There is a lot of talk all over the peptide community about the impacts of peptide degradation byproducts on both the efficacy of peptides, and possible impacts of that degradation on human health. One of the more persistent rumors is that degradation products can travel around the body and into the brain, causing long-term problems resulting in Alzheimer's (a terrifying disease whose very mention freaks people out) or other kinds of damage.

There's a new claim now going around about an adverse health outcome from Cagrilintide that led to an ER-trip, due to near-instant "amyloidosis." Yikes!

Let's state for the record up front that these rumors are false. There isn't any truth to these claims; they seem to be based on misunderstood physiology, and words that sound similar but refer to completely different things.

To help folks separate fact from fiction it seemed like it might be helpful to give a bit of background on how diseases like Alzheimer's really work, what amyloidosis is, and how protein aggregation (clumping, and 'fibrils') is related to that, so you can better understand these claims and evaluate their likelihood.

First off, what is amyloidosis?

Amyloidosis is a process where misbehaving proteins are deposited in parts of the body that they shouldn't be. And there isn't just one kind of amyloidosis; there are dozens[3]. Amyloidosis happens when different kinds of malformed proteins accumulate over many, many years; eventually, this deposition can cause damage to organs.

So why does this happen, and what are the risk factors?

It turns out that some proteins are just stickier than others because of what they need to do inside the body. In certain conditions, some proteins want to start to stack on top of each other, forming dimers (=two of them), trimers (=three) or oligomers (=many!), and eventually, this stacking forms stiff structures like threads called fibrils. And sometimes they clump into plaques or tangles too.

But even healthy people's proteins are just out there sticking to each other relatively regularly, stacking multiple malformed proteins to form these inflexible, relatively large, generally useless structures. Though a few are useful, most are not. And some types of protein are way more prone to this than others. This aggregation, as it's called, can happen due to inflammation stress, due to errors when protein "recipes" are being read off of our DNA (minor errors are surprisingly common: up to 18% might contain at least one mistake!), or due to the protein itself just not being terribly stable to start with[1].

So, the first important point to know is that *everyone* makes bunches of sticky stacking proteins, in an ongoing process, to a greater or lesser extent. Whenever our proteins stick together, they stop being useful as proteins so our ever-vigilant immune system recognizes these interlopers.

It gets to work picking the structures back apart -- sometimes back to their original protein forms, so they can still be re-used! But more often not; the bits just get demolished and chucked into the physiological recycling bin.

Some are much more stable and harder to break apart than others, and in amyloidosis, the immune system *can't keep up* – damage happens when there are just too many misformed or stacked proteins accumulating in large amounts over a long time, and certain people's systems stop being able to get rid of them fast enough.

Alzheimer's is one form of this process. Alzheimer's is a *local* amyloidsis; it happens within the brain, to proteins that are within the brain. The predominant theory behind Alzheimer's is that proteins within the brain misfold and stick together, forming plaques in a toxic process. But cause or effect is disputed, as clearing out the plaques doesn't seem to restore function. The two misfolded proteins in Alzheimer's are the *beta-precursor protein-42*, and the *tau protein*.

Cystic fibrosis is another amyloidosis; same idea as Alzheimer's, but with misfolding and clumping of the cystic fibrosis transmembrane conductance regulator (CFTR) protein (phew) inside the lungs.

So, the key thing to know: in local amyloidoses like Alzheimer's, the misfolded proteins in question are not carried INTO the organs from elsewhere; they're mis-secreted or mis-folded there. [6]

Systemic amyloidosis is a bit different than local. It's when something goes wrong with the secretory cells from an organ. Secretory cells produce things that are designed to enter the bloodstream. But something goes awry, and the organ/tissue starts secreting too many misfolded proteins into the blood – and they get carried everywhere!

This kind of amyloidosis can happen due to cancer, like in multiple myeloma – some switch that gets flipped incorrectly by genetics – or can be caused by inflammation or other damage in the part of an organ that sends things into the blood. Even with this going on, though, it takes a lot of proteins over a long time – years to decades – before the immune system can't deal with them and they start to pile up causing damage.

So, the half-time recap:

1. Many proteins throughout the body like to stack or clump, some a lot more than others. Clumpy proteins are called 'amyloids' and can be created by everything from amylin-secreting cells in the pancreas to apolipoproteins in cholesterol. Because there are many proteins, there are also multiple amyloidosis types – dozens!
2. Local aggregates can damage the organs they get formed in. For example, within the pancreas, the cells that produce amylin (islet cells) can be damaged by amylin fibrils if they aggregate there due to diabetes-induced cellular damage. Aggregates stay there, though, and damage occurs over years or decades of misfolding and local clumping.

