Synaptic Plasticity In Alzheimer’s Disease: Toward Early Detection Using Non-Invasive Protocols

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ABSTRACT

It has been proposed that Alzheimer’s disease is a synaptic failure associated with subtle memory loss during the early stages of the disorder. If this is the case, it should prove useful to elucidate the mechanisms of synaptic plasticity during early stages of the condition. On the other hand, Long Term Potentiation, one of the best-known mechanisms of synaptic plasticity has been recently confirmed absent in Alzheimer’s disease patients. This link may lead to focus efforts in early detection of synaptic failure and development of preventive approaches aiming to improve synaptic plasticity. Here we review some new evidence in the study of cortical plasticity in humans that could be applied to the early detection of the disorder.

Keywords. Alzheimer’s Disease, Long Term Potentiation, Synaptic Failure, Synaptic Plasticity, Event Related Potentials.

RESUMEN

Ha sido propuesto que la enfermedad de Alzheimer es un fallo en el nivel sináptico asociado con leves cambios en la capacidad mnemónica durante las fases tempranas de la dolencia. Si esto es cierto, podría ser de utilidad clínica el analizar los mecanismos de plasticidad sináptica durante estos estadios precoces. Por otro lado, la potenciación de larga duración, uno de los mecanismos de plasticidad sináptica mejor estudiados, se halla ausente en pacientes diagnosticados con Alzheimer. En este artículo revisamos sucintamente evidencia proveniente de estudios psicofisiológicos de la plasticidad sináptica en humanos, basados en potenciales evocados, que podrían ser útiles para la detección temprana de este mal.


Citation. Montoya DAC. Synaptic Plasticity In Alzheimer’s Disease: Toward Early Detection Using Non-Invasive Protocols.

Support for this research was provided by grant P20 MD001089 from the National Institution of Health, NCMHD, and Department of Health and Human Services.

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INTRODUCTION

It has been pointed out that Alzheimer’s Disease (AD) may present itself in its early stages as a breakdown in synaptic communication. These synaptic changes may be at the base of very subtle cognitive impairments expressed, first, as an inability to encode new information, progressing afterward to a complete impairment of declarative and non-declarative memory. On the other side, Long Term Potentiation (LTP) has been considered for some time as the primary candidate for a physiological mechanism responsible for memory encoding. Some studies, using Transcranial Magnetic Stimulation (TMS), had recently revealed the absence of synaptic plasticity in Alzheimer’s Disease’s patients. These findings make clear an underlying association between the early stages of Alzheimer’s disease and physiological mechanisms of synaptic plasticity like LTP. Studying the nature of this association may hold important consequences not only for a timely detection of the disorder but also in the available therapeutic choices. With recent advances in non-invasive techniques, it is possible now to detect changes in cortical plasticity that would signal the onset of Alzheimer’s disease and increase the chances of early detection. In this review, we outline recent developments in the study of synaptic plasticity in human cortex and the possibility of using these technologies for the early recognition of AD symptoms.

Alzheimer’s Disease

Alzheimer’s disease (AD) is known as a neurodegenerative disorder that progressively affects limbic, extralimbic, and neocortical structures of the central nervous system (CNS). Hallmarks of the disorder include abnormal processing of amyloid precursor protein (APP), hyperphosphorylation of tau protein, and apoptotic-like cell death. These molecular features are also accompanied by deficiencies in several neurotransmitter systems, including acetylcholine, serotonin, and norepinephrine, which contributes to a heterogeneous set of symptoms including progressive memory impairment, visuospatial decline, aphasia, and loss of executive function. Other cognitive and behavioral impairments, include depression, delusions, hallucinations, anxiety, sexual disinhibition and aggression, among others. Early studies pointed at the association between synaptic loss and cognitive functioning decline in AD patients (See reference 7 for a review).

Epidemiological data recently extracted from Latin American countries (including Cuba, Dominican Republic, Peru, Mexico and Venezuela) indicates that the prevalence of dementia according to two criteria (10/66 and DSM-IV dementia) is strongly age-dependent, increasing exponentially in people over 80 years old. The most important finding of this study, however, is that prevalence of DSM-IV dementia type in urban areas of Latin America are very similar to data obtained in Europe, approaching sometimes 10% of the population. This is accompanied by figures indicating that the prevalence of Alzheimer’s disease worldwide will quadruple by 2050 from 26.6 million in 2006. This means that 1 in 85 persons worldwide suffer the disorder, but in Latin America, the problem may be compounded by a scarcity of available information to patients and families, which results in an inadequate search, or lack thereof, of medical help. Cost estimation for dementia patient care in developing countries is currently around US$ 73 billion each year, expenses that are only to increase in the future.

