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"Muscarinic Receptor Antagonists: From Pharmacology to Folklore: Discovering Medications that Effectively Treat COPD and Asthma"

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Abstract :

Acetylcholine is released into M3 muscarinic receptors by parasympathetic neurons, which give them dominating control over the smooth muscle of the airways in the lungs. Anticholinergic medications that inhibit muscarinic receptors have been used to treat respiratory disorders for more than 2,000 years. Clinical outcomes for antimuscarinic medications in asthma were inconsistent, despite pharmacologic data suggesting that they should be quite effective. As a result, the use of muscarinic antagonists decreased after β-adrenergic receptor agonists were found to be effective. Numerous reasons, such as undesirable side effects (which might range from dry mouth to coma) and the identification of other muscarinic receptor subtypes in the lungs that occasionally have conflicting effects, contribute to the lack of efficacy of muscarinic antagonists. Possibly the most significant issue is inefficient dosing as a result of poorly understood variations in administration routes is no reliable method for determining if antagonists block receptors that acetylcholine stimulates physically. Asthma and chronic obstructive pulmonary disease seem to respond well to the development of newer muscarinic receptor antagonists that address the issues of side effects and receptor specificity**.**

Keywords: M2 muscarinic receptors; airway hyperreactivity; ipratropium; tiotropium; aclidinium; glycopyrrolate.

Abbreviations: COPD, chronic obstructive pulmonary disease; IUPHAR, LD50, lethal dose for 50% of population; M1–M5, muscarinic receptor subtypes 1–5.

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Introduction:

The lung's muscarinic receptors

Anticholinergic drugs disrupt muscarinic receptors on nerves, glands, and smooth muscle in the lungs to increase neurotransmitter release, inhibit muscle contraction, and suppress gland production. M1 through M5, as defined by the IUPHAR (Caulfield and Birdsall, 1998), are the five subtypes of muscarinic receptors that are part of the vast family of seven transmembrane G-protein coupled receptors. Acetylcholine causes bronchoconstriction in the human lung (as well as in all investigated animal species) via activating smooth muscle M3 (Figure 1) receptors (Roffel et al., 1990). The bulk of muscarinic receptors on airway smooth muscle are actually M2, despite the fact that contraction of the muscle is mediated by M3 receptors (Barnes, 1993). Because these M2 receptors impede β-adrenoceptor-mediated relaxation, they indirectly contribute to the contraction of airway smooth muscle according to Fernandes et al. (1992), adenylate cyclase. M3 muscarinic receptors on submucosal cells are also primarily responsible for mediating glandular secretion (Marin et al., 1976; Borson et al., 1980; Phillips et al., 2002) The parasympathetic neurons that supply the lungs also have muscarinic receptors (Fryer and Maclagan, 1984). A physiologically significant negative feedback control on acetylcholine release is provided by M2 muscarinic receptors on postganglionic parasympathetic nerves (Faulkner et al., 1986; Fryer et al., 1996), which limit acetylcholine release (Fryer and Maclagan, 1984; Baker et al., 1992). Vagally induced bronchoconstriction is markedly enhanced by blocking M2 receptors with muscarinic antagonists, such as atropine and ipratropium, or by utilizing selective M2 receptor antagonists, such as gallamine (Fryer and Maclagan, 1984; 1987; Blaber et al., 1985; Faulkner et al., 1986). Because neuronal M2 receptors are sensitive, exposure to organophosphates or ozone, antigen challenge, or respiratory virus infection all dramatically reduces their function (Empey et al., 1976; Aquilina et al., 1980; Fryer and Jacoby, 1991; Sorkness et al., 1994; Schultheis, 1992; Schultheis et al., 1994). In people who have asthma, they are also less functional (Minette et al., 1989). Multiple processes, such as down-regulation of receptor expression and blockage by endogenous antagonists, contribute to the decreased function of the neuronal M2 receptors. One significant mechanism of airway hyperreactivity is thought to be the increase in acetylcholine release that results from this. In the treatment of asthma and chronic obstructive pulmonary disease (COPD), anticholinergic medications are used as bronchodilators in conjunction with anti-inflammatory steroids. Variable airflow restriction, partly reversible spontaneously or with treatment, is the hallmark of asthma. Chronic inflammation, which heightens airway hyperresponsiveness to diverse stimuli, is the underlying cause of this airflow restriction (EPR-3, 2007). The chronic airflow restriction associated with COPD is not completely reversible. The symptoms of COPD patients can suddenly get worse. Breathlessness and increased sputum output are the hallmarks of these exacerbations (Rabe et al., 2007). The symptoms of asthma and COPD are similar, but the main distinction between the two illnesses is the reversibility of

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airflow limitation. The history of clinically significant anticholinergic medications for COPD and asthma is covered in this article.

