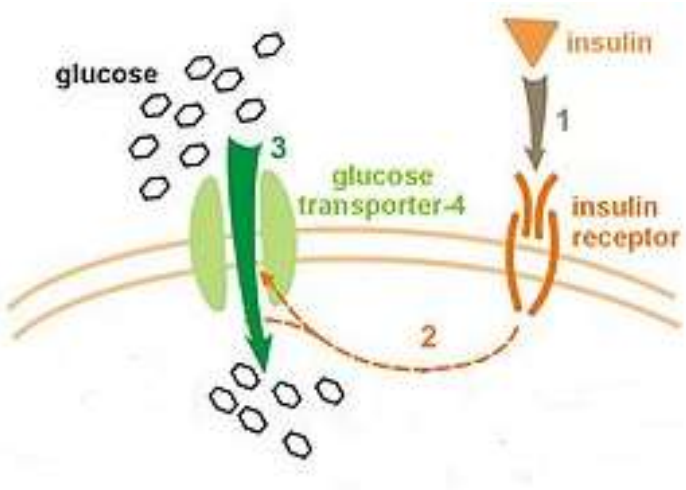
# Adjourning Alzheimer's

## Impaired Brain Insulin Signalling (Day 25)

So far, we've discussed how microtubules, tau, and mitochondria work together to distribute energy within the neuron, but we haven't actually mentioned the raw fuel source they require to make that energy. Under ordinary circumstances, that fuel source is the simple sugar, **glucose**, which circulates in the blood (also known as "blood sugar").

Since neurons need a lot of energy, the brain must constantly regulate how much glucose it extracts from the blood. It does this using the hormone **insulin**, a signalling molecule that regulates glucose entry into the brain for neurons (the effect of insulin on neurons may not be that simple, but we'll leave that aside for now) as well as glia, which are brain cells that support neurons. Insulin regulates glucose entry into neurons and glia by binding to **insulin receptors**, molecules located on the cell's outer membrane that activate glucose transporters, permitting glucose to enter.

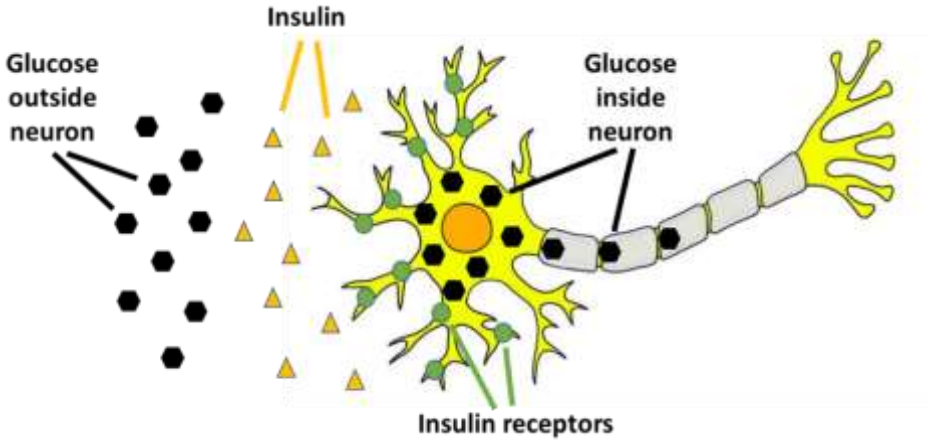



Insulin binds a receptor, which activates a glucose transporter to permit glucose into the cell.

The regulation of brain glucose uptake by insulin and its receptors is collectively called **brain insulin signalling**. Maintaining effective brain insulin signalling is critical for the survival and growth of the neurons and glia of our brain. Effective brain insulin signalling is determined by two things:

(1) **The amount of brain insulin** - The more insulin present, the more glucose will be taken up by the neurons and glia.

(2) **The number of brain insulin receptors** - The more cell receptors, the more glucose will be taken up by the neurons and glia.

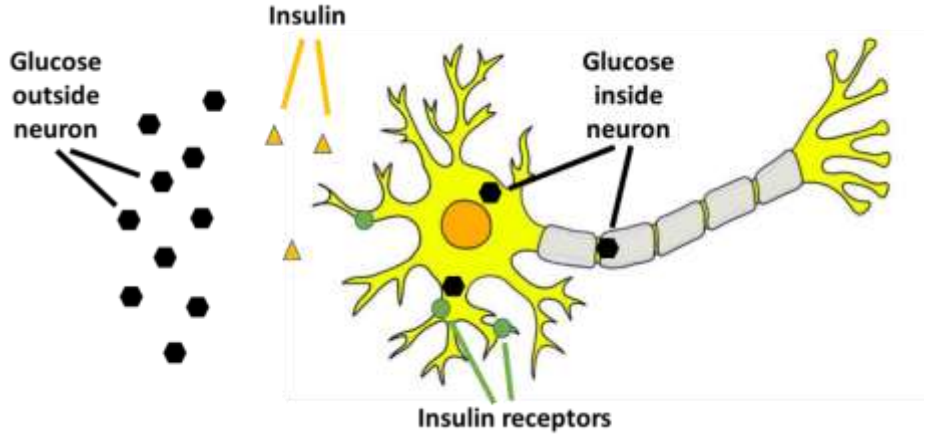



Normally, brain insulin signalling is effective - with insulin and receptors aplenty, lots of glucose is able to enter the neuron, which mitochondria use to produce energy.