These aggregates and fibrils don't typically have a path out of the organ, because they're too big and don't have the right shape to hitch a ride to elsewhere.
3. Systemic amyloidosis is produced by a haywire process in the part of an organ whose job is to secrete things into the blood, but only very specific kinds of damaged proteins can hitch a ride even then.
4. The immune system happily picks apart misfolded and stacked proteins – to a point.[3]

They actually find natural amyloid in all sorts of places in the body when doing unrelated biopsies, and when studied, researchers conclude that these deposits aren't the cause of the problems in question. They're just kinda there because they're… kinda everywhere![8]

And a fun rat fact (who doesn't love these??): When they tried producing a breed of rat to test systemic amyloidoses, they struggled to do so -- because every time they'd inject the rats with amyloid, their immune systems would just chase it all down and clear it back out!

A different kind of stacking…

How does this pertain to peptide byproducts? Well, peptides can degrade and form similar byproducts outside the body as proteins can inside the body. And they can form local amyloidoses inside the body too. Yep! Sounds scary, but recall that our immune system has this covered because of the fact that we're already doing this to ourselves routinely. What's important is how many there are, and what happens to them if we do inject some. Recall back at the beginning I mentioned dimers, trimers, etc? Yes, tirz and cagri and other injected peptides all have the potential to form fibrils or clumps in the right circumstances. But the thing to realize about these fibril, plaque, and other clumpy structures is that they're BIG. They're AT LEAST twice as big as the proteins that make them, since they're made from stacks of proteins, sometimes a few and sometimes dozens. But the clumpiness influences how far they get in the body – spoiler: not far at all.

This is because they no longer have the right shape to hitch a ride into the bloodstream! So let's say we're injecting proteins like degraded peptide bits. If they do manage to aggregate or form fibrils (and note, degradation doesn't always mean fibrillation; they might be too degraded to even stick together at all), well, what happens?

…Nothing!

They stay where they're put. Then our immune system gets busy eating them.

But how do we really know they stay put?

We know because we can study *other peptide amyloids*! Did you know that insulin also forms amyloid!? Yep. The OG peptide. Over decades after injecting in the same spot over and over again, a small percentage of diabetics whose immune systems for whatever reason don't clear them up have ended up with local subcutaneous amyloidoses: in short, they get a lump! [4]

It turns out that there are a few potential "drug-induced amyloidses," and these insulin lumps are a great test bed for studying what might happen if, over time, a lot of fibrils did get injected – it's not the nightmare scenario being painted at all.

1. In every case when investigated, there's been *zero* systemic amyloidosis found.[5] If it was going to be found in the brain like in Alzheimer's, remember, it'd have been found anywhere the blood goes, and in the lungs or heart or other organs. It hasn't been.
2. The aggregation *does* have consequences: they find hyperglycemia/hypoglycemia in these diabetic patients. But that's not the aggregates; that's because injecting into the amyloid lump stops their insulin from being absorbed! – and then the lump excretes that insulin back out again as the immune system *picks the lump back apart*. It just keeps trying to break that lump down. But the rate of injection adds to the lump faster than the body can take it away.
3. This takes *years* of multiple-daily insulin injections to occur. In the cases reported, it's been T1 diabetics after 15-20+ years. And that's to make a 2-3cm lump, all in people who inject in the same spot over and over and over again. In fact, these patients often did it on purpose – it hurts less and less..! Well, sure it does! But this is one of the reasons why they tell people to rotate their injection spots.

Ok, so. These folks, what happens to them? Well, their doc extracts and tests the lump. That's it. And this fixes the issue. Within the lump they find not just amyloid but apolipoproteins and a bunch of other fibrillated proteins mixed up in there too. They theorize that these people just have more difficulty than others clearing the sticky stuff from their systems. Could you be one of them? ....Maybe? But it would take a very, very long time of weekly injections to ever encounter this situation. And the cure is rotating your injection sites.

Insulin, by the way, makes a very good example when talking about the next topic, Cagrilintide, because it has a very similar molecular weight (4.4 kDa) to insulin (5.8 kDa). This means they will behave very similarly with respect to their aggregation sizes and what the body can do with them… .

Okay, but what about amylin and Alzheimer's? Isn't there a link?

There's an *association* between amylin and Alzheimer's, but it's complex and requires several other things to be going on at the same time.

Note first that Cagrilintide is an amylin analog – it's not amylin; it's far more stable. It binds to the same receptors, but it doesn't aggregate nearly as easily. They shouldn't be mistaken for the same thing, even though they are similar.

But yes, amylin does play a role in Alzheimer's disease. It's a very convoluted role, and cause and effect is unclear. First off, when studied, they found that amylin isn't some kind of boogeyman. It's important and necessary. We need it in our brains.

People with high plasma levels of amylin had lower incidence of Alzheimer's. However, there's high levels… and then there's too high. People in the middle stages of Type 2 Diabetes often have chronically high levels of both amylin and insulin. That's where problems show up. These patients have these high levels because insulin and amylin resistance builds up over time as their bodies try to desperately make enough to get their cells to respond properly. These high levels increase up and up over years or decades. In those people, they do find that these drastically higher levels of amylin eventually build up within the pancreas and within the brain, and at a certain volume can form damaging clumps (recall that amylin is particularly clumpy). That process will cause cumulative damage, as the immune system can't keep up -- the clumps both interfere with function, and aren't nice neighbours in big groups.

