Review
Targeting impaired nutrient sensing with repurposed therapeutics to prevent or treat age-related cognitive decline and dementia: A systematic review

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ABSTRACT

Background: Dementia is a debilitating syndrome that significantly impacts individuals over the age of 65 years. There are currently no disease-modifying treatments for dementia. Impairment of nutrient sensing pathways has been implicated in the pathogenesis of dementia, and may offer a novel treatment approach for dementia.

Aims: This systematic review collates all available evidence for Food and Drug Administration (FDA)-approved therapeutics that modify nutrient sensing in the context of preventing cognitive decline or improving cognition in ageing, mild cognitive impairment (MCI), and dementia populations.

Methods: PubMed, Embase and Web of Science databases were searched using key search terms focusing on available therapeutics such as ‘metformin’, ‘GLP1’, ‘insulin’ and the dementias including ‘Alzheimer’s disease’ and ‘Parkinson’s disease’. Articles were screened using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). The risk of bias was assessed using the Cochrane Risk of Bias tool v 2.0 for human studies and SYRCLE’s risk of bias tool for animal studies.

Results: Out of 2619 articles, 114 were included describing 31 different ‘modulation of nutrient sensing pathway’ therapeutics, 13 of which specifically were utilized in human interventional trials for normal ageing or dementia. Growth hormone secretagogues improved cognitive outcomes in human mild cognitive impairment and dementia populations. In animals, all investigated therapeutic classes exhibited some cognitive benefits in dementia models. While the risk of bias was relatively low in human studies, this risk in animal studies was largely unclear.

Conclusions: Modulation of nutrient sensing pathway therapeutics, particularly growth hormone secretagogues, have the potential to improve cognitive outcomes. Overall, there is a clear lack of translation from animal models to human populations.

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1. Introduction

Dementia is a syndrome affecting more than 5% of the world’s population over 60 years of age (Organisation, 2017). Although Alzheimer’s disease (AD) is the most common subtype of dementia, many other subtypes exist including; Vascular Dementia (VD), dementia with Lewy Bodies (LBD), Parkinson’s dementia (PD) and Frontotemporal Dementia (FTD) (Organisation, 2017). Ageing is the major risk factor for the development of all dementia subtypes (Society, 2016). Mechanistically, ageing is defined as an accumulation of molecular and cellular damage leading to a gradual decrease in physiological reserves (Organisation, 2017). As such it has been hypothesized that targeting ageing pathways may be a viable therapeutic option for treating dementia. One such pathway is the nutrient sensing pathway (Lopez-Otin et al., 2013), which relates to the detection of extracellular nutrients, for instance glucose-sensing via the highly evolutionarily-conserved insulin and IGF-1 signaling (IIS) pathway (Lopez-Otin et al., 2013). Other key inter-related effectors of the nutrient sensing pathway include the mammalian Target of Rapamycin (mTOR), which detects high amino acid concentrations, AMPK and sirtuins, which detect low energy states, and transcription factors known as Forkhead Box O proteins (FOXO) (Lopez-Otin et al., 2013; Mc Auley et al., 2017).

Deregulated nutrient sensing is increasingly thought to play a role in the pathophysiology of neurodegenerative diseases such as AD (Fluegge, 2019; Liu and Sabatini, 2020; Shafei et al., 2017). One of the most fundamental pathological mechanisms shared by subtypes of dementia is neurodegeneration (Moya-Alvarado et al., 2016). This process is often accompanied by impaired neurogenesis (Gao et al., 2017), and abnormal protein aggregations (Dugger and Dickson, 2017), which might be driven by dysfunctional autophagy (Wong and Cuervo, 2010). Nutrient sensing is increasingly emerging as a key modulator of the neurogenesis process (Fidaleo et al., 2017), and, via mTOR, of the autophagic process (Jahrling and Laberge, 2015). In mice, higher mTOR signaling has been associated with Aβ accumulation, whilst decreasing mTOR signaling has been shown to reduce Aβ levels (Caccamo et al., 2010). Human post-mortem studies have found higher levels of activated mTOR (Griffin et al., 2005; Li et al., 2005) and its downstream effectors (Tramutola et al., 2015) in affected brain regions of AD and MCI patients compared to controls. The broad role that deregulated nutrient sensing may play in dementia offers a possible therapeutic pathway, as many nutrient sensing-modulating therapeutics, such as metformin, already exist (Rena et al., 2017). To date, however, the therapeutic indications of these medications do not include neurodegenerative diseases (Australian Medicines Handbook Pty Ltd., 2021).

The aim of this systematic review is to summarize the evidence in human and animal populations for the use of Food and Drug Administration (FDA) approved nutrient sensing-modifying therapeutics to prevent age-related cognitive decline or improve cognition in ageing, mild cognitive impairment (MCI), and dementia populations.

2. Methods

2.1. Selection of articles

The protocol of this systematic review was registered at PROSPERO International prospective register of systematic reviews (Reg #: CRD42018091645). PubMed, Web of Science and Embase databases were searched until the 29th March 2019. The search strategy (Heard et al., 2018) focused on key search terms for the dementias, such as; AD, VD, PD, LBD, and ageing. The strategy also included key terms for nutrient modulating proteins and therapeutics, such as; insulin, mTOR, glycogen synthase kinase-3 (GSK-3), metformin, dipeptidyl peptidase-4 (DPP-4) and glucagon-like peptide-1 (GLP-1). The complete search strategy has been previously published (Heard et al., 2018). In addition snowballing was used to search references within included articles.

2.2. Eligibility criteria

Articles included in this review met the following inclusion criteria: 1) Population – animals or humans; normal ageing or neurodegenerative disease, such as dementia (AD, VD, PD, or LBD). Populations likely to have a higher pace of ageing such as Type 2 Diabetes Mellitus (T2DM), insulin-resistant, or obesity, were also included. In animals, normal ageing was defined as a strain not at a greater propensity to develop dementia and not manipulated to mimic dementia. Dementia models were defined as strains at a greater propensity to develop dementia compared to normal ageing strains or being modified to become more likely to develop dementia. In humans, normal ageing was defined as a population not suffering from dementia or mild-cognitive impairment. 2) Study design – interventional studies with comparators; including randomized or quasi-randomised controlled trials, cohort studies, and pre/post studies. 3) Intervention – FDA approved therapeutics known to influence the nutrient sensing pathway. 4) Outcome – cognitive function measured using neuropsychological tests. In animals, using mice as an example, neuropsychological tests may include spatial memory tests (Morris water maze [MWM], radial arm water maze [RAWM]), associative learning tasks (passive avoidance), recognition memory tests, and others (Rozga and Wetsel, 2006). In humans, examples of neuropsychological measures include Mini-Mental State Examination (MMSE), Rowland Universal Dementia Assessment Scale (RUDAS), Neuropsychiatry Unit Cognitive Assessment Tool (NUCOC), Montreal Cognitive Assessment (MOCA), Clinical Dementia Rating Scale Sum of Boxes (CDR-SoB), Addenbrooke’s Cognitive Examination (ACE) or AD Assessment Scale-cognitive subscale (ADAS-Cog) (Lin et al., 2013).

Articles were excluded if they met one of the following exclusion criteria: 1) exercise as the sole intervention, 2) in vitro data only, 3) conference abstract, review, editorial, or letter to the editor, 4) ≤5 population size for human studies, 5) intraperitoneal/intravenous streptozotocin-induced diabetes models unless specifically stated as recapitulating a T2DM phenotype, due to its otherwise inappropriate- ness in mimicking the pathogenesis of age-related dementia following the onset of T2DM diabetes, 6) intracerebroventricular streptozotocin-induced models without reporting a desired cognitive endpoint of either cognitive decline or dementia, due to their inappropriateness in mimicking the pathogenesis of human AD (Grieb, 2016), and 7) published in a language other than English.

2.3. Article selection and data extraction

Three reviewers (DH, CT and TR) independently screened the titles and abstracts for inclusion. Full text articles were then screened by two independent reviewers (DH and TR) to isolate articles of interest. A fourth reviewer (ABM) resolved any disagreements between the reviewers. Articles were screened using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Included studies were separated into the following four groups for data extraction: 1) proteostasis - repurposed therapeutic (please refer to (Heard et al., 2018)), 2) proteostasis - novel intervention (defined as a novel molecule, botanical extract, or dietary manipulation), 3) deregulated nutrient sensing - repurposed therapeutic (reported here) and 4) deregulated nutrient sensing – novel intervention. Where an intervention is thought to modify both pathways (for example the mTOR inhibitor, rapamycin) it was included in the loss of proteostasis group. Therapeutics that were investigated in articles that passed this selection process were then screened using the FDA website to ensure that they met with FDA approval. This systematic review followed the PRISMA guidelines (Supplementary Table F) and focuses on deregulated nutrient sensing and repurposed therapeutics.

