REVIEW ARTICLE

CENTRAL CHOLINERGIC NERVOUS SYSTEM AND CHOLINERGIC AGENTS

Jiří Patočka

Department of Toxicology, Purkyně Military Medical Academy, Hradec Králové;
(Rector: doc. MUDr. S. Býma, CSc.)

Summary: Central cholinergic nervous system play important role in many physiological and behavioral functions in humans. The activity of the cholinergic nervous system depends upon the production and fate of acetylcholine and all compounds influenced its biosynthesis, storage, release, hydrolysis, interaction with different subtypes of cholinergic receptors, etc., there are very important drugs and therapeutics. This paper summarizes current views on many compounds which can interact with different parts of central cholinergic nervous system.

Key words: *Review; Central cholinergic nervous system; Cholinergic and anticholinergic agents; Acetylcholinesterase inhibitors; High affinity choline uptake inhibitors*

Structure of nervous system

The nervous system can be divided into the central nervous system (CNS), composed of the brain and spinal cord, and the peripheral nervous system, consisting of the nerves extending from the brain and spinal cord out to all points of the body. Some of the peripheral nerves connect with the brain, and others with the spinal cord.

The brain is composed of six subdivisions: *cerebrum*, *diencephalon, midbrain, pons, medulla oblongata,* and *cerebellum.* The *cerebellum* and *diencephalon* together constitute the *forebrain* and the *midbrain, pons,* and *medulla* together form the *brainstem*. The brain also contains four interconnected cavities, the *cerebral ventricles,* that contain cerebrospinal fluid. The *spinal cord* is a slender cylinder of soft tissue which lies within the vertebral column (125).

Functional anatomy of neurons (4,91)

The basic unit of the nervous system is the individual nerve cell - the neuron. Nerve cells operate by generating electric signals and passing them from one part of the cell to another and by releasing chemical messengers to communicate with other cells. Neurons occur in a variety of size and shapes, nevertheless, most of them consist of four parts: the cell body, the dendrites, the axon and the axon terminals.

The dendrites form series of highly branched outgrowths and together with the cell body are the sites of most the specialized junctions where signals are received from other neurons. The axon, sometimes also called a nerve fiber, is a single long extension from the cell body. The portion of the axon closest to the cell body is known as the initial segment. The axon may have branched called axon collaterals along its course, and near their ends, axons as well as axon collaterals, are branch endings called axon terminals. These terminals are responsible for transmitting chemical signals from the neuron to the cells contacted by the axon terminals.

Neurons can be divided to three functional classes: afferent neurons transmit information from the tissues and organs of the body into the CNS, efferent neurons transmit electric signals from the CNS out to effector cells, and interneurons connect the afferent and efferent neurons.

The specialized junction between two neurons where one neuron alters the activity of another is called a synapse. At most synapses, a signal is transmitted from one neuron to another by chemical messengers known as neurotransmitters. The neurotransmitter released from one neuron alters the receiving neuron by binding with specific membrane receptors on the receiving neuron.

Synapses generally occur between the axon terminal of one neuron and the cell body of dendrite of a second. In certain areas of the CNS synapses also occur between two dendrites, between a dendrite and a cell body, or between axon terminals of two neurons. A neuron conducting signals toward a synapse is called a presynaptic neuron, neuron conducting signals away from a synapse is called a postsynptic neuron. Certain neurons in the brain receive more than 100,000 synaptic inputs. Only about 10 per cent of the cells in the CNS are neurons, though occupy about 50 per cent of the volume of the CNS. The remainder cells are glial cells, called also neuroglia. Neuroglia has two type of glial cells, oligodendroglia and astroglia.

Central cholinergic nervous system (CChNS)

CChNS is a part of CNS created by cholinergic neurons, where acetylcholine (ACh) is the main chemical neurotransmitter. The specific membrane receptors which bind acetylcholin are called cholinergic receptors and can be divided into muscarinic and nicotinic receptors.

