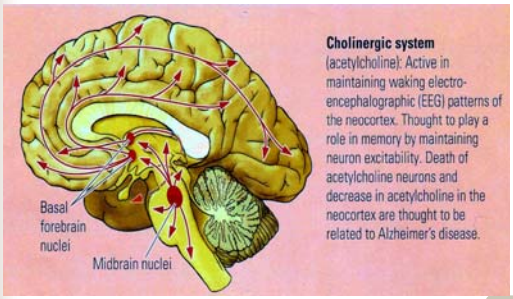


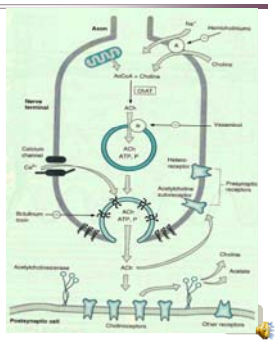
Figure 5.5. The Autonomic and Skeletal Nervous System
Note that the skeletal motor neurons run uninterrupted courses from the spinal cord to the target muscles; the autonomic motor neurons do not.

Cholinergic System



Synthesis Cycle

Acetyl-CoA
(in mitochondria, involved in Krebs cycle) + Choline (from diet)

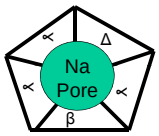


ACh Receptors

- Two Types
- Nicotinic receptors are found in skeletal muscle (ionotropic effect)
  - Agonists: ACh, nicotine
  - Antagonists: d tubocurarine and curare
- Muscarinic receptors are found in heart and smooth muscle (metabotropic effects)
  - Agonists: ACh, muscarine
  - Antagonists: Atropine and scopolamine

Nicotinic Receptor

- Receptor and ion channel are one unit
- Ach binds to alpha subunit
- Beta and Delta subunits are concerned with regulatory functioning



If you put a phosphate group on Beta or Delta subunits – causes endocytosis.
Receptor enters post synaptic element and is destroyed –

Decreases sensitivity

Muscarinic Receptors

- Uses a GP second messenger system

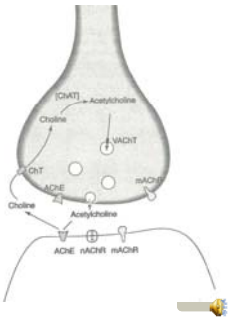
Ach
Muscarinic Ach Receptor
Gp PLC

IP-3 DAG

Ca Release PKC

AChE Inhibitors

- Irreversible
  - Often toxic
  - Include pesticides and nerves gases
- Reversible
  - Cognitive enhancers
  - Treating Alzheimer's

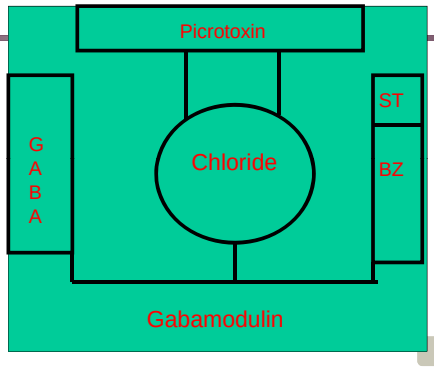


Amino Acid Transmitters

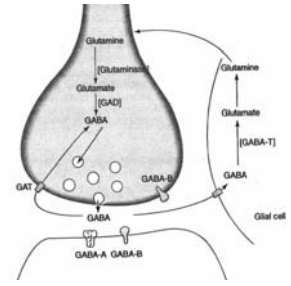
- Synthesis
  - Glutamine
    - Glutaminase
      - » Glutamate = Excitatory
      - » GABA = Inhibitory (more than half the synapses in the brain)

GABA

- Is synthesized from glutamic acid
- Induces IPSPs
- Acts via 2 receptors
  - $GABA_A$: Ionotropic receptor (controls a chloride channel)
  - $GABA_A$ receptors contain 5 distinct binding sites
    - GABA site
    - Benzodiazepine site
    - Barbiturates
    - Steroid binding site
    - Picrotoxin binding site



