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Advances in tacrine for Alzheimer's disease

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Abstract. Alzheimer's disease is a kind of neurodegenerative disease with insidious and progressive onset, which will affect the normal life of patients to varying degrees. At present, there is no specific drug that can completely cure Alzheimer's disease, and there is still a long way to go in the treatment of the disease. In order to provide better ideas for the development of drugs to treat Alzheimer's disease, people have speculated and verified a variety of pathogenesis of the disease as far as possible and developed targeted drugs on this basis. In addition to the need to develop drugs from multiple pathogenetic perspectives, it is also necessary to conduct longitudinal studies on one drug. Since tachrine is one of the drugs with great development potential, this paper will take Tachrine, a representative of cholinesterase inhibitors, as the main drug research object, analyze the structure and efficacy of various existing tachrine drugs, and try to provide the future development direction of Tachrine drug transformation.

Keywords: Cholinergic, Tacrine, Drug modification.

1. Introduction

Since Alzheimer's disease became known to the world, it has remained a major challenge for the medical community until today. With the advancement of medicine, the following possible pathogenic mechanisms of Alzheimer's disease have been explored: cholinergic deficits, of which acetylcholine and butyrylcholine are of great interest; excessive reactive oxygen species produced by abnormal mitochondrial function; neuroinflammation that destroys neurons and affects normal synaptic function, which aggravates the damage to the brain; dysregulation of the homeostatic state of metal ions; hyperphosphorylation of tau proteins and dysfunction of various kinases; and amyloid aggregation and deposition. dysfunction, and amyloid aggregates and deposits. In addition, there are also studies on the pathology of AD from the point of view of the protective mechanism of nerve cells, in which the hypothesis of phosphodiesterase regulation of AD occupies the mainstream [1]. These mechanisms of AD cure are not necessarily complete at present, but they also provide important ideas for the development of anti-AD drugs. Since cholinergic deficiency is currently the more studied pathogenic mechanism, it has prepared the ground for the development of cholinesterase inhibitor drugs. And since cholinesterase inhibitors themselves have good therapeutic effects and can be optimized, this paper summarizes and envisions the modification of some of the anti-AD drugs that have been studied from the perspective of cholinergic deficiency. This work can promote the development of cholinesterase inhibitor drugs as much as possible and help to optimize the pharmacological treatment options for Alzheimer's disease.

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2. Mechanism of Action of Choline

If one wants to develop drugs for AD from a cholinergic perspective, one should first understand the mechanism of action of choline and its effect on brain memory. In the central nervous system, acetylcholine is the neurotransmitter associated with brain memory. Acetyl coenzyme A and choline are catalyzed by choline acetyltransferase to generate acetylcholine, which is released from the presynaptic membrane to the salient gap and binds to receptors on the postsynaptic membrane, realizing the transmission of information between nerve cells. Increasing the amount of acetylcholine can effectively increase cholinergic receptors on target cells of cholinergic neurons [2]. In AD patients, there are four main reasons for the decline in cholinergic energy: a decrease in the amount of acetylcholine synthesized; a decrease in the number of cholinergic receptors (nicotinic-type receptors and muscarinic receptors); a decrease in the amount or activity of the enzyme choline acetyltransferase; and an insufficient uptake of choline.

It is known that cholinesterase breaks down choline, so if the amount of choline needs to be increased, then it is possible to start by decreasing cholinesterase. Tacrine is a typical example of a cholinesterase inhibitor that has been developed. Tacrine can inhibit both blood and tissue cholinesterase, but as a treatment for AD, there are some areas for improvement: high liver toxicity, which can lead to an increase in aminotransferases in some patients; and a higher dosage of tacrine compared to other anti-AD drugs.

Since tacrine itself has an efficient ability to inhibit cholinesterase, it is hoped that a better quality anti-AD drug will be obtained by modifying tacrine for its undesirable properties.

