Ageing Research Reviews 67 (2021) 101302

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

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

Benjamin Kioussis [a,b,1], Camilla S.L. Tuttle [a,c,1], Daniel S. Heard [a,d,e], Brian K. Kennedy [f,g,h], Nicola T. Lautenschlager [d,i], Andrea B. Maier [a,f,g,j,*]

[a] Department of Medicine and Aged Care, @AgeMelbourne, Royal Melbourne Hospital, University of Melbourne, Victoria, Australia
[b] University Hospital Geelong, Barwon Health, Melbourne, Victoria, Australia
[c] Centre for Quantitative Neuroimaging, Department of Radiology, Royal Melbourne Hospital, University of Melbourne, Victoria, Australia
[d] North West Mental Health, Melbourne Health, Melbourne, Victoria, Australia
[e] Older Persons Mental Health Service, Canberra Health Services, Canberra, ACT, Australia
[f] Healthy Longevity Program, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[g] Centre for Healthy Longevity, National University Health System, Singapore
[h] Singapore Institute of Clinical Sciences, A*STAR, Singapore
[i] Academic Unit for Psychiatry of Old Age, Department of Psychiatry, University of Melbourne, Melbourne, Victoria, Australia
[j] Department of Human Movement Sciences, @AgeAmsterdam, Amsterdam Movement Sciences, Vrije Universiteit, Amsterdam, The Netherlands

ARTICLE INFO

Keywords:
Aging
Dementia
Cognition
Therapeutics
Organic chemicals
Clinical trial

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 potentially normal ageing 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.

* Corresponding author at: @Age, Department of Human Movement Sciences, Faculty of Behavioural and Movement Sciences, Vrije Universiteit Amsterdam, Amsterdam Movement Sciences, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands.
E-mail address: a.b.maier@vu.nl (A.B. Maier).
[1] Both authors contributed equally.

https://doi.org/10.1016/j.arr.2021.101302
Received 24 September 2020; Received in revised form 13 February 2021; Accepted 15 February 2021
Available online 17 February 2021

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 (Organization, 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 both 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 tasks, and others (Rodriguiz 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 (NUCOG), 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) $\leq$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 inappropriateness 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, random 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

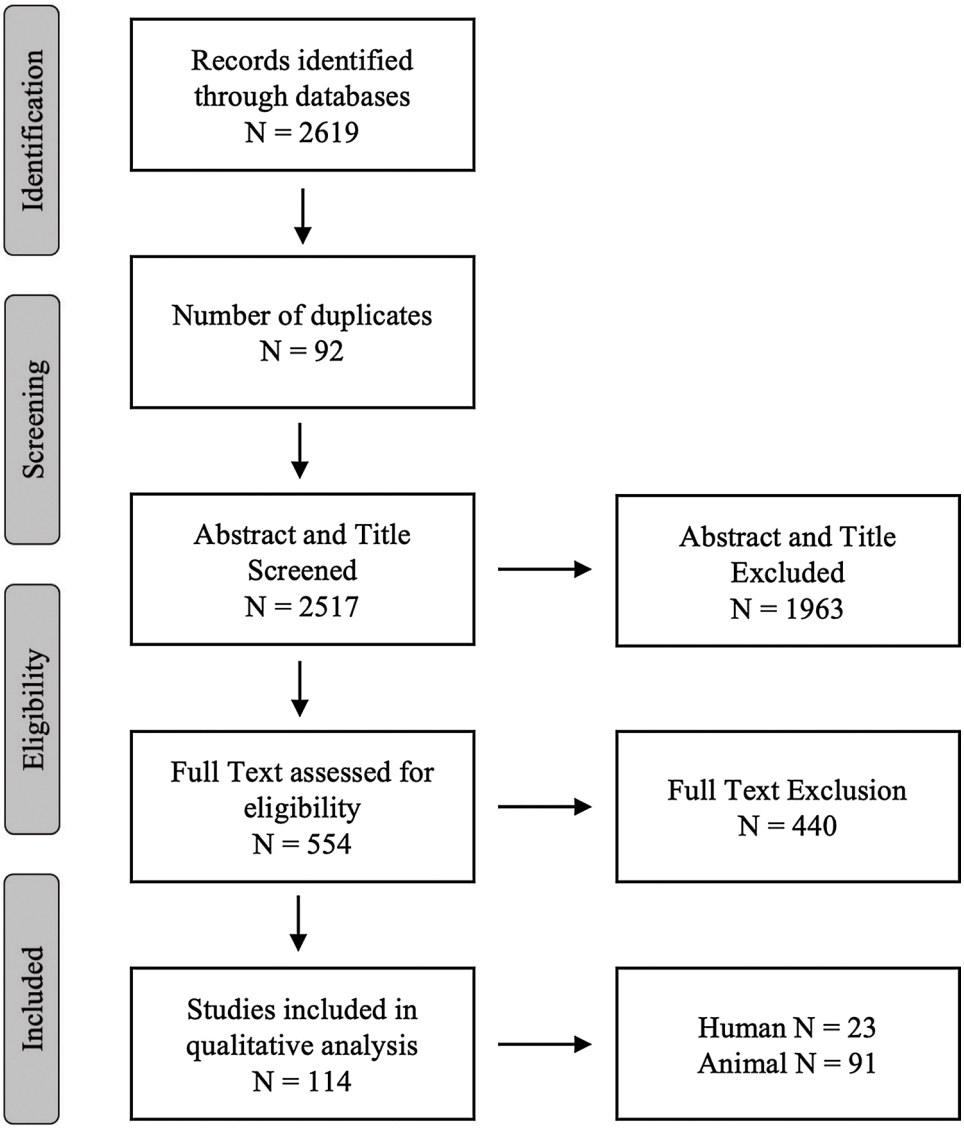

Fig. 1. Schematic overview of the search.

(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 not related to the method of disease induction (T2DM or otherwise), administered therapeutic, dose, duration, sample size, cognitive domain assessed or quality of the article (Fig. 4**a** 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
	D + IR (HFD)	2	2	20	20	ERAM, MWM	Learning and memory, change of learning and memory abilities
	Normal ageing	2	2	20	20	MWM, PAT	Spatial memory, learning and memory performance, change of learning and memory abilities
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, OFT	Spatial memory, object recognition memory, spatial learning, motor activity, speed, anxiety and exploratory behaviour, recognition memory
	D + T2DM (Streptozotocin IV), D (Pentylenetetrazole IP), D + IR (HFD)	3	4	36	30	EPM, PAT, OFT, 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, OFT	Spatial reference learning and memory, object recognition memory, motor activity, speed, anxiety and exploratory behaviour, recognition memory
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-II, D-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	Spatial orientation, time estimation, mental control, clock drawing, incidental recall, inhibition, verbal reproduction
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	Spatial learning and memory
Human	MCI	2	3	39	39	EF, VM, VisM	Memory, executive function, word fluency, episodic memory
	Normal ageing	3	4	86	92	EF, VM, VisM, WAIS-R, SDT, FINDA, LETSET, CATFLU, FAS	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
Metformin							
Mouse	AD (AlCl3), 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	Spatial learning, short-term memory, spatial memory
Rat	D + IR (HFD), D + T2DM (Scopolamine IP)	2	3	44	32	MTP	Cognitive performance
	Normal ageing	1	1	16	16	MTP	Cognitive performance
Human	Normal ageing + IR	1	1	776	755	SEVLT, DSST, AF, LF, CCM	Memory, frontal-executive abilities
Intranasal insulin							

(*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	OFT, 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, DVMC, 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, cross-over	SR, LR, SOPT, SCWT, VS, RBANS, WAIS-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, cross-over	SR, LR, SOPT, SCWT, VS	Verbal declarative memory, visual working memory, selective attention, visual search
Insulin infusion							
Human	AD/MCI	2	4	30	30, pre-post	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, pre-post	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, pre-post	SR, BSRT, SCWIT, SOPT	Verbal memory, complex attention
	Normal ageing	1	1	19	19, pre-post	SR, BSRT, SCWIT, SOPT	Verbal memory, complex attention
Octreotide + insulin infusion							
Human	AD/MCI	1	3	16	16, pre-post	SR, BSRT, SCWIT, SOPT	Verbal memory, complex attention
	Normal ageing	1	1	19	19, pre-post	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, OFT	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
	PD (6OHDA)	1	1	8	8	NOR	Object recognition memory
	Normal ageing	3	4	40	30	MWM, NOR	Cognitive behaviour, cognitive function, 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, OFT, ERAM	Anxiety-behaviour, locomotor and exploratory activity, learning and memory
	Normal ageing	1	1	25	25	EPM, OFT, 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							
Monkey	Normal ageing	1	6	14	14, pre-post	OR	Prefrontal executive function
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 learning and memory
	D (SAMP8 mice), D (Scopolamine SC)	2	5	45	45	MWM, YM	Spatial memory, immediate spatial working memory
	Normal ageing	5	15	158	167	MWM, FCT, FTC, NOR	Spatial memory, contextual memory, hippocampal-dependent context conditioning, long-term memory formation, hippocampal-dependent long-term spatial memory, memory
	Normal ageing	1	2	NR	NR	OFT, VPWM	Hippocampus-independent memory
Rat	VD (4VO), VD (MMI)	2	3	31	20	OFT, MWM, NOR, OT	Locomotor activity levels and anxiety, memory and learning capacity, short-term memory, spatial learning and memory, long-term learning and memory
	Normal ageing	1	1	5	10	NOR, OT, MWM	Short-term memory, spatial learning and memory, long-term learning and memory
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
	Normal ageing stress resistant, Normal ageing stress susceptible	1	2	16	16	MWM	Spatial learning and referential 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
Rat	Normal ageing	1	2	20	10	MWM, YM	Long-term memory, short-term memory
Acarbose							
Mouse	D (SAMP8 mice)	1	1	9	8	MWM	Spatial learning and 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)	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
Rat	AD (Angiotensin II ICV)	1	1	12	12	MWM	Cognitive and behavioural performance
	Normal ageing	1	1	12	12	MWM	Cognitive and behavioural performance
Anti-IL1R antibody							
Mouse	AD (TG)	1	1	8	10	MWM, FCT	Hippocampal-dependent cognition, amygdala and hippocampal function
Bioflavanoid							
Mouse	AD (TG)	1	2	24	12	NOR, MWM	Recognition memory, spatial reference learning and memory
Caffeine							
Mouse	AD (TG)	1	1	6	7	RAWM, PR	Working memory, identification and recognition
	Normal ageing	1	1	8	11	YM, MWM, CP, PR, RAWM	Sensorimotor and cognitive function, spatial learning and reference memory, identification and recognition, working memory
Rat	D + IR (HFD)	1	1	8	8	SAT	Measure of working memory
	Normal ageing	1	1	8	8	SAT	Measure of working memory
Dexibuprofen							
Mouse	AD (TG)	1	1	10	10	NOR	Hippocampal-dependent recognition memory
Gonadotropin releasing hormone agonist							
Mouse	AD + Ovarectomised (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)	1	1	10	10	MWM	Spatial memory
	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*)

Table 1 (*continued*)

