

Discussion

Alzheimer Research Forum Live Discussion: Insulin Resistance: A Common Axis Linking Alzheimer's, Depression, and Metabolism?¹

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June Kinoshita: Welcome, Dr. Rasgon, and thank you for inspiring this discussion. Could we all briefly describe our interest in today's topic? That will provide a frame of reference. I am the editor of the Alzforum and am interested in ideas that might help to pull together a bigger picture of what is going on in Alzheimer disease (AD).

Patricia Heyn: My father supposedly had AD. He demonstrated many characteristics regarding his desire to communicate that were not addressed through the medical community. I have developed a great interest in facilitating communication in this population.

Anne Fagan: I am a researcher interested in AD biomarkers and risk factors.

Mike Marlatt: I have been doing Alzheimer disease research for a few years, especially in the topics of tau phosphorylation and oxidative stress.

David Ewbank: I am a demographer affiliated with Penn's Alzheimer's Center. I have done some work on AD and a bit on depression. I am now starting a project

on alternatives to factor analysis for defining insulin resistance syndrome (IRS). I will be using an alternative to standard meta-analysis that I developed for studying Apolipoprotein E (ApoE), AD, and mortality. Perhaps I can start with a question. There is a huge literature correlating ApoE genotype and anything else you can think of. However, I was struck with your comments on how ApoE might come into the IRS-depression link. I wonder if you could comment on that.

Natalie Rasgon: There is growing data on insulin effects in the central nervous system (CNS). In particular, Suzanne Craft's work on effects of insulin in AD patients suggests that central effects of insulin are selective for memory; for example, insulin effects in hippocampus are of greatest interest with regard to part of AD pathophysiology.

Anne Fagan: What do you think is the biggest issue in the AD/insulin connection? Prevention, mechanisms, risk assessment, etc.?

Natalie Rasgon: In addition, insulin resistance (IR) is clearly driven by various neuroendocrine permutations involved in pathophysiology of depression, and that gives me an idea that IR may link depressive disorders and AD.

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

June Kinoshita: How would ApoE genotype enter into these links?

Natalie Rasgon: In Craft's work, ApoE modulated IR in AD patients. For example, those with $\epsilon 4$ allele had lower glucose disposal than those without.

Michael Marlatt: Getting back to the insulin treatment, are you expecting to increase neurotransmitter levels in the patients?

Natalie Rasgon: We had not thought of that interaction in terms of quantitative analysis, but it is plausible, I am more interested in behavioral and neuroimaging markers of the interaction.

Anne Fagan: What sort of neuroimaging markers would you like to look at?

June Kinoshita: Anne, what do you think about expanding AD biomarker studies to include markers for IR?

Anne Fagan: June, absolutely. It is certainly worth exploring. I will have to do a bit of literature research to see what sort of analyses might be good to look at as a first pass.

Patricia Heyn: I once read that lesions in the hippocampus in AD caused word retrieval difficulties, while lesions lower in the hippocampus caused syntax difficulties in Parkinson's. The effects of insulin on memory are very interesting.

Natalie Rasgon: Currently, there are studies [1,2], and we are starting one as well, to look at the effects of intranasal insulin on memory. My particular interest is in persons at risk, rather than those with mild cognitive impairment (MCI) or an established disease. I hope that we will get funding for it, because it will isolate the central effects of insulin from peripheral, which will further my hypothesis.

Suzanne de la Monte: I could not tell if you think depression is a central or peripheral insulin problem.

Natalie Rasgon: I think that, without a doubt, depression is a central insulin problem. Because depression is a systemic illness, various peripheral events add on to the central component, for example, weight gain, obesity, hypercortisolemia, changes in cytokines, etc.

Suzanne de la Monte: Is there a possibility that the peripheral insulin resistance that would compromise CNS microvascular circulation could cause depression/dementia?

Natalie Rasgon: Suzanne, vascular effects of insulin are not well studied. I think we can infer some of it from imaging studies, which are waiting to be conducted.

David Ewbank: There seem to be two distinct AD-depression literatures: one on depression as a risk factor for MCI or AD, and a second on depressive symptoms in patients with AD. Is it your impression that these represent differences in pathology or merely differences in timing of appearance of symptoms?

