Chew the Fat—Lipids, NMDARs Mediate Neuronal Response to Aβ

22 November 2009. If papers on Aβ mechanism are an Alzforum reporter’s bread and butter, this week offers a triple feast. Broadly speaking, the first two papers suggest ways to dampen Aβ toxicity by targeting underlying signaling pathways. In one study, Canadian scientists have used a lipidomics approach to identify specific phosphocholine metabolites that are elevated in AD. They show that accumulation of these lipids leads to tau hyperphosphorylation, and that blocking signaling downstream of the metabolites can dial down Aβ toxicity. The second study comes from researchers in Ireland who find that selective GluN2B glutamate receptor subunit antagonists can temper Aβ’s disruption of synaptic plasticity. And finally, German scientists have created an ex vivo AD model that recapitulates key pathological features induced not only by Aβ, but also its partner in crime, tau. In this system, tau-induced neuronal death relies on NMDA receptor activation via Aβ. When it comes to Aβ toxicity, these three papers leave plenty to digest.

Abnormal buildup of Aβ peptides in the brain is a prime pathological feature of AD. What’s less of a no-brainer, though, is why some people with heads full of amyloid readily succumb to disease while others resist it. Genetic variations that translate into skewed protein signaling may factor into this conundrum. But those differences are hard-wired, said Steffany Bennett of the University of Ottawa in Ontario, Canada. “Our team is very interested in seeing how the microenvironment impacts on how neurons are sensitive or resistant to Aβ,” she told ARF. Lipidomics, a relative newcomer in the broad-scale profiling world, combines mass spectrometry with other techniques to assess lipid changes as a readout for environmental effects. “The idea is, What changes in lipid species could render the cells or individuals resistant to the disease?” Bennett said.

Her current work, published online this week in PNAS Early Edition, builds on a recent lipidomics analysis by Lemart Mucke and colleagues at the University of California, San Francisco. That study identified the arachidonic acid cascade as a key player in AD pathogenesis, and fingered aberrant activation of cytosolic phospholipase A2 (cPLA2) as the root cause of the changes seen in that pathway (Sanchez-Mejia et al., 2008 and ARF related news story). Whereas Mucke’s team focused on the released arachidonic acid and its metabolites, Bennett and colleagues profiled what was left in the membrane once arachidonic acid was released.

First author Scott Ryan and colleagues extracted glycerophospholipids from posterior/entorhinal cortex of postmortem control and AD brain tissue. They expected to see widespread metabolic disturbances stemming from cPLA2 hyperactivity, but instead found elevations in a particular family of lipids, i.e., alkylacylglycerophospholines, or PAFs (short for “platelet activating factors” though they are found in the brain). The AD brain samples had higher intraneuronal levels of PAF isoforms with 16 carbon saturated (16:0) fatty acid (palmitic acid) side chains at the first position on the glycerol backbone. The finding suggests that phospholipase is particular about what lipids it attacks in the AD brain. “cPLA2 does not just generally hydrolyze membrane glycerophospholipids to generate excess arachidonic acid, but in fact seems to target specific lipids and in doing so disrupts networks of specific lipid messengers,” Bennett explained via e-mail. Her team showed this not only in postmortem AD brain tissue, but also in symptomatic AD transgenic mice (TgCRND8), and in human neurons exposed to soluble, oligomeric Aβ42. Furthermore, the researchers took aim at the PAF metabolic changes by promoting hydrolysis of the accumulated PAF isoform or inhibiting PAF 16:0 signaling. In their hands, these manipulations protected neurons from Aβ-induced toxicity and prevented tau pathology.

Considering this study and newer lipidomics analyses of other phosphocholine networks that her lab hopes to publish soon, Bennett told ARF they seem to be “finding lipid species that are not only damaging, but in animals and people who appear to be resistant [to Aβ pathology], species that are protective.” These data suggest it may be possible to fine-tune lipid networks to help neurons deal with accumulating Aβ. This could tie in with epidemiological observations that some dietary fatty acids, including docosahexanoic acid, may be protective against AD (see ARF related news story).
Another study suggesting therapeutic tweaks to improve neuronal response to Aβ comes from Michael Rowan and colleagues at Trinity College Dublin in Ireland. His team set out to address an apparent paradox—namely, that NMDA receptor activation is needed for long-term potentiation, and yet the AD drug memantine, which blocks NMDA receptors, partly prevents Aβ-induced inhibition of this synaptic strengthening process. “We wondered if subtype-selective NMDA receptor blockers might throw some light on this question,” Rowan wrote in an e-mail to ARF. His study also appears online in this week’s PNAS Early Edition.

