eNeurobiología

Artículo de Revisión

Neurotherapy for Alzheimer's disease

Neuroterapia para la enfermedad de Alzheimer

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Recibido: 20 de febrero de 2020 Aceptado: 13 de junio de 2020
Puedes encontrar este artículo en: www.uv.mx/eneurobiologia/vols/2020/27/27.html

Abstract

One of the world's largest pharmaceutical companies apparently will not continue research and development of new drugs against Alzheimer's disease. This situation will leave millions of people in a vulnerable situation. Drugs approved for the treatment of the disease have not been viable and patients always return to the symptoms of the disease. I am of the idea of a primarily pharmacological therapy, using already approved medications that could delay Alzheimer's disease or alleviate some of the symptoms of the disease. This therapy consists of rehabilitating the brain of the person with Alzheimer's, so that later, the drugs, such as acetylcholinesterase inhibitors and memantine act adequately in the neurons, making the treatment indicated by neurologists more effective. This therapy is not expensive and could help the patient to lead a better quality of life. I practically discussed the translational potential of various drugs that have been tested experimentally.

Keywords: Alzheimer's disease, medications, neuroinflammation, therapy.

Resumen

Una de las mayores compañías farmacéuticas del mundo aparentemente no continuará investigando y desarrollando nuevos medicamentos contra la enfermedad de Alzheimer. Esta situación dejará a millones de personas en una situación vulnerable. Los medicamentos aprobados para el tratamiento de la enfermedad no han sido viables y los pacientes siempre vuelven a los síntomas de la enfermedad. Soy de la idea de una terapia principalmente farmacológica, usando medicamentos ya aprobados que podrían retrasar la enfermedad de Alzheimer o aliviar algunos de los síntomas de la enfermedad. Esta terapia consiste en rehabilitar el cerebro de la persona con Alzheimer, para que posteriormente los fármacos, como los inhibidores de la acetilcolinesterasa y la memantina, actúen adecuadamente en las neuronas, haciendo más efectivo el tratamiento indicado por los neurólogos. Esta terapia no es costosa y podría ayudar al paciente a tener una mejor calidad de vida. Prácticamente he discutido el potencial translacional de varios medicamentos que han sido probados experimentalmente.

Palabras clave: Enfermedad de Alzheimer, medicamentos, neuroinflamación, terapia.

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1. Introduction

The giant of the pharmaceutical industry, at the beginning of 2018, declared that it will not continue with the research of new medicaments against Alzheimer's disease (AD), due to the fact that it is very expensive and not fundable to continue with new researches on this neurodegenerative disease.[1] This leaves millions of people in a vulnerable situation, since it has been estimated that in the USA by 2050 there will be an average of 14 million people over the age of 85 with this disease.[2] The drugs commercialized against AD so far have not been successful, and the question is why? At least 4 drugs used to treat AD are known, three of which are acetylcholinesterase inhibitors such as donepezil (aricept), galantamine (razadyne), and rivastigmine (exelon). Aricept is the most widely used drug, because it has low side effects and the recommended dose is once a day,[3] it can also be used in severe cases of the disease.[4] The drug razadyne, whose recommended dosage is twice daily with meals, has been determined to be involved in inhibiting the aggregation of the amyloid peptide (Aβ), as well as its cytotoxicity [5] showing a protective role against oxidative stress. [6] Another drug utilized in Alzheimer's disease is rivastigmine (exelon) which is used at low doses, due to the risk of severe gastric and hepatotoxic damage associated with its chronic consumption. [7] Another drug used for the treatment of AD is memantine, which is an NMDA receptor antagonist [8] and has only been approved for moderate to severe treatment of AD. Despite the benefits these drugs can give a person with AD, they have not really been seen to improve when they are taken. Relatives always report that at the beginning they notice a slight recovery in the person, however, after the effect is lost and the symptoms continue to deteriorate.

2. Functioning of drugs at the cellular level

Acetylcholinesterase enzyme inhibitors facilitate cholinergic neurotransmission in the brain.[9] This improves attention, working memory, and episodic memory in people with AD.[10] However, studies show that this improvement may be affected because an overexpression of acetylcholinesterase may occur when treated for a long time with enzyme inhibitors. [11] Donepezil and galantamine exert a rapid inhibition of acetylcholinesterase, while rivastigmine has a slower action.[12] Acetylcholinesterase inhibitors are able to potentiate the brain under normal conditions, [13] and in brains with AD function might be more difficult due to the involvement of protein transport along the axon .[14,15] Alterations in axonal transport lead to loss of synapses and this is related to a decrease in cognition due to aggregation of amyloid peptides.[16]

On the other hand, the neurotransmitter glutamate activates several types of both metabotropic and ionotropic receptors (AMPA, kainate and NMDA). Glutamate is neurotoxic in AD because it has been determined to increase NMDA receptor activity and lead to neuronal loss[17] and could be exacerbated by amyloid plaque toxicity. Continued neuronal loss increases cognitive impairment.[18] The drug memantine is a noncompetitive antagonist of moderate affinity, NMDA receptor and is well tolerated when ingested by patients. [19] The effects of memantine have been tested in animals, such as in clinical trials, suggesting that it provides neuroprotection in vascular dementia; [20] however, although it has been widely used in AD to treat moderate to severe symptoms, the brain continues to deteriorate gradually.