The following variables were independently extracted for all articles by two reviewers (BK and DH): author, year of publication, study design, animal model/population (dementia subtype or normal ageing), metabolic status (T2DM, insulin-resistance or normal), sample size, age, sex,
baseline cognition/stage of disease, duration of intervention, cognitive outcome, therapeutic, comparator group, and hallmark(s) of ageing targeted by the intervention. For articles using animal models, the following additional variables were extracted: species, method of dementia induction, and method of metabolic disease induction.

For binary outcomes the number of events and total number in groups, percentage of events or ratios with confidence intervals, were extracted; for continuous outcomes, mean or median, with standard deviation, standard error, confidence intervals or interquartile range, and number of participants, were extracted, along with other reported results such as mean difference, p-values, or F-statistic for overall measures of cognitive function.

2.4. Data analysis

A semi-quantitative data analysis was performed on extracted outcome data. Dementia models were considered preventative if the intervention was administered prior to the onset of dementia, and were considered to be therapeutic if the intervention was administered after dementia onset. For animal and human studies, an overall positive effect of the administered therapeutic on cognitive performance was defined where a positive primary cognitive outcome was reported, or >50% of the cognitive tests demonstrated a statistically significant improvement in the treatment group compared to the comparator group. A moderately-positive result was defined where ≥20% of positive cognitive outcomes were observed, or a single cognitive composite test (e.g. MMSE), demonstrated a statistically significant improvement in the treatment group compared to the comparator group. A finding was considered negative where <20% of the cognitive outcomes were positive in the treatment group compared to the comparator group. Finally, a detrimental treatment outcome was defined as a statistically significant decrease in cognitive performance for the treatment group compared to the comparator group.

Extracted outcome data for each reported population in all therapeutic classes was then stratified according to cohort (normal ageing or MCI/dementia). In both animals and human studies, a therapeutic class was considered overall to have a beneficial effect on cognition if ≥50% of all reported populations (of species) within a given cohort reported an overall positive effect of the administered therapeutic on cognitive performance. The size of each population was also taken into account, whereby a study with larger populations showing no effect of an administered therapeutic on cognition may warrant reconsideration of a therapeutic class’ overall efficacy if studies with smaller populations reported a beneficial cognitive effect.

To investigate for the presence of any correlates that may be found within therapeutic classes (including T2DM status, sample size, population age etc.), populations were ranked in order of: effect of administered therapeutic on cognition (positive, moderately-positive, negative, detrimental effect), followed by population cohort (AD, PD, VD, MCI, dementia, normal ageing), method of induction of dementia/metabolic disease (for animals), duration of administered therapeutic, dose of administered therapeutic, and were visually examined for any indications of bias.

Articles within therapeutic classes were compared for their amenability to meta-analysis, including aspects such as: cohort, cognitive outcome measure, test condition, unit of test, and reported comparative method by which measures of significance were made within the article (Stone and Rosopa, 2017).

2.5. Registered human trials

To provide an overview of the progress in the field of repurposing therapeutics in humans to prevent the onset of age-related cognitive decline or treat mild cognitive impairment (MCI) and dementia, clinical trials registered before 4th of July 2020 that have not yet provided results, were summarized by searching clinicaltrials.gov. The conditions: aging; mild cognitive impairment; Alzheimer disease; vascular dementia; Parkinson disease; Lewy Body disease were key words that were searched for each of the therapeutic classes, for studies of all phases utilizing adult participants.

2.6. Risk of bias

The risk of bias was assessed by two reviewers (BK, DH) using the Cochrane Risk of Bias tool v 2.0 for human studies (Higgins et al., 2011) and SYRCLE’s risk of bias tool for animal studies (Hooijmans et al., 2014). The Cochrane Risk of Bias tool v 2.0 analyses bias using six key sources of bias, specifically: sequence generation, allocation concealment, blinding of participants and personnel, outcome assessment, incomplete outcome data, and selective outcome reporting. Each of these was denoted ‘green’ for ‘low risk’ if this aspect was reported and deemed to mitigate bias, ‘orange’ for ‘some concerns’ if anything less than an absolute mitigation of bias was reported, and ‘red’ for ‘high risk’ if this aspect was reported and deemed to encourage bias. SYRCLE’s risk of bias tool for animal studies analyses bias using the above categories but also includes baseline characteristics, and random housing. Each of these categories was denoted ‘green’ for ‘low risk’ if this aspect was reported and deemed to mitigate bias, ‘blue’ for ‘unclear’ if this aspect was not reported, and ‘red’ for ‘high risk’ if this aspect was reported and deemed to encourage bias. Overall, a given human or animal study was classified as low risk of bias if <2 sources of bias was deemed to have ‘some concerns’, and no source of bias was deemed to have high risk of bias. Possible financial conflict of interest was assessed by evaluating disclosed affiliations to a known pharmaceutical company.

3. Results

3.1. Study selection and characteristics

Overall, 114 articles were analyzed (animals n = 91 articles and human n = 23 articles), of which 81/91 articles focused on a dementia model in animals (58/91 mice as the experimental model), while 17/23 articles focused on MCI/dementia pathology in humans (Fig. 1). Table 1 provides an overview of the population demographics for all articles, and the domains of cognition tested. For a detailed description of all articles please refer to Supplementary Tables A.1 and A.2. Overall 32 nutrient sensing-modifying therapeutics, and seven combinations, have been tested for their effect on cognitive outcomes in either animal or human subjects. Of these, in animal models, GLP-1 agonists were the most tested therapeutic (13/91), followed by glitazones (10/91). In human studies, intranasal insulin was the most tested therapeutic (7/23), followed by glitazones (5/23). Glitazones, GLP-1 agonists, growth hormone, growth hormone secretagogues, metformin, and intranasal insulin, have been assessed in both animal and human subjects. For a detailed description of all reported cognitive outcomes please refer to Supplementary Tables B.1 and B.2. Fig. 2 provides a summary of the results of all interventions tested. Fig. 3 shows the status of interventional trials registered by 4th July 2020 on clinicaltrials.gov that have not yet released their results, investigating the influence of nutrient sensing-modifying therapeutics on cognitive outcomes in human populations. For a detailed description of the status of these registered interventional trials please refer to Supplementary Table C.

3.2. Glitazones

Glitazones regulate gene expression by binding to the nuclear transcription regulator peroxisome proliferator-activated receptor-gamma, to enhance insulin sensitivity and action. They are currently approved by the FDA for use as monotherapy or in combination with sulfonylureas or metformin for the management of T2DM (Eggleton and Jialal, 2019). Overall, 15/114 studies (10 animal, 5 human) investigated the effect of glitazones on cognition in normal ageing (6/15 studies) or dementia...
(15/15 studies) populations. These studies sometimes investigated more than one disease population. In animals, across these 10 studies, 10 normal ageing populations (Baraka and ElGhotny, 2010; Denner et al., 2012; Jiang et al., 2012; Liu et al., 2010; Masciopinto et al., 2012; Rodriguez-Rivera et al., 2011) and 18 dementia populations (Baraka and ElGhotny, 2010; Denner et al., 2012; Gad et al., 2016; Jiang et al., 2012; Kummer et al., 2015; Li et al., 2018; Liu et al., 2010; Masciopinto et al., 2012; Rodriguez-Rivera et al., 2011; Toledo and Inestrosa, 2010) have been assessed, including two studies with preventative models (Masciopinto et al., 2012; Rodriguez-Rivera et al., 2011). Glitazones likely have an overall significant beneficial effect on cognition in animal therapeutic dementia models, but not in preventative dementia models or normal animal ageing models (Fig. 2). This effect was independent of the method of disease induction (T2DM or otherwise), administered therapeutic, dose, duration, sample size, cognitive domain assessed or quality of the article (Fig. 4a and Supplementary Table B.1). In humans, across these five studies, glitazones overall did not positively affect cognitive outcomes in 27 MCI/dementia populations (Gold et al., 2010; Harrington et al., 2011; Sato et al., 2011; Tzimopoulou et al., 2010; Watson et al., 2005) (Fig. 2).