Anatomy of the cholinergic nervous system

Cholinergic neurons participate in both local circuits and projection systems of the brain (4). Local circuit cholinergic neurons are present in the *striatum*, *olfactory nucleus, olfactory bulbs, olfactory tubercle, basolateral hypothalamus,* and *spinal cord*. Cholinergic projection neurons are located in different parts of CNS and can be divided into four major groups: from Ch1 to Ch4 depending on their location and projection of their axons. Ch1 neurons project from the *septal nucleus* to the *hippocampus,* Ch2 neurons correspond to the nucleus of the vertical limb of the diagonal band of Broca and also project to the *hippocampus* and the *hypothalamus,* Ch3 neurons are located in the nucleus of the horizontal limb of the diagonal band and project to the *olfactory bulb, cingulate gyrus,* and *pyriform* and *entorhinal cortex,* Ch4 neurons constitute the *nucleus basalis Meynerti*, whose cells project to the different parts of cortex and *basolateral amygdala* (70,75). The *nucleus basalis Meynerti* consists of an archipelago of neurons distributed along an *anteroposterior axis* beneath the *medial globus pallidus* and the adjacent areas of the *internal capsule* (45).

Cholinergic innervation decreases from high levels in the limbic and prelimbic cortices, through intermediate levels in primary motor and sensory areas, to lowest levels in the frontal and temporoparietal association cortical regions (76). Cholinergic neurotransmission in CNS is very important for its a role in excitation, memory and learning.

Nowadays, at least five subtypes of muscarinic acetylcholine receptors (from M1 to M5) are known in human brain, as well as their differential regional distribution in CNS. The discoveries of the existence of nicotinic acetylcholine receptors in the brain and their involvement in higher functions including learning and memory are relatively new phenomena (87,137). **Nicotine** centrally activates reward mechanism and is therefore presumed to be the reason why people smoke. Also nicotinic receptors exist in various subtypes coded by different genes (19,31). At least three subtypes of nicotinic receptor with different affinity of **nicotine** (superhigh-, high- and low-affinity receptors, Ns, Nh, Nl) have been described in human brain (68,84). Reductions in nicotinic receptors due to aging have been reported in animal and human studies (85,141). Human studies have shown rather large individual differences in the number of nicotinic receptors observed in normal brains with aging (83,85,188). Changes in nicotinic receptors are connected with some neurodegenerative disorders (53). A consistent loss of nicotinic receptors in cortical regions of brain was found in Alzheimers disease (85,88,133). Cholinergic deficit at Alzheimers disease is known very well (26).

Biochemistry of the cholinergic nervous system

The activity of the cholinergic nervous system depends upon the production and fate of ACh. Thus, biosynthesis, storage, release, interaction with different subtypes of cholinergic receptors, and its final enzymatic destruction determine the quality of message transmitted.

Acetylcholine is synthesized from choline and acetylcoenzyme-A (AcCoA) in the cytoplasm of synaptic terminals in a reaction catalyzed by cytoplasmic enzyme choline acetyltransferase (CAT). These nerve terminals have a selective sodium-dependent high-affinity uptake mechanism for choline (HACU) which helps to regulate ACh synthesis. Newly synthesized choline is derived from serine from dietary intake or protein metabolism via ethanolamine. All synthesized ACh is stored in synaptic vesicles (120).

After acetylcholine release and the activation of receptors on the postsynaptic membrane, the concentration of acetylcholine at the postsynaptic membrane is partially reduced by diffusion away from the receptors and mainly by an enzyme, acetylcholinesterase (AChE), that is located on the pre- and postsynaptic membranes and rapidly destroys ACh, releasing choline (120). The choline is then actively transported back into the axon terminals by HACU where is reused in the synthesis of ACh (110).

Metabolism of acetylcholine

Once released into the synapse ACh behaves as a neurotransmitter that associates with specific postsynaptic protein macromolecular receptors. The association of ACh with this receptors iniciates a physiological response, most likely opening of membrane calcium channels, probably organized in a multimolecular complex with receptors and ion channels in the membranes of acetylcholine-receptive cells (13). The action of ACh is terminated by its rapid hydrolysis into choline and acetic acid, a reaction catalyzed by the enzyme AChE (72). The transient discrete and localized action of acetylcholine is attributed in part to the great velocity of this hydrolysis. AChE is associated not only with the postsynaptic membrane, AChE is also located at presynaptic membrane in both soluble and membrane bound forms (71). The choline liberated locally by AChE can be reutilized by presynaptic reuptake and resynthesis into ACh by CAT and AcCoA.