3. Modifications based on the Chemical Structure of Tacrine

Molecular modification or modification of tacrine can be done based on the chemical structure of tacrine first. This paper summarizes three aspects of tacrine: aromatic ring modification, alicyclic modification and side chain free amino modification. Aromatic ring modification of tacrine is divided into two categories, one is to transform the benzene ring into an aliphatic ring or an aromatic ring, but most of these drugs do not have significant therapeutic efficacy; the other is to add substituent groups to the benzene ring, among which 6-chloro(bromo)tacrine and 7-methoxytacrine are relatively prominent in terms of their therapeutic efficacy. There are also two ways to modify the alicyclic ring, one is to modify the original alicyclic ring to other alicyclic ring, and the other is to add substituents on the alicyclic ring. Lipocyclic modification is further divided into three categories, which are heterocyclic lipocyclic modification, thickened lipocyclic modification and lipocyclic size modification. Among them, tacrine analogs 17-19 obtained after single alicycle size modification were weaker than tacrine. Among the tacrine derivatives modified by adding substituents to the alicyclic ring, 1-hydroxytacrine is a typical representative, which has a stronger anticholinesterase effect and at the same time a weaker toxicity than tacrine. Further study of 1-hydroxytacrine derivatives revealed that 6-fluorotacrine-1-ol was slightly more potent than tacrine, while 6-chlorotacrine-1-ol was 30 times more potent than tacrine. The side-chain amino modification of tacrine is to add hydrocarbon group to its side-chain amino group, and on the basis of side-chain amino modification, the more valuable direction of research lies in the synthesis of tacrine duplex. It has been found that the use of straight-chain saturated aliphatic hydrocarbons as a bridge for tacrine can effectively reduce the toxicity of tacrine [3].

The tacrine dications can be structurally categorized into four groups, AnA, AnX, XnX and AnH (A for tacrine and its substituted derivatives, H for hesperidin A, X for other aryl ring groups, and n for the number of carbon atoms in the bridged alkane group). It was found that the toxicity of tacrine decreases with the increase of the carbon chain in the side-chain aminoalkane substituents in the dications, but the decreasing trend levels off again when the toxicity weakens to a certain extent. This pattern led to the identification of A7A, a representative product of the AnA-type tacrine complex, which is more active, selective, and therapeutically effective than tacrine, with toxicity of only ten-thousandth of that of tacrine and which has strong advantages of a shorter synthesis period and lower production costs. The study of AnX-type compounds did not find any drugs with outstanding therapeutic effects, but it further proved that the toxicity of AnA-type duplex compounds varies with the number of carbon atoms in the bridge,

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i.e., the toxicity of compounds is the weakest when the number of carbon atoms is 7. XnX refers to tacrine duplex analogs, representing the drug galantamine, whose efficacy has been tested to be greater than that of tacrine. the structure of the AnH(A)-type duplexes Unlike the other three diplexes, it is not connected by a bridge group, but rather consists of the tacrine 1,3-position carbon attached to itself or to other structures. As sarcosine methyl itself is a reversible cholinesterase inhibitor, the synthesis of tacrine and sarcosine methyl into a duplex (AnH15) produces a greater potency than tacrine and sarcosine methyl alone [4].

Tacrine-indole heterodimer (1a~1f,2a~2f) is also an acetylcholinesterase inhibitor. In vitro activity assay experiments of the modified compounds using Ellman's method revealed that the dicotyledons had strong inhibitory ability against fish skate acetylcholinesterase, and compounds 2a~2f inhibited acetylcholinesterase more strongly than 1a~1f [5].

4. Modifications based on Improved Tacrine Cholinesterase Inhibition and Toxicity Reduction

Although tacrine itself has a strong ability to inhibit cholinesterase, continuing to enhance tacrine's enzyme inhibition is an effective way to increase its potency. Tacrine-isohydroxamic acid derivatives (A1-A28) are a promising anti-AD molecule that have been investigated on the basis of their ability to enhance cholinesterase inhibition. These 28 tacrine-derived compounds showed strong inhibition of both acetylcholinesterase and butyrylcholinesterase, and most of them inhibited the enzymes more strongly than tacrine, represented by compounds A10 and A28.The advantage of A10 over A28 is that it is selective and more efficient against acetylcholinesterase. Under general conditions, the longer the linker between the 9-position nitrogen atom located on the tacrine and the isohydroxamic acid, the easier it is for the compound to bind to the enzyme. Further experimental analyses yielded that under conditions containing a benzene ring, tacrine-derived compounds inhibit cholinesterase most effectively when the linker portion contains a chain length of seven carbon atoms. Based on the existing experiments it is known that the 6-chloro substitutes of tacrine have an enhanced inhibitory effect on acetylcholinesterase, so in the future attempts can be made to investigate derivatives that enhance the inhibitory effect of butyrylcholinesterase. The antioxidant activity of in vitro tacrine-isohydroxamic acid derivatives was tested by ABTS free radical scavenging assay, and the results of the assay showed that the compounds possessed good antioxidant activity almost the same as that of Trolox, and have an excellent potential as drugs. By depolymerization Aβ experiments, it was found that tacrine did not depolymerize under the same conditions, whereas compounds A5 and A12 both possessed more than half the depolymerization rate. In recent years, it has been suggested that the deposition of Aβ42 in the brain is one of the causes of Alzheimer's disease, and the above experiments further confirmed that the compounds have a mitigating effect on AD symptoms and are able to promote memory function in the brain. HepG2 cytotoxicity experiments were conducted with tacrine and A5 and A10 of the compound, respectively, and the experimental data showed that there was no significant difference between the hepatotoxicity of the compound and that of tacrine within the range of appropriate concentrations. In vitro permeability is also an important indicator of whether tacrine derivatives, a central nervous system drug, can effectively exert their drug effects. By predicting the permeability of the compounds, it was found that all the compounds possessed a certain degree of membrane permeability, but their ability was lower than that of the parent drug, tacrine. A10 was selected for enzyme kinetic analysis as well as molecular docking experiments, which showed that the compounds were mixed-type inhibitors that could simultaneously bind to both sites of action of acetylcholinesterase and were more selective for acetylcholinesterase than for butyrylcholinesterase. Cytotoxicity and antioxidant properties of the compounds were examined by MTT assay, and the results showed that all the compounds were cytotoxic to a certain extent and could not protect the oxidatively damaged cells [6].

