Pharmacology of Acetylcholine and Cholinergic Receptors

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Abstract

Acetylcholine is a neurotransmitter that plays a significant role in a variety of physiological functions. Cholinergic neurons synthesize, store, and release acetylcholine and are also responsible for sympathetic and parasympathetic responses of the autonomous nervous system. The wide range of functions that the cholinergic system plays explains the diverse range of therapeutic potential that targets this system. Over the decades, cholinergic and anticholinergic drugs are utilized as treatment options for various conditions including ophthalmology, neurogenic bladder, myasthenia gravis, dementia, postoperative urinary retention, xerostomia, anticholinergic overdose, snakebites, Parkinson's disease, and

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Alzheimer's disease. Alongside, they are also investigated for various promising therapeutics. This chapter provides an overview of the cholinergic system pharmacology, functions in the body, cholinergic and anticholinergic compounds, and their potential role in the medical field. Further, the chapter highlights the updates on the cholinergic compounds currently used to treat various conditions as well as compounds under investigation.

Keywords

Acetylcholine · Cholinergic system · Nicotinic receptors · Muscarinic receptors · Acetylcholinesterase inhibitors · Cholinergic ligands

Abbreviation

ACh	Acetylcholine
AChE	Acetylcholinesterase
AD	Alzheimer's disease
ADHD	Attention deficit hyperactivity disorder
ANS	Autonomic nervous system
ASDs	Autism spectrum disorders
BQCA	Benzyl quinolone carboxylic acid+
BTX	Botulinum toxin
BuChE	Butyrylcholinesterase
ChAT	Choline acetyltransferase
ChE	Cholinesterase
CNS	Central nervous system
CoA	Coenzyme A
COPD	Chronic obstructive pulmonary disease
DMN	Default mode network
DS	Down syndrome
ECT	Electroconvulsive therapy
EDHF	Endothelium-derived hyperpolarizing factor
EDRF	Endothelium-derived relaxing factors
EPSP	Excitatory postsynaptic potential
FDA	Food and Drug Administration
GPCR	G-protein-coupled receptor
LAMA	Long-acting muscarinic receptor antagonist
mAChR	Muscarinic acetylcholine receptor
MCI	Mild cognitive impairment
MTL	Medial temporal lobe
nAChR	Nicotinic acetylcholine receptor
NAL	Neutral allosteric ligand
NAM	Negative allosteric modulator
NMJ	Neuromuscular junction
NO	Nitric oxide

OPC	Organophosphate compound
OSCC	Oral squamous cell carcinoma
OSF	Oral submucous fibrosis
PAM	Positive allosteric modulator
PD	Parkinson's disease
PLA2	Phospholipase A2
PNS	Peripheral nervous system
UAB	Underactive bladder

3.1 Introduction

Autonomic nervous system (ANS) is a collection of ganglia (motor nerves) situated in pelvis, abdomen, thorax, neck, and head, in addition to motor neurons axonal connections. Acetylcholine (ACh) is the neurotransmitter found in sympathetic and parasympathetic preganglionic autonomic neurons (Blessing and Gibbins 2016). ACh also elicits activity on the postsynaptic dendrite and nerve cell body of nicotinic receptor subclass that innervate the ganglia (Taylor 2012). The first neurotransmitter to be identified was ACh. It has also been detected in primitive plants, fungi, algae, protozoa, and bacteria, which indicates the wide distribution of cholinergic system in living organisms before its identification as a part of the nervous system (Greig et al. 2013). Acetylcholine was first synthesized in 1867. However, its biological importance was only discovered 50 years later (Bylund 2016). Cholinergic neurons are responsible for ACh synthesis, storage, and release. The ionotropic neuronal nicotinic acetylcholine receptors (nAChRs) and the muscarinic metabotropic receptors are the two primary receptors that transduced the signal of ACh (Picciotto et al. 2012). Moreover, cholinergic neurons control peripheral sympathetic and parasympathetic responses of the ANS. The "rest and digest" functionalities are mediated by the release of ACh by the parasympathetic terminals in the ANS (Tiwari et al. 2013). While in the central nervous system (CNS), ACh acts as a neuromodulator and neurotransmitter when released from cholinergic neurons and interneurons in the brain and spinal cord (Naser and Kuner 2018). In the ANS, ACh is released from postganglionic parasympathetic and sympathetic nerves and preganglionic neurons. In the somatic system, Ach is released at the neuromuscular junction. ACh is a quaternary ammonium parasympathomimetic compound; it produces a transient action due to its rapid destruction by cholinesterase enzyme, which limits the therapeutic application of ACh. Another limiting factor is the fact that acetylcholine possesses no specificity as it interacts with all nicotinic and muscarinic receptors making it particularly not a useful therapeutic agent (Bylund 2016). Nevertheless, ACh chloride is used topically after cataract surgeries to reduce a possible postoperative increase in intraocular pressure (Drudi et al. 2017). Many compounds that target the cholinergic system are currently used for the treatment of various conditions, and these compound include muscarinic antagonists (e.g., darifenacin, fesoterodine, oxybutynin, and tolterodine) for the treatment of urinary incontinence, scopolamine for motion sickness, and aerosol ipratropium for COPD management (Ehlert 2019a). Acetylcholinesterase inhibitors have also shown great therapeutic importance in the treatment of diseases such as myasthenia gravis, Alzheimer's

disease, and glaucoma (Potter and Kerecsen 2017). Nicotinic receptors stimulation has shown to improve cognitive functioning after several studies on animal models. Besides, some preclinical and clinical studies suggested that nicotinic receptors also play a role in depression, mood, and anxiety (Aboul-Fotouh 2015; Quik et al. 2015). In this chapter, we present an overview of the cholinergic system pharmacology, functions in the body, cholinergic and anticholinergic compounds, and their role in the medical field. Finally, an update on the cholinergic compounds currently used to treat various conditions as well as compounds under investigation are discussed.

3.1.1 Chemistry of Acetylcholine

Acetylcholine (2-acetoxy-*N*,*N*,*N*-trimethylethanaminium) is a small molecule with the chemical formula $CH_3COOCH_2CH_2N^+(CH_3)_3$ and a molecular mass of 146.2074 g/mol. It has a simple chemical structure composed of an ester of choline and acetic acid as shown in Fig. 3.1 (Tunç et al. 2016; Ueda et al. 2016).

ACh plays a crucial role in maintaining homeostasis in the brain by acting as a neurotransmitter in both the peripheral nervous system (PNS) and CNS. Choline acetyltransferase is the enzyme responsible for synthesizing acetylcholine from the substrates choline and acetyl CoA (coenzyme A) (Fig. 3.2) (Akaike and Izumi 2018). Pyruvate that results from glucose breakdown serves as the key source of acetyl CoA inside the neurons. The rate-limiting factor of ACh synthesis is the choline uptake by neurons. Choline acetyltransferase is found as a particulate membrane-bound enzyme in cholinergic neurons and as a soluble enzyme in the cytoplasm. Acetylcholine storage takes place in small synaptic spherical vesicles

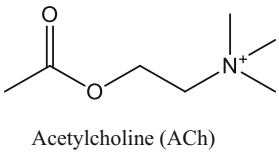


Fig. 3.1 Chemical structure of ACh

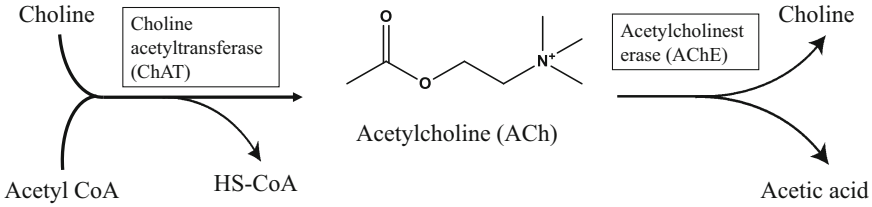


Fig. 3.2 Synthesis of acetylcholine by choline acetyltransferase (ChAT) using choline and acetyl coenzyme A, releasing coenzyme A (HS-CoA). Metabolism of acetylcholine is catalyzed by acetylcholinesterase (AChE) producing acetic acid and choline

where it is protected from being destroyed by the enzyme acetylcholinesterase (Browning 2010; Colzato et al. 2017).