Long Term Potentiation

Long Term Potentiation is one of the most important mechanisms considered as a physiological correlate of learning and memory. LTP is defined as a long-lasting enhancement in communication between two neurons that results from high frequency trains of electrical stimulation, called tetani. LTP is a useful index of synaptic plasticity and can be established by recording excitatory post-synaptic potentials (EPSP) directly from brain tissue of animals (see Figure 1). Largely ignored outside the research community, the process was discovered several decades after Donald Hebb’s prediction that the repeated activation of a neuron by a neighboring cell through synaptic communication would lead, eventually, to the enhancement or facilitation of communication between both cells. This phenomenon launched a long history of animal research, but direct evidence for its presence in the human brain is still unverified. However, human tissue obtained from surgical patients displays synaptic plasticity with the same characteristics as the LTP demonstrated in non-human preparations.
Over the decades, it has been established that LTP is endowed with a series of specific features that differentiate it from other plastic mechanisms. These properties make it useful as a neural correlate of memory\textsuperscript{18}. Among one of the most interesting characteristics is its long duration which fulfill a basic requirement for a mechanism of memory encoding\textsuperscript{13}. Surprisingly, some studies show evidence of synaptic changes lasting for a year\textsuperscript{19}. These changes only occur in the pathways receiving high frequency stimulation without affecting neighboring pathways, a property called input-specificity\textsuperscript{20}. Another quality, associativity, means that a weak train of stimulation produces LTP only when is linked with a strong tetanus\textsuperscript{21}.

Previous studies had also demonstrated that LTP can be reversed by activation of the same set of pathways that were tetanized before\textsuperscript{22}. LTP can also be reversed by trains of low frequency stimulation which produce a lasting depression of the response known as “depotentiation”\textsuperscript{23}. At the level of neurotransmitters, LTP is dependent for its induction on the activation of the N-Methyl-D-Aspartate (NMDA) receptor and expressed as an increase in glutamate release\textsuperscript{24}.

LTP is not a single phenomenon, but an event presenting itself in multiple phases, each one sustained by a particular mechanism. These phases have been recently named LTP1, LTP2 and LTP3, based on their persistence.
over time. Each one of these phases is sustained by different molecular and physiological mechanisms. With repeated use of the activated pathways, LTP stabilizes, producing changes in spine morphology, a necessary step to establish the elusive relationship between physiological changes and learning.

A neurophysiologic correlate of the EPSP obtained from animal models is the event related potential (ERP) which can be recorded non-invasively in humans. ERP uses electroencephalographic (EEG) data locked to a particular stimulus and, after averaging these responses, changes in amplitude can be detected (see Figure 2). Like EEG, it has a precise time definition but poor spatial localization, which means that we can follow minute variations in electrical activity over time, but cannot pinpoint accurately the sources of these electrical changes in the brain. Using this technique, however, Teyler and collaborators recently reported that rapidly presented stimulation (“photic tetanus”) could induce LTP in the human visual cortex. This was detected as an increase in the visual evoked potential recorded over the occipital cortex contralateral to the visual stimulus. A similar study, using functional magnetic resonance showed that the hemodynamic responses in the extrastriate visual cortex were significantly increased to checkerboards presented at a low frequency after the administration of the visual tetanus. In addition, event related desynchronization (ERD) of the alpha rhythm, an index of cortical activity, indicated that this photic tetanization can produce an hour-long increase of cellular activity in the occipital lobe. In addition, LTP has also been described in the human auditory cortex as an increase in the N1 (N1 component of the ERP is a negative change at around 100 ms after the stimulus) component of the ERP. The phenomenon described in humans seems to be NMDA dependent and, not surprisingly, it is not present in patients diagnosed with Alzheimer’s disease.

While not all of the known properties of LTP have been tested in humans, these techniques could be successfully applied to the examination of patients with mild cognitive impairment (MCI), to assess synaptic plasticity in the cortex.

![Figure 2](image-url)
Studying the Underlying Relationship Between Synaptic Plasticity and Alzheimer’s Disease

The association between Alzheimer’s disease and synaptic plasticity is currently stronger than ever. Early on, evidence suggested that synaptic functioning is the first target of Alzheimer’s disease. Studies involving the neurochemical analysis of brain tissue established that the synaptic mechanisms mediated by acetylcholine are significantly impaired in Alzheimer patients\textsuperscript{32}. Moreover, the presence of neuritic plaques and neurofibrillary tangles in hippocampal and basal forebrain-neocortical cholinergic pathways plus the associated cell loss in these pathways, completes a general picture of early cellular effects produced by the disorder\textsuperscript{33}. At a physiological level, cortical coherence (\textit{coherence is defined as a quantitative index of synchronization of activity between brain regions}), compared over a one-year period, is irregular (specially in frontal areas) in patients with a dementia of the Alzheimer’s type compared to controls\textsuperscript{34}, which points to synaptic impairments readily detectable with non-invasive methods. Moreover, the role of a soluble Amyloid β oligomer has been recently documented in Alzheimer’s disease\textsuperscript{35}, adding to evidence that this oligomer is capable of inhibiting the development of Long Term Potentiation in vivo\textsuperscript{36, 37}.