Cholinergic agents

The term cholinergic agents can be used in broadest sense, i.e. to include agents that not only act to imitate the effect of ACh, but also to include the various substances that interfere with the action of this neurotransmitter. The wide scale of these agents may be divided into compounds

interacting with cholinergic receptors,, i.e. their agonists and antagonists, compounds which inhibit ACh metabolism as for example AChE inhibitors, inhibitors of ACh storage, and some others.

Because the cholinergic system play very important role in many systems of all organisms, these compounds influencing its function are biologically active and there are important pharmaceuticals (57).

Subtypes of cholinergic receptors

The recognition of subpopulations of acetylcholine receptors began with the studies of Dale in 1914 (27) who observed that ACh had dual actions. The hypotensive, cardiac inhibitory effects caused by low doses of ACh were similar to those produced by naturally occurring alkaloid **muscarine** (8) whereas the hypertensive effect by high doses in atropinized animals was nicotine-like (28). Strong evidence has suggested subsequently that these actions, now referred to as muscarinic and nicotinic, are produced by activation of specific subtypes of acetylcholine receptors. The principal effects of cholinergic agonist and antagonist drugs are mediated via muscarinic acetylcholine receptors at postganglionic parasympathetic terminals whereas the effects at autonomic ganglia and the skeletal neuromuscular junction result from nicotinic acetylcholine receptors. There is evidence that both these receptor subtypes may be present in the CNS, but muscarinic acetylcholine receptors appears to predominate (8,60).

Ever since the first experiments with pharmacological effect of **muscarine** was recognized that the muscarinic receptors in the heart are different from those in the gastrointestinal tract, suggesting the occurrence of at least two subtypes of muscarinic acetylcholine receptor, M1 and M2. These findings were fortified by different studies. The M1 receptor shows a high degree of sensitivity to the muscarinic antagonist pirenzepine, the M2 receptor shows low affinity to this compound. The neuromuscular blocking agent gallamine shows selectivity for the M2 receptor (52). At this time at least five subtypes of muscarinic receptors are known, with different selectivity and affinity to different pharmaceuticals.

All these muscarinic receptor subtypes, M1 to M5, were demonstrated in the CNS with a differential regional distribution (43). M1 receptors are located on cholinoceptic neurons of the *cortex, striatum* and *hippocampus*, M2 receptors are found mainly on cholinergic neurons of the *pons, thalamus, medial striatum, medulla*, and *basal forebrain nuclei*. M3 receptors were observed in *hippocampus, striatum,* and *olfactory tubercle,* M4 receptors are most concentrated in *striatum* and *olfactory tubercle* and regional distribution of M5 receptors remains to be fully delineated (43).

Nicotinic acetylcholine receptors also exist in more different subtypes (107). It is a well characterized neurotransmitter receptor and transmembrane ionic channel, composed of five subunits in a stoichiometry of $\alpha_2\beta\gamma\delta$ (126). The role of nicotinic receptors at neuromuscular junctions of skeletal muscle is well known (1), but the discoveries of the existence of nicotinic receptors in the CNS and their involvement in learning and memory processes are relatively new phenomena (86,137).

Cholinergic receptor agonists (cholinergics)

Although ACh is essential for neurotransmission in the nervous system it has almost no therapeutic applications. This is the consequence of its short duration of action because of its metabolism by both AChE and butyrylcholinesterase (BuChE). At this time many cholinergic agonists are known. Some of them have both muscarinic and nicotinic actions, others are more or less selective to these receptors or to their different subtypes (57).

The known cholinergic agonists of therapeutic interest are for example methacholine, carbachol, bethanechol or furthretonium (132). All these compounds are derived from the structure of ACh. Very known cholinergic agonists are some plant alkaloids, for example arecoline (from *Areca catechu*), pilocarpine (from *Pilocarpus jaborandi* and *P.microphyllus)*, **muscarine** (from *Amanita muscaria*) or their some synthetic derivatives and analogues as for instance dilvazene or dioxolane (119). Also oxotremorine and its many derivatives are strong cholinergic agonists (35), as well as some quinuclidines of aceclidine type (131).

