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# Alzheimer's Disease and Neuronal Network Activity

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The amyloid β-peptide (Aβ) theory of AD has proven invaluable for advancing our understanding of AD, and for the development of many therapeutic strategies including vaccination against Aβ, inhibition of amyloid precursor protein (APP) cleaving enzymes, glutaminyl cyclase inhibitors, and drugs targeting cholesterol synthesis or apoplipoprotein function. The Aβ theory of AD originated from the discovery that Aβ is the main constituent of amyloid plaques in the brains of AD patients, and was subsequently supported by genetic findings that linked gene mutations in the APP and Presenilin (PS) genes to increased Aβ production. In the last decade the Aβ theory of AD subtly shifted its emphasis away from amyloid plaques which, although most likely detrimental to brain tissue (Meyer-Luehrmann et al., 2008), are not necessarily regarded as the root cause of cognitive decline. Rather the emphasis has turned to soluble Aβ oligomers or fibrils which have been shown to have an inhibitory influence on synaptic transmission and can reduce the number of synapses in experimental models (Kamenetz et al., 2003). The debate about which specific form of Aβ transmits these effects is still ongoing. For example, Aβ dimers isolated from brain extracts from AD patients were found to have these inhibitory properties (Shankar et al., 2008), whereas with synthetic peptides Aβ oligomers of at least 100 molecules were needed to exert similar effects (Lauren et al., 2009). While the final word is still out on this matter, the change in focus from amyloid plaques to Aβ oligomers has advanced our knowledge in several ways. Firstly, there is evidence for a possible physiological function for soluble Aβ, serving as a negative feedback mechanism in synaptic transmission that protects neurons from overexcitation. Accordingly, Aβ generation has been shown to increase in depolarized neurons. Secondly, soluble Aβ provides a direct link to synaptic transmission, the basis of all information processing in the brain. Therefore the soluble Aβ theory of AD also provides a rationale for how in early stages of AD neuronal information processing may be affected without neuron loss or significant structural brain damage.

The pathogenesis of AD, however, may be much more complex than a simple increase in levels of Aβ and, indeed, many elderly individuals exhibit extensive Aβ plaque pathology with no major impairment of cognitive function (Forman et al., 2007). While neurofibrillary tangles are better correlated with cognitive impairment, some individuals may also have relatively high numbers of neurofibrillary tangles and yet maintain normal cognitive function. Moreover, recent studies of animal models of AD and tauopathies have shown that cognitive performance can be improved without lessening of Aβ or tau pathology (Halagappa et al., 2007). Aging is the major risk factor for the most common late-onset cases of AD, and so it is not surprising that links have been discerned between the molecular mechanisms of normal aging and AD. Three age-related changes that are relevant to perturbed network activity are: 1) increased oxidative damage to cellular proteins, membranes and nucleic acids (Mattson, 2004;

Markesbery and Lovell, 2007); 2) reduced neurotrophic factor signaling (Zuccato and Cattaneo, 2009); and 3) dysregulation of neuronal calcium homeostasis (Bezprozvanny and Mattson, 2008). Oxidative stress can affect neuronal excitability by inhibiting ion-motive ATPases, modifying ligand- and voltage-gated ion channels and altering neurotransmitter signaling pathways. Neurotrophic factors, particularly BDNF, have been shown to affect network excitability and play pivotal roles in cognitive processes. Aβ, oxidative stress and altered neurotrophic factor signaling can perturb calcium homeostasis and, on the other hand, aberrant calcium signaling can alter APP processing, can promote oxidative stress and can impair neurotrophic signaling. Intuitively, it seems likely that some of the earliest abnormalities that occur in AD are subtle alterations in neurotransmitter and neurotrophic factor signaling associated with increased oxidative stress and perturbed cellular calcium homeostasis.

A next logical step is to move from the level of individual synapses and neuron to a higher level of organization and study how neuronal network function is altered in AD. It is on this aspect that the current issue of *NeuroMolecular Medicine* will focus, discussing some of the more recent exciting findings. As has been pointed out previously (Palop et al., 2006; Mesulam 2000), a sustained alteration of synaptic transmission is likely to elicit compensatory responses in the brain. Some of these compensatory responses may be beneficial and others may be detrimental to cognitive function or neuronal survival and, moreover, the responses may occur in both short- and long-term time periods. Short-term adaptive responses of neuronal network activity are a possible explanation for the remarkable day to day fluctuations typically seen in AD patients (Palop et al., 2006, Palop and Mucke 2009), which can not be explained through structural changes in the brain. In any case the compensatory responses, which can be considered indirect effects of Aβ, are likely to become part of the overall clinical picture in more advanced stages of the disease. A clear understanding of these compensatory responses should help us understand endogenous processes that help the brain cope with increased levels of Aβ and oxidative stress to keep synaptic transmission working despite impaired synaptic drive. Having a closer look at neuronal adaptive responses to aging and increased Aβ levels also will likely help us understand some of the apparent discrepancies that have emerged. For example, despite the inhibitory effect of Aβ on synaptic transmission in slice culture experiments, several mouse models of AD exhibit epileptic seizures, in part before the onset of plaque deposition and memory deficits (LaFerla et al., 1995; Moechars et al., 1999; Kumar-Singh et al., 2000;Lalonde et al., 2005). However, the increased excitability may contribute to cognitive dysfunction because hippocampal epileptiform discharges can also occur without any observable seizure activity in mice (Palop et al., 2007).

