The Nicotinic Acetylcholine Receptor (nAChR)

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Introduction

- Overview
- Receptor composition
- Structure of the receptor
- How the receptor is activated
  - What activates the receptor
  - How the ion channel opens
- Types and functions of the receptor
- Why this receptor is important to the practice of anesthesia
Overview

- **Locations:**
  - Peripheral Nervous System
  - Central Nervous System

- **Types:**
  - Muscle-type
  - Neuronal-type
  - Non-neuronal type

- **Functions**
  - Dependent upon location and composition

http://www.jbc.org/content/283/32.cover-expansion
## Receptor Composition

### SUBUNITS

<table>
<thead>
<tr>
<th>Receptor</th>
<th>α subunit</th>
<th>Non-α subunits</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle-type nAChR&lt;sup&gt;5&lt;/sup&gt;</td>
<td>α1</td>
<td>β1, γ, δ, and ε</td>
<td>α1β1γδ</td>
</tr>
<tr>
<td>Neuronal-type nAChR&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heteromeric</td>
<td>α2, α3, α4, α5, α6, α7, α8, α9, and α10</td>
<td>β2, β3, and β4</td>
<td>α4β2</td>
</tr>
<tr>
<td>Homomeric</td>
<td>α7, α8, and α9</td>
<td>None</td>
<td>α7</td>
</tr>
<tr>
<td>Nonneuronal-type nAChR</td>
<td>α</td>
<td>a</td>
<td>a</td>
</tr>
</tbody>
</table>

### SUBTYPES

**Table 1. Types of nAChRs and Their Subunit Makeup**

All 17 subtypes listed for the muscle and neuronal types have been found throughout the tissues and cells of the body where the nonneuronal-type nAChR is located.<sup>9</sup>

Abbreviation: nAChR, nicotinic acetylcholine receptor.

Rossman, 2011
Subunits and Subtypes

http://www.jyi.org/research/re.php?id=88
1. Extracellular domain
   - Binding sites
2. Transmembrane domain
   - Channel gate
3. Intracellular domain
   - Regulates expression

Zouridakis et al., 2009
Conformational States

1.

2.

3.
# Types of Binding Proteins

<table>
<thead>
<tr>
<th>Binding protein</th>
<th>Effect</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agonist</td>
<td>Binds to the ligand binding sites activating the receptor and results in the opening of the gated channel.</td>
<td>Acetylcholine and succinylcholine (^1^0)</td>
</tr>
<tr>
<td>Competitive antagonist</td>
<td>Binds to the ligand binding sites prohibiting the binding of an agonist and, therefore, the receptor cannot be activated. This effect is overcome if there is an increase in the concentration of an agonist (acetylcholine) in the area surrounding the nAChR.</td>
<td>Vecuronium, pancuronium, and mivacurium (^1^0)</td>
</tr>
<tr>
<td>Noncompetitive antagonist</td>
<td>Does not bind directly to the ligand binding sites and can block the opening of the channel or bind to an allosteric site on the nAChR and cause inhibition of the receptor.</td>
<td>Lidocaine, (^1^2) procaine, (^1^2) and isoflurane (^1^1)</td>
</tr>
</tbody>
</table>

*Table 2. Effects of Binding Proteins on the nAChR*

Abbreviation: nAChR, nicotinic acetylcholine receptor.
Opening of the Gate

Bulky hydrophobic Leu side chains of M2 helices close the channel.

Binding of two acetylcholine molecules causes twisting of the M2 helices.

With receptor sites occupied, the M2 helices have smaller, polar residues lining the channel.

http://www.biochem.arizona.edu/classes/bioc462/462a/NOTES/LIPIDS/transport.html
Muscle-Type nAChR

http://physiwiki.wetpaint.com/page/Autonomic+Nervous+System
Muscle-Type nAChR Cont’d

http://www.frca.co.uk/article.aspx?articleid=100618#
Neuronal-Type nAChR

Kalamida et al., 2007

Neuronal-Type nACHr Cont’d

- Selective to calcium
- Increases intracellular calcium by:
  - Direct influx
  - VOCC
  - Release from intracellular stores

http://www.bath.ac.uk/bio-sci/research/profiles/wonnacott-s.html
Non-neuronal Type nAChR

- **Location**
  - Endocrine
  - Endothelial
  - Epithelial
  - Immune

- **Composition**
  - Hetero/Homomeric
  - All 17 subunit subtypes

http://www.hindawi.com/journals/mi/2010/642462/fig1/
Importance for the CRNA

MEMORY

MUSCLE CONTRACTION
Memory Formation

- General anesthetics
  - Non-competitive antagonist

- Inhibits calcium permeability of the cell
Muscle Contraction

- Local anesthetics
- Non-depolarizing muscle relaxants
- Depolarizing muscle relaxants
- Inhalational agents

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# Effects of Anesthetic Agents

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Drug</th>
<th>Cation involved</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle-type</td>
<td>Ester and amide local anesthetics</td>
<td>Sodium</td>
<td>Act as noncompetitive antagonists inhibiting the influx of sodium into the muscle cell, preventing muscle contraction.(^{11,12})</td>
</tr>
<tr>
<td></td>
<td>Nondepolarizing muscle relaxants</td>
<td>Sodium</td>
<td>Act as competitive antagonists blocking the binding of acetylcholine to the receptor, thus preventing activation of the receptor and muscle contraction.(^{10})</td>
</tr>
<tr>
<td></td>
<td>Depolarizing muscle relaxants</td>
<td>Sodium</td>
<td>Act as agonists transforming the receptor into the desensitized state, inhibiting activation of the nAChR, thus preventing contraction of the muscle.(^{10})</td>
</tr>
<tr>
<td>Neuronal-type</td>
<td>Inhalation anesthetics</td>
<td>Calcium</td>
<td>Act as noncompetitive antagonists and prevent an influx of calcium into the neuronal cells, thus inhibiting the initiation of mechanisms that lead to memory formation.(^{9,10})</td>
</tr>
</tbody>
</table>

**Table 3. The Effects of Anesthetic Agents and Adjuncts on the nAChR**

Abbreviation: nAChR, nicotinic acetylcholine receptor.

Rossman, 2011
# Pathophysiology

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Upregulated Receptors</th>
<th>Downregulated Receptors</th>
</tr>
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<tbody>
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<td>Upper/Lower motor neuron lesions, burns,</td>
<td></td>
<td>Myasthenia Gravis, congenital myasthenic syndromes</td>
</tr>
<tr>
<td>immobilization, denervation injuries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depolarizing muscle relaxants</td>
<td>X</td>
<td>Upward arrow</td>
</tr>
<tr>
<td>Nondepolarizing muscle relaxants</td>
<td>Upward arrow</td>
<td>Downward arrow</td>
</tr>
</tbody>
</table>

- **Diseases**: Upper/Lower motor neuron lesions, burns, immobilization, denervation injuries
- **Upregulated Receptors**: Myasthenia Gravis, congenital myasthenic syndromes
- **Downregulated Receptors**: Myasthenia Gravis, congenital myasthenic syndromes
Located widely throughout the body and is involved in numerous bodily functions.

- Muscle, neuronal, and non-neuronal types

This is the target of many anesthetics that we will use.

- Muscle contraction and memory

Understanding of this receptor will help us to appropriately reach the anesthetic goals for our patient.
Questions


References