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Title:

Effects of incretin-based therapies on neurocognitive function in humans: a systematic review of the literature

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Abstract

We performed a PRISMA systematic review of incretin-based therapies and effects on neurocognitive function in humans. There was observational evidence to support dipeptidyl peptidase-IV inhibitors in improving cognition, whilst glucagon-like peptide-1 had positive effects on cerebral glucose metabolism. Powered clinical trials are now needed in patients with- and without diabetes.

1. Introduction

Dementia is expected to increase in worldwide prevalence from around 35.6 million in 2010 to approximately 65.7 million by 2030 [1]. However, current treatments for dementia are not disease-modifying and produce only modest effects on cognitive decline [2]. As such, novel treatment strategies are needed.

Incretin-based therapies, including dipeptidyl peptidase-IV (DPP-IV) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, act primarily to stimulate insulin secretion via the incretin effect [3]. More recently, however, incretin-based therapies been found to improve Alzheimer-like pathology in animal models [4,5]. However, human studies of incretin-based therapies on cognition have been far fewer. As more clinical trials are proposed, an appraisal of the current evidence base for incretin-based therapies on human cognition is warranted.

We have therefore conducted a PRISMA systematic review examining the effects of incretin-based therapies on neurocognitive outcomes in human studies. We hypothesised that both GLP-1 receptor agonists and DPP-IV inhibitors would be associated with improvements in cognitive function.

2. Methods

2.1. Design and literature search

Following PRISMA guidelines, we systematically searched Web of Science, MEDLINE and PubMed for papers dating from 1st January 1900 to 23rd November 2016 using the following search strategy (OR's omitted here):

(cognit*; dement*; alzheimer*; memory; brain; cerebral; positron emission; hippocamp*; csf; cerebrospinal; cerebro-spinal) AND (lixisenatide; glucagon-like peptide-1; glp-1; albiglutide; dulaglutide; alogliptin; linagliptin; dpp-iv; dipeptidyl; incretin; exenatide; sitagliptin; incretin-based; liraglutide; exendin; saxagliptin; vildagliptin) NOT (rat; mouse; mice).

2.2. Inclusion criteria

Studies were included if they used all of the following: 1) a licensed incretin-based therapy in human subjects; 2) pre-and post-treatment testing using i) a validated cognitive test; ii) cerebrospinal fluid amyloid/tau levels; iii) cerebral amyloid burden or glucose metabolism using positron emission tomography (PET); or iv) change in hippocampal atrophy using MRI; 3) a clinical trial or longitudinal observational study design; and 4) a minimum of 10 patients. Exclusion criteria were: 1) reanalysis of published data, 2) review article without original data; 3) study not published in English; and 4) isolated case reports. Reference lists of included papers were also searched.

2.3. Data extraction

The following were extracted for each paper: year, design, baseline diabetes status, baseline cognitive status, sample size, age, gender, treatment and duration, cognitive testing and central biomarkers of cognition.

2.4. Meta-analysis

For studies reporting clinical outcomes against controls, we planned to perform meta-analysis. However, as only three studies reported such data [6-8], all with varying study populations, meta-analysis was not performed.

3. Results

3.1. Overview

From 1787 titles examined after duplicates removed, 141 abstracts were read, 13 full-text papers studied and 7 studies met inclusion criteria (Figure 1). Five studies were interventional and two observational. There was significant heterogeneity in baseline cognitive status and in comorbidities. Both DPP-IV inhibitor studies and one GLP-1 receptor agonist study

specifically targeted patients with T2D, whilst the remaining four GLP-1 receptor agonists studies excluded diabetes patients. Study characteristics are summarized in [Table 1](#).

3.2. DPP-IV inhibitors

In an observational study of 240 people with T2D, DPP-IV inhibition was associated with 2-year improvement in a range of cognitive parameters compared to sulphonylurea, despite no difference in HbA1c change [8]. In a pilot study (n=11), addition of vildagliptin to metformin produced no change in cognitive performance after an average of 11 months. However, this study was severely limited by its brief cognitive assessment and small sample size [9].

3.3. GLP-1 receptor agonists

3.3.1. Liraglutide

In a 6-month double-blinded trial, liraglutide produced increased cerebral metabolism of glucose versus placebo in multiple regions of interest [7], although the study was not powered to detect clinical outcomes. In an open-label study in 19 patients with comorbid affective disorder, 4 weeks of liraglutide was associated with improvements in multiple cognitive domains, although the study was uncontrolled [10]. In a cross-over trial of liraglutide versus placebo, 17 days of liraglutide was not associated with improvements on any measure of cognition compared to placebo [11].

3.3.2. Exenatide

In a 2-year open-label randomised trial, exenatide produced greater improvement in cognitive function compared to usual care [6]. However, the study was limited its open-label design and potential confounding effects of comorbid Parkinson's disease. In a single-dose cross-over trial, exenatide was found to increase cerebral glucose metabolism in various regions compared to placebo [12]. No cognitive testing was performed.

4. Discussion

We systematically reviewed the effects of incretin-based therapies on neurocognitive function in humans. Despite a wide-ranging literature search, only seven studies were includable. We found promising observational evidence for DPP-IV inhibitors, whilst GLP-1 receptor agonists had positive effects on cerebral glucose metabolism in areas relevant to cognitive processing. No clinical trial of GLP-1 receptor agonists was powered to detect clinical effects and patients with diabetes were largely excluded. Trials of DPP-IV inhibitors were lacking.

Implications

Our review highlights the need for powered clinical trials of both GLP-1 receptor agonists and DPP-IV inhibitors for cognitive function in humans. Whilst several cognition trials are ongoing for GLP-1 receptor agonists, all exclude people with diabetes [13]. This may be a missed opportunity. Injectable GLP-1 therapies are likely to be safer and more acceptable in patients with T2D, whilst GLP-1 receptor agonists have positive effects on candidate pathways linking T2D with dementia, including hyperglycaemia, inflammation and depression [14,15].

4.1. Limitations

This review is limited by a lack of includable papers and lack of high-quality trial evidence. There was also significant between-study heterogeneity in terms of population, intervention and outcomes. In several studies, inclusion of patients with normal cognitive function may have limited effects.

4.2. Conclusion

There is currently inadequate evidence that incretin-based therapies prevent cognitive decline. However, observational findings for DPP-IV inhibitors are promising and GLP-1 receptor agonists produce consistently positive effects on cerebral glucose metabolism. Powered clinical trials are needed in patients at risk of cognitive decline, including those with- and without diabetes.

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Conflict of interest

None

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