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Butyrylcholinesterase: Structure and Physiological Importance

[Butirilkolinesteraz: Yapısı ve Fizyolojik Önemi]

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ABSTRACT

Butyrylcholinesterase is involved three different enzymatic activities in its structure like its sister enzyme, acetylcholinesterase: esterase, aryl acylamidase and peptidase (or protease). Whereas the clear role of acetylcholinesterase in cholinergic neurotransmission is well defined, the real physiological function of butyrylcholinesterase is still unknown. Both enzymes have similar molecular forms with different tissue distribution. Esteratic activity of butyrylcholinesterase becomes more important in scavenging of organophosphate and carbamate inhibitors before they reach to acetylcholinesterase; in regulating cholinergic transmission in the absence of acetylcholinesterase and in inactivation of some drugs such as cocaine aspirin, amitriptyline or in activation of others such as bambuterol, heroin. It is suggested that aryl acylamidase activity plays a role in crosstalking between seratonergic and cholinergic neurotransmission systems. In addition, peptidase activity of butyrylcholinesterase has a function in the development and progression of Alzheimer disease due to cause the production of β-amyloid protein and to help its diffusion to β-amyloid plaques.

Key Words: Butyrylcholinesterase; esteratic function of; aryl acylamidase function of; peptidase funtion of.

ÖZET

Butirilkolinesteraz, kardeş enzimi asetilkolinesteraza benzer şekilde yapısında üç farklı enzimatik aktivite barındırır: esteraz, aril açilamidaz ve peptidaz (proteaz) aktiviteleri. Asetilkolinesterazın kolinerjik sinir iletimindeki rolü tamamen anlaşılmış olmasına karşın, butirilkolinesterazın gerçek fizyolojik işlevi bugün halen bilinememektedir. Her iki enzim farklı doku dağılımları gösteren benzer moleküler formlara sahiptir. Butirilkolinesterazın esteraz aktivitesi, organofosfat ve karbamat yapılı inhibitörlerin asetilkolinesteraza ulaşamadan dolaşımdan temizlenmesinde, asetilkolinesteraz yoksunluğunda kolinerjik sinir iletiminin kontrolünde ve kokain, aspirin, amitriptilin gibi bazı ilaçların inaktivasyonu veya bambuterol, heroin gibi bazı ilaçların ise aktivasyonunda önem kazanmaktadır. Enzimin aril açilamidaz aktivitesinin ise seratonerjik ve kolinerjik sinir ilemi sistemleri arasında iletişim sağlama işlevi olduğu ileri sürülmektedir. Ek olarak, enzimin peptidaz veya proteaz aktivitesinin Alzheimer hastalığının gelişmesi ve ilerlemesinde işlevi vardır. Butirilkolinesteraz bu hastalıkta β-amyloid proteinin üretimine ve proteinin β-amyloid plaklara difüzlenmesine neden olmaktadır.

Anahtar Kelimeler: Butirilkolinesteraz; esteratik aktivitesi; aril açilamidaz aktivitesi; peptidaz aktivitesi.

CONTENTS

1. INTRODUCTION

Animal cholinesterases are widespread enzymes present in cholinergic and noncholinergic tissues as well as in their plasma and other body fluids (1-3). They are divided into two classes according to differing in their subtrate specificity, behaviour in excess substrate and susceptibility to inhibitors: acetylcholinesterase or "true cholinesterase" (AChE; acetylcholine acetylhydrolase, E.C. 3.1.1.7) and butyrylcholinesterase (BChE; acylcholine acylhydrolase, E.C. 3.1.1.8). BChE is also known as pseudocholinesterase, non-specific cholinesterase or simply cholinesterase. AChE hydrolyzes acetylcholine faster than other cholinesters and is much less active on butyrylcholine. On the contrary, BChE pereferentially acts on butyrylcholine, but also hydrolyzes acetylcholine (2,4). The inhibition of AChE by excess substrate is one of the key features that distinguishes it from BChE. BChE exhibits the substrate activation in excess substrate (5,6). AChE is inhibited selectively by 1,5-bis (4-allyldimethylamminopropyl) pentan-3-on dibromide (BW 284C51), while BChE is selectively inhibited by 10-[2-diethylaminopropyl]-phenothiazid (ethopropazine) and isotetra monoisopropyl pyrophopsphate tetramid (iso-OMPA) (7). Their tissue-specific distribution is also different from each other: AChE is known to be abundant in brain, muscle and erythrocyte membrane, whereas BChE has higher activity in liver, intestine, heart, kidney and lung (8,9). Many species such as human, horse, mice exhibit high BChE activity in their plasma, while rat has higher AChE activity than BChE in its plasma (2,9,10). Serum BChE is synthesized in liver and secreted into plasma (2).

