Neuroscience and Biobehavioral Reviews 173 (2025) 106159

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Role of Glucagon-Like Peptide-1 on Amyloid, Tau, and α-Synuclein: Target Engagement and Rationale for the Development in Neurodegenerative Disorders

Hezekiah C.T. Au [a], Pak Ho Lam [b], Poh Khuen Lim [a], Roger S. McIntyre [c,*]

[a] Brain and Cognition Discovery Foundation, Toronto, Ontario, Canada
[b] Institute of Epidemiology and Health Care, University College London, London, United Kingdom
[c] Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

ARTICLE INFO

Key Words:
GLP-1
GLP-1 Receptor Agonists
Neurodegeneration
Alzheimer's
Parkinson's
Cognition

ABSTRACT

Introduction: Glucagon-like Peptide-1 (GLP-1) and Glucagon-Like Peptide-1 receptor agonist (GLP-1 RA) administration has been associated with neuroprotective effects in neurodegenerative disorders. We conducted a comprehensive synthesis of known effects of GLP-1 and GLP-1 RAs on the cognitive, cellular, and molecular changes in neurodegenerative diseases.
Methods: We examined preclinical and clinical paradigms that investigated changes in neurodegenerative disease pathology following administration of GLP-1 and GLP-1 RAs. Relevant articles were retrieved through OVID (MedLine, Embase, AMED, PsychINFO, JBI EBP Database), PubMed, and Web of Science from database inception to September 27th, 2024. Primary studies investigating the aforementioned changes following GLP-1 and GLP-1 RA administration were retrieved for analysis (n = 62).
Results: GLP-1 and GLP-1 RAs (i.e. dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, and tirzepatide) improved cognitive and motor function in neurodegenerative diseases in preclinical and clinical paradigms. Additionally, GLP-1 and GLP-1 RAs were associated with modulating changes in neuroinflammation, oxidative stress, and proliferative pathways.
Discussion: We observed that GLP-1 and GLP-1 RAs modulate molecular and cellular changes known to govern the phenomenology of neurodegenerative diseases. Future research should examine the interaction between signaling molecules, neuronal subpopulations, and cognitive effects affected by GLP-1 and GLP-1 RA administration.

1. Introduction

Glucagon-Like Peptide-1 (GLP-1) is a gut-derived incretin hormone commonly used in antidiabetic therapy, promoting insulin secretion and inhibition of glucagon secretion (Lutz and Osto, 2016). GLP-1 is also synthesized and released locally by neurons within the nucleus tractus solitarius (NTS), where it binds to GLP-1 receptors distributed on neurons and glial cells of the central nervous system, with notable expression in the hypothalamus and cerebral cortex (Lee and Lee, 2017; Muscogiuri et al., 2017; Lopez-Ferreras et al., 2023).

Neurodegenerative diseases are conditions characterized by the progressive loss of neurons, which are classified based on clinical features and symptoms, anatomical location of neurodegeneration, or molecular abnormalities (Dugger and Dickson, 2017). Neurodegenerative diseases manifest through symptoms such as cognitive deficits, motor impairments, and depressive symptoms (Baquero and Martín, 2015). Various molecular and immunological processes such as oxidative stress and neuroinflammation have been associated with the progression of neurodegenerative diseases (Teleanu et al., 2022). Additionally, various molecular markers serve as hallmarks for disparate neurodegenerative diseases. For example, phosphorylation of α-synuclein (α-syn) is associated with Parkinson's Disease (PD), whereas amyloid beta (Aβ) plaque accumulation and tau neurofibrillary tangles are characteristic of Alzheimer's Disease (AD) (Sengupta and Kayed, 2022).

Extant literature has highlighted the neuroprotective role of GLP-1 and GLP-1 receptor agonists (GLP-1 RAs) (Velmurugan et al., 2012;

* Correspondence to: Brain and Cognition Discovery Foundation, 77 Bloor Street West, Suite 617, Toronto, ON M5S 1M2, Canada.
E-mail addresses: hezekiah.au@mail.utoronto.ca (H.C.T. Au), pak.lam.24@ucl.ac.uk (P.H. Lam), pohkhuen@um.edu.my (P.K. Lim), roger.mcintyre@bcdf.org (R.S. McIntyre).

https://doi.org/10.1016/j.neubiorev.2025.106159
Received 28 November 2024; Received in revised form 8 April 2025; Accepted 13 April 2025
Available online 17 April 2025

Perry et al., 2003; McIntyre et al., 2013, 2025). GLP-1 has been shown to attenuate the accumulation of Aβ and tau hyperphosphorylation through the activation of Akt and GSK3β signaling (Bak et al., 2011; Shu et al., 2019). Additionally, GLP-1 RAs exert anti-inflammatory effects in the brain by attenuating hyperactivity of microglia and astrocytes, which subsequently reduces the production of downstream cytokines such as IL-1β and TNF-α (Kopp et al., 2022; Hogan et al., 2014). Furthermore, GLP-1 RAs have also been linked with ameliorating oxidative stress, which may partially subserve the mechanisms wherein GLP-1 RAs induce neuroprotective effects (Kopp et al., 2022). In addition, GLP-1 RAs may ameliorate cognitive symptoms associated with neurodegenerative conditions via increased levels of neurogenesis (Li et al., 2010a). Notwithstanding, the mechanism whereby GLP-1 RAs subserve improvements in symptoms for neurodegenerative diseases remains to be elucidated.

Herein, we examine the effects of GLP-1 RAs on the cognitive effects of neurodegenerative diseases, simultaneously examining changes in neuronal populations, molecular pathways, and signaling molecules that may subserve phenomenology. The overarching aim is to distinguish the molecular pathways modulated by GLP-1 RAs that may contribute to improvements in neurodegenerative symptoms.

2. Methods

2.1. Search strategy

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021). Web of Science, OVID (MedLINE, Embase, AMED, PsychInfo, JBI EBP), and PubMed were systematically searched for relevant articles from database inception to September 27, 2024. The search string for the search included: ("GLP-1" OR "Glucagon-Like Peptide-1" OR "Glucagon-Like Peptide 1" OR “GLP-1 Agonist” OR “Glucagon-Like Peptide-1 Agonist” OR “Glucagon-Like Peptide 1 Agonist” OR "Semaglutide" OR “Ozempic” OR “Rybelsus” OR “Wegovy” OR "Dulaglutide" OR “Trulicity” OR "Exenatide" OR “Byetta” OR “Bydureon” OR “Liraglutide” OR “Lixisenatide” OR “Tirzepatide”) AND (“Beta Amyloid” OR “Amyloid Beta” OR “β-Amyloid” “Amyloid*” OR “Amyloidopath*” OR “Tau” OR “Tau Protein” OR “aSyn” OR “a-Syn” OR “a-Synuclein” OR “Synuclein*” OR “Synucleinopath*”) AND (“Parkinson*” OR “Parkinsonian” OR “Alzheimer*” OR “Neurodegenerative” OR “Neurodegeneration” OR “Neuroprotect*”).

2.2. Study selection and inclusion criteria

Articles obtained from the systematic search were screened via Covidence, wherein duplicate articles were removed (Covidence, 2024). Two reviewers (H.A. and P.H.L.) individually screened the title and abstracts based on the inclusion and exclusion criteria (Table 1). Primary articles were extracted for full-text screening by both reviewers if they reported on changes associated with neurodegenerative disease pathology (i.e. concentration of tau protein, cognitive deficits induced by amyloidopathy) as a result of GLP-1 or GLP-1 RA prescription.

2.3. Data extraction

The piloted data extraction template was used to organize and extract relevant data from included studies. Information of interest was established *a priori* for human studies, including (1) author, (2) study type, (3) sample size, (4) diagnoses, (5) mean age, (6) measurement tools, (7) outcome of interest. Similarly, information to be extracted was established *a priori* for animal studies, including (1) author, (2) study type, (3) sample size, (4) diagnoses, (5) measurement tools, (6) outcome of interest. Extraction was conducted by two independent reviewers (H.A. and P.H.L.), wherein all conflicts were immediately resolved via discussion. Outcomes of interest pertained to changes in amyloid, tau, or synuclein pathologies mediated by GLP-1 and GLP-1 RAs.

Table 1
Eligibility criteria.

Inclusion Criteria	1. A primary study, 2. Human Studies, 3. Participants must have a diagnosis of a neurodegenerative condition (i.e. Alzheimer’s Disease, Parkinson’s Disease), 4. Animal Studies, 5. Measurement of changes in β-amyloid, tau, α-synuclein, and associated genes, 6. Full-text article available online, 7. English language.
Exclusion Criteria	1. Non-primary or secondary research (i.e., literature reviews, systematic reviews, meta-analyses, posters, abstracts, guidelines, protocols and theses), 2. Participants must not be diagnosed with co-morbidities or mixed diagnoses between different disorders, 3. Case Studies, 4. Cell Culture Studies, 5. Reports an association without statistics, 6. Full-Text is not available.

