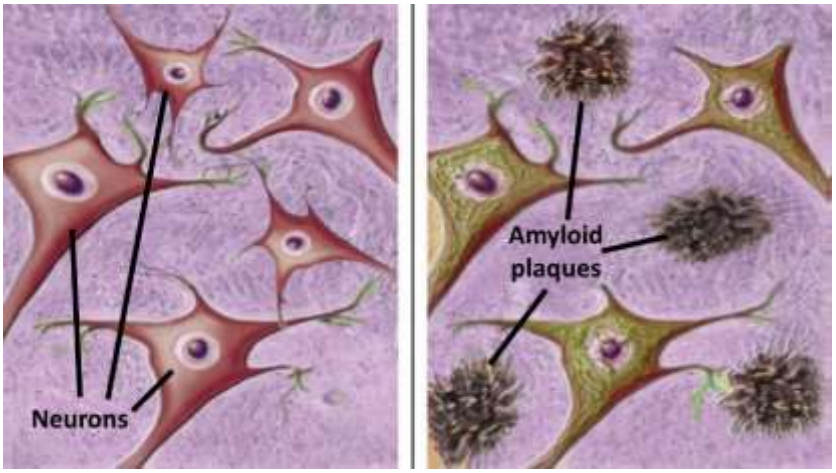
Adjourning Alzheimer's

Excess Amyloid Beta (Day 11)

Alzheimer's is a long chain of pathological events that culminates in neuron loss. However, Alzheimer and Fischer noted another pathological feature of Alzheimer's: **amyloid beta (Aβ) plaques**, abnormal protein deposits that accumulate **outside** neurons. The main component of these plaques is **Aβ**, a small protein formed from the larger **Aβ precursor protein** (which may regulate the formation of synapses, the junctions where neurons communicate).



Aβ plaques (right figure) are abnormal protein deposits that accumulate outside neurons.

Many researchers believe that excess Aβ is the main culprit driving neuron loss in Alzheimer's. They continue to support the **amyloid cascade hypothesis,** which essentially posits that Aβ builds up outside neurons, aggregating to form Aβ plaques. The excess Aβ somehow interferes with neuron function, followed by neuron loss.

Over the last 30 years, a lot of **evidence linking Aβ to neuron loss** has accumulated in support of the amyloid hypothesis. However, although the strongest evidence supporting the hypothesis appears impressive at first glance, a bit of reflection reveals several major shortcomings:

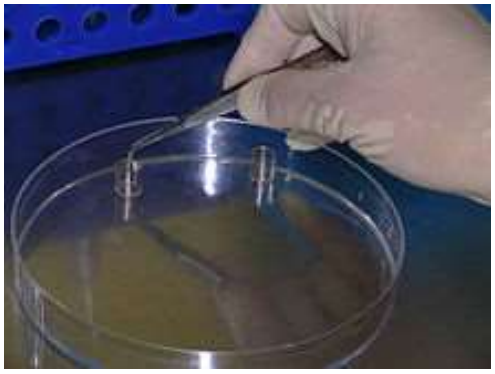
(1) **In vitro, Aβ can kill neurons** - It has been shown that Aβ can kill neurons in vitro (in an artificial environment, like a lab); however, neurons in such an environment experience utterly different conditions compared to neurons in their natural environment such that what applies to one does not necessarily translate to the other.

(2) **In mice, Aβ precursor protein mutations increase Aβ deposition and neuron loss -** Like in vitro studies, many things that can be shown in mice do not actually work when they are attempted in humans; once again, what happens in one does not necessarily translate to the other.

(3) **Familial Alzheimer's can arise from mutations in the Aβ precursor protein gene** - This fact is exciting to some, but it lacks relevance to the vast majority of people with Alzheimer's (familial Alzheimer's accounts for less than 5% of all Alzheimer's cases; over 95% of people with Alzheimer's have the sporadic form, in which these mutations are not present).

(4) **In Down's syndrome, Aβ is overproduced, and people with Down's develop Alzheimer's** - This is only a correlation, and does not prove that Aβ is the culprit in Down's syndrome (moreover, it is not relevant to the vast majority of people with Alzheimer's, most of whom do not have Down's).

Basically, the strongest evidence for the amyloid cascade hypothesis is drawn from **in vitro studies**, **animal studies**, and **humans with rare genetic alterations** such as familial Alzheimer's and Down's syndrome. None of which are directly relevant to the vast majority of people with Alzheimer's.



It is perilous to extrapolate the results of in vitro and animal studies to people.

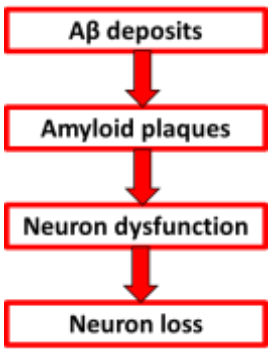
Keep in mind, the above forms the **strongest** evidence for the amyloid cascade hypothesis; we have yet to mention its **weaknesses**, which are considerable. Obviously, if excess Aβ is the main culprit driving Alzheimer's, **Aβ plaques ought to correlate with neuron loss** (where there is more Aβ, there should be more neuron loss). Let's see if this holds:

(1) If excess Aβ is the main culprit in Alzheimer's, **the greatest number of Aβ plaques ought to occur in structures most affected by neuron loss**, particularly the hippocampus. Yet most plaques appear in the cerebral cortex (moreover, in regions of cerebral cortex less prone to neuron loss).

(2) If excess Aβ is the main culprit driving dementia in Alzheimer's**, the greatest numbers of Aβ plaques ought to occur in the most severe dementia cases**. Yet the correlation between plaque numbers and dementia severity is poor; people ranging from very mild to very severe Alzheimer's in life often have similar plaque burdens at autopsy.

(3) If excess Aβ is the main culprit in Alzheimer's, **Aβ plaques ought to be rare in cognitively normal elderly people**. Yet this is not so - observational studies show that by 70 years of age, up to 40% of cognitively normal people possess large numbers of plaques in their brain.

Thus, the facts reveal that **excess Aβ does not correlate well with neuron loss**; Aβ plaques appear in the wrong place, at the wrong time. This is a very big flaw in the amyloid cascade hypothesis.



The amyloid cascade hypothesis posits that excess Aβ is the main culprit driving neuron loss…but excess Aβ and neuron loss do not occur in the same place or time, a difficult fact to reconcile.

Yet even if excess Aβ and neuron loss do not strongly correlate in place and time, there is still a weak correlation; **Aβ plaques are still a feature associated with Alzheimer's.** What are the possibilities?

There are several. One possibility is that Aβ plaques are **partial contributors** to the neuron-killing process; not the main culprits, but sidekicks. Another possibility is that the plaques are **neutral bystanders** produced by the Alzheimer's process, with no actual role in driving that process. Yet another possibility may even be that Aβ plaques are **protective reservoirs**, collecting excess β and keeping it away from neurons. We simply do not know.

To sum up, **it is extremely unlikely that excess Aβ is the main culprit driving the pathological process that is Alzheimer's**. The strongest evidence supporting the amyloid cascade hypothesis comes from in vitro and animal studies, as well as humans with familial Alzheimer's and Down's syndrome; it is perilous to extrapolate findings from these studies to people with sporadic Alzheimer's. Fatally, excess Aβ does not explain the pattern of neuron loss in Alzheimer's; it appears in the wrong place and time. We must keep looking.

Matt (Neurologist, Waikato Hospital).

References

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