AUTONOMIC HOMEOSTASIS

CORE CONTENT

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AUTONOMIC NERVOUS SYSTEM (ANS)

The ANS is a neuronal network that enables us to function without consciously controlling and managing our bodies. In order to accomplish this specific neurotransmitters and neuromodulators are involved working through many different pathways. The system is also an integral part of neuroendocrine and immunomodulatory systems.
ACETYLCHOLINE

Acetylcholine (ACh) was the first neurotransmitter (NT) discovered and is the major NT in the peripheral nervous system (PNS)

- Acetylcholine
  - Produced from acetyl-CoA (glucose metabolism) and choline
  - Acetyl-CoA and choline are independently synthesized in the neuronal cell body and transported along the axon to the synapse for conjugation into ACh
  - Release is mediated via Ca influx and presynaptic vesicles interacting with cell membrane docking complex (process disrupted by botulinum toxin)
  - In order to allow repolarization, ACh must be removed rapidly (ie, AChE)
  - Two classes of ACh receptors
    - Nicotinic
    - Muscarinic

Nicotinic Receptors (nAChRs)

- CNS (mainly spinal cord)
- Preganglionic autonomic neurons (sympathetic and parasympathetic)
- Adrenal neuronal receptors
- Skeletal muscle neuromuscular junction

- Nicotinic Receptor Agonists
  - Initial activation of nicotinic receptors
    - Prolonged depolarization leads to inhibition
    - Initial sympathomimetic, GI distress, fasciculations, seizures
    - Then ↓ BP, ↓ HR, paralysis, coma
  - Nicotine alkaloids (nicotine, coniine)
    - Trick to remember the hemlocks –
      - Water Gate Candidate Scandal (Water hemlock, GABA, Cicutoxin, Seizures)
      - Poison Control Network (Poison hemlock, Coniine, Nicotine)
  - Carbachol (mainly muscarinic effects, primarily in ophthalmic use)
  - Methacholine (minimal effects, does not cross BBB, methacholine test in asthma)
  - Succinylcholine (initial effects)

- Nicotinic Receptor Antagonists
  - Neuromuscular junction (NMJ) blockers: weakness, paralysis
    - Curare, atracurium, alpha-bungarotoxin (prevents AChR channel opening)
  - Peripheral neuronal blockers: autonomic ganglionic blockade
    - Trimethaphan (not entirely specific, may produce NMJ blockade)

- Nicotinic Indirect Agonists
  - Bind to distinct allosteric sites on the nicotinic receptor, not ACh binding site (enhanced channel opening)
    - Phystostigmine
    - Tacrine
    - Galantamine
• Nicotinic Indirect Antagonists
  o Bind to distinct allosteric sites on the nicotinic receptor, not ACh binding site (decreased channel opening)
    ▪ Chlorpromazine
    ▪ Ketamine
    ▪ Phencyclidine (PCP)
  ▪ Local anesthetics
  ▪ Ethanol
  ▪ Corticosteroids

• Muscarinic Receptors
  o CNS (mainly brain)
  o Postganglionic parasympathetic nerve endings
  o Postganglionic sympathetic receptors for most sweat glands

• Muscarinic Agonists
  o Peripheral: DUMBBELS
  o Central: Sedation, dystonia, coma, seizures
  o Muscarine
  o Bethanachol
  o Pilocarpine

• Muscarinic Antagonists
  o Peripheral: mydriasis, anhidrosis, tachycardia, urinary retention, ileus, dry and flushed skin
  o Central: delirium, agitation, hallucinations, coma
    ▪ Atropine
    ▪ Benztropine
    ▪ Scopolamine
    ▪ Phenothiazines
    ▪ Cyclic antidepressants

• Agents that Induce ACh Release
  o Aminopyridines
  o Latrodectus venom (acts as a transmembrane pore and allows Ca influx into cells)
  o Carbachol
  o Guanidine
  o Alpha₂-adrenergic antagonists (↑ ACh release from parasympathetic nerve endings)

• Acetylcholinesterase Inhibitors
  o ↑ [ACh] at both nicotinic and muscarinic receptors
  o Produce a variety of CNS, sympathetic, parasympathetic, and NMJ effects (DUMBBELS)
  o Carbamates
  o Organophosphorus compounds
  o Nerve agents
  o ‘Central’ AChE inhibitors (donepezil)

