Autonomic Nervous System – A Quick Review of Clinical Concepts

Cardiology 64 and 65

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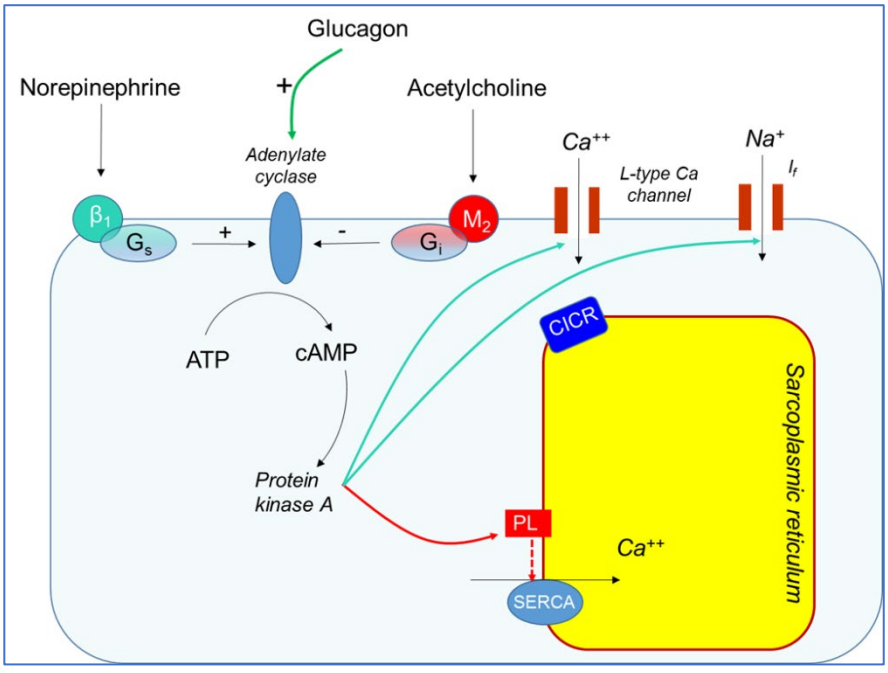
1. Beta Blocker Toxicity

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**.

    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 Simulation	**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

- *Remember that bronchoconstriction is found with **non-selective β-blockers** such as propranolol (due to their **blockade of β-2 receptors**). 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

i. Epinephrine

1. **First line drug** used in the **treatment of β-blocker overdose**
2. Activates **β1 and β2** receptors
3. Results: ↑ contractility, ↑ HR, ↑ CO, ↑ BP, bronchodilation (↓ wheezing and dyspnea)
4. Often need to use very high doses due to the β-blockade

ii. Glucagon

1. If inadequate response to treatment with epinephrine, should consider administration of glucagon
2. Independently activates myocardial adenylate cyclase, bypassing the impaired β-receptor – **see figure above**
3. 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 the treatment of 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.

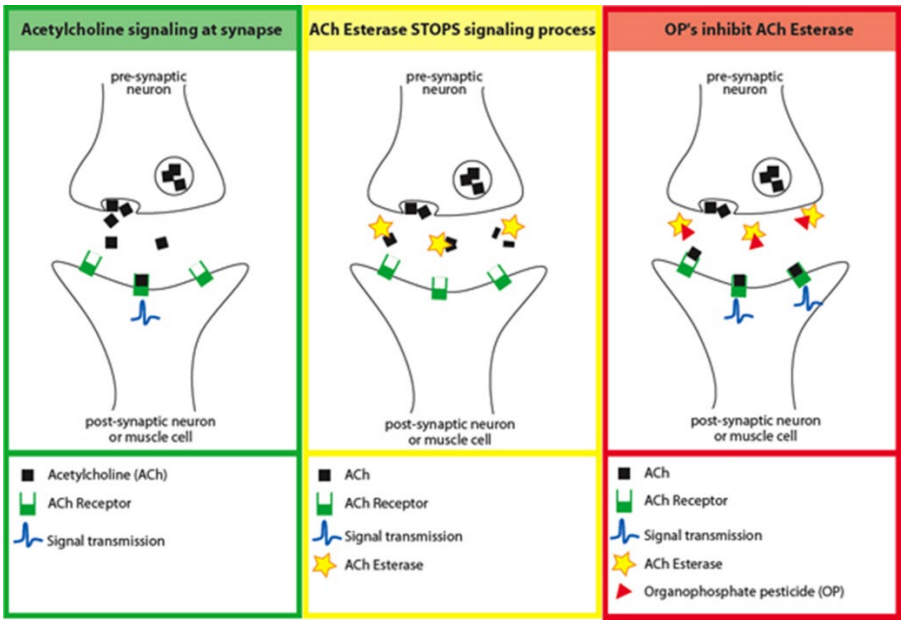
iii. Atropine - inhibits parasympathetic action on heart but the problem in a β-blocker overdose is not excessive parasympathetic activity but blockade of the sympathetic NS.

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. 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.

Remember, you got this!