Structural and Functional Aspects of Muscarinic Receptors in Correlation with Anticholinergic Drugs

13

Pramod Kumar Singh, Rajendra Nath, Ram Naraian, and Manish Kumar Gupta

Abstract

The muscarinic acetylcholine receptors (mAChRs) are receptors that produce the GPCR complex in the membrane of specific neurons and other cells. It performs a key role at the end of the receptor stimulated by the neurotransmitter. Ach liberates from postganglionic neurons in a parasympathetic region of ANS. The mAChRs constitute a family of five interrelated GPCRs that come under the category of α branch of GPCRs' Class A. The five different subtypes of the mAChR family are designated as M1–M5. M1, M3 and M5 subtype receptors exhibit to pair through the Gq/11 family of G proteins, but the M2 and M4 subtype receptors particularly indicate through Gi/o family of G protein. The mAChRs play multifunctional peripheral and central roles in human physiology including regulation of muscle contraction, heartbeat, lung, secretion by gland and other functions of the CNS.

Keywords

Muscarinic receptors · Acetylcholine receptor · Anticholinergic drugs · Central nervous system · *Atropa belladonna*

The original version of this chapter was revised due to the error in the affiliation of the co-authors. A correction to this chapter is available at https://doi.org/10.1007/978-981-15-5530-5_18

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D. B. Singh, T. Tripathi (eds.), *Frontiers in Protein Structure, Function, and Dynamics*, https://doi.org/10.1007/978-981-15-5530-5_13

13.1 Introduction

Acetylcholine receptor (AChR) is an intrinsic membranous type of protein, which reacts to the binding of the neurotransmitter acetylcholine (ACh) molecule. It is classified into muscarinic and nicotinic receptors based on their pharmacology and relative target to molecules (Verma et al. 2018). Muscarinic and nicotinic receptors are the main type of the cholinergic system. The cholinergic system, portion of the visceral or autonomic nervous system (ANS), plays a significant role in many functions such as circadian rhythmicity, digestion, addiction, control of heartbeat, motivation, blood pressure, cognitive flexibility, pain and reward, spatial learning and perceptual memory (Prado et al. 2017). mAChRs are well-known metabotropic acetylcholine receptors that are mainly reactive to muscarine. mAChRs are termed after muscarine, a lethal alkaloid produced by the highly poisonous mushroom *Amanita muscaria* (Jo et al. 2014). Scopolamine and atropine are the best known naturally occurring muscarinic antagonist, which is reported in the fatal nightshade plant: *Atropa belladonna* (Albuquerque et al. 2009). Nicotinic acetylcholine receptors (nAChRs) are famous ionotropic acetylcholine receptors particularly responsive to nicotine, Na^+, Ca^{2+} and K^+ ion channel (Corradi and Bouzat 2016). nAChR is named after nicotine, an ideal agonist. D-tubocurarine compound, a toxic alkaloid isolated from the curare poison, is a very well-known nicotinic antagonist (Malca Garcia et al. 2015) (Fig. 13.1).

13.1.1 Structure and Function of Muscarinic Receptor and Their Subtypes

The mAChRs are acetylcholine receptors, which produce the GPCR complex in the membrane of specific neurons and other cells (Eglen 2006). It performs a key role at the end of the receptor stimulated by the neurotransmitter. Ach liberates from postganglionic neurons in a parasympathetic region of ANS. The mAChRs constitute a family of five interrelated GPCRs that comes under the category of α branch of GPCRs Class A (Fredriksson et al. 2003). The five different subtypes of the mAChR family are designated as M1–M5 (encoded by CHRM1–CHRM5 genes). M1, M3 and M5 subtype receptors exhibit to pair through the Gq/11 family of G proteins, but the M2 and M4 subtype receptors particularly indicate through Gi/o family of G protein (Haga 2013). The mAChRs play multifunctional peripheral and central roles

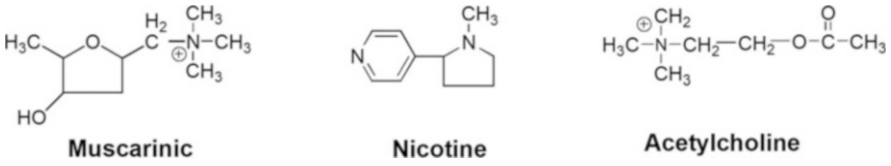

Fig. 13.1 Chemical structures of muscarine, acetylcholine and nicotine

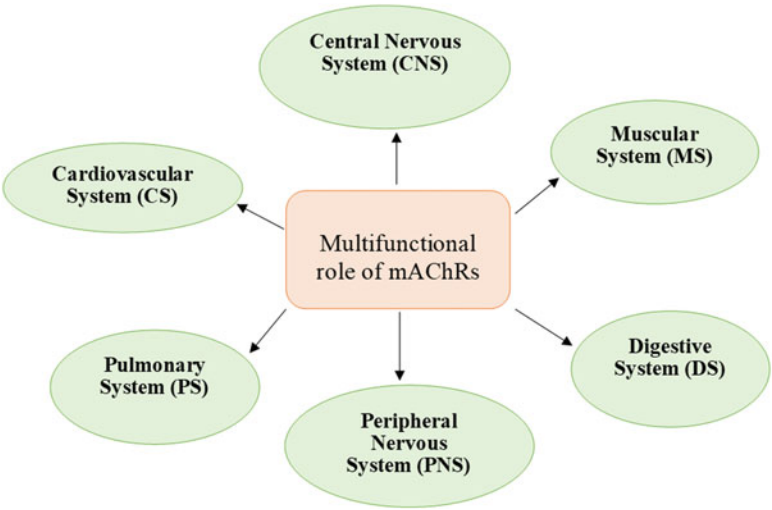

Fig. 13.2 Multifunctional role of mAChRs

in human physiology including regulation of muscle contraction, heartbeat, lung, secretion by gland and other functions of the CNS (Wess et al. 2007) (Fig. 13.2).