• Agents that Block ACh Release
  o Alpha₂-adrenergic agonists
  o Botulinum toxin (prevents NT vesicle from docking with cell membrane)
  o Crotalinae venoms
  o Elapidae beta-neurotoxins
  o Hypermagnesemia (blocks presynaptic N-subtype calcium channels)
HISTAMINE

Histamine interacts with four types of receptors $H_1$-$4$. $H_1$ receptors use G-protein second messenger systems. $H_1$ receptors are diverse and have the most clinical toxicity in overdose. They are located in the CNS, heart and vasculature, airways, sensory nerves, Gastrointestinal smooth muscles cells, immune cells, and adrenal medulla. $H_2$ receptors are located mainly in the gastric mucosa, but also exist in the heart, lungs, CNS, uterus, and immune cells. $H_3$ receptors serve as neuromodulators for the release of other NT, including histamine. $H_4$ receptors are involved in hematopoietic functions and eosinophil chemotaxis.

- Antihistamines
  - 1st generation
    - Cross the BBB
    - Diphenhydramine most clinically relevant for boards
  - 2nd generation
    - Classified as non-sedating
    - Selectively bind peripheral $H_1$ receptors
    - Lower binding affinity for cholinergic receptors
    - Reduced antimuscarinic effects and CNS depression

- $H_1$ Receptor Antagonists
  - Historical perspective
    - Terfenadine $\rightarrow$ CYP3A4 $\rightarrow$ terfenadine carboxylate
    - Astemizole $\rightarrow$ CYP3A4 $\rightarrow$ desmethylastemizole
      - Parent compounds block $I_{kr}$
      - Increased risk of TdP
      - Withdrawn from market in 1998
  - Clinical manifestations
    - Rapid onset with potential for long duration
    - CNS depression
    - Antimuscarinic effects
    - Cardiac
      - Sodium channel and $I_{kr}$ blockade with diphenhydramine (QRS and QT prolongation)
  - $H_2$ Receptor Antagonists
    - Hydrophilic – poor access to CNS
    - Alter gastric pH
    - May impact absorption of acid-labile drugs
      - e.g., ketoconazole
    - Cimetidine
      - Only $H_2$ receptor antagonists to inhibit P450 isozymes (specifically CPY3A4)
      - Useful in dapsone-induced methemoglobinemia
      - Useful in toxicity from Gyromitra esculenta
      - Associated with myelosuppression if taken with drugs associated with BM suppression
      - Rapid IV dosing has resulted in bradycardia, hypotension, and cardiac arrest
ADENOSINE

Adenosine is a neuromodulator primarily involved in the reduction of excitatory NT release including glutamate, GABA, norepinephrine, serotonin, and ACh. Its greatest effect is in the inhibition of glutamate release and neuronal excitation.

- Adenosine receptor antagonism
  - CNS: excitation due to sustained and unmodulated release of glutamate and other excitatory neurotransmitters (A<sub>1</sub> receptors)
  - Cardiac: tachycardia due to an increase rate of signaling in pacemaker cells (A<sub>1</sub> receptors)
  - Vasculature: vasoconstriction of CNS, cardiac, and peripheral vascular (A<sub>2</sub> receptors)

- Adenosine A<sub>1</sub> Receptors - CNS
  - Postsynaptic
  - Enhances outward potassium channels
  - Enhances inward Chloride influx
  - Results in induced hyperpolarization

- Adenosine A<sub>2</sub> Receptors - CNS
  - Presynaptic
  - Activates adenyl cyclase increasing cAMP levels
  - Inhibits L-type & N-type calcium channels
  - Vasodilation
  - Only the A<sub>2A</sub> subtype of A<sub>2</sub> receptors have significant activity

- Effects of A1 receptors predominate over A<sub>2A</sub>
  - A1 receptors are more numerous
  - Adenosine affinity for A<sub>1</sub> > A<sub>2A</sub> receptors
  - Adenosine A<sub>2A</sub> Receptors
  - Adenosine A<sub>2A</sub> receptors are prominent in endothelial cells (vasodilation)
  - A<sub>2A</sub> receptor activity inhibits locomotor activity by inhibiting dopamine at D2 receptors
  - A<sub>2A</sub> receptors serve as check-balance for A1