AChE and BChE share 65% amino acid sequence homology and have similar molecular forms and active center structure despite being products of different genes on human choromosomes 7(specifically 7q22) and 3(specifically 3q26), respectively (11). The main function of AChE is rapid hydrolysis of the neurotransmitter acetylcholine at cholinergic synapses, and it is one of the fastest enzyme known (12). But individuals whose BChE is absent does not correlate with any physiological abnormality. Its importance as a detoxification enzyme is growing interest in recent years. BChE is of pharmacological and toxicological importance, because it hydrolyzes ester-containing drugs and scavenges cholinesterase inhibitors including potent organophosphporus nerve agents before they reach their synaptic targets (13).

The presented review focusses on function of BChE as a detoxification enyme and the using as a prophylactic and therapeutic drug against toxicity of some chemicals.

2. MOLECULAR FORMS OF CHOLINESTERASES

AChE and BChE present a similar amphiphilic or soluble molecular forms in tissues and body fluids with different tissue distribution. These homo- and hetero-oligomeric forms are summarized as follows:

1. Type I amphiphilic dimers: Glycophosphatidyl inositol anchored dimers to plasma membranes exit in mammalian muscles, erythrocytes and lymphocytes. It is abundant form of AChE. It is only solubilized by detergents and it aggregates in the absence of detergents.

2. Type II amphiphilic monomers and dimers: Distinguished from Type I due to devoid of glycolipid anchore and does not aggregate in the absence of detergents. They are solubilized by salt solutions. These forms are abundant in mammalian brains, muscles and intestine for both cholinesterases.

3. Hydrophobic-tailed tetramers: Anchored to plasma membranes by a hydrophobic, 20 kDalton length polypeptid subunit. This form is abundant for AChE in mammalian central nervous system.

4. Collagen-like tailed forms or asymetric forms: This form is characterized by the presence of a collagen-like tail for anchorage to the basal lamina. It is formed by the triple helical structure of three collagenic subunits Q, each associated with one (A_4), two(A_8) or three (A_{12}) tetramers of cholinesterases. It is more abundant for AChE than BChE in nervous-muscle junctions.

5. Soluble tetrameric form (G_4): Composed of the four identical monomers and stabilized by hydrophobic interactions of hydrophobic amino acids at C terminal of monomers. This form is abundant for BChE in

mammalian body fluids and in the soluble fraction of tissue homogenates (14,15).

3. STRUCTURE AND ACTION MECHANISM OF ESTERATIC ACTIVE CENTER

For many species, monomer is made up approximately 574 amino acids and carries a few asparagine-linked carbohydrate chains. It has also three interchain disulphide bridges that help to gain specific three dimentional globular structure of monomer. For many mammalian species, monomers make dimers via disulphide bridge with cysteines at position 571. The function of this intrachain disulphide bridge is to stabilize the dimeric structure. Some species such as horse donot have this intrachain disulphide bridge. Monomers or disulphide-linked dimers can also make tetramers with hydrophobic interactions via aromatic amino acids at their carboxy terminal (15).

Each monomer has a 20Å deep and narrow active site gorge lined approximately 55 residues. In Fig. 1, the structure of the human BChE active site gorge is schematized. Peripheral anionic site (PAS) is located at the mouth of the gorge. Asp70 and Tyr332 residues of PAS are involved in the initial binding of positively charged subtrates such as quaternary ammonium containing choline esters and in activation control. BChE has a hydrogen bond between Asp70 and Tyr332 which controls the functional architecture of the BChE active site gorge. When a positively charged substrate is bound to the enzyme by forming a cation-π complex with the aromatic ring of Tyr332, at the same time the substrate interacts the negatively charged Asp70 and this process triggers the conformational change in the momomer. Then, the two flexible arms of Ω loop come close to each other and the substrate slides down to Trp82 residue of choline binding site or cation-π site of the active site. This site was formerly named as anionic site, but now it is known that there is not any residue with negative charge that is responsible for binding of quaternary ammonium group. Trp82 also forms cation-π complex with this group of substrate (6,16,17).