13.1.1.1 Muscarinic-1 Receptor (M1 Receptor)

Muscarinic-1 receptor (M1 receptor) is a cholinergic muscarinic type of receptor found in humans, rats and mice encoded by the CHRM1 gene (CHRM1 2020). The receptor belongs to the GPCR family and bound to Gq proteins (Qin et al. 2011). This is one of the five muscarinic receptors that act as the metabotropic roles of ACh in the CNS of humans. M1 receptors mostly found in nerve cells of the hippocampus and cerebral cortex. Initiation of the M1 receptor yields many reactions including the activation of ion channels such as Cl^-, K^+, inhibition of cAMP production and the upregulation of phospholipase C (Sanchez et al. 2009). M1 receptor agonists may also lead to secretion from the bronchoconstriction, stomach and salivary gland. M1 receptors generally participate in many processes including cardiac muscle contraction, control of seizure and cognitive activity (Hamilton et al. 2001; Bakker et al. 2018). The beginning of these receptors by selective agonists reduces harmful β-amyloid secretion and increases the secretion of the non-toxic α-amyloid peptide from amyloid precursor proteins (Jiang et al. 2014).

The M1 receptor is made up of 521 amino acid residues (Fig. 13.3). These are made up of five transmembrane domains: residues 1–239, 403–515, 240–255, 298–402, 256–298, respectively. The M1 muscarinic receptor interacts with the inhibitor tiotropium. Orthosteric and allosteric interaction sites play a significant role in drug specificity. It also reveals how allosteric modulation may be spread involving the two spatially discrete domains (Thal et al. 2016).

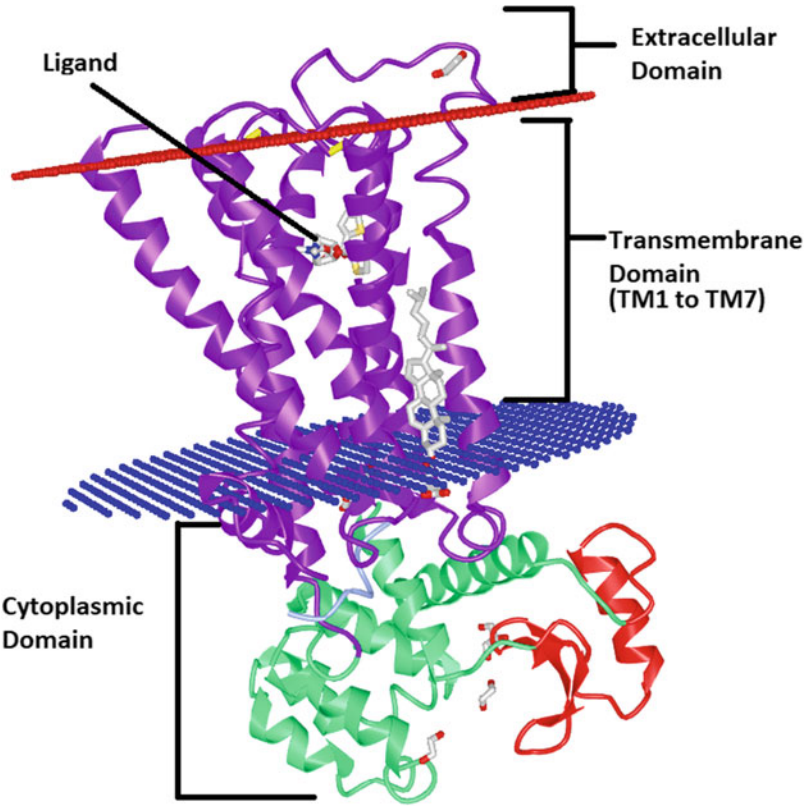

Fig. 13.3 Structure of muscarinic receptor-1 (PDB Id: 5CXV)

13.1.1.2 Muscarinic-2 Receptor (M2 Receptor)

The mAChR M2 is also known as the cholinergic receptor M2, which is encoded by the CHRM2 gene of mice, rats and humans (CHRM2 2020). M2 receptor is a member of the GPCRs family that binds to Gi protein, generally leading to inhibitory effects (Douglas et al. 2001). It regulates the metabotropic function of ACh in the CNS. The receptor is tightly engaged in brain regions, heart and smooth muscle. Initiation of the M2 receptor produces several responses such as initiation of Ca^{2+}, K^+ channels and the inhibition of adenylyl cyclase (Harvey and Belevych 2003). M2 receptor also participates in several processes such as regulation of atrial contraction, AV node conduction velocity, acquiring and retention of smooth muscle contraction (Andersson and Olshansky 2007). The receptor antagonist has been suggested useful in the remedy of Alzheimer's disease (Clader and Wang 2005; Kumar et al. 2016; Wang et al. 2020) (Fig. 13.4).

