

Eat your way to dementia

Is the western diet poisoning our brains, asks Bijal Trivedi

SUZANNE DE LA MONTE's rats were disoriented and confused. Navigating their way around a circular water maze – a common memory test for rodents – they quickly forgot where they were, and couldn't figure out how to locate the hidden, submerged safety platform. Instead, they splashed around aimlessly. "They were demented. They couldn't learn or remember," says de la Monte, a neuropathologist at Brown University in Providence, Rhode Island.

A closer look at her rats' brains uncovered devastating damage. Areas associated with memory were studded with bright pink plaques, like rocks in a climbing wall, while many neurons, full to bursting point with a toxic protein, were collapsing and crumbling. As they disintegrated, they lost their shape and their connections with other neurons, teetering on the brink of death.

Such changes are the hallmarks of Alzheimer's disease, and yet they arose in surprising circumstances. De la Monte had interfered with the way the rats' brains respond to insulin. The hormone is most famous for controlling blood sugar levels, but it also plays a key role in brain signalling. When de la Monte disrupted its path to the rats' neurons, the result was dementia.

Poor sensitivity to insulin is typically associated with type 2 diabetes, in which liver, fat and muscle cells fail to respond to the hormone. But results such as de la Monte's

have led some researchers to wonder whether Alzheimer's may sometimes be another version of diabetes – one that hits the brain. Some have even renamed it "type 3 diabetes".

If they are right – and a growing body of evidence suggests they might be – the implications are deeply troubling. Since calorific foods are known to impair our body's response to insulin, we may be unwittingly poisoning our brains every time we chow down on burgers and fries. People with type ▶

115m

people globally will get Alzheimer's by 2050

DIABETES OF BRAIN AND BODY

Type 1: Only about 5 per cent of people with diabetes have type 1, also called juvenile diabetes, which is typically diagnosed in children and young adults. It starts when an autoimmune response destroys the insulin-producing cells in the pancreas, meaning the body can no longer regulate levels of blood sugar. Insulin therapy helps these individuals lead a healthy life.

Type 2: Most people with diabetes have type 2. Here, the pancreas either does not produce enough insulin or the muscle, liver and fat cells ignore the insulin and fail to suck excess sugar from the blood.

This can lead to both high insulin levels and high blood sugar – the hallmarks of type 2 – which can raise the risk of heart disease, stroke, blindness, nerve damage and amputation. Being overweight, particularly if you have excess abdominal fat, increases your risk of developing type 2 diabetes.

Type 3: This controversial new category, coined by Suzanne de la Monte, refers to Alzheimer's disease, which she and a growing number of other researchers believe arises when brain tissue becomes resistant to insulin. In that sense it is like type 2 but primarily concerns the brain.

FOOD FOR THOUGHT

Brain food isn't just an expression. Recent studies have revealed that consuming a lot of foods high in saturated fat and sugar or anything with a high glycaemic index are bad for your brain because they keep your insulin levels high.

A recent study from the University of California, Los Angeles, showed that rats consuming water laced with high-fructose corn syrup, a sweetener in soft drinks, condiments and many processed foods, had learning and

memory problems after just six weeks, and their brain tissue became less responsive to insulin.

But certain dishes may offer some protection against these effects. Rats consuming high-fructose corn syrup water alongside omega-3-fatty acids from flaxseed oil seemed to escape the cognitive problems the other group encountered (*Journal of Physiology*, vol 590, p 2485). Omega-3 acids are also found in oily fish.

There is also some tentative

evidence that certain compounds called flavonoids, found in tea, red wine and dark chocolate, can reduce the risk of dementia. All of which may explain why the Mediterranean diet is associated with less cognitive decline, dementia and Alzheimer's disease. This diet is known to be rich in fish and vegetable oils, non-starchy vegetables, low glycaemic fruits, less added sugar and a moderate helping of wine (*Current Alzheimer Research*, vol 8, p 520).

