Time for a Change in the Research Paradigm for Alzheimer's Disease: The Value of a Chaotic Matrix Modeling Approach

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The amyloid cascade hypothesis, based on the genetic data from early onset, familial forms of the disease, has been the dominant model for many years and involves over production and deposition of the beta amyloid protein as causal in the disease process. However, it does not apply very well to the more common, later onset, sporadic form of the disease, where a wider range of factors appear to be involved in disease progression. Over recent years, data illustrating reciprocal interactions between the amyloid precursor protein (APP) and its various metabolites with many factors involved in normal synaptic plasticity have emerged. These feedback relationships have the potential to affect the complex kinase cascades involved in every aspect of neuronal function. Further, data regarding the multiple roles of the presenilins have the potential to allow the over expression and deposition of the amyloid beta protein to be both a cause and consequence of disease progression, with relevance in both sporadic and familial of Alzheimer's disease (AD). Disease progression might be better explained by a chaotic matrix of factors and raises the question again whether AD should be approached as a single entity or as a syndrome, with important consequences for disease identification and treatment.

Introduction

Alzheimer's disease (AD), is a neurodegenerative disease characterized by progressive cognitive impairment with no known cause or treatment. With no unique qualitative marker, AD diagnosis is difficult, requiring both clinical and neuropathological assessments of continuously varying characteristics with great inter-individual heterogeneity both in range and extent of symptoms [1,2]. AD is currently classified by age at onset and genetic status [3]. Sporadic AD, (SAD), is characterized by later age at onset and accounts for ~99% of cases. Familial AD, (FAD), accounting for ~1% of cases, is characterized by early age at onset and a genetic component [3].

Since the proposal of the Amyloid Cascade Hypothesis in 1992 [4], the Alzheimer's research community has been split into two broad groups; those that support the amyloid cascade hypothesis and those that do not [5,6].

The genetic evidence that has been accumulating over the last quarter of a century is interpreted as providing convincing support for the amyloid cascade model [7–9], and it is easy to see why. Various mutations in the APP, and presenilins (PS) in FAD are fully penetrative and lead to an increased expression of the amyloid- β protein, ($A\beta$), and an early onset of dementia [7–10]. Trisomy of chromosome 21 in Down's syndrome leads to an increase in expression of APP and early onset dementia. The only known case of Down's syndrome reaching the usual age at risk and not suffering early onset dementia was found to have a deletion in APP [11]. In addition, the presence of cortical $A\beta$ -containing plaques is a neuropathological diagnostic feature of AD. In summary, the genetic data from these different sources can be interpreted as sharing an increased expression of $A\beta$ and this increased expression and follow on deposition in the brain is linked with cognitive decline. This interpretation of the genetic

evidence is given as evidence for the causal role of $A\beta$ in Alzheimer's type dementia and is widely accepted.

The interpretation above is based on the physical presence of $A\beta$, either as monomers or oligomers. It disregards contributions to cognition from the dynamic, self-organizing nature of the brain at many levels including cellular homeostatic mechanisms involved in synaptic plasticity, the interactions between different cell types in the brain and the organization of neural networks across brain regions. Contributions to disease progression from brain development are also not well accounted for by the amyloid cascade hypothesis.

While animal models for FAD have been developed, based on the amyloid cascade hypothesis, there are no fully convincing animal models of SAD. Rodents do not naturally develop AD-like neuropathology so that any rodent model requires genetic manipulations to achieve this, with unknown consequences for the usefulness of the model itself. The rodent models for FAD may also be confounded by differences in cholesterol metabolism [12].

The metabolic processing of APP by the α -, β - and γ -secretases has been well reviewed [3,7,13,14]. However, the regulation of APP processing and the effects of the different cellular compartments and the metabolic processes in different cell types are not well understood. The flow of metabolic information through APP processing has at least three possible routes: the neuroprotective α -pathway, interactions of the full length APP and the β -pathway. The relative flow through these pathways leads to a dynamic balance between them over time in the cell as a whole. This allows APP to act as a point of balance, integrating biological information from the various factors that regulate APP processing and passing this information on in the form of its metabolites. Anything that increases $A\beta$ by increasing flow through the β pathway has the effect of shifting this balance [15]. The effects of the loss of function in the α - and full length pathways may be as important in disease progression as the increase in $A\beta$.