### 3.3. GLP-1 agonists

GLP-1 agonists function by stimulating insulin secretion via the incretin response, and are approved for use in T2DM (Collins and Costello, 2019). Overall, 15/114 studies (13 animal, 2 human) investigated the effect of GLP-1 agonists on cognition in normal ageing (6/15 studies) or dementia (13/15 studies) populations. These studies sometimes investigated more than one disease population. In animals, across these 13 studies, 8 normal ageing populations (Huang et al., 2012; Isacson et al., 2011; McClean and Holscher, 2014a, b; Wang et al., 2016) and 20 dementia populations (Bomba et al., 2013; Bomfim et al., 2012; Gad et al., 2016; Gumuslu et al., 2016; Kamble et al., 2016; Lennox et al., 2014; Li et al., 2016; McClean and Holscher, 2014a, b; Solmaz et al., 2015; Wang et al., 2016) have been assessed, including one study with a preventative model (Wang et al., 2016). GLP-1 agonists likely have an overall significant beneficial effect on cognition in animal therapeutic dementia populations (including a therapeutic VD model (Li et al., 2016)), but not in normal ageing populations (Fig. 2). Additionally, a single rat preventative model showed a beneficial effect on cognitive outcomes (Fig. 2). This effect was independent of the method of disease induction (T2DM or otherwise), administered therapeutic, dose, duration, sample size, cognitive domain assessed or quality of the article.
## Table 1

Study designs of nutrient sensing-modifying therapeutics and cognitive tests in animal and human subjects, stratified by species.

| Species | Experimental model | A, n | G, n | Rx, n | Ctrl, n | Cognitive tests                                      | Domains of cognition                                                                 |
|---------|--------------------|------|------|-------|---------|------------------------------------------------------|---------------------------------------------------------------------------------------|
| **Glitazones** |                     |      |      |       |         |                                                      |                                                                                       |
| Mouse   | AD (TG), AD + T2DM (TG + Streptozotocin IV) | 5    | 12   | 145   | 124     | FCT, MWM, NOR                                       | Contextual memory, hippocampal memory formation, cognitive function, short and long-term spatial memory, ability to build spatial relationships, fear-conditioned learning |
|         | AD (TG)            | 1    | 1    | NR    | NR      | MWM, MFT                                            | Spatial memory, memory flexibility                                                   |
|         | D + T2DM (Streptozotocin IV + HFD) | 1    | 2    | 20    | 10      | MWM, YM                                             | Learning and memory behaviour                                                        |
| Normal ageing |                  | 4    | 8    | 99    | 85      | FCT, STT, YM, MWM, NOR                               | Contextual memory, learning and memory behaviour, short and long-term spatial memory, ability to build spatial relationships, fear-conditioned learning |
| Rat     | AD (AB ICV)        | 1    | 1    | 9     | 8       | MWM, PAT                                            | Spatial memory, learning and memory performance, change of learning and memory abilities |
|         | D + IR (HFD)       | 2    | 2    | 20    | 20      | ERAM, MWM                                           | Spatial memory, learning and memory performance, change of learning and memory abilities |
| Normal ageing |                | 2    | 2    | 20    | 20      | MWM, PAT                                            |                                                                                       |
| Human   | AD/MCI             | 5    | 27   | 3524  | 917     | ADAS-Cog, CIBIC+, NPI, DAD, MMSE, Q1 & 7 from ADAS-Cog, CDR-SB, ADAS-Jcog, WMS-R logical memory I, FAB, CF, BSRT, SR, SSA | Cognition, global function, behavioural and psychological symptoms of dementia, ability to perform activities of daily living, cognitive status, short-term memory, changes in cognition and global function, verbal memory, selective attention, category fluency |
| **GLP-1 agonists** |                    |      |      |       |         |                                                      |                                                                                       |
| Mouse   | AD (TG)            | 4    | 10   | 95    | 59      | MWM, NOR, RMWM, OPT                                 | Spatial memory, object recognition memory, spatial learning, motor activity, speed, anxiety and exploratory behaviour, recognition memory |
|         | D + T2DM (Streptozotocin IV), D (Pentyleneetrazole IP), D + IR (HFD) | 3    | 4    | 36    | 30      | EPM, PAT, OPT, MWM, NOR                              | Spatial memory function, emotional memory function, locomotor activity, anxiety-behaviour, motor activity, speed, anxiety and exploratory behaviour, recognition memory |
|         | VD + T2DM (MCAO + db/db mice) | 1    | 1    | 6     | 6       | NSB                                                 | Motor and cognitive function                                                          |
| Normal ageing |                | 3    | 6    | 85    | 49      | MWM, NOR, RMWM, OPT                                 |                                                                                       |
| Rat     | AD (Streptozotocin ICV), AD (AB ICV) | 2    | 2    | 17    | 17      | PAT, MWM                                           | Cognitive performance, spatial learning and memory ability                             |
|         | D + IR (HFD), D (Scopolamine IP) | 2    | 3    | 26    | 16      | ERAM, MWM                                           | Learning and memory, cognitive behaviour                                               |
| Normal ageing |                | 2    | 2    | 21    | 23      | ERAM                                               | Hippocampus-based cognitive performance                                               |
| Human   | AD                 | 1    | 1    | 15    | 11      | BVRT, CVLT-IL, &-KEFS, RCFT, PP, WAIS-III, WASI: Vocabulary and Matrix Reasoning | Working memory, processing speed, visuospatial and constructional abilities, verbal and visual memory, verbal fluency, executive functioning, and fine motor abilities |
| Normal ageing |                | 1    | 1    | 18    | 20      | WMS-IV                                             |                                                                                       |
| **Growth hormone** |                  |      |      |       |         |                                                      |                                                                                       |
| Rat     | Normal ageing      | 1    | 1    | 12    | 12      | MWM                                                 | Spatial learning                                                                      |
| Human   | Normal ageing      | 1    | 1    | 26    | 26      | TB, MMSE, DSST                                      | Visual and motor tracking and attention, orientation, attention, calculation, language, memory, cognitive impairment |
| **Growth hormone secretagogues** |                |      |      |       |         |                                                      |                                                                                       |
| Mouse   | AD + T2DM (TG + HFD) | 1    | 1    | 9     | 10      | MWM                                                 | Spatial learning                                                                      |
| Rat     | AD (Monosodium L-glutamate IP) | 1    | 1    | 6     | 6       | BMT                                                | Memory, executive function, word fluency, episodic memory                             |
| Human   | MCI                | 2    | 3    | 39    | 39      | EF, VM, VisM                                        | Memory, executive function, word fluency, episodic memory, problem solving and psychomotor processing speed, working memory, reaction time, cognitive processing speed, highly over-learned verbal knowledge/crystallised intelligence |
| Normal ageing |                | 3    | 4    | 86    | 92      | EF, VM, VisM, WAIS-R, SDT, FINDA, LETSET, CATFLU, FAS |                                                                                       |
| **Metformin** |                     |      |      |       |         |                                                      |                                                                                       |
| Mouse   | AD (AIC3), AD (TG) | 2    | 2    | 16    | 16      | MWM                                                 | Spatial learning, short-term memory, spatial learning and memory                       |
|         | D + T2DM (db/db mice), AD + IR (HFD) | 3    | 3    | 38    | 38      | MWM                                                 | Spatial learning, short-term memory, cognitive performance, spatial learning and memory |
| Normal ageing |                | 2    | 4    | 58    | 58      | MWM, DAT                                            |                                                                                       |
| Rat     | D + IR (HFD), D + T2DM (Scopolamine IP) | 2    | 3    | 44    | 32      | MTP                                                | Cognitive performance                                                                 |
| Normal ageing |                | 1    | 1    | 16    | 16      | MTP                                                |                                                                                       |
| Human   | Normal ageing + IR | 1    | 1    | 776   | 755     | SEVLT, DSST, AF, LF, CCM                            | Memory, frontal-executive abilities                                                  |