Therapeutic strategies in Alzheimers disease based on cholinergic receptor agonists administration

Alzheimers disease, the major cause of dementia in the elderly, is progressive neurodegenerative disorder characterized by synaptic loss, amyloid plaques, neurofibrillary tangles, and degeneration of cholinergic neurons in some brain areas (22). A presynaptic cholinergic hypofunction, as one of the major neuronal events in Alzheimers disease, is characterized by reduced levels of ACh, CAT and AChE. The cholinergic neuronal tracts are involved in memory and learning processing and the extent of the degeneration of the cortical projections correlate with the severity of the dementia (7). The cholinergic hypothesis in Alzheimers disease implies that a cholinergic replacement therapy might be beneficial in alleviating some of the cognitive dysfunctions in this disorder. Thus it can be deduced that restoration of ACh levels or replacement with muscarinic agonist may be effective in treating at least some of the cognitive symptoms in Alzheimers disease (106). Because postsynaptic M1 muscarinic acetylcholine receptors are relatively unchanged in Alzheimers disease, highly selective M1 agonists, producing cellular excitation, could be considered a direct and rational strategy to treat Alzheimers disease patients (39). The design of selective M1 muscarinic agonists is an area of intense research and development of numerous laboratories. Recent findings show that activation of M1 receptors induces neurotrophic-like activities (3,44), decreases synthesis of β-amyloid peptide (49,82), decreases

of phosphorylation of tau microtubule-associated protein and inhibits cell apoptosis (65). It will suffice to mentioned that some new M1 agonists (AF 102B and **xanomeline**) have reached already some phases of clinical trials.

Cholinergic receptors antagonists (anticholinergics)

It is known for a long time that the alkaloids **atropine** and scopolamine block the action of ACh at muscarinic receptors to produce many potentially useful therapeutic actions. The extensive search of synthetic anticholinergics was carried out at many laboratories and the big number of different compounds of this type with more or less selectivity and affinity to different subtypes of cholinergic receptors are known (115).

The main characteristic of anticholinergics is that they inhibit ACh and acetylcholine-like compounds from exerting their effects on acetylcholine receptors. These compounds do not inhibit the release of ACh at the nerve endings, but they compete with it for the cholinergic receptor sites. From the point of their pharmacological effects, anticholinergics may be divided into peripherally and centrally active compounds. But mostly it is not so simple to separate both peripheral and central effects of these compounds.

The most known anticholinergics are alkaloids **atropine** and scopolamine and their numerous synthetic derivatives and analogues (6,50). Numerous anticholinergics demonstrated great enantioselectivity that is especially characteristic for muscarinic antagonists (50). Thus S-(-)-scopolamine is very potent muscarinic receptor antagonists whereas R-(+)-scopolamine is practically uneffective (6). The similar situation is also in other groups of chiral anticholinergics (12).

Other examples of atropine-like cholinergic receptor antagonists are for example **3-quinuclidinyl benzilate** (**QB** or **BZ**) (114), 3-quinuclidinyl atrolactate (QNA), 3-quinuclidinyl xanthene-9-carboxylate (QNX), N-methyl-4-piperidyl benzilate (4-NMPB), 4-diphenylacetoxy-N-methylpiperidine (4-DAMP), procyclidine, adiphenine, benactyzine**,** oxybutynine, trihexyphenidyl**, biperiden,** and many others. For example see (5,12,100,114). Other interesting anticholinergics are for instance pirenzepine (15), AF-DX116 (42), secoverine (20) or dexetimide (57).

Anticholinergic incapacitating chemical agents (INCAPS)

These compounds were developed as modern chemical weapons without deadly effect, which are in relative small doses caused psychical and physical harmless of live power (17,101). From the military points of view the most important INCAPS are compounds with anticholinergic effect (40,46). INCAPS are also known as psychodysleptics, fantastics, psychedelics, psycholytics or hallucinogens (41).