Species	Experimental model	A, n	G, n	Rx, n	Ctrl, n	Cognitive tests	Domains of cognition
							Spatial memory, non-spatial recognition and memory
Subcutaneous insulin							
Rat	AD (AB ICV)	1	1	8	8	MWM	Place navigation and spatial probing
	D + T2DM (Streptozotocin IP)	1	1	10	10	MWM, YM	Long-term memory, short-term memory
Sulfonylureas							
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							
Rat	AD + T2DM (AB ICV + Streptozotocin IP)	1	1	15	15	PAT	Measure of cognitive decline
Glitazone + GLP-1 agonist							
Rat	D + IR (HFD)	1	2	20	10	ERAM	Learning and memory
ICV 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
	D + T2DM (db/db mice)	1	1	8	10	MWM, NOR	Spatial cognition, episodic memory
Metformin + GLP-1 agonist							
Mouse	D + T2DM (db/db mice)	1	2	20	10	MWM	Spatial learning and memory

4VO: 4 vessel occlusion, A: articles, AB: amyloid beta, ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale, ADAS-Jcog: Japanese version, ADCS-ADL: Alzheimer's Disease Cooperative Study - activities of daily living, AF: Animal fluency, AlCl3: aluminium chloride, AMPK: AMP-activated protein kinase, BMT: Barnes maze test, BNT: Boston naming test, BSRT: Buschke selective reminding test, BVRT: Benton Visual Retention Test, CATFLU: Category fluency task, CCM: Composite cognition measure, CDR-SB: Clinical Dementia Rating Scale sub of boxes, CF: Category Fluency, CIBIC+: Clinician's Interview-Based Impression of Change plus caregiver input, CP: Circular platform, Ctrl: control, CVLT: California Verbal Learning Test, DAD: Disability Assessment for Dementia, DAT: Discrimination avoidance task, D-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, DSST: Digit symbol substitution test, EF: 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's task, FTC: Freezing to context, G: populations, GLP-1: glucagon-like peptide 1, HBT: Hole-board task, HFD: high-fructose diet, ICV: intracerebroventricular, IG: intragastric, IGF: 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, MMI: multiple microinfarction, MMSE: Mini-Mental State Examination, MTP: Matching to position, NMTP: Non-matching to position, NOR: Novel object recognition, NR: not reported, NSB: Novel sniffing behavior, OFT: Open field test, OR: Object retrieval, ORL: Odor reversal learning, OT: Odor test, PAT: Passive avoidance test, 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, RCFT: Rey Complex Figure Test, RMWM: Reverse Morris Water Maze, Rx: treatment, SAT: Spontaneous alternation testing, SC: subcutaneous, SCWT: Stroop Color-Word Test, SCWIT: Stroop Color-Word Interference Task, SDT: Single-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: Stroop selective attention, STT: 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, TOD: 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.

(Fig. 4**a** and *Supplementary Table B.1*). Across 2 human studies, GLP-1 agonists do not have a significant effect on cognition in the human normal ageing population (Watson et al., 2019) or dementia population (Gejl et al., 2016) (Fig. 2).

3.4. Growth hormone

Whilst growth hormone (GH) receptors are present in many organs, the many metabolic and growth-related effects of GH are accomplished both directly via receptor-signaling, and indirectly via insulin-like growth factor (IGF) (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. 4**b** and *Supplementary Table B.2*). The number of participants in each population varied between the two studies examining MCI/dementia cohorts (eight (Friedman et al., 2013) to 31 (Baker et al., 2012) participants receiving treatment) and the three studies examining normal ageing cohorts (six (Friedman et al., 2013) to 67 in the mixed normal ageing/MCI (Baker et al., 2012) receiving

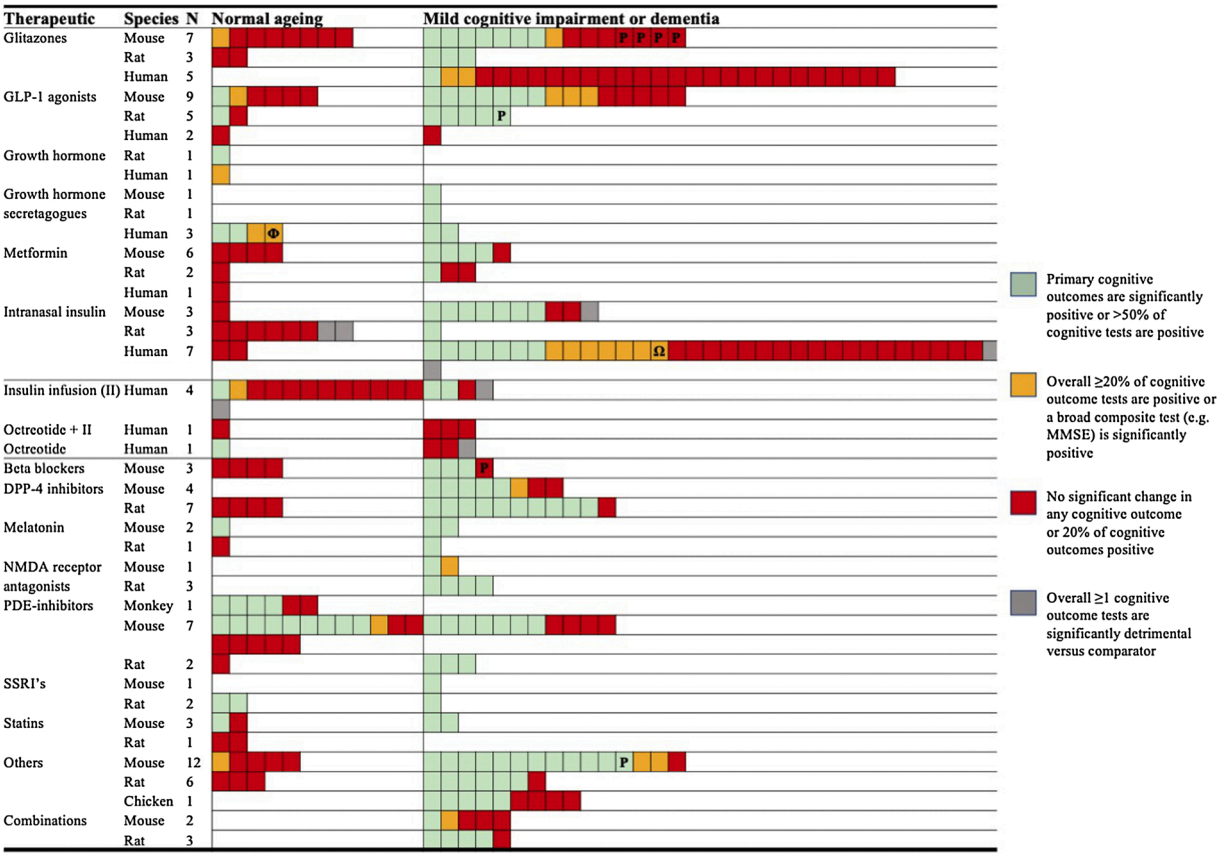

Fig. 2. Outcome of trials in animals and humans investigating nutrient sensing-modifying therapeutics on cognitive performance.
A, n = number of articles, DPP-4 = dipeptidyl peptidase-4, GH = growth hormone, GLP-1 = glucagon-like peptide 1, II = insulin infusion, NMDA = N-methyl -D-aspartate, PDE = phosphodiesterase, RA = receptor antagonist, SSRI = selective serotonin reuptake inhibitor. P = Preventative model, with therapeutic being given prior to the cognitive onset of dementia.
Φ = These two populations were mixed, with ~55% being Normal Ageing and ~45% being MCI.
Ω = Statistical run-in plots suggested that this 'improvement' in ADAS-Cog could have followed a chance worsening and represent regression to the mean.

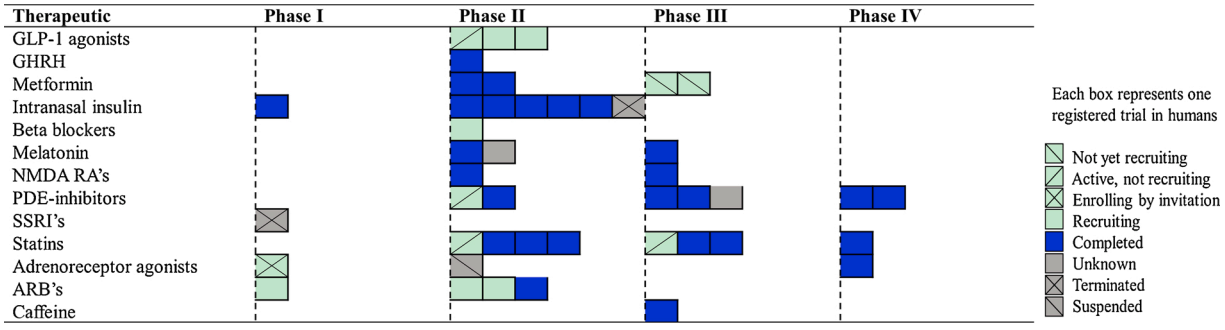

Fig. 3. Overview of registered trials in humans investigating nutrient sensing-modifying therapeutics on cognitive performance, that have not yet released results. ARB = angiotensin receptor blocker, GHRH = growth hormone releasing hormone, GLP-1 = glucagon-like peptide 1, NMDA = N-methyl-D-aspartate, PDE = phosphodiesterase, RA = receptor antagonist, SSRI = selective serotonin reuptake inhibitor.

treatment).

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; McNeilly 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**a** and *Supplementary Table B.1*). In humans, in a single study, one normal ageing population with insulin resistance

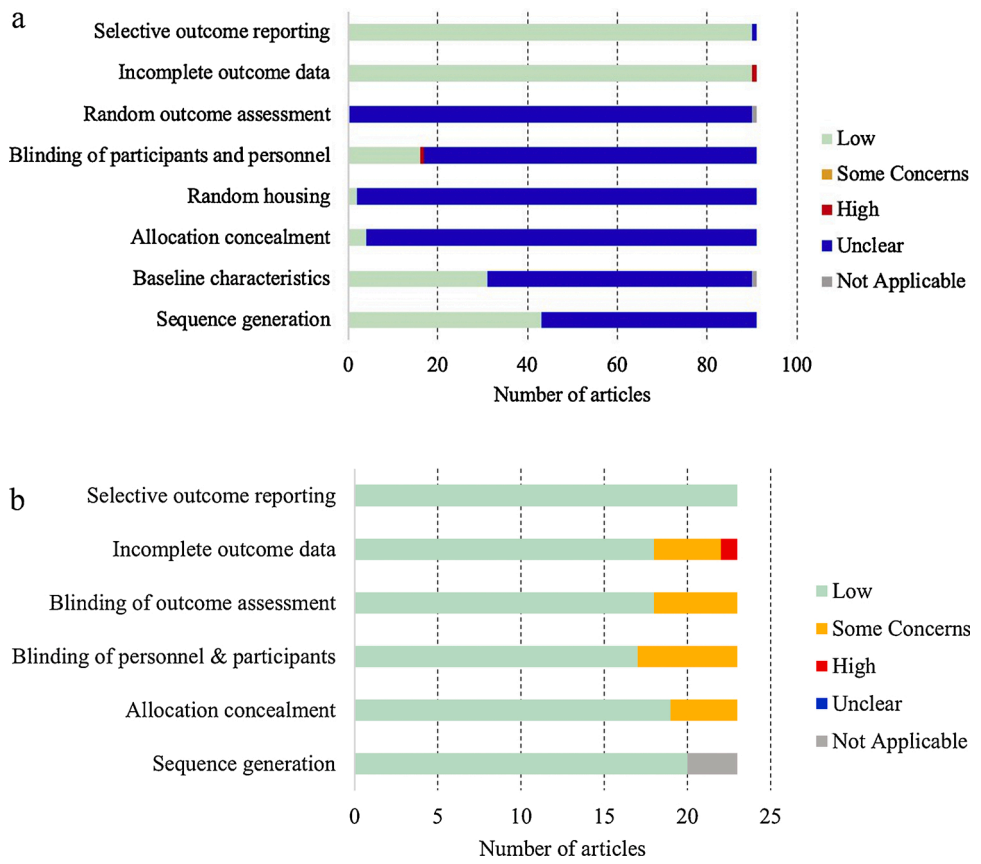

Fig. 4. Risk of bias for animal (a) and human (b) studies Overview of.
(a) SYRCLE risk of bias for animal studies.
(b) Cochrane risk of bias for human studies.

(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 (Fig. 2), which was not related to the method of disease induction (T2DM or otherwise), dose, duration, sample size, cognitive domain assessed or quality of the article (Fig. 4**a** and Supplementary Table B.1). 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 gastro-enteropancreatic system (such as glucagon and insulin), and is primarily approved for the treatment of thyrotropinomas 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 model (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; Kosaraju 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 (Bahramian et al., 2016; Ettcheto 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 SSRI'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 SSRI's 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 a beta-blocker as an intervention did not benefit cognitive outcomes (Fig. 2). Significant beneficial effects on cognition were found in normal ageing monkeys with four out of six different therapeutic dosages of PDE-inhibitors (Rutten et al., 2008), and in normal ageing mice populations receiving PDE-inhibitors (Barad et al., 1998; Burgin et al., 2010; Li et al., 2011). Two normal ageing rat populations showed a significantly positive effect of SSRI's on cognitive outcomes (Wu et al., 2018). These results were independent of the method of disease induction (T2DM or otherwise), dose, duration, sample size, cognitive domain assessed or quality of the article, and the results for DPP-4 inhibitors, PDE-inhibitors, and SSRI's were also independent of the type of administered therapeutic (Fig. 4**a** and Supplementary Table B.1).

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 protein kinase (AMPK) activator, amylin & analogues, angiotensin receptor blockers, an anti-interleukin 1 receptor antibody, bioflavonoids, caffeine, dexibuprofen, 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 ElGhotny, 2010; Carro et al., 2006; Ettcheto 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 ElGhotny, 2010; 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. 4**a** 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. 4**b** 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., 2010; Harrington et al., 2011; Kern et al., 2001; Luchsinger et al., 2017; Tzimopoulou 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 been estimated to increase an individual's risk of developing dementia by 50% (Biessels et al., 2014), though the precise mechanism is likely to be multi-aetiological (Verdile et al., 2015). Whilst many animal studies utilized insulin resistant/T2DM models, this review did not note an association between T2DM status and cognitive outcomes in animal studies. In human studies however, with the exception of (Luchsinger et al., 2017), no human cohorts were reported as having insulin resistance or T2DM.

GLP-1 agonists and DPP-4 inhibitors, also known as incretin mimetics, frequently showed an improvement in cognitive outcomes in experimental dementia models. Incretin mimetics work by mimicking the functions of the natural incretin hormones. It has been demonstrated that incretins can act directly upon the brain, as peripherally secreted GLP-1 can cross the blood brain barrier (Groeneveld et al., 2016). DPP-4 inhibitors may additionally target the brain by impacting its vasculature (Groeneveld et al., 2016). Furthermore, several *in vitro* studies have demonstrated that incretins have neurotrophic (Faivre et al., 2011; Liu et al., 2006; Nyberg et al., 2005; Perry et al., 2002) and neuroprotective (Kimura et al., 2009; Liu et al., 2007, 2009; Perry et al., 2002) properties in the brain. Importantly, studies have also demonstrated that incretins may influence synaptic plasticity – long term potentiation (LTP) and cognition (Gault and Hölscher, 2008a, b; McClean et al., 2010). As such the positive effects of GLP-1 agonists and DPP-4 inhibitors observed in this review may be explained by a combination of mechanisms that are neurotrophic, neuroprotective, and modulatory of synaptic plasticity. Furthermore, whether a combination of GLP-1 agonist/DPP-4 inhibitor could provide a synergistic increase in GLP-1 levels and improve cognition has not yet been studied.

Similar to the incretin mimetics, growth hormones, specifically, growth hormone secretagogues, were also likely to improve cognitive outcomes in MCI, and dementia models. Currently there is uncertainty around whether growth hormone elicits this cognitive effect directly, indirectly via IGF, as a combination of the two, or through a disparate mechanism (Devesa et al., 2018). Growth hormone may also be able to induce and function through the local expression of IGF-1 in the brain (Pathipati et al., 2011). There are two isoforms of IGF – IGF-1 and IGF-2 – both of which are further structurally related to proinsulin (Lewitt and Boyd, 2019). Additionally, growth hormone secretagogues have been shown to effectively increase IGF levels, a key constituent of the IIS pathway (Lopez-Otin et al., 2013), whilst potentially mitigating the side effects of direct GH administration (Sigalos and Pastuszak, 2018). The relationship between cognition and IGF is yet to be fully understood, although the activity of the IGF axis is well understood to decrease with age (Williams et al., 2018). A study of healthy older men of mean age 69.1 (range 65–76) showed a significant correlation between higher circulating levels of IGF-1 and better performance on measures of perceptual-motor and processing speed (Aleman et al., 1999), whilst an eight year follow-up study of 286 men of mean age 67.2 (range 48–88) found that higher IGF-1 levels at baseline are associated with worse future cognitive function in processing capacity and the MMSE (a measure of global cognition) (Tumati et al., 2016). Historically, IGF-2 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 healthspan 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 (Kickstein 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; Venna 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 (Impey 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 amylin & analogues, caffeine, ICV 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-Minguez, 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 ($n \leq 10$–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 outcomes 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.

Acknowledgements

An unrestricted grant by the University of Melbourne supported the work. We thank Patrick Condron from the Brownless Biomedical Library, University of Melbourne, for his assistance with the search strategy.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2021.101302.

References

Adler, B.L., Yarchoan, M., Hwang, H.M., Louneva, N., Blair, J.A., Palm, R., Smith, M.A., Lee, H.G., Arnold, S.E., Casadesus, G., 2014. Neuroprotective effects of the amylin analogue pramlintide on Alzheimer's disease pathogenesis and cognition. Neurobiol. Aging 35, 793–801.

Ahmed, S., Mahmood, Z., Javed, A., Hashmi, S.N., Zerr, I., Zafar, S., Zahid, S., 2017. Effect of metformin on adult hippocampal neurogenesis: comparison with donepezil and links to cognition. J. Mol. Neurosci. 62, 88–98.

Akintola, A.A., van Heemst, D., 2015. Insulin, aging, and the brain: mechanisms and implications. Front. Endocrinol. (Lausanne) 6, 13-13.

Aleman, A., Verhaar, H.J., De Haan, E.H., De Vries, W.R., Samson, M.M., Drent, M.L., Van der Veen, E.A., Koppeschaar, H.P., 1999. Insulin-like growth factor-I and cognitive function in healthy older men. J. Clin. Endocrinol. Metab. 84, 471–475.

Allard, J.S., Perez, E.J., Fukui, K., Carpenter, P., Ingram, D.K., de Cabo, R., 2016. Prolonged metformin treatment leads to reduced transcription of Nrf2 and neurotrophic factors without cognitive impairment in older C57BL/6J mice. Behav. Brain Res. 301, 1–9.

Anderson, K.L., Frazier, H.N., Maimaiti, S., Bakshi, V.V., Majeed, Z.R., Brewer, L.D., Porter, N.M., Lin, A.L., Thibault, O., 2017a. Impact of single or repeated dose intranasal zinc-free insulin in young and aged F344 rats on cognition, signaling, and brain metabolism. J. Gerontol. A Biol. Sci. Med. Sci. 72, 189–197.

Anderson, R.M., Le Couteur, D.G., de Cabo, R., 2017b. Caloric restriction research: new perspectives on the biology of aging. J. Gerontol. A Biol. Sci. Med. Sci. 73, 1–3.

Arendash, G.W., Mori, T., Cao, C., Mamcarz, M., Runfeldt, M., Dickson, A., Rezai-Zadeh, K., Tane, J., Citron, B.A., Lin, X., Echeverria, V., Potter, H., 2009. Caffeine reverses cognitive impairment and decreases brain amyloid-beta levels in aged Alzheimer's disease mice. J. Alzheimers Dis. 17, 661–680.

Ariyasu, H., Takaya, K., Tagami, T., Ogawa, Y., Hosoda, K., Akamizu, T., Suda, M., Koh, T., Natsui, K., Toyooka, S., Shirakami, G., Usui, T., Shimatsu, A., Doi, K., Hosoda, H., Kojima, M., Kangawa, K., Nakao, K., 2001. Stomach is a major source of circulating ghrelin, and feeding state determines plasma ghrelin-like immunoreactivity levels in humans. J. Clin. Endocrinol. Metab. 86, 4753–4758.

Australian Medicines Handbook Pty Ltd., Australian medicines handbook. Australian Medicines Handbook. Adelaide, S.Aust.

Bahramian, A., Rastegar, K., Namavar, M.R., Moosavi, M., 2016. Insulin potentiates the therapeutic effect of memantine against central STZ-induced spatial learning and memory deficit. Behav. Brain Res. 311, 247–254.

Baker, L.D., Barsness, S.M., Borson, S., Merriam, G.R., Friedman, S.D., Craft, S., Vitiello, M.V., 2012. Effects of growth hormone-releasing hormone on cognitive function in adults with mild cognitive impairment and healthy older adults: results of a controlled trial. Arch. Neurol. 69, 1420–1429.

Barad, M., Bourtchouladze, R., Winder, D.G., Golan, H., Kandel, E., 1998. Rolipram, a type IV-specific phosphodiesterase inhibitor, facilitates the establishment of long-lasting long-term potentiation and improves memory. Proc. Natl. Acad. Sci. U.S.A. 95, 15020–15025.

Baraka, A., ElGhotny, S., 2010. Study of the effect of inhibiting galanin in Alzheimer's disease induced in rats. Eur. J. Pharmacol. 641, 123–127.

Bell, G.A., Fadool, D.A., 2017. Awake, long-term intranasal insulin treatment does not affect object memory, odor discrimination, or reversal learning in mice. Physiol. Behav. 174, 104–113.

Biessels, G.J., Strachan, M.W.J., Visseren, F.L.J., Kappelle, L.J., Whitmer, R.A., 2014. Dementia and cognitive decline in type 2 diabetes and prediabetic stages: towards targeted interventions. Lancet Diabetes Endocrinol. 2, 246–255.

Bomba, M., Ciavardelli, D., Silvestri, E., Canzoniero, L.M., Lattanzio, R., Chiappini, P., Piantelli, M., Di Ilio, C., Consoli, A., Sensi, S.L., 2013. Exenatide promotes cognitive enhancement and positive brain metabolic changes in PS1-KI mice but has no effects in 3xTg-AD animals. Cell Death Dis. 4, e612.

Bomfim, T.R., Forny-Germano, L., Sathler, L.B., Brito-Moreira, J., Houzel, J.C., Decker, H., Silverman, M.A., Kazi, H., Melo, H.M., McClean, P.L., Holscher, C., Arnold, S.E., Talbot, K., Klein, W.L., Munoz, D.P., Ferreira, S.T., De Felice, F.G., 2012. An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease- associated Abeta oligomers. J. Clin. Invest. 122, 1339–1353.

Bonham, L.W., Geier, E.G., Steele, N.Z.R., Holland, D., Miller, B.L., Dale, A.M., Desikan, R.S., Yokoyama, J.S., A.s.D.N.I, 2018. Insulin-like growth factor binding protein 2 is associated with biomarkers of alzheimer's disease pathology and shows differential expression in transgenic mice. Front. Neurosci. 12.

Brooks, A.J., Waters, M.J., 2010. The growth hormone receptor: mechanism of activation and clinical implications. Nat. Rev. Endocrinol. 6, 515–525.

Burgin, A.B., Magnusson, O.T., Singh, J., Witte, P., Staker, B.L., Bjornsson, J.M., Thorsteinsdottir, M., Hrafnsdottir, S., Hagen, T., Kiselyov, A.S., Stewart, L.J., Gurney, M.E., 2010. Design of phosphodiesterase 4D (PDE4D) allosteric modulators for enhancing cognition with improved safety. Nat. Biotechnol. 28, 63–70.

Caccamo, A., Majumder, S., Richardson, A., Strong, R., Oddo, S., 2010. Molecular interplay between mammalian target of rapamycin (mTOR), amyloid-beta, and Tau: effects on cognitive impairments. J. Biol. Chem. 285, 13107–13120.

Campbell, J.M., Stephenson, M.D., de Courten, B., Chapman, I., Bellman, S.M., Aromataris, E., 2018. Metformin use associated with reduced risk of dementia in patients with diabetes: a systematic review and meta-analysis. J. Alzheimers Dis. 65, 1225–1236.

Carro, E., Trejo, J.L., Gerber, A., Loetscher, H., Torrado, J., Metzger, F., Torres-Aleman, I., 2006. Therapeutic actions of insulin-like growth factor I on APP/PS2 mice with severe brain amyloidosis. Neurobiol. Aging 27, 1250–1257.

Chen, D.Y., Stern, S.A., Garcia-Osta, A., Saunier-Rebori, B., Pollonini, G., Bambah-Mukku, D., Blitzer, R.D., Alberini, C.M., 2011. A critical role for IGF-II in memory consolidation and enhancement. Nature 469, 491–497.

Chen, T., Wang, C., Sha, S., Zhou, L., Chen, L., Chen, L., 2016. Simvastatin enhances spatial memory and long-term potentiation in hippocampal CA1 via Upregulation of alpha7 nicotinic acetylcholine receptor. Mol. Neurobiol. 53, 4060–4072.

Chen, J.L., Luo, C., Pu, D., Zhang, G.Q., Zhao, Y.X., Sun, Y., Zhao, K.X., Liao, Z.Y., Lv, A. K., Zhu, S.Y., Zhou, J., Xiao, Q., 2019a. Metformin attenuates diabetes-induced tau hyperphosphorylation in vitro and in vivo by enhancing autophagic clearance. Exp. Neurol. 311, 44–56.

Chen, S., Tang, Q., Wang, Y., Xu, Z., Chen, S.T., Sun, Y., Yao, W.B., Gao, X.D., 2019b. Evidence of metabolic memory-induced neurodegeneration and the therapeutic effects of glucagon-like peptide-1 receptor agonists via Forkhead box class O. Biochim. Biophys. Acta Mol. Basis Dis. 1865, 371–377.

Chin-Hsiao, T., 2019. Metformin and the risk of dementia in type 2 diabetes patients. Aging Dis. 10, 37–48.

Cianfarani, S., 2012. Insulin-like growth factor-II: new roles for an old actor. Front. Endocrinol. (Lausanne) 3.

Claxton, A., Baker, L.D., Wilkinson, C.W., Trittschuh, E.H., Chapman, D., Watson, G.S., Cholerton, B., Plymate, S.R., Arbuckle, M., Craft, S., 2013. Sex and ApoE genotype differences in treatment response to two doses of intranasal insulin in adults with mild cognitive impairment or Alzheimer's disease. J. Alzheimers Dis. 35, 789–797.

Claxton, A., Baker, L.D., Hanson, A., Trittschuh, E.H., Cholerton, B., Morgan, A., Callaghan, M., Arbuckle, M., Behl, C., Craft, S., 2015. Long acting intranasal insulin detemir improves cognition for adults with mild cognitive impairment or early-stage alzheimer's disease dementia. J. Alzheimers Dis. 45, 1269–1270.

Collins, L., Costello, R.A., 2019. Glucagon-like Peptide-1 Receptor Agonists.

Corcoran, C., Jacobs, T.F., 2018. Metformin, StatPearls [Internet]. StatPearls Publishing.

Corpas, R., Griñán-Ferré, C., Palomera-Ávalos, V., Porquet, D., García de Frutos, P., Franciscato Cozzolino, S.M., Rodríguez-Farré, E., Pallàs, M., Sanfeliu, C., Cardoso, B. R., 2018. Melatonin induces mechanisms of brain resilience against neurodegeneration. J. Pineal Res. 65, e12515.

Craft, S., Baker, L.D., Montine, T.J., Minoshima, S., Watson, G.S., Claxton, A., Arbuckle, M., Callaghan, M., Tsai, E., Plymate, S.R., Green, P.S., Leverenz, J., Cross, D., Gerton, B., 2012. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Arch. Neurol. 69, 29–38.

Craft, S., Claxton, A., Baker, L.D., Hanson, A.J., Cholerton, B., Trittschuh, E.H., Dahl, D., Caulder, E., Neth, B., Montine, T.J., Jung, Y., Maldjian, J., Whitlow, C., Friedman, S., 2017. Effects of regular and long-acting insulin on cognition and alzheimer's disease biomarkers: a pilot clinical trial. J. Alzheimers Dis. 57, 1325–1334.

Cuadrado-Tejedor, M., Hervias, I., Ricobaraza, A., Puerta, E., Perez-Roldan, J.M., Garcia-Barroso, C., Franco, R., Aguirre, N., Garcia-Osta, A., 2011. Sildenafil restores cognitive function without affecting beta-amyloid burden in a mouse model of Alzheimer's disease. Br. J. Pharmacol. 164, 2029–2041.

Cummings, J.L., Tong, G., Ballard, C., 2019. Treatment combinations for alzheimer's disease: current and future pharmacotherapy options. J. Alzheimers Dis. 67, 779–794.

de la Monte, S.M., 2013. Intranasal insulin therapy for cognitive impairment and neurodegeneration: current state of the art. Expert Opin. Drug Deliv. 10, 1699–1709.

Debnath, D., Cheriyath, P., 2019. Octreotide, StatPearls [Internet]. StatPearls Publishing.

Denner, L.A., Rodriguez-Rivera, J., Haidacher, S.J., Jahrling, J.B., Carmical, J.R., Hernandez, C.M., Zhao, Y., Sadygov, R.G., Starkey, J.M., Spratt, H., Luxon, B.A., Wood, T.G., Dineley, K.T., 2012. Cognitive enhancement with rosiglitazone links the hippocampal PPARgamma and ERK MAPK signaling pathways. J. Neurosci. 32, 16725–16735a.

Devesa, J., Núñez, I., Agra, C., Bejarano, A., Devesa, P., 2018. Treatment with Growth Hormone (GH) Increased the Metabolic Activity of the Brain in an Elder Patient, Not GH-Deficient, Who Suffered Mild Cognitive Alterations and Had an ApoE 4/3 Genotype. Int. J. Mol. Sci. 19, 2294.

Dobarro, M., Gerenu, G., Ramirez, M.J., 2013a. Propranolol reduces cognitive deficits, amyloid and tau pathology in Alzheimer's transgenic mice. Int. J. Neuropsychopharmacol. 16, 2245–2257.

Dobarro, M., Orejana, L., Aguirre, N., Ramirez, M.J., 2013b. Propranolol reduces cognitive deficits, amyloid beta levels, tau phosphorylation and insulin resistance in response to chronic corticosterone administration. Int. J. Neuropsychopharmacol. 16, 1351–1360.

Dobarro, M., Orejana, L., Aguirre, N., Ramirez, M.J., 2013c. Propranolol restores cognitive deficits and improves amyloid and Tau pathologies in a senescence-accelerated mouse model. Neuropharmacology 64, 137–144.

Dong, Q., Teng, S.W., Wang, Y., Qin, F., Li, Y., Ai, L.L., Yu, H., 2019. Sitagliptin protects the cognition function of the Alzheimer's disease mice through activating glucagon-like peptide-1 and BDNF-TrkB signalings. Neurosci. Lett. 696, 184–190.

Dubey, S.K., Lakshmi, K.K., Krishna, K.V., Agrawal, M., Singhvi, G., Saha, R.N., Saraf, S., Saraf, S., Shukla, R., Alexander, A., 2020. Insulin mediated novel therapies for the treatment of Alzheimer's disease. Life Sci. 249, 117540.
Dugger, B.N., Dickson, D.W., 2017. Pathology of neurodegenerative diseases. Cold Spring Harb. Perspect. Biol. 9.
Eggleton, J.S., Jialal, I., 2019. Thiazolidinediones, StatPearls [Internet]. StatPearls Publishing.
Elder, G.A., Gama Sosa, M.A., De Gasperi, R., 2010. Transgenic mouse models of Alzheimer's disease. Mt. Sinai J. Med. 77, 69–81.
Ettcheto, M., Sánchez-López, E., Pons, L., Busquets, O., Olloquequi, J., Beas-Zarate, C., Pallas, M., García, M.L., Auladell, C., Folch, J., Camins, A., 2017. Dexibuprofen prevents neurodegeneration and cognitive decline in APPswe/PS1dE9 through multiple signaling pathways. Redox Biol. 13, 345–352.
Ettcheto, M., Sánchez-López, E., Gómez-Mínguez, Y., Cabrera, H., Busquets, O., Beas-Zarate, C., García, M.L., Carro, E., Casadesus, G., Auladell, C., Vázquez Carrera, M., Folch, J., Camins, A., 2018. Peripheral and central effects of memantine in a mixed preclinical mice model of obesity and familial alzheimer's disease. Mol. Neurobiol. 55, 7327–7339.
Faivre, E., Gault, V.A., Thorens, B., Hölscher, C., 2011. Glucose-dependent insulinotropic polypeptide receptor knockout mice are impaired in learning, synaptic plasticity, and neurogenesis. J. Neurophysiol. 105, 1574–1580.
Fawzy Fahim, V., Wadie, W., Shafik, A.N., Ishak Attallah, M., 2019. Role of simvastatin and insulin in memory protection in a rat model of diabetes mellitus and dementia. Brain Res. Bull. 144, 21–27.
Fidaleo, M., Cavallucci, V., Pani, G., 2017. Nutrients, neurogenesis and brain ageing: from disease mechanisms to therapeutic opportunities. Biochem. Pharmacol. 141, 63–76.
Fluegge, K., 2019. A model of lipid dysregulation and altered nutrient status in Alzheimer's disease. Alzheimers Dement. N. Y. (N Y) 5, 139–145.
Franco, R., Cedazo-Minguez, A., 2014. Successful therapies for Alzheimer's disease: why so many in animal models and none in humans? Front. Pharmacol. 5, 146-146.
Friedman, S.D., Baker, L.D., Borson, S., Jensen, J.E., Barsness, S.M., Craft, S., Merriam, G. R., Otto, R.K., Novotny, E.J., Vitiello, M.V., 2013. Growth hormone-releasing hormone effects on brain gamma-aminobutyric acid levels in mild cognitive impairment and healthy aging. JAMA Neurol. 70, 883–890.
Gad, E.S., Zaitone, S.A., Moustafa, Y.M., 2016. Pioglitazone and exenatide enhance cognition and downregulate hippocampal beta amyloid oligomer and microglia expression in insulin-resistant rats. Can. J. Physiol. Pharmacol. 94, 819–828.
Galle, S.A., van der Spek, A., Drent, M.L., Brugts, M.P., Scherder, E.J.A., Janssen, J.A.M. J.L., Ikram, M.A., van Duijn, C.M., 2019. Revisiting the role of insulin-like growth Factor-I receptor stimulating activity and the apolipoprotein e in alzheimer's disease. Front. Aging Neurosci. 11.
Gao, C., Wang, Q., Chung, S.K., Shen, J., 2017. Crosstalk of metabolic factors and neurogenic signaling in adult neurogenesis: implication of metabolic regulation for mental and neurological diseases. Neurochem. Int. 106, 24–36.
García-Osta, A., Cuadrado-Tejedor, M., García-Barroso, C., Oyarzábal, J., Franco, R., 2012. Phosphodiesterases as therapeutic targets for Alzheimer's disease. ACS Chem. Neurosci. 3, 832–844.
Gault, V.A., Hölscher, C., 2008a. GLP-1 agonists facilitate hippocampal LTP and reverse the impairment of LTP induced by beta-amyloid. Eur. J. Pharmacol. 587, 112–117.
Gault, V.A., Hölscher, C., 2008b. Protease-resistant glucose-dependent insulinotropic polypeptide agonists facilitate hippocampal LTP and reverse the impairment of LTP induced by beta-amyloid. J. Neurophysiol. 99, 1590–1595.
Gejl, M., Gjedde, A., Egefjord, L., Moller, A., Hansen, S.B., Vang, K., Rodell, A., Braendgaard, H., Gottrup, H., Schacht, A., Moller, N., Brock, B., Rungby, J., 2016. In alzheimer's disease, 6-Month treatment with GLP-1 analog prevents decline of brain glucose metabolism: randomized, placebo-controlled, double-blind clinical trial. Front. Aging Neurosci. 8, 108.
Gems, D., Partridge, L., 2013. Genetics of longevity in model organisms: debates and paradigm shifts. Annu. Rev. Physiol. 75, 621–644.
George, K., Woollett, G., 2019. Insulins as Drugs or Biologics in the USA: What Difference Does it Make and Why Does it Matter? BioDrugs 33, 447–451.
Gibbs, M.E., Gibbs, C.L., 2013. Deleterious effects of soluble beta amyloid on cognition, antagonism by saline and noradrenaline, a role for microglia. Neuroscience 230, 62–71.
Gold, M., Alderton, C., Zvartau-Hind, M., Egginton, S., Saunders, A.M., Irizarry, M., Craft, S., Landreth, G., Linnamagi, U., Sawchak, S., 2010. Rosiglitazone monotherapy in mild-to-Moderate alzheimer's disease: results from a randomized, double-blind, placebo-controlled phase III study. Dement. Geriatr. Cogn. Disord. 30, 131–146.
Green, C.J., Holly, J.M., Bayer, A., Fish, M., Ebrahim, S., Gallacher, J., Ben-Shlomo, Y., 2014. The role of IGF-I, IGF-II, and IGFBP-3 in male cognitive aging and dementia risk: the Caerphilly Prospective Study. J. Alzheimer Dis. 41, 867–875.
Grieb, P., 2016. Intracerebroventricular streptozotocin injections as a model of alzheimer's disease: in search of a relevant mechanism. Mol. Neurobiol. 53, 1741–1752.
Griffin, R.J., Moloney, A., Kelliher, M., Johnston, J.A., Ravid, R., Dockery, P., O'Connor, R., O'Neill, C., 2005. Activation of Akt/PKB, increased phosphorylation of Akt substrates and loss and altered distribution of Akt and PTEN are features of Alzheimer's disease pathology. J. Neurochem. 93, 105–117.
Groeneveld, O.N., Kappelle, L.J., Biessels, G.J., 2016. Potentials of incretin-based therapies in dementia and stroke in type 2 diabetes mellitus. J. Diabetes Investig. 7, 5–16.
Gumuslu, E., Mutlu, O., Celikyurt, I.K., Ulak, G., Akar, F., Erden, F., Ertan, M., 2016. Exenatide enhances cognitive performance and upregulates neurotrophic factor gene expression levels in diabetic mice. Fundam. Clin. Pharmacol. 30, 376–384.
Guo, Z., Chen, Y., Mao, Y.-F., Zheng, T., Jiang, Y., Yan, Y., Yin, X., Zhang, B., 2017. Long-term treatment with intranasal insulin ameliorates cognitive impairment, tau hyperphosphorylation, and microglial activation in a streptozotocin-induced Alzheimer's rat model. Sci. Rep. 7, 45971.
Harrington, C., Sawchak, S., Chiang, C., Davies, J., Donovan, C., Saunders, A.M., Irizarry, M., Jeter, B., Zvartau-Hind, M., van Dyck, C.H., Gold, M., 2011. Rosiglitazone does not improve cognition or global function when used as adjunctive therapy to AChE inhibitors in mild-to-Moderate alzheimer's disease: two phase 3 studies. Curr. Alzheimer Res. 8, 592–606.
Hasegawa, Y., Hayashi, K., Takemoto, Y., Cheng, C., Takane, K., Lin, B., Komohara, Y., Kim-Mitsuyama, S., 2017. DPP-4 inhibition with linagliptin ameliorates the progression of premature aging in klotho−/− mice. Cardiovasc. Diabetol. 16, 154.
Heard, D.S., Tuttle, C.S.L., Lautenschlager, N.T., Maier, A.B., 2018. Repurposing proteostasis-modifying drugs to prevent or treat age-related dementia: a systematic review. Front. Physiol. 9, 1520.
Hettich, M.M., Matthes, F., Ryan, D.P., Griesche, N., Schröder, S., Dorn, S., Krauβ, S., Ehninger, D., 2014. The anti-diabetic drug metformin reduces BACE1 protein level by interfering with the MID1 complex. PLoS One 9, e102420.
Higgins, J.P.T., Altman, D.G., Gøtzsche, P.C., Jüni, P., Moher, D., Oxman, A.D., Savović, J., Schulz, K.F., Weeks, L., Sterne, J.A.C., 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343, d5928.
Hooijmans, C.R., Rovers, M.M., de Vries, R.B.M., Leenaars, M., Ritskes-Hoitinga, M., Langendam, M.W., 2014. SYRCLE's risk of bias tool for animal studies. BMC Med. Res. Methodol. 14, 43.
Hsu, C.-C., Wahlqvist, M.L., Lee, M.-S., Tsai, H.-N., 2011. Incidence of dementia is increased in type 2 diabetes and reduced by the use of sulfonylureas and metformin. J. Alzheimer Dis. 24, 485–493.
Huang, H.J., Chen, Y.H., Liang, K.C., Jheng, Y.S., Jhao, J.J., Su, M.T., Lee-Chen, G.J., Hsieh-Li, H.M., 2012. Exendin-4 protected against cognitive dysfunction in hyperglycemic mice receiving an intrahippocampal lipopolysaccharide injection. PLoS One 7, e39656.
Hwangbo, D.-S., Lee, H.-Y., Abozaid, L.S., Min, K.-J., 2020. Mechanisms of lifespan regulation by calorie restriction and intermittent fasting in model organisms. Nutrients 12, 1194.
Impey, S., Mark, M., Villacres, E.C., Poser, S., Chavkin, C., Storm, D.R., 1996. Induction of CRE-mediated gene expression by stimuli that generate long-lasting LTP in area CA1 of the hippocampus. Neuron 16, 973–982.
Infante-Garcia, C., Ramos-Rodriguez, J.J., Hierro-Bujalance, C., Ortegon, E., Pickett, E., Jackson, R., Hernandez-Pacho, F., Spires-Jones, T., Garcia-Alloza, M., 2018. Antidiabetic polypill improves central pathology and cognitive impairment in a mixed model of alzheimer's disease and type 2 diabetes. Mol. Neurobiol. 55, 6130–6144.
Isacson, R., Nielsen, E., Dannaeus, K., Bertilsson, G., Patrone, C., Zachrisson, O., Wikstrom, L., 2011. The glucagon-like peptide 1 receptor agonist exendin-4 improves reference memory performance and decreases immobility in the forced swim test. Eur. J. Pharmacol. 650, 249–255.
Ishida, J., Saitoh, M., Ebner, N., Springer, J., Anker, S.D., von Haehling, S., 2020. Growth hormone secretagogues: history, mechanism of action, and clinical development. JCSM Rapid Commun. 3, 25–37.
Jahrling, J.B., Laberge, R.-M., 2015. Age-related neurodegeneration prevention through mTOR inhibition: potential mechanisms and remaining questions. Curr. Top. Med. Chem. 15, 2139–2151.
Janson, J., Laedtke, T., Parisi, J.E., O'Brien, P., Petersen, R.C., Butler, P.C., 2004. Increased risk of type 2 diabetes in alzheimer disease. Diabetes 53, 474.
Jiang, L.H., Zhang, Y.N., Wu, X.W., Song, F.F., Guo, D.Y., 2008. Effect of insulin on the cognizing function and expression of hippocampal Abeta1-40 of rat with Alzheimer disease. Chin. Med. J. 121, 827–831.
Jiang, L.Y., Tang, S.S., Wang, X.Y., Liu, L.P., Long, Y., Hu, M., Liao, M.X., Ding, Q.L., Hu, W., Li, J.C., Hong, H., 2012. PPAR? Agonist pioglitazone reverses memory impairment and biochemical changes in a mouse model of type 2 diabetes mellitus. CNS Neurosci. Ther. 18, 659–666.
Jiang, T., Yu, J.T., Zhu, X.C., Wang, H.F., Tan, M.S., Cao, L., Zhang, Q.Q., Gao, L., Shi, J. Q., Zhang, Y.D., Tan, L., 2014. Acute metformin preconditioning confers neuroprotection against focal cerebral ischaemia by pre-activation of AMPK-dependent autophagy. Br. J. Pharmacol. 171, 3146–3157.
Jin, Q., Cheng, J., Liu, Y., Wu, J., Wang, X., Wei, S., Zhou, X., Qin, Z., Jia, J., Zhen, X., 2014. Improvement of functional recovery by chronic metformin treatment is associated with enhanced alternative activation of microglia/macrophages and increased angiogenesis and neurogenesis following experimental stroke. Brain Behav. Immun. 40, 131–142.
Kamble, M., Gupta, R., Rehan, H.S., Gupta, L.K., 2016. Neurobehavioral effects of liraglutide and sitagliptin in experimental models. Eur. J. Pharmacol. 774, 64–70.
Kern, W., Peters, A., Fruehwald-Schultes, B., Deininger, E., Born, J., Fehm, H.L., 2001. Improving influence of insulin on cognitive functions in humans. Neuroendocrinology 74, 270–280.
Khalaf, S.S., Hafez, M.M., Mehanna, E.T., Mesbah, N.M., Abo-Elmatty, D.M., 2019. Combined vildagliptin and memantine treatment downregulates expression of amyloid precursor protein, and total and phosphorylated tau in a rat model of combined Alzheimer's disease and type 2 diabetes. Naunyn Schmiedebergs Arch. Pharmacol. 392, 685–695.
Kickstein, E., Krauss, S., Thornhill, P., Rutschow, D., Zeller, R., Sharkey, J., Williamson, R., Fuchs, M., Köhler, A., Glossmann, H., Schneider, R., Sutherland, C., Schweiger, S., 2010. Biguanide metformin acts on tau phosphorylation via mTOR/protein phosphatase 2A (PP2A) signaling. Proc. Natl. Acad. Sci. U S A 107, 21830–21835.

Kimura, R., Okouchi, M., Fujioka, H., Ichiyanagi, A., Ryuge, F., Mizuno, T., Imaeda, K., Okayama, N., Kamiya, Y., Asai, K., Joh, T., 2009. Glucagon-like peptide-1 (GLP-1) protects against methylglyoxal-induced PC12 cell apoptosis through the PI3K/Akt/mTOR/GCLc/redox signaling pathway. Neuroscience 162, 1212–1219.
Kitazawa, M., Cheng, D., Tsukamoto, M.R., Koike, M.A., Wes, P.D., Vasilevko, V., Cribbs, D.H., LaFerla, F.M., 2011. Blocking IL-1 signaling rescues cognition, attenuates tau pathology, and restores neuronal beta-catenin pathway function in an Alzheimer's disease model. J. Immunol. 187, 6539–6549.
Kosaraju, J., Murthy, V., Khatwal, R.B., Dubala, A., Chinni, S., Muthureddy Nataraj, S.K., Basavan, D., 2013. Vildagliptin: an anti-diabetes agent ameliorates cognitive deficits and pathology observed in streptozotocin-induced Alzheimer's disease. J. Pharm. Pharmacol. 65, 1773–1784.
Kosaraju, J., Holsinger, R.M.D., Guo, L., Tam, K.Y., 2017. Linagliptin, a dipeptidyl Peptidase-4 inhibitor, mitigates cognitive deficits and pathology in the 3xTg-AD mouse model of alzheimer's disease. Mol. Neurobiol. 54, 6074–6084.
Kumar, M., Bansal, N., 2018. Fasudil hydrochloride ameliorates memory deficits in rat model of streptozotocin-induced Alzheimer's disease: involvement of PI3-kinase, eNOS and NFκB. Behav. Brain Res. 351, 4–16.
Kummer, M.P., Schwarzenberger, R., Sayah-Jeanne, S., Dubernet, M., Walczak, R., Hum, D.W., Schwartz, S., Axt, D., Heneka, M.T., 2015. Pan-PPAR modulation effectively protects APP/PS1 mice from amyloid deposition and cognitive deficits. Mol. Neurobiol. 51, 661–671.
Kunath, N., van Groen, T., Allison, D.B., Kumar, A., Dozier-Sharpe, M., Kadish, I., 2015. Ghrelin agonist does not foster insulin resistance but improves cognition in an Alzheimer's disease mouse model. Sci. Rep. 5, 11452.
Lee, J.Y., Lee, H., Yoo, H.B., Choi, J.S., Jung, H.Y., Yoon, E.J., Kim, H., Jung, Y.H., Lee, H.Y., Kim, Y.K., 2019. Efficacy of cilostazol administration in alzheimer's disease patients with white matter lesions: a positron-emission tomography study. Neurotherapeutics 16, 394–403.
Lennox, R., Flatt, P.R., Gault, V.A., 2014. Lixisenatide improves recognition memory and exerts neuroprotective actions in high-fat fed mice. Peptides 61, 38–47.
Lewitt, M.S., Boyd, G.W., 2019. The Role of Insulin-Like Growth Factors and Insulin-Like Growth Factor-Binding Proteins in the Nervous System. Biochem. Insights 12, 1178626419842176-1178626419842176.
Li, X., Alafuzoff, I., Soininen, H., Winblad, B., Pei, J.J., 2005. Levels of mTOR and its downstream targets 4E-BP1, eEF2, and eEF2 kinase in relationships with tau in Alzheimer's disease brain. FEBS J. 272, 4211–4220.
Li, Y.-F., Cheng, Y.-F., Huang, Y., Conti, M., Wilson, S.P., O'Donnell, J.M., Zhang, H.-T., 2011. Phosphodiesterase-4D knock-out and RNA interference-mediated knock-down enhance memory and increase hippocampal neurogenesis via increased cAMP signaling. J. Neurosci. 31, 172–183.
Li, J., Deng, J., Sheng, W., Zuo, Z., 2012. Metformin attenuates Alzheimer's disease-like neuropathology in obese, leptin-resistant mice. Pharmacol. Biochem. Behav. 101, 564–574.
Li, P.C., Liu, L.F., Jou, M.J., Wang, H.K., 2016. The GLP-1 receptor agonists exendin-4 and liraglutide alleviate oxidative stress and cognitive and micturition deficits induced by middle cerebral artery occlusion in diabetic mice. BMC Neurosci. 17.
Li, H., Wu, J., Zhu, L., Sha, L., Yang, S., Wei, J., Ji, L., Tang, X., Mao, K., Cao, L., Wei, N., Xie, W., Yang, Z., 2018. Insulin degrading enzyme contributes to the pathology in a mixed model of Type 2 diabetes and Alzheimer's disease: possible mechanisms of IDE in T2D and AD. Biosci. Rep. 38.
Lin, J.S., O'Connor, E., Rossom, R.C., Perdue, L.A., Burda, B.U., Thompson, M., Eckstrom, E., 2013. U.S. Preventive Services Task Force Evidence Syntheses, Formerly Systematic Evidence Reviews, Screening for Cognitive Impairment in Older Adults: an Evidence Update for the U.S. Preventive Services Task Force. Agency for Healthcare Research and Quality (US), Rockville (MD).
Liu, G.Y., Sabatini, D.M., 2020. mTOR at the nexus of nutrition, growth, ageing and disease. Nat. Rev. Mol. Cell Biol. 21, 183–203.
Liu, J., Zheng, X., Yin, F., Hu, Y., Guo, L., Deng, X., Chen, G., Jiajia, J., Zhang, H., 2006. Neurotrophic property of geniposide for inducing the neuronal differentiation of PC12 cells. Int. J. Dev. Neurosci. 24, 419–424.
Liu, J., Yin, F., Zheng, X., Jing, J., Hu, Y., 2007. Geniposide, a novel agonist for GLP-1 receptor, prevents PC12 cells from oxidative damage via MAP kinase pathway. Neurochem. Int. 51, 361–369.
Liu, J.H., Yin, F., Guo, L.X., Deng, X.H., Hu, Y.H., 2009. Neuroprotection of geniposide against hydrogen peroxide induced PC12 cells injury: involvement of PI3 kinase signal pathway. Acta Pharmacol. Sin. 30, 159–165.
Liu, X.P., Luo, D.Z., Zheng, M., Hao, Y.W., Hou, L., Zhang, S.M., 2010. Effect of pioglitazone on insulin resistance in fructose-drinking rats correlates with AGEs/RAGE inhibition and block of NAPDH oxidase and NF kappa B activation. Eur. J. Pharmacol. 629, 153–158.
Lopez-Otin, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2013. The hallmarks of aging. Cell 153, 1194–1217.
Lu, Y.F., Kandel, E.R., Hawkins, R.D., 1999. Nitric oxide signaling contributes to late-phase LTP and CREB phosphorylation in the hippocampus. J. Neurosci. 19, 10250–10261.
Lu, C.-H., Yang, C.-Y., Li, C.-Y., Hsieh, C.-Y., Ou, H.-T., 2018. Lower risk of dementia with pioglitazone, compared with other second-line treatments, in metformin-based dual therapy: a population-based longitudinal study. Diabetologia 61, 562–573.
Luchsinger, J.A., Ma, Y., Christophi, C.A., Florez, H., Golden, S.H., Hazuda, H., Crandall, J., Venditti, E., Watson, K., Jeffries, S., Manly, J.J., Pi-Sunyer, F.X., 2017. Metformin, lifestyle intervention, and cognition in the diabetes prevention program outcomes study. Diabetes Care 40, 958–965.
Ma, J., Gao, Y., Jiang, L., Chao, F.L., Huang, W., Zhou, C.N., Tang, W., Zhang, L., Huang, C.X., Zhang, Y., Luo, Y.M., Xiao, Q., Yu, H.R., Jiang, R., Tang, Y., 2017. Fluoxetine attenuates the impairment of spatial learning ability and prevents neuron loss in middle-aged APPswe/PSEN1dE9 double transgenic Alzheimer's disease mice. Oncotarget 8, 27676–27692.
Ma, Q.H., Jiang, L.F., Mao, J.L., Xu, W.X., Huang, M., 2018. Vildagliptin prevents cognitive deficits and neuronal apoptosis in a rat model of Alzheimer's disease. Mol. Med. Rep. 17, 4113–4119.
Madhavadas, S., Kutty, B.M., Subramanian, S., 2014. Amyloid beta lowering and cognition enhancing effects of ghrelin receptor analog [D-Lys (3)] GHRP-6 in rat model of obesity. Indian J. Biochem. Biophys. 51, 257–262.
Maimaiti, S., Anderson, K.L., DeMoll, C., Brewer, L.D., Rauh, B.A., Gant, J.C., Blalock, E. M., Porter, N.M., Thibault, O., 2016. Intranasal insulin improves age-related cognitive deficits and reverses electrophysiological correlates of brain aging. J. Gerontol. A Biol. Sci. Med. Sci. 71, 30–39.
Mao, Y.F., Guo, Z., Zheng, T., Jiang, Y., Yan, Y., Yin, X., Chen, Y., Zhang, B., 2016. Intranasal insulin alleviates cognitive deficits and amyloid pathology in young adult APPswe/PS1dE9 mice. Aging Cell 15, 893–902.
Masciopinto, F., Di Pietro, N., Corona, C., Bomba, M., Pipino, C., Curcio, M., Di Castelnuovo, A., Ciavardelli, D., Silvestri, E., Canzoniero, L.M.T., Sekler, I., Pandolfi, A., Sensi, S.L., 2012. Effects of long-term treatment with pioglitazone on cognition and glucose metabolism of PS1-KI, 3xTg-AD, and wild-type mice. Cell Death Dis. 3.
Mattison, J.A., Colman, R.J., Beasley, T.M., Allison, D.B., Kemnitz, J.W., Roth, G.S., Ingram, D.K., Weindruch, R., de Cabo, R., Anderson, R.M., 2017. Caloric restriction improves health and survival of rhesus monkeys. Nat. Commun. 8, 14063-14063.
Mc Auley, M.T., Guimera, A.M., Hodgson, D., McDonald, N., Mooney, K.M., Morgan, A. E., Proctor, C.J., 2017. Modelling the molecular mechanisms of aging. Biosci. Rep. 37, BSR20160177.
McClean, P.L., Holscher, C., 2014a. Liraglutide can reverse memory impairment, synaptic loss and reduce plaque load in aged APP/PS1 mice, a model of Alzheimer's disease. Neuropharmacology 76 Pt A, 57–67.
McClean, P.L., Holscher, C., 2014b. Lixisenatide, a drug developed to treat type 2 diabetes, shows neuroprotective effects in a mouse model of Alzheimer's disease. Neuropharmacology 86, 241–258.
McClean, P.L., Gault, V.A., Harriott, P., Hölscher, C., 2010. Glucagon-like peptide-1 analogues enhance synaptic plasticity in the brain: a link between diabetes and Alzheimer's disease. Eur. J. Pharmacol. 630, 158–162.
McNeilly, A.D., Williamson, R., Balfour, D.J., Stewart, C.A., Sutherland, C., 2012. A high-fat-diet-induced cognitive deficit in rats that is not prevented by improving insulin sensitivity with metformin. Diabetologia 55, 3061–3070.
Mietelska-Porowska, A., Gasiorowska, A., Palasz, E., Koss, D.J., Riedel, G., Niewiadomska, G., 2019. Pore-former enabled seeding of tau in rats: alleviation by memantine and lithium chloride. J. Neurosci. Methods 319, 47–59.
Morris, J.K., Vidoni, E.D., Mahnken, J.D., Montgomery, R.N., Johnson, D.K., Thyfault, J. P., Burns, J.M., 2016. Cognitively impaired elderly exhibit insulin resistance and no memory improvement with infused insulin. Neurobiol. Aging 39, 19–24.
Mostafa, D.K., Ismail, C.A., Ghareeb, D.A., 2016. Differential metformin dose-dependent effects on cognition in rats: role of Akt. Psychopharmacology (Berl.) 233, 2513–2524.
Moy, G.A., McNay, E.C., 2013. Caffeine prevents weight gain and cognitive impairment caused by a high-fat diet while elevating hippocampal. BDNF 109, 69–74.
Moya-Alvarado, G., Gershoni-Emek, N., Perlson, E., Bronfman, F.C., 2016. Neurodegeneration and alzheimer's disease (AD). What can proteomics tell us about the alzheimer's brain? Mol. Cell Proteomics 15, 409–425.
Muhammad, T., Ali, T., Ikram, M., Khan, A., Alam, S.I., Kim, M.O., 2019. Melatonin rescue oxidative stress-mediated neuroinflammation/ neurodegeneration and memory impairment in scopolamine-induced Amnesia mice model. J. Neuroimmune Pharmacol. 14, 278–294.
Ng, T.P., Feng, L., Yap, K.B., Lee, T.S., Tan, C.H., Winblad, B., 2014. Long-term metformin usage and cognitive function among older adults with diabetes. J. Alzheimers Dis. 41, 61–68.
Nyberg, J., Anderson, M.F., Meister, B., Alborn, A.M., Ström, A.K., Brederlau, A., Illerskog, A.C., Nilsson, O., Kieffer, T.J., Hietala, M.A., Ricksten, A., Eriksson, P.S., 2005. Glucose-dependent insulinotropic polypeptide is expressed in adult hippocampus and induces progenitor cell proliferation. J. Neurosci. 25, 1816–1825.
Ongali, B., Nicolakakis, N., Tong, X.K., Aboulkassim, T., Papadopoulos, P., Rosa-Neto, P., Lecrux, C., Imboden, H., Hamel, E., 2014. Angiotensin II type 1 receptor blocker losartan prevents and rescues cerebrovascular, neuropathological and cognitive deficits in an Alzheimer's disease model. Neurobiol. Dis. 68, 126–136.
Orejana, L., Barros-Minones, L., Jordan, J., Puerta, E., Aguirre, N., 2012. Sildenafil ameliorates cognitive deficits and tau pathology in a senescence-accelerated mouse model. Neurobiol. Aging 33, 625 e611-620.
Orejana, L., Barros-Minones, L., Aguirre, N., Puerta, E., 2013. Implication of JNK pathway on tau pathology and cognitive decline in a senescence-accelerated mouse model. Exp. Gerontol. 48, 565–571.
Organisation, W.H., 2017. Global Action Plan on the Public Health Response to Dementia 2017-2025.
Organization, W.H., 2017. Global Strategy and Action Plan on Ageing and Health.
Ostrowski, P.P., Barszczyk, A., Forstenpointner, J., Zheng, W., Feng, Z.-P., 2016. Meta-analysis of serum insulin-like growth factor 1 in alzheimer's disease. PLoS One 11 e0155733-e0155733.
Ou, Z., Kong, X., Sun, X., He, X., Zhang, L., Gong, Z., Huang, J., Xu, B., Long, D., Li, J., Li, Q., Xu, L., Xuan, A., 2018. Metformin treatment prevents amyloid plaque deposition and memory impairment in APP/PS1 mice. Brain Behav. Immun. 69, 351–363.
Palm, R., Chang, J., Blair, J., Garcia-Mesa, Y., Lee, H.G., Castellani, R.J., Smith, M.A., Zhu, X., Casadesus, G., 2014. Down-regulation of serum gonadotropins but not

