AUTONOMIC NERVOUS SYSTEM 2
Receptors
Learning Objectives

1. List the different types of cholinergic and adrenergic receptors.

2. Describe the cellular actions of ACh and NE in terms of receptors activated and second messenger systems involved.

3. Explain the differential effect on NE on cardiac muscle and smooth muscle.

4. Describe the role of $\alpha_2$ receptors in regulating NE release from sympathetic nerve terminals.
Types of Receptors

SNS:
Postganglion: Nicotinic
Effector Organ: $\alpha_1, \alpha_2, \beta_1, \beta_2$ & Muscarinic

PNS:
Postganglion: Nicotinic
Effector Organ: Muscarinic

The physiological event elicited by a neurotransmitter depends on the RECEPTOR being occupied… NOT by the transmitter
Cholinergic Receptors

Cholinergic receptors are divided into *nicotinic* and *muscarinic* receptors

All *nicotinic* receptors are ligand-gated cation-selective channels (ionotropic receptors)

*Muscarinic* receptors are G protein-linked (GTP-binding proteins) transmembrane receptors (metabotropic receptors) - activation can effect changes in intracellular 2nd messengers – Ca\(^{2+}\) and cAMP
Nicotinic and Muscarinic: Both receptor types bind Ach (named after nicotine & muscarine that bind to them and mimic ACh effects)

Nicotinic receptors:
Effect of ACh binding is always stimulatory
Found on
(a) Motor end plates of skeletal muscle
(b) ALL postganglionic neurons of both SNS & PNS
(c) Chromaffin cells of the adrenal medulla

Muscarinic receptors:
Effect of ACh binding can be either inhibitory or excitatory
Found on
(a) ALL effector organs of PNS (heart, GI tract, bronchioles, bladder, male genitalia)
(b) Certain effector organs of SNS (sweat glands, vascular smooth muscle of skeletal muscle)
Adrenergic Receptors

Found in target tissues of SNS

Activated by catecholamines NE (from postganglionic neurons) & E (from adrenal medulla)

Divided into 2 types: $\alpha$ and $\beta$

Each type is subdivided into $\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$

Each type has a different mechanism of action = different physiologic effects

Physiologic responses to NE binding are tissue-specific and cell-type specific...so although the mechanism is the same (increased cAMP) the responses are different
The physiological event elicited by a neurotransmitter depends on the RECEPTOR being occupied… NOT by the transmitter.

Receptors act through different second messenger pathways involving G proteins.
Which receptor type is found on the chromaffin cells of the adrenal medulla?

1. Alpha 1
2. Alpha 2
3. Beta 1
4. Beta 2
5. Nicotinic
6. Muscarinic
Cholinergic System
Cholinergic Pharmacology

**Somatic Nervous System**

Motor neuron → ACH → Nicotinic receptor (N1 or Nm) → Skeletal muscle

**Autonomic Nervous System**

Preganglionic neuron → ACH → Nicotinic receptor (N2 or Nn) → Post gang. neuron → ACH → Parasymp → Muscarinic receptor

Smooth and cardiac muscle and glands
The Parasympathetic NS

Target Organ (Effector)

Sacral

Preganglionic Neuron

Neuroeffector Junction

Post-ganglionic

ACh

Cranio- (CNs 3, 7, 9, 10)

Pelvic Ns

Parasympathetic ganglion

CHOLINERGIC SYSTEM
Cholinergic Neurons

- Acetylcholine secreted at preganglionic synapses of autonomic neurons and postganglionic neurons of parasympathetic neurons and some sympathetic neurons.
- Choline acetylated and the acetylcholine packaged.
- Acetylcholine hydrolyzed by cholinesterase to acetate and choline.
- Choline taken up by preganglionic neuron by a Na\(^+\)-coupled secondary transport system.
Nicotinic ‘ionotropic’ Receptors

• Located in CNS Autonomic Ganglia and neuromuscular junction (NMJ)

• CNS and Ganglionic receptors ($N_2/N_n$) distinct from NMJ nicotinic receptors ($N_1/N_m$)

• Consists of 5 subunits: Requires 2 ACh molecules binding to two α subunits for channel opening
Nicotinic Receptor: Ion channel Selective for \( \text{Na}^+ \) & \( \text{K}^+ \)

Equally permeable to \( \text{Na} \) and \( \text{K} \)

More \( \text{Na}^+ \) entry
Than \( \text{K}^+ \) leaving
Causes depolarisation
G Proteins

Autonomic receptors are coupled to HETEROTRIMERIC GTP binding proteins (G proteins)