Gaba Cycle



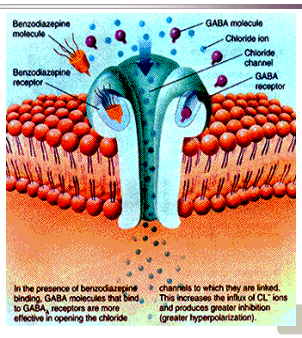
- Metabolized by GABA-transaminase (GABA-T)
- Termination
  - reuptake with transporters on neuron or glial cells

$GABA_B$

- Activates a metabotropic receptor (controls a K^+ channel)
- Formed by subunits (GABA-B1 [has 2 forms] and GABA-B2).

Amino Acids

- Drugs
  - Glutamate
    - PCP/ketamine (antagonists)
  - GABA
    - Sedative-hypnotics – tranquilizers, alcohol… (agonists)



Glutamate

- Comes from metabolic pathway (Krebs cycle) or from glutamine via glutaminase.
- Binds to several receptor types.
  - NMDA, kainate, AMPA
    - NMDA mediated by glutamate and glycine/serine.
    - NMDA requires membrane depolarization by kainate or AMPA.
    - NMDA involved in memory formation.

Glutamate

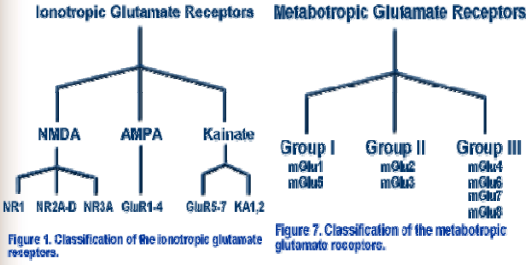
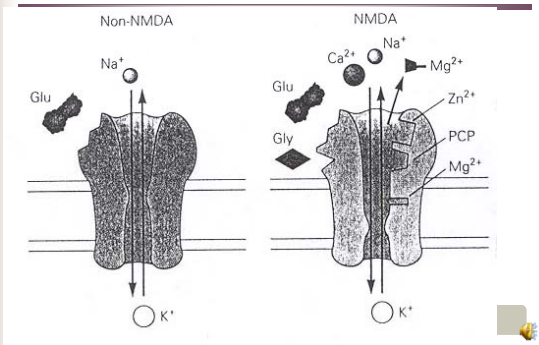


Figure 1. Classification of the ionotropic glutamate receptors.

Figure 7. Classification of the metabotropic glutamate receptors.

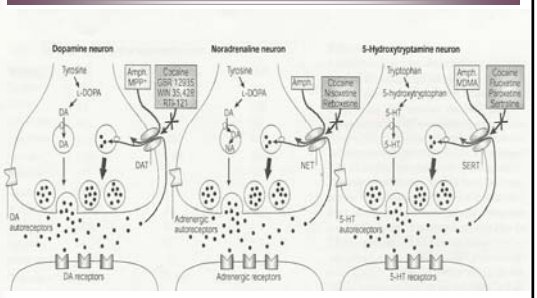
Glutamate



Disorders

- Glutamate
  - Epilepsy / seizure
  - Dementias?
- GABA
  - Epilepsy / seizure

Biogenic Amine Transmitters



Catecholamine Synthesis

Dopamine

- Is used by several neural systems
  - Nigrostriatal system
    - Projects from the substantia nigra to the caudate nucleus and putamen
  - Mesolimbic system
  - Projects from ventral tegmental area to the limbic system (including the nucleus accumbens, amygdala, and hippocampus)
  - Mesocortical system projects from the ventral tegmental area to the cortex

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- Dopamine receptors are metabotropic
  - D1 receptors are postsynaptic, whereas D2 receptors are pre - and postsynaptic

