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PERSPECTIVE

The potential for one drug, administered at the earliest preclinical stage, to prevent the subsequent decline of cognition that eventuates in dementia

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Abstract

In the process that eventuates in mild cognitive impairment (MCI) and ultimately in Alzheimer's dementia, the earliest identifiable change is in the function of synapses. If started at that early point in time, when there is subjective but not objective memory loss plus abnormal brain imaging with fluorodeoxyglucose and Pittsburgh compound B, treatment with a single drug directed at synaptic dysfunction might prevent development of cognitive impairment. Each of four drugs, dantrolene, lithium, minocycline, and piracetam, benefits synaptic impairment. This presentation has two sections. In the first, evidence is discussed at length, for abnormality in the axo-spinous synapse as being the earliest change before objective cognitive decline. The second section explains the benefits to synapses provided by the four mentioned drugs. Dantrolene and lithium perhaps have the strongest supporting data for use as single agents: their efficacy should be subjected to clinical trial.

KEYWORDS
dantrolene, drug treatment, dysfunctional synaptic transmission, elderly persons, lithium, preceding loss of cognition, preclinical Alzheimer's dementia, prevention of cognitive loss, prevention of dementia

1 | INTRODUCTION

In a prior article, I suggested that commencing treatment when mild cognitive impairment (MCI) is diagnosed may prevent progression from MCI to Alzheimer's disease (AD).[1] The recommendation was made to use a combination of three or four drugs chosen from among a list of eight (dantrolene, erythropoietin, lithium, memantine, minocycline, piracetam, riluzole, and silymarin). However, because for most medical conditions, treating earlier requires fewer drugs than treating later, in the present essay I argue that administering just one drug may prevent cognitive decline from happening even before it has become MCI. This statement is based upon data that show synaptic dysfunction in persons who have no objective loss of cognition on neuropsychological testing. Those individuals are readily found; they would be further filtered by brain imaging with fluorodeoxyglucose (FDG) and Pittsburgh compound B (PiB) to select those with synaptic hypometabolism and amyloid deposition. That group is at high risk of progressing to MCI, thence to AD.

This review is in two sections. In the first, data are reviewed showing that abnormality in the axo-spinous synapse precedes both cognitive impairment and neuronal loss. The second section explains why erythromycin, memantine, riluzole, and silymarin/silibinin are unsuitable to use in a single-drug regimen, although as previously discussed they have value in a three- or four-drug combination; and details are provided about how dantrolene, lithium, minocycline, and piracetam address synapses. Among the four, dantrolene and lithium seem to

offer the strongest possibility of being able to forestall cognitive impairment if administered as single drugs, and should be evaluated in a clinical trial.

2 | THE EARLIEST PRECLINICAL STAGE, EVEN PRECEDING MCI, HAS REDUCED SYNAPSES BOTH IN NUMBER AND FUNCTION, BUT NORMAL NEURONS

2.1 | The earliest, "preclinical AD" stage

Sperling et al. postulated that AD begins with a long asymptomatic period during which the pathophysiological process is progressing, and that individuals with biomarker evidence of early AD are at increased risk for developing cognitive and behavioral impairment with eventual progression to AD dementia. Those individuals who are cognitively normal but whose brains, at autopsy, show the neuropathology of AD, were labeled by Sperling et al. as having the diagnostic category, "preclinical AD," with two possible stages.[2] Their model was based on that proposed earlier by Jack et al.[3]: the features of stage 1 were asymptomatic cerebral amyloidosis shown on amyloid tracer positron emission tomography (PET) scan, and low cerebrospinal fluid (CSF) amyloid beta ($A\beta)_{1\text{-}42}$; those of stage 2 were cerebral amyloidosis plus neurodegeneration shown on FDG-PET/MRI scan, high CSF tau/p-tau, and cortical thinning/hippocampal atrophy on MRI (Sperling et al.).[2] More recently, a committee of the National Institute on Aging and the Alzheimer's Association, updated the recommendations with a schema that has eight stages and includes the possibility of a PET scan to identify deposition of tau.[4] Here we will use the earlier staging proposal, modified to include in the preclinical stage those with normal cognition, abnormal FDG scan with abnormal PiB scan, because the studies reviewed here were made several years before the most recent proposals, and it is not always possible to categorize subjects with complete accuracy.