3.1.2 Acetylcholine Functions

Acetylcholine (ACh) is a neurotransmitter that functions in both the PNS and the CNS. The ANS (sympathetic and parasympathetic) uses acetylcholine to generate a nerve impulse. In PNS, ACh mainly acts on the muscular system by activating muscle contraction after being released in the neuromuscular junction. In the central nervous system, ACh has various effects on cognitive functions, alertness, learning, and memory (Haerter and Eikermann 2016; Maurer and Williams 2017; Panus et al. 2009). When ACh gets released from somatic nerve endings into the neuromuscular junction, it causes the nicotinic ligand-gated ion channels to open, leading to sodium entrance into muscle cells. The sodium ions produce an excitatory postsynaptic potential (EPSP) that generates an action potential which eventually stimulates muscle contraction (Pappano 2018). Also, serum ACh has shown to produce vasodilation by activating vascular endothelial muscarinic receptors, which causes the release of endothelium-derived relaxing factors (EDRF) including prostanoids, endothelium-derived hyperpolarizing factor (EDHF), and nitric oxide (Tangsucharit et al. 2016). The chapter further presents the role of acetylcholine and cholinergic system together with few specific ligands and their clinical utility.

3.2 Cholinergic Receptors

Cholinergic receptors were named "cholinergic" due to their activation by Ach, and these receptors are mostly parasympathetic and transduce signal in the autonomic and somatic nervous system (Wehrwein et al. 2016). Based on the stimulation by muscarine or nicotine, cholinergic receptors are classified into muscarinic and nicotinic receptors, respectively. Nicotinic receptors are ionotropic ligand-gated channels, unlike muscarinic receptors, which are G-protein-coupled receptors (GPCRs) (Kruse et al. 2014; Papke 2014). Both receptor types are present within the CNS; however, nicotinic receptors are also found at the neuromuscular junction. The difference in signal transduction upon activation of the two receptor types results in distinctive physiological functions.

3.2.1 Muscarinic Receptors

Muscarinic receptors are mostly present at parasympathetic target organs, but it can also be found at specific sympathetic target organs such as the eccrine sweat glands that produce copious secretion for thermoregulation purpose, and in blood vessels of the skeletal muscles. In the PNS, muscarinic receptors are mainly found on autonomic effector cells, which are innervated by postganglionic parasympathetic nerves

Table 3.1 Classification of muscarinic receptors, their distribution and role

Subtype	Distribution	Role
M_1	Brain (cortex, hippocampus), salivary glands	Cognitive functioning and memory, salivary secretion
M_2	Heart, brain, smooth muscle	Regulation of heart rate and heart rate variability, behavioral flexibility
M_3	Smooth muscle, glands, eye	Smooth muscle contraction, gland secretion, iris contraction
M_4	Brain (forebrain, striatum)	Modulation of several important dopamine-dependent behaviors
M_5	Brain (substantia nigra), eye	Regulation of striatal dopamine release

Table 3.2 Muscarinic receptors subtypes localization and role in the brain

Subtype	Presence in brain	Functional aspect
M_1	All major areas of the forebrain including cerebral cortex, hippocampus, thalamus, and corpus striatum. Cellular localization at striatum nigrum neurons and glutamatergic pyramidal neurons	Highly responsible for cholinergic functions. Synaptic plasticity, learning and memory (cognition), neuronal differentiation during development, and neuronal excitability
M_2	Throughout the brain especially in hippocampus and neocortex. Abundant in non-cholinergic neurons in these areas	Inhibitory effect on dopaminergic action. Antinociceptive effect reported
M_3	Highly expressed in hypothalamus, lesser expression in hippocampus	Major role in food intake, body growth
M_4	Major presence in corpus striatum	An important role in psychosis, an involvement in pathology of Parkinson's disease, inhibits D1 receptor of dopamine signaling
M_5	Pars compacta of substantia nigra, ventral tegmental region	Rewarding effect of abusive drugs

(Tiwari et al. 2013). Muscarinic receptors are classified into five subtypes; each subtype distribution and role are listed in Table 3.1 (Glavind and Chancellor 2011).

These five muscarinic receptor subtypes are expressed throughout the human brain and are involved in various functional processes, such as learning, memory, attention, sleep-wake cycles, sensorimotor processing, and arousal (Lebois et al. 2018). Table 3.2 summarizes the details concerning muscarinic receptors distribution and function in the brain (Verma et al. 2018). Muscarinic receptors are GPCRs in which M_1, M_3, and M_5 are Gq/11 G-proteins which mediate excitatory neuromodulatory acetylcholine actions while M_2 and M_4 receptors are Gi/o G-proteins that produce inhibitory neuromodulatory acetylcholine actions (Brown 2019; Felder 1995; Lebois et al. 2018).

All five muscarinic receptor subtypes express throughout the mammalian brain. However, different regions in the brain contain different receptor subtype concentrations exemplified by M1 and M2 receptors. In the major forebrain areas,

the expression of these receptors is comparatively higher to that of other subtypes. M1 receptor is the highest muscarinic receptor expressed in the cortex, striatum, and hippocampus. M2 receptor is highly expressed in the occipital cortex and nucleus basalis, while M4 receptor is more prominent within caudate putamen and the striatum. The least muscarinic receptor expressed compared to the other subtypes is M5 receptor (Carruthers et al. 2015; Scarr et al. 2016).

3.2.2 Nicotinic Receptors

Nicotinic acetylcholine receptors (nAChRs) are hetero- or homo-pentameric structured ligand-gated ion channels. Nicotinic receptors possess an essential role in various biological processes such as learning, memory, locomotion, anxiety, and attention. Recent researches showed that nicotinic receptors play a role in regulating inflammation by α7 nicotinic acetylcholine receptors activation in macrophages (Egea et al. 2015). The nAChRs are mainly divided into two subclasses: neuronal and muscular. In the neuromuscular junctions, the muscular nAChRs contribute to the neuromuscular transmission, and the neuronal nAChRs are located in both the PNS and the CNS. The nAChRs have a large number of homologous subunits that can form many different combinations of pentamers which produce various receptors with diverse functionalities (Kulbatskii et al. 2018).

Composition of nicotinic acetylcholine receptors (nAChRs) consists of five subunits surrounding a water-filled pore. Neuronal nAChRs are classified based on the presence of adjacent cysteine groups within the extracellular part of the α subunits into two types: the alpha and beta. The alphas are α2, α7, α9, and α10, while the betas are β2–β4 (Dani 2015; Fasoli and Gotti 2015). There have been 17 subunits of nAChRs identified (α1–10, β1–4, γ, δ, and ε). All those subunits were found in mammals except for α8, which is found in avian species. In muscular nicotinic receptors, the binding sites are at the interfaces of the δ or γ subunits and the α subunit, while in neuronal nicotinic receptors, the binding sites are found at the interfaces of the β subunit and α subunit or at two adjacent α subunits. Alpha subunits are the only ones containing two cysteine residues near the binding site of acetylcholine (Lukas et al. 1999; Melroy-Greif et al. 2016). The characteristics of nAChRs are listed in Table 3.3 (Akaike and Izumi 2018; Dani 2015).

In the brain, the predominant subtypes expressed are α7 subunit containing receptors which are either homo- or heteromeric. Different subtypes of nAChRs have shown the ability to modulate synaptic transmission in various brain parts, including thalamic nuclei, cortical interneurons, the visual cortex, and supraoptic nuclei. nAChR subtypes are distributed differently in the CNS (Table 3.4) (Akaike and Izumi 2018; Dineley et al. 2015).

Table 3.3 Nicotinic acetylcholine receptors characteristics

Subtype	Primary subunit composition	Ca^{2+} permeability	Major location
α1	$(\alpha1)_2\beta1\gamma\delta$, $(\alpha1)_2\beta1\delta\varepsilon$	Low	Neuromuscular junction
α2	α2β2, α2β4	Low	CNS
α3	α3β2, α3β4	Low	CNS, autonomic ganglion
α4	$(\alpha4)_3(\beta2)_2$, $(\alpha4)_2(\beta2)_3$	Low	CNS
α5	α3β2α5, α3β4α5, $(\alpha4)_2(\beta2)_2\alpha5$	High	CNS, autonomic ganglion
α6	α6β2β3, α6α4β2β3	High	CNS
α7	$(\alpha7)_5$	High	CNS, non-neuronal cells
α8	$(\alpha8)_5$	High	CNS
α9	$(\alpha9)_5$, α9α10	High	Mechanosensory hair cells
α10	α9α10	High	Mechanosensory hair cells

3.3 Pharmacology of Cholinergic Receptors

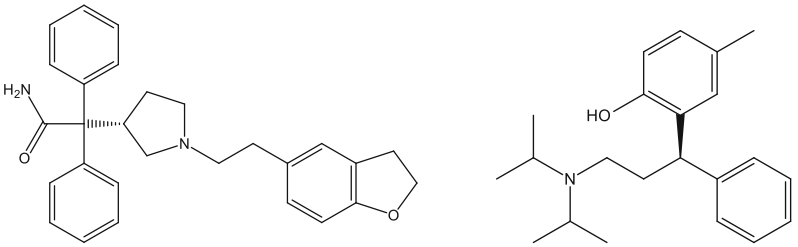
Cholinergic ligands provide a wide range of therapeutic applications, many are currently on the market for various medical conditions including scopolamine, neostigmine, tacrine, oxybutynin, donepezil, tolterodine, ipratropium, ambenonium, and edrophonium (Bukala et al. 2019; Potter and Kerecsen 2017; Ramaswamy et al. 2018; Vozmediano-Chicharro et al. 2018). Other compounds are under investigation for further therapeutic options in the future such as xanomeline, cevimeline, tazomeline, benzyl quinolone carboxylic acid (BQCA), and bispyridinium oximes (Antonijevic et al. 2016; Lorke and Petroianu 2018; Verma et al. 2018).