The presenilins are cofactors involved in many neural processes including amongst others; Notch processing [16], regulation of β -catenin stability in the Wnt pathway [16,17], interactions with the inflammatory pathway [18], and regulation of Ca^{2+} stores in the endoplasmic reticulum [16,19–21]. Any increase in APP processing by PS1 would lead to a reduction in these other processes due to competition, a well-recognized mechanism of metabolic control.

The genetic data can be interpreted as leading not only to increased $A\beta$ but also to loss of the extracellular, neuroprotective fragment released via the α -pathway, (sAPP α), and to a decrease in PS function due to com-

petition. In fact, all the categories of genetic data, including the evidence from Down's syndrome, share alterations in PS function in other pathways and this forms the basis of the presenilin hypothesis [22]. This is significant as the Wnt pathway is seen as neuroprotective and perturbations in Ca^{2+} homeostasis will disrupt mechanisms of synaptic plasticity [23] and contribute to neural excitotoxicity [24,25]. It may be that loss of function in other PS pathways is a major contributor to cognitive impairment and that $A\beta$ deposition is a marker for this. The contributions of PS to other systems allow $A\beta$ to be both a cause and a consequence of disease progression, depending on other contributing factors.

The interactions of PS with other pathways can be seen as a second point of balance in APP processing. Perturbed functions in the various pathways affected by presenilins may contribute substantially to the earlier onset seen in FAD, perhaps in addition to any effects of increased $A\beta$ and loss of sAPP α . The changes associated with PS mutations may be associated with very early perturbations in synaptic processes before any symptoms become apparent [26–28] and may be subtly different depending on the effects of specific PS mutations [29]. The balance in information flow between the different APP processing pathways coupled with the balance between the different pathways involving PS generates a matrix of possible outcomes.

This interpretation of the genetic data, involving regulatory mechanisms and the loss of function in the APP α and the other PS dependent pathways can be expanded by including other factors involved in AD progression, a few of which are summarized in Tables 1–4.

The relationships summarized in Tables 1–4 are in no way comprehensive and important areas such as the immune system [30], second messenger systems e.g., cyclic adenosine monophosphate, (cAMP)/CREB signaling [31] and cyclic guanosine monophosphate, (cGMP) signaling [32], and the involvement of kinase cascades [33] have been omitted due to considerations of space.

Investigations into the roles of APP, its metabolites and PS with other systems involved in synaptic plasticity may use different *in vitro* cell types, e.g., [34,35], various tissue preparations, e.g., [36,37], different *in vivo* models, e.g., [38,39] and different concentrations of $A\beta$ ranging from pico- to milli-molar. It becomes difficult to interpret the experimental findings as APP/PS may behave slightly differently in different cell types and under different conditions. However it is clear that $A\beta$ has physiological roles in the pico- to nano-molar range. Any imbalance in APP/PS signaling is likely to have decoherent effects before $A\beta$ reaches the higher concentrations associated with the amyloid cascade hypothesis.

Table 1 Relationships between APP, its metabolites and selected neurotransmitter systems

Relationship	Reference
Review: the balance between the α - and β -pathways and the effects of A β on the cholinergic system	[49]
Review: neuro-protection associated with nAChRs including interactions with kinase cascades	[50]
Down regulation of the muscarinic M2 and up regulation of M1/M3 mAChRs increases expression of BACE1, (SK-SH-SY5Y cells <i>in vitro</i>)	[34]
Stimulation of α 4 and α 7 nAChRs promotes APP processing through the α -pathway, (SH-SY5Y, SH-SY5Y/APPsw and HEK 293/APPsw)	[35]
Electrical stimulation, M1 mAChR activation and inhibition of M2 mAChRs increases secreted sAPP α (Rat tissue slices)	[36]
Pico molar concentrations of A β modulate synaptic plasticity and memory through actions on α 7nAChRs, (mouse tissue slices)	[37]
Review: modulation of the glutamatergic system by A β including loss of AMPAR and the role of NMDAR in excitotoxicity	[51]
Stimulation of metabotropic glutamate receptor up-regulates secretion of sAPP α (<i>in vivo</i> rat retina)	[38]
Review: NMDA receptor signaling pathways and A β effects on LTP	[52]
sAPP α selectively, reversibly and rapidly suppresses NMDA currents at concentration of 0.011 nM via a mechanism involving cGMP (cultured embryonic rat hippocampal neurons)	[32]
sAPP α is involved in hippocampal synaptic plasticity and memory via tetanus-evoked NMDA receptor-mediated currents, (intrahippocampal infusion in adult rats)	[39]
A β modulates glutamatergic signals involving nAChRs and metabotropic glutamate receptors, (rat forebrain tissue slices)	[53]
A β promotes endocytosis of NMDA receptors in cortical neurons, (mouse cortical neurons <i>in vitro</i>)	[54]
Impaired hippocampal GABAergic synaptic transmission may be a consequence of A β induced reduction in α 7nAChR-containing cells, (<i>in vivo</i> rat)	[55]
A β associated with a reduction in M2mAChR-immunoreactivity and a reduction in GABAergic interneurons containing M2mAChR and an impairment of GABAergic synaptic transmission, (<i>in vivo</i> rat)	[56]

