Muscarinic Pharmacology: No Need to Memorize

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PROLOGUE
The following is a summary of a one hour lecture on muscarinic receptor agonists provided to pharmacy students in their second semester of professional study. During the previous semester students complete prerequisite courses in physiology and biochemistry. The lecture is preceded by lectures covering pharmacokinetics, pharmacodynamics, receptor theory, and the autonomic nervous system (ANS). The lecture represents the students’ first exposure to a pharmacologic class of agents. In conjunction with the pharmacology course, students are enrolled in a medicinal chemistry course. The objectives of the lecture are to present the pharmacology of direct muscarinic receptor agonists, and to assist the students develop an approach to the application of prerequisite knowledge to the study of pharmacology.

Muscarinic pharmacology is frequently one of the first topics covered in entry-level pharmacology courses. As a result, it is important that students apply prerequisite knowledge (e.g., physiology, biochemistry, pharmacodynamics, and receptor theory) to the comprehension of pharmacology. If students attempt to understand pharmacology, the quantity of memorization decreases. Although muscarinic agonists are generally not found among lists of the “Top 200” prescription medications they serve as a useful model class. Prior to the lecture students are provided a few scenarios and exercises to prepare them for the study of muscarinic pharmacology (Appendix).

The pharmacology of muscarinic agonists is presented using an organ system approach. The major target organs of muscarinic agonists include: blood vessels, heart, eyes, lungs, and gastrointestinal and urinary smooth muscle. For each organ system the effect of stimulation of muscarinic receptors is presented with emphasis on correlation to the activities of the parasympathetic nervous system. Based upon the effect on organ function, potential therapeutic uses and adverse effects are discussed. Examples of agents are provided and distinguishing features presented. It is hoped that at the conclusion of the lecture students will be able to apply knowledge of the ANS to muscarinic pharmacology and the only information required in preparation is knowledge of the five muscarinic receptor subtypes. (Appendix).

Direct Muscarinic Agonists
Agents that mimic the effects of acetylcholine include direct receptor agonists and indirect agonists. An example of an indirect cholinergic agonist would be an agent that inhibits the breakdown of acetylcholine by acetylcholinesterase. The indirect agonists will not be discussed during this lecture.

The study of cholinergic pharmacology begins with the neurotransmitter acetylcholine. Acetylcholine activates muscarinic and nicotinic receptors. Pharmacologically, it is generally desirable to develop agents that are “selective” for one receptor type. With regard to cholinergic pharmacology, agents that are relatively selective for muscarinic receptors have been developed. These selective muscarinic agonists offer the advantage of lack of nicotinic effects (e.g., stimulation of skeletal muscle contraction).

The clinically available direct muscarinic agonists are divided into two classes. The choline esters are structural analogs of acetylcholine and the alkaloids are analogs of naturally occurring substances. With the exception of acetylcholine, agents are selective for muscarinic receptors as compared to nicotinic receptors, but do not distinguish between the subtypes of muscarinic receptors. That is, they activate M1, M2, M3, M4, and M5 receptors. Muscarinic receptors are classified as M1- M3 based upon the results of cloning and pharmacologic experimentation. All muscarinic receptors are G-protein linked receptors. The second messenger systems of the muscarinic receptors are generally thought to be inhibition of adenylate cyclase for the M2 and M4 subtypes and activation of phospholipase C for the M1, M3, and M5 subtypes. Additional second messenger systems probably exist for some subtypes.

Muscarinic receptors are located in many areas of the body (Table I). As a result of the lack of selectivity, muscarinic agonists have diverse and far reaching effects. Nevertheless due to their inability to activate nicotinic receptors, as compared to acetylcholine, the muscarinic agonists are pharmacologically preferred. In theory, development of an agent selective for one of the subtypes of muscarinic receptors would possess enhanced efficacy and decreased adverse effects. A few experimental agents exist, but no selective agents are currently approved for use in the United States.

