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Research report

Prophylactic liraglutide treatment prevents amyloid plaque deposition, chronic inflammation and memory impairment in APP/PS1 mice

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HIGHLIGHTS

- Liraglutide can prevent the development of key biomarkers in a mouse model of AD.
- The study shows that the drug has the potential to prevent the development in the first place.
- The drug is on the market as a type 2 diabetes drug.
- It is currently in clinical trials in patients with AD.

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ABSTRACT

Type 2 diabetes is a risk factor for Alzheimer's disease (AD). Previously, we have shown that the diabetes drug liraglutide is protective in middle aged and in old APP/PS1 mice. Here, we show that liraglutide has prophylactic properties. When injecting liraglutide once-daily ip. in two months old mice for 8 months, the main hallmarks of AD were much reduced. Memory formation in object recognition and Morris water maze were normalised and synapse loss and the loss of synaptic plasticity was prevented. In addition, amyloid plaque load, including dense core congophilic plaques, was much reduced. Chronic inflammation (activated microglia) was also reduced in the cortex, and neurogenesis was enhanced in the dentate gyrus. The results demonstrate that liraglutide may protect from progressive neurodegeneration that develops in AD. The drug is currently in clinical trials in patients with AD.

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1. Introduction

Type 2 diabetes has been identified as a risk factor for Alzheimer's disease [25,31], presumably linked to an impairment in insulin signalling in the brain. In the brains of people with Alzheimer's disease, insulin signalling was found to be much impaired, even independently of a medical history of diabetes [29,44]. The incretin hormone Glucagon like peptide-1 (GLP-1) facilitates insulin signalling, and long-lasting GLP-1 analogues such as Liraglutide (Victoza®) are on the market as diabetes therapies [24]. Liraglutide crosses the blood-brain barrier and increases synaptic plasticity [16,27]. Liraglutide and other GLP-1 mimetics have been found to be neuroprotective in a range of neurodegenerative disorders [14,35].

We reported previously that liraglutide treatment improved cognitive function, reduced amyloid plaque deposition, inflammation, overall amyloid precursor protein (APP) and amyloid oligomer levels and enhanced long-term potentiation of synaptic transmission (LTP) in the hippocampus in 9 months old APP*swe*/PS1 ΔE9 (APP/PS1) mice that had been treated for 8 weeks [26]. At this stage, animals had already developed amyloid plaques and the first synaptic and memory impairments, comparable to patients in the early stage of Alzheimer's disease. Liraglutide also reversed disease progression in 16 months old APP/PS1 mice that had been treated for two months. Liraglutide significantly improved recognition and spatial memory, reduced beta amyloid plaque load, total APP and aggregated beta amyloid levels and chronic inflammation in the brain [28]. At 14 months, the amyloid plaque load of APP/PS1 mice

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had increased to maximum levels, and damage in the brain had already been established.

Insulin signalling is impaired in the brain of this APP/PS1 mouse model, similar to the insulin signalling impairment observed in the human brain [4]. Importantly, liraglutide has been shown to prevent this insulin de-sensitisation in the brain, as well as an ability to reverse some of the insulin signalling impairments in human AD brain tissue in an ex vivo assay [45].

The current study was designed to elucidate if liraglutide has a prophylactic effect when administered before plaque deposition and associated memory impairments are present in the APP/PS1 model. Animals were treated from 8 weeks of age onwards for 8 months once-daily at the previously established effective dose [26].

2. Materials and methods

2.1. Animals

$APP_{swe}/PS1_{\Delta E9}$ mice with a C57Bl/6 background were bred at the animal unit of the University of Ulster. Heterozygous males were bred with wild-type C57/Bl6 females bought locally (Harlan, UK). Offspring were ear punched and genotyped using PCR with primers specific for the APP-sequence (Forward "GAATTC-CGACATGACTCAGG", Reverse: "GTTCTGCTGCATCTTGGACA"). For details see [11]. Mice not expressing the transgene were used as wild-type controls. Male animals were used in all studies. Animals were caged individually and maintained on a 12/12 light–dark cycle (lights on at 08:00 h, off at 20:00 h), in temperature-controlled room (T:21.5 °C ± 1). Food and water were available ad libitum. Animals were handled daily for two weeks prior to commencement of the study.

APP/PS1 and wild-type animals were 8 weeks of age when treatment began. Mice were randomized and had blood glucose measured before initiation of their designated treatment, liraglutide (25 nm/kg bw) or saline (0.9% w/v). Liraglutide and saline were made up to a final volume of 10 ml/kg, with 0.9% saline used as vehicle for liraglutide and were injected intraperitoneally (i.p.) once daily (at 15:00 h). Treatment groups comprised $n = 12$. All experiments were licensed by the UK home office in accordance with the Animal (scientific procedures) Act of 1986.

2.2. Peptides

Liraglutide was purchased from GL Biochem Ltd. (Shanghai). The purity of the peptide was analysed by reversed-phase HPLC and characterised using matrix assisted laser desorption/ionisation time of flight (MALDI-TOF) mass spectrometry, with a purity >99%.

Peptides were reconstituted in ultrapure® water to a concentration of 1 mg/ml in polypropylene tubes and frozen in aliquots to permit fresh preparation of doses required for injection.

2.3. Blood glucose measurement

Blood glucose was measured from tail vein blood blood by an automated glucose oxidase procedure using the Ascencia® Contour® Blood Glucose Meter and corresponding analysis strips (Bayer Healthcare, Berkshire, UK).

2.4. Object recognition task

The object recognition task was conducted in a grey-coloured aluminium open-field arena (58 cm in diameter; 31 cm high wall) as previously described [1]. Objects for exploration were red cubes (1.8 cm diameter) and white balls (2.6 cm diameter). The arena and objects were cleaned with 70% ethanol between trials to prevent the build-up of olfactory cues.

Mice received a session of 5 min in the empty open-field, 24 h prior to exposure to objects, in order to habituate them to the apparatus and test room. Motor activity was recorded by total path, number of lines crossed, and speed. The number of rearing events (forepaws elevated from the floor) was considered to be an index of exploratory behaviour. The number of grooming sessions and the number of fecal pellets were recorded as measures of anxiety in mice.

Twenty-four hours after habituation, each mouse was subject to a 10 min acquisition trial, during which they were placed in the open-field in presence of two identical objects (cube or ball) situated at 15 cm from the arena wall. After a 3 h retention interval, the mice were placed back into the arena and exposed to the familiar object and to a novel object for a further 10 min. Object location and novel and familiar objects were randomized throughout the trial.

Total time spent exploring each of the two objects (when the animal's snout was directly toward the object at a distance ≤2 cm), was recorded. Recognition index was defined as the amount of time exploring the novel object over the total time spent exploring both objects multiplied by 100, and was used to measure recognition memory $(TB/(TA + TB)) \times 100$ where A represents familiar object and B, novel object. Object recognition data from all groups was analysed by Student *t*-test for each group, to compare time spent exploring the familiar object to time spent exploring the novel object. Animals were injected for 8 months prior to, and received their injection as normal at 3 pm on the day prior to open field and object recognition tasks, which were commenced at 9am to avoid acute drug effects.

2.5. Morris water maze task

The maze was made of white opaque plastic with a diameter of 120 cm and 40 cm high walls, and was filled with water at 25 °C to avoid hypothermia. A small escape platform (10 × 6.5 × 21.5 cm) was placed at a fixed position in the centre of one quadrant, 25 cm from the perimeter, and was hidden 1 cm beneath the water surface. The room contained a number of fixed visual cues on the walls.

2.5.1. Acquisition phase

The acquisition trial phase consisted of 4 training days (Day 1–4) and four trials per day with a 15-min inter-trial interval. Four points equally spaced along the circumference of the pool (North, South, East, West) served as the starting position, which was randomised across the four trials each day. If an animal did not reach the platform within 90 s, it was guided to the platform where it had to remain for 30 s, before being returned to its home cage. Mice were kept dry, between trials, in a plastic holding cage filled with paper towels. The path length and escape latencies were recorded ($n = 12$ per group).

2.5.2. Probe Trial

One day after finishing the acquisition task (Day 5), a probe trial was performed in order to assess the spatial memory (after a 24 h delay). The platform was removed from the maze and animals were allowed to swim freely for 60 s. Time spent in the target quadrant was assessed, as was spatial acuity, which measured the amount of time spent in the exact area where the escape platform had been located.

2.5.3. Reversal Morris water maze task

One day after completion of the Morris water maze task, a reversal training programme commenced. This involved changing the location of the escape platform and a 3-day acquisition phase, fol-

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