2.4. Quality assessments

Quality assessment of randomized control trials was conducted using the Quality Assessment of Controlled Intervention Studies from the National Institute of Health (Ma et al., 2020; Study Quality Assessment Tools, 2024). For animal studies, quality assessment was conducted using the SYRCLE’s risk of bias analysis tool for animal studies (Hooijmans et al., 2014). Relevant literature was assessed by two independent reviewers (H.A. and P.H.L.), wherein all conflicts were resolved via immediate discussion. Further information on methodological quality assessments have been listed in the supplementary materials (Table S1, Table S2).

3. Results

3.1. Search results

A systematic database search generated a total of 591 studies, wherein 4 articles were further obtained through citation searching. Thirty-one duplicates were manually identified, and 192 duplicates were identified by Covidence. Three hundred sixty eight studies underwent title and abstract screening, with 268 articles deemed irrelevant. One hundred relevant full-text articles were retrieved and screened based on the eligibility criteria (Table 1). Thirty-nine studies were excluded as a result of wrong outcomes (n = 4), wrong comparator (n = 5), wrong intervention (n = 11), wrong study design (n = 7), comorbid diagnoses (n = 4), or wrong subject population (n = 8) (Fig. 1). In total, 62 studies were selected and retrieved for this systematic review.

3.2. Methodological Quality

All controlled intervention studies employed adequate methods of randomization, clearly defined exposure and outcome measures, and reported that the sample size was sufficient to detect a clinically significant difference. No clinical studies exhibited a high risk of bias. Varied limitations were present across studies, wherein an elevated drop-out rate and use of single-blind rather than double-blinded procedures was observed in disparate studies. Notwithstanding, these limitations did not significantly affect the quality of the results.

Most preclinical studies were devoid of selective outcome reporting, employed similar populations at baseline, and adjusted for confounders in the analysis. Common limitations varied across animal studies, with a lack of random housing, blinding, and random outcome assessment being commonly observed. Most clinical studies did not exhibit a high