estrogen replacement improves cognition in aged-ovariectomized 3xTg AD female mice. J. Neurochem. 130, 115–125.
Papadakis, M.A., Grady, D., Black, D., Tierney, M.J., Gooding, G.A., Schambelan, M., Grunfeld, C., 1996. Growth hormone replacement in healthy older men improves body composition but not functional ability. Ann. Intern. Med. 124, 708–716.
Papadopoli, D., Boulay, K., Kazak, L., Pollak, M., Mallette, F., Topisirovic, I., Hulea, L., 2019. mTOR as a central regulator of lifespan and aging. F1000Res 8. F1000 Faculty Rev-1998.
Park, S.H., Kim, J.H., Bae, S.S., Hong, K.W., Lee, D.S., Leem, J.Y., Choi, B.T., Shin, H.K., 2011. Protective effect of the phosphodiesterase III inhibitor cilostazol on amyloid beta-induced cognitive deficits associated with decreased amyloid beta accumulation. Biochem. Biophys. Res. Commun. 408, 602–608.
Pathipati, P., Gorba, T., Scheepens, A., Goffin, V., Sun, Y., Fraser, M., 2011. Growth hormone and prolactin regulate human neural stem cell regenerative activity. Neuroscience 190, 409–427.
Perry, T., Haughey, N.J., Mattson, M.P., Egan, J.M., Greig, N.H., 2002. Protection and reversal of excitotoxic neuronal damage by glucagon-like peptide-1 and exendin-4. J. Pharmacol. Exp. Ther. 302, 881–888.
Picone, P., Nuzzo, D., Caruana, L., Messina, E., Barera, A., Vasto, S., Di Carlo, M., 2015. Metformin increases APP expression and processing via oxidative stress, mitochondrial dysfunction and NF-κB activation: use of insulin to attenuate metformin's effect. Biochim. Biophys. Acta 1853, 1046–1059.
Pintana, H., Apaijai, N., Chattipakorn, N., Chattipakorn, S.C., 2013. DPP-4 inhibitors improve cognition and brain mitochondrial function of insulin-resistant rats. J. Endocrinol. 218, 1–11.
Pipatpiboon, N., Pintana, H., Pratchayasakul, W., Chattipakorn, N., Chattipakorn, S.C., 2013. DPP4-inhibitor improves neuronal insulin receptor function, brain mitochondrial function and cognitive function in rats with insulin resistance induced by high-fat diet consumption. Eur. J. Neurosci. 37, 839–849.
Poels, J., Spasić, M.R., Callaerts, P., Norga, K.K., 2009. Expanding roles for AMP-activated protein kinase in neuronal survival and autophagy. Bioessays 31, 944–952.
Qi, D.S., Tao, J.H., Zhang, L.Q., Li, M., Wang, M., Qu, R., Zhang, S.C., Liu, P., Liu, F., Miu, J.C., Ma, J.Y., Mei, X.Y., Zhang, F., 2016. Neuroprotection of Cilostazol against ischemia/reperfusion-induced cognitive deficits through inhibiting JNK3/caspase-3 by enhancing Akt1. Brain Res. 1653, 67–74.
Ramsey, M.M., Weiner, J.L., Moore, T.P., Carter, C.S., Sonntag, W.E., 2004. Growth hormone treatment attenuates age-related changes in hippocampal short-term plasticity and spatial learning. Neuroscience 129, 119–127.
Ran, I., Laplante, I., Lacaille, J.C., 2012. CREB-dependent transcriptional control and quantal changes in persistent long-term potentiation in hippocampal interneurons. J. Neurosci. 32, 6335–6350.
Reger, M.A., Watson, G.S., Frey 2nd, W.H., Baker, L.D., Cholerton, B., Keeling, M.L., Belongia, D.A., Fishel, M.A., Plymate, S.R., Schellenberg, G.D., Cherrier, M.M., Craft, S., 2006. Effects of intranasal insulin on cognition in memory-impaired older adults: modulation by APOE genotype. Neurobiol. Aging 27, 451–458.
Ren, Q.G., Wang, Y.J., Gong, W.G., Xu, L., Zhang, Z.J., 2015. Escitalopram ameliorates tau hyperphosphorylation and spatial memory deficits induced by protein kinase a activation in Sprague Dawley Rats. J. Alzheimer Dis. 47, 61–71.
Rena, G., Hardie, D.G., Pearson, E.R., 2017. The mechanisms of action of metformin. Diabetologia 60, 1577–1585.
Reneerkens, O.A.H., Rutten, K., Steinbusch, H.W.M., Blokland, A., Prickaerts, J., 2009. Selective phosphodiesterase inhibitors: a promising target for cognition enhancement. Psychopharmacology 202, 419–443.
Richter, W., Menniti, F.S., Zhang, H.-T., Conti, M., 2013. PDE4 as a target for cognition enhancement. Expert Opin. Ther. Targets 17, 1011–1027.
Rodriguez-Rivera, J., Denner, L., Dineley, K.T., 2011. Rosiglitazone reversal of Tg2576 cognitive deficits is independent of peripheral gluco-regulatory status. Behav. Brain Res. 216, 255–261.
Rodriguiz, R.M., Wetsel, W.C., 2006. Assessments of cognitive deficits in mutant mice. In: Levin, E.D., Buccafusco, J.J. (Eds.), Animal Models of Cognitive Impairment. Boca Raton (FL).
Rosenbloom, M.H., Barclay, T.R., Pyle, M., Owens, B.L., Cagan, A.B., Anderson, C.P., Frey 2nd, W.H., Hanson, L.R., 2014. A single-dose pilot trial of intranasal rapid-acting insulin in apolipoprotein E4 carriers with mild-moderate Alzheimer's disease. CNS Drugs 28, 1185–1189.
Rudnitskaya, E.A., Maksimova, K.Y., Muraleva, N.A., Logvinov, S.V., Yanshole, L.V., Kolosova, N.G., Stefanova, N.A., 2015. Beneficial effects of melatonin in a rat model of sporadic Alzheimer's disease. Biogerontology 16, 303–316.
Rutten, K., Basile, J.L., Prickaerts, J., Blokland, A., Vivian, J.A., 2008. Selective PDE inhibitors rolipram and sildenafil improve object retrieval performance in adult cynomolgus macaques. Psychopharmacology 196, 643–648.
Salameh, T.S., Bullock, K.M., Hujoel, I.A., Niehoff, M.L., Wolden-Hanson, T., Kim, J., Morley, J.E., Farr, S.A., Banks, W.A., 2015. Central nervous system delivery of intranasal insulin: mechanisms of uptake and effects on cognition. J. Alzheimers Dis. 47, 715–728.
Sato, T., Hanyu, H., Hirao, K., Kanetaka, H., Sakurai, H., Iwamoto, T., 2011. Efficacy of PPAR-gamma agonist pioglitazone in mild Alzheimer disease. Neurobiol. Aging 32, 1626–1633.
Schaler, A.W., Myeku, N., 2018. Cilostazol, a phosphodiesterase 3 inhibitor, activates proteasome-mediated proteolysis and attenuates tauopathy and cognitive decline. Transl. Res. 193, 31–41.
Shafei, M.A., Harris, M., Conway, M.E., 2017. Divergent Metabolic Regulation of Autophagy and mTORC1-Early Events in Alzheimer's Disease? Front. Aging Neurosci. 9, 173-173.
Sigalos, J.T., Pastuszak, A.W., 2018. The safety and efficacy of growth hormone secretagogues. Sex. Med. Rev. 6, 45–53.
Society, A.s., 2016. Risk Factors for Dementia.
Solmaz, V., Cinar, B.P., Yigitturk, G., Cavusoglu, T., Taskiran, D., Erbas, O., 2015. Exenatide reduces TNF-alpha expression and improves hippocampal neuron numbers and memory in streptozotocin treated rats. Eur. J. Pharmacol. 765, 482–487.
Stein, M.S., Scherer, S.C., Ladd, K.S., Harrison, L.C., 2011. A randomized controlled trial of high-dose vitamin D2 followed by intranasal insulin in Alzheimer's disease. J. Alzheimers Dis. 26, 477–484.
Stone, D.L., Rosopa, P.J., 2017. The advantages and limitations of using meta-analysis in human resource management research. Hum. Resour. Manag. Rev. 27, 1–7.
Thangthaeng, N., Rutledge, M., Wong, J.M., Vann, P.H., Forster, M.J., Sumien, N., 2017. Metformin impairs spatial memory and visual acuity in old male mice. Aging Dis. 8, 17–30.
Tian, M., Zhu, D., Xie, W., Shi, J., 2012. Central angiotensin II-induced Alzheimer-like tau phosphorylation in normal rat brains. FEBS Lett. 586, 3737–3745.
Toledo, E.M., Inestrosa, N.C., 2010. Activation of Wnt signaling by lithium and rosiglitazone reduced spatial memory impairment and neurodegeneration in brains of an APPswe/PSEN1DeltaE9 mouse model of Alzheimer's disease. Mol. Psychiatry 15, 272–285, 228.
Tramutola, A., Triplett, J.C., Di Domenico, F., Niedowicz, D.M., Murphy, M.P., Coccia, R., Perluigi, M., Butterfield, D.A., 2015. Alteration of mTOR signaling occurs early in the progression of Alzheimer disease (AD): analysis of brain from subjects with pre-clinical AD, amnestic mild cognitive impairment and late-stage AD. J. Neurochem. 133, 739–749.
Tully, T., 1997. Regulation of gene expression and its role in long-term memory and synaptic plasticity. Proc. Natl. Acad. Sci. U S A 94, 4239–4241.
Tully, T., Bourtchouladze, R., Scott, R., Tallman, J., 2003. Targeting the CREB pathway for memory enhancers. Nat. Rev. Drug Discov. 2, 267–277.
Tumati, S., Burger, H., Martens, S., van der Schouw, Y.T., Aleman, A., 2016. Association between cognition and serum insulin-like growth Factor-1 in middle-aged & older men: an 8 year follow-up study. PLoS One 11 e0154450-e0154450.
Turnes, J.d.M., Bassani, T.B., Souza, L.C., Vital, M.A.B.F., 2018. Ineffectiveness of saxagliptin as a neuroprotective drug in 6-OHDA-lesioned rats. J. Pharm. Pharmacol. 70, 1059–1068.
Tzimopoulou, S., Cunningham, V.J., Nichols, T.E., Searle, G., Bird, N.P., Mistry, P., Dixon, I.J., Hallett, W.A., Whitcher, B., Brown, A.P., Zvartau-Hind, M., Lotay, N., Lai, R.Y.K., Castiglia, M., Jeter, B., Matthews, J.C., Chen, K.W., Bandy, D., Reiman, E. M., Gold, M., Rabiner, E.A., Matthews, P.M., 2010. A multi-center randomized proof-of-Concept clinical trial applying [F-18]FDG-PET for evaluation of metabolic therapy with rosiglitazone XR in mild to moderate alzheimer's disease. J. Alzheimer Dis. 22, 1241–1256.
Venkat, P., Chopp, M., Zacharek, A., Cui, C., Landschoot-Ward, J., Qian, Y., Chen, Z., Chen, J., 2019. Sildenafil treatment of vascular dementia in aged rats. Neurochem. Int. 127, 103–112.
Venna, V.R., Li, J., Hammond, M.D., Mancini, N.S., McCullough, L.D., 2014. Chronic metformin treatment improves post-stroke angiogenesis and recovery after experimental stroke. Eur. J. Neurosci. 39, 2129–2138.
Verdile, G., Fuller, S.J., Martins, R.N., 2015. The role of type 2 diabetes in neurodegeneration. Neurobiol. Dis. 84, 22–38.
Vitiello, M.V., Moe, K.E., Merriam, G.R., Mazzoni, G., Buchner, D.H., Schwartz, R.S., 2006. Growth hormone releasing hormone improves the cognition of healthy older adults. Neurobiol. Aging 27, 318–323.
Wang, D.M., Li, S.Q., Wu, W.L., Zhu, X.Y., Wang, Y., Yuan, H.Y., 2014. Effects of long-term treatment with quercetin on cognition and mitochondrial function in a mouse model of Alzheimer's disease. Neurochem. Res. 39, 1533–1543.
Wang, C., Chen, T., Li, G., Zhou, L., Sha, S., Chen, L., 2015. Simvastatin prevents beta-amyloid(25-35)-impaired neurogenesis in hippocampal dentate gyrus through alpha7nAChR-dependent cascading PI3K-Akt and increasing BDNF via reduction of farnesyl pyrophosphate. Neuropharmacology 97, 122–132.
Wang, X., Wang, L., Jiang, R., Xu, Y., Zhao, X., Li, Y., 2016. Exendin-4 antagonizes Abeta1-42-induced attenuation of spatial learning and memory ability. Exp. Ther. Med. 12, 2885–2892.
Wang, Y.-W., He, S.-J., Feng, X., Cheng, J., Luo, Y.-T., Tian, L., Huang, Q., 2017. Metformin: a review of its potential indications. Drug Des. Devel. Ther. 11, 2421–2429.
Watson, G.S., Peskind, E.R., Asthana, S., Purganan, K., Wait, C., Chapman, D., Schwartz, M.W., Plymate, S., Craft, S., 2003. Insulin increases CSF Abeta42 levels in normal older adults. Neurology 60, 1899–1903.
Watson, G.S., Cholerton, B.A., Reger, M.A., Baker, L.D., Plymate, S.R., Asthana, S., Fishel, M.A., Kulstad, J.J., Green, P.S., Cook, D.G., Kahn, S.E., Keeling, M.L., Craft, S., 2005. Preserved cognition in patients with early Alzheimer disease and amnestic mild cognitive impairment during treatment with rosiglitazone: a preliminary study. Am. J. Geriatr. Psychiatry 13, 950–958.
Watson, G.S., Baker, L.D., Cholerton, B.A., Rhoads, K.W., Merriam, G.R., Schellenberg, G. D., Asthana, S., Cherrier, M., Craft, S., 2009. Effects of insulin and octreotide on memory and growth hormone in Alzheimer's disease. J. Alzheimers Dis. 18, 595–602.
Watson, K.T., Wroolie, T.E., Tong, G., Foland-Ross, L.C., Frangou, S., Singh, M., McIntyre, R.S., Roat-Shumway, S., Myoraku, A., Reiss, A.L., Rasgon, N.L., 2019. Neural correlates of liraglutide effects in persons at risk for Alzheimer's disease. Behav. Brain Res. 356, 271–278.
Williams, D.M., Karlsson, I.K., Pedersen, N.L., Hägg, S., 2018. Circulating insulin-like growth factors and Alzheimer disease: a mendelian randomization study. Neurology 90, e291–e297.
Wong, E., Cuervo, A.M., 2010. Autophagy gone awry in neurodegenerative diseases. Nat. Neurosci. 13, 805–811.