2.2 | The published data

Combining shotgun proteomics of the CSF with an exhaustive search of the literature and public databases, Lleó et al. found 22 proteins in CSF that participate in core synaptic processes, and among those they were able to visualize 9 of them at the human synapse by using Array Tomography microscopy.[5] Some are presynaptic (Calsynytenin-1, Neurexin-3A, Syntaxin-1B, Vamp-2), some are postsynaptic (Calsynytenin-1, GluR2, GluR4, Neuroligin-2, Thy-1). In a cross-cohort meta-analysis, 6 of these (Calsyntenin-1, GluR4, Neurexin-2A, Neurexin-3A, Syntaxin-1B, and Thy-1) were reduced 0.8-fold ($P < .05$) in stage-1 preclinical AD. Inspection of fig 2 in Lleó et al.[5] shows the clear separation between preclinical stage 1 and stage 2, such that in stage 1 the levels of CSF synaptic proteins are overall decreased but in stage 2 are increased—possibly reflecting a compensatory mechanism. In brief, in preclinical AD, some synaptic proteins have reduced levels and others are unchanged.

As detailed below, Terry et al. described imaging studies demonstrating decreases in synaptic density in the very earliest stage of preclinical AD.[6] Further, those imaging studies showed a strong correlation between results of cognition tests and mid-frontal synaptic density ($r = 0.76$). Very few autopsy studies are available, so after describing those, we provide the studies that showed abnormal imaging in persons who had either stage 1 or stage 2 preclinical AD.

A report from the Baltimore Longitudinal Study of Aging (BLSA) indicated a total of 3006 subjects, of whom 238 had died, and 211 had undergone autopsy, with a mean age at death of 86.9 years and a mean interval between last evaluation and death of 8.7 months.[7] Baseline evaluations included information on history of cerebrovascular disease, impairment of cognition or behavior due to secondary causes or medical treatments and, after the age of 75 years, annual physical and cognitive assessments. The evaluation included a neuropsychological battery, and informant- and subject-structured interview that was based on the Clinical Dementia Rating (CDR) scale or the Dementia Questionnaire.

O'Brien et al. examined the *post mortem* brains from 8 subjects with preclinical AD and 11 age-matched controls.[7] Relevant to present-day case finding, they estimated preclinical AD subjects as representing approximately 50% of the individuals with preserved cognition beyond 75 years of age who were enrolled in in the BLSA. Using unbiased stereology, they estimated the total number of neurons in the granule cell layer, hilus, CA3-2, CA1, and subiculum and did not observe a significant loss of neurons in CA1 or any of the other subdivisions of the hippocampus in subjects with preclinical AD. However, there were significant decrements in the levels of synaptic proteins, Rab3A, synaptobrevin, and synaptotagmin.

The BLSA is the only report of subjects with preclinical AD that provides data obtained from the same cohort, for both synapses and neurons; the remaining reports inform about either synapses or neurons. Price et al. confirmed that neurons themselves are unaffected: they studied 4 individuals with presymptomatic AD having CDR scores of 0; 4 with MCI having CDR scores of 0/0.5; 5 with MCI having CDR scores of 0.5; and 14 healthy, non-demented controls.[8] Nissl and Bielchovsky stains were applied to slides containing sections from the CA1 area of the hippocampus and entorhinal cortex. Importantly, all slides were coded to the slide readers. In the entorhinal cortex, the number of neurons and tissue volume did not differ between the healthy controls (11.85 million and 99/mm^3, respectively) and those with presymptomatic AD (10.84 million and 102/mm^3, respectively), whereas those with very mild MCI had significantly reduced numbers of neurons and tissue volume. In the hippocampal CA1, the number of neurons and tissue volume also did not differ between the healthy controls (1.17 million and 131/mm^3, respectively) and those with presymptomatic AD (1.04 million and 138/mm^3, respectively) whereas those with very mild MCI had significantly and substantially reduced numbers of neurons and tissue volume (0.63 million and 93/mm^3, respectively). Thus, in presymptomatic AD the neurons are anatomically normal, whereas in early AD they were seen by Hampel et al. as being reduced.[9]

