ORIGINAL RESEARCH

Carbamates as Acetylcholinesterase (AChE) inhibitors: Mechanism and Theoretical Implications

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Received: 23 June, 2023 Accepted: 26 July, 2023

ABSTRACT
The inhibition of acetylcholinesterase (AChE) has emerged as a significant strategy in the treatment of disorders characterized by impaired cholinergic neurotransmission. Carbamates, a class of compounds defined by the carbamate functional group (R-O-C(=O)-NR2), have garnered substantial attention as potent AChE inhibitors. This article highlights the mechanisms underlying the interaction of carbamates with AChE and their diverse therapeutic applications.

INTRODUCTION

The study of carbamates as acetylcholinesterase inhibitors is an important area of research within the fields of chemistry, biochemistry, and pharmacology. Acetylcholinesterase (AChE) is an enzyme that plays a crucial role in terminating the transmission of nerve signals at cholinergic synapses by breaking down the neurotransmitter acetylcholine[1]. Inhibiting AChE can lead to an accumulation of acetylcholine, which can result in excessive stimulation of cholinergic pathways and has potential applications in various medical contexts, including neurodegenerative disorders like Alzheimer's disease[2] and as insecticides. A major use of AChEIs is in agriculture where they are used for the control of insects and some other arthropod pests.

Among the most common acetylcholinesterase inhibitors are organophosphorus compounds (OPs), carbamates and some chlorinated derivatives of nicotine. As such, AChEIs are attracted in 1:1 ratio to the active site of the enzyme AChE, where they act as substrates for the enzymes. At the active site, the inhibitors mimic the normal hydrolysis of Ach. The original AChEIs used were OPs which bind irreversibly to AChE[4]. The organophosphorus compounds (OPs) such as phosphoramidates are potent inhibitors of AChE. Up to now inhibitory effect of two types of OP on AChE have been studied: oxono (P=O) and thiono (P=S) derivatives[5]. The concept of using carbamates as AChEIs arose from the finding that the carbamate group was found to be a necessary part of physostigmine for AChEI activity, so they can be said to have been developed from a natural product lead[6]. The carbamates were introduced as much less toxic alternatives to the OP.

Carbamates are a class of organic compounds that contain the carbamate functional group (NH2COO-). They have been extensively studied as AChE inhibitors due to their structural similarity to acetylcholine and the reversible nature of their inhibition, which makes them a more favorable choice compared to the reversible inhibitors[7,8].

MEDICAL APPLICATIONS OF CARBAMATE BASED ACHE INHIBITORS

Carbamate-based acetylcholinesterase (AChE) inhibitors have several medical applications, particularly in the treatment of conditions where cholinergic neurotransmission is impaired. Some notable medical applications of carbamate AChE inhibitors are:

1. **Alzeimer's Disease:** One of the most significant applications of carbamate AChE inhibitors is in the treatment of Alzheimer's disease[9]. Alzheimer's is characterized by a decline in cognitive function, memory loss, and reduced cholinergic neurotransmission due to the loss of cholinergic neurons. Carbamate AChE inhibitors help increase the availability of acetylcholine in the brain, mitigating some of the cognitive

deficits associated with the disease. Donepezil and rivastigmine are examples of carbamate-based AChE inhibitors that are FDA-approved for treating mild to moderate Alzheimer's disease.

2. **Mild Cognitive Impairment:** Mild cognitive impairment (MCI) is a transitional state between normal age-related cognitive decline and more severe cognitive impairment seen in conditions like Alzheimer's disease. Carbamate AChE inhibitors may be used to manage the cognitive symptoms associated with MCI[10].
3. **Parkinson's Disease Dementia:** Parkinson's disease can progress to involve cognitive deficits and dementia. In these cases, carbamate AChE inhibitors may be used to address both the motor symptoms of Parkinson's disease[11] and the associated cognitive impairments.
4. **Lewy Body Dementia:** Lewy body dementia[12] is characterized by cognitive fluctuations, visual hallucinations, and parkinsonian motor symptoms. Carbamate AChE inhibitors can be used to manage the cognitive symptoms and potentially alleviate some of the motor symptoms**.**
5. **Myasthenia Gravis:** Myasthenia gravis is an autoimmune neuromuscular disorder where antibodies attack acetylcholine receptors, leading to muscle weakness and fatigue[13]. Carbamate AChE inhibitors can increase the availability of acetylcholine at the neuromuscular junction, helping to improve muscle strength and function.
6. **Glucoma:** Some forms of glaucoma involve reduced cholinergic neurotransmission, leading to increased intraocular pressure. Carbamate AChE inhibitors can be used topically as eye drops to increase acetylcholine levels in the eye, thereby reducing intraocular pressure and managing glaucoma[14].
7. **Organophosphate poisoning:** Carbamate AChE inhibitors have been used as antidotes for organophosphate poisoning[15]. Organophosphates are potent AChE inhibitors used in pesticides and nerve agents. Carbamates can compete with and displace organophosphates from AChE, providing temporary relief from their toxic effects.
8. **Neuromuscular Disorder:** Apart from myasthenia gravis, carbamate AChE inhibitors might be used in other neuromuscular disorders where enhanced cholinergic neurotransmission is desired, such as Lambert-Eaton myasthenic syndrome[16].