The receptor is made up of 467 amino acids with 68% helical (24 helices; 322 residues) and 2% beta sheet (4 strands; 13 residues). M2 receptor is devoid of the third intracellular loop and the natural glycosylation sites in the majority of cases.

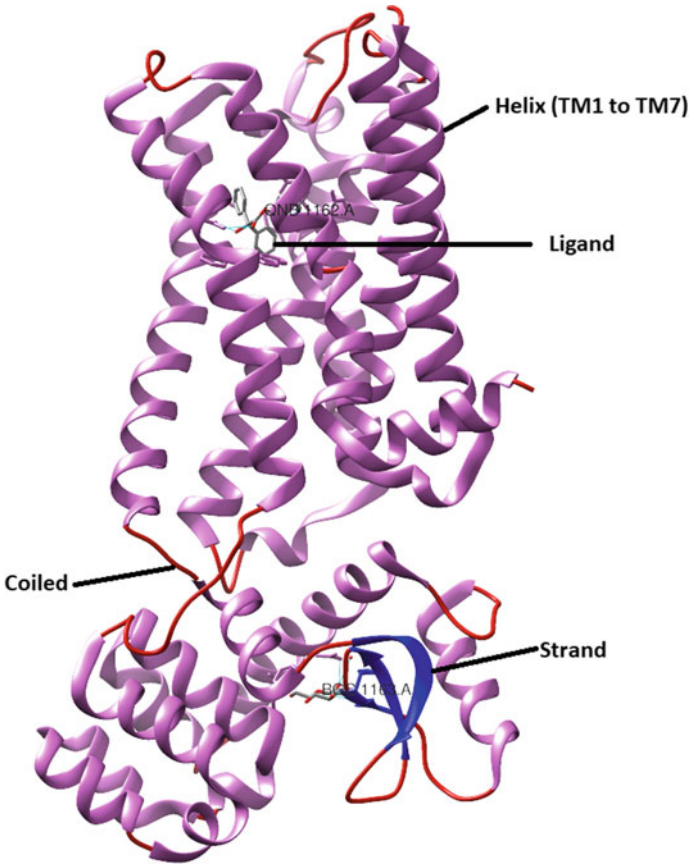

Fig. 13.4 Structure of muscarinic receptor-2 (PDB ID: 3UON)

There are ample hydrophobic interactions that occur between receptor proteins within the transmembrane. The ligand QNB in the interior buried pocket specified by the side chains of TM3–TM7 (Haga et al. 2012). A hydrophobic layer formed by three amino acids, viz. Leu 65 in TM2, Leu 114 in TM4 and Ile 392 in TM6. The orthosteric binding pocket is produced by residues that are identical in M1–M5 receptors. All the muscarinic receptors (M1–M5) show common structural homology with other activity distinct acetylcholine interacting proteins from diverse species. M2 receptor structure imparts molecular insights into the contests of creating specific ligands for muscarinic receptors and their predisposition for allosteric control.

13.1.1.3 Muscarinic-3 Receptor (M3 Receptor)

The mAChR M3 is known as acetylcholine/cholinergic receptor M3, which is encoded by the CHRM3 gene of the mouse, rats and humans (CHRM3 2020). M3 receptor is a member of the GPCRs family that binds to Gq protein, which

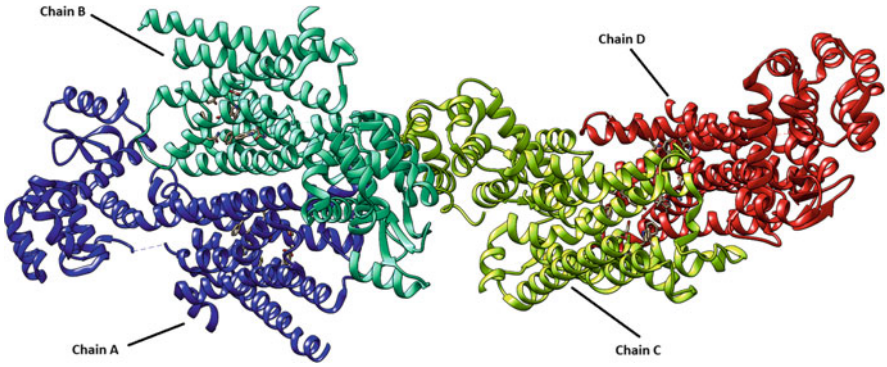

Fig. 13.5 Structure of muscarinic receptor-3 (PDB Id: 4DAJ)

upregulates inositol triphosphate (IP3) and phospholipase C and increases the intracellular Ca^{2+} (Qin et al. 2011). It acts as the metabotropic role of ACh in the CNS. These receptors are generally found in the lungs, endocrine, exocrine glands, smooth muscle and CNS (Weston et al. 2012). The receptor agonist performs an important function in bronchoconstriction and smooth muscle constriction. Activation of the M3 receptor leads to various secretions from the pancreas, stomach and salivary gland (Gautam et al. 2006). Therefore, the M3 receptor actively participates in many metabolic activities such as regulation of the insulin release and the glucose homeostasis. Additionally, the receptor is a potentially beneficial target site in the case of the pulmonary block and in the progression of colon cancer (Moulton and Fryer 2011; Tolaymat et al. 2019). Moreover, initiation of the M3 receptor by selective agonists may also be useful in the case of type-2 diabetes (Gautam et al. 2006; Ito et al. 2019).

