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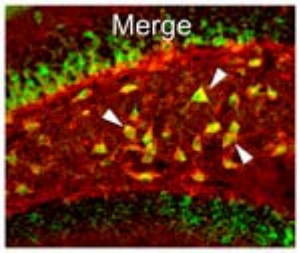
# Chronic Stress and Phosphorylated Tau: suggestions for Alzheimer's

By Scicurious | March 26, 2012

Could stress play a role in the development of Alzheimer's? Right now we're not sure, but this latest study shows that it may play a role, though exactly how? Well, we're *still* not sure.

Rissman et al. "Corticotropin-releasing factor receptor-dependent effects of repeated stress on tau phosphorylation, solubility, and aggregation" PNAS, 2012.

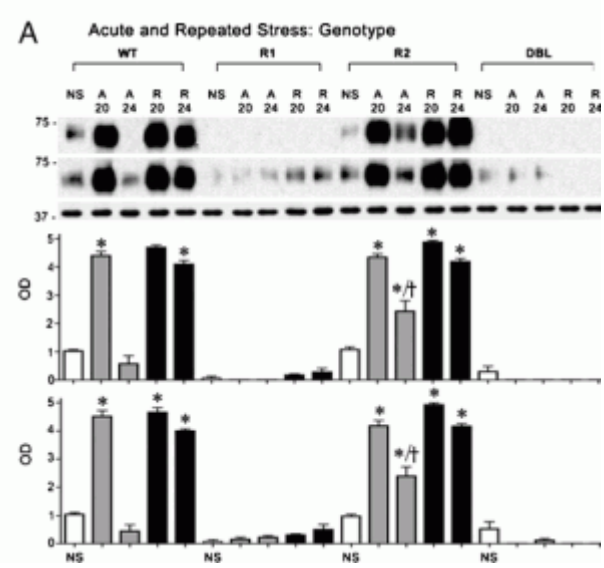



So what does stress have to do with Alzheimer's? To look at this we'll have to start by bringing two areas of study together: stress, and Tau.

Alzheimer's Disease is characterized by the development of two different globs of proteins, beta-amyloid plaques and neurofibrillary tangles. This study focuses on neurofibrillary tangles, or NFTs, which are made up of aggregates of a protein called tau. Tau is normally a protein used in the cytoskeleton to build and maintain cellular structure. In the case of Alzheimer's Disease, tau proteins end up getting phosphorylated, have phosphorous attached to them, which causes them to be able to aggregate in groups, and if those get large enough, into neurofibrillary tangles. These tangles in your brain cells **correlate with the cognitive decline** associated with Alzheimer's (*though as yet we have no definitive proof that they CAUSE Alzheimer's*). Studying the tau protein, how it becomes phosphorylated and then aggregates, could thus allow us to study one of the hallmarks of Alzheimer's disease, and if these tangles cause some of the symptoms of Alzheimer's, studies of tau could also provide us with new methods to attack the development of the disease.

And now what about stress? Stress has been linked to the development of many psychiatric diseases such as anxiety and depression, but it is also a natural **response to, well, stressful situations**. During times of physical or psychological stress, the hypothalamus of the brain releases corticotropin releasing hormone (previously called corticotropin releasing factor) toward the pituitary gland (located directly beneath the hypothalamus). In the pituitary gland, corticotropin releasing hormone stimulates receptors (called corticotropin releasing factor receptors, or CRF receptors, either type 1 or 2) to stimulate cells to synthesize adrenocorticotropic hormone, which will then promote the release of the stress hormone cortisol from places like the adrenal glands. This means that corticotropin releasing hormone and its receptors are the first line of the stress response. And it turns out **they may have something to do with the tau proteins** I just mentioned in Alzheimer's disease.

To look at the link between stress and tau proteins, the authors of this study subjected a group of mice to an acute stress: a **brief period** of restraint. During this stress, the animals are put in a tube where they can't turn around and held there for 20 minutes. It doesn't seem particularly severe, but it's certainly enough to get some stress from the mice. And it's **also enough to cause the tau proteins in the hippocampi of the mice to become phosphorylated:**



(Click to embiggen)

What you can see if you look on the left of this picture at the grey bars are the amounts of phosphorylated tau in the hippocampus following an acute stress at 20 minutes and again at 24 hours after the stress. You can see that in normal wild-type mice (WT), the acute stress increases the amounts of phosphorylated tau, but that this decreases again after about 24 hours.