Although carbamate AChE inhibitors offer therapeutic benefits, they are not without potential side effects. Increased cholinergic stimulation can lead to adverse effects like nausea, vomiting, diarrhea, and muscle cramps. The development of AChE inhibitors, including carbamates, requires a balance between inhibitory potency, selectivity, and safety. The understanding of the enzyme's structure and the interactions between inhibitors and the active site has been instrumental in designing compounds with desired pharmacological properties for the treatment of conditions like Alzheimer's disease and other neurodegenerative disorders.

MECHANISM OF ACTION OF CARBAMATE AS ACHE INHIBITORS

The mechanism of action of carbamates as acetylcholinesterase (AChE) inhibitors involves their interaction with the active site of the AChE enzyme, leading to inhibition of its activity. Carbamate compounds contain the carbamate functional group (R-O-C(=O)-NR2), where R can be various substituents. These compounds are designed to structurally mimic the acetylcholine substrate that normally binds to the active site of AChE. When a carbamate inhibitor interacts with the active site of AChE, the carbonyl oxygen of the carbamate group undergoes nucleophilic attack by a serine hydroxyl group present in the active site of the enzyme. This nucleophilic reaction results in the formation of a covalent bond between the carbonyl carbon of the carbamate and the hydroxyl group of the serine residue in the active site of AChE. This covalent bond is reversible, but the dissociation of the inhibitor from the enzyme is often slow, leading to prolonged inhibition. The formation of this covalent bond prevents the AChE enzyme from effectively breaking down acetylcholine molecules in the synaptic cleft.