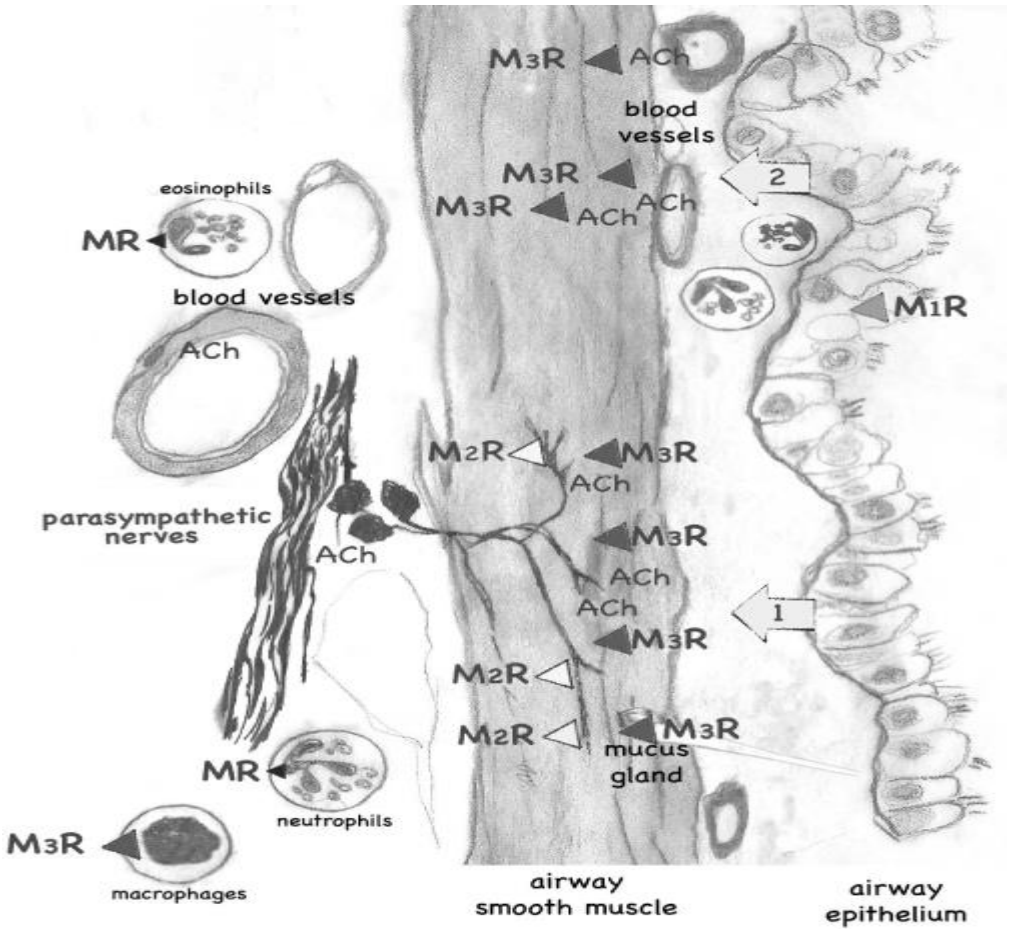

Figure 1: Muscarinic receptors in lungs. Muscarinic receptors (MR) are present throughout the lungs and control smooth muscle contraction, gland secretion, acetylcholine (ACh) release from parasympathetic nerves and probably also inflammatory cells. Only receptors with dominant physiological effects are shown, thus for example M2 receptors in airway smooth muscle are not included. The major physiological source of ACh is from postganglionic parasympathetic nerves that supply both muscle and glands (1); ACh release is normally limited by M2 receptors on these nerves. However, muscarinic receptors are distributed throughout smooth muscle and can be stimulated by exogenous acetylcholine administered i.v. or by inhalation**.**

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Atropine and its derivatives