(continued on next page)
**Table 1 (continued)**

| Species | Experimental model | A, n | G, n | Rx, n | Ctrl, n | Cognitive tests | Domains of cognition |
|---------|--------------------|------|------|-------|---------|-----------------|---------------------|
| Mouse   | AD (TG), AD (SAMP8 mice) | 2    | 10   | 103   | 54      | OFT, MWM, RMWM, TMT, NOR | Anxiety and exploratory activities, spatial learning and memory, Behavioural plasticity, hippocampal dependence of memory, declarative memory |
|         | Normal ageing      | 1    | 1    | 5     | 5       | TOD, ORL, NOR | Short and long-term object memory recognition, olfactory discrimination, odour reversal learning |
| Rat     | AD (Streptozotocin ICV) | 1    | 1    | 15    | 14      | OFF, MWM | Cognitive function |
|         | Normal ageing      | 2    | 8    | 80    | 50      | MWM | Spatial learning, short-term memory, spatial learning and memory |
| Human   | AD/MCI             | 5    | 29   | 228   | 108     | DSR, DSRS, ADAS-Cog, ADCS-ADL, VM, DNB, BVRT, SCWIT, IVMC, ADAS-Cog12, WMS-RLM | Cognition, verbal memory, verbal working memory, visuospatial working memory, executive function, functional ability, delayed memory, functional status, memory, praxis, orientation, and language, ADL’s, delayed verbal memory, memory and disability |
|         | AD/MCI             | 2    | 5    | 35    | 35      | SR, LR, SOPT, SCWIT, VS, RBANS, WAS-IV, TM, BNT, SMT | Verbal declarative memory, selective attention, visual search, learning/memory, language, attention/executive function, visuospatial function, olfaction |
|         | Normal ageing      | 1    | 2    | 35    | 35      | SR, LR, SOPT, SCWIT, VS | Verbal declarative memory, visual working memory, selective attention, visual search |
| Insulin infusion | Human AD/MCI | 2    | 4    | 30    | 30      | MR, SCWIT, DLM, SRT, SR, BSRT, SOPT | Attention and working memory, verbal episodic memory, logical memory, verbal memory, complex attention |
|         | Normal ageing      | 1    | 2    | 30    | 0       | MR, SCWIT | Attention and working memory |
|         | Normal ageing      | 3    | 3    | 72    | 72      | DLM, SRT, SR, MMSE, SCWIT, BSRT, SOPT | Verbal episodic memory, logical memory, declarative memory, general orientation and cognitive ability, selective attention, verbal memory, complex attention |
| Octreotide | Human AD/MCI | 1    | 3    | 16    | 16      | SR, BSRT, SCWIT, SOPT | Verbal memory, complex attention |
|         | Normal ageing      | 1    | 1    | 19    | 19      | SR, BSRT, SCWIT, SOPT | Verbal memory, complex attention |
| Octreotide + insulin infusion | Human AD/MCI | 1    | 3    | 16    | 16      | SR, BSRT, SCWIT, SOPT | Verbal memory, complex attention |
|         | Normal ageing      | 1    | 1    | 19    | 19      | SR, BSRT, SCWIT, SOPT | Verbal memory, complex attention |
| Beta blockers | Mouse AD (TG), AD (SAMP8 mice) | 2    | 3    | 24    | 24      | NOR, FCT | Spatial working memory, recognition memory, cognitive memory |
|         | D + IR (corticosterone) | 1    | 1    | 8     | 8       | NOR | Recognition memory |
|         | Normal ageing      | 3    | 4    | 32    | 32      | NOR, FCT | Spatial working memory, recognition memory, cognitive memory |
| DPP-4 inhibitors | Mouse AD (TG) | 2    | 5    | 34    | 13      | MWM, YM, OPT | Reference and working memory, spatial learning function, spontaneous exploratory activity and anxiety-like behaviour |
|         | D (Pentylenetetrazole IP), D (Klotho +/- mice) | 2    | 3    | 21    | 21      | EPM, PAT | Anxiety-behaviour, cognitive impairment |
|         | Rat AD (Streptozotocin ICV), AD + T2DM (AB ICV + Streptozotocin IP), AD (AB ICV) | 3    | 6    | 65    | 35      | RAM, HBT, PAT, MWM | Reference and working memory, learning deficits in a food-motivated complex HB apparatus, measure of cognitive decline, spatial learning and memory |
|         | D (Scopolamine IP), D + IR (HFD) | 3    | 4    | 38    | 28      | MWM | Cognitive behaviour, cognitive function |
|         | Normal ageing      | 3    | 4    | 40    | 30      | MWM, NOR | Object recognition memory |
|         | Melatonin         | Mouse AD (TG) | 1    | 1    | 11    | 13      | NOR | Learning and memory |
|         | D (Scopolamine IP) | 1    | 1    | 14    | 14      | MWM, YM | Spatial working memory |
|         | Normal ageing      | 1    | 1    | 12    | 16      | NOR | Learning and memory |
|         | Rat AD (OXYS rats) | 1    | 1    | 25    | 25      | EPM, OPT, ERAM | Anxiety-behaviour, locomotor and exploratory activity, learning and memory |
|         | Normal ageing      | 1    | 1    | 25    | 25      | EPM, OPT, ERAM | Anxiety-behaviour, locomotor and exploratory activity, learning and memory |
|         | N-methyl-D-aspartate receptor antagonist | Mouse AD (TG), AD + IR (TG + HFD) | 1    | 2    | 20    | 20      | MWM, NOR | Spatial memory and learning, hippocampal-dependent recognition memory |
|         | Rat                | 3    | 4    | 35    | 33      | MWM, PAT | (continued on next page) |
Table 1 (continued)

| Species Experimental model | A, n | G, n | Rx, n | Ctrl, n | Cognitive tests | Domains of cognition |
|----------------------------|------|------|-------|---------|-----------------|----------------------|
| AD (Streptozotocin ICV), AD + T2DM (AB ICV + Streptozotocin IP), AD (Poly-APS/Tau ICV) | | | | | | Learning and memory capacity, measure of cognitive decline, spatial reference memory |
| **PDE-inhibitors** | | | | | | Prefrontal function |
| Monkey Normal ageing | 1 | 6 | 14 | 14, pre-post | OR | |
| Mouse AD (TG) | 2 | 2 | 21 | 20 | MWM, FCT | Spatial memory, contextual memory, spatial learning and cognitive performance |
| AD (AB ICV) | 1 | 4 | NR | NR | MWM | Spatial memory, immediate spatial working memory |
| D (SAMP8 mice), D (Scopolamine SC) Normal ageing | 2 | 5 | 45 | 45 | MWM, YM | Spatial memory, contextual memory, hippocampal-dependent context conditioning, long-term memory formation, hippocampal-dependent long-term spatial memory, memory |
| Normal ageing | 5 | 15 | 158 | 167 | MWM, FCT, FTC, NOR | |
| **Selective serotonin reuptake inhibitors** | | | | | | |
| Mouse AD (TG) | 1 | 1 | 20 | 20 | MWM | Spatial learning ability |
| Rat D (Forskolin ICV) | 1 | 1 | 12 | 12 | MWM | Spatial learning and memory |
| **Statins** | | | | | | |
| Mouse AD (AB ICV) | 2 | 2 | 18 | 18 | MWM, YM | Spatial memory, long-term memory, short-term memory |
| Normal ageing | 2 | 2 | 22 | 22 | MWM, YM | Spatial cognitive performance, spatial memory |
| Normal ageing | 1 | 2 | 20 | 10 | MWM, YM | Long-term memory, short-term memory |
| **Acarbose** | | | | | | |
| Mouse D (SAMP8 mice) Normal ageing stress resistant, Normal ageing stress susceptible | 1 | 2 | 16 | 16 | MWM | Spatial learning and referential memory |
| **Adrenoceptor agonist** | | | | | | |
| Chicken AD (AB intra-cortical) | 1 | 9 | 108 | 48 | DAT | Memory retention |
| **AMPK activator** | | | | | | |
| Mouse AD + T2DM (TG + Streptozotocin ICV) | 1 | 1 | 10 | 10 | MWM, NOR | Cognitive function |
| **Amylin & analogues** | | | | | | |
| Mouse AD (TG), AD (SAMP8 mice) Normal ageing | 2 | 3 | 30 | 30 | YM, MWM, NOR | Short-term memory, long-term spatial memory |
| Normal ageing | 1 | 1 | 10 | 10 | YM, MWM | Short-term memory, long-term spatial memory |
| **Angiotensin receptor blockers** | | | | | | |
| Mouse AD (TG) | 1 | 2 | 14 | 14 | MWM | Learning and memory |
| Normal ageing | 1 | 2 | 14 | 14 | MWM | Learning and memory |
| **Anti-IL1R antibody** | | | | | | |
| Mouse AD (TG) | 1 | 1 | 8 | 8 | MWM | Cognitive and behavioural performance |
| **Bioflavanoid** | | | | | | |
| Mouse AD (TG) | 1 | 2 | 24 | 12 | NOR, MWM | Hippocampal-dependent cognition, amygdala and hippocampal function |
| **Caffeine** | | | | | | |
| Mouse AD (TG) | 1 | 1 | 6 | 7 | RAWM, PR | Recognition memory, spatial reference learning and memory |
| Normal ageing | 1 | 1 | 8 | 11 | YM, MWM, CP, PR, RAWM | Working memory, identification and recognition |
| **Dexibuprofen** | | | | | | |
| Mouse AD (TG) | 1 | 1 | 10 | 10 | NOR | Hippocampal-dependent recognition memory |
| **Gonadotropin releasing hormone agonist** | | | | | | |
| Mouse AD + Ovariectomised (TG) | 1 | 1 | 6 | 6 | MWM | Hippocampal-dependent spatial learning and memory |
| **ICV insulin** | | | | | | |
| Rat AD (Streptozotocin ICV) | 1 | 1 | 7 | 7 | MWM | Learning and memory capability |
| IGF-1 Mouse AD (TG) | 1 | 1 | 12 | 12 | MWM | Spatial memory |
| JNK inhibitor | | | | | | |
| Mouse AD (SAMP8 mice) Normal ageing | 1 | 1 | 10 | 10 | MWM | Spatial memory |
| **Rho-kinase inhibitor** | | | | | | |
| Rat AD (Streptozotocin ICV) | 1 | 1 | 6 | 6 | MWM, NOR | |