Another open question is: how might alterations in neuronal network activity contribute to increased production and/or reduced clearance of Aβ in AD? Aβ production can be increased by neuronal depolarization and intriguingly Aβ deposition is increased in areas of the “default network”, i.e. brain regions that are active in restive state and are silenced during learning and memory tasks (Sperling et al., 2009). Importantly, in patients with minimal cognitive impairment and MCI patients the default network remains active during learning and memory tasks (Sperling et al., 2009).

Exposure of neurons to Aβ peptide in culture and in vivo causes an increased intracellular calcium concentration (Mattson et al., 1992; Kuchibhotla et al., 2008). One possible explanation would be that the primary action of Aβ is inhibition of synaptic transmission and that an adaptive response in neurons then causes an increase in cytosolic calcium, which will then render the neurons more susceptible to epileptic discharges and excitotoxicity. A variation of this hypothesis would be that Aβ primarily inhibits N-methyl D-aspartate (NMDA) receptor mediated currents and that a compensatory increase in AMPA/kainate receptor currents then leads to increased vulnerability to seizures (Moechars, 1999). Of course the reverse may be the case as well, i.e. that the primary action of Aβ is to increase excitability and compensatory

responses then inhibit the strength of synaptic transmission. These points underscore that much more work must be done to establish the sequence of events underlying neuronal network dysfunction in AD, and the role of Aβ in those events.

In this issue of *Neuromolecular Medicine* Lennart Mucke and Jorge Palop discuss the latest developments and insights in the area of neuronal network activity in AD, the molecular mechanism that may underlie altered network activity and how mouse models of AD can be used to unravel the effects that Aβ has at the molecular, synaptic and network level. Andrew Larner considers the clinical side of the issue reviewing the current knowledge about epileptic seizures in AD patients. It has been known for a long time that epileptic seizure frequency is increased in AD patients, but it has until recently been considered to be a late stage epiphenomenon. And while it is unlikely that seizures precede the clinical onset of AD in patients as clearly as in some mice models, more recent studies have shown that seizures in fact can occur fairly early in the course of the disease. A greater knowledge about seizure type and origin may help us understand if and how subclinical seizures can have an impact on cognitive function in AD patients.

While Aβ production seems to be a fairly straightforward process involving two proteases (β- and γ-secretases), APP processing in fact is a quite intricate and complex procedure that can be considered a miniature network that is likely to have multiple sites of feedback regulation. More functions have evolved for most of APP's cleavage products in addition to Aβ including secreted forms of APP (sAPPα and sAPPβ) and intracellular C-terminal domains including AICD (Furukawa et al., 1996; Mattson, 2004). In addition, more substrates have been discovered for APP processing enzymes. Reducing Aβ formation through inhibition of APP processing enzymes therefore is likely to affect non-APP substrate cleaving and possibly also inhibit the functions of non-Aβ fragments of APP, making the search for suitable yet potent β- and γ-secretase inhibitors a formidable task. The Vivian Chow and Philip Wong together with the authors of this article will review this aspect of AD.

Stress can be considered a modulator of brain network activity and Sarah Rothman and Mark Mattson will review the evidence that suggests a link between stress and AD.

Mouse models of AD replicate only specific aspects of the disease which in most cases is increased Aβ production and deposition in plaques. They lack neurofibrillary tangles unless a mutation in the microtubule associated protein tau is introduced in addition to APP and PS1 mutations, as in the so-called triple transgenic AD mice (Oddo et al., 2003a). While these triple transgenic mice have proven very useful in addressing some of the basic questions regarding Aβ and tau pathologies (Oddo et al., 2003b., 2006, 2007, 2008a., 2008b) one must keep in mind that in sporadic AD no mutations are observed in the tau gene and tau mutations alone will cause neurofibrillary tangles without plaques. So it remains to be seen whether the same interactions between Aβ and tau that are observed in the triple transgenic mice actually take place in sporadic AD patients. Similarly, it has to be taken into account that the PS1 mutations used for most mouse models of AD increase neuronal cytosolic calcium via release from the endoplasmic reticulum (Guo et al., 1997; Chan et al., 2000; Tu et al., 2006, Nelson et al., 2007, Cheung et al., 2008), causing severe calcium dysregulation (Lopez et al., 2008) that is possibly independent of the γ-secretase activity of PS1. This is another aspect of AD mouse models that is unlikely to appear in this form in sporadic AD. Also aging is the single most powerful risk factor for developing AD. However, aging induced changes in the human brain are somewhat different (and arguably more severe) from those observed in mice (Loerch et al., 2008). Accordingly, studying AD mouse models can only provide an addition but no substitute for studying AD patients. In addition to neuropathological studies with brain tissue the emergence of functional MRI and advanced software analysis now allows us to study neuronal network interactions in human brains. Reisa Sperling will introduce us to this technique and

review some of the findings from AD patients. These studies are likely to provide us with clues about the effect of AD on neuronal network activity and how network activity in AD patients may shape the disease. Ultimately the challenge will be to reconcile and integrate the findings from basic research at single synapse level with functional MRI and clinical data. We hope that this issue of *NeuroMolecular Medicine* provides some food for thought for our readers towards this goal.

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