When too-high levels of insulin and amylin become chronic, this leads to:

> …system insulin resistance, impaired insulin transport across the blood-brain barrier (BBB), and thus decreased insulin signaling within the brain. Loss of insulin signaling in the brain is associated with a number of AD [Alzheimer's Disease]-related pathological features, including increased Aβ[amyloid-beta protein] production, tau phosphorylation, and neuroinflammation. …
>
> [W]hether amylin is a toxic insult in these diseases or whether its functional loss through aggregation or late stage β-cell loss in T2D contributes to the development of an AD remains unclear. [6]

What they're saying here is that whatever caused that excess amylin to aggregate in the brain also plays a role in amyloid-beta plaque formation too. Then once clumped there, amylin is not able to do its job properly. They find that there's a U-shaped curve in the stats:

- **not enough** amylin **bad**
- **a lot** of amylin **good**, but
- **way way too much** amylin… also **bad**.

Now, amylin is the hormone that Cagrilintine mimics. But Cagrilintide is designed to be much more stable than amylin – while they bind to the same receptors, they are not the same molecule. Amylin is much more prone to aggregation, and that's important to remember.

Because of this structural difference, there's even a suggestion in the research that Pramilintide, the prior generation of Cagrilintide, could be used to treat Alzheimer's! – it can take over the job of binding to amylin receptors in the brain in the place of missing or aggregated amylin! Now, of course, this is all theoretically interesting, but kind of beside the point. The original concern wasn't amylin or Cagrilintide – the question was whether if Cagrilintide aggregates were injected, will they make it into the brain to cause damage?

The answer to that is no.

These big aggregates and stiff fibrils **can't get into the brain.** The blood brain barrier (BBB) is far too small to let through anything the size of these aggregates; they're a minimum of 3x as large as the BBB can let past. They're just **too big** to even get there in the first place. Amylin must be able to get into the brain, and Cagrilintide too, to have their amazing effects on appetite. ***But aggregates or fibrils can't even get through the door.*** . .

Sticking it all together…

Amyloidosis is a fascinating process of badly-behaved proteins doing things they shouldn't. There are around 27 different types of amyloidosis, and they're caused by malfunctioning systems or disease processes that happen over years and decades of constant mis-folding and aggregation in the location where the damage occurs.

Degradation of any peptide is not something that's good, and the goal is to keep that to a minimum, because forcing your immune system to do extra work isn't great. There are very real pH limits within which pharmaceutical formulations should be kept during storage, and this is to ensure that the drug is at the same dose whether it's taken now or two years from now – degraded peptide is functionally useless, and triggering an immune reaction isn't fun. Degradation can happen due to incorrect pH, heat, and time, but it isn't a switch that gets flipped in an instant, either; there are safe ranges within which everything can be used.

But if for whatever reason there is degradation, what then? For subcutaneous administration... nothing. Now, note that there's a big difference between saying all this and saying aggregation is *good*, or that fibrils are benign -- in the wrong place, in the wrong quantity, they're bad. We should do what we can to avoid them! (Although, sidenote: I hear the word "toxic!" thrown about, but this is a very specific term in biology. Lots of things are toxic to cells, including lack of blood flow, autoimmune reactions, getting a bruise, or too low or high pH – like from, say, injecting spicy NAD+... all stuff toxic to cells! Thankfully, we've got lots and they're self-replicating.)

Injecting a large quantity of amylin fibrils directly into your bloodstream, say, would *not* be great, as they discovered when they did so to mice -- that increased toxic (the bad kind) aggregation in the pancreases of diabetic mice vs the control diabetic mice.[10] But in humans, we have many layers of protective mechanisms that come into play long before that point that the mice didn't. Molecular chaperones stop amylin oligomers from turning into fibrils, antibodies specifically recognize and target amylin aggregates of all sorts, and there are even ingredients in our blood that stop amylin aggregation and fibrilization too.[9] Amylin is just clumpy, so we evolved multiple ways to deal with its bullshit.

But if you...
1. HAD injected a hot vial of Cagrilintide chock full of aggregates one day and
2. Some of these managed, *somehow*, to leave where you injected them subcutaneously and bind to the albumin in your bloodstream to hitch a ride – despite there being no evidence of that being able to happen with insulin aggregates in *millions* of T1 diabetics! – and they then
3. circumvented all your body's immune and other protections,

...there's still no way for degradation byproducts to get into the brain to cause Alzheimer's. Your immune system will do its job and pick aggregates apart wherever it finds them. The amount is manageable, and your body does way worse to itself every day. It's got this.

And some final words from the nerds:

> …although aggregation and amyloidosis correlate to a certain extent, they are different processes and should be treated as such.[2]

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