Blocking muscarinic receptors is one of the earliest methods of treating asthma. For millennia, atropine and scopolamine, two naturally occurring anticholinergic alkaloids, were employed in traditional medicine. It is said that henbane, or Hyoscyamus, was distilled and the smoke was inhaled by ancient Egyptians suffering from respiratory ailments who placed the bricks on fire (Ebell, 1937; Ellul-Micallef, 1997). The deadly nightshade bush was the source of atropine in medieval Europe. Linnaeus named this plant Atropa belladonna in honor of Atropos, the Fate that tears the thread of life, because this plant was also used as poison (Goodman et al., 2006). Atropine was utilized in Western medicine in the 19th century after being purified from datura, jimsonweed, and deadly nightshade Atropine reverses bronchoconstriction caused by parasympathetic nerve stimulation or by intravenous or inhaled acetylcholine in a dose-dependent manner in both animal and human studies (Cavanaugh and Cooper, 1976; Sheppard et al., 1982; Holtzman et al., 1983), indicating that anticholinergic medications may be effective in treating asthma. We will talk about why, at the moment, atropine or other anticholinergic drugs are not the first line of treatment for airway disorders. The route of administration affects atropine's bronchodilator potency (Holtzman et al., 1983; Sheppard et al., 1983). Whether bronchoconstriction was caused by vagal stimulation or intravenous acetylcholine, more intravenous atropine is needed to counteract it than inhaled atropine (Holtzman et al., 1983). The route in which atropine works for asthma also affects its efficacy of management. Inhaled atropine is a more potent bronchoconstriction inhibitor than intravenous atropine, regardless of whether bronchoconstriction is brought on by inhaled methacholine or the vagal reflex (which is triggered by cold, dry air) (Sheppard et al., 1983). These findings could indicate that the best bronchodilator would be breathed atropine. Inhaled atropine, however, is far more effective at inhibiting bronchoconstriction induced by inhaled acetylcholine than it is at blocking bronchoconstriction induced by vagal stimulation (Holtzman et al., 1983), and this is a crucial finding of these research. The process for determining an anticholinergic medication's clinically effective dose (the amount that prevents bronchoconstriction brought on by inhaled acetylcholine) is much smaller than the amount needed to prevent the parasympathetic nervous system, which is the body's natural source of acetylcholine nerves. These studies on asthmatic humans and dogs show that the amount of atropine that is inhaled is insufficient to prevent the release of acetylcholine into the vagus. The idea that enhanced acetylcholine release from the parasympathetic nervous system is not a factor in asthma hyperreactivity has been supported by the ineffectiveness of atropine and other anticholinergic medications un treating asthma. The clinical dosage of atropine is most likely too low, though. Pharmacologically, 50% of muscarinic receptors in the lungs must be blocked by 0.67 mg/kg−1 (47 mg in an adult weighing 70 kg) with systemic atropine (Chen et al., 1981). Currently, the maximum clinical dose for asystolic arrest is 3 mg intravenously per adult (ACC/AHA, 2005). Atropine has an LD50 of 453 mg per adult; nevertheless, 10–20 mg is

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debilitating for an adult (Goodman, 2010). As a result, atropine's pharmacologically useful dose range is extremely near to its hazardous range. The existence of several muscarinic receptor subtypes, including neuronal M2 receptors on parasympathetic neurons supplying the lungs, further complicates the atropine dosage. These neuronal M2 receptors restrict vagally mediated bronchoconstriction and prevent the release of acetylcholine under physiological conditions (Fryer and Maclagan, 1984; 1987; Minette and Barnes, 1988). Atropine at levels that have little inhibitory impact on post junctional M3 receptors promotes acetylcholine release and inhibits neuronal M2 receptors in guinea pigs (Fryer and Maclagan, 1987). Furthermore, because multiple muscarinic receptor subtypes are present in humans, atropine has a complicated dose-response curve (Wellstein and Pitschner, 1988).

After being absorbed orally, atropine passes through drug elimination using first-order kinetics (Hinderling et al., 1985a,b). One-fourth to one-third of atropine taken orally is present in urine as a pharmacologically active substance twenty-four hours after administration (Kalser, 1971). Atropine's systemic side effects include urine retention and dry mouth. Additionally, atropine passes the placenta and the blood-brain barrier (Mirakhur, 1978; Proakis and Harris, 1978). With increased dosages, its capacity to enter the central nervous system causes a high fever, hallucinations, and coma. Because of these numerous, serious side effects, atropine's therapeutic usage is restricted to the treatment of life-threatening arrhythmias and toxic prodromes, even though the World Health Organization recognizes it as a fundamental, necessary medication (WHO, 2010). The therapeutic dose of atropine that can be utilized is strongly constrained by these effects To reduce harmful side effects, efforts were made to create an anticholinergic medication that was less well absorbed.

Ipratropium

A synthetic quaternary ammonium molecule having an isopropyl group at atropine's N atom is called isotropium bromide When ipratropium is breathed, this quaternary ammonium restricts systemic availability to 6.9%, and when it is administered orally, it limits availability to 2% (Ensing et al., 1989). Due to its low absorption, ipratropium, when inhaled, targets muscarinic receptors in the lung without having the systemic adverse effects associated with atropine (Cugell, 1986; Gross, 1988; Goodman et al., 2006). For instance, breathing in ipratropium has no effect on heart rate at rest. Since 90% of an aerosolized dose is probably swallowed, the low oral absorption is especially significant (Davies, 1975; Cugell, 1986). Regardless of the mode of administration, ipratropium has a half-life of 3.2 to 3.8 hours (Pakes et al. et al., 1980). The assessment of airflow limitation showed that the start of action for a >15% increase in forced expiratory volume in 1 s was <15 min, with a peak onset at 1-2 h and a duration of action of 5 h (Gunther and Kamburoff, 1974; Tashkin et al., 1986).In the early 1980s, ipratropium became a popular treatment for COPD in clinics. This use may be partially explained by other bronchodilator therapy's relative ineffectiveness un treating COPD. In particular, β-agonists

