ACHEIs bind ACHE

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references

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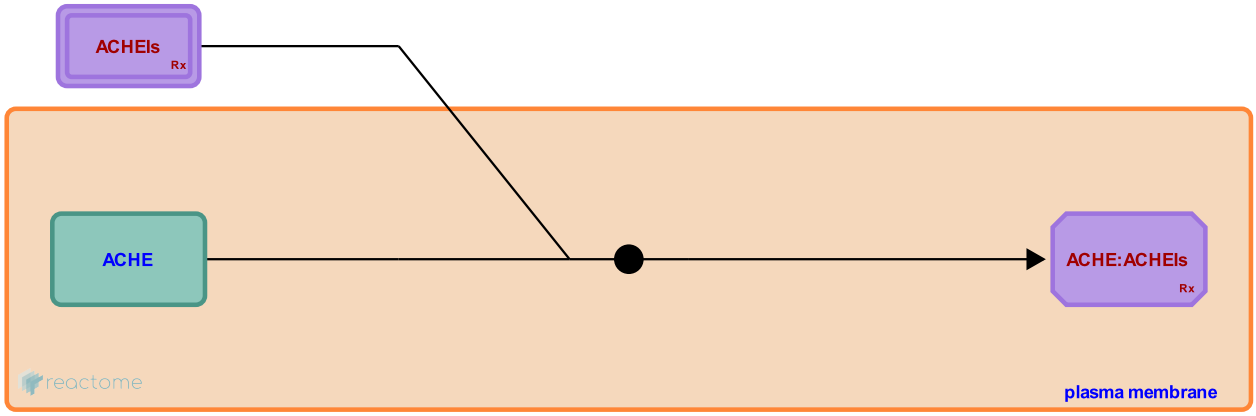
Stable identifier: R-HSA-9634834

Type: binding

Compartments: plasma membrane, extracellular region



Acetylcholinesterase (ACHE) is involved in the termination of impulse transmission by rapid hydrolysis of the neurotransmitter acetylcholine in numerous cholinergic pathways in the central and peripheral nervous systems. The enzyme inactivation, induced by various inhibitors (Stahl 2000), leads to acetylcholine accumulation, hyperstimulation of nicotinic and muscarinic receptors, and disrupted neurotransmission (Pohanka 2011, Colović et al. 2013). ACHE inhibitors (ACHEIs) are classified as reversible, irreversible, or quasi-irreversible. Compounds which function as reversible competitive or noncompetitive inhibitors of cholinesterase are those most likely to have therapeutic uses. Compounds which function as quasi-irreversible inhibitors of cholinesterase are those most likely to have use as chemical weapons or pesticides. Acetylcholinesterase inhibitors are also found naturally in venoms and poisons. When used medicinally, ACHEIs are used to treat neurodegenerative conditions such as Alzheimer's, Parkinson's and schizophrenia. They are also used for myasthenia gravis, autism and glaucoma. The following reversible ACHEIs are used as therapeutic drugs.

Rivastigmine (trade name Exelon) is a reversible carbamate ACHEI used in the treatment of mild to moderate Alzheimer's disease (Rosler et al. 1999, Birks et al. 2015) and Parkinson's (Emre et al. 2004, Barone et al. 2008). The drug is taken orally or applied as a transdermal patch (the latter method of delivery can reduce nausea and vomiting) (Inglis 2002). Galantamine (trade name Razadyne) is a reversible phenanthrene ACHEI used in the treatment of cognitive decline in mild to moderate Alzheimer's disease and in other memory impairment disorders (Lilienfeld 2002, Mohammad et al. 2017). Galantamine has a unique, dual mode of action; as a reversible inhibitor of AChE and as an allosteric modulator of nicotinic acetylcholine receptors (nAChRs) (Albuquerque et al. 2001). Physostigmine (trade names Antilirium and Isopto Eserine) is a reversible carbamate ACHEI used to treat glaucoma (Lindén & Alm 1997), anticholinergic poisoning (Watkins et al. 2015) and recently, sepsis and septic shock (Zimmermann et al. 2017). It was discovered to be the active ingredient in the Calabar bean found in Nigeria and was used as a poison test for individuals accused of witchcraft. If they survived, they were set free (Proudfoot 2006, Scheindlin 2010).