(continued on next page)
Alzheimer agonists do not have a significant effect on cognition in the human population, with only 5/114 studies showing a beneficial effect on cognition in normal ageing populations. Growth hormone secretagogues likely have a significant effect on cognition in animal therapeutic dementia models.

### 3.4. Growth hormone

Growth hormone (GH) receptors are present in many organs, and the many metabolic and growth-related effects of GH are accomplished both directly via receptor-signaling, and indirectly via insulin-like growth factor (IGF) signaling (Brooks and Waters, 2010). GH use is approved by the FDA for the treatment of GH deficiency, hypopituitarism, AIDS wasting syndrome, and short bowel syndrome (Sigalos and Pastuszak, 2018). Overall, 2/114 studies (1 animal, 1 human) each investigated the effect of GH on cognition in one normal ageing population. GH may have a beneficial effect on cognition in normal ageing animals (Ramsey et al., 2004), and a possible positive effect in normal ageing humans (Papadakis et al., 1996) (Fig. 2).

### 3.5. Growth hormone secretagogues

Growth hormone secretagogues, which include growth hormone releasing hormone agonists, and growth hormone secretagogue receptor agonists (the natural ligand of which is ghrelin), have been evaluated for use in growth retardation, altered body composition, and gastrointestinal dysfunction, some of which have been approved by the FDA (Ishida et al., 2020). Overall, 5/114 studies (2 animal, 3 human) investigated the effect of growth hormone secretagogues on cognition in normal ageing (3/5 studies) or dementia (4/5 studies) populations. These studies sometimes investigated more than one disease population. In animals, across 2 studies, growth hormone secretagogues have a significant beneficial effect on cognition in animal therapeutic dementia populations (Fig. 2) (Kunath et al., 2015; Madhavadas et al., 2014). In humans, across 3 studies, three normal ageing populations and one mixed normal ageing/MCI population (Baker et al., 2012; Friedman et al., 2013; Vitiello et al., 2006), and two MCI populations (Baker et al., 2012; Friedman et al., 2013) were investigated for changes in cognitive outcomes. Growth hormone secretagogues likely have a significant beneficial effect on cognition in human MCI populations, and may have a beneficial effect on cognition in human normal ageing populations (Fig. 2). In humans, this effect was independent of administered therapeutic, dose, duration, cognitive domain assessed, quality of the article, or number of participants (Fig. 4a and Supplementary Table B.1). Across 2 human studies, GLP-1 agonists do not have a significant effect on cognition in the human population (Watson et al., 2019) or dementia population (Gojl et al., 2016) (Fig. 2).

### Table 1 (continued)

| Species | Experimental model | A, n | G, n | Rx, n | Ctrl, n | Cognitive tests | Domains of cognition |
|---------|--------------------|------|------|-------|---------|-----------------|---------------------|
| Rat     | AD (AB ICV)        | 1    | 1    | 8     | 8       | MWM            | Spatial memory, non-spatial recognition and memory |
|         | D × T2DM (Streptozotocin IP) | 1   | 1    | 10    | 10      | MWM, YM        | Place navigation and spatial probing |
| Sulfonylureas |                  |      |      |       |         |                 | Long-term memory, short-term memory |
| Rat     | AD (AB ICV)        | 1    | 1    | 9     | 8       | MWM, PAT       | Spatial memory, learning and memory performance |
| Normal ageing |                  | 1   | 1    | 10    | 10      | MWM, PAT       | Spatial memory, learning and memory performance |
| DPP-4 inhibitor + memantine |            |      |      |       |         |                 | Measure of cognitive decline |
| Rat     | AD × T2DM (AB ICV + Streptozotocin IP) | 1  | 1    | 15    | 15      | PAT            | |
| Glitazone + GLP-1 agonist |            |      |      |       |         |                 | |
| Rat     | D + IR (HF)        | 1    | 2    | 20    | 10      | ERAM           | Learning and memory |
| IGF insulin + memantine |            |      |      |       |         |                 | |
| Rat     | AD (Streptozotocin ICV) | 1  | 2    | 14    | 7       | MWM            | Learning and memory capability |
| Metformin + drug cocktail |            |      |      |       |         |                 | |
| Mouse   | AD × T2DM (TG + db/db mice), AD (TG) | 1  | 2    | 20    | 23      | MWM, NOR       | Spatial cognition, episodic memory |
| Metformin + GLP-1 agonist |            |      |      |       |         |                 | |
| Mouse   | D × T2DM (db/db mice) | 1  | 1    | 8     | 10      | MWM, NOR       | Spatial cognition, episodic memory |
|         | D × T2DM (db/db mice) | 1  | 2    | 20    | 10      | MWM            | Spatial learning and memory |

**Abbreviations:** AD: Alzheimer’s disease, MCI: mild cognitive impairment, Dementia: dementia, VD: vascular dementia, PP: Purdue Pegboard, PR: Platform recognition, RAWM: Reverse Morris Water Maze, Rx: treatment, SAT: Spontaneous alternation testing, SC: subcutaneous, SCWT: Stooexp Color-Word Test, SCWIT: Stooexp Color-Word Interference Task, SDT: Single-trial dual task, SEVLT: Spanish English Verbal Learning Test, TTC: Tissue Tolerance Challenge, T2DM: Type 2 Diabetes Mellitus, T2DM (db/db mice), AD: Alzheimer’s disease, D: dementia, PD: Parkinson’s disease, VD: vascular dementia, PP: Purdue Pegboard, PR: Platform recognition, RAWM: Radial arm water maze, RBANS: Repeatable battery for the Assessment of Neuropsychological Status, CDR: Clinical Dementia Rating Scale, CIBIC: Clinician’s Interview-Based Impression of Change plus caregiver input, CB: California Verbal Learning Test, DAT: Disability Assessment for Dementia, IC: Category fluency, CCIM: Composite cognition measure, CDR-SB: Clinical Dementia Rating Scale sub of boxes, CF: Category Fluency, CIBIC+1: Clinician’s Interview-Based Impression of Change plus caregiver input, CP: California platform, Ctrl: control, CVLT: California Verbal Learning Test, DAD: Disability Assessment for Dementia, Discrimination avoidance task, e-KEFS: Delis-Kaplan Executive Functioning System, DLM: Delayed logical memory, DMTS: Delayed match to sample, DNB: Dot N-Back, DPP-4: dipeptidyl peptidase-4, DSRS: Dementia Severity Rating Scale, DG: digit symbol substitution test, EV: Executive function, EPM: Elevated plus maze, ERAM: Eight radial arm maze, FAB: Frontal Assessment Battery, FAS: FAS verbal fluency task, FCT: Fear conditioning task, FINDA: Finding A, pt: Freezing to context, G: populations, GLP-1: glucagon-like peptide 1, HBT: Hole-board task, HFD: high-fructose diet, ICV: intracerebroventricular, IG: intragastric, In: insulin-like growth factor, IL1R: interleukin-1 receptor, IP: intraperitoneal, IR: insulin-resistant, IV: intravenous, JNK: c-Jun N-terminal kinase, LETSET: Verbal sets task, LF: Letter fluency, LR: List recall, MCAO: middle cerebral artery occlusion, MFT: Memory flexibility test, MMSE: Mini-Mental State Examination, MTP: Matching to position, N: number of participants, NO: non-obesity recognition, NR: not reported, NST: Novel sniffing behavior, OBT: Open field test, OR: Object retrieval, ORL: Odor reversal learning, OT: Odor test, PAT: Passive avoidance task, PDE: phosphodiesterase, Population: [AD: Alzheimer’s disease, D: dementia, PD: Parkinson’s disease, VD: vascular dementia], PP: Purdue Pegboard, PR: Platform recognition, RAWM: Radial arm water maze, RBANS: Repeatable battery for the assessment of neuropsychological status, RCT: Rey Complex Figure Test, RMWM: Reverse Morris Water Maze, Rx: treatment, SAT: Spontaneous alternation testing, SC: subcutaneous, SCWT: Stooexp Color-Word Test, SCWIT: Stooexp Color-Word Interference Task, SDT: Single-trial dual task, SEVLT: Spanish English Verbal Learning Test, SMT: Sniff magnitude test, SOPT: Self-ordered pointing task, SR: Story Recall; Immediate (ISR) and delayed (DSR), SRT: Free and Cued Selective Reminding Test, SSA: Stoop selective attention, ST: Shock threshold test, T2DM: Type 2 Diabetes Mellitus, TB: Trails B, TG: transgenic, TM: Trail making, TMSA: Trail making test selective attention, TMT: T-maze test, TOAD: Two odour discrimination, VisM: Visual memory, VM: Verbal memory, VMC: Verbal memory composite; delayed (DVMC), VPWM: Visible platform water maze, VS: Visual search, WAIS: Wechsler Adult Intelligence Scale, WAIS-R: Wechsler Adult Intelligence Scale Revised, WASI: Wechsler Abbreviated Scale of Intelligence, WMS: Weschler Memory Scale, WMS-R: Wechsler Memory Scale Revised, YM: Y-Maze test.
3.6. Metformin

