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Discussion

Alzheimer Research Forum Live Discussion: Is Alzheimer's a Type 3 Diabetes?[1]

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June Kinoshita: I am June Kinoshita of the Alzforum. Suzanne, perhaps we can start by having you quickly state your main concepts of the articles appearing in the Journal of Alzheimer's Disease [1,2].

Suzanne de la Monte: Our main concepts are that Alzheimer disease (AD) may represent a neuroendocrine disease in which substantial abnormalities arise due to impairments in insulin and insulin-like growth factor (IGF) signaling. Insulin and IGF are critical for neuronal survival, and what we have found is that the levels of the polypeptide genes and their receptors are substantially reduced, preventing neurons from responding to the trophic influences. We believe these effects may be critical to neuronal function and neurodegeneration.

Nancy Emerson: Excellent reviews of the literature and the extant theories relating diabetes, insulin resistance, and AD. I am still absorbing the details of the two articles [1,2]. My primary interest now is in designing, with Tufts, a nutritional intervention for early-stage patients. I noted that you suggest treatment with insulin might be helpful. What are your thoughts about dietary interventions designed to increase insulin sensitivity or reduce insulin resistance?

Suzanne de la Monte: One of the interesting findings was that insulin is made in the brain. Actually, we have known this for some time, and it fits with our knowledge that all other pancreatic polypeptides are made in the central nervous system (CNS). I also believe that diet may influence this story. For example, vanadate inhibits tyrosine phosphatases, so vanadium, which is present in shellfish and lobster, may be a great supplement.

June Kinoshita: What is different about CNS insulin signaling pathways versus peripheral pathways?

Suzanne de la Monte: CNS and peripheral insulin signaling work the same way, but we think the peripheral and CNS pathways are separated – that is good. It may explain why diabetics with acute and chronic metabolic impairments are cognitively okay for the most part.

Nancy Emerson: So how do we encourage increased insulin production in the brain? And are levels of endogenous insulin as difficult to influence as brain cholesterol, as opposed to peripheral cholesterol? This is immensely complex, biochemically, as you showed in your papers.

[1] Note: The transcript has been edited for clarity and accuracy.

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Suzanne de la Monte: Our latest work shows increased brain cholesterol in AD. I do not know if this is caused by abnormalities in local insulin, but it may interfere with signaling. Maybe insulin sensitizers would be useful, for example, peroxisome proliferator activated receptor (PPAR) agonists.

Nancy Emerson: Other studies suggest the importance of docosahexaenoic acid (DHA) (omega-3 fatty acid) deficiencies and supplementation as important for AD pathology/treatment, at least in transgenic mice. What are your thoughts on how polyunsaturated fatty acids (PUFAs) in brain cell membrane relate to action of insulin and IGF-1? You did show how the insulin/glucose metabolic impairments can be related to oxidative stress or extra vulnerability to oxidative stress.

Shaharyar Khan: Suzanne, why would the brain be reducing its insulin production at the same time as it is also reducing its insulin sensitivity by downregulation of insulin receptor signaling – if I understand the observations correctly?

Suzanne de la Monte: Maybe the cells that make the insulin also have receptors, or loss of insulin causes insulin-dependent neurons to die. We cannot tell if individual neurons have lost receptors or insulin-receptor-bearing cells have died.

Craig Atwood: Is it because there needs to be a balance between overall insulin signaling; if the receptor is decreased, then you need less insulin?

Suzanne de la Monte: Not sure, Craig. If we deplete insulin receptors from the brain, we get neurodegeneration.

Craig Atwood: Yes, but if the insulin signaling remained high, you might get more degeneration.

Shaharyar Khan: Through desensitization?

Suzanne de la Monte: As a follow-up to my last comment, ethanol inhibits insulin receptor responsiveness and the neurons die, but the receptor number does not decline.

Shaharyar Khan: Through what mechanism?

Suzanne de la Monte: We have data that I hope will come out soon showing reduced insulin and IGF receptor responsiveness in AD, and associated loss of the receptors. I would think reduced growth factors would increase sensitivity temporarily, at least.

Marcos Marques: What is your hypothesis for the etiology of reduced neuronal insulin, IGF-1, and insulin receptor in AD cases?

Suzanne de la Monte: Marcos, that is a great question and I am looking at regular diabetes to try to understand why type 2 diabetes mellitus (DM-2) increases with aging. My guess is that there will be susceptibility polymorphisms in the brain.

Cyrus Raji: A growing number of papers over the past few years suggest that type 2 diabetics are at greater risk for getting AD due to impaired insulin degrading enzyme (IDE) function with respect to amyloid degradation. To Dr. de la Monte, how do you synthesize this knowledge with your own proposed mechanisms for the role of glucose and insulin in AD?

Craig Atwood: DM-2 is primarily driven by obesity, no?

Cyrus Raji: Correct.