The M3 receptor is made up of 479 amino acid residues having four chains A, B, C, D and two domains (Fig. 13.5). The domain 1 lies from 1–202 to 368–479 range, whereas domain 2 ranges from 203 to 367 amino acid residues. No structure alignment results are available for all the four chains of PDB ID: 4DAJ (A to D) explicitly. Structural conservation comprises of intracellular loops 1 and 2. It also includes extracellular loops 1, 2 and 3, having extremely common resemblance in character; overall folds even though little sequence conservation. The M3 receptor shows distinctive characteristics, having a big extracellular vestibule as part of a lengthened hydrophilic route comprising the orthosteric binding pocket (Kruse et al. 2012). Molecular dynamics simulations study advocates that ligand tiotropium interacts momentarily to an allosteric site on the way to the cavity in the interior of the receptor that possesses suitable properties for binding a ligand. The binding pocket of the receptor may also provide an opportunity to design a novel ligand with enhanced therapeutics for the M3 receptors. The conserved residue (Thr234 of TM 5 and Tyr506 of TM 6) in all muscarinic receptors may perform a significant role in the designing of a novel stimulator for the activation of muscarinic receptors (Wess et al. 1992).

13.1.1.4 Muscarinic 4 Receptor (M4 Receptor)

The mAChR M4 receptor is also known as the cholinergic receptor M4. M4 receptor is present in rats, humans and mice, which is encoded by the CHRM4 gene (CHRM4 2020; Birdsall et al. 2019). This receptor is a participant of the GPCRs family, mostly bind to Gi proteins, leading to inhibitory effects (Douglas et al. 2001). It regulates the metabotropic functions of acetylcholine in the brain. This receptor is tightly involved in the lung and striatum. Activation of the M4 receptor response to several reactions includes the inhibition of adenylyl cyclase (Guo et al. 2010). The function of the M4 receptor is the indirect mediation of dopaminergic neurotransmission through cholinergic activity. M4 receptor is also reported to be involved in neuropathological diseases (Tzavara et al. 2004; Stepnicki et al. 2018).

The M4 receptor is made up of two domains and two chains (A & B). The first domain ranges from residues 1–204 to 326–422 and domain 2 ranges from residues 205 to 325 (Fig. 13.6). An alteration in the rotamer of D112 amino acid transmembrane 3 is conserved all over the biogenic amine G and acts as the counter ion for positively charged neurotransmitters (Van Rhee and Jacobson 1996). This rotameric alteration indicates that D112 of TM3 is beyond ligand tiotropium. The residues Y439 and Y443 play a significant affair to stabilize the various inoperative states of conformation to ligand interact with it. The orthosteric site of the M4 receptor is nearer to the M1 than the M2 subtypes. A deviation in amino acids covering allosteric site stresses the significance of this zone for designing specific drugs (Thal et al. 2016).

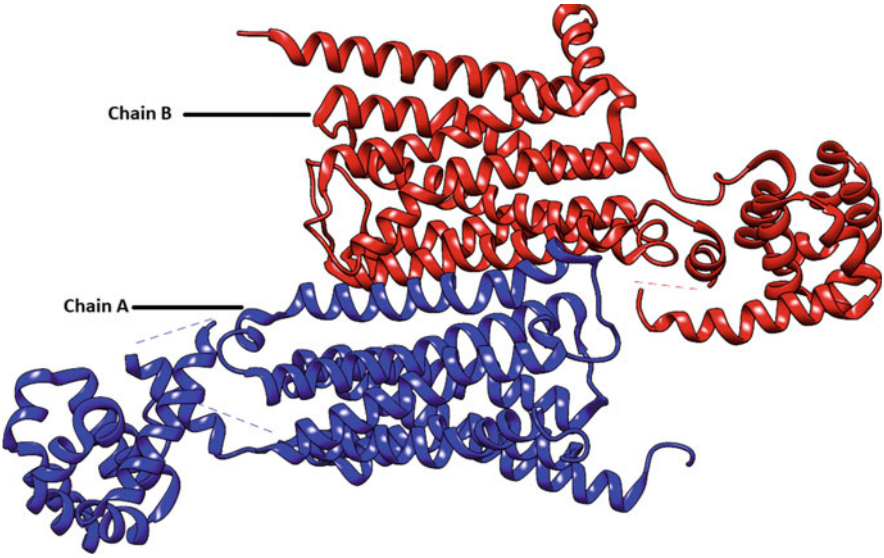

Fig. 13.6 Structure of muscarinic receptor-4 (PDB Id: 5DSG)

13.1.1.5 Muscarinic 5 Receptor (M5 Receptor)

The M5 receptor is encoded by the CHRM5 gene of rats, mouse and human, which is a member of the GPCRs subfamily of the integral membrane protein (CHRM5 2020). The receptor is coupled to Gq protein (Qin et al. 2011). It regulates the metabotropic function of ACh in the CNS. M5 receptor is the most closely occupied in the neurotransmitter containing neuronal cells in the cerebral cortex, striatum, hippocampus along substantia nigra of the brain (Foster et al. 2014). M5 receptor agonists regulate the level of the dopaminergic neuron and release dopamine into the striatum, which facilitates rude substances such as cocaine (Fink-Jensen et al. 2003). The clinical effect of this receptor is not very well-known; however, activation of the M5 receptor is identified which reduces the level of cyclic AMP and the activities of protein kinase C (Bender et al. 2018). M5 receptors may also probably beneficial in the treatment of memory deficits produced by diminished cerebrovascular function (Araya et al. 2006; Vuckovic et al. 2019).