Natalie Rasgon: Ewbank is right. I refer only to the presence of clinical depression long before any cognitive decline is evident; in fact, there is evidence, albeit not consistently replicated, that depression preceding AD for more than 10 years is a risk factor for AD [3].

Suzanne de la Monte: I agree about the depression and AD story – no controversy there. We see AD as a mixed bag with about 40 percent having overlapping cerebrovascular disease with moderate AD or AD and little vascular disease. We are doing postmortem studies to detect insulin resistance in AD, AD plus vascular, and aging microvessels. We are not sure how to detect it *in vivo*.

Natalie Rasgon: I think that is exactly the case – that AD is, to a large extent, a vascular disease and as such is compounded with all consequences of atherosclerosis, and if you could show IR comparably represented in vascular versus AD brain, that will be a great contribution to the field.

Suzanne de la Monte: So, how do you think insulin resistance in the brain causes depression? Is the depression you refer to different from psychotic depression in terms of basic etiology? This is a really interesting concept because it may have relevance to psychosis.

Natalie Rasgon: I do not think that IR causes depression. IR has been described in patients with major depressive disorder (MDD) before treatment, and my work suggested that women with bipolar disorder have high homeostasis model assessment (HOMA, and index of insulin sensitivity based on fasting glucose and insulin levels) ratios suggesting IR. In addition, women

with primary IR syndromes have much higher rates of depression. Pathophysiologically, insulin is driving hypercortisolemia and *vice versa*, which may in turn further promote central IR.

June Kinoshita: Does Dr. Rasgon hypothesize that the effect of IR on brain disorders is primarily through effects on vasculature? Does this contrast with Dr. de la Monte's concept of a brain-specific insulin-signaling pathway that is disrupted in AD?

Natalie Rasgon: No, June, I am not suggesting a microvasculature component. I do not know of any evidence for that. I agree that it may be one of the components of connection, however.

Suzanne de la Monte: So, to help clarify, do you think the neurons and/or glia versus CNS vessels are insulin resistant in the depression that precedes AD? How about depression that does not precede AD?

Nancy Emerson Lombardo: Could Dr. Rasgon more fully reply to Suzanne's earlier question about the type of depression involved, etiologically.

Natalie Rasgon: I refer to depressive disorders, both bipolar and major depression. I do not think that psychotic depression is the main culprit, because IR has been described in non-psychotic MDD. I do not have pathology data, but neuroimaging data clearly suggest that in some patients with depression, clinical recovery is not followed by improvement in glucose utilization patterns; thus, it is possible that these patients may have an underlying IR.

David Ewbank: I worked on a study on late-onset depression, brain atrophy, and medical illness. I seem to remember that there were almost no late-onset depression patients who did not have other medical conditions. Given the complex interactions among affective disorders (Ad), AD, and IRS, what is the best age group to be studying to understand the IR-Ad link?

Natalie Rasgon: Late-life depression has a different pathophysiology, and I think in many cases is a precursor, or a prodrome for AD. I believe that we need to study IR in early depressives, because we know that neurodegeneration starts decades before it is manifested clinically.

June Kinoshita: What age ranges would you target for studying IR in early depressives?

Natalie Rasgon: Age 35–55.

David Ewbank: So would you start with depressives and look for IR rather than starting with IR and looking for (or waiting for) depression?

Natalie Rasgon: Actually, I would do both.

Suzanne de la Monte: Agreed – early depression should be studied. Would it be helpful to do experiments in animals by looking for the molecular phenotypes of depression with insulin resistance in the brain?

Natalie Rasgon: Absolutely; what animals would you use? Rats, monkeys?

Suzanne de la Monte: Probably rats. We have several models now. What do you think we should look for that would be clinically relevant? We could look with different severities and time durations as well as brain regions.

June Kinoshita: Dr. Rasgon, are you currently studying this group with behavioral tests and neuroimaging?

Nancy Emerson Lombardo: I have a couple of questions. One, what about anxiety, both in current AD patients and as a precursor? Any connection there with IR? Your article refers to affective disorders, but I was not clear which you were including.