Suzanne de la Monte: DM-2 is insulin resistance, and some individuals are not obese at all; Asians, in particular, have this problem. A growing number of papers on this topic are very confusing. I am doing a systematic study of DM-2 and brain pathology. As far as I can tell, there is no increase [in DM-2] in classical AD. Instead, there is substantial microvascular disease with white matter ischemia, which we already know contributes to AD. If there were IDE abnormalities, that would be interesting. We have not found them, yet.

Craig Atwood: I agree that you do not have to be obese, but at least have more fuel than the body can handle.

Cyrus Raji: As far as I know, only one study has examined AD pathology in postmortem diabetic brains. This was done at Albert Einstein College of Medicine in 1997 [3] and found nothing, but it was spotty because it included DM-1 and DM-2 samples. Does anyone know of any new work done in this area? My Medline searches have turned up nothing.

Suzanne de la Monte: The postmortem DM studies are horrible because they require medical input to clar-

ify whether or not the original diagnoses were correct. Systematic study is now needed. We are trying, but other sites need to get involved.

June Kinoshita: Suzanne, are you talking about genetic studies looking at IDE?

Suzanne de la Monte: One other comment about IDE is that it would not explain mRNA problems.

June Kinoshita: Can you elaborate?

Suzanne de la Monte: We searched for abnormalities in IDE expression in AD brains and did not find them. IDE should degrade insulin polypeptide, and as far as I know, it has no impact on insulin gene expression. The mRNA levels for insulin are reduced [in AD brain]. If anything, degradation of a needed growth factor would lead to compensatory increased, not reduced, gene expression.

Shaharyar Khan: Suzanne, I am interested in the mitochondrial role in AD and diabetes. What, would you hypothesize would be the consequence of perturbed insulin signaling on mitochondrial function?

Suzanne de la Monte: Mitochondrial function is certainly abnormal in both DM-2 and AD. It may be linked to insulin because insulin regulates mitochondrial function and oxidative metabolism.

Marcos Marques: Do you think infection or oxidative stress caused by a high carbohydrate diet may trigger an "immune" response causing all the insulin impairment in the brain?

Suzanne de la Monte: Marcos, I think stress can push the AD cascade over the line. I do not know about carbohydrate-rich diets, except they are possibly related to DM-2 and microvascular disease.

June Kinoshita: Suzanne, by stress, do you mean oxidative?

Suzanne de la Monte: June, yes, ischemia, anesthesia, hypoxia. I am not sure about life stresses; there is no epidemiological proof for a connection with AD or dementia.

Shaharyar Khan: Would you hypothesize that perturbed insulin signaling is capable of initiating the oxidative stress seen in AD? Do you see oxidative stress in, say, the insulin receptor substrate 2 (IRS2) knockout (KO) mice?

Suzanne de la Monte: Shaharyar, I think that is certainly one pathway that is operative. However, we are looking into the role of oxidative stress on insulin signaling. This could bring in the role of Aβ. IRS2 KO mice have increased glycogen synthase kinase-3beta (GSK3beta) activity on the link between GSK3beta and the microtubule-binding protein tau, the major component of the neurofibrillary tangles found in AD brain. That would push the oxidative stress cascade.

Marcos Marques: What about stress mechanisms such as infection? Could they cause an autoimmune response that would deregulate insulin/receptors and so on in AD brain?

Suzanne de la Monte: Marcos, that is interesting. I do not know the answer. What is your sense?

Shaharyar Khan: Many in the Aβ camp postulate that Aβ fails to be sufficiently degraded by IDE because IDE is possibly occupied by increased insulin, but you are finding that CNS insulin is actually down, meaning that if IDE levels were invariant, more amyloid ought to be degraded.

Suzanne de la Monte: Shaharyar, that is correct. I think we need to know more about IDE and its substrates. I still have not given up because it may function differently in the presence or absence of Abeta.

Shaharyar Khan: Sure. Would you expect perturbed insulin signaling in familial AD (FAD) cases as you have seen in sporadic?

Craig Atwood: I would not expect to see differences in insulin signaling in FAD.

June Kinoshita: Suzanne, Columbia University is embarking on a big epidemiological study of diabetes and AD. Over time, they will have individuals who come to autopsy.

Suzanne de la Monte: I think familial AD as well as Down syndrome should have abnormalities in insulin signaling. Did you know there was an association between Down syndrome and DM? I cannot find great references, but apparently there is.

Craig Atwood: Why?

Suzanne de la Monte: Why not, Craig? The familial genes are not sufficient to trigger AD because the patients are not born with AD; they must age or have something else happen.

Craig Atwood: But it could be any age-related hormonal change. Does insulin signaling change that much up to 40 years of age? That is, there are individuals with FAD before 40–45, but their insulin signaling is likely not changed.

Suzanne de la Monte: Insulin signaling certainly goes down with aging of the brain. I am not sure about prior to 40. That would be a good thing to check.