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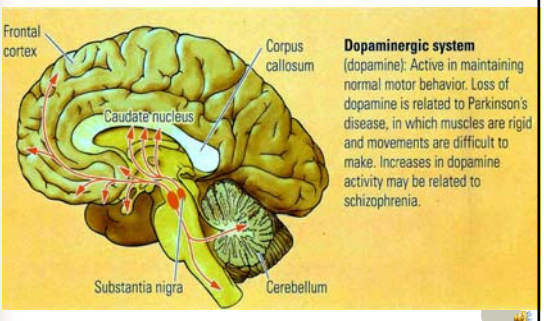
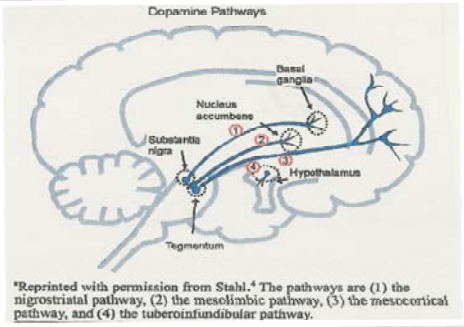


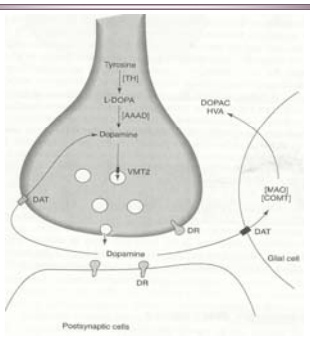
- Receptors
  - Dopamine
    - Two families: D1 and D2
  - DA and NE do not directly activate ion channels, but trigger sequence of chemical events.

Neurotransmitter	Receptor Subtype
Acetylcholine	M_1
	M_2
	M_3
	M_4
	M_5
	Nicotinic
Dopamine	D_1
	D_2
	D_3
	D_4
	D_5
Epinephrine and norepinephrine	$\alpha_{1A, B, C, \text{and } D}$
	$\alpha_{2A, B, \text{and } C}$
	$\beta_{1, 2, \text{and } 3}$
Histamine	H_1
	H_2
	H_3
Serotonin	5-HT_{1A}
	5-HT_{1B}
	5-HT_{1C}
	5-HT_{1D}
	5-HT_{1E}
	5-HT_{1F}
	5-HT_{2A}
	5-HT_{2B}
	5-HT_{2C}
	5-HT_3
	5-HT_4
	5-HT_{5A}
	5-HT_{5B}
	5-HT_6
	5-HT_7

Dopamine Pathways



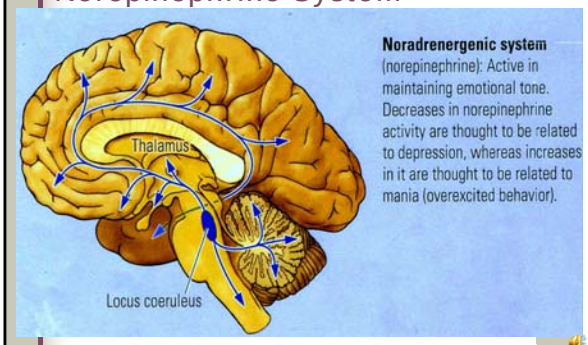
*Reprinted with permission from Stahl.[4] The pathways are (1) the nigrostriatal pathway, (2) the mesolimbic pathway, (3) the mesocortical pathway, and (4) the tuberoinfundibular pathway.



Norepinephrine

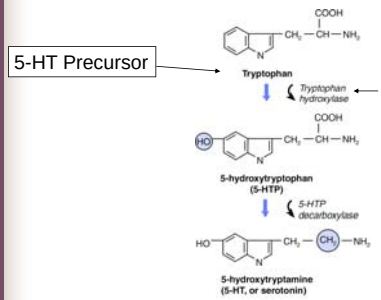
- Norepinephrine is synthesized from dopamine within vesicles
- The locus coeruleus gives rise to NE fiber systems
  - NE is secreted from varicosities along fibers
- NE interacts with four receptor types in brain
  - α-adrenergic (subtypes 1 and 2)
  - β-adrenergic (subtypes 1 and 2)
  - Adrenergic receptors are metabotropic

Norepinephrine System



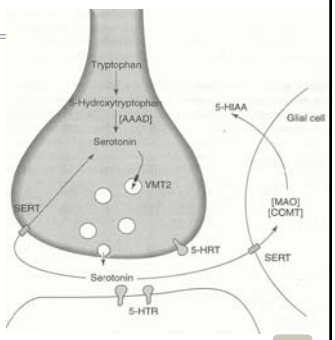
Noradrenergenic system (norepinephrine): Active in maintaining emotional tone. Decreases in norepinephrine activity are thought to be related to depression, whereas increases in it are thought to be related to mania (overexcited behavior).

