Autonomic Nervous System – A Quick Review of Clinical Concepts

Cardiology 63 and 64

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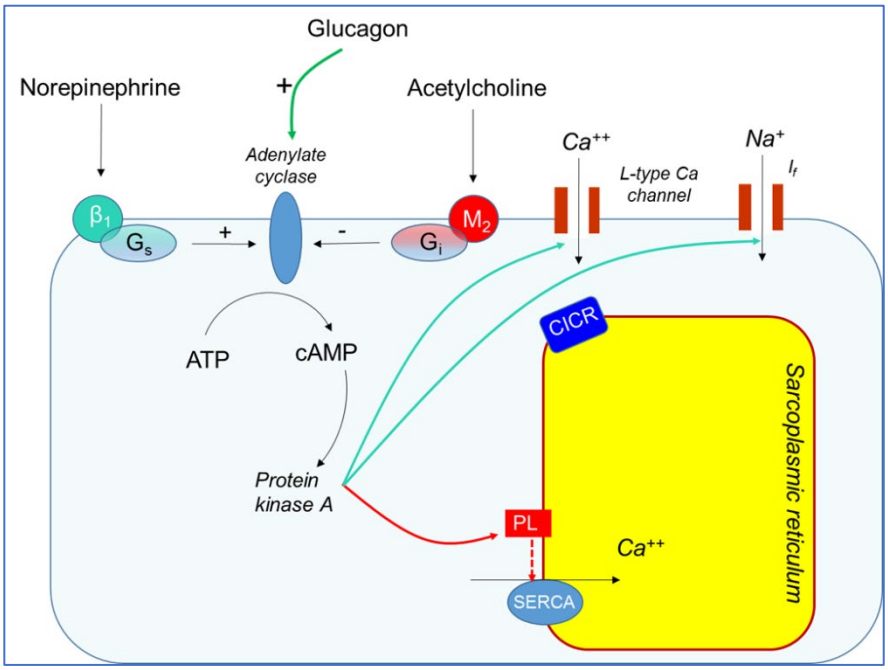
1. Beta Blocker Toxicity

a. Beta Receptors - review

i. B1 - receptors are coupled to Gs-proteins, which activate adenylyl cyclase to form cAMP from ATP. Stimulation of β-receptors results in ↑ cAMP levels in the cell.

ii. ↑ cAMP activates a cAMP-dependent protein kinase (PK-A) that phosphorylates L-type calcium channels, which causes **increased calcium** entry into the cell.



iii. B-1 – receptors in the heart

1. ↑ **calcium** entry leads to enhanced release of calcium by the sarcoplasmic reticulum (SR) - **increases contractility**.

2. PK-A also phosphorylates sites on the SR, which leads to increased release of calcium through the ryanodine receptors (ryanodine-sensitive, calcium-release channels) associated with the SR.

    a. Provides more calcium for binding troponin-C, which then **increases contractility**.

3. PK-A can phosphorylate myosin light chains, which may contribute to the positive inotropic effect of β- stimulation.

4. Gs-protein activation also **increases heart rate**.

iv. B-2 Receptors

1. Vascular smooth muscle

    a. β2-receptors are **activated by norepinephrine** released by sympathetic adrenergic nerves **or** by circulating **epinephrine**.

    b. These receptors are coupled to a Gs-protein, which also stimulates the formation of cAMP.

    c. Although ↑ cAMP enhances cardiac myocyte contraction**, in vascular smooth muscle** an ↑ in cAMP leads to **smooth muscle relaxation** and **vasodilation**

    d. **Why?** cAMP inhibits myosin light chain kinase responsible for phosphorylating smooth muscle myosin. Thus, ↑ in intracellular cAMP caused by β2-agonists inhibits myosin light chain kinase thereby producing less contractile force.

    e. **Blockade of β2-receptors** causes a **small degree of vasoconstriction** by removing the small β2-receptor vasodilator influence which normally opposes the more powerful alpha-adrenoceptor mediated vasoconstrictor effects.

2. Bronchial smooth muscle

    a. Same mechanism as in vascular smooth muscle

    b. In **bronchial smooth muscle** an ↑ in cAMP leads to smooth muscle relaxation and therefore **bronchodilation**.

    c. **Blocking the β-2 receptors** will therefore inhibit this bronchodilation and lead to **bronchoconstriction**.

b. **B-blockers** modulate activity of myocyte & vascular smooth muscle contraction by **↓ Ca^{++} entry into the cell.**

	Normal Response to Receptor Stimulation	**Effects of Receptor Blockade**
B1-receptors in heart	↑ contractility, ↑ HR, ↑ CO	**↓ Contractility, ↓ HR, ↓ CO, hypotension**
β2-receptors in bronchial smooth muscle	Smooth muscle relaxation with bronchodilation	**Bronchoconstriction*** Wheezing, dyspnea, ↑ RR
β2-receptors in vascular smooth muscle	Smooth muscle relaxation with mild vasodilation	Loss of **β2** receptor induced vasodilation resulting in **unopposed α-1 vasoconstriction** Skin is pale and cool

Note: Clinically β-blockers actually have relatively little vascular effect because β2-adrenoceptors have only a small modulatory role on basal vascular tone. Nevertheless, blockade of β2-adrenoceptors is associated with a small degree of vasoconstriction in many vascular beds.