3.3.1 Muscarinic Receptor

Muscarinic acetylcholine receptors play a significant role in modulating physiological processes related to mental health, respiration, salivation, excretion, and motion perception. In recent years, investigations on the mAChR ligands have accelerated the discovery of various novel chemical entities and some were approved for certain conditions, including psychosis (Foster and Conn 2017), Alzheimer's disease (Bradley et al. 2017), asthma, motion sickness, and incontinence. An ideal therapeutic agent for these diseases should not exert any adverse effects that can be caused by nonspecific interaction with other mAChR subtypes. However, the orthosteric sites of the mAChR subtypes have high amino acid sequence similarities, which explains the current difficulties in designing drugs that target specific receptor subtype (Korczynska et al. 2018). For example, darifenacin and tolterodine (Fig. 3.3) are mAChR antagonists that treat incontinence by targeting M3 receptors, often cause adverse effects such as dry mouth by interacting with glandular M1 and M3 receptors, and increase heart rate due to effects on M2 receptors and increase drowsiness (Glavind and Chancellor 2011; Korczynska et al. 2018; Naicker et al.

Table 3.4 Distribution of nicotinic receptors in CNS

α2	α3	α4	α5	α6	α7
Cortex		Cortex	Cortex		Cortex
Hippocampus	Hippocampus	Hippocampus	Hippocampus		Hippocampus
		Striatum	Striatum	Striatum	
Amygdala		Amygdala			Amygdala
		Thalamus			
Hypothalamus		Hypothalamus			Hypothalamus
	Substantia nigra	Substantia nigra	Substantia nigra	Substantia nigra	Substantia nigra
	Cerebellum	Cerebellum			Cerebellum
	Spinal cord	Spinal cord			Spinal cord



Darifenacin Tolterodine

Fig. 3.3 Chemical structures of darifenacin and tolterodine

2017). Such adverse effects of muscarinic receptor antagonists have reduced their convenience as treatment options; nevertheless they are highly active compounds (Korczynska et al. 2018) with scope for further structural optimization.

In CNS disorders, the majority of studies are focused on compounds targeting M1 and M4 mAChRs subtypes. On the other hand, M5 mAChRs expresses itself in highly variable regions of therapeutic interest, and it is the least mAChR expressed in the brain by 2% of the total mAChRs population. Despite the fact, M5 receptors are the only subtype with an identifiable mRNA transcript in dopamine-containing neurons. This factor makes it a viable target for drug addiction treatment by supporting the hypothesis that mAChR subtype may be responsible for regulating the transmission of midbrain dopamine and reward mechanisms (Berizzi et al. 2016; Gunter et al. 2018).

3.3.1.1 Muscarinic Agonists

Arecoline (methyl-1,2,5,6-tetrahydro-1-methyl-nicotinate), an alkaloid, is considered the primary active constituent of A. *catechu.* In recent years, many studies have been carried out to further investigate arecoline's pharmacological and toxic effects (Bhat et al. 2017). Several pharmacological activities produced by arecoline have been reported such as anti-parasitic effects, in addition to effects on the digestive, cardiovascular, nervous, and endocrine systems. The main toxic effects of arecoline are genotoxicity, oral squamous cell carcinoma, and oral submucous fibrosis. However, arecoline has an agonistic effect on muscarinic receptors which upon further investigation have shown to reverse memory impairment and scopolamine-induced memory loss in male rats model of Alzheimer's disease (Kuca et al. 2016; Liu et al. 2016).

In preclinical studies, muscarinic receptor agonists have exhibited atypical antipsychotic effects. Xanomeline is a mAChR agonist that can reverse certain dopamine-mediated behaviors. Cevimeline, milameline, sabcomeline, and xanomeline have all progressed into different clinical development stages for possible treatment of Alzheimer's disease (AD) and schizophrenia. Phase II clinical trials of xanomeline have demonstrated its effect and efficacy for various cognitive symptoms domains such as hallucinations and behavioral disturbances associated

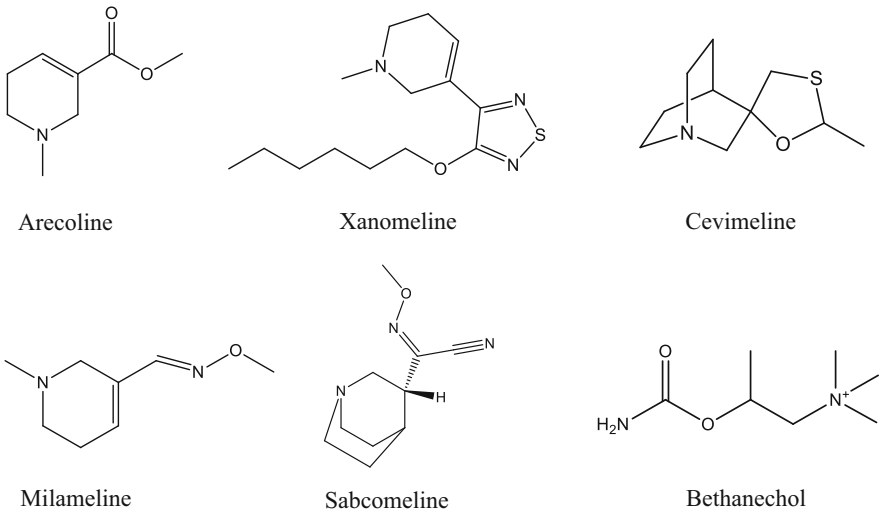


Fig. 3.4 Structures of mAChR agonists

with AD (Congreve et al. 2018; Sivaraman et al. 2019). Figure 3.4 depicts the chemical structures of some mAChR agonists mentioned in this section.

Bethanechol is a cholinergic agonist that acts on M1 and M2 muscarinic receptors. It is a methyl analogue of acetylcholine and used clinically for women with underactive bladder (UAB). Stimulation of mAChRs at the neuromuscular junction of smooth muscle with bethanechol can induce the contraction of the detrusor muscle, which eventually improves bladder emptying. However, various clinical evidence supporting bethanechol efficacy for UAB is limited and poor (Sivaraman et al. 2019; Gaitonde et al. 2018). Bethanechol has also been investigated in the treatment of tracheomalacia. However, further trials are required to ensure the safety and efficacy of bethanechol as a treatment regimen (Bass et al. 2018).