Mufson et al. compared presynaptic proteins (synaptophysin and synapsin-1) and postsynaptic proteins (Debrin, SAP-97, PD-95), in the

hippocampus of persons with low pathology and no cognitive impairment in their neuropsychological test results (roughly corresponding to the preclinical AD stage-1 of Sperling et al.), high pathology and no cognitive impairment (roughly corresponding to preclinical AD stage-2), and amnestic MCI.[10] With a single exception (PSD-95), those with low pathology and no cognitive impairment had levels of both presynaptic and postsynaptic proteins that were significantly higher than in the other two categories. Although there is an uncertain correspondence between the stages of the patients described by Lleó et al. and Mufson et al., the overall results show that there are synaptic changes at preclinical AD stage-1 and that neuronal loss does not account for the synaptic decrease.

Reductions in glucose metabolism of the brain is another technique that reflects either anatomical loss or diminished function (see below) of synapses. Mosconi et al. reported seventy-seven 50- to 80-year-old subjects with normal cognition, who received longitudinal clinical examinations over 6 to 14 years (561 person-years, mean per person 7.3 years); all had a baseline FDG-PET scan.[11] Eight years after baseline, 6 had AD and 19 had MCI. The baseline hippocampal CMRglc (cerebral metabolic rate of glucose consumption) predicted decline from normal to AD with 83% sensitivity and 79% specificity, and from normal to MCI with 74% sensitivity and 70% specificity. Compared to those who remained normal, those who developed AD had baseline hippocampal CMRglc that was 26% reduced ($P = .002$), and those who developed MCI had baseline hippocampal CMRglc that was 15% reduced ($P = .01$). It is important that these effects remained significant after correcting for partial volume effects, because this shows that the early CMRglc reductions in MCI are independent of tissue (ie, mainly neuronal) loss and represent a real reduction of glucose consumption per gram of brain tissue, presumably from synaptic decline.[11] The energy requirement of axo-spinous synapses is discussed in detail by Jang et al., from whom the following is taken.[12] The brain accounts for ≈20% of total body energy consumption. Within the brain, synapses are primary sites of adenosine triphosphate (ATP) synthesis and the synaptic vesicle is one of the main sources of activity-driven metabolic demands. Even brief interruptions of activity-stimulated ATP synthesis can result in severe impairment of synaptic function. Thus, the hypometabolism of the brain, in presymptomatic individuals, shown both above and in the next paragraph, reflects decreased synaptic activity: the evidence for this is further discussed by Attwell and Iadecola[13] and by Pellerin and Magistretti.[14]

Mosconi et al. also confirmed synaptic abnormality in an FDG-PET and MRI study of persons who were asymptomatic carriers of mutant presenilin-1.[15] They were examined an average of 13 years (range was 1 to 27 years) prior to the estimated age at disease onset in their families. The subjects were seven at-risk individuals from three unrelated Italian families, who were enrolled in an ongoing longitudinal clinical/MRI/FDG-PET study. The control subjects, matched by age, sex, and education, were three siblings from the same Italian families but who did not carry the genetic mutations and four healthy subjects derived from the clinical/MRI/FDG-PET database of healthy volunteers. Their data showed that the medial temporal lobe (MTL) is also hypometabolic in presymptomatic familial AD (FAD), and that CMRglc reductions exceed tissue loss in these individuals. They compared CMRglc and volumes in several brain regions, including the hippocampus, entorhinal cortex (EC), posterior cingulate cortex (PCC), parietal and temporal cortices, and the whole brain, between patients with FAD and the age-matched noncarriers. Whereas volume reductions were seen only in the parietal cortex, CMRglc reductions on FDG-PET were observed in every region examined and remained significant even after corrections for MRI-observed regional volumes. Volume-corrected CMRglc reductions ranged from 13% (whole brain) to 21% (PCC), reflecting true reductions of brain glucose use per unit of brain volume. CMRglc was reduced 12% in the hippocampus and 20% in the EC. Overall, presymptomatic FAD patients showed generalized and widespread CMRglc reductions in the same brain regions as those that are typically hypometabolic in AD itself, and these reductions primarily reflect synapse loss rather than neuron loss.[15]