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lose some of their efficacy when used continuously for COPD (Donohue et al., 2003).But when it comes to dosage, ipratropium and atropine have the same issue. The FDA capped dosages at 18 µg per puff, mostly because of worries about possible adverse effects on the anticholinergic system. Considering that ipratropium's maximum dilating dosage is For COPD patients, 500 µg is less than the current suggested dose of 36 µg (Ward et al., 1981; Gross et al., 1989). Ipratropium side effects are usually not severe; the most frequent complaints are of dry mouth and sporadic coughing. Similar to β-agonists, there is no proof that using ipratropium on a regular basis lowers the rate at which lung function declines in people with COPD (Anthonisen et al., 1994). Compared to β-agonists, ipratropium is less effective at bronchodilation (Ruffin et al., 1977). Once more, a greater dose was used due to concern about possible adverse effects, which reduced the bronchodilation. On the other hand, ipratropium added to β-agonists for acute asthma enhanced results, leading to a faster and more significant improvement in lung function (Rebuck et al., 1987; Stoodley et al., 1999; Rodrigo and Rodrigo, 2000; Castro-Rodriguez and Rodrigo (2005). Nonetheless, the average dosage for severe asthma was 504µg of ipratropium per hour. This highlights the fact that bronchodilation is clinically relevant when ipratropium is given at dosages that are close to the maximal dilating dose (Gross et al., 1989; Rodrigo and Rodrigo, 2000). Ipratropium is also advised by current expert opinion, albeit at a greater dosage, for acute severe asthma exacerbations (EPR-3, 2007). All muscarinic receptor subtypes, including the inhibitory neuronal M2 receptors, are, nevertheless, equally well-blocked by ipratropium (Fryer and Maclagan, 1987; Restrepo, 2007). Ipratropium can intensify vagally induced bronchoconstriction by blocking these neural receptors, and this action is observed at doses that are comparable to those employed in clinical settings (Fryer and Maclagan, 1987). Asthma sufferers already have diminished M2 function. (Ayala and Ahmed, 1989; Minette et al., 1989), anticholinergic medications that are specific for M3 receptors were therefore created to prevent further blockage of neural receptors.

Tiotropium

Tiotropium bromide monohydrate is the first anticholinergic drug ever that is effective in treatment of poorly controlled asthma (Peters et al., 2010). This trial showed tiotropium bromide in combination with corticosteroids was more effective than corticosteroids alone and equally effective as corticosteroids in combination with salbutamol, a long-acting beta receptor agonist. Tiotropium is structurally related to ipratropium bromide, but it has a significantly higher affinity for muscarinic receptors (Haddad et al., 1994). Tiotropium has similar affinity for all muscarinic receptor subtypes; however, unlike ipratropium, tiotropium is functionally selective for M3 receptors. This selectivity is provided by the ability of tiotropium to dissociate from M2 receptors 10 times faster than it does from M3 receptors (T1/2 3.6 h for M2 vs. T1/2 34.7 h for M3) (Disse et al., 1993). It has even been suggested that in the lungs, tiotropium is a kinetically irreversible antagonist at M3 muscarinic receptors (Swinney, 2004). This functional muscarinic receptor selectivity is likely related to the two thiophene rings that are a

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part of tiotropium's structure (Price et al., 2009). Tiotropium has 2–3% bioavailability when taken orally. When inhaled, 80% of tiotropium is swallowed with 19.5% reaching the lung, which is almost entirely bioavailable. Clearance of tiotropium is primarily renal with 14% of an inhaled dose excreted unchanged in the urine with active renal secretion of tiotropium (Price et al., 2009). The advantage of low oral bioavailability and increased renal clearance is fewer systemic side effects. The prolonged duration of action, higher affinity and functional selectivity of tiotropium for M3 receptors produces greater improvement in airflow limitation when compared to ipratropium (Vincken et al., 2002; Brusasco et al., 2003). Extended half-life of tiotropium allows once daily dosing with subsequent doses progressively increasing efficacy up to 1 week after starting tiotropium (Disse et al., 1993; Haddad et al., 1994; Maesen et al., 1995; Barnes, 2001; Casaburi et al., 2002; Restrepo, 2007). This combination of functional selectivity and extended half-life overcomes many of the drawbacks of ipratropium, including the need for frequent dosing and confounding effects of M2 receptor blockade, and may explain improved outcomes of tiotropium compared with ipratropium in COPD (Casaburi et al., 2002; Vincken et al., 2002; Brusasco et al., 2003).

Asthma is associated with decreased neuronal M2 receptor function leading to increased acetylcholine release (Ayala and Ahmed, 1989; Minette et al., 1989). Tiotropium more rapidly dissociates from M2 receptors than from M3 receptors sparing additional inhibition of neuronal M2 receptors. Thus, unlike other cholinergic antagonists (Fryer and Maclagan, 1987), tiotropium, by not exacerbating acetylcholine release from parasympathetic nerves (Takahashi et al., 1994), further improves bronchodilation. However, as with all muscarinic antagonists dosing of tiotropium may still be inadequate for treatment of stable asthma. As described above for atropine and ipratropium, dose was determined by the ability of tiotropium to inhibit bronchoconstriction induced by inhaled methacholine and bronchoconstriction induced by i.v. acetylcholine but not vagally induced bronchoconstriction (Barnes et al., 1995; O'Connor et al., 1996; Buels et al., 2010). As with other antimuscarinic drugs 18 μg dose was chosen to limit systemic side effects and not to induce maximal bronchodilation, (Littner et al., 2000) and thus there is potential for under dosing of tiotropium. In humans tiotropium significantly delayed and reduced COPD exacerbations including hospitalizations for exacerbations (Tashkin et al., 2008). Increased mucus production is a hallmark of COPD exacerbations. Stimulation of muscarinic receptors on epithelial cells promotes cell proliferation, cell survival and mucociliary clearance in vitro (Acevedo, 1994; Wessler and Kirkpatrick, 2001; Klein et al., 2009). The role of muscarinic receptors in mucociliary clearance is complex. Mucus glands express M1 and M3 receptors while acetylcholine release from nerves supplying these glands is limited by neuronal M2 receptors. Epithelial cells express M1, M2 and M3 receptors (Acevedo, 1994; Wessler and Kirkpatrick, 2001; Klein et al., 2009). Stimulation of M3 muscarinic receptors increases serous secretions and increases mucociliary beat frequency while M2 receptors inhibit mucociliary beat frequency and decrease particle transport (Klein

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et al., 2009). The balance of effects of these muscarinic receptors is not fully understood either under physiological or pathological conditions, but does provide opportunity to manipulate secretions with selective muscarinic antagonists. Therefore, as tiotropium has greater affinity for M3 than M1 and M2 receptors this may explain the reduced exacerbations in COPD (Disse et al., 1999; Tashkin et al., 2008). Tiotropium was also significantly better than ipratropium in reducing COPD exacerbations when combined with corticosteroids (Tashkin et al., 2008). In antigen challenged animals, tiotropium reduces bronchoconstriction independently of the bronchodilator effects (Buels et al., 2010). This increase effect of tiotropium may result from its anti-inflammatory properties. Muscarinic receptors are found on inflammatory cells in lungs including mast cells (M1), macrophages (M3), neutrophils (M4/M5) and eosinophils (M3/M4) (Mak and Barnes, 1989; Reinheimer et al., 1997; Bany et al., 1999; Verbout et al., 2006). Acetylcholine increases chemotactic mediator leukotriene B4 thereby increasing neutrophil migration. Tiotropium blocks neutrophil migration demonstrating a role for acetylcholine and muscarinic receptors in inflammation (Buhling et al., 2007). Tiotropium reduces airway remodelling that results from prolonged inflammation in allergic guinea pigs (Bos et al., 2007). Severe asthmatic patients responded better to tiotropium than to inhaled corticosteroids further suggesting that tiotropium has anti-inflammatory effects in asthma and COPD (Tashkin et al., 2008; Peters et al., 2010).

Bromide of aclidinium

Similar to tiotropium, an anticholinergic medication called aclidinium bromide also contains a quaternary ammonium group and two thiophene rings (Norman, 2006; Prat et al., 2009). Aclidinium has kinetic selectivity for M3 receptors over M2 receptors, which is also comparable to tiotropium. Aclidinium has a lower half-life at muscarinic receptors in the lung of guinea pigs—29 hours—than tiotropium, which is 34 hours—but its beginning of action is noticeably quicker (Gavalda et al., 2009). In contrast to tiotropium, aclidinium undergoes rapid metabolism in the plasma, leading to a remarkably brief half-life of 2.4 minutes in circulation. In animal tests, this quick metabolism reduces negative effects on the central and systemic neurological systems (Gavalda et al., 2009). Early clinical studies seem to support the absence of of systemic effects (Joos et al., 2010; Schelfhout et al., 2010a), allowing for higher dosage without the fear of harmful side effects that prevented muscarinic receptor antagonists from being used earlier. When 300 µg was administered once daily, phase I tests in both COPD patients and normal people demonstrated a 23.3% improvement in airflow limitation two hours after the dose and sustained bronchodilation for 24 hours (Joos et al., 2010; Schelfhout et al., 2010b). For aclidinium, a phase III clinical investigation is presently being conducted.