BuTAC ([5*R*-(exo)]-6-[4-butylthio-1,2,5-thiadiazol-3-yl]-1-azabicyclo-[3.2.1]-octane) is a muscarinic receptor agonist that produces full agonist activity on M2 receptor and partial agonist activity on both M1 and M4 receptors. Contrarily, it exhibits full antagonist activity on M3 and M5 receptors. BuTAC has shown to produce antipsychotic activity on schizophrenic animal models (Andersen et al. 2015; Watt et al. 2013). Another muscarinic agonist is cevimeline, which activates both M1 and M3 receptors, and it was originally developed for the treatment of Alzheimer's-type senile dementia. Currently, this compound is used to treat xerostomia, which is a condition that causes numerous disorders in oral functions, including swallowing, taste, speech, and mastication. Other than pilocarpine, cevimeline is the only agent available for the therapeutic intervention of xerostomia (Kishimoto et al. 2016; Mitoha et al. 2017). Table 3.5 summarizes various

Table 3.5 Muscarinic receptor agonists in preclinical and clinical phases

Agonist	Muscarinic receptor	Status	Therapeutic application	Reference
AF102B, AF150, AF267B, AF292	mAChR	*In vivo* passed	Alzheimer's disease	Ferreira-vieira et al. (2016); Fisher (2012); Sehgal et al. (2018)
77-LH-28-1	mAChR	*In vivo* passed	Alzheimer's disease and schizophrenia	Langmead et al. (2008a, b); Zhao et al. (2019)
VU0357017 and VU0364572	M1 mAChR	*In vivo* passed	Cognitive deficits (schizophrenia, Alzheimer's disease)	Digby et al. (2010); Lebois et al. (2017); Rogers and Gray (2012)
Xanomeline	M1/M4 mAChR	Phase 2 trials	Schizophrenia	Bender et al. (2017); Khatwal et al. (2014)
Arecoline	M1, M2, M3, M4 mAChR	*In vivo*	Wide pharmacological activities (nervous, cardiovascular, endocrine, digestive system, and anti-parasitic effects)	Langmead et al. (2008a, b); Liu et al. (2016)
CI-1017	M1 mAChR	*In vivo*	Cognitive deficits (Alzheimer's disease and schizophrenia)	Brady et al. (2008); Weiss et al. (2000)
Cevimeline	M3 mAChR	Passed in *in vitro* and *in vivo* study but failed in clinical trial	Primary Sjögren's syndrome (dry mouth)	Garlapati et al. (2019); Langmead et al. (2008a, b)
Tazomeline, talsaclidine, milameline, and arecoline	M1 mAChR	Passed in *in vitro* and *in vivo* study but failed in clinical trial	Schizophrenia	Langmead et al. (2008a, b)
AF102B	mAChR	Clinical trial phase 2/3	Alzheimer's disease	Digby et al. (2010); Kumar and Kumar (2018)
SB202026	M1, M2, M3 mAChR	Discontinued due to cholinergic adverse effects	Alzheimer's disease	Digby et al. (2010)
Benzyl quinolone carboxylic acid (BQCA)	M1 mAChR	*In vivo* passed	Alzheimer's disease	Digby et al. (2010); Hepnarova et al. (2018)

(continued)

Table 3.5 (continued)

Agonist	Muscarinic receptor	Status	Therapeutic application	Reference
MK-7622	M1 mAChR	Discontinued after phase 1 trials	Alzheimer's disease	Cummings et al. (2016)
AC-260854	M1 mAChR	*In vivo* study	Schizophrenia and Alzheimer's disease	Berizzi et al. (2016)
VU0152099, VU0152100	M4 mAChR	*In vivo* study	Alzheimer's disease	Lebois et al. (2017)
TBPB	M1 mAChR	*In vivo* study	Schizophrenia	Conn et al. (2009)

muscarinic receptor agonists in different developmental stages (Berizzi et al. 2016; Cummings et al. 2016; Verma et al. 2018).

3.3.1.2 Muscarinic Antagonists

As discussed earlier, muscarinic receptors are present in autonomic ganglia, peripheral tissues, and various regions of the brain innervated by parasympathetic nerves. Antagonism of muscarinic receptors can produce therapeutic effects in several clinical conditions. For instance, during eye examination, muscarinic receptor antagonist is applied topically to the eye inducing relaxation in the pupillary constrictor muscles and circular ciliary, which results in pupil dilation, thereby making it easier to view the retina and measure refractive errors of the lens (de Linder Henriksen et al. 2019; Yi et al. 2015). Muscarinic antagonists have also been considered for the treatment of COPD and asthma due to the constricting effect in vagal tone in the pulmonary airways (Busse et al. 2016; Oba et al. 2016). Muscarinic antagonists are sometimes used to treat diarrhea associated with inflammatory bowel conditions and dysenteries due to their ability to reduce gastrointestinal tract mobility (Aleem and Janbaz 2018). Muscarinic antagonists (trospium, oxybutynin, tolterodine, solifenacin, fesoterodine, and darifenacin) can also relieve symptoms of frequency, urgency, and incontinence of an unstable bladder, which reduces micturition frequency, and are currently used for the treatment of overactive bladder and urge incontinence (Andersson 2019). Muscarinic antagonists inhibit the vestibular apparatus of the inner ear, which reduces motion sickness. Scopolamine has been used topically as a patch to be placed on the skin behind the ear for the treatment of motion sickness (Zhang et al. 2016). Muscarinic antagonists can also act as antidotes in cases such as muscarine poisoning from mushrooms, insecticides poisoning, and war gases that contain cholinesterase (ChE) inhibitors. Pharmacokinetic properties of the muscarinic antagonist and the route of administration are the main factors affecting which muscarinic antagonist is of choice to treat each health condition. Table 3.6 summarizes the currently used muscarinic antagonists (Ehlert 2019a, b).

Long-acting muscarinic receptor antagonists (LAMA) such as tiotropium has been used for years in the management of COPD. LAMAs antagonize

Table 3.6 Muscarinic receptor antagonists that are currently used and their therapeutic applications

Agent	Use
Tertiary amines	
Atropine	Treatment of anticholinergic poisoning
Scopolamine	Treatment of motion sickness
Homatropine	Mydriatic and cycloplegic; for mild uveitis
Dicyclomine	Alleviates GI spasms, pylorospasm, and biliary distention
Darifenacin	Treatment of urinary incontinence
Fesoterodine	Treatment of urinary incontinence
Oxybutynin	Treatment of urinary incontinence
Tolterodine	Treatment of urinary incontinence
Oxyphencyclimine	Antisecretory agent for peptic ulcer
Cyclopentolate	Mydriatic and cycloplegic
Tropicamide	Mydriatic and cycloplegic
Benztropine	Treatment of Parkinson's and Huntington's diseases
Trihexyphenidyl	Treatment of Parkinson's and Huntington's diseases
Pirenzepine	Antisecretory agent for peptic ulcer
Quaternary ammonium derivatives	
Methylatropine	Mydriatic, cycloplegic, and antispasmodic
Methylscopolamine	Antisecretory agent for peptic ulcer, antispasmodic
Ipratropium	Aerosol for COPD
Glycopyrrolate	Antisecretory agent for peptic ulcer, antispasmodic
Tolterodine	Treatment of urinary incontinence
Propantheline	GI antispasmodic
Tiotropium	Aerosol for COPD

parasympathetic bronchoconstriction in the airways reversing airflow obstruction. Recently, several new agents have been developed and studied for COPD management such as aclidinium bromide, umeclidinium bromide, and glycopyrronium bromide. For COPD management, many LAMAs are under development, and some are already available, including bencycloquidium, V0162, CHF 5407, AZD8683, AZD9164, and TD-4208 (Mark A. Mastrodicasa et al. 2017). Tiotropium was the only LAMA in clinical use for almost two decades, and it was the first LAMA prepared as daily single-dose treatment. Tiotropium exerts its anticholinergic effects by binding to M1 and M3 receptors (Alvarado-Gonzalez and Arce 2015). Tiotropium has shown to decrease hospitalization, symptoms, and exacerbations and improve health status in COPD patients. It also showed an improvement in the effectiveness of pulmonary rehabilitation. As compared to salmeterol, tiotropium has proven to show a higher increase in the time to first exacerbation occurrence, thus decreasing exacerbation rate in general (Han and Lazarus 2016).

3.3.1.3 Allosteric Modulators

Many efforts were made to produce specific M1 and M4 receptor targeting agents to maintain therapeutic efficacy and reduce adverse side effects (Foster et al. 2014; Jones et al. 2012). The targeting of a specific subtype of muscarinic receptors is difficult due to the highly conserved orthosteric binding site between the receptor subtypes. Allosteric modulators have been developed to overcome this problem since the allosteric binding sites are considered less conserved among the receptor subtypes. Allosteric modulators show higher selectivity and can modulate receptor activation either by acetylcholine or other agonists, or it can activate the receptor. Allosteric activators can either be allosteric agonists or positive allosteric modulators (PAMs). Allosteric agonists act on the allosteric site of the receptor, hence activating the receptor without the presence of acetylcholine, while PAMs cannot activate the receptor directly but only potentiate the activation by acetylcholine (Jakubik and El-Fakahany 2016). One compound can also act as both an allosteric agonist and PAM. However, since allosteric mechanisms are affected by cooperativity factors and affinity, they present challenges and practical implications for drug discovery and development (Conn et al. 2014; Yohn and Conn 2018).