Serotonin Synthesis



Serotonin

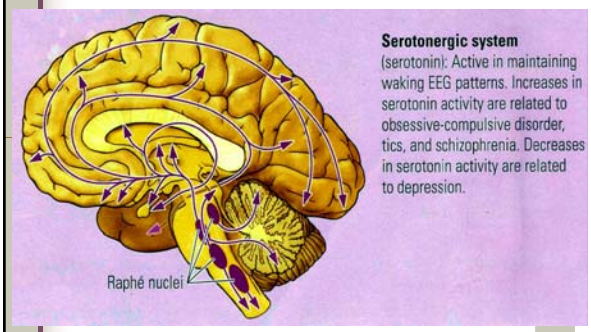
- Synthesis
  - Tryptophan
- Receptors
  - Ionotropic
    - 5-HT_3
  - G protein-coupled
    - 5-HT_1, 5-HT_2,
    - 5-HT_4
- Pathways
  - Largely parallel DA



- (5-HT) cells are mostly located in the gut (98%) with only 2% of serotonin cells in brain
- Serotonin cell bodies are located in brainstem raphe nuclei and project to cortex
- Serotonin systems:
  - D system originates in the dorsal raphe nucleus but does not form synapses (5-HT as a neuromodulator)
  - M system originates from the median raphe nucleus and these varicosities form synapses

5-HT: Release and Termination

- Serotonin release:
  - 8-OHDPAT is an autoreceptor agonist that reduces 5-HT release
  - No selective release blocker
  - Fenfluramine is a 5-HT releasing drug
- Serotonin termination:
  - Reuptake is blocked by fluoxetine (elevates 5HT)
  - Degradation: MAO converts serotonin to 5-HIAA



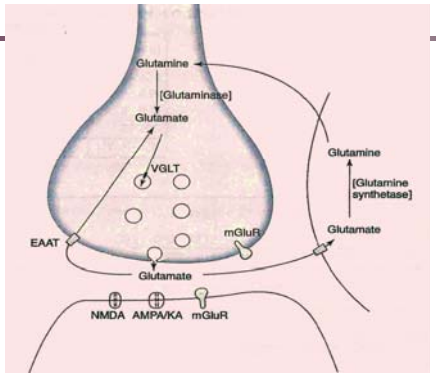
Serotonin Receptors

- There are at least 9 types of 5-HT receptors
  - 5-HT_1 : 1A, 1B, 1D, 1E, and 1F
  - 5-HT_2 : 2A, 2B, and 2C
  - 5-HT_3
- 5-HT_3 receptors are ionotropic, the remainder are metabotropic
- 5-HT_{1B} and 5-HT_{1D} are presynaptic autoreceptors

4.41

Glutamate

- Glutamate (glutamic acid) is an excitatory neurotransmitter
- Glutamate interacts with four receptor types
  - NMDA receptor: controls a CA^{++} channel
    - Activation by glutamine requires glycine binding and displacement of magnesium ions
  - AMPA receptor: controls sodium channels
  - Kainate receptor: controls sodium channels
  - Metabotropic glutamate receptor



Peptides

- Consist of 2 or more amino acids
- Are synthesized in the soma and transported to the presynaptic element in vesicles
- Are released from all parts of the presynaptic element
- After release are enzymatically degraded (no reuptake)
- Peptides can be co-released with other NTs
  - Serves as neuromodulators

- Peptides
  - More than 100 types
  - Are small proteins
    Have 30 - 40 amino acids

  Are critical for fine tuning the NS

Conclusions

- Lots of different types
- Lots of different functions
- Impact multiple brain systems

- Important to have a general idea about what they do and the systems they impact