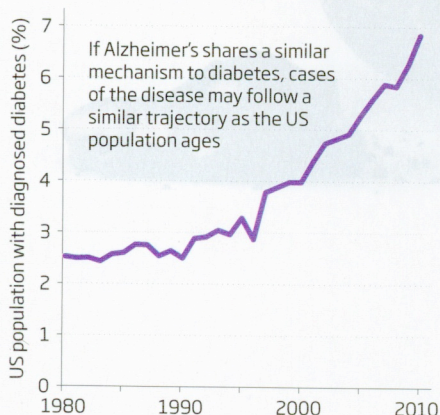
2 diabetes, who have already developed insulin resistance, may be particularly at risk. "The epidemic of type 2 diabetes, if it continues on its current trajectory, is likely to be followed by an epidemic of dementia," says Ewan McNay of the University at Albany in New York. "That's going to be a huge challenge to the medical and care systems."

All of which highlights the importance of eating healthier foods and taking exercise to reduce your risk of dementia. It may even be possible to reverse – or at least decelerate – some of the cognitive decline in people who already have Alzheimer's, by targeting the underlying insulin resistance. If so, that would suggest new treatments for the disease, which has so far evaded any attempt to treat it.

A new understanding of Alzheimer's can't come soon enough; it plagues an estimated 5.4 million adults in the US, whose care cost \$130 billion in 2011 alone. Worldwide, 36 million people have the disease, a figure that will rise as the population continues to grow. "We are desperate for an effective therapy," says John Morris, a neurologist specialising

A ticking time bomb?

A poor diet, filled with high-fat, high-sugar foods has led to a rapid rise in cases of type 2 diabetes



35.7%

of people in the US are obese, putting them at greater risk of Alzheimer's

in Alzheimer's disease at the Washington University School of Medicine in St Louis.

For a long time, the finger of blame has pointed squarely at the beta amyloid plaques that amass in the brains of people with the disease. Alois Alzheimer, the German psychiatrist and neuropathologist for whom the disease is named, first described these strange protein deposits over a century ago, when he noticed apparently normal brain cells filled with strange fibrils. In the areas where the disease had progressed, the fibrils had merged and moved to the surface inside the cell, where they folded together in thick bundles. "Eventually, the nucleus and the cell disintegrate, and only a tangled bundle of fibrils indicates the place which had formerly been occupied by a ganglion cell," he wrote.

The origin of these plaques is only partially understood; we know that beta amyloid is a fragment of a larger protein that helps form cell membranes in the brain and other parts of the body. It is also thought to carry out important functions of its own, such as fighting microbes, transporting cholesterol and regulating the activity of certain genes. What prompts the protein to clump into the deadly plaques is something of a mystery, but if the new research is right, a diabetes-like illness might be a trigger.

This new focus follows a growing



DIGITAL VISION/GETTY

recognition of insulin's role in the brain. Until recently, the hormone was typecast as a regulator of blood sugar, giving the cue for muscles, liver and fat cells to extract sugar from the blood and either use it for energy or store it as fat. We now know that it is a master multitasker: it helps neurons, particularly in the hippocampus and frontal lobe, take up glucose for energy, and it also regulates neurotransmitters, like acetylcholine, which are crucial for memory and learning. What's more, it encourages plasticity – the process through which neurons change shape, make new connections and strengthen others. And it is important for the function and growth of blood vessels, which supply the brain with oxygen and glucose.

As a result, reducing the level of insulin in the brain can immediately impair cognition. Spatial memory, in particular, seems to suffer when you block insulin uptake in the hippocampus; the effect is almost the same as that of morphine, says McNay. Conversely, a boost of insulin seems to improve its functioning.

McNay points out that this role in the brain "makes evolutionary sense", since it would help us to remember the location of a food



Being overweight increases your risk of Alzheimer's

source. As our ancestors gorged on berries in the savannah, for instance, the spike in glucose and the subsequent rush of insulin would signal “remember this, it’s important”, causing the brain to crystallise the memory.

But as we know from type 2 diabetes, processes that evolved to help us meet the challenges of prehistory can easily backfire in the modern world. When people frequently gorge on fatty, sugary food their insulin spikes repeatedly until it sticks at a higher level. Muscle, liver and fat cells then stop responding to the hormone, meaning they don’t mop up glucose and fat in the blood. As a result, the pancreas desperately works overtime to make more insulin to control the glucose – and levels of the two molecules skyrocket. “It’s like you are knocking on the door and the person inside is ignoring your call. So you knock louder and louder,” says de la Monte. The pancreas can’t keep up with the demand indefinitely, however, and as time passes people with type 2 diabetes often end up with abnormally low levels of insulin.