Positive Allosteric Modulators

As mentioned before, PAMs possess higher selectivity than muscarinic agonists because the allosteric sites of the muscarinic receptors have higher sequence divergence as compared to orthosteric site. Generally, PAMs are considered as compounds with an excellent safety profile because they do not cause the induction of independent agonistic activity, which means they cannot exert their effect without the presence of the endogenous agonist. Thiochrome is a natural compound that results from the oxidation and metabolism of thiamine. Thiochrome acts as a PAM to M4 muscarinic receptors (Takai and Enomoto 2018). Recently, there has been much successful development of selective mAChR PAMs, especially M1 and M4 selective compounds that have shown promising results including excellent brain penetration and pharmacokinetic profiles. After the discovery of the M4 selective PAMs (VU10010 and LY2033298), many efforts were directed towards developing M4 selective compounds. M4 mAChR possesses a potential role in dopaminergic systems' regulations, which are highly related to the positive symptoms of schizophrenia, and these receptors are also significant in reducing negative symptoms and cognitive impairment in AD patients (Chan et al. 2008; Foster and Conn 2017). M4 receptor PAMs are also considered as a potential therapeutic approach for drug addiction, Huntington's disease, and Parkinson's disease (PD). The thieno[2,3-*c*] pyridazine analogues received most of the attention due to the limited chemical diversity of M4 PAMs discovered, and one of the promising analogue for further preclinical trials is VU6005806/AZN-00016130 (Engers et al. 2019). Recently, the discovery of selective M1 receptor PAMs showed their ability to enhance both hippocampal and prefrontal cortex-dependent forms of cognitive functions in non-human primates and rodents, which agrees with many studies suggesting that activating M1 receptors produce cognitive-enhancing effects (Digby et al. 2012; Gould et al. 2015; Lange et al. 2015; Vardigan et al. 2015). For example, MK-7622,

a potent and selective M1 PAM, is under preclinical and clinical trials to reduce cognitive dysfunction in AD patients (Uslaner et al. 2018).

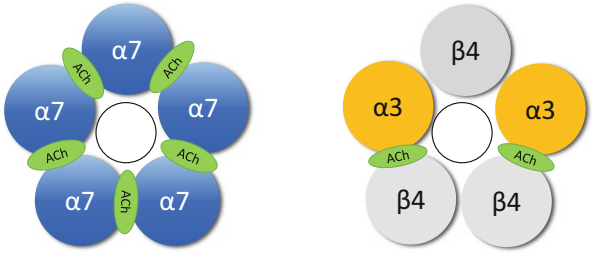
Negative Allosteric Modulators

Allosteric ligands for individual muscarinic receptors subtypes are currently under investigations. Allosteric ligands exhibit selective cooperativity between the ligand and the receptor at the receptor after targeting allosteric site(s) (Berizzi et al. 2018). Lately, ML375 (VU0483253) became the first negative allosteric modulator (NAM) that displayed selectivity for M5 muscarinic receptor (Gentry et al. 2013). Studies have shown that there is a functional interlink between M5 receptor and addiction/reward pathways, and further substantiated by the attenuation of cocaine addiction liabilities in a rodent model with cocaine addiction by ML375 (Gunter et al. 2018).

However, ML375's elimination half-life is excessively long, with approximately 80 h in rats. An equipotent M5 receptor NAM (VU6008667) has been developed later with a more appropriate shorter elimination half-life (2.3 h) in rats, excellent selectivity, and high CNS penetration (Bender et al. 2019; Gentry et al. 2013; McGowan et al. 2017).

3.3.2 Nicotinic Receptor

The nAChRs are a part of the "Cys-loop" receptor superfamily, which are multi-subunit transmembrane receptors. nAChRs mediate excitatory neurotransmission in autonomic ganglia, specific synapses in both the spinal cord and brain, and at the vertebrate neuromuscular junction (Albuquerque et al. 2009; Alcaino et al. 2017). These nAChRs generate complex calcium signals that influence neuronal processes and signaling molecules. The combination of the nicotinic receptor subtype, Ca^{2+} signaling pathway, neuronal type, and developmental stage all together translate the stimulation of the nicotinic receptors into a neuronal response and eventually into a physiological outcome (Dajas-Bailador and Wonnacott 2004; Kabbani and Nichols 2018). As stated before, nicotinic receptors are ligand-gated ion channels, which are pentamers assembled from five subunits either as homomeric or heteromeric pentamers (Fig. 3.5) (Improgo et al. 2010; Millar and Gotti 2009; Wu et al. 2016).



Homomeric nAChR (e.g., α7)

Heteromeric nAChR (e.g., α3β4)

Fig. 3.5 Schematic representation of homomeric and heteromeric nicotinic receptors with the ACh binding site location

During the inactivated state, the pentamers exist as a funnel shape structural motif with a central core, and it remains closed. When activated by ACh, the channel undergoes a conformational change in all subunits, and the core opens to allow Na^+ and K^+ flow according to electrochemical gradients leading to cellular response (Svorc 2018). The nAChRs in the CNS are responsible for regulating various processes including neuronal integration, neurotransmitter release, and cell excitability and can also affect certain physiological functions including cognition, pain, arousal, sleep, and mood (Rahman et al. 2015).

Nicotine, a prototypic tobacco alkaloid, had received interest as a potential therapeutic compound 30 years ago, which was the time when tobacco smoking was discovered to affect the performance of a particular cognitive task positively. Further investigations substantiated that nicotine administration indeed affects pro-cognitive performances (Terry and Callahan 2018; Heishman et al. 1994; Sherwood 1993). Nowadays, growing pieces of evidence corroborate nicotine's effect in enhancing cognitive function and information processing in both experimental animals and human nonsmokers (Levin et al. 2013). Additionally, other effects of nicotine have been reported from *in vivo* and *in vitro* studies such as sustained attention, working memory (Newhouse 2019) and recognition memory in rats (Nikiforuk et al. 2015), attention, processing of visual information, and short term memory in humans. *In vivo* and *in vitro* studies have also shown that nicotine possesses neuroprotective activity in specific disease models which proposes that nicotine can be used not only for symptomatic control but also to produce effects that enhance cognition in neurodegenerative diseases such as AD and PD (Newhouse 2019). However, nicotine has limited therapeutic potentials for psychiatric and neurologic conditions due to several factors including cardiovascular side effects, abuse potentials, and its relatively short half-life. Nicotine transdermal patches used for smoking cessation have shown no cardiovascular side effects while exhibiting improved cognition in patients with mild cognitive impairment (MCI) (Newhouse et al. 2012). Various types of nicotine formulations have been developed for smoking cessation such as tablets, patches, nasal sprays, gums, inhalers, and lozenges to reduce cravings and withdrawal symptoms (Shahab et al. 2013). Nicotinic acetylcholine receptor ligands other than nicotine have various therapeutic potentials which are listed in Fig. 3.6 (Terry and Callahan 2018).

Nicotinic cholinergic receptors (nAChRs) are pentameric proteins that are activated by acetylcholine at central and peripheral synapses. Neuronal nicotinic receptors in the brain, autonomic ganglia, adrenal gland, and immune cells are composed of either α subunits or both α and β subunits. One of the primary phenomena that nicotinic receptors exhibit upon continued nicotinic agonist exposure is desensitization, which occurs in both muscular and neuronal nicotinic receptors.

3.3.2.1 Nicotinic Agonists

Nicotinic agonists are any compound that can mimic ACh action on nAChRs. Nicotine (Fig. 3.7) is the most popular nicotinic agonist. After the discovery of the positive effects of nicotine, the approach to investigate and design more nicotinic

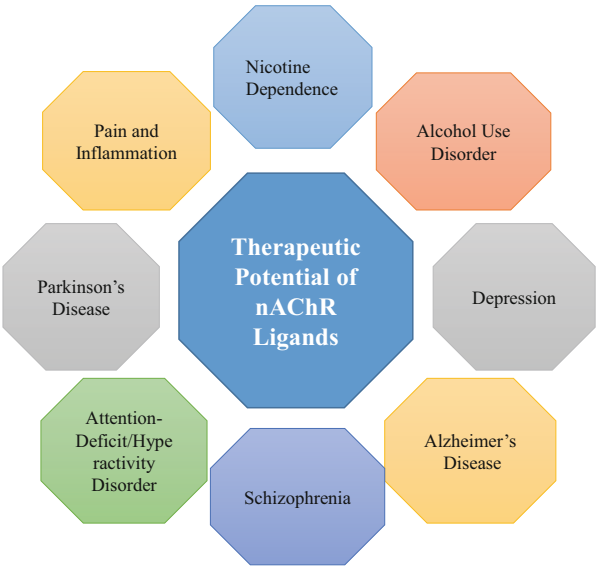


Fig. 3.6 Potential therapeutic applications of nicotinic acetylcholine receptors (nAChRs) ligands