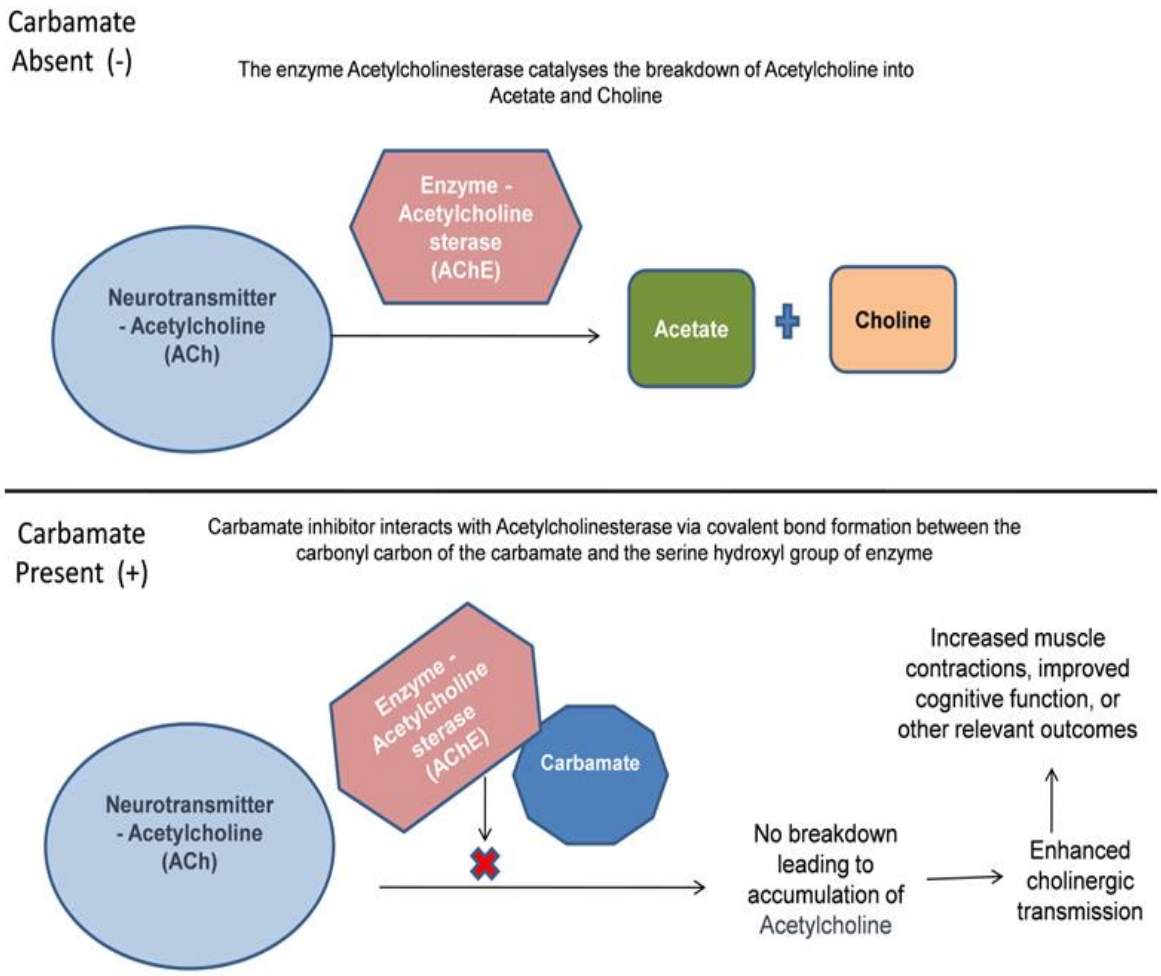

Figure1: Mechanism of Action of Carbamate AChE Inhibitors

As a result, acetylcholine accumulates in the synaptic gap, leading to prolonged stimulation of cholinergic receptors on the postsynaptic neuron. (Figure1) The increased concentration of acetylcholine enhances cholinergic neurotransmission, which is critical for various physiological processes such as muscle contraction, cognitive function, and regulation of autonomic functions. While the initial covalent bond formation is reversible, the carbamate-AChE complex can often dissociate slowly. This leads to a prolonged inhibitory effect, as new enzyme molecules are required to replace the inhibited ones. This slow dissociation is an important factor in the duration of action of carbamate inhibitors[17-20]. Over time, carbamate inhibitors can undergo hydrolysis and degradation in the body. The carbamate bond may be cleaved, restoring the active site of AChE. Additionally, the body's detoxification mechanisms can metabolize and eliminate the carbamate compounds. The challenge in developing carbamate-based AChE inhibitors lies in achieving selectivity for AChE over other cholinesterases and minimizing off-target effects. This selectivity helps to minimize side effects associated with excessive cholinergic stimulation, such as nausea, vomiting, diarrhea, and muscle cramps.

CARBAMATE ACETYLCHOLINESTERASE (ACHE) INHIBITORS AS INSECTICIDES

Carbamate acetylcholinesterase (AChE) inhibitors have been widely used as insecticides due to their ability to disrupt the nervous systems of insects. These compounds target the cholinergic neurotransmission in insects, leading to overstimulation of nerve cells and eventually paralysis and death. In insects, cholinergic neurotransmission is crucial for transmitting nerve signals. Acetylcholine is the neurotransmitter responsible for transmitting signals between nerve cells and muscles. Acetylcholinesterase is the enzyme that breaks down acetylcholine after it has transmitted the signal, ensuring that the nerve cell can reset and respond to new signals. Carbamate AChE inhibitors interfere with this process by binding to and inhibiting acetylcholinesterase, preventing the breakdown of acetylcholine. As a result, acetylcholine accumulates, causing prolonged stimulation of the insect's nervous system[21-23]. The overstimulation of the nervous system leads to a range of effects in insects. Initially, insects may experience tremors, convulsions, and increased muscle activity. As the exposure continues, insects become paralyzed and eventually die due to

the inability of their nervous system to function properly.

Compared to some other classes of insecticides, carbamates generally have shorter residual activity. This means that their effects on insect populations can diminish more quickly after application, which can be advantageous in situations where shorter control periods are desired. While carbamates have been effective as insecticides, their use has raised environmental and health concerns. Non-target organisms, including beneficial insects, birds, and mammals, can be affected by these chemicals. Additionally, some carbamates can persist in the environment and pose risks to aquatic ecosystems.

While carbamate AChE inhibitors hold therapeutic potential, challenges exist in achieving the delicate balance between efficacy and safety. Excessive cholinergic stimulation can result in adverse effects, necessitating careful dosing and patient monitoring. Furthermore, environmental and health concerns associated with carbamate insecticides underscore the need for judicious application and the exploration of alternative strategies.

In conclusion, the study of carbamates as AChE inhibitors represents a dynamic avenue in medicinal chemistry and neuropharmacology. Understanding the intricate interplay between these inhibitors and AChE informs the design of compounds with tailored pharmacological profiles. The therapeutic impact of carbamate AChE inhibitors spans multiple medical contexts, reaffirming their role in addressing disorders characterized by disrupted cholinergic signaling.

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