The experimental structure of the M5 receptor is not available till date. M5 receptor participates in various cellular activities such as K^+ channel modulation, phosphoinositide degradation and adenylate cyclase inhibition (UniprotID: P08912). All five subtypes (M1–M5) of mAChRs play a significant role in biological processes like renal, cardiac, intestinal function, motor control, cognitive and attention mechanisms. Different functions and diseases associated with these five subtypes along with their locations are given in Table 13.1.

13.2 Anticholinergic Drugs

Anticholinergic drugs are substances which inhibit the action of acetylcholine at the synapse of the PNS and CNS (Xu et al. 2017). It blocks the parasympathetic nerve impulse by non-selectively or selectively linking the neurotransmitter acetylcholine to its receptor site of neurons (Prommer 2013). These drugs are also called parasympatholytics or cholinergic antagonists. Anticholinergics drugs are divided into two main categories based on their specific target to PNS and CNS: antinicotinic drugs and antimuscarinic drugs.

13.2.1 Antinicotinic Drugs

The antinicotinic drugs attack on the nAChRs. The majority of antinicotinic drugs are non-depolarizing and depolarizing drivers. Non-depolarizing agents such as vecuronium, rocuronium, pancuronium, cisatracurium, atracurium and mivacurium are a type of neuromuscular blocker, which does not depolarize the motor end plate and causing action potential (Kim et al. 2017). Depolarizing agents such as succinylcholine, decamethonium, and others are a type of neuromuscular blocker which depolarize the motor end plate and produce an action potential (Ahmad et al. 2018). Both agents are used in muscle relaxants for clinical purposes (Clar and Liu 2020; Gulenay and Mathai 2020).

Table 13.1 Location and function of M1–M5 receptor and their associated diseases

S. no.	mAChRs subtypes	Brain regions	Other tissue	Function	Associated diseases	References
1.	M1	Rich in hippocampus, neostriatum, cerebral cortex, and constitute 50–60% of total acetylcholine receptor	Sympathetic ganglia, salivary gland	Cognition, salivation	Alzheimer's disease, cognitive dysfunction	Lee et al. (2016); Lebois et al. (2018)
2.	M2	Situated throughout brain	Cardiac muscle, smooth muscle	Cardiac inhibition	Cardiac dysfunction, pain	Saternos et al. (2018); Kobayashi et al. (2007)
3.	M3	Low levels throughout brain	Salivary glands, smooth muscle, eyes	Contraction of blood vessel, lachrymal secretion, regulation of GIT	COPD, irritable bowel syndrome, urinary incontinence	Saternos et al. (2018); Kobayashi et al. (2007); Muise et al. (2017)
4.	M4	Rich in hippocampus, cortex and neostriatum	Salivary gland	Regulatory action on Ca^{+2} and K^{+} channel	Schizophrenia, Parkinson's disease, neuropathic pain	Lebois et al. (2018); Langmead et al. (2008); Kobayashi et al. (2007)
5.	M5	Estimate neuron of hippocampus, substantia nigra, pars compacta and ventral tegmental region	Muscle (eye)	Regulation of dopamine liberation at terminal end inside substantia nigra	Parkinson's disease, schizophrenia, drug addiction	Lebois et al. (2018); Langmead et al. (2008)

13.2.2 Antimuscarinic Drugs

Antimuscarinic drugs act on the mAChRs. Muscarinic antagonists (muscarinic anticholinergic drugs) disrupt the learning and memory processes (Table 13.2). These drugs are involved in causing cognitive and memory deficits in an experimental animal model for the pathological conditions identified in several human neuropathological diseases such as Alzheimer's, Schizophrenia and other diseases (Robinson et al. 2011). Majority of anticholinergic drugs have been used in a wide range of clinical conditions like amnesia, mydriasis, bronchodilation and sedation (Prommer 2013).

13.3 Sources of Antimuscarinic Drugs

The most common sources of anticholinergic drugs are (1) *Datura species* (Datura 2016), (2) *Atropabelladonna* (Ulbricht et al. 2004; Belladonna 2020), (3) *Hyoscyamusniger* (Roberts and Wink 1999), (4) *Brugmansia species* (toxic plants 2020), (5) *Garrya species* (Nesom 2012) (6) and *Mandragora officinarum* (Duke 2002) plants.

13.4 Classification of Antimuscarinic Drugs

13.4.1 Based on Their Sources

Antimuscarinic drugs are classified into three groups (Fig. 13.7): (1) natural alkaloids, (2) semi-synthetic drugs and (3) synthetic drugs.

13.4.1.1 Natural Alkaloids

Natural alkaloids are mostly natural organic compounds, which usually consist of a basic nitrogen atom. It also includes some correlated compounds with both neutral and weak acidic in nature (IUPAC 2012; Sheela 2013). Some alkaloids are synthetic or semisynthetic compounds of dissimilar or similar structures like natural alkaloids. Alkaloids have various important physiological roles in humans and animals (Lahlou 2014). Natural alkaloids such as scopolamine, atropine and tubocurarine are well known and may be toxic to the animal. They exhibit a broad range of pharmacological and biological properties (Yadav et al. 2014).