In the case of modifications whose main purpose is the attenuation of toxicity to tacrine, there are tacrine-phenol-biphenyl bis ester heterodimers (7a to 7e, 8a to 8e). Acetylcholinesterase has two active sites, a catalytic anionic active center (CAS) and a peripheral anion binding site (PAS). The primary function of the CAS is to catalyze the hydrolysis of acetylcholine. If the drug can act on both binding sites simultaneously, it will have the following three advantages: it enhances the affinity of the drug to

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cholinesterase; it improves the selectivity to cholinesterase, and it reduces the polymerization rate of Aβ protein. The cholinesterase inhibitory activity of the compound was tested using Ellman's method with tacrine as a control. The results showed that the compound has strong inhibitory activity against both acetylcholinesterase and butyrylcholinesterase, with the most active compound being 8d. Thus, this compound has more advantages than drugs that inhibit acetylcholinesterase alone. Further, by performing an enzyme kinetic test and analytical docking test on 8d, it was confirmed that the compound 8d acted on both peripheral and catalytic binding sites of Ach E, which acted as an inhibitor of acetylcholinesterase to a greater extent. The in vitro toxicity of the compounds and tacrine on normal hepatocytes and hepatocellular carcinoma cells was tested using the thiazolyl blue tetrazolium bromide assay with tacrine as a control group, and the test results showed that the compounds were less toxic than tacrine to the above two types of hepatocytes under the same effective drug-acting concentration, which somewhat ameliorated the problem of tacrine having hepatotoxicity. In order to solve the hepatotoxicity problem further, it can be considered from the point of view of improving the antioxidant activity of the drug. However, the compound was not found to have antioxidant activity by oxygen radical absorbance capacity assay. Since the hydroxyl-containing precursor compounds showed a certain degree of antioxidant capacity, combined with the fact that the tacrine-phenol-biphenyl diester hybrid carries an ester bond, it is envisioned whether a synergistic drug that promotes the decomposition of the ester bond of the compound in vivo could be developed to reduce the degree of oxidative damage in hepatocytes by sequentially administering the two drugs so as to decompose the ester bond. High intracellular ROS levels will induce apoptosis and low ROS levels will inhibit cell proliferation, so it was necessary to determine the effect of the compounds on intracellular ROS levels [7]. The effects of compound 8d and tacrine on intracellular ROS levels in Hep G2 cells were determined by 2,7-dichlorodihydro-fluorescein diacetate, setting a blank control, respectively. The experimental results showed that compound 8d did not produce significant changes in ROS levels relative to tacrine, which implies that the side effects of 8d will be less than those of tacrine [8].

5. Multi-targeted Tacrine Drug Studies

In addition to modifying a drug from the perspective of basing it on the structure of tacrine itself, there is another way of thinking about drug modification, i.e., multi-target drug research. Although the concept of designing a drug for a single target is reasonable, the causes of AD are numerous and complex, and it is possible to try to design a drug to act on multiple targets to improve the therapeutic efficiency of the drug. The simplest idea is to combine tacrine with other molecules that have the potential to reduce the effects of AD, and then test the drug to find one that is more potent than tacrine alone.