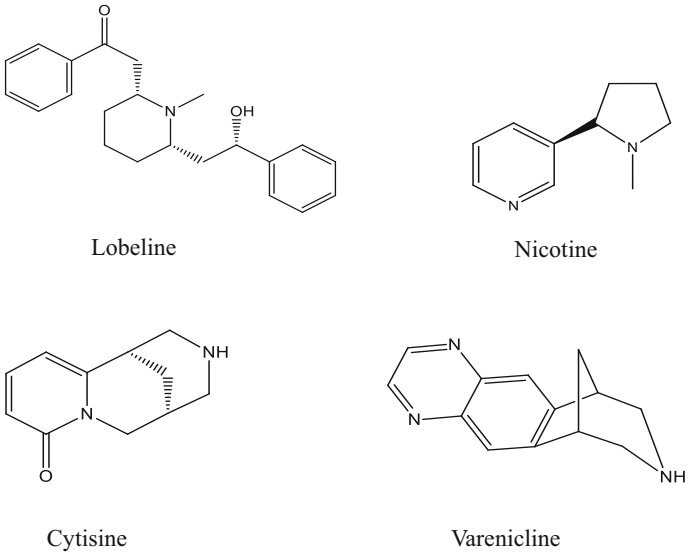


Fig. 3.7 Chemical structures of nicotinic agonists

agonists started in the early 1990s. ABT-418 was one of the first nicotinic agonists developed by Abbott Labs. Further investigations of ABT-418 have shown cognitive-enhancing effects that are three to ten times more potent than nicotine. Clinical trials on ADHD patients with ABT-418 have shown promising results in

reducing ADHD symptoms (Buccafusco 2004; Takechi et al. 2016). Lobeline (Fig. 3.7) like nicotine is a naturally occurring alkaloid and has similar effects with less potency as compared to nicotine. Both nicotine and lobeline are full agonists; they lead to nicotinic receptor activation in sympathetic and parasympathetic ganglia, on immune cells, in the brain, and at the adrenal medulla which leads to a wide range of physiological effects. Lobeline has been investigated for drug abuse treatment such as cocaine, alcohol abuse, opioid, and methamphetamine (Martin et al. 2018; Zheng and Crooks 2015). Both the cytisine (natural plant alkaloid) and varenicline (a synthetic compound) act as full agonists on (α3β4 and α7) nicotinic receptor subtypes and as partial agonists on (α4β2) receptors. Both the compounds were investigated for smoking cessation (Walker et al. 2018).

Nicotinic receptors are involved in various behavioral and cognitive functions, which makes nicotinic ligands good candidates for the treatment of conditions with cognitive dysfunction, such as schizophrenia. Postmortem studies of schizophrenic patients have shown that both protein expression and binding levels of α7 nicotinic acetylcholine receptor (α7 nAChR) were decreased in prefrontal cortex and hippocampus (cognition-related areas). A study was conducted on sub-chronic schizophrenic rats, by using α7 nAChR partial agonist (A-582941) for treatment. Results showed improvement in cognitive dysfunctions and social deficits on spatial and visual memory (Unal and Aricioglu 2017; Verma et al. 2018).

ABT-126, an α7 nAChR agonist, showed high potency and affinity in mouse, rat, and human in nonclinical studies. 25 mg once daily of ABT-126 in a phase 2a study resulted in cognitive improvement in subjects with both mild and moderate Alzheimer's dementia (AD) (Gault et al. 2016; Valle's et al. 2014).

3.3.2.2 Nicotinic Antagonists

Nicotinic antagonists block acetylcholine action at the autonomic ganglia, adrenal medulla, and neuromuscular junction. Neuromuscular blockers act on muscle-type nicotinic receptors, and ganglionic blockers act on neuronal ganglionic nicotinic receptors. Neuromuscular blockers are categorized based on the mechanisms of action and their use into two categories: depolarizing and non-depolarizing agents (Ding 2017). Neuromuscular blockers produce skeletal muscle relaxation which makes them useful in specific clinical situations such as electroconvulsive therapy (ECT), scoping procedures, endotracheal intubation, orthopedic procedures, and as a surgical adjunct (Keating 2016). Ganglionic blockers, on the other hand, can be used to control hypotension during procedures and for the treatment of hypertensive emergencies. Non-depolarizing neuromuscular blockers include benzylisoquinolines (doxacurium, mivacurium, atracurium), aminosteroids (rocuronium, pipecuronium, pancuronium), and natural alkaloids like d-tubocurarine. All these compounds are considered relatively large and contain multiple rings, making them bulky molecules that block acetylcholine from binding to the receptor. Besides, these compounds are competitive antagonists that produce flaccid paralysis and increasing acetylcholine concentration at synapsis by acetylcholinesterase inhibitors reverses their effect (D'Souza and Johnson 2019; Smetana et al. 2017).

Similarly, depolarizing neuromuscular blockers such as succinylcholine that binds and activates the receptor causes muscle relaxation that also leads to flaccid paralysis. Although succinylcholine activates the receptor, it resists hydrolysis by acetylcholinesterase, remaining bound to the receptor for a longer time than acetylcholine leading to blockage (Bertrand and Terry 2018; Hager and Burns 2018). Trimethaphan and mecamylamine are ganglionic blockers with different structures and mechanisms of action. While mecamylamine is a voltage-dependent noncompetitive antagonist that prevents activation by blocking the open cation channel, trimethaphan is a competitive antagonist that competes with ACh for receptor binding. Trimethaphan is used rarely for hypertensive emergencies during surgeries to produce controlled hypotension (Petrakis et al. 2018; Sear 2019).

3.3.2.3 Nicotinic Allosteric Modulators

Acetylcholine binds at a site on the interface of two subunits from the extracellular part of the nicotinic receptors. Many compounds were discovered that compete on the same site and exert either an agonistic or antagonistic effect. The site where acetylcholine binds is called the orthosteric binding site. However, researchers have identified compounds that show a modulatory effect on nicotinic receptors by binding to different sites other than the orthosteric-binding site, including the transmembrane domain. These compounds are termed as allosteric modulators, and the sites where they bind to are called allosteric sites (Abdel-Magid 2015; Chatzidaki and Millar 2015).

Allosteric modulators do not all exert the same effect, as mentioned in Sect. 3.3.1.3. The allosteric modulators that initiate an agonist-mediated response are termed as positive allosteric modulators (PAMs), while negative allosteric modulators (NAMs) are those that inhibit the effects of agonist activation. PAMs are different from allosteric agonists, as allosteric agonists can activate the receptor directly when binding to the allosteric site. Conversely, neutral allosteric ligands (NALs) do not cause changes in the receptor activity or its binding ability to the ligands (Cecchini and Changeux 2015; Chatzidaki and Millar 2015; Gentry et al. 2015).

PAMs binding to the receptor causes potentiation of agonist-evoked responses, which means they neither activate the receptor nor compete with acetylcholine binding. PAMs acting on α7 nicotinic receptors show therapeutic potentials for the treatment of inflammatory and neurological disorders. PAMs possess advantageous characteristics that make them more promising as compared to exogenous agonists, such as higher target selectivity, less tolerance due to desensitization, and their ability to maintain the spatial and temporal characteristics of the endogenous activation processes (Corradi and Bouzat 2016; Uteshev 2014). Based on the effect on macroscopic currents of receptors, PAMs are classified into two types, type I and II. Type I PAMs such as NS-1738, genistein, 5-HI, and ivermectin do not significantly affect current decay but enhance the agonist-induced peak currents. Type II PAMs, on the other hand, show slow desensitization onset and reactivate receptors that are desensitized (Bouzat and Sine 2018; Corradi and Bouzat 2016).

3.3.3 Cholinesterase Inhibitors

There are two types of cholinesterases in the body, acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), which differ in substrate specificity and their distribution within the body. While AChE terminates the action of ACh at synapses in the nervous system, BuChE concentrates in non-neuronal sites such as liver and plasma. BuChE is also responsible for metabolizing certain drugs (e.g., ester-type local anesthetics, succinylcholine) (Colovic et al. 2013; Kishore et al. 2012; Mehrpouya et al. 2017).