G PROTEINS:
Serpentine cell membrane proteins: span the cell membrane 7 times winding like a “snake”
3 subunits: $\alpha$, $\beta$, $\gamma$
- 16 $\alpha$; 6 $\beta$; 12 $\gamma$ – provides various members of 5 g protein families
Stimulatory ($G_s$) or inhibitory ($G_i$)
- $\alpha$ subunit binds to either GDP (inactive) /GTP (active) – stimulatory/inhibitory activity in a subunit
Couple receptors to enzymes (adenylyl cyclase/ PLC) generating 2nd messengers (cAMP/ IP$_3$) which amplifies message and executes final physiological action
Muscarinic ‘metabotropic’ Receptors

Extracellular acetylcholine

$M_1, M_3, M_5$  $M_2, M_4$

Key Effectors
(examples)

$\uparrow$PLC$\beta$
$\uparrow$[Ca$^{2+}$]$_i$
$\uparrow$MAP kinases
$\downarrow$M current

$\downarrow$Adenylyl cyclase
$\uparrow$MAP kinases
$\uparrow$GIRK channels
$\downarrow$Voltage-operated Ca$^{2+}$ channels

Intracellular
Muscarinic ‘metabotropic’ Receptors

G-Protein Coupled Receptors

Muscarinic Receptors

M1 / M5
Gq

↑IP$_3$ / DAG

↑Ca$^{2+}$

↑PKC

M2 (SA Node) / M4
Gi

↓cAMP

↑K$^+$ channel open

↑Ca$^{2+}$

↑PKC

M3 (non vascular smooth muscle)
Gq

↑IP$_3$ / DAG
Physiological Effects of Muscarinic Receptor Activation

Muscarinic Receptors

M1
CNS
Autonomic Ganglia
Exocrine gland
Parietal Cell

M2
Cardiac; SA & AV node
Autonomic Ganglia

M3
Smooth Muscle contraction
GI Glands Secr
Bronchial Secr
Salivation
Sweat
Vasodilation

M4
CNS

M5
CNS
<table>
<thead>
<tr>
<th>Target Organ</th>
<th>Effect</th>
<th>Outcome</th>
<th>Receptor Type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The Eye</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circular muscle</td>
<td>Contraction</td>
<td>Pupil constriction (miosis)</td>
<td>$M_3$</td>
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<tr>
<td>Ciliary muscle</td>
<td>Contraction</td>
<td>Accommodation for near vision</td>
<td>$M_3$</td>
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<tr>
<td><strong>Exocrine Glands</strong></td>
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<td></td>
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<tr>
<td>Lacrimal, Nasal, Salivary</td>
<td>Secretion</td>
<td>Secretion</td>
<td>$M_3$</td>
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<tr>
<td><strong>The Lungs</strong></td>
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<tr>
<td>Bronchial Smooth Muscle</td>
<td>Contraction</td>
<td>Some bronchoconstriction</td>
<td>$M_3$</td>
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<tr>
<td>Bronchial glands</td>
<td>Increased secretion</td>
<td></td>
<td>$M_3$</td>
</tr>
<tr>
<td><strong>Heart</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SA node</td>
<td>↓ excitability</td>
<td>↓ HR</td>
<td>$M_2$</td>
</tr>
<tr>
<td>AV node</td>
<td>↓ conduction velocity</td>
<td></td>
<td></td>
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<tr>
<td>Myocardial muscle</td>
<td>↓ in contractile force (atria only)</td>
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<td><strong>Gastrointestinal</strong></td>
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<tr>
<td>GIT wall muscles</td>
<td>Contraction</td>
<td>↑ motility and tone</td>
<td>$M_3$</td>
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<tr>
<td>Sphincters:</td>
<td>Relaxation</td>
<td></td>
<td>? Peptides</td>
</tr>
<tr>
<td>Pancreas</td>
<td>↑ enzyme secretions</td>
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<td><strong>Urinary Bladder</strong></td>
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<tr>
<td>Detrusor</td>
<td>Contraction</td>
<td>Micturition</td>
<td>$M_3$</td>
</tr>
<tr>
<td>Trigone (sphincter)</td>
<td>Relaxation</td>
<td></td>
<td>? Peptides</td>
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<td><strong>Reproductive Tract</strong></td>
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<tr>
<td>Male</td>
<td>Vasodilation</td>
<td>Erection</td>
<td>ACh / NO</td>
</tr>
</tbody>
</table>
Activation of the receptor on postganglion cells lead to:

A. opening of ligand-gated Ca$^{+2}$ channels
B. opening of ligand-gated Na$^{+}$ channels
C. increased levels of cAMP
D. increased levels of diacylglycerol
E. increased levels of IP$_{3}$

B.