Glycopyrrole

Glycopyrrolate has been used in surgery to lessen the adverse effects of neostigmine-induced paralytic reversal, namely bradycardia and increased salivary flow. Compared to tiotropium

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and aclidinium, glycopyrrolate lacks kinetic selectivity, but it is marginally selective for M3 muscarinic receptors, having an affinity for M3 receptors that is 3-5 times higher than that at M1 and M2 receptors (Haddad et al., 1999). In phase III studies for COPD, glycopyrrolate is presently being studied (Norman, 2006). According to a phase II trial, 30 hours after inhaling methacholine-induced bronchospasm, a 0.5 mg dosage of nebulized glycopyrrolate avoided the occurrence (Hansel et al., 2005). As previously mentioned with regard to atropine and tiotropium (Holtzman et al., 1983; Sheppard et al., 1983; O'Connor et al., 1996), however, preventing bronchoconstriction brought on by inhaled muscarinic opting for an antagonist dosage that is insufficient to sufficiently prevent vagally-induced bronchoconstriction due to agonists (Sheppard et al., 1982; 1983; Holtzman et al., 1983). Consequently, during acute asthma exacerbations or COPD exacerbations, bronchoconstriction does not improve even when glycopyrrolate prevents methacholine-induced bronchoconstriction (Cydulka and Emerman, 1994; 1995; Hansel et al., 2005).

Other muscarinic receptor antagonists

Additional long-acting muscarinic receptor antagonists are being developed. These include OrM3 and CHF 5407. OrM3's affinity for M3 receptors is 120 times greater than its affinity for M2 receptors . It was formulated in tablets to allow for oral dosing for those patients who had difficulty using inhaled medications. Unfortunately, it was less effective than ipratropium with increased side effects; most notably dry mouth (Lu et al., 2006). CHF 5407 appears more promising. Early trials show it is as potent and long-acting antagonist of M3 receptors as tiotropium (with 54% still bound to M3 receptors at 32 h) with a significantly shorter half-life at M2 receptors (21 min for CHF 5407 vs. 297 min for tiotropium)(Peretto et al., 2007a,b; Cazzola and Matera, 2008). Studies are currently ongoing to determine the clinical effectiveness of CHF 5407. 2008). Research is presently being conducted to ascertain CHF 5407's clinical efficacy.

Muscarinic receptor antagonist formulation

Muscarinic antagonists may not be delivered to the important parts of the lung in the best possible way when inhaled. At the moment, portable nebulizers, pressurized metered dose inhalers, and dry powder inhalers are used to provide anticholinergic medications. These techniques lead to distinct patterns of lung deposition and increased delivery to the lungs as opposed to the gastrointestinal route. Nevertheless, the various inhalers do not differ in terms of ipratropium or tiotropium's effectiveness or adverse effects (Vincken et al., 2004; van Noord et al., 2009; Ichinose et al., 2010). In order to improve the clinical efficacy of newer generation muscarinic receptor antagonists, distribution modalities are not as crucial as the pharmacology of the antagonists, notably their receptor selectivity.

In summary

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It makes sense that preventing M3 receptors on smooth muscle in the airways would prevent bronchoconstriction. Anticholinergic medications, while helpful in the lab, have struggled to effectively block bronchoconstriction in individuals with asthma and COPD due to issues with dosage, side effects, and muscarinic receptor specificity. Muscarinic antagonists have become more selective, longer acting, less well absorbed, and, most recently, more easily digested with each new generation. Nevertheless, none of them have yet addressed the question of appropriate dosage or whether antagonists administered at doses that will prevent acetylcholine from being inhaled or methacholine from causing bronchoconstriction will also prevent acetylcholine from being released from the vagus nerves, which is the body's natural supply of acetylcholine. One mechanism of airway hyperreactivity in asthma is increased acetylcholine (Holtzman) et al., 1980; Evans et al., 1997; Costello et al., 1999; Yost et al., 1999; Nadel and Barnes, 1984; Minette and Barnes, 1988). Therefore, it is still unclear if anticholinergic medications can be administered in vivo to the appropriate M3 receptors in the lungs, reach pharmacologically efficacious concentrations, and cause bronchodilation without having harmful side effects**.**

References

1. Acevedo M (1994). Effect of acetyl choline on ion transport in sheep tracheal epithelium. Pflugers Arch 427: 543–546.
2. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS et al. (1994). Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. JAMA 272: 1497–1505.
3. Aquilina AT, Hall WJ, Douglas RG Jr, Utell MJ (1980). Airway reactivity in subjects with viral upper respiratory tract infections: the effects of exercise and cold air. Am Rev Respir Dis 122: 3–10.
4. Ayala LE, Ahmed T (1989). Is there loss of protective muscarinic receptor mechanism in asthma? Chest 96: 1285–1291.
5. Baker DG, Don Ksiezopolska-Pietrzak K, Jozwicka M, Klimczak E, Ryzewski J et al. (1999). Expression of mRNA encoding muscarinic receptor subtypes in neutrophils of patients withrheumatoid arthritis. Ann NY Acad Sci 876: 301–304.
6. Barnes PJ (1993). Muscarinic receptor subtypes in airways. Eur Respir J 6: 328–331.
7. Barnes PJ (2001). Tiotropium bromide. Expert Opin Investig Drugs 10: 733–740.
8. Barnes PJ, Belvisi MG, Mak JC, Haddad EB, O'Connor B (1995).Tiotropium bromide (Ba 679 BR), a novel long-acting muscarinicantagonist for the treatment of obstructive airways disease. Life Sci 56: 853–859.
9. Blaber LC, Fryer AD, Maclagan J (1985). Neuronal muscarinicreceptors attenuate vagally-induced contraction of feline bronchial smooth muscle. Br J Pharmacol 86: 723–728.