As a cause for the hypometabolism in synapses, the low-density lipoprotein (LDL) receptor LRP1 also attracts attention. Bacskai et al. showed that after LRP1 becomes ligated on neurons, there is calcium influx via *N*-methyl-D-aspartate receptor (NMDAR) channels which (see below in the dantrolene section) causes a synaptic function change.[16] (The critical importance of the calcium influx is discussed below in the section on dantrolene.) May et al. showed that the postsynaptic density protein, PSD-95, can be co-precipitated with LRP1, suggesting a function-dependent interaction of the two proteins.[17]

Another way to show synaptic impairment as the earliest measurable event preceding cognitive decline uses electroencephalography (EEG), because EEG fields provide measures of the modulation of synaptic activity potentials around their background levels.[18] Event-related brain potentials (ERPs) are comprised primarily of summed excitatory and inhibitory postsynaptic potentials, and provide non-invasive measures of synaptic dysfunction underlying cognitive alternations. One such EEG study records event-related brain ERPs while the subject reads pairs of words in which the words in a given pair are linked either appropriately or inappropriately, and the subject responds that a pair is appropriately or inappropriately linked. Responses to word pairs which are appropriately linked elicit a brain potential (labeled as P600) that is distinct from the one (labeled as N400) that contains inappropriately linked words. The P600 effect has consistently been found as correlated with episodic verbal memory and declarative memory. Olichney et al. followed seven "normal" elderly controls, who were most probably in the early stages of preclinical AD at the time of their ERP recordings, having median Mini-Mental State Examination scores of 29 (27–30), and who continued to perform within normal limits on an annually administered, extensive neuropsychological test battery.[19] But in the years after the ERPs these seven cases showed cognitive decline to AD or MCI, and some had AD pathology verified at autopsy. Compared to 12 normal elderly participants, all of whom had remained cognitively normal with longitudinal neuropsychological testing over 9.1 years, the group of seven with preclinical AD had significantly smaller P600 repetition effects than had the 12 normal elderlies (mean amplitude 0.10 vs 3.28 μV). These abnormal P600 effects may reflect the earliest stages of synaptic dysfunction.

Finally, a mouse model provides supporting evidence: in the brain of hAPP-J20 transgenic mice, Talantova et al. noted marked synaptic loss despite minimal neuronal loss.[20]

In brief, many studies have shown that, in the earliest preclinical stage before AD has occurred, there is synaptic loss without neuronal loss. In this regard, Terry et al. reminded their readers that a large cortical neuron may well have hundreds if not thousands of axonal terminals, and while loss of a large portion of those synapses may cause a clinical or physiologic change, the perikaryon will probably survive because it can still receive sufficient maintenance (trophic) factors from its remaining terminals.[6] This is why demonstration of synaptic loss in persons whose cognition has not yet deteriorated offers a therapeutic opportunity to prevent subsequent development of cognitive impairment.

3 | POSSIBLE TREATMENTS TO AMELIORATE THE EARLY PATHOPHYSIOLOGY BEFORE PROGRESSION TO EITHER MCI OR AD

Because, as shown above, synaptic changes occur before cognitive deterioration and precede all others, it is essential that the chosen agent provide the best chance to benefit synaptic function. In deciding which among the eight drugs might be most effective as a single agent, four of them are immediately eliminated. These are erythromycin, because it crosses the blood brain barrier only if used in such a high dose as to cause hematologic complications;[21] riluzole, because it inhibits vascular endothelial growth factor,[22] which might adversely affect the cerebral microcirculation; silymarim/silybin, because a preparation of pharmaceutical grade is unavailable; and memantine, because besides blocking the ion channel of NMDARs it also blocks, to a high degree, an acetylcholine receptor (a7-nAchR).[23] That leaves dantrolene, lithium, minocycline, and piracetam, which are next considered in alphabetical order.