- *Remember that **bronchoconstriction** is found with **non-selective β-blockers** such as propranolol (due to their **blockade of both β-1 and β-2 receptors**).
    - Propranolol is also the **most lipophilic** β-blockers – can cross blood-brain-barrier and cause **altered mental status**

- Selective β-blockers such as atenolol, esmolol, and metoprolol will typically **not** produce bronchoconstriction unless at very high doses (in which case they behave more like non-selective blockers).

- Esmolol - has a very **short half-life** and can only be **given IV** – thus often used to control tachyarrythmias in the perioperative setting.

c. **Common drugs used to treat β-blocker overdose** (**can be considered "first line"**)

i. Vasopressors – Epinephrine and Norepinephrine

1. **Vasopressors** used in the **treatment of β-blocker overdose**

2. Epinephrine
   a. Activates **β1 and β2** receptors
   b. Results: ↑ contractility, ↑ HR, ↑ CO, ↑ BP, bronchodilation (↓ wheezing and dyspnea)

3. Norepinephrine
   a. **Primarily an agonist at α_1-adrenergic receptors,** with **modest β_1-adrenergic activity**
   b. Many guidelines suggest norepinephrine before using epinephrine due to the increased risks associated with epinephrine infusion (tachyarrhythmias, splanchnic hypoperfusion, metabolic abnormalities).

4. Often need very high doses of vasopressors due to the β-blockade

ii. Glucagon

1. Independently **activates myocardial adenylate cyclase**, bypassing the impaired β-receptor – **see figure above**
2. Produces same sympathetic NS effects as stimulation of the actual β-receptors by epi / norepinephrine

d. Other autonomic drugs that are **not** generally useful in treating β-blocker toxicity

i. Phenylephrine - a pure **alpha agonist** and won't ↑ heart rate or contractility

ii. Dobutamine - a **positive inotrope** but does not have any significant chronotropic effect. **Won't** ↑ heart rate which is an important component of improving cardiac output.

1. Dobutamine can also cause **vasodilation** which could **worsen hypotension**

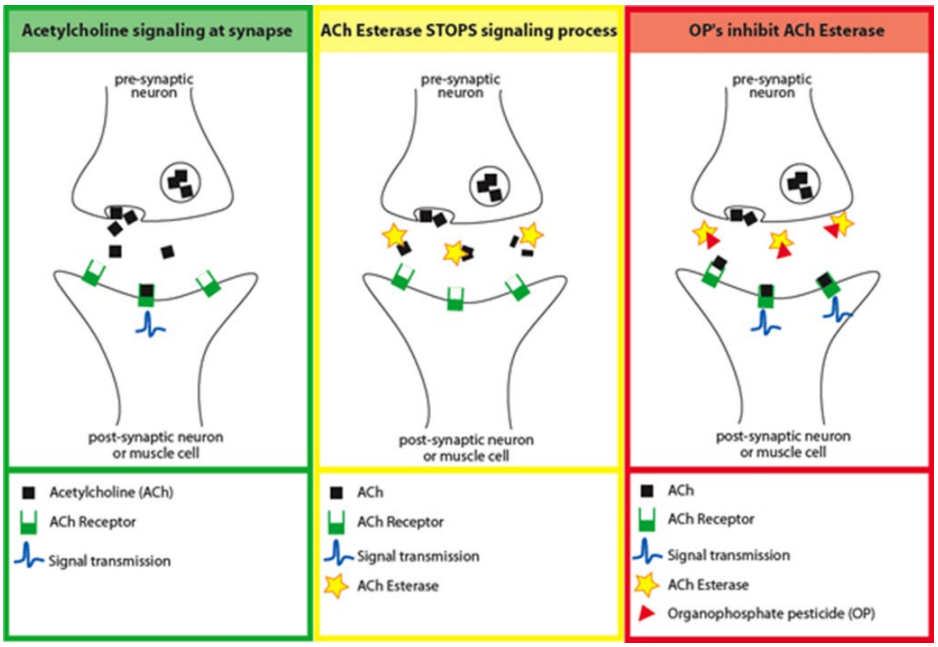
iii. Atropine - inhibits parasympathetic action on heart by blocking muscarinic receptors, but the problem in a β-blocker overdose is not excessive parasympathetic activity but blockade of the sympathetic NS.