Unfortunately, convincing studies in humans demonstrate the presence of severely **impaired brain insulin signalling** in Alzheimer's:

(1) **Insulin deficiency** - In Alzheimer's, **overall brain insulin is reduced by 80%** compared to the brain of a cognitively normal elderly person; this "insulin deficiency" is widespread throughout the brain.

(2) **Insulin resistance** - In Alzheimer's, **the number of brain insulin receptors in the hippocampus and cerebral cortex temporal lobe is reduced by 90%** compared to the brain of a cognitively normal elderly person; with fewer receptors available, more insulin is needed to transport glucose into neurons and glia, so the neurons and glia essentially become "insulin resistant."



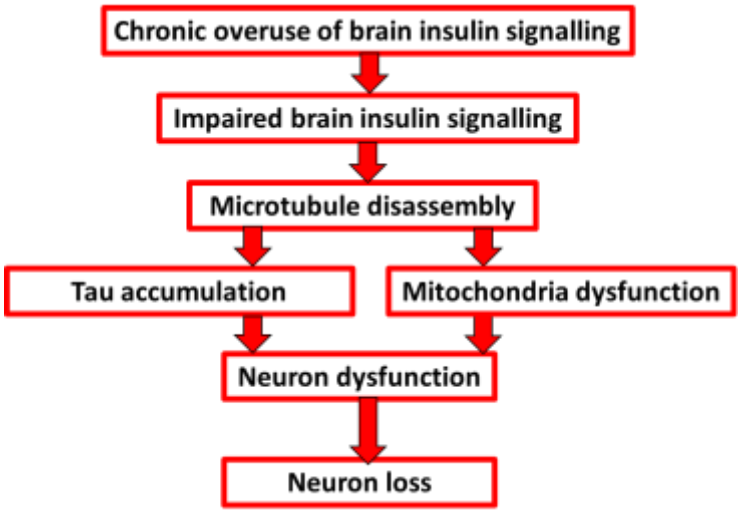

In Alzheimer's, brain insulin signalling is impaired - there is both insulin deficiency and resistance, so little glucose enters the neuron and it is starved of energy, even though there is plenty of glucose.

The 80-90% shortfall in both brain insulin and brain insulin receptors results in little glucose entering the neurons, so they are literally "starved" of their main fuel despite there being plenty of glucose

outside the cell. In fact, **brain glucose metabolism is reduced by 20-40% in Alzheimer's**, a marked shortfall that makes life difficult for energy-demanding neurons.

In 2005, United States neuropathologist **Suzanne De la Monte** and colleagues argued that since Alzheimer's shows features of both insulin deficiency (similar to type 1 diabetes) and insulin resistance (similar to type 2 diabetes), Alzheimer's should be considered as a combined form of diabetes, one that is brain-specific. In fact, De la Monte refers to Alzheimer's as **"type 3" diabetes**.

The **impaired brain insulin signalling hypothesis** posits that chronic overuse leads to impairments in the brain insulin signalling system; this compromises brain glucose metabolism, which then drives microtubule disassembly, tau accumulation, mitochondria dysfunction, and neuron loss.




The impaired brain insulin signalling hypothesis posits that reduced glucose uptake leads to excessive hyperphosphorylated tau, which triggers excessive microtubule disassembly, leading to tau accumulation, mitochondria dysfunction, and neuron loss.

The impaired brain insulin signalling hypothesis addresses the two **weaknesses** recently mentioned:

(1) **It addresses the formation of hyperphosphorylated tau in Alzheimer's**. It has been shown that excessive amounts of hyperphosphorylated tau are produced when neuron glucose uptake is reduced.

(2) **It explains the selectivity of Alzheimer's for the hippocampus**. Interestingly, the hippocampus contains **hundreds of times** as many insulin receptors as other brain structures. Since it relies so heavily on effective insulin signalling, losing 90% of its insulin receptors poses a particularly serious energy problem for the hippocampus in comparison with other brain structures.

To sum up, the impaired insulin signalling hypothesis posits that chronic overuse of the brain's insulin signalling system produces Alzheimer's, which at its core may be a **metabolic brain disorder initiated and driven by impaired brain insulin signalling**, instigating the long chain of pathological events that culminates in neuron loss in the hippocampus and cerebral cortex.

Finally, we may have arrived at the origin.

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**References**

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