- Adenosine A<sub>1</sub> Antagonism
  - Cardiac
    - ↑ HR
    - ↑ Atrial inotropicity
    - ↑ Response to epinephrine
  - CNS
    - ↑ Excitatory amino acid (EAA) release
  - Renal
    - Diuresis

- Other methylxanthine effects
  - Increased catecholamine release
  - Phosphodiesterase (PDE) inhibition: results in increased levels of cyclic adenosine monophosphate (cAMP) that serves to augment adrenergic effects
  - Increased intracellular calcium uptake and storage: clinical significance is unknown
SEROTONIN

Serotonin is an indole alkylamine synthesized from tryptophan. Serotonergic neurons lie in or near midline nuclei in brainstem and project to various parts of cerebrum. There are 7 current serotonin receptor classes (5-HT<sub>1-7</sub>) with at least 15 subtypes. Serotonin has a wide variety of functions including vasoconstriction, inhibition of gastric secretion, enhanced platelet aggregation, stimulation of smooth muscle, and is naturally present in the central nervous system (CNS) as a neurotransmitter. Hallucinogenic drugs produce their electrophysiologic effects primarily through partial agonism at 5-HT<sub>2</sub> receptors. Serotonin syndrome involves 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors.

- Serotonin synthesis and metabolism
  
  ![Tryptophan Metabolism Diagram](image-url)

  - **Tryptophan**
    - tryptophan hydroxylase (rate limiting)
    - 5-OH-Tryptophan
      - l-aromatic acid decarboxylase
    - Serotonin
      - MAO, aldehyde dehydroxylase
    - 5HIAA

- Serotonin Agonists
  - Enhanced synthesis
    - L-tryptophan (associated with Eosinophilia Myalgia Syndrome – see Pharmaceutical Additives handout)
    - 5-OH-tryptophan
  - Direct Serotonin Agonists

<table>
<thead>
<tr>
<th>5-HT1A</th>
<th>Buspirone</th>
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<tbody>
<tr>
<td>5-HT1B</td>
<td>Triptans</td>
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<tr>
<td>5-HT1D</td>
<td></td>
</tr>
<tr>
<td>5-HT2A</td>
<td>Ergot alkaloids, LSD, mescaline, psilocibin</td>
</tr>
<tr>
<td>5-HT4</td>
<td>Metoclopramide, Cisapride</td>
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</tbody>
</table>

- Increased Serotonin Release
  - Amphetamines (MDMA)
  - Cocaine
  - Codeine derivatives
  - Dexfenfluramine
  - Fenfluramine
  - L-Dopa
- Inhibit Serotonin Metabolism
  - MAO-I
- Unknown Serotonin Effect
  - Lithium
- Inhibit Serotonin Uptake

<table>
<thead>
<tr>
<th>Amphetamines</th>
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<tr>
<td>Cocaine</td>
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<tr>
<td>Cyclic antidepressants</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>SSRIs</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>St. John’s Wart (Hypericum perforatum)</td>
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- Direct Serotonin Antagonists

<table>
<thead>
<tr>
<th>5-HT&lt;sub&gt;1&lt;/sub&gt;</th>
<th>Methysergide, cyproheptadine</th>
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<tbody>
<tr>
<td>5-HT&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Trazadone, nefazodone</td>
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<td>5-HT&lt;sub&gt;2&lt;/sub&gt;</td>
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<tr>
<td>5-HT&lt;sub&gt;2A&lt;/sub&gt;</td>
<td>Risperidone, olanzapine, ziprasidone, quetiapine, cyclic antidepressants</td>
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<tr>
<td>5-HT&lt;sub&gt;2C&lt;/sub&gt;</td>
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</tr>
<tr>
<td>5-HT&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Ondansetron, granisetron, metoclopramide</td>
</tr>
</tbody>
</table>