2. Organophosphate poisoning

a. Organophosphate compounds (which can include insecticides and chemical nerve agents) inhibit the enzyme **cholinesterase**

b. Inhibition of cholinesterase leads to **acetylcholine accumulation** at nerve synapses and NMJ resulting in overstimulation of acetylcholine receptors – **excess parasympathetic activity**

c. Excess acetylcholine results in a **cholinergic crisis** with both central and peripheral findings



http://depts.washington.edu/opchild/acute.html

d. Classic clinical presentation due to effects of excessive parasympathetic activity

i. SLUDGE

1. S: Salivation
2. L: Lacrimation
3. U: Urinary incontinence
4. D: Defecation
5. G: GI distress
6. E: Emesis

ii. DUMBELS

1. D: Defecation
2. U: Urination
3. M: Muscle weakness; miosis
4. B: **Bradycardia, bronchorrhea, bronchospasm*** (**Killer B's**)
5. E: Emesis
6. L: Lacrimation
7. S: Salivation

e. Management

i. **Atropine** – **most important**

1. **Competitive antagonist of acetylcholine** at central & peripheral **muscarinic** receptors
2. Reverses effects of excessive cholinergic stimulation
3. Does not work at nicotinic receptors - will **not reverse muscle weakness**

ii. **Pralidoxime** (2-PAM Chloride)

1. Displaces organophosphates from active site of acetylcholinesterase - **reactivates the enzyme**
2. Must be given as soon as possible for maximum effectiveness. The organophosphate (or nerve agent) / acetylcholinesterase complex "**ages**" and the longer they are bound, the less likely that pralidoxime will be able to displace the organophosphate from cholinesterase and regenerate the enzyme.

I will not test you on these ☺ **– just providing them as a very basic review of what Dr. Smith covered in case they are helpful in preparing for boards, etc.**

Drug(s)	Mechanism of Action	Physiologic Effects	Additional Notes
Ca^{++} channel blockers	Block inward movement of Ca^{++}	Bradycardia, ↓ cardiac output, vasodilation May cause hyperglycemia (vs. hypoglycemia in B-blocker overdose)	Dihydropyridines (amlodipine): effect on vasculature **>>>** heart; vasodilation Non-dihydropyridines (diltiazem, verapamil): effect on heart **>>>** vasculature; ↓ HR and contractility
Digoxin	Inhibits sodium-potassium (ATPase)	Bradyarrhythmias, heart blocks Yellow-green halos around objects	Labs - hyperkalemia
Alpha blockers	Antagonizes α1-adrenergic receptors	↓ peripheral vascular resistance (PVR) (vasodilation); ↓ blood pressure (BP) Reflex ↑ HR	
Hydralazine	Relaxes arteriolar smooth muscle; ↑ intracellular cGMP	Vasodilation ↓ BP	Mechanism not completely understood
Phenylephrine	Pure alpha agonist	Vasoconstriction, ↑ BP No direct effect on HR	
Nitrates (nitroglycerine, nitroprusside), PDEI	↑ intracellular cGMP	Vasodilation, smooth muscle relaxation ↓ BP	PDEI = phosphodiesterase inhibitor
Fenoldopam, Dopamine (low dose)	Dopamine D1 receptor stimulation	↓ PVR primarily in renal capillary beds ↑ renal blood flow, natriuresis, and diuresis ↓ BP	

Drug(s)	Mechanism of Action	Physiologic Effects	Additional Notes
Doxazosin, prazosin	α1-receptor blockade –	Doxazosin, prazosin: smooth muscle relaxation in arterioles (alpha-1b receptors); Vasodilation and ↓ BP Alfuzosin, tamsulosin: smooth muscle relaxation in bladder neck and prostate (alpha-1a receptors)	
Physostigmine	Reversibly binds/inactivates acetylcholinesterase; ↑ amount of acetylcholine at cholinergic synapse	SLUDGE/MUDPILES Muscle twitching/fasciculations	Used to manage and treat anticholinergic (antimuscarinic) toxicity and glaucoma
Edrophonium	Reversible acetylcholinesterase inhibitor ↑ of acetylcholine at synapse, NMJ	↑ muscle tone and strength; twitching SLUDGE/MUDPILES	No longer used for dx of myasthenia gravis Reversal of non-depolarizing neuromuscular blocking agents - however, neostigmine is preferred due to its longer duration of action
Donepezil	Centrally acting acetylcholinesterase inhibitor; relatively specific for ACHase in brain	Overdose can cause cholinergic crisis w/ SLUDGE/MUDPILES	Used in treatment of Alzheimer disease
Methyldopa	Alpha-2 agonism in the CNS to ↓ central adrenergic outflow	↓ PVR, ↓BP	Methyldopa is converted to alpha-methylnorepinephrine in the central nervous system which then binds to alpha-2 adrenergic receptors in the brainstem

Remember, you got this!