It has been hypothesized that amyloid aggregation results in the formation of two types of substances, soluble protofibrils and insoluble protofibrils and plaques, and that these aggregated substances cause a pathological response in the brain. Oxidation of proteins strengthens their aggregation tendency, and ferulic acid can resist the oxidation of Aβ proteins to the extent of attenuating protein aggregation, so it is hoped to synthesize tacrine and ferulic acid into a new substance to form a potent drug. Dysregulation of the homeostatic state of metal ions in patients with AD is also a key factor in the deterioration of the disease, so if we use a linker arm with metal-ion chelating activity to connect tacrine and ferulic acid, then a drug with triple therapeutic effects can be obtained. a drug with triple efficacy. Later experiments revealed that these compounds not only have stronger inhibitory ability of acetylcholinesterase and butyrylcholinesterase than tacrine, but also have good inhibitory activity of Aβ protein aggregation at the same time. One of the representative compounds is C3 5 H4 3 N5 O6, whose cholinesterase inhibitory activity as well as Aβ protein inhibitory activity is higher than that of the control, making it an excellent potential anti-AD drug [9].

Besides ferulic acid, we can find other suitable antioxidants. Lipoic acid, for example, not only has antioxidant capacity, but also attenuates the cytotoxicity induced by Aβ protein. By linking lipoic acid to tacrine using a methylene chain of a certain length, it is possible to synthesize drugs with both cholinesterase inhibitory and antioxidant properties. The compounds of this series are more effective than the parent drug tacrine when the number of methylene groups ranges from 2 to 7, and when the

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number of methylene groups is 3, the efficacy of the drug is 60 times higher than that of tacrine itself at a certain concentration. If, on the basis of the number of methylene groups equal to 3, the 6 position of the compound is replaced by a chlorine atom, the strongest drug of this type of compound can be obtained, and its efficacy is up to nearly two thousand times that of tacrine. Melatonin is effective in scavenging free radicals and is also a strong antioxidant. Similar to lipoic acid, a series of drugs are obtained by connecting the indole ethylamine structure of tacrine and melatonin with a methylene chain. The most potent drug in this series is when the number of methylene groups is 6 (R=R1=H), which can be up to 350 times more potent than tacrine. When the compounds are substituted with chlorine at the 6 and 8 positions (R=6,8-diC1,R1=H), one of the most potent cholinesterase inhibitors is obtained. In addition to both cholinesterase inhibitory and antioxidant abilities, such compounds also have the advantage of easily crossing the blood-brain barrier, making them an anti-AD drug with developmental advantages.

Calcium ion, as a second messenger molecule, plays a crucial role in functions such as memory for intracellular learning. Although current research on AD drug development is mostly based on the hyperphosphorylation of Tau protein and the amyloid hypothesis, as the research on the pathogenesis of AD by calcium ions matures, more and more research results indicate that persistent homeostatic dysregulation of calcium ions in vivo may lead to the disruption of normal neuronal function, and therefore attempts have been made to synthesize both calcium antagonists and tacrine into a new anti-AD drug [10]. Currently, researchers have synthesized a hybrid between the 1,4-dihydropyridine structure and the acridine ring structure of tacrine, which has the ability to inhibit both cholinesterase and calcium uptake.

The 5-hydroxytryptamine receptors (5-HT receptors) are located in the central part of the central nervous system and in the periphery of the peripheral nervous system and regulate the transmission of both inhibitory and excitatory neurotransmitters. The combination of tacrine and 5-HT receptors results in a drug that has both cholinesterase inhibitory and 5-HT3 receptor antagonistic effects, which effectively improves the neurological symptoms of AD patients [11].

Homeostasis of metal ions is also crucial for the central nervous system to remain healthy. It has been experimentally confirmed that free trivalent and divalent iron ions promote tau protein aggregation, while copper and zinc ions promote amyloid formation, thus exacerbating the condition of AD patients. Therefore, the combination of tacrine and substances with metal-chelating effects will hopefully result in a drug with dual efficacy [11].

6. Conclusion

As a cholinesterase inhibitor, is an anti-AD drug with good development potential. Tacrine can be modified based on its molecular structure, or it can be combined with other anti-AD molecules from the perspective of multi-target drug design. The modified drug should maintain the excellent anti-AD characteristics of tacrine while minimizing its side effects on the patient's body [12]. In addition to summarizing the existing tacrine modification schemes, this paper also provides new modification ideas. Future modification of tacrine can be more attempts based on this theory, and it is expected that anti-Alzheimer drugs with stronger potency and fewer side effects will be researched.

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