Tiotropium Bromide Binding to Muscarinic (M3) Acetylcholine Receptor

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ABSTRACT [9]

Tiotropium bromide (Spiriva®) is a long acting, inhaled anti-cholinergic agent used for maintenance of chronic obstructive pulmonary disease (COPD). Tiotropium bromide acts by competitively and reversibly inhibiting muscarinic receptors M1, M2, and M3. This mechanism of action causes bronchodilation and relaxation of smooth muscle in the lungs. The tiotropium bromide molecular structure provides higher binding specificity to the M3 receptor when locally administered. Our goal was to clarify the interactions between the tiotropium molecule and its receptors.

CASE STUDY

A patient presents to the pharmacy with prescriptions for tiotropium bromide and aclidinium bromide (Tudorza®). Both medications are long-acting antimuscarinic inhalation medications for COPD.

- Past Medical History: COPD
- Family History: cardiac disorder
- Patient prefers the drug to be covered by insurance, dosed once daily, and for it not to have a bad taste.

THE MOLECULE [1, 4-5, 7]

Use & Dosing

- Long-term treatment of bronchospasms and exacerbation reduction associated with COPD
- Tiotropium bromide is available as a once-daily regimen in two different dosage forms:
  - 18 mcg inhalation powder administered via the HandiHaler®; and
  - 5 mcg inhalation spray administered via via the Respimat® Inhaler

Known ADRs and DDIs

- Tiotropium bromide is limited in systemic absorption (~14%)
- Minimal crossing of the Brain Barrier (BBB) limits additional toxicities
- Any systemic absorption may increase risk of other off-target effects such as
  - Dry mouth: 4% (spray); 14-16% (powder)
  - Upper respiratory infection (URI): 41-43% (powder only)

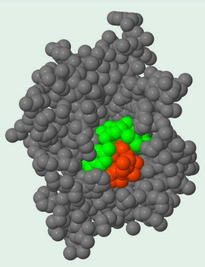
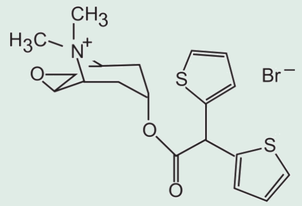


Figure 1 (above): Tiotropium bromide (red) bound to receptor tyrosine lid (green)



Structure 1 (above): The molecular structure of tiotropium bromide.

THE PROTEIN RECEPTOR [4-5, 7]

Once the tiotropium bromide molecule encounters the receptor, it binds deep inside the core and is covered by a tyrosine lid (Fig. 1). The tyrosine lid creates an environment where the drug can interact with the hydrophobic regions inside the receptor.

The M3 receptor (Fig. 2) has a leucine in the ECL2 portion of the binding site, unlike M2 which has a phenylalanine in the ECL2 portion. The substitution creates a larger binding pocket which does not cause a disruption of the hydrogen bond created by the thiophene ring of tiotropium bromide and the tyrosine of the receptor (Fig. 3). This unique interaction accounts for its higher affinity and slower dissociation of tiotropium bromide from the M3 receptor and provides a 24-hour duration of action.

Receptor	Location	Anticholinergic Effect
M1	Brain	Delirium, increased body temperature
M2	Heart	Tachycardia
M3	Smooth muscle	Decreased secretions/urination, constipation

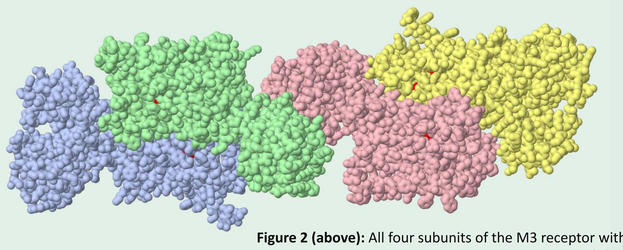


Figure 2 (above): All four subunits of the M3 receptor with tiotropium bromide (red) bound

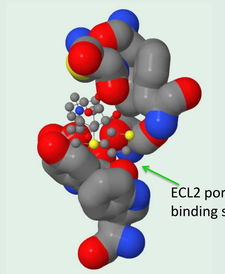


Figure 3 (above): The molecular structure of tiotropium bromide showing its interactions in the binding site of the M3 receptor

MOLECULAR STORY [1, 5]

Optimal Muscarinic Competitive Antagonists Structural Features

R1 and R2: Two large carbocyclic or heterocyclic rings prevent a conformational change required to signal the G-coupled protein. The rings bind outside the active site, allowing the drug molecule to act as an antagonist.