3.1 | How dantrolene benefits synapses

Calcium dynamics are crucial for synaptic functions, so dantrolene, which antagonizes the ryanodine receptors (RyR) and blocks Ca^{2+} release, has potential to be a major player in the preventative treatment of cognitive decline. A brief description is appropriate of the mechanism by which calcium dynamic affects synaptic function. Glutamate, released from activated presynaptic neurons, is bound to the metabotropic glutamate receptors (mGluR) of the astrocytes that are adjacent to the synaptic terminals. This triggers the production of the second messenger, inositol (1,4,5)-trisphosphate (IP3) and release of Ca^{2+} into astrocyte cytoplasm from the endoplasmic reticulum (ER). These calcium elevations propagate via gap junctions into nearby astrocytes, producing intercellular calcium waves. Because of the increased intracellular Ca^{2+} concentration, the astrocytes release gliotransmitters such as glutamate and ATP into the extracellular space and, through them, regulate pre- and postsynaptic neurons. Three points are important to note. First, that a brain-wide network forms via gap-junction channels that link adjacent astrocytes; second, that released Ca^{2+} initiates the entire process; third, that it is an excessive release of Ca^{2+} that causes the neuronal cytotoxicity and neuronal loss that characterize established AD.

Dantrolene benefits synaptic function both by direct action on the NMDAR and by an indirect effect caused by its prevention of release of intracellular calcium. It accomplishes the former by antagonizing the glycine coreceptor at the NMDAR, and the latter by inhibiting RyR at the ER stores. Salinska et al. used MK-801, a noncompetitive antagonist of the NMDAR, to demonstrate that dantrolene blocked the attachment of MK-801 to the NMDAR in a concentration-dependent manner.[24] Glycine is a co-agonist with NMDA at NMDA receptors and is required for channel activation by glutamate or NMDA; Salinska et al. also showed that dantrolene blocks the glycine binding site of the NMDAR. Emptage et al. demonstrated that stimulation of the NMDAR causes calcium release from intracellular stores.[25] Emptage et al. accomplished this by using confocal microscopy to monitor synaptically evoked Ca^{2+} transients in dendritic spines of hippocampal pyramidal cells. They then applied a specific inhibitor of calcium release from intracellular stores, and showed that this greatly reduced the excitatory postsynaptic calcium transition; moreover, this effect was duplicated by ryanodine, a specific blocker of RyR. Dantrolene also blocks the RyR and an earlier report by Lei et al. had shown that depletion of intraneuronal calcium stores by ionomycin reduced the NMDA response by about 50%, and that dantrolene accomplished the same result.[26]

Inhibiting discharge of Ca^{2+} from the ER and reducing calcium release from intracellular stores makes dantrolene an important neuroprotective agent. There are examples of this. Low-frequency stimulation (1 Hz for 15 minutes) of slices of the dentate gyrus from the rat brain induced robust long-term depression (LTD) of baseline, excitatory postsynaptic potentials as well as depotentiation of previously established long-term potentiation (LTP).[27] Dantrolene completely prevented both the LTD and the depotentiation of LTP. Peng et al. used a triple transgenic Alzheimer mouse model, and treated the mice with dantrolene from 2 to 13 months of age measuring learning and memory with the Morris Water Maze.[28] Dantrolene treatment significantly reduced both memory deficits and amyloid plaque load in the hippocampus.

Kelliher et al. showed that in the earliest stage of AD there is increased RyR2 binding in the CA1 area of patients with AD.[29] Similarly, in presymptomatic AD-model mice, that is, prior to histopathology and memory loss, Chakroborty et al. also saw increased expression of RyR2, and heightened Ca^{2+} release.[30]

3.2 | How lithium benefits synapses

Lithium benefits synapses in many ways. It was shown by Kim and Thayer to increase synapse formation between hippocampal neurons in culture.[31] Postsynaptic densities (PSDs) are composed of many proteins, including NMDA receptors. In hippocampal neurons transfected with PSD95-GFP, PSDs were identified microscopically

as fluorescent puncta; by double-labeling the PSD-95 synapses with antibodies to the NR2A and NR2B subunits of the NMDA receptor, Kim and Thayer showed that lithium increased PSD-95 expressing synapses by 69%. Likewise, Green et al. showed significantly more synapses in hippocampal cultures treated with 3 mM lithium, whereas 100 mM glutamate caused the expected excitotoxicity and synapse loss.[32] Kerr et al. pointed to data showing that lithium enhances synaptic transmission via inhibition of both inositol monophosphatase and inositol polyphosphate 1-phosphatase, thus maintaining high levels of IP3.[33] IP3 activates IP3 receptors that induce Ca^{2+} release from IP3-sensitive ER stores, which in turn regulates synaptic plasticity.

