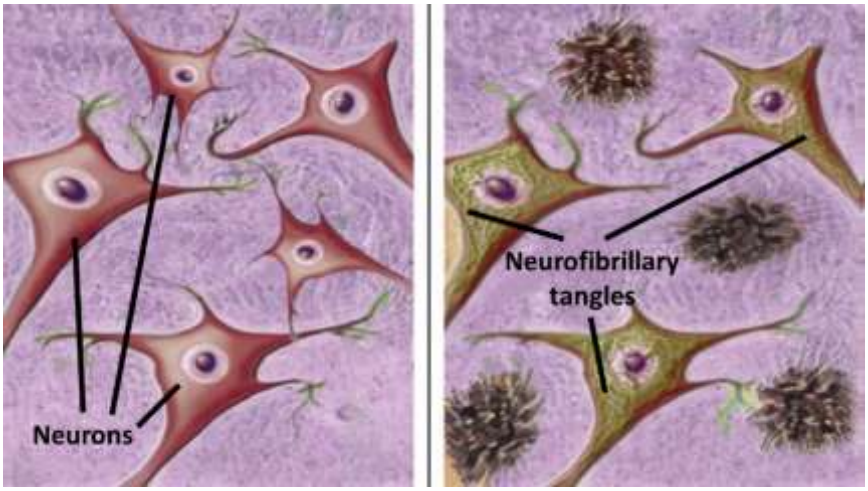
Adjourning Alzheimer's

Tau Accumulation (Day 15)

Alzheimer and Fischer both noted neuron loss and amyloid beta (Aβ) plaques, but Alzheimer noted another feature of the disorder that would later bear his name: **neurofibrillary tangles**, abnormal protein deposits that accumulate **inside** neurons. The main component of these tangles is **tau**, a protein that normally binds and stabilizes **microtubules** (proteins that move substances from one place to another within the neuron). Tau is vital for normal neuron function.



Neurofibrillary tangles (right figure) are abnormal protein deposits that accumulate inside neurons.

Some researchers believe that excessive tau accumulation is the main culprit driving neuron loss in Alzheimer's. Essentially, the **tau hypothesis** posits that tau builds up inside neurons, gradually forming **pretangles** (early tau deposits) that coalesce to form neurofibrillary tangles. The tangles interfere with neuron function, followed by neuron loss.

In a massive 2011 study, German neuropathologist **Heiko Braak** and colleagues examined the origin and spread of pretangles, neurofibrillary tangles, and Aβ plaques in 2,332 brains aged 1-100 years at autopsy. Unexpectedly, the earliest pretangles appeared in the **brainstem**, followed by pretangles and tangles in the **hippocampus** and **entorhinal cortex** (a tiny adjacent region of cerebral cortex), followed by pretangles and tangles in the rest of the **cerebral cortex**; incredibly, the earliest pretangles occurred by 10 years of age (in contrast, the earliest Aβ plaques appeared in the cerebral cortex, and not until 40 years of age).

This well-conducted study revealed compelling **evidence linking tau accumulation to neuron loss** by showing that:

(1) **Both pretangles and neurofibrillary tangles strongly correlate with neuron loss** - After the initial appearance of pretangles in the brainstem, pretangles and tangles follow the same pattern as neuron loss in Alzheimer's, first afflicting the hippocampus and entorhinal cortex, followed by the rest of the cerebral cortex.

(2) **The earliest pretangles appear well before the earliest Aβ plaques** - In fact, Braak showed that the earliest pretangles appear up to 30 years before the earliest Aβ plaques. In every single case that his team examined, the pretangles appeared before the plaques showed up.

The tau hypothesis stands on firmer ground than the amyloid cascade hypothesis. Unlike Aβ, **tau accumulation correlates well with the pattern of neuron loss in Alzheimer's**. Moreover, given that the earliest pretangles appear decades before the earliest Aβ plaques, **it seems far more plausible that tau is involved in the origin of Alzheimer's**, rather than Aβ. One last notable strength of the evidence for the tau hypothesis is that the Braak data comes from studies on **humans**, not in vitro or animal studies.

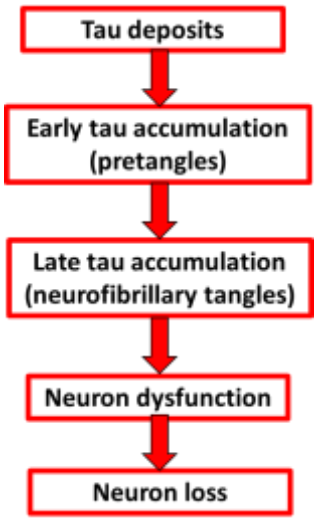
If possible, studies of disorders in people are best done in people.

So far, the tau hypothesis sounds quite plausible. However, we have discussed its **strengths**, but not yet addressed its **weaknesses**. If tau kills neurons, **neurons containing neurofibrillary tangles ought to die**. Let's see if this holds:

(1) If tau is the main culprit in Alzheimer's, **neurofibrillary tangles ought to kill the neurons in which they reside**. However, many neurons survive for decades with tangles inside them.

(2) If tau is the main culprit in Alzheimer's, **neurofibrillary tangles ought to be rare in cognitively normal elderly people**. However, observational studies show that by 70 years of age, a majority of cognitively normal people have large numbers of tangles…but still no neuron loss.

Thus, tau accumulates alongside neuron loss and occurs early in Alzheimer's, but **tau accumulation itself does not seem to be particularly lethal**; it does not explain the selective neuron loss seen in Alzheimer's.



The tau hypothesis posits that tau accumulation is the main culprit driving neuron loss; however, although tau accumulates alongside neuron loss, tau itself does not seem lethal.

Yet even if tau accumulation is not the factor driving neuron loss in Alzheimer's, **tau accumulation is tightly correlated with neuron loss**, so it must be involved in some way**.** What possibilities remain?

There are two. One possibility is that tau accumulation **partially contributes** to the neuron-killing process; not the main culprit, but a sidekick. The other possibility is that tau accumulation is a **neutral bystander** somehow produced by the Alzheimer's process, but not the actual driver of that process.

To sum up, high-quality evidence in humans shows that tau accumulation and neuron loss affect similar brain structures, and tau accumulates decades before neuron loss or excess Aβ occur; however, many neurons survive containing large amounts of tau, and for a very long time. Logically, **tau accumulation is tightly linked to the main culprit driving neuron loss in Alzheimer's, but tau itself is not the lethal factor**. We must go deeper.

Matt (Neurologist, Waikato Hospital).

References

(1) Braak et al. 2011. Stages of the Pathologic Process in Alzheimer Disease: Age Categories From 1 to 100 Years. J Neuropathol Exp Neurol 70(11), 960-969.

(2) Price and Morris. 1999. Tangles and Plaques in Nondemented Aging and "Preclinical" Alzheimer's Disease. Ann Neurol 45, 358-368.

(3) Wischik et al. 2014. Tau-aggregation inhibitor therapy for Alzheimer's disease. Biochem Pharmacol 88, 529-539.