Wu, C., Gong, W.G., Wang, Y.J., Sun, J.J., Zhou, H., Zhang, Z.J., Ren, Q.G., 2018. Escitalopram alleviates stress-induced Alzheimer's disease-like tau pathologies and cognitive deficits by reducing hypothalamic-pituitary-adrenal axis reactivity and insulin/GSK-3β signal pathway activity. Neurobiol. Aging 67, 137–147.

Yan, W.W., Chen, G.H., Wang, F., Tong, J.J., Tao, F., 2015. Long-term acarbose administration alleviating the impairment of spatial learning and memory in the SAMP8 mice was associated with alleviated reduction of insulin system and acetylated H4K8. Brain Res. 1603, 22–31.

Yin, J.C., Tully, T., 1996. CREB and the formation of long-term memory. Curr. Opin. Neurobiol. 6, 264–268.

Zhao, W.Q., Townsend, M., 2009. Insulin resistance and amyloidogenesis as common molecular foundation for type 2 diabetes and Alzheimer's disease. Biochim. Biophys. Acta 1792, 482–496.

Zhi, W.H., Zeng, Y.Y., Lu, Z.H., Qu, W.J., Chen, W.X., Chen, L., Chen, L., 2014. Simvastatin exerts antiamnesic effect in Abeta25-35 -injected mice. CNS Neurosci. Ther. 20, 218–226.

Zhu, H.H., Xue, X.H., Wang, E.M., Wallack, M., Na, H.N., Hooker, J.M., Kowall, N., Tao, Q.S., Stein, T.D., Wolozin, B., Qiu, W.Q., 2017. Amylin receptor ligands reduce the pathological cascade of Alzheimer's disease. Neuropharmacology 119, 170–181.