Despite efforts to find a drug or cure for Alzheimer's disease, it has not been possible to develop a drug that can eradicate the symptoms of the disease. Therefore, what remains for us to do? most importantly, is to stay as healthy as possible in adulthood, so as not to suffer from AD in old age.

What could we do when we already have the disease? Or when we already have some warning signs. Unfortunately, we go to the physician when we already have symptoms of the disease and may be at some point of "no return". A drug would be almost impossible for AD to cure. There are some drugs that have been used as part of the treatment of AD that have been shown to have certain advantages in relieving the symptoms of the disease. Examples are antidepressants that inhibit serotonin reuptake, to which escitalopram belongs, used to treat depression in patients with AD, and could help generate new neural connections in brains with AD.[21]

New drugs have been developed that consist of modifying agonists of acetylcholine receptors, as they are more tolerable and with less risk for patients [22] and the same is being carried with gabaergic drugs that could attenuate the symptoms of AD. [23] There is no doubt that these new drugs and their modifications will work properly, but in healthy neurons and unfortunately, they will fail again in people with AD. One option that we suggest in this article is a neuronal rehabilitation therapy, what does this therapy consist of? In our experience, relatives of patients with AD repeatedly express concern about drugs that at first seem to work, however, after a while the signs of the disease reappear and the relative becomes disillusioned and loses hope for the recovery of the patient with AD. It is known that anti-AD drugs have a limited period of efficacy and are not capable of stopping the neurodegenerative process, which once it starts seems not to stop. We propose a integral rehabilitation therapy that consists of two main aspects:

3. Physical therapy

1. Never isolate the patient, it is most likely that isolated lose stimuli that are necessary for your brain. Enriched environments have been shown to reduce Aβ peptide levels in transgenic mice.[24]

2. Occupational therapy. It has been demonstrated that when patients take occupational therapy, they have a tendency to have a better behavior and it is suggested that functional abilities of daily life could be recovered.[25]

Physical Therapy. Physical therapy in people with Alzhiemer's disease is beneficial in functions of daily life, this will allow the patient to be more independent.[26]

4. Pharmacological therapy

It is believed that pharmacological therapy is not new, however, neurologists have not yet tested it on their patients (Table1).

Brain Rehabilitation

Drug	Dosage	Time
Nimesulida	100mg per day/morning.	A month
Citalopram	20mg per day/night.	At least 6 months
ω-3 Acids (DHA+EPA)	1000mg per day/morning.	At least 6 months
Resveratrol	100mg per day/morning.	At least 6 months
Ginkgo biloba (Tebonin-OD)	240mg per day/morning.	At least 6 months

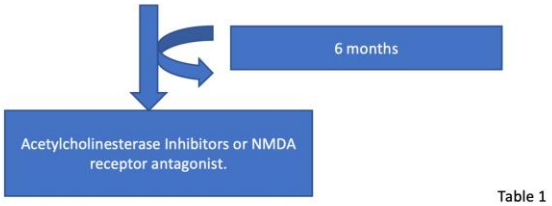

Table 1

Table 1. Neuronal rehabilitation protocol.

1. One of the important aspects that must be resolved is the problem of neuroinflammation, where cytotoxicity has been determined, carrying out an inflammatory response that includes the protein β-amyloid, cytokines, and prostaglandins that activate the enzyme cyclooxygenase type 2 (COX-2).[27] An effective way to reduce neuroinflammation is to use non-steroidal anti-inflammatory drugs (NSAID), which are capable of decreasing COX-2 activity. The most used have been celecoxib and nimesulide. In clinical trials celecoxib has not adequately decreased activity levels of the COX-2 enzyme, [28] however, nimesulide has worked effectively, reducing levels of prostaglandins and COX-2.[29] In AD, the neuroinflammatory process is of major importance, as neuroinflammation has been determined to be a trigger for the disease.[30,31] Nonsteroidal anti-inflammatory drugs have a protective effect in rodents where they have been treated with quisqualic acid injected into the basalis nucleus, the excitotoxin induces cholinergic degeneration and intense reaction of the glia, as well as the production of inflammatory mediators. When rodents are treated with nimesulide (10mg/kg/day, i.m.) it strongly attenuates the microglia reaction, reducing the activity of the nitric oxide synthase and completely inhibiting the formation of prostaglandin-E2.[32] Nimesulide is an NSAID that selectively inhibits COX-2, which may be useful in the treatment of Alzheimer's disease,[33] due to the neuroinflammation process characteristic of this pathology, including activated microglia and astrocytes accumulation, as well as some T-cells, accompanied by a molecular alteration of inflammatory characteristics such as cytokines, partially triggered by extracellular accumulation and precipitation of neurofibrillary tangles.[34] Some epidemiological studies of people using NSAIDs observed a delay in the onset of Alzheimer's disease, for example in identical twins who had received anti-inflammatory therapy, which is associated with damage caused by neuroinflammation.[35] Recent studies indicate that a possible mechanism of action of NSAIDs is by modulating the activity of the gamma secretase which is required for proteolytic anchoring of APP and producing the peptide β-amyloid.[36] The recommended dose due to the pharmacokinetics of nimesulide is 100 mg daily, as plasma levels of 4.58 mg/L are reached in about 3 hours.[37] It is