13.4.1.2 Semi-Synthetic Drugs

Semi-synthetic drugs are produced by the biochemical reaction between naturally occurring compounds to form a new product (Lahlou 2014). Semi-synthesis, a kind of biochemical synthesis, which uses chemical compound extracted from a natural source (plant material or microbial cell cultures) as the initial materials to yield other innovative compounds (Cragg and Newman 2013). These drugs are neither synthetic nor natural completely, which is a mixture of both. Semi-synthetic drugs are

Table 13.2 Features of muscarinic receptor antagonists and their functions

S. no.	Characteristics	Antagonists	Functions	References
1.	Tertiary amines	Atropine	Increases heart rate.	McEvoy (2018); De Caen et al. (2015)
	Lipophilic (good oral bioavailability and CNS penetration)		Diminishes secretions of exocrine glands.	
			Diminishes motility and tone of smooth muscle.	
			Diminishes cholinergic overactivity in the brain.	
			Mydriasis and Cycloplegia	
		Scopolamine (hyoscine)	CNS depression	McEvoy (2005); Rang (2003)
			Diminishes vestibular disturbances (antiemetic)	
		Homatropine	Mydriasis	Agrawal et al. (2010); Yazdani et al. (2018)
		Tropicamide	Impair accommodation	
		Cyclopentolate		
		Benztropine	Diminishes cholinergic overactivity in CNS	McEvoy (2003); Harvey et al. (2018)
		Biperiden		
		Trihexyphenidyl		
		Tolterodine	Diminishes motility and tone of muscle cells	De Caen et al. (2015); Katzung and Trevor (2014)
		Oxybutynin		
		Solifenacin		
		Dicyclomine		
		Darifenacin	Enhances sphincter tone	De Maagd and Davenport (2012)
2.	Quaternary amines hydrophilic (less oral bioavailability and CNS penetration)	Butyl scopolamine (hyoscine butyl bromide)	Reduces motility and tone of the gut (antispasmodic effects)	Tytgat (2007)
		Methscopolamine	Diminishes secretion of exocrine gland	Ivanovic et al. (2016)
		Glycopyrrolate		
		Pirenzepine		
		Propantheline		
		Ipratropium bromide	Bronchodilation	Rang (2003)
		Tiotropium bromide		Cheyne et al. (2013)

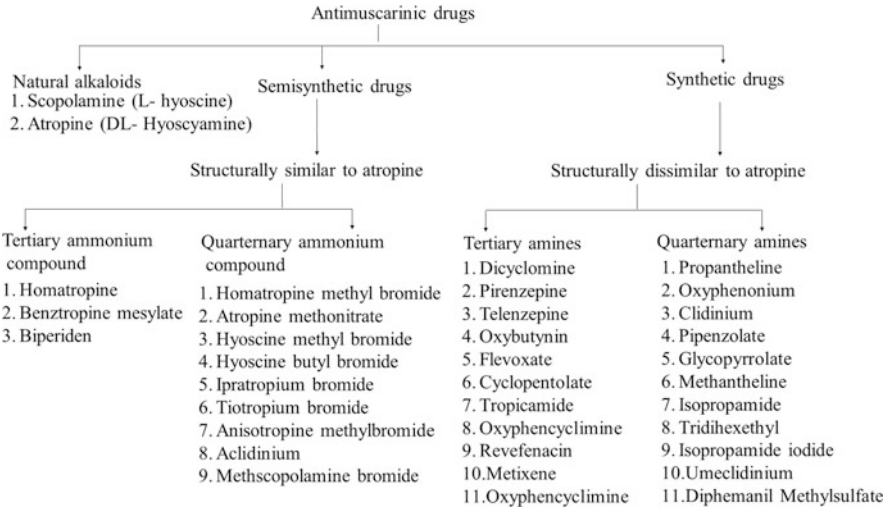

Fig. 13.7 Classification of antimuscarinic drugs: natural, semisynthetic and synthetic muscarinic receptor antagonist

structurally related to atropine including tertiary ammonium compound (homatropine, biperiden, etc.), quaternary ammonium compound (homatropine methyl bromide, atropine methonitrate, etc.) and novel antibiotics (tetracycline, doxycycline, tigecycline and chemotherapy drug) which exhibit a wide variety of chemical and pharmacological properties (Lahlou 2014; Nelson and Levy 2011; Liu and Myers 2016).

13.4.1.3 Synthetic Drugs

The synthetic drug is a drug having similar properties and belongings to hallucinogen or narcotic drugs (Garcia-Romeu et al. 2016). These drugs are structurally dissimilar to atropine including tertiary amines (pirenzepine, dicyclomine, oxybutynin, etc.) and quaternary amine (propantheline, glycopyrrolate, trihexyphenidyl, etc.) which exhibits a wide variety of biological, physicochemical and pharmacological properties (Grynkiewicz and Gadzikowska 2008). Synthetic drugs are prepared from the beginning substance, which is not present in the environment; instead, they are formed from building blocks of a chemical substance (Lahlou 2014). The common process of synthetic drug discovery is analogous to the discovery of natural drugs (Mathur and Hoskins 2017). In the natural drugs discovery, the compounds are obtained from sources like the plant, animal and microorganism. In the case of synthetic drug discovery, the compound generally produces in vitro laboratory through combinatorial technique, which manufactured a hundred to million molecules from the building block of smaller chemical substances (Valecha et al. 2010).