The clinical course of intoxication by INCAPS is practically the same as at overdose of **atropine** or natural belladonna alkaloids (99). Intoxication course cover up changes in autonomial, motorical, central, neurological, behavioral, and psychological functions (11,103). In the military context there are important effects of INCAPS based on the entire disorientation and the loss of contact with environs and connected with disorders of imagination, receptivity, and speech as well as the senses of deseparation and anxiety (48).

Practically all military useful INCAPS are chemically characterized as an esters of diphenylacetic and/or benzilic acid with different basic aminoalcohols. The most known INCAPS are JB-336**,** ditran (JB-329)**,QB**, i.e. **3-quinuclidinyl benzilate** and TB.

Potential risk of anticholinergics for the elderly

At typical centrally active anticholinergics as for instance **QB** the psychical incapacitance appeared at very low doses of them (103). But also weak centrally active anticholinergics may be dangerous, mainly for the elderly (77,121). In the old age the level of ACh in the brain is reduced, mainly at different forms of dementia as for example Alzheimers disease (98). This matter of fact is insufficiently appraised in the treatment of patients by drugs with central anticholinergic affect and there is not important if it is their major pharmacological effect (anticholinergical antiparkinsonics trihexyphenidyl, biperidene etc.) or undesirable side effect (some antidepresives as for instance amitryptyline, dosulepine, analgetics, anxiolytics and numerous others) (127). Among twenty-five most frequent prescribed drugs to elderly, fourteen of them produced anticholinergic effect. At nine of them (codeine, digoxine, dipyridamol, isosorbit dinitrate, nifedipin, ranitidin, theophylline, prednisolon and warfarine) significant effect in the test of short memory was observed in the group of healthy old volunteers (77). In order to reduce the risk of centrally anticholinergic syndrom at elderly, exposure to anticholinergics should be minimized.

Anticholinergic drugs abuse

Belladonna alkaloids **atropine** and scopolamine are natural occuring anticholinergics of some *Solanaceae* (*Atropa bella-donna, Hyoscyamus niger, Datura stramonium*) that have been used as both medicinal and hallucinogenic agents for centuries. Ancient Romans and Egyptians used these substances to dilute the pupils of young girls and enhance their beauty, hence the name „belladonna“. These two alkaloids were also used as poisons during the Roman Empire and in the Middle Ages (14).

Anticholinergics, most often used in psychiatry to treat antipsychotic-induced extrapyramidal symptoms (33), are also used by some patients for their mood altering and psychedelic effects. The first case of anticholinergic drug abuse was described in 1960, when a young woman with severe torticollis escalated the prescribed dosage up to 30 mg per

day in order to experience euphoria and a sense of well-being (10). From this time the abuse and misuse of the centrally acting anticholinergic agents is a phenomenon occasionally reported in the medical literature - for example (24,25,38,63). From an analysis of 110 published cases of anticholinergic drugs abuse followed that the most often anticholinergics was trihexyphenidyl used in 76 (69 per cent) of cases followed by benzatropine, **biperiden**, diphenhydramine, and procyclidine (69). The individuals were mostly young, with an average age of 29 years, and predominantly male (70 per cent). Most of them purchased anticholinergics illegally and take them for the toxic effects of euphoria or psychosis (32,55,67,138).

Acetylcholinesterase inhibitors

AChE inhibitors are compounds of different structure and different origin, which are able to inactivate this enzyme by binding to its active surface. The inhibitors bind to the same site as substrate, i.e. catalytic center created by anionic and esteratic subsites (61). The anionic subsite is represented as a negative charge of carboxyl group of glutamic acid and esteratic subsite as hydroxyl group of serine (135). Aminoacid residues that participate in the catalytic process of ACh hydrolysis and ligand interactions of AChE are positioned within the deep, narrow, active-site gorge. Catalytic center is localized on the bottom of the gorge, regions rich in hydrophobic aminoacid residues lining the gorge created so called hydrophobic binding area (112).