We propose that non-invasive techniques can be used to detect early failures of synaptic plasticity. We describe briefly an ABA protocol, based on Clapp et al.\textsuperscript{30}, currently in use in our lab to study auditory plasticity in humans. The stimulus presented to the participant consists in a hundred beep sounds (1000 Hz sound with 50 ms duration), played binaurally through headphones. The protocol is divided in three parts: a) a basal recording phase where the stability of the ERP signal is established for all electrodes. This basal phase is used as a control to compare subsequent changes. b) An induction phase, where Long Term Potentiation is produced. The same sound stimuli presented during the basal phase is utilized for the tetanic stimulation, but this time monaurally (either left or right ear only) at the rate of 13 per second during a period of two minutes. After this high frequency stimulation, the participants seat for five minutes in silence to eliminate any ringing in their ears. c) After fifteen minutes, the same low frequency stimulation used during the basal phase can be applied again, repeating recordings every fifteen minutes for up to an hour. During this phase, after averaging, increases in the N1 component should be detected, which is believed to indicate activity within auditory cortex (see Figure 2). After retanization has been delivered to one auditory pathway, the increase in the N1 component in this pathway, compared with the non-retanized pathway, could last for, at least, an hour, which is an indicator of long term plasticity. This kind of procedure can be readily applied to elderly patients as part of a general cognitive checkup with minimum discomfort and cost for the patient. The study of patients with minimal cognitive impairment (MCI)\textsuperscript{31}, a forerunner of AD, has been proposed as a more profitable heuristic framework, instead of focusing on the late stages of the disorder\textsuperscript{1}.

Consequences for Therapeutic Approach

Once a failure in synaptic communication has been detected, what would be the best strategy to avoid further deterioration? How can synaptic plasticity be enhanced or restored?

There are several suggestions discussed in the literature, including those proposing targeting calcium regulation as a therapeutic line of attack\textsuperscript{38} or, specially useful in developing countries, the use of traditional diets and medicinal plants extracts\textsuperscript{11}, with procholinergic, antioxidant, anti-amyloid and anti-inflammatory effects (see reference 39 for a recent review). Non-pharmacological approaches include the use of cognitive training (\textit{consists on the guided practice of a set of tasks designed to improve specific cognitive function such as memory or attention - see reference 40}); introduction of consistency, structure and visual cues in the patient’s environment and encouragement of physical exercise\textsuperscript{40}. Several pharmacological options exist for the treatment of AD, but they lay out of the scope of the present review.

CONCLUSIONS

Significant progress has been made in the understanding of synaptic plasticity of Alzheimer’s Disease. The loss of synapses during the early stages of AD will eventually lead to an impairment of synaptic plasticity, which could not be sustained when a minimum of...
synapses is not longer available in cortical networks. This is an important element to consider when providing an accurate and timely diagnostic. Epidemiological data indicates that the use of DSM-IV criteria alone have the tendency to underestimate the prevalence of dementia in developing regions. Other criteria may be used in conjunction with DSM-IV principles to improve the chances of early detection. In addition, new technological developments had made possible the use of non-invasive techniques applied to early detection of synaptic failure. We propose that the recently developed approaches described above for the study of synaptic plasticity in humans, and the wealth of information about its mechanisms acquired on more than 30 years of research, can be used for exploratory diagnosis in patients with mild cognitive impairment and thus reduce their chances of developing full blown Alzheimer’s disease.

More parametric studies are clearly required to understand the cellular mechanisms of auditory plasticity registered trough the use of ERP. For example, other components may be altered or enhanced, in addition to N1. Moreover, there is the need to establish a direct relationship between the loss of cortical plasticity and the development of Alzheimer’s symptoms. We also must remember one of the particular limitations of the EEG technique, which is its poor spatial resolution and thus not useful to spot subcortical damage that may not be readily detectable with the ERP method.

To sum up, technology has brought a wealth of new approaches to deal with the early diagnostic and treatment of Alzheimer’s. The application of these new technologies, available as a common neurological diagnostic tool, can only benefit patients by increasing the chances of detecting early plastic failures and preventing or postponing the development of more generalized symptoms.

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