Most compounds used clinically to inhibit cholinesterase work on both the enzymes without discrimination. Cholinesterase inhibitors are classified into two main types based on the nature of the compound-enzyme binding, *viz.* reversible and irreversible. Reversible compounds can either be covalent or non-covalent inhibitors. Edrophonium is a non-covalent inhibitor that binds reversibly to the anionic part of the acetylcholinesterase enzyme. Drug-enzyme bond characteristics mainly determine the duration of these compounds. For instance, edrophonium binds weakly to the enzyme and is rapidly cleared by the kidney, which results in a short duration of action that is approximately 10 min long (Romano et al. 2017; dos Coelho et al. 2018). Other examples of non-covalent ChE inhibitors are donepezil and tacrine used for the treatment of AD. These two compounds possess a longer duration of action due to their partition into lipids and their higher affinities (Birks and Harvey 2018; Sameem et al. 2017). Carbamic acid ester derivatives such as neostigmine and physostigmine are covalent inhibitors, sometimes termed as carbamate inhibitors. After their binding to the AChE enzyme, they get hydrolyzed, which results in carbamylation of the serine residue in the active site of the enzyme (Arens and Kearney 2019; Lauretti 2015).

On the other hand, irreversible ChE inhibitors act on the serine group in the active site of the enzyme and phosphorylate it. Nerve gases such as tabun, sarin, and soman are examples of irreversible ChE inhibitors. Other examples include insecticides (malathion, parathion) and therapeutic agents such as isofluorophate and echothiophate referred to as organophosphate or organophosphorus ChE inhibitors. The reason why these compounds are considered irreversible is that the resultant phosphorylated enzyme is exceptionally stable, which means that the dephosphorylation process can take hours to occur. The possibility of dephosphorylation of phosphorylated enzyme by secondary and tertiary alkyl-substituted phosphates (soman and isofluorophate) cannot be achieved to restore the enzyme activity until further biosynthesis of new enzyme molecules (Sánchez-Santed et al. 2016; Thapa et al. 2017).

Inhibition of ChE enzyme by anticholinesterase results in augmentation of acetylcholine and the effects get relayed throughout the whole nervous system leading to both therapeutic actions and associated adverse effects. Hence those compounds lead to a nonselective indirect activation of both muscarinic and nicotinic receptors. Therefore, the receptors in the peripheral nervous system and the brain get activated, including peripheral tissues innervated by parasympathetic nerves, sympathetic and parasympathetic ganglia, and at the neuromuscular junction

(Ehlert 2019b). Many acetylcholinesterase inhibitors are available on the market for the treatment of various conditions (Table 3.7) (Potter and Kerecsen 2017).

3.3.4 Release Inhibitors

Release inhibitors' primary mechanism of action is preventing ACh release from the presynaptic end of the neuron. Botulinum toxin (BTX) is produced by *Clostridium botulinum* bacteria that target cholinergic receptors at neuromuscular junctions in skeletal muscles, inhibiting ACh release leading to neuromuscular blockage and paralysis. The inhibition of ACh occurs after the toxin enters the nerve and reaches the cytoplasm, then cleaves the (SNARE) proteins that are responsible for vesicle fusion mediation. Prevention of vesicle fusion means that the ACh vesicles can no longer bind into the intracellular cell membrane and release ACh into the synaptic cleft (Dressler and Saberi 2005; Zhao et al. 2016). Some snake venoms produce an irreversible blockade of neuromuscular transmission such as Crotoxin (CTX). CTX is a heterodimeric phospholipase A2 (PLA2) neurotoxin produced by a **Brazilian rattlesnake** (*Crotalus durissus terrificus*). This neurotoxin causes prevention of acetylcholine release from presynaptic ends, which depends on intrinsic PLA2 activity (Cavalcante et al. 2017). Blockage of ACh release leads to interruption of neuromuscular transmission and eventual muscle paralysis. Crotoxin exerts postsynaptic level effects too by stabilizing desensitized acetylcholine receptors (Faure et al. 2017).

3.4 Therapeutic Applications

Cholinergic and anticholinergic drugs have a wide range of therapeutic application including myasthenia gravis, dementia, ophthalmology, neurogenic bladder, xerostomia, anticholinergic overdose, snakebites, and postoperative urinary retention including tensilon test. Further explanation will be presented later in this section.

3.4.1 Nicotinic Receptor Ligands

The most established therapeutic outcomes of nicotinic stimulation are cognitive improvements. Nicotine was the first compound to bring attention to this since it can improve performance cognitively and attention requiring vigilance tasks, which suggests that nicotine possesses an optimizing ability to response and attention mechanisms and enhances working memory (Gandelman et al. 2018; Grundey et al. 2015). Figure 3.8 illustrates a potential model explaining how nicotinic stimulation can enhance network function leading to improved cognitive performance. Nicotine has been shown to enhance the efficacy of cognitive/function control networks in frontal attention while decreasing the activity in default mode network nodes in parietal regions, frontal lobe, and cingulate. These effects

Table 3.7 Currently used acetylcholinesterase inhibitors (AChEIs) for various therapeutic applications

Drug	Brand name	Class/type of binding	Duration	CNS effect	Uses
Physostigmine	Eserine	Carbamate, reversible	0.5–2 h	Yes	Treatment of atropine poisoning, glaucoma
Neostigmine	Prostigmin	Carbamate, reversible	0.5–4 h	No	Reversal of NMJ blockade, myasthenia gravis
Pyridostigmine	Mestinon, Regonol	Carbamate, reversible	4–6 h	No	Reversal of NMJ blockade, myasthenia gravis, prevention of organophosphate poisoning
Ambenonium	Mytelase	Carbamate, reversible	3–8 h	No	Reversal of NMJ blockade, myasthenia gravis
Tacrine	Cognex	Pyridine, reversible	4–6 h	Yes	Alzheimer's disease (discontinued)
Donepezil	Aricept	Piperidine, non-covalent, reversible	>6 h Yes	Yes	Alzheimer's disease
Galantamine	Reminyl, Razadyne	Tertiary alkaloid, reversible	>6 h Yes	Yes	Alzheimer's disease
Rivastigmine	Exelon	Carbamate, pseudo-irreversible	10–12 h	Yes	Alzheimer's disease
Edrophonium	Tensilon	Electrostatic, rapidly reversible	5–15 min	No	Diagnosis of myasthenia gravis, reversal of NMJ blockade
Echothiophate	Phospholine	Organophosphate, irreversible	>24 h	N/A (topical)	Glaucoma

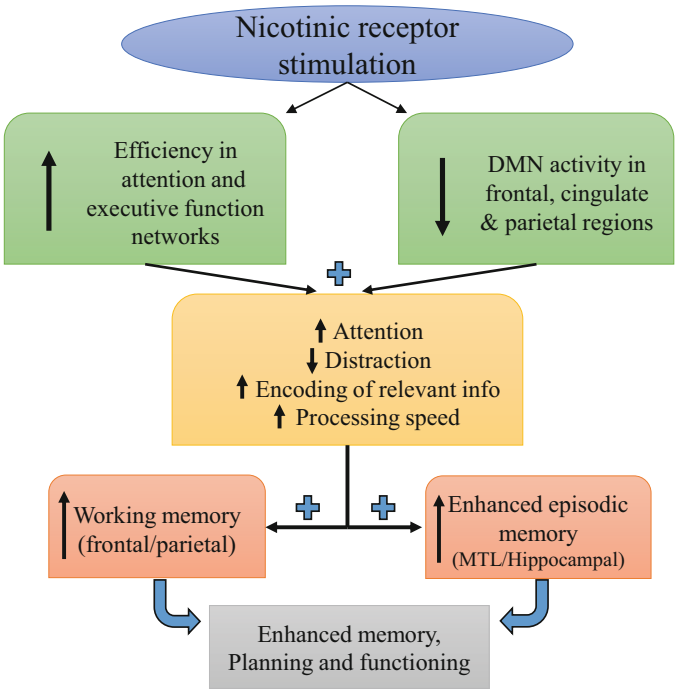


Fig. 3.8 Simplified model of nicotinic receptor stimulation effect in the enhancement of cognitive functioning. Abbreviations: MTL: medial temporal lobe; DMN: default mode network

altogether may enhance processing speed, attention, and response inhibition, eventually leading to improved memory and attention to external stimuli and decreased internally focused processing (Hahn 2019; Newhouse 2019).

Nicotine and nAChRs ligands have shown a different level of enhancement in cognitive functions after many studies carried out on animal models, including attention, memory, and learning. Further clinical trials have shown that these cognitive effects are also present when varenicline has improved cognitive impairment in schizophrenic patients and increased lapses in attention in smokers. Recent clinical trials have shown that activating α7 nAChRs has procognitive effects on patients with AD and schizophrenia. Likewise, a randomized placebo-controlled double-blinded study with TC-1734, a β2-selective nicotinic agonist, had shown an improved cognition when given to patients with age-associated memory impairment (Hoskin et al. 2019; Quik et al. 2015). Some preclinical and clinical studies supported that nicotinic receptors have a role in anxiety, mood, and depression. A study revealed that the treatment of Tourette's disorder with mecamylamine, a nAChR antagonist, showed considerable improvement in depression symptoms (Aboul-Fotouh 2015; Silver et al. 2001).