The inhibitors which interact with catalytic center are called isosteric and their main representants are many organophosphates and carbamates. These inhibit AChE very fast by irreversible mechanism and many of them are very toxic (73). The inhibitors which are ligands of peripheral sites, mainly of the hydrophobic area, are know as reversible inhibitors and are called allosteric for their allosteric mechanism of action (78,79).

Isosteric inhibitors

Isosteric inhibitors of AChE bind to the same site as substrate and their major representatives are organophosphates and carbamates.

Organophosphates

The first organophosphates were prepared in the past century but only some time in the 1930s were intensive studied as potential chemical warfare agents in England and Germany (89). Their anticholinesterase properties were found with diisopropylfluorophosphate (DFP) in 1941 in Britain but these findings were published in 1947 (1).

Insecticidal organophosphates

These compounds were studied intensively in Germany by G. Schrader and his coworkers and by the end of the 2nd World War had made many of the insecticidal phosphates in use today. Thus, dimefox was made in 1940, schradan in 1942, and parathion in 1944 (89). The first organophosphates were toxic not only for insects but also for all mammals including a man. Hundreds and perhaps thousands of organophosphates were up to-date synthesized and tested on their insecticidal activity in different species of insects (36,37), before partially ecological compounds with low toxicity for man were selected (74). There are for example **dicrotophos** or dichlorvos (DDVP).

Nerve gases

The class of chemical warfare agents known as nerve agents or nerve gases are organophosphorus compounds that are extremely potent inhibitors of AChE (101). Nerve gases are odorless, colorless and so toxic that they can kill a man within minutes in extremely small dosages. All these, and still some other compounds, became to chemical warfare agents in many countries. The most important organophosphates with military meaning are tabun, sarin, soman**,** and **VX**.

Carbamates

The carbamates are esters of hypothetical carbamic acid. The first known naturally occured carbamate was **physostigmine**. This compound is an alkaloid obtained from the leguminous plant Calabar or ordeal bean - the dried, ripe seed of *Physostigma venenosum*, a perennial plant in the tropical West Africa (47). Carbamates act by carbamylating of AChE by the same way that organophosphates phosphorylate (51,129,136). Also other synthetically prepared carbamates are strong anticholinesterases and are used as pharmaceuticals. The widely used pharmaceutical carbamates are neostigmine (prostigmin) and pyridostigmine (2,18).

Insecticidal carbamates

The carbamate insecticides are relatively easy to classify. With a few exceptions, these are either N-methyl- or N,N-dimethyl-carbamates. The N-methyl-carbamates predominate in number and importance. Also the **physostigmine** is N-methyl-carbamate.

Following the development of the early 1950s, a flood of candidate insecticidal carbamates were synthesized. They numbered in the thousands, but as well as the organophosphates, relatively few became commercial insecticides (130). Typical insecticidal carbamates are for example carbaryl (sevin), **pyrimicarb**, isolan, moban, carbofuran or aldicarb.

Allosteric inhibitors

Relatively the most examined allosteric inhibitors of AChE are different compounds which interact with hydrophobic area of the active surface of enzyme (113). There are very often different condensed heteroaromatic compounds where the heteroatome is mostly nitrogen, as for instance

derivatives of chinoline, isochinoline, acridine (113), phenantroline (29), protoberberine (123), etc. These compounds have planar molecular structure and there are able to create mesomeric structure with delocalized charge (93, 94).

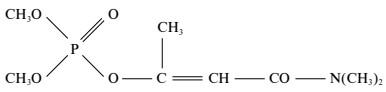
The most important hydrophobic-site-directed allosteric inhibitor of AChE is tacrine (94,113) and its derivatives and analogues (95,113).

Acetylcholinesterase inhibitors in the treatment of Alzheimers disease

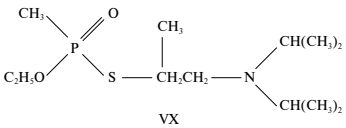
Alzheimers disease is a human progressive most common neurodegenerative disorder (58) (see also Chapter 3.2.1 of this work) characterized by cholinergic deficit (23). ACh plays a major role in the memory processes, therefore its shortening in the brain of Alzheimer patients closely correlated with degree of dementia (34). One possibility as to increase ACh level in the brain is partially inhibition of AChE activity by centrally effective inhibitors (80).