Shaharyar Khan: What would you suppose is the locus of the interaction for presenilins (PS), amyloid-β protein precursor (AβPP), insulin, and insulin receptor (IR) – maybe at the plasma membrane?

Suzanne de la Monte: AβPP and IR – plasma membrane. I am not sure about PS.

Cyrus Raji: Dr. de la Monte, you said, I think, that you did not find altered IDE levels in the brains you looked at, but at least one study [4] suggests that hippocampal levels of IDE are reduced, although only in apolipoprotein E4 positive AD cases.

Nancy Emerson: A recent study, not published yet, at Veteran Affairs Medical Center, Bedford, with Richard Fine, J. Wells, and Pat Einenhauer, found abnormalities in IDE in epithelial (vascular) cells in human AD brain tissue samples.

Suzanne de la Monte: The IDE story needs sorting and more attention; that is clear.

Cyrus Raji: I agree with what Dr. de la Monte has said, and I think it is also important to be able to tease out the molecular mechanisms of vascular dementia versus AD in DM-2 and where the two may intersect, since this is a major point of confusion.

Marcos Marques: I believe it is quite possible we are dealing with an autoimmune disease. There is intense debate about infectious agents associated with AD. As for dietary impact, Lane and Farlow [5] proposed that a Western diet may tip the balance toward fatty acid proinflammatory eicosanoids. They also observed that a high carbohydrate diet may increase insulin levels and insulin growth factor signaling, leading to a decrease in lipoprotein lipase activities that may trigger inefficient essential fatty acids to neurons that would inhibit glucose transport.

June Kinoshita: It would be worth looking at markers of insulin signaling in families with FAD mutations.

Suzanne de la Monte: We do not know that. We need to look at the impact of the genetic factors as an A+B story (two or three hits in the genome). How would we do this if the impairments are in CNS and possibly not affecting the periphery? Cerebrospinal fluid (CSF) could certainly help and could provide interesting information. positron emission tomography (PET) scans to measure glucose utilization would also help.

June Kinoshita: Suzanne, what is on your wish list for how to push this area of inquiry forward? Access to certain reagents? Collaborations with people doing big DM-2 studies, and so on?

Suzanne de la Monte: I think access to reagents and collaborations with other human investigators regarding DM and having brain tissue available would be great. We will be seeking NIH funding to do this type of work.

June Kinoshita: Suzanne, what existing drugs, nutraceuticals, and so on, would be interesting to study regarding effects on insulin signaling pathways and penetration across the blood-brain barrier?

Suzanne de la Monte: I would like to try insulin sensitizers directly in the CNS, and also agents that reduce membrane cholesterol in the CNS to improve ligand binding.

Marcos Marques: Did you study or plan to study mild cognitive impairment (MCI) cases? Or do you have any preliminary data on them?

Suzanne de la Monte: We have data on early AD – insulin abnormalities occur very early in disease. We have a paper in revision showing that Braak stages I-II have impaired insulin signaling. Those patients have MCI.

June Kinoshita: Where does the impairment lie?

Suzanne de la Monte: The impairment exists in the hippocampus, hypothalamus, and frontal lobe. I think the basic problem stems from basal forebrain and corticolimbic structures. This happens to be the distribution of insulin gene expression.

Nancy Emerson: Marilyn Albert says there seem to be two main types of MCI: those who progress to develop AD and those who remain abnormal but stable, cognitively. It would be interesting if it is the insulin signaling impairment that predicts progression. Have you explored this possibility? Right now the MCI folks do not know how to predict which will progress and which will not, and, of course, knowing that is key to whether to intervene or not, especially if the treatment is non-benign.

June Kinoshita: That is an interesting idea, Nancy.

Suzanne de la Monte: MCI of the type that goes on [to develop AD] (like our postmortem cases) I would predict to have abnormalities in insulin signaling. Perhaps looking for this could help sort the problem clinically.

Marcos Marques: Interesting. In MCI cases, is the [insulin signaling] impairment worse or better than in AD? I am trying to make a longitudinal picture of this impairment. Would it be possible that this is a consequence of an exhaustion brain response to insulin?

June Kinoshita: What about a list of potential biomarkers related to defects in CNS insulin signaling? The Alzheimer Disease Neuroimaging Initiative (ADNI) study is going to be collecting biomarker data, and there are other collaborations looking at antecedent biomarkers, so these are important opportunities to include some novel candidate biomarkers.

Nancy Emerson: One key challenge that Suzanne has pointed out repeatedly is the likely heterogeneity of the human cases we are looking at, and sometimes the confusion over the diagnoses, as well. That is why working with a larger AD center, with very careful clinical and postmortem diagnoses, will be important going forward for you, Suzanne.

June Kinoshita: I am afraid we are at the end of our hour. Thanks to all of today's participants.

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