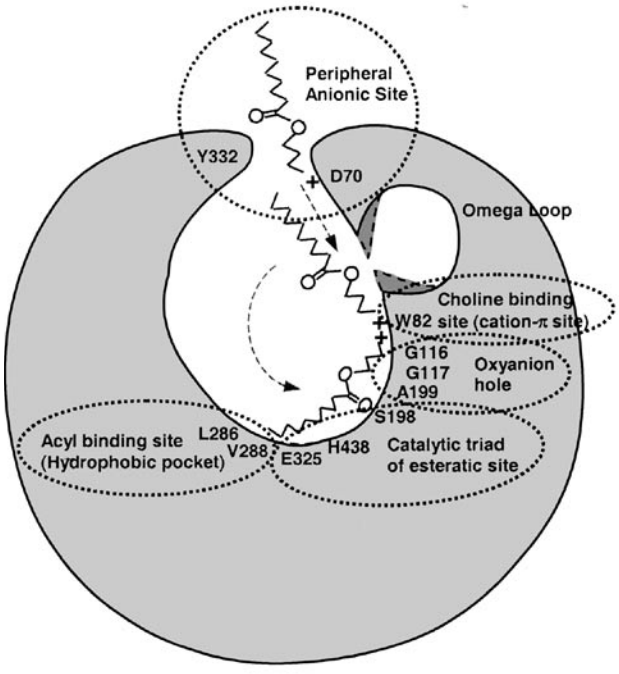

Figure 1 Schematic structure of cholinesterase active site of butyryl-cholinesterase monomer.

A, alanine; D, aspartic acid; E, glutamic acid; G, glycine; H, histidine; L, leucine; S, serine; V, valine; W, tryptophan; Y, tyrosine.

Oxyanion hole found near the choline binding site includes Gly116, Gly117 and Ala199 and helps to rotate the substrate from vertical to horizontal position by where the substrate can be hydrolyzed by Ser198. The amino acids of oxyanion hole have peptidic NH functions with the carbonyl or phosphoryl oxygen of the ester bond (18,19).

Acyl portion of the substrate binds to "acyl binding pocket" when the substrate rotates horizontally. Acyl binding pockets of AChE and BChE contain different amino acid residues. In acyl binding pocket of AChE, phenyl rings of Phe295 and Phe297 restrict the degree of the freedom of the bound substrate and enhance the catalysis of shortest acyl group containing substrate such as acetylcholine. On the otherhand, Leu286 and Val288 are found in acyl binding pocket of BChE and replacement of phenylalanines with the aliphatic residues allows the catalysis of larger acyl group containing substate such as buytrylcholine (7).

Stabilized substrate between oxyanion hole and acyl binding pocket is ready for hydrolysis of "catalytic triad", composed of Ser198, His438 and Glu325, of esteratic site of active center. The mechanism of catalysis is an example of the "charge relay" system. Imidazol ring of His438 relays electrons from Glu325 to Ser198 and hydroxyl oxygen of Ser198 becomes a nucleophil. Nucleophilic attact of this hydroxyl oxygen to ester bond of substrate leads the acyl-enzyme intermediate and free choline moiety. Then acyl group is hydrolyzed from Ser198 by nucleophilic attact of a water molecule activated by taking a proton from His438. BChE or AChE with carbamylated or phosphor(phosphon)ylated serine by carbamates or organophosphate can carry out last hydrolysis step very slowly and generaly is inhibited irreversibily (16,19).