The first inhibitor of AChE tested in the treatment of Alzheimers disease was **physostigmine** (109). **Physostigmine** has been shown to produce a modest facilitation of learning and memory, but the magnitude and duration of changes, as well as safety consideration greatly diminish the practical significance of this therapeutic (21,31,117).

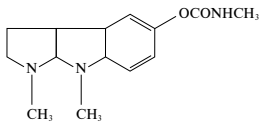
Much better results were obtained in studies where tacrine was administered orally in combination with lecithin as ACh precursor to treat patient with Alzheimers disease (115). At last time new centrally active AChE inhibitors were developed as potential drugs for the Alzheimers disease treatment, as for as **donepezil (**16,139), amiridin (62, 122), SM-10888 **(**90) or alkaloids **huperzin A** (66,104,140) or galanthamin (118).



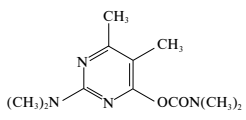
Dicrotophos



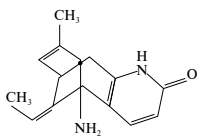
VX



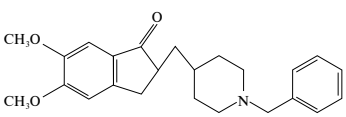
Physostigmine



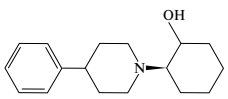
Pirimicarb



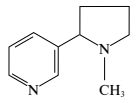
Huperzin A



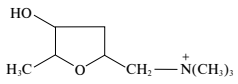
Donepezil



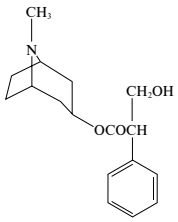
Vesamicol



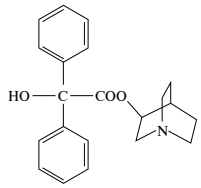
Nicotine



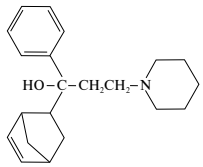
Muscarine



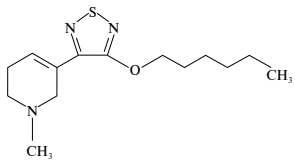
Atropine



3-Quinuclidinyl benzilate (QB, BZ)



Biperiden



Xanomeline

Inhibitors of the high affinity choline uptake (HACU)

The most important precursor of ACh, choline, is transported into the cholinergic nerve terminals by a sodium-dependent high-affinity choline uptake system. This uptake mechanism is one of the serious regulatory steps in the ACh synthesis (97). Inhibitors of the HACU blocks the stimulus-induced release of ACh in synapses. The observation that the capacity of the HACU changes with the neuronal activity indicates that this system is important in the impulse-regulation of the ACh synthesis for physiological regulation of cholinergic innervation (105). Several classes of choline uptake inhibitors are known, for example hemicholinium-3, troxonium, 1-pyrenebutyrylcholine**, vesamicol** and others. All these inhibitors are generally quaternary ammonium compounds which poorly pass the blood-brain barrier (64).

Conclusions

Today is commonly accepted that central cholinergic nervous system play important role in many physiological and behavioral functions in humans (30,56,128). Cholinergic system has been implicated in a wide variety of behaviors (59,81), aggression (102), exploration (124), social play (92), odor aversion (9), depression (54), sleep (111), memory (134) etc. It is thus readily apparent that the cholinergic system is involved in many different behavioral functions and that its role in neural activities is complex and widespread. New area of neuropsychopharmacological investigation in the last decade is the role of ACh in learning and memory which reached to the cholinergic hypothesis of geriatric memory dysfunction (7). Some neurological disor-

ders connected with cognitive decline are associated with decreased central cholinergic transmission (134).

The number of compounds which influenced cholinergic transmission is very high of various types and various pharmacological effects. Many of them are also very important therapeutics of many diseases.

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Submitted May 1998.
Accepted June 1998.

Doc. RNDr. Jiří Patočka, DrSc.,
Purkyně Military Medical Academy,
500 01 Hradec Králové,
Czech Republic.