Natalie Rasgon: I am not sure about anxiety; I was not including anxiety disorders in the hypothesis.

Nancy Emerson Lombardo: Question two: I am studying the relationship between nutrition and dementia, especially AD, and I recently spoke with a Tufts University professor who is studying the link between nutrition and depression and anxiety. It turns out that the recommended diet is very similar, as both seem to be related to, among other things, deficiencies in omega-3s, especially docosahexaenoic acid (DHA)/eicosapentaenoic acid (EPA) long-chain omega-3s, and too few antioxidants.

Natalie Rasgon: Nancy, the antioxidant part of the link is there, as they are a ubiquitous part of cell function. I do agree that with dietary modification we may get changes in peripheral IR; I am not sure about central IR, but this could be tested, again with brain imaging.

Suzanne de la Monte: Nancy, do the AD patients actually eat more before they are demented?

Nancy Emerson Lombardo: No, there are only a few studies contrasting diets of AD patients with age-matched controls, and they tend to show AD patients with lower amounts of omega-3s, excess omega-6s (which would also cause inflammation), too much sugar (think IR), and fewer antioxidants [4].

June Kinoshita: Are there blood biomarkers that one might look at to gain insight into the IR, Ad, and AD connection?

Natalie Rasgon: You can look at glucose disposal via several tests: glucose tolerance test (GTT), or euglycemic clamp, etc. [The euglycemic clamp measures the amount of glucose necessary to compensate for a set amount of insulin infused. If a patient is infused with insulin, the blood sugar levels fall. This can be compensated for by infusing glucose, as well. The clamp measures how much glucose must be infused to maintain blood sugar levels between 5 and 5.5 mmol/l. The rate of glucose infusion is determined by checking the blood sugar levels every 5 minutes. The rate of glucose infusion during the last 30 minutes of the test determines insulin sensitivity. If high levels (7.5 mg/min or higher) are required, the patient is insulin-sensitive. Very low levels (4.0 mg/min or lower) suggest that the body is resistant to insulin action. Levels between 4.1 and 7.4 mg/min are indeterminate and might point at “impaired glucose tolerance”, considered an early form of insulin resistance.]

Suzanne de la Monte: I could be wrong, but I always consider anxiety as the flip of depression, but very related.

Natalie Rasgon: Not really; anxiety is very comorbid with MDD but has distinct pathophysiology.

Nancy Emerson Lombardo: Suzanne and Natalie, how about an animal study using Suzanne’s rat models, where we look at the effect of specific dietary components on both peripheral and, more important, central (brain-based) IR? And memory or executive function?

Suzanne de la Monte: Animal models and diet? That may be too difficult, but the effects on treating or reducing the depression/dementia markers could be studied.

Natalie Rasgon: I agree with Suzanne; diet is difficult to study in general, and I would think humans would be a better model.

Nancy Emerson Lombardo: At the Bedford VA we have access to AD transgenic animals, and some of the animal researchers are interested in working with me on the diet concept. However we have to design a diet also that looks like the typical American diet that people eat, since the usual mouse chow is actually pretty healthy. But I have to agree with Natalie and Suzanne. Diets are difficult to study, period, and I have been learning that if you want to do something more complex than study a single substance, it is very challenging to do in animals. But sometimes the review panels want you to first test anything in animals. In humans, we use dietary guidelines to achieve an overall objective; in animals, they have a precise diet. They eat the same thing at every meal, generally.

Natalie Rasgon: I believe there is a need for a number of studies, both in animals and humans. We need to better quantify IR in humans with depressive disorders, and we need to test relationships between IR and other neuromarkers in animals and humans.

Nancy Emerson Lombardo: I like June’s suggestion about making sure the biomarker and imaging studies now underway – especially the supersize NIA neuroimaging studies – include markers for IR. I think the investigators would be open to this if they have not already done it.

Suzanne de la Monte: I think the CNS IR story is not simple, as you all probably agree. Just as diabetes can have different severities and adverse effects with regard to peripheral organs, there will have to be a way to look at the CNS selectively. Maybe going back to the depression would be a good one.

June Kinoshita: We have come to the end of our hour. Thank you all very much for today’s discussion.

References

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