Table 2 Relationships between APP, its metabolites and factors associated with oxidative stress

Relationship	Reference
Review: A β contributes to Ca ²⁺ -dependent oxidative stress by activating an astrocytic NADPH oxidase	[57]
Review: neurotrophic and neurotoxic properties of A β	[58]
Review: reciprocal relationship between A β and oxidative stress	[59]
Review: Control of APP processing by oxidative stress signalling	[60]
Review: oxidative stress caused by A β	[61]
Review: oxidative damage in neurodegenerative disease	[62]
Review: Redox factors in the brain	[63]
A β and NMDA induce ROS from NADPH oxidase and Arachidonic Acid release from cytosolic phospholipase A2 in cortical neurons and their contributions to synaptic plasticity, (cultured embryonic rat cortical neurons)	[64]
A β inhibits the nitric oxide-cGMP-CREB pathway, (hippocampal slices from male mice)	[65]
Memory and amyloid changes are preceded by NO up-regulation in the hippocampus of hypoperfused rats, (<i>in vivo</i> rat)	[66]
A β induced changes in nitric oxide production and mitochondrial activity lead to apoptosis, (<i>in vitro</i> PC12 and HEK cells)	[67]
Oxidative stress activates the γ - and β -secretase cleavages of the β -amyloid precursor protein leading to increased A β , (SK-N-BE neuroblastoma cells and wild-type, PS1/PS2-deficient, APP deficient and JNK-deficient mouse embryonic fibroblasts)	[68]

Interpretations of experimental data with reference to A β neurotoxicity may be misleading where A β has a normal physiological role.

The high affinity of A β for the homodimeric α 7 nicotinic receptor suggests that APP/PS and its metabolites have important roles in regulating acetylcholine signaling. This coupled with effects on *N*-methyl-D-Aspartate, (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, (AMPA) glutamatergic receptors suggests that PS, APP and the various metabo-

lites play a central role in the regulation of synaptic plasticity, Table 1, and that these relationships may be at the heart of disease progression to dementia. Evidence from other areas, such as oxidative stress, Table 2, cholesterol metabolism, Table 3 and Ca²⁺ regulation, Table 4, suggests that there are many reciprocal relationships which feed into the matrix of interactions involved in the tight regulation of synaptic plasticity and that not all regulatory relationships involved in disease progression necessarily include PS, APP and its metabolites.

Table 3 Relationships between APP, its metabolites and cholesterol homeostasis

Relationship	Reference
Review: effects of cholesterol homeostasis on APP processing	[69]
Review: reciprocal relationship between cholesterol and sphingomyelin and APP processing	[70]
Review: oxysterol-mediated LXR activation reduces A β production	[71]
Inhibition of glycosphingolipid synthesis reduces APP and A β , (various human and mouse cell types <i>in vitro</i>)	[72]
Regulation of APP processing: cerebrosterol (24-hydroxycholesterol) up regulates processing of APP via the α -secretase pathway, (human SH-SY5Y cells <i>in vitro</i>)	[73]
ApoE alters APP processing and may be involved in neuronal responses to stress via increased ERK activation and decreased JNK activation, (rat <i>in vivo</i>)	[74]
ApoE ϵ 4 increases A β production, (rat neuroblastoma B103 cells)	[75]
ApoE modulates γ -secretase cleavage of APP, (various cell lines <i>in vitro</i>)	[76]
ApoER2 expression increases A β production and decreases APP endocytosis with consequences for γ -secretase regulation, (various cell types <i>in vitro</i>)	[77]
Loss of γ -secretase function leads to reduced endocytosis of low-density lipoprotein receptor and increased cholesterol synthesis, (Embryonic fibroblasts of wild-type (WT), PS1/PS2 double knock-out (PS dKO) mice and other cell lines <i>in vitro</i>)	[78]
A β modulates ApoE isoform specific receptor binding, (Cultured fibroblasts <i>in vitro</i>)	[79]