Six of 14 aromatic amino acid residues lining in the active site gorge of AChE are replaced by aliphatic amino acid residues in BChE. This situation causes that the volume of BChE active site gorge is larger (~ 200 $Å^3$) than that of AChE active site gorge. The replacement of aromatic amino acids with aliphatic amino acids is also responsible for selective sensitivity against different inhibitor of the two enzymes (20). Three distinct domains in active site gorge confer selectivity for AChE and BChE inhibitors: First domain is acyl binding pocket. Studies with the mutant BChE were showed that Leu and Val residues are responsible for binding of larger substrate and selective iso-OMPA inhibition. Replacement of these residues with phenylalanines as found in AChE causes to prefer smallest substrates and iso-OMPA is not an inhibitor of AChE. Second domain is found near the lip of active site gorge. At this domain

of AChE, Tyr72, Tyr124 and Trp286 have critical role for binding of BW284C51. Third domain defines as the choline binding site (or cation-π site). Tyr337 and Trp82 at this site are responsible for sensitivity to ethopropazine in BChE (7).

4. GENETIC VARIANTS OF BChE

In human, point mutations and frameshifts in BChE gene localyzed on chromosome 3 at q26 cause the different BChE genotypes that have different levels of enzyme activity.

The enzyme has normal BChE activity (8440±1780 IU/L for butyrylthiocholine used as substrate) in serum is called as usual BChE. Atypical BChE (Asp70Gly mutant or dibucain resistant mutant) is best known variant and has reduced activity, because Asp70 plays an important role for initial binding of positively charged substrates to active site gorge. K variant (Ala539Thr mutant), J variant (Glu497Val mutant) and fluoride resistant variants (Thr247Met or Gly390Val mutants) also shows reduced BChE activities. Furthermore, approximately 20 different silent genotypes have been recognized with 0-2% of normal activity. On the otherhand, C5+ variant (combination of BChE with an unidentified protein), Cynthiana variant (increased amount of BChE than normal level) and Johannesburg variant (increased BChE activity with normal enzyme level) have increased activity than usual BChE (21-23).

5. FUNCTIONS OF BChE

5.1. As a Detoxification Enzyme:

Although the real substrate(s) is still unknown, BChE can hydrolyze hydrophobic and hydrophilic carboxylic or phosphoric acid ester contaning compounds. Its toxicological and pharmacological importance becomes clear when an individual exposures to poisonous compounds targeting to acetylcholine binding sites. Loss of AChE function leads to muscle paralysis, seizure and may cause death by asphyxiation. BChE can be considered as an endogenous scavenger of anticholinesterase compounds. BChE detoxifies them before they reach to AChE at physiologically important target sites. Some important compounds detoxified by BChE are illustrated as follows:

5.1.1 Succinyldicholine (SuCh)

SuCh is a neuromuscular blocking drug used for endotracheal intubation during operation, endoscopies and electroconvulsive therapy. It is hydrolyzed by BChE to succinylmonocholine and choline. Whereas the diester is a powerfull muscle relaxant, monoester is not. When SuCh is injected intravenously, about 90% of its dose is hydrolyzed by BChE within 1 min and rest amount reaches the nerve-muscle junctions and binds to a receptor. In result, the nerve-end plate is depolorized and losses sensitivity to acetylcholine (21,24). SuCh administration to individuals carrying no or reduced BChE activity variants results in prolonged apnea, since a large overdose reaches to the nerve-muscle junctions. In order to avoid from this result, the assay of serum BChE activity is used in the assessment of patients with prolonged apnea after administration of SuCh during anesthesia. If prolonged apnea occurs, well-timed intravenous administration of highly purified human serum BChE decreases the duration of the induced apnea (25).

5.1.2. Organophosphates (OPs) and Carbamates

Organophosphate or carbamate esters are used as pesticides, insecticides, chemical warfare agent and drugs for treatment of medical disorders such as glaucoma, parasite infections and Alzheimer disease. This compounds are potent inhibitors of both AChE and BChE. The most toxic OPs are soman (*O*-pinacolyl methylphosphonofluoridate), VX (ethyl-S-(2-diisopropylaminoethyl) methylphosphonothiolate), sarin (*O*-isopropyl methylphosphonofluoridate) and tabun (N,N-dimethylamido-*O*-ethyl phosphorocyanidate) which can be used as nerve gases against civilian or military populations. The progresive inhibitions of cholinesterases by OPs is due to phosphylation (phosphorylation or phosphonylation) of their active site serine (Ser198 for BChE and Ser200 for AChE in human). Loss of AChE functions leads to acetylcholine accumulation in synaptic clefts, and it is resulted with muscle paralysis, seizure and death by asphyxiation (26).

Therapy against acute nerve gases toxicity includes the pretreatment with pyridostigmine, which is a carbamate and reversible AChE inhibitor, capable of partial and temporary masking of AChE active site. Post exposure treatment is continious with administration of cholinolytic agents such as atropine, oxime reactivator such as pralidoxime chloride and anticonvulsant drug such as diazepam. Although multidrug combination therapy is effective in increasing survival, it cannot prevents the occurance of post exposure toxic symtoms such as tremors, convulsions, apnea, fasciculation. Another disadvantage of this therapy is the dependence of its efficacy on timing of their administration (27,28). On the otherhand, pyridostigmine is also AChE inhibitor and causes acetylcholine accumulation. To prevent of its side effects and for higher prophylactic efficacy, it is proposed that pyridostigmine should be administered with an anticholinergic drug such as benactyzine (29).

Mechanism of this therapy can be explained as follow: Phosphylated cholinesterases can be reactivated by strong nucleophilic compounds such as oximes. So, pralidoxime salts or obidoxime dichloride is used for the reactivation of phosphylated AChE and highly reactive phosphoryloximes (POX) occur. But it is found that POX are able to re-inhibit the cholinesterases. This re-inhibited form of enzymes is called as “aged enzyme” and its reactivation is not possible. Thus, in vivo the activity of aged plasma enzyme only returns to normal level by re-synthesis of new enzymes in liver (30,31).

As discussed above, the traditional approach has several disadvantages. So, it is thought that exogenously administration of pure AChE or BChE can be more effective therapy for sequestration of OPs in the

circulation before they inhibit AChE at physiologically important target sites. Human serum BChE as a prophylactic antidote has been used in marmosets, rhesus monkey, mice and rat. It has more advantages than AChE:

1. It makes 0.1% of human plasma protein, but AChE activity is found in erythrocyte membrane for human.
2. It binds to OP poisons rapidly and irreversibily in a molar stoichiometric ratio of 1:1.
3. It can be easly purified from human serum in a large amount. So, it will be well tolareted in blood of humans. AChE purified from fetal bovine serum can be immunoreactive.
4. Human BChE has a large space within its active site gorge that can accomadate a wide variety of OPs.
5. It has long half-life in vivo (8-12days).
6. It is thermally stable on prolonged storage (13,26,32-34).

When stoichiometric data obtained from rhesus monkey is extrapolated to human, administration of 150 mg human BChE can provide a reasonable protection against $2xLD_{50}$ of soman and $1.5xLD_{50}$ of VX for an individual weighing 70 kg without the need for postexposure treatment (13).

Results of the investigations on obtaining more potent BChE mutants which have acquired ability to hydrolyze all kinds of OPs with a high efficacy will give more chance to all humans exposed to the nerve gases in a war (35).

5.1.3. Cocaine

BChE plays an important role in cocain metabolism. It is the major detoxification enzyme of both natural (-) cocain and unnatural (+) cocain in plasma. The inactive metabolites produced by BChE is ecgonine methyl ester and benzoic acid that are rapidly excreted from circulation by kidney (36,37). Cocain abuse is a medical problem in all around of the world. Symptoms of cocaine toxicity include grand-mal seizure, cardiac arrest, stroke, elevated body temperature. Animal studies showed that administration of purified human serum BChE protected mice and rats from the lethal effects of cocaine as well as from hypertention and arrythmia (38,39).

Although BChE protects against cocain toxicity, it acts slowly. Turnover number (k_{cat}) of natural (-) cocaine is found to be as 3.9 min^{-1}. To increase the catalytic efficiency of BChE towards cocaine by increasing its binding affinity and hydrolysis rate, different mutants of the enzyme have been tested. It is found that Ala328Tyr mutant has an improved cocaine hydrolase activity (40).

5.1.4. Aspirin

Aspirin is an example of the negatively charged substrates of BChE. BChE is the major plasma esterase involved in hydrolysis of aspirin to salicylate. Usual and atypical BChEs can hydrolyze aspirin with the same kinetic manner. The rates of hydrolysis plotted as a function of aspirin concentrations gives symmetrical bell-shaped curve. BChE inhibition seen in the high aspirin concentrations (> 6 mM) is due to increasing salicylate concentrations by spontaneous hydrolysis of aspirin which also causes the decrease in pH. Turnover number is found to be 5000-12000 min^{-1} for usual and atypical BChEs. This result shows that Asp70 is not major site for initial binding of aspirin to enzyme. But Trp82 mutant does not hydrolyze aspirin, indicating that the presence of Trp82 ring is essential for aspirin binding in the active center (41).

5.1.5. Amitriptyline

Amitriptyline, fluoxetine, sertraline as clinical antidepresssant are used worldwide. Besides of their confirmed efficiency, especially amitriptyline is characterized by anticholinerjic side effects including memory impairment, delirium, behavioural toxicity and cardiovascular dysfunctions. Reason of these side effects is the inhibition of AChE and BChE activities. It is reported that AChE from cerebral cortex (42) and erythrocyte membrane (43) are inhibited by imipramine, desipramine and amitriptyline at high concentrations. We also found that amitriptyline is partial competitive inhibitor of human serum BChE (44). Long-term treatment with amitriptyline causes acquired BChE and AChE deficiency at relatively close to the cinical levels. If these patients have to be operated on because of emergency, the possibilty of succinylcholine apnea must be considered.

5.1.6. Anticonvulsant Drugs

As mentioned before, exposure to nerve gases, even with carbamate pretreatment, produce a variety of toxic cholinergic signs such as secretions, convulsions. Since carbamates are also inhibitors of AChE and BChE. After carbamate pretreatment, a multidrug complex including a cholinolytic agent (generaly atropin), an oxime reactivator and an anticonvulsant is necessary for posttreatment of patients. Diazepam has been generally used as anticonvulsant together with atropin, but its injectable form has associated with its drawback such as abuse liability, nonaqueos formulation and delibilitating side effects which make it less preferable for military personnel in the battle field (45). It is proposed that benactyzine has more efficiency in preventing soman-induced convulsions in the tested animals. When benactyzine is used, cholinolytic agent is not necessary (46). But our investigation on the effect of benactyzine on human serum BChE showed that benactyzine and drofenine are competitive inhibitors of the enzyme. They both are carboxylic acids esters and hydrolyzed by BChE (47).

5.2. As Activator Enzyme

Some prodrugs are converted to active forms by BChE. Some examples of these kinds of prodrugs are given as follow:

5.2.1. Bambuterol

It is a new dicarbamate prodrug and is converted to terbutalin by BChE that has antiasthamatic effect (48).

5.2.2. Heroin

It is hydrolyzed by BChE to 6-acetylmorphine which penetrates the blood-brain barrier and is hydrolzed to morphine by the enzymes in the brain. BChE is only enzyme in human serum that hydrolyzes heroin. Persons having silent BChE variants are not able to hydrolyze heroin (49).

5.2.3. CPT-11 (Irinotecan)

It is an anticancer prodrug and converted to SN-38 (7-ethyl-10-hydroxy-camptothecin), which is a potent topoisomerase I poison, by BChE (50).

5.3. As a Diagnostic Marker

Alzheimer disease (AD) is a chronic and progressive neurodegenerative disease that is characterized by degeneration of cholinergic neurons in the areas of the brain particularly associated with memory, higher intellectual functions and consciousness. Although other neurotransmitter systems are affected, the most profound loss is that of cholinergic tranmission. β-Amyloid plaques and neurofibrillary tangles constitute the patological hallmarks of AD. The biochemical deficits of AD are reduced levels of acetylcholine because of substantial reduction in the activity of choline acetyltransferase, reduced activity of AChE, and by contrast, increased activity of BChE. Both AChE and BChE, that have differentiated kinetic and molecular properties than normal neuronal forms found in the brain, accumulate within amyloid plaques and tangles (51).