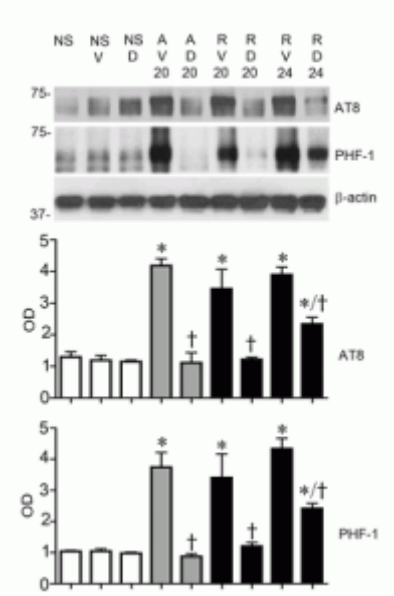
But that's just an acute stress. What about chronic stress? In this case, the authors put the mice in restraint stress for two weeks before looking at their levels of phosphorylated tau. They found that after two weeks of stress, the phosphorylated tau levels were high 20

minutes after the final stress, and the levels *remained* high 24 hours later, instead of going down again like those in the acute stress group.

What does this mean? It means that stress can increase levels of phosphorylated tau, which is the first step to causing tau to aggregate, and which could play a role in creating the neurofibrillary tangles present in Alzheimer's disease. But how is stress causing this change?

To look at this, the authors looked at mice with the two kinds of CRF receptors knocked out, either CRF 1 was knocked out, CRF 2 was knocked out, or both receptors were knocked out at once. They found that if CRF 2 was knocked out (the second group of high bars in the figure), it didn't really affect the levels of phosphorylated tau. **But it CRF 1 was knocked out, the mice showed no effects of stress on tau phosphorylation**. This means that **stress increases tau phosphorylation via actions at the CRF 1 receptor** (though the cellular mechanisms behind it are still unknown). They also showed that the TYPE of tau phosphorylation made a difference. tau phosphorylation can be of two types, the type that is soluble in detergent, and the type that isn't. The type that is soluble is the kind that participates in neurofibrillary tangles, and it appears to be the type that is most increased after stress.

Of course, a knockout mouse has had the knockout from birth, and there could be important changes taking place within the brain. So the authors also looked at the effects of using an antagonist of the CRF 1 receptor.



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You can see here that, if you give an antagonist to CRF 1 (which blocks the ability of corticotropin releasing factor to activate the CRF 1 receptor), you can block the effects of acute stress (in the grey bars) and chronic stress (in the black bars), as long as you give it during the stress exposure.

*What this suggests is not only that the CRF 1 receptor may play a role in how stress could increase phosphorylated tau, it also could be a good drug target, to try and stop the effects of stress on this protein.*

Of course, there are many caveats to this study. While it may have important implications for the development of Alzheimer's, there is not yet evidence that neurofibrillary tangles themselves CAUSE Alzhiemer's disease. Not only that, while the increases in phosphorylated tau (which could eventually become neurofibrillary tangles) remained elevated after 24 hours, this is still not very long. It's possible that the levels could decline if the animals were given long enough to recover and that the increases here might not be relevant to the development of Alzheimer's. In addition, the increased in phosphorylated tau were not linked to any cognitive impairment in the mice like you might see in Alzheimer's, and the study has not gone far out enough to determine if the increases in phosphorylated tau are here to stay, or if they have a function in the mouse's behavior. Finally, the authors used repeated restraint stress for two weeks for their chronic stress. While that is indeed stressful, mice become habituated to repeated stress like this, which might change the responses in tau that they are looking for. So it might be interesting to see if a different type of stress (like chronic unpredictable stress, which is much more varied) might have different effects.

So while there are many caveats to the story and a lot more work remains to be done, I think **it's an interesting new potential mechanism**, and it will be interesting to see if these results bear out over the long term, and if they have behavioral and cognitive consequences for stressed mice, and in turn, potentially for stressed humans.

Robert A. Rissmann, Michael A. Staup, Allyson Roe Lee, Nicholas J. Justice, Kenner C. Rice, Wylie Vale, and Paul E. Sawchenko (2012). Corticotropin-releasing factor receptor-dependent effects of repeated stress on tau phosphorylation, solubility, and aggregation *PNAS*