13.4.2 Based on Their Mode of Action

Antimuscarinic drugs are classified into two groups (Fig. 13.8): (1) nonselective muscarinic receptor antagonist and (2) selective muscarinic receptor antagonist.

13.4.2.1 Nonselective Muscarinic Receptor Antagonist

The nonselective muscarinic antagonist is a drug, which is not selective for all subtypes of the muscarinic receptors on therapeutic doses (Svoboda et al. 2017). Most of the anticholinergic drugs such as scopolamine, atropine and homatropine are nonselective for the subtypes M1–M5 receptors. However, these drugs are specific to the muscarinic receptor (Svoboda et al. 2017). A nonselective muscarinic drug is used as a medication for clinical events like obstruction of muscle contraction, salivary secretion and cardio-protection; conversely, their beneficial function in the treatment of long standing is known (Chapple et al. 2002). Ipratropium and oxitropium are also nonselective antimuscarinic drugs that successfully retract airway hyperactivity and bronchoconstriction in humans (Coulson and Fryer 2003).

13.4.2.2 Selective Muscarinic Receptor Antagonists

The muscarinic receptor is well-defined by selective agonists and antagonists. A selective muscarinic receptor grouping preceded the identification of acetylcholine (Schiechl et al. 2008). Telenzepine and pirenzepine antagonists have a comparatively strong binding affinity for the M1 receptor, which permitted for use in the therapy of peptic ulcer disease (Okabe et al. 2002). Conversely, M2 receptor antagonist includes Otenzepad peripherally acting in the remedy of bradycardia (Lanzafame et al. 2001). Darifenacin inhibitor is applied in the remedy of irritable bowel syndrome, urinary incontinence and is a specific M3 receptor (McFerren and Gomelsky 2015). Biperiden, a comparative specific M1 receptor antagonist, therapeutically applied to reduce the symptoms of Parkinson's disease, memory and learning deficit in Alzheimer's disease (Witkin et al. 2014).

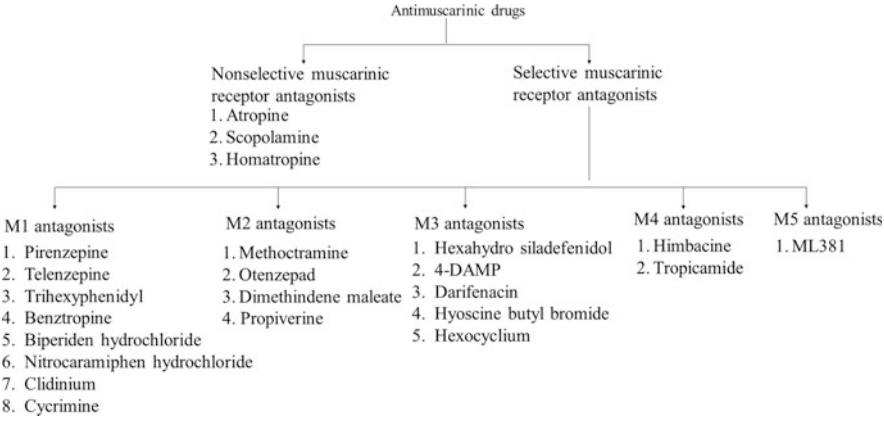

Fig. 13.8 Classification of antimuscarinic drugs: nonselective and selective receptor antagonist

A recent study was done in the chick model of myopia, which proved that the best selective M4 receptor antagonist himbacine is the most effective drug in the regulation of myopia (Carr et al. 2019; Cottriall et al. 2001). However, the M5 receptor has least worked out due to the absence of selective ligand subtypes of mAChRs. After the detection, characterization and synthesis of the first highly muscarinic and specific M5 orthosteric inhibitor, ML381 or VU0480131 have been reported (Gentry et al. 2014).

13.5 Mechanism of Antimuscarinic Drugs

The antimuscarinic drugs including atropine, scopolamine and others are more liposoluble because of their lipophilic nature, which act rapidly and are being absorbed from the gastrointestinal tract (GIT). However, it is less absorbed from injured or intact skin and easier to cross the blood–brain barrier (BBB), which upset the CNS and other organ systems (Rajput 2013; He et al. 2011). Most of the antimuscarinic drugs are usually observed to be safe taking at dose level 1.5 mg/day (Beyer et al. 2009; Ulbricht et al. 2004). Toxicity usually occurs after the ingestion of drugs at a dose level more than 1.5 mg/day in the brain, which caused unclear vision, delirium, incomprehensive speech, fatigue and unconsciousness (Milanlioglu 2011; Apfel et al. 2010; Bogan et al. 2009).

Antimuscarinic drugs competitively bind and inhibit acetylcholine from the binding site of the muscarinic receptors (Pergolizzi et al. 2012). However, their antagonistic actions may be decreased by elevating the concentration of the muscarinic agonists. The main action of antimuscarinic drugs like scopolamine, atropine and associated drugs competitively blocks the action of ACh agonists (Fig. 13.9). These drugs compete with such agonists for normal requisite on the muscarinic receptor. Many evidences support the idea that scopolamine- and atropine-related compounds compete with agonists for normal requisite on the muscarinic receptors (Snyder et al. 2005; Malik et al. 2015).