Power System Technology
ISSN:1000-3673
Received: 06-06-2024 Revised: 15-07-2024 Accepted: 28-08-2024

10. Borson DB, Chin RA, Davis B, Nadel JA (1980). Adrenergic and cholinergic nerves mediate fluid secretion from tracheal glands of ferrets. J Appl Physiol 49: 1027–1031.
11. Bos IS, Gosens R, Zuidhof AB, Schaafsma D, Halayko AJ, Meurs H et al. (2007). Inhibition of allergen-induced airway remodelling by tiotropium and budesonide: a comparison. Eur Respir J 30: 653–661.
12. Brusasco V, Hodder R, Miravitlles M, Korducki L, Towse L, Kesten S (2003). Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. Thorax 58: 399–404.
13. Buels KS, Jacoby DB, Fryer AD (2010). Selectively blocking M3 muscarinc receptors at the time of antigen challenge prevents airway hyperreactivity 24 h later in guinea pigs. Am J Respir Crit Care Med 181 (1_MeetingAbstracts): A3974.
14. Buhling F, Lieder N, Kuhlmann UC, Waldburg N, Welte T (2007). Tiotropium suppresses acetylcholine-induced release of chemotactic mediators in vitro. Respir Med 101: 2386–2394.
15. Casaburi R, Mahler DA, Jones PW, Wanner A, San PG, ZuWallack RL et al., Jr (2002). A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. Eur Respir J 19: 217–224.
16. Casarosa P, Bouyssou T, Germeyer S, Schnapp A, Gantner F, Pieper M (2009). Preclinical evaluation of long-acting muscarinic antagonists: comparison of tiotropium and investigational drugs. J Pharmacol Exp Ther 330: 660–668.
17. Caulfield MP, Birdsall NJ (1998). International Union of Pharmacology. XVII. Classification of muscarinic acetylcholine receptors. Pharmacol Rev 50: 279–290.
18. Cavanaugh MJ, Cooper DM (1976). Inhaled atropine sulfate: dose-response characteristics. Am Rev Respir Dis 114: 517–524.
19. Cazzola M, Matera MG (2008). Novel long-acting bronchodilators for COPD and asthma. Br J Pharmacol 155: 291–299.
20. Chen WY, Brenner AM, Weiser PC, Chai H (1981). Atropine and exercise-induced bronchoconstriction. Chest 79: 651–656.
21. Costello RW, Evans CM, Yost BL, Belmonte KE, Gleich GJ, Jacoby DB et al. (1999). Antigen-induced hyperreactivity to histamine: role of the vagus nerves and eosinophils. Am J Physiol 276 (5 Pt 1): L709–L714.
22. Cugell DW (1986). Clinical pharmacology and toxicology of ipratropium bromide. Am J Med 81: 18–22.
23. Cydulka RK, Emerman CL (1994). Effects of combined treatment with glycopyrrolate and albuterol in acute exacerbation of asthma. Ann Emerg Med 23: 270–274.
24. Cydulka RK, Emerman CL (1995). Effects of combined treatment with glycopyrrolate and albuterol in acute exacerbation of chronic obstructive pulmonary disease. Ann Emerg Med 25: 470–473.

Power System Technology
ISSN:1000-3673
Received: 06-06-2024 Revised: 15-07-2024 Accepted: 28-08-2024

