Leptin fragments as a treatment for Alzheimer's disease

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What is the problem?

Alzheimer's disease (AD) is a form of dementia. It is a progressive neurodegenerative disorder which leads to severe cognitive impairments, including profound memory loss. It devastates lives. The World Health Organisation has predicted that by 2050, 152 million people will suffer from it. We urgently need a therapeutic strategy for AD.

What are we interested in?

Leptin is a hormone found in the body and is critical for weight regulation. But like many other hormones, it has another effect in brain, acting on communications between nerve cells (neurons). Brain leptin has been linked to AD and leptin-based therapies may be a treatment option. In early AD, build-up of a toxic protein called amyloid beta (Aβ), disrupts the proper working of the brain. Leptin has been shown to prevent this harmful effect of Aβ. Fragments of leptin also seem to have neuroprotective and cognitive enhancing effects. We wanted to further investigate the effect of fragments of leptin to see if they mirror the neuroprotective action of the whole leptin protein.

What did we do?

We investigated two 6 amino acid long fragments of leptin (hexamers): leptin(116-121) and leptin(117-122) to find out if they had anti-AD properties. We measured this by looking at a protein found on the surface of neurons, called GluA1. We know that in AD models, toxic Aβ causes a reduction in the amount of GluA1 at the cell surface, an effect that can be prevented by leptin. We grew neurons in the lab and used a technique called immunocytochemistry to fluorescently label GluA1 in the neurons. We used confocal microscopy to see where and how much GluA1 was present in neurons under different treatment combinations of Aβ and the leptin hexamers.

What did we find?

Treatment with Aβ induced a significant reduction in the amount of GluA1 seen at the surface of the cells, as seen in AD. Leptin(116-121) prevented this. In neurons treated with both Aβ and this leptin hexamer there was no significant change in the relative GluA1 intensity compared with untreated neurons (control) (see Figure 1A).

The ability of Aβ to reduce GluA1 surface expression was significantly inhibited in neurons treated with both Aβ and leptin(117-122). There was no significant change in the relative GluA1 intensity compared with untreated neurons (control) (See Figures 1B and 2).

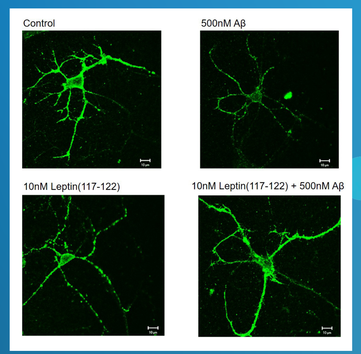

Figure 2 shows neurons grown in the lab under different treatment combinations of Aβ and the leptin hexamers. The neurons were viewed with a confocal microscope, with GluA1 stained green.

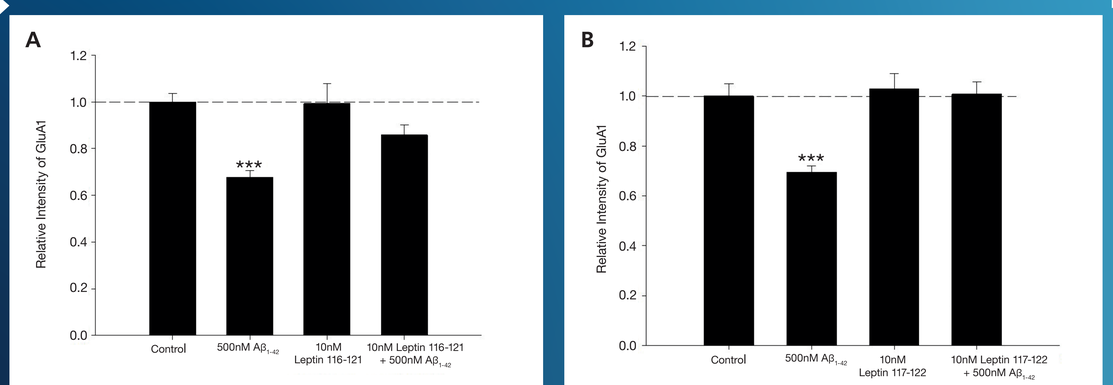

Figure 1 Aβ reduces the amount of GluA1 seen at the surface of neurons grown in the lab, as measured by the intensity of immunocytochemistry staining relative to untreated (control) cells. Both of the hexamers prevented this reduction, as seen when cells were treated with both Aβ and leptin(116-121) **(A)** or Aβ and leptin(117-122) **(B)**. (1nM = 1 billionth of a mole.)

What does this mean?

These results show that both leptin(116-121) and leptin(117-122) prevent the Aβ induced reduction of GluA1 surface expression. Leptin(117-122) was more potent, with a more complete blocking effect. The hexamers seem to mirror the neuroprotective actions of the full molecule, but further experiments will be required to clarify their effects in other AD models using cells grown in the lab as well as experiments in animal models, to investigate the potential cognitive effects. These findings add to the evidence that leptin could be a potential therapeutic target in AD treatment, and maybe in other neurodegenerative disorders.

Who am I?

I am a fourth year Neurosciences student at the University of Dundee. I completed my honours project where I investigated the effects of the (116-121) hexamer in a cellular model of Alzheimer's Disease, and am currently in my last semester of my BSc degree. After graduation I plan to travel before finding a job in the science sector.

Beth was supervised during her Vacation Scholarship project, *"Evaluation of the potential use of novel leptin-based hexamers in the treatment of neurodegenerative disease"*, by Dr Jenni Harvey.