13.5.1 Epidemiology of Anticholinergic Drug

The epidemiological study suggests that about 20–50% of individuals of old age are regularly put in danger to anticholinergic drugs with possible activity (Fox et al. 2011). This shows that more than one half of the drug usually given for grown-up people is possible due to anticholinergic action (Chew et al. 2008). Anticholinergic agent's actions in adult individuals differ with sex, age and comorbidities (Wawruch et al. 2012; Chatterjee et al. 2010; Agar et al. 2009).

13.5.2 Clinical Significance of Anticholinergic Drugs

Anticholinergic drugs with potential properties have been significantly used in medicine for many years to treat disease conditions including the following:

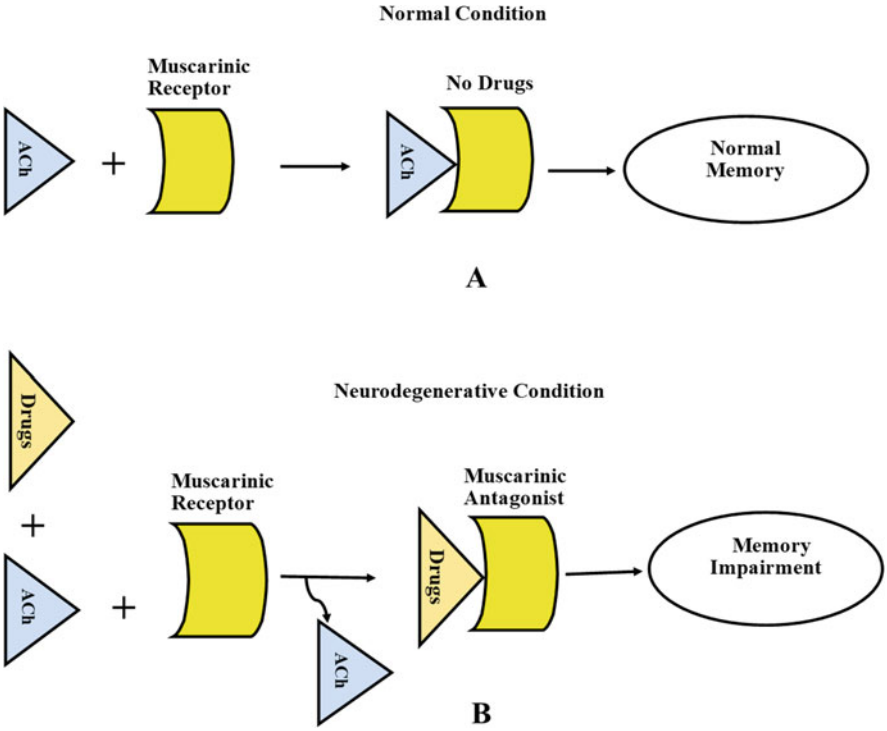

Fig. 13.9 Mechanism of action of agonist and antimuscarinic drugs on muscarinic receptor site: (**a**) normal condition and (**b**) neurodegenerative condition

(1) motion sickness, (2) Parkinson's disease, (3) overactive bladder and urinary incontinence, (4) psychiatric disorders, (5) gastrointestinal disorders, (6) diarrhoea, (7) asthma, (8) chronic obstructive pulmonary disease (COPD), (9) surgery and anaesthesia for muscle relaxation, (10) anaesthesia during surgery, (11) insomnia, (12) Alzheimer's disease and (13) toxicity of certain poisonings (Cahalan et al. 2009; Kees et al. 2015).

13.5.3 Side Effects of Anticholinergic Drugs

Different studies have indicated the side effects of anticholinergic drugs on different organ systems of the human body. The highly significant side effects of anticholinergic drugs are mentioned in Table 13.3.

Table 13.3 Side effects of anticholinergic drugs on organs and other tissues

S. no.	Organ/tissue	Side effects	References
1.	Exocrine glands	Reduce respiratory tract secretions	Le and Bhushan (2014); Macdiarmid (2008)
		Sore throat and dry mouth	
		Dry skin, warm and hyperthermia	
2.	Cardiovascular system	Elevate heart rate (tachycardia)	Katzung and Trevor (2014); Cetinel and Onal (2013)
3.	Smooth muscle	Obstipation or ileus	Lieberman (2004); Mintzer and Burns (2000)
		Gastroesophageal reflux	
		Urinary retention/impaired maturation	
		Flush and vasodilatation	
4.	Eye	Photophobia and mydriasis	Mintzer and Burns (2000); Ramnarine (2020)
		Blurred vision	
5.	CNS	Agitation, hallucination and excitement together with lipophilic antimuscarinic drugs such as atropine and scopolamine, disorientation, confusion, seizure, coma and rarely death (elderly patients)	Cetinel and Onal (2013); Berdai et al. (2012)

13.6 Conclusions

The muscarinic receptor can be distinguished structurally, physiologically and pharmacologically. The muscarinic receptor is a family of GPCRs and commonly distributed in the human body. Each subtype performs a specific function and plays a significant biological activity in the PNS and CNS. Muscarinic receptor antagonists competitively inhibit postganglionic muscarinic receptor which regulates several essential functions and structures of the PNS and CNS. Thus, antagonistic activity of antimuscarinic drug acts as a target in correlation with muscarinic acetylcholine receptor subtypes in animal and is associated with human health risk.

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