• Nicotine and similar alkaloids first stimulate then inactive nAChRs
• Botulinum toxin prevents release of ACh
• Alpha-latrotoxin (black widow) stimulates release of ACh and NE
• Cimetidine CYP3A4 inhibitor
  o Useful in dapsone-induced methemoglobinemia
  o Useful in toxicity from Gyromitra esculenta
• Terfendine and astemizole withdrawn for increased risk of TdP
• Hallucinogenic drugs produce their effects primary through 5-HT_2 receptors
• Serotonin syndrome primarily involves 5-HT_1A and 5-HT_2A receptors
• Methysergide (serotonin antagonist) linked to retroperitoneal fibrosis
• Fenfluramine and phentermine: weight loss drugs linked thickening of the leaflet and chordae tendineae of aortic and mitral valves, withdrawn from U.S. market in 1997
• Nicotine alkaloids (nicotine, coniine)
  o Trick to remember the hemlocks –
    ▪ Water Gate Candidate Scandal (Water hemlock, GABA, Cicutoxin, Seizures)
    ▪ Poison Control Network (Poison hemlock, Coniine, Nicotine)
QUESTIONS

1. A 22-year-old woman with resistant depression discontinued her phenelzine (Nardil) last week and arrives to hospital after using crack cocaine with complaints of abdominal pain. The medical resident prescribes the patient meperidine. She becomes agitated, hyperthermic, rigid, and hypereflexic with a profound startle response. What best explains her reaction?
   A. Excessive GABA release from the meperidine
   B. Excessive glutamate stimulation in the cerebellum from cocaine
   C. Excessive serotonin release from the cocaine and meperidine
   D. Serotonin antagonism from the phenelzine
   E. Probable concomitant methamphetamine abuse

   This patient’s symptoms are consistent with excessive serotonin or serotonin syndrome. The recent use of phenelzine along with the exposure to cocaine and administration of meperidine likely lead to significant amounts of serotonin in the CNS.

2. Which of the following statements is correct regarding neurotransmitters?
   A. Acetylcholine release is mediated via transmembrane pores unlike other neurotransmitters that use synaptic vesicles
   B. Adenosine antagonism leads to reduction in glutamate transmission
   C. Hallucinogenic drugs produce their effects primarily through partial agonism at 5-HT_4 receptors
   D. Nicotine first stimulates but then blocks nicotinic receptors both in the CNS and in skeletal muscle
   E. Norepinephrine is the neurotransmitter of preganglionic sympathetic neurons

   Nicotine first stimulates but then blocks nicotinic receptors both in the CNS and in skeletal muscle. Acetylcholine uses synaptic vesicles primarily for its release. Adenosine antagonism leads to an increase glutamate transmission. Hallucinogenic drugs primarily stimulate 5-HT_2 receptors. Norepinephrine is a neurotransmitter of postganglionic sympathetic neurons.

3. Which of the following systems is involved with an organophosphate poisoning but not encountered in a diphenhydramine overdose?
   A. Central nervous system
   B. Glands (salivary, sweat, lacrimal)
   C. Skeletal muscle
   D. Stomach and intestines
   E. Urinary (bladder)

   All of the organ systems listed except skeletal muscles contain muscarinic receptors. The nicotinic receptors of skeletal muscles would no be effected with an exposure to a drug with antimuscarinic properties such as diphenhydramine.

4. The antagonism of adenosine A1 receptors is most likely to result in which of the following clinical manifestations?
   A. Bradycardia
   B. Diaphoresis
   C. Hyperkalemia
   D. Hypotension
E. Seizures

Adenosine is primarily involved in the reduction of excitatory neurotransmitter release including glutamate, GABA, norepinephrine, serotonin, and acetylcholine. Its greatest effect is in the inhibition of glutamate release and neuronal excitation. Seizures are a manifestation of this excitation and may occur with adenosine A1 antagonism.

5. Which of the following best explains the mechanism of action for the botulinum toxin?
   A. Blocks presynaptic N-subtype calcium channels
   B. Inhibits magnesium binding at the NMDA receptor
   C. Phosphodiesterase (PDE) inhibition with increase cyclic adenosine monophosphate (cAMP)
   D. Prevents neurotransmitter vesicle from docking with cell membrane
   E. Sodium channel and I_{kr} blockade

The botulinum toxin enters the presynaptic terminal as two chains. Its primary mechanism of action is preventing synaptic vesicles containing acetylcholine from binding to the terminal membrane. This results in a reduction of acetylcholine release and post-synaptic acetylcholine receptor changes.

1C 2D 3C 4E 5D