Weight gain seems to amplify the problem – 80 per cent of people with type 2 diabetes are also overweight or obese. Though the

mechanism is still unclear, obesity seems to trigger the release of inflammatory and metabolic stress molecules inside liver and fat cells that disrupt insulin action, leading to high blood glucose levels and, eventually, insulin resistance.

If McNay and de la Monte are correct, a similar process may lead to Alzheimer’s. They think that constantly high levels of insulin, triggered by the fat and sugar content of the western diet, might begin to overwhelm the brain, which can’t constantly be on high alert. Either alongside the other changes associated with type 2 diabetes, or separately, the brain may then begin to turn down its insulin signalling, impairing your ability to think and form memories before leading to permanent neural damage. “I believe it starts with insulin resistance,” says de la Monte. “If you can avoid brain diabetes you’ll be fine. But once it gets going you are going to need to attack on multiple fronts.”

Her study on the demented rats was one of the first experiments to make this link. At the time she was interested in the impact of alcohol on the brain, which is known to decrease its number of insulin receptors. To

probe the consequences she used a chemical to wipe out all the brain cells carrying the insulin receptor; the result looked surprisingly similar to Alzheimer’s, including the build-up of the deadly beta amyloid plaques.

De la Monte’s finding is now just one of many discoveries to confirm that a disrupted insulin system can lead to the symptoms of Alzheimer’s. William Klein at Northwestern University in Evanston, Illinois, for instance, has found that triggering diabetes created Alzheimer’s-like brain changes in rabbits, including a sharp rise in the number of beta amyloid proteins (*The Journal of Alzheimer’s Disease*, DOI: 10.3233/JAD-2012-120571). “It’s the first time that any culprit has been singled out as an instigator of sporadic Alzheimer’s disease pathology, one of the big mysteries in the field,” he says. McNay and Suzanne Craft at the University of Washington in Seattle, meanwhile, fed rats a high fat diet for 12 months, which destroyed their ability to regulate insulin and led to diabetes. Once again, the change was accompanied by high beta amyloid levels in the brain. They also had trouble navigating a maze and looked “much like an Alzheimer’s patient”, says McNay.

Of course, animal studies can only tell you so much about a human disease, but an almost Frankensteinian demonstration confirms that the brains of people with Alzheimer’s are insulin-resistant. Using brains from cadavers, Steven Arnold at the University of Pennsylvania bathed various tissue samples in insulin to see how they would react. Tissue from people who had not had Alzheimer’s seemed to spring back to life, triggering a cascade of chemical reactions suggestive of synaptic activity. In contrast, the neurons of those who had had Alzheimer’s barely reacted at all (*Journal of Clinical Investigations*, vol 122, p 1316). “The insulin signalling is paralysed,” says Arnold.

It’s not yet fully understood exactly why disrupted insulin signalling would lead to the other kinds of brain damage associated with

\$130^b

the cost of Alzheimer’s care in the US in 2011

40%

decrease in the risk of Alzheimer's from regular exercise

Alzheimer's, such as the build up of plaques, though the emerging research suggests many, possibly interlinked, mechanisms (see "A toxic cycle", below). One line of evidence, for instance, has shown that insulin and beta amyloid are both broken down by the same protein-chomping enzyme. Under normal circumstances that enzyme can successfully deal with both, but if too much insulin is washing around, the enzyme gets overwhelmed by the hormone, and the beta amyloid gets neglected. Instead of being broken down, it accumulates, perhaps building into the toxic plaques that kill brain cells (*Proceedings of the National Academy of Sciences*, vol 100, p 4162).

Exacerbating the problem, beta amyloid can then stop neurons from responding to insulin, leading to further damage. By studying dishes of rat neurons, Klein has found that toxic clusters of the protein attack and destroy regions of synapses that are covered in insulin

receptors; they also stop new receptors appearing, making the neuron insulin-resistant (*FASEB Journal*, vol 22, p 246). The result would be an immediate impairment in cognition. Worse still, this insulin resistance tells the cells to make even more beta amyloid, which then goes on to harm more brain cells. "It triggers a vicious cycle," says Klein.