To test their hunch, first author Neng-Wei Hu and colleagues injected soluble Aβ into the lateral cerebral ventricle of anaesthetized rats and tested if co-injection of NMDA receptor subtype antagonists could protect against Aβ-induced LTP inhibition. Of three NMDAR compounds initially tested, only the one selective for GluN2B (>200-fold preference for GluN2B subunits) prevented the effects of Aβ at doses that did not affect control LTP. A more specific GluN2B antagonist (>3,000-fold selectivity over other GluN2 subunits), Ro 25-6981, was able to prevent the Aβ effects when offered systemically. Systemic treatment with similar doses of memantine could only restore LTP to levels two- to threefold lower than those achieved with Ro 25-6981. These researchers previously found that TNFα, a proinflammatory cytokine, mediates Aβ toxicity (Wang et al., 2005), and here they report that the cytokine inhibited LTP in a GluN2B-dependent manner and that the Aβ-induced LTP inhibition required TNFα activity.

Taken together, the data suggest that GluN2B selective antagonists are “potentially a major advance on memantine and lend support to proposed clinical trials of (these compounds) and possibly anti-TNFα agents in the treatment of cognitive deficits of AD,” Rowan noted. Perispiral treatment with an anti-TNFα antibody has been reported to produce quick cognitive improvement in a small, open-label trial (Tobinick and Gross, 2008), but these findings are controversial and have yet to be reproduced in a randomized, controlled trial (see ARF related news story and Live Discussion).

A third study affords a different sort of look at how neurons respond to Aβ. Writing in the November 18 Journal of Neuroscience, Christian Tackenberg and Roland Brandt at the University of Osnabrück, Germany, have developed an ex vivo system that demonstrates what many AD animal models cannot—Aβ-induced spine changes and tau-dependent cell death. (Most AD models have the former but not the latter, even though it’s the neurodegeneration that more closely correlates with disease progression.)

To recapitulate these two key AD pathologies, the researchers prepared hippocampal slice cultures from AD transgenic mice (SDL) expressing triply mutated human amyloid precursor protein, and brought in fluorescent-tagged wild-type or mutant tau using virus-mediated gene transfer. “With this model, it was possible to look at signal transduction mechanisms involved in both (Aβ and tau) pathways, to see whether they are overlapping or whether they are different,” Brandt told ARF.

By introducing different tau constructs onto APP and non-APP backgrounds, and assessing spine changes and cell death in the presence or absence of inhibitors to various signaling pathways, the researchers could quickly determine which components are required for Aβ or tau pathology. “I think we are the first to show that the tau pathology is dependent on NMDAR activation via Aβ,” Brandt said. Furthermore, the researchers found that some tau mutants behaved differently than wild-type tau in the ex vivo system. Several tau mutations are known to cause tau aggregation and neurodegeneration in frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), but the new data call into question the validity of using these mutations to model AD. For example, R406W tau shows increased toxicity in the presence of Aβ, but another FTDP-17 tau mutant (P301L) does not. (The P301L mutation is present in the 3xTg mouse model of AD that exhibits both plaques and tangles; see ARF related news story.) Furthermore, blocking NMDAR activity tones down the toxicity of both wild-type and R406W tau, while GSK-3β inhibition only protects against the toxic effects of the former. All told, the data suggest that “Aβ-induced spine pathology and tau-dependent neurodegeneration are mediated by divergent pathways downstream of NMDAR activation,” the authors write.

The ex vivo model should be useful for screening potential AD therapeutics. “The system is more accessible than a mouse would be,” Brandt said. “You can simply add the drug, and in a relatively short time, determine its effect on two pathologies.” His lab is currently testing compounds from AstraZeneca, and from Probiodrug in Halle, Germany. The group is also using the new system to
delve further into mechanisms. “We really want to understand what happens downstream (of the two pathologies),” Brandt said. “What is the mechanism that actually kills the neurons? What comes after the tau? It is now possible to pinpoint the changes that happen and identify the mechanisms involved.” —Esther Landhuis.

References:
