Progress Report

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Title of Project: Treating cholinergic degeneration in sleep apnoea to prevent Alzheimer's disease

Summary: (approximately 1,000 words)
Alzheimer's disease is the most common form of dementia, affecting ~30% of the elderly population. However, individuals who suffer from sleep apnoea are at 2-3 fold increased risk of developing this condition. Emerging evidence indicates that sleep apnoea, causing hypoxia, is a major risk factor for the development of sporadic Alzheimer's disease due to the death of a group of cholinergic neurons in the brain. This in turn leads to the production of amyloid plaques and cognitive decline. Here we will investigate (in mice and humans) whether continuous positive airway pressure (CPAP) treatment can stop or slow the cholinergic neuronal degeneration. We will also investigate (in mice) a possible alternative treatment strategy to CPAP therapy that could be developed to prevent cholinergic neuronal dysfunction in people with sleep apnoea, so as to reduce their risk of developing Alzheimer's disease. As sleep disturbances can occur up to 10 years prior to Alzheimer's disease, our findings could have major ramifications for initiating early intervention in patients with sleep apnoea with hypoxia, as a prophylactic, with the aim of lowering their risk of developing dementia.

Hypothesis vs Findings

Aim 1 Can CPAP treatment prevent basal forebrain degeneration?

Study 1. Human study: We aimed to test this hypothesis by determining whether the basal forebrain volumes of patients with obstructive sleep apnoea who are undergoing 12 month CPAP therapy are maintained compared to the volumes of untreated subjects. We obtained the MRI scans and clinical data for elderly subjects where 8 CPAP subjects were available. In addition, we obtained structural MRI scans from a number of longitudinal cohorts of sleep apnoea patients before and after CPAP treatment (n=15). We determined basal forebrain volumes from the MRI scans of subjects over the age of 55, at baseline and at 12 months, and calculated whether there was a significant decrease in basal forebrain volume in the untreated and CPAP-treated groups. In a retrospective analysis, we have found a significant decrease in basal forebrain volume after 12 months without CPAP treatment in OSA subjects, but only those people that showed cognitive decline leading to a diagnosis of AD within 24 months. No change in volumes was found in the CPAP group. However, because our CPAP treatment group was small and their age was much younger than the untreated AD group, we can not make any conclusions about the efficacy of CPAP. We will require a dedicated prospective study to answer this question in humans.

Study 2. Mouse study: In order to determine whether 'CPAP treatment' can protect cholinergic basal forebrain (cBF) neurons from the disordered breathing-induced hypoxia induced by mesopontine

(MPT) lesion, we placed mice in 'chambers' in which the oxygen (O_2) levels was 40% O_2 (normoxia is 20%), the level required to restore blood oxygen levels in MPT-lesioned mice to above 95% saturation. Mice were treated for 8-12 hours a day (during their sleep cycle) for 4 weeks in the high O_2 environment. Following immunostaining for the cholinergic marker cholinergic acetyl transferase (ChAT) in histological brain sections, the number of MPT and cBF neurons were counted. In support of our hypothesis, that hypoxia is responsible for cBF neuronal degeneration, the high O_2 environment prevented cBF neuron loss without affecting MPT cell number (Fig 1).

Unanswered Questions

Aim 1 Can CPAP treatment prevent basal forebrain degeneration (and therefore amyloid accumulation) Previous work has suggested that cBF neuronal loss is sufficient to induce Aβ accumulation. Therefore, we are currently testing whether the high O_2 treatment following MPT neuron lesioning can prevent accumulation of amyloid-beta, and cognitive dysfunction in the Alzheimer's disease APP/PS1 mouse model. Lesions have been performed but analysis is ongoing.

Aim 2 Can pharmacologically blocking $p75^{NTR}$ stop cBF death in the MPT lesion model?

Study 3. We will determine whether the cBF neurons of cBF-$ROSA^{c29/c29}$ mice are protected from MPT-induced degeneration. We have performed lesions on the mice from the cBF-$ROSA^{c29/c29}$ strain, which expresses our neuroprotective peptide, and their control non-c29-expressing littermates. Sections are currently being analysed. We hypothesise that c29 will block the $p75^{NTR}$ death signalling induced by hypoxia.

Study 4. If transgenic expression of c29 inhibits MPT lesion-induced cBF neuronal loss, we will next systemically administer c29 peptide (5mg/kg) via i.p. injections once a day to MPT-lesioned mice, starting 1 week after UTII-saporin toxin injection (before cBF neuron loss) for 4 weeks. A scrambled peptide will be administered as a control.

What these research outcomes mean

Outcomes: So far our experiments suggest that basal forebrain loss occurs coincident with cognitive decline in OSA patients and that (fig 1) maintaining blood O_2 saturation can prevent cBF degeneration induced by disordered breathing in mice.

Fig 1 unpublished data – for reporting purposes only- please do not reproduce or publicise