Understanding the pharmacology of muscarinic agonists relies upon knowledge of the parasympathetic nervous system. The parasympathetic nervous system is active mainly at rest and is responsible for maintaining homeostasis and conserving energy. The effect of stimulation of muscarinic receptors on the function of various organ systems will in general mimic parasympathetic stimulation. Based upon the effects of parasympathetic stimulation, it is easy to predict therapeutic uses and adverse effects of the muscarinic receptor agonists.

Cardiovascular System
The cardiovascular effects of any agent include two components. First the direct effects of stimulating or blocking receptors on the blood vessels and the heart must be considered. Second, a change in blood pressure and/or heart rate can...
The direct effect of activation of M2 receptors in the heart is to decrease myocardial activity, namely negative chronotropic, dromotropic, and inotropic effects occur. M2 receptors inhibit adenylyl cyclase activity and enhance potassium current, both of which lead to decreased activation of the myocardial cells(7). In pacemaker cells this slows the rate of spontaneous depolarization. A negative inotropic effect decreases myocardial oxygen demand. These cardio-depressant effects are a predictable consequence of mimicking the parasympathetic nervous system and are consistent with energy conservation.

Changes in blood pressure can activate baroreceptors and produce a centrally mediated reflex. Administration of a muscarinic agonist which lowers blood pressure could stimulate a reflex tachycardia. The direct effect of a muscarinic agonist is to lower heart rate. Several factors are important in determining if the direct or indirect effects predominate including: (i) the rate of administration; (ii) the dose; and (iii) the baseline blood pressure and heart rate. Generally large, rapid changes in arterial blood pressure are more likely to provoke a reflex as compared to gradual or small changes in blood pressure. Intravenous administration of a muscarinic agonist would be more likely to stimulate a reflex than oral administration(1). If a large dose is administered the direct effects could overcome the reflex. For example, a low dose will decrease blood pressure and produce a reflex increase in heart rate. A large dose will lower blood pressure and heart rate. In this case the direct effect on the M2 receptors in the heart overcomes the baroreceptor reflex mediated increase in heart rate. The baseline blood pressure and heart rate of the patient can influence the magnitude of the change. The cardiovascular effects produced by administration of acetylcholine are complicated by the potential for stimulation of nicotinic receptors in autonomic ganglia(1).

Theoretically the decrease in myocardial activity could be utilized to decrease oxygen demand following a myocardial infarction, however, agents with greater specificity are preferable. Similarly, a patient with hypertension could expect a lowering of blood pressure if a muscarinic agonist is administered. However, several factors prevent the clinical use of muscarinic agonists for this purpose, including adverse effects, reflex tachycardia, and potential for development of tolerance.

Cardiovascular adverse effects are the major reason muscarinic agonists have limited therapeutic utility. In fact, the only clinically useful agents are associated with a lower incidence of cardiovascular effects. Adverse effects include bradycardia, hypotension, bradyarrhythmias, flushing, and headache(1). Production of vasodilation can be associated with a pattern of adverse effects. Vasodilation can lower blood pressure (i.e., hypotension). Increases in peripheral blood flow due to vasodilation can produce flushing. Increases in cerebral blood flow can lead to increases in cranial pressure and may produce a headache. As discussed previously, reflex tachycardia can also occur.

From a cardiovascular perspective, the importance of muscarinic agonists is related to the potential for producing adverse cardiovascular consequences. Changes in cardiovascular function can be particularly troubling for patients with underlying cardiovascular diseases or in elderly patients. Adverse effects are greater if the agents are administered intravenously and would be minimal if used topically(1).

Gastrointestinal Tract

Parasympathetic stimulation of the gastrointestinal tract increases secretions, contracts the smooth muscle (peristalsis), and relaxes the sphincters (7). These effects are predictable from an understanding of the ANS. Parasympathetic activity predominates at rest when it is appropriate to digest food and stimulate bowel function. Although all of the receptors involved have not been identified, it is believed that M3 receptors located on the gastrointestinal smooth muscle stimulate motility (7). M1 receptors stimulate phospholipase C increasing intracellular calcium levels and enhancing contraction and stimulating secretions.