recommended to ingest it only for one month due to the risk that could be presented by hepatotoxicity.[38]

2 Citalopram is a selective inhibitor of serotonin recapture. Pharmacological evidence suggests that it has a role in the cholinergic modulation of monoamines in Alzheimer's disease. Studies related to this drug are primarily aimed at evaluating its efficacy in decreasing agitation in Alzheimer's patients.[39] In addition, it has been identified that in rat hippocampus it has an effect on Tau hyperphosphorylation. In this experiment, rodents were placed in social isolation, and reported that the increased level of phosphorylated Tau observed in social isolation can be reversed by citalopram [40]. Its effect on acetylation of Tau or its hyperphosphorylation under the effect of peptide β-amyloid is unknown. The recommended dose in elderly patients is 20 mg per day, this would allow the drug to maintain its effect.[41]

3. Resveratrol, which is a polyphenol known for its cardioprotective effect for cardiovascular disease, cancer and modulates pathological mechanisms of some diseases such as stroke, ischemia and Huntington's disease.[42] Several studies suggest that it has therapeutic value, it has been reported that it reduces the generation of the peptide β-amyloid and may also reduce Tau hyperphosphorylation, as well as its abnormal aggregation in animal models, [43] however it is not yet clear what effect it has on Tau protein. It is proposed that its mechanism of action could be through the activation of SIRT1, which is a deacetylase with antioxidant effects, deacetylates the Tau protein preventing the destabilization of microtubules and decreases the formation of neurofibrillary tangles, inhibits p53 and thus decreases apoptosis, reduces the inflammatory process and neurotoxicity, increases alpha-secretase activity and decreases peptide production β-amyloid.[44] It has been determined that a dose of 75 mg daily is sufficient to prevent microvascular dysfunction in people with type II diabetes [45] where it has been determined that this condition may be a determining factor for the onset of Alzheimer's disease. [46]

4. To maintain healthy neurons, the first thing we have to do is to maintain the integrity of the plasma membrane and avoid oxidative stress. [47] Attention has been focused on the ω-3 acids that are necessary for the integral maintenance of the plasma membrane.[48,49] It has been determined that ω-3 acids are capable of maintaining brain structure and function and potentially delay dementia.[50]

An 800 mg dose of omega-3 acids has been recommended to reduce the risk of dementia in older adults.[51]

5. Ginkgo biloba extract has been used to treat memory problems[52, 53] with good results in cognitive function. Studies have determined that a dose of 240 mg per day of ginkgo biloba extract Egb 761 is able to increase prefrontal dopamine [54] and this dose can be safely consumed. [55]

5. Conclusion

Unfortunately, there is as yet no cure for Alzheimer's disease and the number of cases, according to studies, predict that there will be more and more people with this condition every day. Practically one of the largest pharmaceutical companies in the world, declined to continue research and development of new drugs against AD.

The only thing we have is prevention or the use of drugs that could delay the development of the disease.

Perhaps neurologists and geriatricians are faced with the question of whether or not to use nimesulide, which is the most controversial drug at least of this proposed therapy, since there are studies that show the risk of hepatotoxicity and this has made its use and management prohibited in countries of the first world. The use of nimesulide for one month could be very beneficial for the person with AD and then suspend it.

The therapy is to rehabilitate the brain, so that FDA-approved drugs function properly and help patients effectively. I suggest that this therapy may improve a person's cognitive ability and it is advisable to start when the first warning signs appear. This therapy is proposed for people with sporadic AD, although it could be used in cases of genetic type, but we would not know if it could be effective. Neurologists and geriatricians would have to evaluate the application of this therapy in their patients, follow them monthly and determine if it is effective.

6. Conflict of interests

No conflict of interest.

7. Acknowledgements

I thank the Centro de Investigaciones Cerebrales/Universidad Veracruzana, for all the support provided to me in the development of my line of research.

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