Things only get worse if the pancreas becomes exhausted by the high demand for insulin, lowering levels of the hormone in the brain. Klein has found that a moderate level of insulin is protective, offsetting beta amyloid damage by blocking its landing sites on brain cells. "But when people age or have diabetes, the insulin signalling in the brain becomes weaker, possibly opening a window for amyloid beta toxin to start destroying the neurons," he says.

It is still early days for this work – and the researchers are keen to point out that they haven't solved every aspect of the puzzle. Klein, for example, thinks that lack of insulin in the brain may be just one of many triggers for beta amyloid toxins, so he's searching for other culprits. Suzanne Craft, who has been a pioneer in insulin and Alzheimer's research, agrees that it is probably one of many paths to the disease. After all, most people with Alzheimer's don't have full-blown type 2 diabetes – though many do have some problems with the insulin signalling in their bodies, even if they don't match every criterion for the disease.

Even so, the research should ring warning

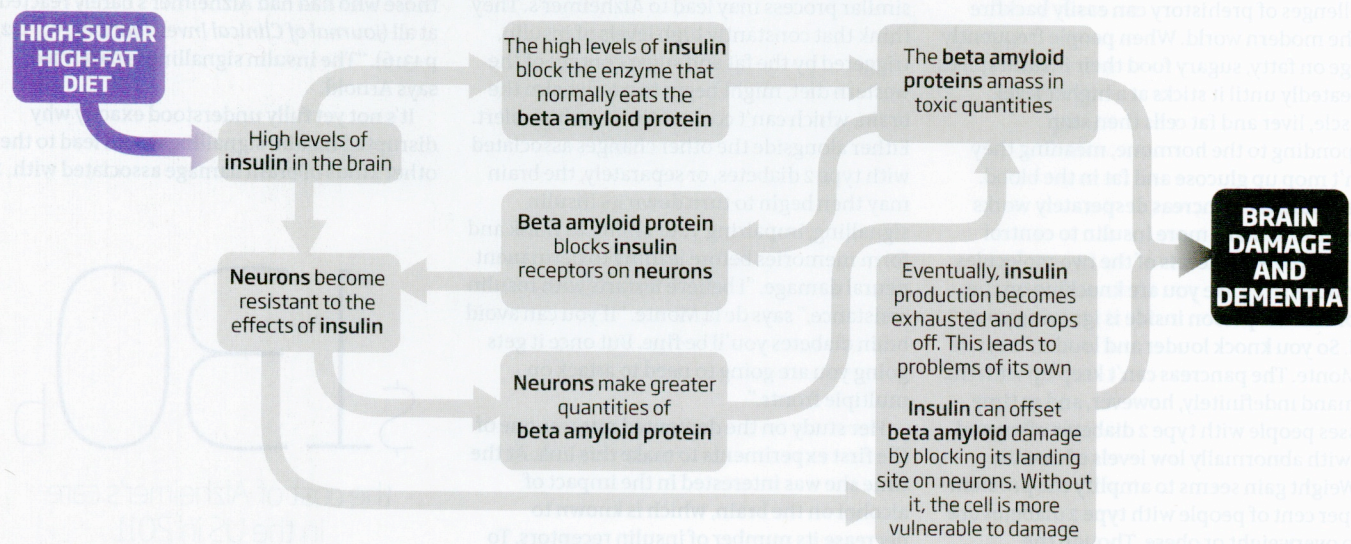
bells for the future. Thanks to our addiction to fast food, type 2 diabetes is constantly on the rise (see graph, page 34). In the US alone, 19 million people have now been diagnosed with the condition, while a further 79 million are considered "prediabetic", showing some of the early signs of insulin resistance. If Alzheimer's and type 2 diabetes do share a similar mechanism, levels of dementia may follow a similar trajectory as these people age.