BChE and AChE in brain can cleave >10 000 molecules of acetylcholine per second. It is shown that AChE knockout mouse survives for several weeks, since BChE compensates the absence of AChE and serves as a backup to AChE in supporting and regulating cholinergic transmission (52). In a similar way, cytochemical studies have revealed that cholinergic neurons contain BChE instead of AChE, suggesting that specific cholinergic pathways are regulated by BChE in the brain of patients with AD (53).

Symptoms of AD are related to decreased levels of acetylcholine due to decreased rate of its synthesis. In order to protect acetylcholine levels, potent AChE and BChE inhibitors are used to allivate the symptoms. Tacrine has been used for this purpose (54). But recent studies show that selective inhibition of BChE elevates acetylcholine levels and is correlated more strongly with cognitive improvement (55, 56).

BChE has an important role in the development and progressing of AD. It has peptidase activity besides of esterase activity (57). It cleaves the amyloid procurser protein, which is found in abundance in normal brain, to β-amyloid protein in AD. Then β-amyloid proteins deposit and constitute β-amyloid plaques. Selective BChE inhibitors also prevents the formation of new β-amyloid plaques (58).

Important point is to find specific markers which help in accurate and early diognosis of AD. It is found that cerebrospinal fluid (CSF) of the patirnts with AD has a specific form of BChE that its glycosylation is altered. It is suggested that assay of this form in CSF can be used in sensitive and specific detection of AD (59).

5.4. Non-Classical Functions of BChE

5.4.1. Cellular Differentiation and Morphogenesis

Besides of cholinergic and detoxification functions, it is shown that AChE and BChE involve in embryonic neural developmant in the animals. BChE has an influence both on cellular proliferation and morphogenetic movements, and on AChE expression (60). In turn, AChE expression stimulates differentiation (61) and cellular adhesion (62) during neurogenesis.

5.4.2. Aryl Acylamidase Activity

Other than the cholinesterase activity, both AChE and BChE display a geunine aryl acylamidase (AAA) activity with unknown phyiological function, capable of hydrolyzing the synthetic substrate, o-nitroacetanilide into o-nitroaniline and acetate. AAA activity of BChE is susceptible to selective inhibition by seratonin besides of classical cholinesterase inhibitors, but several fold activation by tyramine. AAA and BChE active sites have close relationship in the enzyme molecule. It is known that some of the classical neurotransmitter systems are linked with each other, and AAA and BChE can be well representation of a crosstalk between seratonergic and cholinergic neurotransmitter systems (63). Potent cholinesterase inhibitors, that are effective against some symptoms of Alzheimer disease such as tacrine, physostigmine, inhibit AAA activity more strongly than cholinesterase activity. So, it is suggested that the therapeutic effectiveness of these drugs is related in some way to their action on AAA activity of the enzymes (64).

5.4.3. Peptidase (Proteinase) or Amidase Activity

As mentioned before in “Section 5.3.”, both BChE and AChE also have peptidase or amidase activity (57). This activity becomes more important in AD pathogenesis. It is shown that pepdidase activity of AChE cleave amyloid precursor protein at a nonamyloidogenic site (65), but BChE is able to produce β-amyloid proteins and also helps it to diffuse into β-amyloid plaques (58,66).

6. RESULTS

In the near future, we will have more information about BChE value as a new threapeutic target and as a diagnostic marker in AD treatment. In embryonic life, definition of the role of cholinesterases in cellular proliferation and differentiation have started the investigations on possible involvement of BChE and AChE in tumorogenesis. Abnormal expression of both BChE and AChE, and in vivo amplification of their genes have been observed in intracranial neoplasms such as meningioma (67), glioma (68), and acuostic neurinomas (69), lung cancers (70), megakaryocytopoietic disorders and leukemias (71), ovarian tumors (72). It is also shown that AChE and BChE modulate cell adhesion in human neuroblastoma cells (62). Antisense blocking of BChE has been shown

to result in an inhibition of megakaryocytopoiesis and application of similar techniques in embryonic chick retinal cell resulted in an inhibition of proliferation (61,71). So we will read more about the relationship between BChE and tumorogenesis and the usage of specific BChE inhibitors used as chemothreapeutic agents in the future also.

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