Table 4 Relationships between APP, its metabolites and Ca²⁺ homeostasis

Relationship	Reference
Review: Ca ²⁺ homeostasis in neurodegenerative disease	[23]
Review: the balance between α and β pathways with reference to ER function, Ca ²⁺ homeostasis and synaptic plasticity	[80]
Review: oxidative stress with increased A β as a response	[81]
Processing of the Alzheimer amyloid protein precursor by phospholipase 2 involves both protein kinase C and Ca ²⁺ independently (cultured cells <i>in vitro</i>)	[82]
Increased Ca ²⁺ concentration triggers A β _{1–42} production which induces neuronal death, (rat cortical neurons <i>in vitro</i>)	[83]
PS mutations are associated with over filling of calcium stores leading to altered calcium signalling, (fibroblasts isolated from mutant PS1 knockin mice <i>in vitro</i>)	[84]

Using ideas of decoherence[33], a chaotic matrix model of disease progression based on the regulation of biological information flow can be developed (see Figure 1).

It is clear that the balance between the competing pathways in APP coupled with the balance between PS involvement with APP and other systems is a point highly likely to lose coherence in flow of biological information. While all systems are reacting to their environments within biological tolerance, these systems will integrate and information will flow. However, during the ageing process these systems may lose tolerance, perhaps due to oxidative stress and metabolic changes, and this balance may be disrupted. It is of note that oxidative stress, lowered metabolic rate and an involvement of the immune system are commonly reported in both FAD and SAD. In FAD, the balance between the interactions involving PS and APP coupled with PS and other systems is already skewed so that factors associated with aging, such as oxidative stress, may be enough to trigger decoherence earlier.

Decoherence at the level of the synapse may have follow-on effects at the level of neural networks. Analysis of noise in functional magnetic resonance imaging, (fMRI) has shown significant differences between patients with early AD and age-matched controls consistent with the possibility that the electrical activity of the AD brain becomes less dynamic [40]. The results from EEG show loss of functional coupling between brain regions early in disease progression [41–43] suggesting that both normal cognition and loss of cognition may involve a chaotic matrix of factors at many levels of consideration.

The amyloid cascade hypothesis can be approximated to a linear model with a definite start point, (increased A β expression), a progression (the effects of A β species on other neural systems and increased A β deposition in the brain) and a definite end point, (Alzheimer's type dementia). The model predicts clearly that reduction and/or removal of A β is the key to treating the clinical effects of Alzheimer's dementia and finding a cure. With the

Figure 1 Model of disease progression based on decoherence in flow of biological information through the matrix of factors underlying synaptic plasticity.

publishing of the trial showing removal of $\text{A}\beta$ in patients but with no improvement in cognition [44] and mouse studies showing presenilin but not $\text{A}\beta$ dependent cognitive impairment [45–47], the cascade hypothesis has been brought into question.

A complex picture is beginning to emerge where contributions from APP and PS mutations may be far more subtle and disease progression may occur over a longer period than the amyloid cascade model allows for, with disruption of the signaling pathways involved in synaptic plasticity at very early stages of disease progression.

The matrix model not only reflects the complex neuronal environment that contributes to synaptic plasticity, it also has the power to accommodate data from both SAD and FAD via the complex interactions between cell signaling pathways that converge on kinase cascades and Ca^{2+} regulation. It can also explain findings from

population studies where cognitive decline in SAD is associated with a wide range of neuropathological features that may or may not involve $\text{A}\beta$ [48]. The matrix model allows AD to be a syndrome of different disease pathways, perhaps due to different initiating factors, that ultimately converge on the dysregulation of synaptic plasticity and follow-on progressive loss of cognitive function.

Given the potential for various disease pathways, there may not be one treatment that will work in all cases. A challenge here is to investigate possible variations in clinical disease progression in SAD with a view to classification of possible disease subtypes. Early interventions may be possible to stabilize the systems involved in synaptic plasticity, bringing with it the challenge of identifying those cases where decoherence and decoupling are beginning to develop and correctly identifying appropriate interventions. New techniques that are able to

analyze complex chaotic systems and identify relevant factors need to be developed.

The matrix of factors involved both in normal cognition and disease progression is iterative and self-referencing. A disturbance in the behavior of any contributing factor can potentially be both a cause of and a consequence in disease progression. The PS and APP interactions in FAD may be the best starting point we have for teasing apart the complexity of the neurochemistry involved.

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Conflict of Interest

The authors declare no conflict of interest.

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