Metformin is a biguanide which lowers blood glucose levels by decreasing intestinal absorption, decreasing production of hepatic glucose, and increasing insulin sensitivity, and is the preferred approved first-line therapeutic for use in T2DM (Collins and Costello, 2019; Corcoran and Jacobs, 2018). Overall, 9/114 studies (8 animal, 1 human) investigated the effect of metformin on cognition in normal ageing (4/9 studies) or dementia (7/9 studies) populations. These studies sometimes investigated more than one disease population. In animals, across 8 studies, five normal ageing populations (Ahmed et al., 2017; McNeilly et al., 2012; Thangthaeng et al., 2017) and eight dementia populations (Ahmed et al., 2017; Allard et al., 2016; Chen et al., 2019a, b; McNeill et al., 2012; Mostafa et al., 2016; Ou et al., 2018) have been assessed. Metformin shows a beneficial effect on cognition in animal therapeutic dementia populations, but not normal ageing populations (Fig. 2). This effect was independent of the method of disease induction (T2DM or otherwise), dose, duration, sample size, cognitive domain assessed or quality of the article (Fig. 4 and Supplementary Table B.1). In humans, in a single study, one normal ageing population with insulin resistance
Luchsinger et al. (2017) showed a non-significant effect of Metformin on cognition (Fig. 2).

3.7. Intranasal insulin

Insulin receptors are widely distributed throughout the brain, and intranasal delivery of insulin has been shown to achieve excellent penetration into the brain – potentially augmenting roles played by endogenous insulin such as the regulation of neuronal processes of metabolism, plasticity, growth, cholinergic function, and survival (de la Monte, 2013). Overall, 13/114 studies (6 animal, 7 human) investigated the effect of intranasal insulin on cognition in populations of normal ageing (4/13 studies) or dementia (10/13 studies). These studies sometimes investigated more than one disease population. In animals, across 6 studies, nine normal ageing populations (Anderson et al., 2017a; Bell and Fadool, 2017; Maimaiti et al., 2016) and eleven dementia populations (Guo et al., 2017; Mao et al., 2016; Salameh et al., 2015) have been assessed. Intranasal insulin has an overall significant beneficial effect on cognition in animal therapeutic dementia populations, but not normal ageing populations (4/13 studies) or dementia (10/13 studies). These studies sometimes investigated more than one disease population. In humans, across 7 studies, two normal ageing populations (Reger et al., 2006) and 34 MCI/dementia populations (Claxton et al., 2015, 2013; Craft et al., 2012, 2017; Reger et al., 2006; Rosenbloom et al., 2014; Stein et al., 2011) were investigated for changes in cognitive outcomes. Overall, intranasal insulin does not have a positive effect on cognition in human normal ageing populations or MCI/dementia populations (Fig. 2).

3.8. Insulin infusion

All levels of human physiology are influenced by insulin, which signals through the insulin receptor glycoprotein present on the surface of many different tissues (Akintola and van Heemst, 2015). In clinical settings it is currently utilized for the treatment of T1DM and T2DM (George and Woollett, 2019). Overall 4/114 studies (4 human) investigated the effect of insulin infusion on cognition in normal ageing (4/4 studies) or dementia (2/4 studies) populations. These studies sometimes investigated more than one disease population. In humans, across 4 studies, 15 normal ageing populations (Kern et al., 2001; Morris et al., 2016; Watson et al., 2009, 2003) and ten MCI/dementia populations (Morris et al., 2016; Watson et al., 2009) were investigated for changes in cognitive outcomes. One of these studies (Watson et al., 2009) examined the effect of insulin infusion, octreotide + insulin infusion, or octreotide infusion, on cognition in normal ageing or dementia populations. Insulin infusion may have a beneficial effect on cognition in human MCI/dementia populations (Watson et al., 2009), but worse cognitive outcomes have been reported in one study (Morris et al., 2016). The number of participants in each population was similar between the two studies examining MCI/dementia cohorts, ranging from seven receiving treatment in the Apolipoprotein E4 positive population, to 16 receiving treatment in the full population of the same study (Watson et al., 2009). In normal ageing populations, the majority of studies showed negative results (Fig. 2) (Kern et al., 2001; Watson et al., 2009).

3.9. Octreotide + insulin infusion, and octreotide infusion

Octreotide is a somatostatin analogue which inhibits the release of
hormones from the anterior pituitary and hormones of the gastroenteropancreatic system (such as glucagon and insulin), and is primarily approved for the treatment of thyrotopinomas and acromegaly (Debnath and Cheriyath, 2019). Overall 1/114 studies (1 human) investigated the effect of octreotide + insulin infusion, and octreotide infusion alone on cognition in normal ageing and dementia populations. This study (Watson et al., 2009) investigated more than one disease population - examining one normal ageing population, and three dementia MCI/dementia populations, for changes in cognitive outcomes. Octreotide infusion may have a significant beneficial effect on cognition in human normal ageing populations (Fig. 2). Neither octreotide + insulin infusion nor octreotide infusion alone had a significant effect on cognition in human MCI/dementia populations (Fig. 2).

3.10. Animal studies only: Beta blockers, dipeptidyl peptidase (DPP)-4 inhibitors, melatonin, N-methyl-D-aspartate (NMDA) receptor antagonists, Phosphodiesterase (PDE)-inhibitors, Selective serotonin reuptake inhibitors (SSRIs), and statins