Based upon the increased motility, stimulation of muscarinic receptors in the gastrointestinal tract could be useful in patients with abdominal distension, gastric atony, or esophageal reflux(1). Abdominal distension and gastric atony can occur following abdominal surgery. Stimulation of muscarinic receptors can lead to resumption of normal bowel motility. The effect in gastroesophageal reflux may be harder to predict. More rapid emptying of the stomach will decrease the likelihood of acidic contents irritating the esophagus and should relieve heartburn.

It is easy to imagine the adverse effects a patient could experience as a result of a parasympathomimetic effect on the gastrointestinal tract. The effects include nausea and vomiting, belching, cramps, and diarrhea. Of special concern would be the potential for the enhanced acid secretion to aggravate patients with peptic ulcer disease(1). In summary, muscarinic agonists could be used to stimulate gastrointestinal activity.

### Table I. Potential sites of action of muscarinic receptor agonists

<table>
<thead>
<tr>
<th>Site</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasympathetic Effector</td>
<td>Effects mimic parasympathetic activation</td>
</tr>
<tr>
<td>Organs</td>
<td>Limited by distribution to the brain</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td>Mimic modulating signals not the primary signal, few effects result</td>
</tr>
<tr>
<td>Autonomic Ganglia</td>
<td></td>
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</tbody>
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*aSee references 1 and 7.*
**Table II. Direct muscarinic receptor agonists**

<table>
<thead>
<tr>
<th>Choline esters</th>
<th>Unique properties</th>
<th>Most common use</th>
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</thead>
<tbody>
<tr>
<td>Acetylcholine (Miochol®)</td>
<td>Muscarinic and nicotinic agonist; short half-life; not orally bioavailable</td>
<td>Rapid miosis (topically)</td>
</tr>
<tr>
<td>Methacholine (Provocholine®)</td>
<td>Analog of ACH</td>
<td>Rarely used clinically</td>
</tr>
<tr>
<td>Carbachol (Miostar®, Isopto Carbachol®)</td>
<td>Retains some nicotinic activity; fewer cardiovascular effects; longer half-life; orally bioavailable</td>
<td>Wide angle glaucoma</td>
</tr>
<tr>
<td>Bethanechol (Urecholine®)</td>
<td>Fewer cardiovascular effects; longer half-life; orally bioavailable</td>
<td>Urinary or gastrointestinal hesitancy</td>
</tr>
<tr>
<td>Alkaloids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscarine</td>
<td>Derived from poison mushrooms; prototypical muscarinic agonist</td>
<td>Not clinically useful</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>Muscarinic selective; produces prominent effects on glands</td>
<td>Wide angle glaucoma</td>
</tr>
<tr>
<td>(Akarpine®, Isopto Carpine®, OcusertPilo®)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*See references 1, 9 and 12.*

Several agents are used clinically for this purpose, but the use is limited due to the potential for adverse effects.

**Urinary Tract**

Parasympathetic stimulation of the urinary tract increases ureteral peristalsis, contracts the detrusor muscle, increases maximum voiding pressure, decreases the capacity of the bladder, and relaxes the sphincters(7). These effects are explainable if one considers the receptors involved, probably M2 receptors (see gastrointestinal tract). During parasympathetic stimulation at times of rest, housekeeping activities such as urination can occur. 

Based upon the increased motility stimulation of muscarinic receptors in the urinary tract could be useful in patients suffering from urinary retention. Urinary retention can occur following catheterization or surgery. These agents stimulate contraction of the detrusor muscle, but they may not alter outflow resistance and have the potential for producing adverse effects(8). Therefore, muscarinic agonists have limited clinical utility for treatment of urinary retention. It is easy to imagine the adverse effects a patient could experience as a result of a parasympathomimetic effect on the urinary tract. The main effect would be incontinence.

**Eye**

Parasympathetic stimulation of the eye stimulates contraction of the sphincter muscle and produces miosis. Contraction of the ciliary muscle produces visual accommodation for near vision(9). At times of rest, visual focus should be on the immediate environment and light is assumed to be adequate, therefore pupil size is small. As a result of the miosis and the contraction of the ciliary muscle, a decrease in intraocular pressure can occur(7). It is believed that the M2 receptor mediates the miosis and changes in vision(9).