R3: Increased binding strength due to a hydroxyl group forming an extra hydrogen bond with M3.

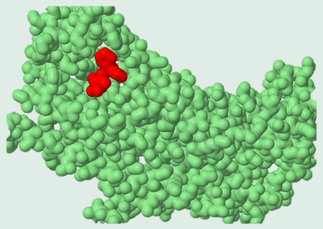
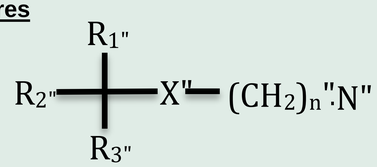


Figure 4 (above): Tiotropium bromide (red) sitting in the active site of an M3 subunit (green)



X: Esters are rapidly hydrolyzed in the acidic environment of our gastrointestinal tract (GIT). This limits systemic bioavailability, while increasing potency of tiotropium bromide. Esterases in the plasma also prevent the molecule from binding muscarinic receptors outside of the lungs.

$(CH_2)_n$: Provides separation of the ester and the quaternary ammonium and maximizes potency.

N: A quaternary ammonium with cationic action limits systemic bioavailability. It is not hydrophobic enough to be absorbed from the GIT and will not pass the BBB. Lack of hydrophobicity prevents tiotropium from binding other muscarinic receptors in the brain.

Important Structural Features of the Molecule and an Alternative Anticholinergic

Tiotropium bromide

- Two thiophene rings increase functional muscarinic receptor selectivity
- Dithienyl derivative of N-methyl scopolamine
- Two methyl groups on nitrogen rather than one (scopolamine)
- Quaternary ammonium
- Epoxide on amino ring
- Six-carbon + 1-nitrogen ring

Aclidinium bromide:

- N-methyl scopolamine moiety replaced with N-phenoxypropyl (-1-azabicyclo [2.2,2] octane, resulting in kinetic selectivity for M3 v M2
- Two thiophene rings
- Seven-carbon + 1-nitrogen ring

THE NEXT QUESTION [8]

The HandiHaler® is the original delivery system that uses an encapsulated dry powder dosage form. Delivery of the drug to the lungs requires a specific breathing pattern; complete exhalation of breath, sealing lips around the HandiHaler® mouthpiece, and one slow and deep breath that is strong enough to vibrate the powder from the capsule and into the lungs.

The FDA recently approved a new dosage form and delivery system of tiotropium bromide, the Respimat® Inhalation Spray. This system is comprised of solution that is delivered in a pre-measured and slow-moving mist, activated by the press of a button. There is no difficult breathing pattern required for delivery of the new formula into the lungs.

Both tiotropium bromide dosage forms are safe and efficacious for preventing exacerbations of COPD. The same active drug is delivered in the two dosage forms, providing selectivity for the M3 receptor and local delivery to the lungs. The two dosage forms also share the same half-life of 5 to 6 days.

Differences between the dosage forms are as follows:

	HandiHaler®	Respimat®
Bioavailability	19.5%	33%
Excretion (urine)	14%	18.6%
Dry mouth	14-16%	4%
URI	41-43%	0%

Due to the safety and efficacy of tiotropium bromide, there is no need to modify the molecular structure. Both forms of the drug are administered once daily and only available as name brand, but are relatively affordable for patients.

Future studies should focus on a greater understanding of the metabolism of tiotropium bromide and any long-term side effects.

SUMMARY [2-3, 6, 9]

The antagonist action of tiotropium bromide on the M1, M2, and M3 receptors creates an anti-cholinergic effect in the body. The M3 receptor drug target of COPD is located in the lungs, making inhaled medication a first-line therapy due to quick and local delivery of the drug. Inhibition of the M1, M2, and M3 receptors reduces secretions and airway constriction in the lungs, giving the patient reduced COPD symptoms.

We clarified that tiotropium bromide has higher affinity to the M3 receptor which promotes a longer duration of action and limits side effects. Our patient was given tiotropium bromide rather than aclidinium bromide due to the highly specific inhibition of the M3 receptor and the once daily regimen. A Respimat® dosage form was chosen for the ease of use and reduced side effects.

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