These studies sometimes investigated more than one disease population. Three out of 114 studies investigated beta blockers (four normal ageing populations (Dobarro et al., 2013a, b, c), four dementia populations (Dobarro et al., 2013a, b, c) including one study with a preventative treatment (Dobarro et al., 2013b)), 10/114 investigated DPP-4 inhibitors (four normal ageing populations (Pintana et al., 2013; Pipatpiboon et al., 2013; Turnes et al., 2018), 19 dementia populations (Dong et al., 2019; Hasegawa et al., 2017; Kamble et al., 2016; Khalaf et al., 2019; Kosaaraju et al., 2017, 2013; Ma et al., 2018; Pintana et al., 2013; Pipatpiboon et al., 2013; Turnes et al., 2018), 3/114 studies investigated Melatonin (two normal ageing populations (Corpas et al., 2018; Rudnitskaya et al., 2015), three dementia populations (Corpas et al., 2018; Muhammad et al., 2019; Rudnitskaya et al., 2015)), 4/114 studies investigated NMDA receptor antagonists (six dementia populations (Brahmanian et al., 2016; Etcheto et al., 2018; Khalaf et al., 2019; Mietelska-Porowska et al., 2019)), 10/114 studies investigated PDE-inhibitors (24 normal ageing populations (Barad et al., 1998; Burgin et al., 2010; Cuadrado-Tejedor et al., 2011; Li et al., 2011; Orejana et al., 2012; Rutten et al., 2008; Venkat et al., 2019), 14 dementia populations (Burgin et al., 2010; Cuadrado-Tejedor et al., 2011; Orejana et al., 2012; Park et al., 2011; Qi et al., 2016; Schaler and Myeku, 2018; Venkat et al., 2019)), 3/114 studies investigated SSRIs’s (two normal ageing populations (Wu et al., 2018), two dementia populations (Ma et al., 2017; Ren et al., 2015)), and 4/114 studies investigated statins (four normal ageing populations (Chen et al., 2016; Fawzy Fahim et al., 2019; Wang et al., 2015), two dementia populations (Wang et al., 2015; Zhi et al., 2014)). Beta-blockers, DPP-4 inhibitors, Melatonin, NMDA receptor antagonists, and statins, overall have a significantly beneficial effect on cognition in animal therapeutic dementia populations, but not normal ageing (Fig. 2). PDE-inhibitors and SSRIs show benefits on cognitive outcomes in both therapeutic dementia (including a VD model receiving a therapeutic PDE-inhibitor (Qi et al., 2016)) and normal ageing populations (Fig. 2). A single mouse preventative dementia model receiving an angiotensin receptor blocker as an intervention exhibited improved cognitive outcomes versus a dementia control (Fig. 2).

3.11. Other therapeutics and combinations

Sixteen other nutrient sensing therapeutics were investigated for cognitive outcomes in animals, including acarbose, an adrenoreceptor agonist, an adenosine monophosphate-activated kinase (AMPK) activator, amylin & analogues, angiotensin receptor blockers, an anti- interleukin 1 receptor antibody, bioflavonoids, caffeine, dexamphetamine, a gonadotropin-releasing hormone agonist, intracerebroventricular (ICV) insulin, IGF-1, a c-Jun N-terminal kinase inhibitor, a rho-kinase inhibitor, subcutaneous insulin, and sulfonylureas. As a cohort, these other therapeutics have a significant beneficial effect on cognitive outcomes in therapeutic dementia populations (Adler et al., 2014; Arendash et al., 2009; Bahramian et al., 2016; Baraka and Elghotmy, 2016; Carro et al., 2006; Etcheto et al., 2017; Gibbs and Gibbs, 2013; Jiang et al., 2008; Kitazawa et al., 2011; Kumar and Bansal, 2018; Li et al., 2018; Moy and McNay, 2013; Ongali et al., 2014; Orejana et al., 2013; Palm et al., 2014; Wang et al., 2014; Yan et al., 2015; Zhu et al., 2017), but not normal ageing populations (Fig. 2) (Arendash et al., 2009; Baraka and Elghotmy, 2016; Moy and McNay, 2013; Ongali et al., 2014; Tian et al., 2012; Zhu et al., 2017). A single mouse preventative dementia model receiving an angiotensin receptor blocker as an intervention exhibited improved cognitive outcomes versus a dementia control (Fig. 2).

Five combinations of nutrient sensing therapeutics were investigated for their effect on cognitive outcomes in 11 animal dementia populations (Bahramian et al., 2016; Chen et al., 2019b; Gad et al., 2016; Infante-Garcia et al., 2018; Khalaf et al., 2019); DPP-4 inhibitor/ memantine (Khalaf et al., 2019), glitazone/GLP-1 agonist (Gad et al., 2016), ICV insulin/memantine (Bahramian et al., 2016), metformin/statin/aspirin/angiotensin-converting enzyme inhibitor (Infante-Garcia et al., 2018), and metformin/GLP-1 agonist (Chen et al., 2019b). Combinations of nutrient sensing therapeutics may have a significant beneficial effect on cognition in animal dementia populations (Fig. 2), although each combination was not explored in more than one study.

3.12. Risk of bias across studies

Fig. 4a shows the SYRCLE risk of bias ratings for animal studies. The majority of animal studies had an unclear risk of bias, as none reported on random outcome assessment, and the majority of studies did not report on the blinding of personnel, random housing, allocation concealment, or baseline characteristics. The risk of bias was similar across animal models of normal ageing, therapeutic dementia models, and preventative dementia models. The method of sequence generation (e.g. randomized) was reported in 43/91 articles. Overall, 91/91 studies had a low risk of bias for selective outcome reporting, and most studies provided all cognitive outcome information, although some did not provide detailed information in cases where cognitive outcome findings were reported to be non-significant. Overall the risk of bias was similar across animal studies regardless of the therapeutic being tested. Fig. 4b shows the Cochrane risk of bias rating for human studies. Overall, 18/23 studies were classified as having an overall low risk bias. Furthermore, 20/23 studies utilized randomized sequence generation, 17/23 studies were double-blinded, and 18/23 studies blinded the outcome assessment. With regards to incomplete outcome data, 18/23 studies were of low concern. Overall the risk of bias was similar across human studies regardless of the therapeutic being tested, with the exceptions of intranasal insulin, and insulin infusion, in which more than half of the studies raised some concerns for bias potential in one or more categories. Financial conflict of interest is an important possible source of bias that is not taken into account with the Cochrane risk of bias tool. Financial interests may be a potential bias in 7/23 studies (Gold et al., 2016; Harrington et al., 2011; Kern et al., 2001; Luchsinger et al., 2017; Tzimopoulos et al., 2010; Vitiello et al., 2006; Watson et al., 2019), which either disclosed affiliations to a known pharmaceutical company or did not provide a statement reporting any conflicts of interest.
For a detailed description of each article’s risk of bias refer to Supplementary Table D and Supplementary Table E.

4. Discussion

Nutrient sensing-modifying therapeutics may improve ameliorate cognitive decline in MCI or dementia populations but there is limited evidence supporting their preventative effect for ageing populations. Specifically, GLP-1 agonists, growth hormone secretagogues, metformin, DPP-4 inhibitors and PDE-inhibitors were identified as the therapeutics with the most promising cognitive improvements in dementia populations.

It has been reported that greater than 80% of patients with AD have either T2DM or impaired fasting glucose (Janson et al., 2004), and has only been considered to play a significant role in the central nervous system during embryonic development (Lewitt and Boyd, 2019), due largely to its limited expression in the brain compared to IGF-1 (Cianfarani, 2012; Lewitt and Boyd, 2019). However, whilst its roles and molecular mechanisms through which it functions in the central nervous system and on metabolism are still largely unknown (Cianfarani, 2012), a prospective study exploring the associations between the various IGF’s, their binding proteins, and cognitive function found higher circulating levels of IGF-2 are associated with better cognitive function (Green et al., 2014). In rats and mice, IGF-2 has been found to play a critical role in memory (Chen et al., 2011). It may be that only optimum levels of IGF-1 in conjunction with higher circulating IGF-2 are associated with improved long-term cognitive function – with levels of IGF-1 too high or too low, or a deficiency of IGF-2 leading to detriment. Additionally, ghrelin - the natural ligand of growth hormone secretagogue receptor agonists – has been shown to increase when fasting (Ariyasu et al., 2001). The increase in both lifespan and health-span that results from caloric restriction has been clearly elucidated across all studied organisms (although not yet proven in humans) (Anderson et al., 2017b; Gems and Partridge, 2013; Mattison et al., 2017), and despite being less studied, there is growing evidence also indicating a positive effect of intermittent fasting on ageing (Hwangbo et al., 2020). Because a fundamental component of the beneficial effects of fasting are believed to be achieved through the suppression of mTOR (Papadopoli et al., 2019), it is also possible that the mechanism through which the potential cognitive benefits of growth hormone secretagogues are achieved is through mimicking the effects of fasting/caloric restriction. Suppression of the mTOR pathway might be in general a more effective way to reduce Aβ levels (Caccamo et al., 2010), as it is presumably over-activated in AD patients (Zhao and Townsend, 2009).