Nicotinic receptors are the principal receptors affecting the regulatory pathways of nicotinic and cholinergic signaling, as suggested by recent studies. These signals

regulate both cell growth and migration, as well as regulation of angiogenesis of endothelial cells during pathological and physiological conditions (Schaal and Chellappan 2016). The nicotinic receptor that showed most of the oncogenic responses in cancer is α7-nAChR. However, in breast cancer cells (estrogen receptor-positive), the α9-nAChR was found to be upregulated. α9-nAChR coalition with estrogen receptors stimulates both the initiation and progression of breast cancer. Accordingly, these recent studies suggest that nicotinic receptors-mediated oncogenic signaling has a significant role in cancer initiation and progression, which supports that cytotoxic and mutagenic effects of tobacco smoke promote growth and angiogenesis of tobacco-related cancers. Hence, nicotinic receptors are presenting promising new targets for diagnosis, treatment, and prevention of cancers associated with tobacco consumptions (Dang et al. 2016; Zhao 2016).

Currently, there has not been a medication developed that can target defects in social communication and repetitive, restrictive patterns of behaviors in patients with autism spectrum disorders (ASDs). Although individuals with Down syndrome (DS) exhibit a progressive decline in adaptive functioning, that is also associated with AD patients. Unfortunately, for DS patients and people with ASDs, there has not been any effective medication strategy to stop or retard the worsening of adaptive functions. However, α7-nAChRs present a potential therapeutic target in the treatment of these disorders due to their involvement in the pathophysiology of these disorders (Deutsch et al. 2014, 2015).

3.4.2 Muscarinic Receptor Ligands

Xanomeline, an M1/M4 receptor muscarinic agonist, exhibited positive effects on psychotic and cognitive-like symptoms, including delusions and hallucinations in patients with AD, which also makes it a therapeutic option to treat patients with schizophrenia. Studies supported this notion when xanomeline had an antipsychotic effect on rodent models (Yohn and Conn 2018). These studies and trials have revealed the importance of muscarinic receptors in the modulation of neuronal activity and release of neurotransmitter in various brain regions. Muscarinic receptors additionally play a crucial role in shaping neuronal plasticity and affect a wide range of functions from sensory and motor function to cognitive processes. In recent years, with the development in gene targeting technology, knockout mice offer valuable insight into the physiology and pathophysiology of the brain, thus accelerating the efforts to develop new medications for analgesia and certain conditions such as schizophrenia, addiction, PD, and AD (Thomsen et al. 2017). Analgesic therapy by muscarinic agonists has been proposed in preclinical and clinical models long ago. In a recent study, an M1 selective agonist has shown analgesic activity *in vivo*. However, the pharmacokinetic/pharmacodynamic measures have shown that to have the productive analgesic activity, a tenfold of higher exposure is needed as compared to cognitive effects in a rodent model (Wood et al. 2017).

3.4.3 Cholinesterase Inhibitors

Acetylcholinesterase (AChE) inhibitors prevent acetylcholine breakdown. There are already many AChE inhibitors currently used, such as galantamine, donepezil, tacrine, and physostigmine in the treatment of AD (Fig. 3.9) (Verma et al. 2018). These compounds have shown to positively affect psychosis, visual hallucinations, and cognitive dysfunction in schizophrenia. Additionally, preclinical studies showed that clinically used AChEIs could improve memory and learning in rodent models for schizophrenia. However, clinical trials on schizophrenic patients treated with AChEIs showed dose-limiting adverse effects due to their intrinsic ability to activate the peripheral receptors (Thakurathi et al. 2013; Yohn and Conn 2018).

The two popular hypotheses, the cholinergic and the amyloid hypothesis, explain the pathological mechanism for AD progression based on observed biochemical and morphological changes in the brain of AD patients (Huang et al. 2014). The amyloid hypothesis focuses on deposits accumulation in extracellular space formed from β-amyloid peptides and tau proteins, which causes oxidative stress on neurons causing inflammation leading to neurons degeneration (Jiang et al. 2014). On the other hand, the cholinergic hypothesis is characterized by alterations in the biochemical state of the brain due to ACh decrease in the cholinergic neurons present in the cerebral cortex and the hippocampus. AD patients have a stunted Meynert nucleus basalis, which is responsible for producing the enzyme ChAT that plays a central role in acetylcholine synthesis and results in acetylcholine deficiency (Kuhn et al. 2015; Liu et al. 2015). The last treatment approved by the FDA for AD was memantine, an NMDA (*N*-methyl-D-aspartate) glutamate receptor antagonist. Memantine is currently indicted for moderate to severe phases of AD (Matsunaga et al. 2015; de Souza et al. 2016). Postmortem studies have shown that patients with PD have concomitant degeneration of nigrostriatal and cholinergic pathways. This impairment in both neurotransmitter systems is related to specific motor and non-motor features of the disease, such as cognitive and gait dysfunction (Aarsland et al. 2017). Although the neurochemical trait in patients with PD is depletion in dopamine, cognitive decline in PD is also associated with defects in the activity of cortical acetylcholinesterase. Concomitant of dementia and classical gait

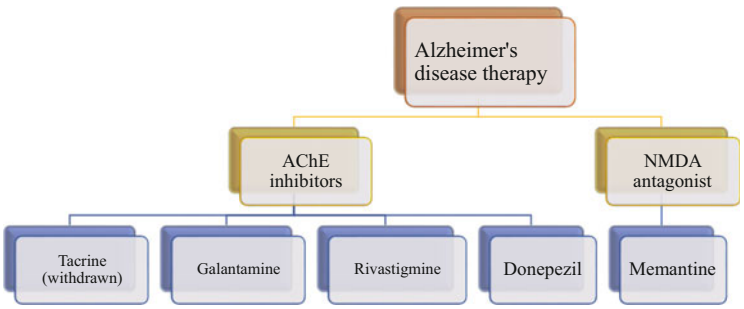


Fig. 3.9 Currently approved therapy regiment for Alzheimer's disease

dysfunction in those patients increases the risk of falls and hospitalizations. 80% of PD patients develop dementia after 20 years, which makes dementia the leading risk factor for falls. Treatments that interfere with both dopaminergic and cholinergic imbalance can improve long-term outcomes of PD patients (Hiller et al. 2015; Pagano et al. 2015).

Organophosphorus compounds (OPCs) are primarily a group of pesticides that inhibit acetylcholinesterase, and they are considered a severe health hazard. Current therapy for OPCs exposure is oxime-type enzyme reactivators such as obidoxime and pralidoxime, while atropine is administered for symptomatic treatment sometimes with unsatisfactory therapeutic outcomes. Better therapeutic results are observed when AChE inhibitors (reversible) are administered before the exposure to organophosphorus compounds. Recent studies showed that bispyridinium oximes K027 and K203, AChE inhibitors under development, are highly effective (K027 more than K203) in protecting against OPCs when administered pre-exposure. This strategy makes it a promising prophylactic agent and preventing possible occupational hazard (Antonijevic et al. 2016; Lorke and Petroianu 2018).

3.5 Conclusion

Cholinergic ligands possess great importance for various medical conditions. Over the years, studies and research have provided substantial evidence of positive outcomes from cholinergic ligands, such as nicotinic stimulators and muscarinic agonist and their ability to improve cognitive performance. Currently, there are potential cholinergic ligands approved for medical applications such as acetylcholinesterase (AChE) inhibitors including galantamine, donepezil, and rivastigmine for the treatment of AD. Furthermore, several AChE inhibitors displayed promising and appreciable therapeutic benefit for glaucoma, atropine poisoning, myasthenia gravis, and reversal of NMJ (neuromuscular junction) blockade. Another example is muscarinic receptor antagonists (tertiary amines, quaternary ammonium derivatives) used for conditions such as urinary incontinence, motion sickness, GI antispasmodic, COPD, Parkinson's disease, Huntington's disease, and as an antisecretory agent for peptic ulcer. The involvement and pathophysiology of cholinergic receptors in certain medical conditions are subsequently investigated to provide more potential therapeutic targets in the future. For example, α9-nAChR upregulation in estrogen-positive breast cancer suggests that nicotinic receptors can mediate oncogenic signaling, making them a potential new target in treating and preventing certain cancers. Gene knockout technology is currently being used to provide a further understanding of the cholinergic receptors, especially in the brain to present new potential therapeutic agents for various conditions.

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