Even if someone doesn't develop diabetes, a bad diet might be enough to set the wheels in motion for brain degeneration, according to an ongoing study led by Craft. For one month a group of volunteers – none of whom had diabetes – ate foods that were high in saturated fat and sugar while a control group ate a diet low in sugar and saturated fat. In just four weeks, those gorging on the high-sugar diet had higher levels of insulin and significantly higher beta amyloid levels in their spinal fluid. The control group showed decreases in both. "An unhealthy diet disrupts normal insulin function in the brain, increases inflammation and oxidative stress, and impairs amyloid regulation," says Craft. When these three converge they can lead to Alzheimer's, she says. When you consider that obesity is a big risk factor for both diabetes and dementia, all the signs suggest that our addiction to junk foods could spell trouble for our mental health in the future.

On the plus side, a new understanding of the disease might lead to new treatments for

A toxic cycle

Caloric foods cause levels of insulin in the brain to spike. Although the mechanism is not completely understood, it seems to trigger a vicious cycle that ultimately results in dementia





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One of the
biology is how
take on their
of forms
But

As dementia develops, memories of the past slowly slip away

those who already have Alzheimer's. Craft, for instance, is investigating whether a boost of insulin might improve symptoms. So far, she has tested out a device that delivers insulin deep into the nose, where it then travels to the brain. The study was short, lasting just four months and involving only 104 people, but the results were promising. In memory tests those who received the treatment could recall more details of stories, had longer attention spans, regained more interest in their hobbies and were better able to care for themselves. The glucose metabolism in their brains also improved (*Archives of Neurology*, vol 69, p 29).

Given insulin's many roles in the brain, the nasal spray may work for a number of reasons. A blast of the hormone might help struggling cells to return to normal activity. Alternatively, Craft points out that it might decrease inflammation and oxidative stress caused by reactive oxygen-containing

compounds – both of which are problems for people with Alzheimer's. Klein, meanwhile, thinks that Craft's approach may work because insulin helps prevent the beta amyloid toxins from docking with brain cells. "It is a struggle between insulin and the toxins for synaptic survival," he says. He suspects it might also curb the build-up of these toxins in the first place.

A better understanding of this process might come from Craft's next project; she has just been awarded \$7.9 million by the US National Institutes of Health in Bethesda, Maryland, to test the nasal insulin spray on 240 volunteers showing signs of dementia. Teams across the US will monitor learning, memory, daily function and any brain changes using PET scans.

There are several other possible lines of attack: clinical trials are investigating the use of approved diabetes drugs such as metformin, exenatide, liraglutide and pioglitazone, which try to restore the balance of insulin and glucose in the blood or improve the insulin sensitivity of an organ. Arnold, for instance, plans to study the effect of metformin by measuring amyloid levels in the spinal fluid and testing the blood flow in the brain before and after treatment. "We want to see if these medicines work to decrease levels of these abnormal proteins in Alzheimer's disease and ultimately improve the patients' cognitive abilities, or at least prevent them from getting worse," he says. "We'll also see whether the drugs restore

other insulin functions like promoting synapse formation and regrowing neural connections." Other groups plan to use advanced brain imaging to see if these diabetes medications can shrink the beta amyloid plaques, which might reverse some of the brain damage.

For the time being, there are measures that everyone can take to help stave off cognitive decline. Since insulin resistance emerges from a bad diet, laying off fatty and sweet foods might help to reduce the risk of developing Alzheimer's. Conversely, diets rich in certain kinds of fatty acids might help the brain to maintain good insulin signalling (see "Food for thought", page 34). Exercise, too, can encourage the body to conquer insulin resistance – which may explain why regular physical activity reduces your risk of Alzheimer's by 40 per cent (*Annals of Internal Medicine*, vol 144, p 73).

"Even if you are 400 pounds and you haven't seen the back of the couch for six months, it's not too late. It's likely that any exercise will help, even in patients who've been diabetic for a long time. Get some of the insulin sensitivity back and stop accumulating so much amyloid," says McNay. "Potentially, even some of the amyloid that's built up might get broken down. As for the rest of us, extra trips to the gym are always a good idea, and this work shows that they help your brain as well as your body." ■

Bijal Trivedi is a writer based in Washington DC

98m

people in the US show some signs of insulin resistance, putting them at greater risk of Alzheimer's