The results of our review suggest that growth hormone secretagogues may have beneficial impacts on cognition in MCI populations, and potentially normal ageing populations. Yet, the relationship between IGF levels and dementia is also contentious; a meta-analysis of nine studies identified no significant association between serum IGF-1 levels and AD (Ostrowski et al., 2016), and a study of British men found no association between baseline circulating IGF-1, IGF-2 and dementia risk after 17 years of follow-up (Green et al., 2014). Furthermore, the relationship between circulating levels of IGF-binding proteins in AD patients, which may reduce the amount of bioactive IGF for a given total serum IGF level, is poorly understood (Bonham et al., 2018; Galle et al., 2019). It may be that the efficacy of growth hormone secretagogues is related to the progression of dementia – that administration of these therapeutics to individuals with MCI, before significant dampening of IGF-signaling has occurred, could retain IGF-1 and IGF-2 levels in the optimum range and prevent further cognitive decline (Baker et al., 2012; Friedman et al., 2013).

Overall metformin may have some cognitive benefit in animal models of dementia, but this did not translate to humans or normal ageing animal models. The interplay between metformin, T2DM, and neurodegenerative disease is complex and studies examining metformin in these populations are often inconsistent (Wang et al., 2017). There is evidence that metformin given in clinical settings with diabetic populations reduces the risk of dementia (Campbell et al., 2018; Chin-Hsiao, 2019), and cognitive impairment (Ng et al., 2014). It has been hypothesized metformin may act via modulation of tau, and studies examining metformin’s neuroprotective effects have largely focused on tau levels and Aβ production (Wang et al., 2017). While there are inconsistencies in its effect on Aβ production (Hettich et al., 2014; Picone et al., 2015), metformin may decrease total tau levels and phosphorylated tau (Kirkstein et al., 2010; Li et al., 2012), and may further instigate neuroprotection through the activation of AMPK (Wang et al., 2017). AMPK activation may enable neuroprotection through the induction of autophagy, angiogenesis, and neurogenesis (Jiang et al., 2014; Jin et al., 2014; Poels et al., 2009; Venema et al., 2014).

The current available evidence does not support glitazones as a beneficial therapeutic for MCI and dementia populations. However, a
longitudinal observational study (Lu et al., 2018) demonstrated a lower incidence of dementia in populations taking pioglitazone and metformin, than with other metformin-based dual therapies. This may indicate that glitazones are effective in preventing dementia only in combination with another therapeutic. Similarly, administration of insulin did not appear to benefit cognitive performance. Although intranasal insulin, which effectively bypasses the systemic circulation and blood-brain barrier to directly enter the cerebrospinal fluid, may have some role in improving cognition in dementia patients with shorter-term use (Dubey et al., 2020).

In contrast to glucose-lowering therapeutics, PDE-inhibitors exhibit their likely beneficial cognitive effect on experimental dementia models through increasing levels of cAMP and/or cGMP (García-Osta et al., 2012). PDE-inhibitors activate the cAMP response element-binding, which may promote gene transcription (Jimpey et al., 1996; Lu et al., 1999) that has been implicated in long-term memory formation and persistent long-term potentiation (Tully, 1997; Yin and Tully, 1996). This may involve the formation of new synaptic connections in the hippocampus (Ran et al., 2012; Tully et al., 2003), and it has been suggested that this can mitigate the cognitive impacts of dementia by enhancing synaptic function (García-Osta et al., 2012). Further mechanisms may be cognitive vasodilatory properties, and/or as a consequence of emotional arousal (Reneerkens et al., 2009). As elicited by articles examining normal ageing animals in this review, cognitive-enhancing effects of PDE-inhibitors have been observed in a number of different normal healthy animal species (Richter et al., 2013). Currently two phase IV clinical trials (one AD cohort, one VD cohort) examining the effect of PDE-inhibition of cognition in humans have been completed – no improvement in cognitive outcomes were reported for the AD cohort (Lee et al., 2019), and the results of the VD cohort remain unpublished.

It is possible that combinations of therapeutics may provide synergistic improvements in cognitive outcomes. In this review, our search elicited studies examining a number of therapeutic combinations in animals. All, except the metformin/GLP-1 agonist combination, demonstrated improvements in cognitive outcomes in dementia models. Metformin may have a benefit in combination with glitazones (Lu et al., 2018) and sulfonylureas (Hsu et al., 2011). Mechanistically, targeting multiple pathways would seem to be necessary for treatment of dementia, which is a complex multi-aetiological pathological entity. Currently approved agents are limited to cholinesterase inhibitors, memantine, or a combination of these agents, but many other therapeutics are currently in clinical studies as add-on therapies to the standard of care (Cummings et al., 2019).

Therapeutics classified as ‘Other’ were not investigated in any human population and were examined in <3 studies in animals, thus making it difficult to draw tenable conclusions relating to their efficacy in human normal ageing and dementia populations. Some of the more promising ‘other’ therapeutics included in this review are amylín & analogues, caffeine, IV C insulin, and subcutaneous insulin. Our search of registered human trials found a number of ‘other’ therapeutics currently being investigated, including melatonin, statins, adrenoreceptor agonists, and angiotensin receptor blockers.

There has consistently been a poor translation of successful therapeutics of pre-clinical animal dementia models to successful interventions in human dementia clinical trials (Franco and Cedazo-Mínguez, 2014). Aspects such as the wide range of animal dementia models available - the questionable accuracy of these in mimicking human age-related dementia, and differences in study design between animal and human studies, must presumably all contribute to this lack of translation. The majority of animal dementia models utilized by studies in this review were transgenic, overexpressing or producing mutant products of human genes such as amyloid precursor protein (APP), tau, and presenilin 1 (PS1). However, a wide variety of other dementia models were also utilized, such as administration of ICV Aβ or streptozotocin. It remains contentious how extrapolatable findings are from animal models such as these, which are at best incomplete representations of a complex multi-aetiological disease process – an example being that transgenic models do not fully recapitulate neuronal loss (Elder et al., 2010) which is a fundamental pathological mechanism of dementia (Moya-Alvarado et al., 2016). Although human interventional trials are often carried out for a much shorter portion of time relative to the individual’s lifespan than in animal trials, the longer duration of animal trials are often carried out using a much smaller number of animals. In the future, animal studies may more clearly define the dementia model’s baseline level of cognition, and their own aims of exploring interventions as being either neuroprotective, cognitive enhancing, or disease-modifying agent, to help discriminate the various modes by which successful pre-clinical interventions may be having their effect.

4.1. Limitations

Our search strategy was based primarily on key terms related to the main nutrient sensing pathways, with the addition of a selection of therapeutics well-known to modulate these processes. Therefore, our search may have missed studies that examine drugs that modulate nutrient sensing not named in our search and not mentioning nutrient sensing pathway or related key terms. Secondly, whilst the therapeutics included in this review have had prior FDA approval, certain specific administration methods of these therapeutics have not; namely intranasal insulin, insulin infusion, octreotide infusion, and combination insulin infusion + octreotide infusion. Thirdly, we cannot exclude publication bias, particularly in animal studies which are unlikely to be registered and may be less likely to be published if results are negative. Fourth, we did not perform any formal statistical analysis and results are based on reported p-values. The significance of p-values is influenced by sample size. This is likely to have impacted our findings as the majority of animal studies included in this review had a low sample size (<10–15, with n = 5 for some mouse studies), and 11/23 human studies utilized human populations with <15 individuals. The small sample size of these studies specifically, the animal studies is a widespread structural problem within animal research. Studies with small sample sizes are likely to produce ambiguous or misleading results as smaller numbers can inflate the effect size. Ensuring experiments use appropriate sample sizes are critical for reproducibility of findings and future animal research should focus on utilizing power calculation to ensure the appropriate number of animals are included in all treatment arms. Fifth, due to the variation in reported data - different; animal models, FDA therapeutics, dosages, duration of treatment, length of study and control groups - a meta-analysis reporting overall effects on cognition could not be performed. Sixth, whilst the age of animals was largely consistent, mice utilized as preventative and therapeutic dementia models may have been slightly younger than normal ageing models. Finally, this review has also identified some reporting omissions within this research field. Specifically, the use of the SYRCLE bias tool has highlighted large gaps in reporting of the trial design in animal studies. Aspects such as random outcome assessment, blinding of personnel, random housing, allocation concealment, baseline characteristics, and sequence generation, was often unclear. Future animal trials should consider following the SYRCLE guidelines (Hooijmans et al., 2014).

5. Conclusions

The results of this review indicate that nutrient sensing-modifying therapeutics have the potential to alter cognitive outcome in MCI or dementia populations. Overall, the translation of therapeutic efficacy from animal models to human populations is limited. Further studies are required to fully elucidate the potential of GLP-1 agonists, growth hormone secretagogues, metformin, DPP-4 inhibitors, and PDE-inhibitors in dementia.
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