Decreases in intraocular pressure can be useful in the treatment of wide angle glaucoma(9). Muscarinic receptor agonists are used clinically for the treatment of wide angle glaucoma. Many of the disadvantages of the muscarinic agonists become clinically unimportant when the agents are used topically in the eye. The majority of adverse effects will be ocular and include difficulty in visual accommodation, enhanced myopia, and the potential for local irritation(9). Systemic adverse effects are also possible (See other organ systems).

**Central Nervous System (CNS)**

Although not part of the peripheral ANS, muscarinic receptors are located in various areas of the CNS. The complete role of muscarinic receptors in brain function has not been elucidated. Muscarinic receptors are believed to be important in learning, memory and cortical arousal(1). Currently direct muscarinic receptor agonists are not used for treatment of any CNS disease states, but agents that penetrate the blood brain barrier can produce CNS effects. The main effects could be hallucinations and delirium. Researchers are interested in determining the subtype of muscarinic receptor involved in learning and memory with the potential to develop agents useful in the treatment of Alzheimer’s disease(10). Agents that increase acetylcholine concentrations in the brain (i.e., indirect cholinergic agonists) are currently the only agents available to treat Alzheimer’s disease(10). It remains unclear if a muscarinic receptor agonist would offer a clinical advantage as compared to the indirect agonists.

**Miscellaneous Effects**

In addition to the detailed effects above, muscarinic receptor agonists can stimulate the activity of most glands(7). Excess sweating, salivation, and lacrimation are potential adverse effects. Of therapeutic utility would be the potential to treat xerostomia (dry mouth) with a muscarinic agonist(11). Parasympathetic stimulation can produce bronchoconstriction, which could present a problem to a patient receiving a muscarinic agonist who has a history of asthma(1).

**Agents**

Table II lists the muscarinic agonists. Limitations of acetylcholine include activation of nicotinic receptors and rapid hydrolysis by acetylcholinesterase. Therefore, acetylcholine’s therapeutic utility is limited to rapid production of miosis via direct ocular instillation(1). The choline esters were developed to provide muscarinic selectivity and a longer duration of action(1,12). Specific modifications of the acetylcholine structure lead to a relative increase in muscarinic receptor binding and to resistance to acetylcholinesterase(1,12). Both carbachol and Bethanechol are reported to produce a lower incidence of cardiovascular effects(1).

The alkaloid pilocarpine tends to produce greater effects...
on the glands, and therefore, sweating is a common adverse effect. On the other hand, pilocarpine has been used to treat dry mouth as a result of its prominent effect on salivary glands. Acetylcholine, carbachol, and pilocarpine are available as ocular preparations decreasing the incidence of peripheral adverse effects. Pilocarpine is also available in an ocular drug-delivery system (Ocusert). Muscarine is of historical importance as the first compound identified to selectively activate muscarinic receptors, but is not used clinically due to toxicities.

SUMMARY

The pharmacology of muscarinic receptor agonists correlates directly with the effects of activation of the parasympathetic nervous system. Due to lack of specificity the muscarinic agonists have limited clinical utility, but are excellent examples of the power of applying knowledge of physiology to the comprehension of pharmacology.


References


APPENDIX. SAMPLER AUTONOMIC NERVOUS SYSTEM EXERCISES

1. Diagram the parasympathetic innervation of the heart. Include neurotransmitters, receptors, neurons, and the effect on the heart.
2. Theoretically if you had an agent which is a selective agonist of M2 receptors, the drug would produce what effect on heart rate?
3. Think about cholinergic neurotransmission. Draw or list all the components involved beginning with synthesis and ending with gastrointestinal smooth muscle contraction. Identify potential sites where agonists or antagonists could interfere with cholinergic neurotransmission.
4. Describe the effect of activation of muscarinic receptors on the eyes, blood vessels, gastrointestinal tract, and urinary tract. Include the receptor subtype and the second messenger system.