25. Davies DS (1975). Pharmacokinetics of inhaled substances. Postgrad Med J 51 (7 Suppl.): 69–75.
26. Disse B, Reichl R, Speck G, Traunecker W, Ludwig Rominger KL, Hammer R (1993). Ba 679 BR, a novel long-acting anticholinergic bronchodilator. Life Sci 52: 537–544.
27. Disse B, Speck GA, Rominger KL, Witek TJ, Jr, Hammer R (1999).Tiotropium (Spiriva): mechanistical considerations and clinical profile in obstructive lung disease. Life Sci 64: 457–464.
28. Donohue JF, Menjoge S, Kesten S (2003). Tolerance to bronchodilating effects of salmeterol in COPD. Respir Med 97: 1014–1020.
29. Ebell B (1937). The Papyrus Ebers. Levin Munksgaard: Copenhagen. Ellul-Micallef R (1997). History of bronchial asthma. In: Barnes PJ, Grunstein MM, Leff AR (eds). Asthma. Lippincott Raven: Philadelphia, PA, pp. 9–25.
30. Empey DW, Laitinen LA, Jacobs L, Gold WM, Nadel JA (1976). Mechanisms of bronchial hyperreactivity in normal subjects after upper respiratory tract infection. Am Rev Respir Dis 113: 131–139.
31. Ensing K, de Zeeuw RA, Nossent GD, Koeter GH, Cornelissen PJ (1989). Pharmacokinetics of ipratropium bromide after single dose inhalation and oral and intravenous administration. Eur J Clin Pharmacol 36: 189–194.
32. EPR-3 (2007). Expert Panel Report 3 (EPR-3): guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol 120 (5 Suppl.): S94–S138.
33. Evans CM, Fryer AD, Jacoby DB, Gleich GJ, Costello RW (1997). Pretreatment with antibody to eosinophil major basic protein prevents hyperresponsiveness by protecting neuronal M2 muscarinic receptors in antigen-challenged guinea pigs. J Clin Invest 100: 2254–2262.
34. Faulkner D, Fryer AD, Maclagan J (1986). Postganglionic muscarinic inhibitory receptors in pulmonary parasympathetic nerves in the guinea-pig. Br J Pharmacol 88: 181–187.
35. Fernandes LB, Fryer AD, Hirshman CA (1992). M2 muscarinicreceptors inhibit isoproterenol-induced relaxation of canine airway smooth muscle. J Pharmacol Exp Ther 262: 119–126.
36. Fryer AD, Jacoby DB (1991). Parainfluenza virus infection damages inhibitory M2 muscarinic receptors on pulmonary parasympathetic nerves in the guinea-pig. Br J Pharmacol 102: 267–271.
37. Fryer AD, Maclagan J (1984). Muscarinic inhibitory receptors in pulmonary parasympathetic nerves in the guinea-pig. Br J Pharmacol 83: 973–978.
38. Fryer AD, Maclagan J (1987). Pancuronium and gallamine are antagonists for pre- and post-junctional muscarinic receptors in the guinea-pig lung. Naunyn Schmiedebergs Arch Pharmacol 335: 367–371.

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39. Fryer AD, Elbon CL, Kim AL, Xiao HQ, Levey AI, Jacoby DB (1996). Cultures of airway parasympathetic nerves express functional M2 muscarinic receptors. Am J Respir Cell Mol Biol 15: 716–725.
40. Gavalda A, Miralpeix M, Ramos I, Otal R, Carreno C, Vinals M et al. (2009). Characterization of aclidinium bromide, a novel inhaled muscarinic antagonist, with long duration of action and a favorable pharmacological profile. J Pharmacol Exp Ther 331: 740–751.
41. Goodman E (2010). Historical Contributions to the Human Toxicology of Atropine : Behavioral Effects of High Doses of Atropine and Military Uses of Atropine to Produce Intoxication, 1st edn. Eximdyne: Wentzville, MO.
42. Goodman LS, Gilman A, Brunton LL, Lazo JS, Parker KL (2006). Goodman & Gilman's the Pharmacological Basis of Therapeutics, 11th edn. McGraw-Hill: New York. Gross NJ (1988). Ipratropium bromide. N Engl J Med 319: 486–494.
43. Gross NJ, Petty TL, Friedman M, Skorodin MS, Silvers GW, Donohue JF (1989). Dose-response to ipratropium as a nebulized solution in patients with chronic obstructive pulmonary disease. A three-center study. Am Rev Respir Dis 139: 1188–1191.
44. Gunther W, Kamburoff PL (1974). The bronchodilator effect of a new anticholinergic drug, Sch 1000. Curr Med Res Opin 2: 281–287.
45. Haddad EB, Mak JC, Barnes PJ (1994). Characterization of [3H]Ba 679 BR, a slowly dissociating muscarinic antagonist, in human lung: radioligand binding and autoradiographic mapping. Mol Pharmacol 45: 899–907.
46. Haddad EB, Patel H, Keeling JE, Yacoub MH, Barnes PJ, Belvisi MG (1999). Pharmacological characterization of the muscarinic receptor antagonist, glycopyrrolate, in human and guinea-pig airways. Br J Pharmacol 127: 413–420.
47. Hansel TT, Neighbour H, Erin EM, Tan AJ, Tennant RC, Maus JG et al. (2005). Glycopyrrolate causes prolonged bronchoprotection and bronchodilatation in patients with asthma. Chest 128: 1974–1979.
48. Hinderling PH, Gundert-Remy U, Schmidlin O (1985a). Integrated pharmacokinetics and pharmacodynamics of atropine in healthy humans. I: pharmacokinetics. J Pharm Sci 74: 703–710.
49. Hinderling PH, Gundert-Remy U, Schmidlin O, Heinzel G (1985b). Integrated pharmacokinetics and pharmacodynamics of atropine in healthy humans. II: pharmacodynamics. J Pharm Sci 74: 711–717.
50. Holtzman MJ, Sheller JR, Dimeo M, Nadel JA, Boushey HA (1980). Effect of ganglionic blockade on bronchial reactivity in atopic subjects. Am Rev Respir Dis 122: 17–25.