Neostigmin (brand name Prostigmin), is a is a reversible carbamate ACHEI (Calvey et al. 1979) with a slightly shorter duration of action than physostigmine. It is primarily used to treat myasthenia gravis (Grob & Namba 1976, Aquilonius et al. 1983) and to reverse the effects of muscle relaxants such as gallamine and tubocurarine. Neostigmine, unlike physostigmine, does not cross the blood-brain barrier. By inhibiting ACHE, neostigmine indirectly stimulates both nicotinic and muscarinic receptors which are involved in muscle contraction. Pyridostigmine (trade name Mestinon) is a peripherally acting, orally active reversible ACHEI used to treat MG (Aquilonius et al. 1983, Maggi & Mantegazza 2011) and to combat the effects of curariform drug toxicity. During the first Gulf War, pyridostigmine bromide was given prior to exposure to the nerve agent Soman in order to increase survival. Pyridostigmine bromide has been implicated as a causal factor in Gulf War syndrome (Golomb 2008). Pyridostigmine is also used for postural orthostatic tachycardia (Gales & Gales 2007, Kanjwal et al. 2011). Donepezil (trade name Aricept) is a reversible piperidine ACHEI used in the palliative treatment of mild to moderate Alzheimer's disease (Sabbagh et al. 2013, Lee et al. 2015). It is generally accepted that the symptoms of Alzheimer's disease are related to a substantial loss of cholinergic neurons in the CNS that correlates with the severity of cognitive impairment. The precise mechanism of action of donepezil in patients with Alzheimer's disease is not fully understood but by inhibiting ACHE breakdown, acetylcholine levels at cholinergic synapses is prolonged.

Tacrine (trade name Cognex) is a dual inhibitor of butyrylcholineesterase and acetylcholinesterase (ACHE) being the first centrally acting cholinesterase inhibitor approved for the treatment of Alzheimer's disease in 1993. Tacrine

appears to have little beneficial effect on congnition in AD patients (Qizilbash et al. 1998) and currently, it is no longer used as a treatment for AD due to serious hepatotoxicity which limited its clinical use (Qizilbash et al. 2007, Patocka et al. 2008). Edrophonium (trade name Tensilon) is a reversible ACHEI In the treatment of myasthenia gravis, edrophonium reduces muscle weakness by prolonging the presence of acetylcholine in the synaptic cleft. The Tensilon test uses edrophonium to differentiate myasthenia gravis from cholinergic crisis and Lambert-Eaton (Pascuzzi 2003). In practice, the edroophonium test has been replaced by testing for autoantibodies (Benatar 2006, Meriggioli & Sanders 2012). The Tensilon test may also be used to predict if neurotoxic paralysis caused by snake envenomation is presynaptic or postsynaptic. If it is a postsynaptic then paralysis will be temporally reversed, indicating that can be reversed by adequate antivenom therapy. If the neurotoxic is presynaptic then the Tensilon test will show no response and antivenom will not reverse such paralysis.

Pralidoxime is an antidote to organophosphate poisoning in conjunction with atropine and diazepam. Organophosphates such as sarin bind to the hydroxy component (the esteric site) of the active site of the acetylcholinesterase enzyme, thereby blocking its activity. Pralidoxime binds to the other half (the unblocked, anionic site) of the active site and then displaces the phosphate from the serine residue. The conjoined poison/antidote then unbinds from the site, and thus regenerates the fully functional enzyme (Jokanović & Prostran 2009, Jokanović 2009). Echothiophate (Trade name Phospholine) is an irreversible ACHEI used as an ocular antihypertensive in the treatment of chronic glaucoma (Schmidt et al. 2010, Kraus et al. 2015). Echothiophate covalently binds its phosphate group to a serine in the active site of acetylcholinesterase, rendering the enzyme permanently inactive.

Literature references

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Editions

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