Further demonstration of lithium benefitting synapses is provided by studies of LTP and LTD. LTP is a synaptic response enhancement and LTD a synaptic response decrement; they follow brief, high- or low- frequency, respectively, electrical stimulation. In 10 healthy adults, Voytovych et al. tested the effects of a single oral dose of 900 mg of lithium on LTP or LTD, which they induced in the motor cortex by transcranial magnetic stimulation.[34] Lithium switched the induced LTD plasticity to LTP. Son et al. induced LTP in hippocampal slices taken from rats that had been treated with either lithium or saline intraperitoneally for 14 days.[35] In the rats treated with lithium, on day 28 their blood level of lithium was 0.97 mM/mL (therapeutic in humans < 1.2 mM/mL) and on that day there was significantly enhanced LTP in the rats treated with lithium as compared with the saline controls.

Some of these synaptic benefits of lithium are because the AD brain contains increased levels of GSK-3β.[36] Llorens-Martin et al. showed that mice with overexpression of GSK-3β have a marked decrease of PSD-95-expressing synapses.[37] An important action of lithium is inhibition of GSK-3β, with two beneficial consequences for synapses: (1) preventing GSK-3β from phosphorylating and inactivating β-catenin, which can now translocate to the nucleus where it activates transcription of genes involved in synaptogenesis; and (2) Aβ activates GSK-3β, which induces hyperphosphorylation of tau and formation of neurofibrillary tangles, neuronal death, and synaptic loss.

3.3 | How minocycline benefits synapses

Jiang et al. demonstrated that minocycline increased the postsynaptic PSD-95 levels in the CA1 and dentate gyrus.[38] Minocycline also facilitates synaptic function by upregulation of CREB (cAMP responsive element binding protein). Zhao et al. occluded the carotid arteries of rats and then administered minocycline.[39] As compared to controls, the rats given minocycline had improved swimming behavior, increased expression of brain-derived neurotrophic factor, CREB, and phospho-CREB. Phosphorylation of CREB is required for it to become functionally active; minocycline prevents the block to CREB's phosphorylation caused by Aβ.[40] An increased expression of CREB was seen by Huang et al. as enhancing the function of the NMDAR in the nucleus accumbens, as shown by increases of both the duration of the active state of spiny neurons and action potential firings.[41]

Phencyclidine is an antagonist of the NMDAR. Fujita et al. administered either phencyclidine or saline to mice for 10 days then for 2 weeks minocycline, which gave significant improvement to the cognitive defects cause by the phencyclidine.[42]

3.4 | How piracetam benefits synapses

Piracetam shifted the balance of mitochondrial fission or fusion toward fusion, which is more favorable for ATP production, which would indirectly benefit synaptic function because of the energy requirements of synapses.[43] A review indicated favorable effects on neurotransmission and neuroplasticity.[44] Another report showed that the increased neurite length after piracetam treatment was accompanied by increased expression of the synaptic marker GAP43, thus improving neural plasticity.[45]

4 | CONCLUSION

The best chance of preventing AD is when synaptic function becomes impaired, which is long before cognition deteriorates. Each of four drugs, dantrolene, lithium, minocycline, piracetam, benefits some aspects of synaptic dysfunction, and choosing between them is problematic. Arguably, the evidence favors dantrolene and lithium, although minocycline comes close; and the least is for piracetam. Dantrolene and lithium should be tested for safety and efficacy in a clinical trial of duration 3 years, and whose subjects have neuropsychologically determined normal cognition and abnormal brain imaging results from FDG-PET to demonstrate synaptic hypometabolism; positive results from imaging with PiB would increase the risk of future cognitive loss without treatment.

CONFLICT OF INTEREST

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