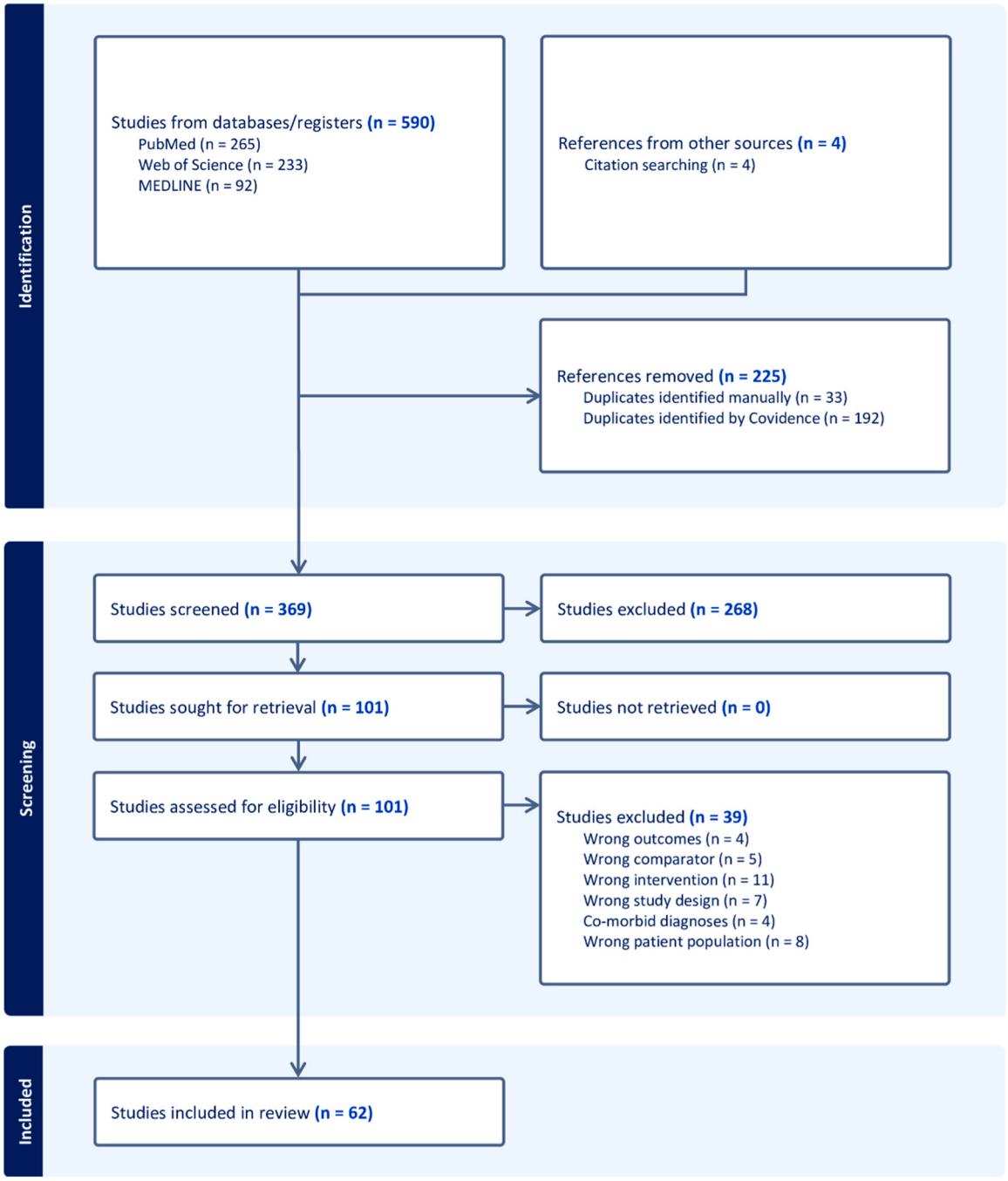

Fig. 1. PRISMA flow diagram of literature search (Covidence, 2024).

risk of bias. However, An et al. (2019) exhibited notable methodological concerns, specifically due to the lack of the aforementioned limitations, along with the absence of allocation concealment, impacting the reliability and quality rating of the study's outcomes. Similarly, Long-Smith et al. (2013) reported comparable methodological issues associated with An et al. (2019), though the study lacked baseline characteristics reporting rather than allocation concealment. As such, only objective results were examined for both studies. Specifically, only the cellular and molecular changes associated with GLP-1 RA administration have been referenced.

3.3. Effects of GLP-1 and GLP-1 RAs on neurodegenerative diseases in humans

3.3.1. Effects of GLP-1 and GLP-1 RAs on Alzheimer's diseases in humans

We identified 3 studies examining the effects of GLP-1 and GLP-1 RAs on AD in humans (Long-Smith et al., 2013; Akimoto et al., 2020; Mullins et al., 2019).

3.3.1.1. Effects of Dulaglutide on Alzheimer's disease in humans. In a pharmacovigilance study conducted using the FDA Adverse Event Reporting System (FAERS) database, dulaglutide administration was associated with significantly lowered risk of AD in all populations (ROR = 0.39, 95 % CI [0.17, 0.77], p = 0.014, n = 961) (Akimoto et al., 2020). This trend was significantly replicated in females (ROR = 0.40,

95 % CI [0.12, 0.98], p = 0.048, n = 560), but not significantly in males (ROR = 0.41, 95 % CI [0.10, 1.10], p = 0.131, n = 401) (Akimoto et al., 2020). These results suggest that dulaglutide may reduce risk of AD. Notwithstanding, further research is required to elucidate the role of dulaglutide on AD.

3.3.1.2. Effects of exenatide on Alzheimer's disease in humans. In addition to examining the role of dulaglutide on AD, Akimoto et al. (2020) also examines the association between exenatide administration and AD. Exenatide administration was associated with significantly reduced risk of AD in all populations (ROR = 0.22, 95 % CI [0.11, 0.37], p < 0.001, n = 3158) (Akimoto et al., 2020). This relationship was observed disparately in both female (ROR = 0.20, 95 % CI [0.08, 0.40], p < 0.001, n = 1904) and male (ROR = 0.25, 95 % CI [0.09, 0.55], p = 0.002, n = 1254) populations (Akimoto et al., 2020).

In a randomized clinical trial by Mullins et al. (2019) (n = 21), administration of exenatide was not significantly associated with improving scores on multiple cognitive tests, including the Clinical Dementia Rating (CDR), Mini-Mental State Exam (MMSE) (Table 2). Notwithstanding, administration of exenatide was associated with within-subject differences in Digit-Span forward total score (F[3,36.2] = 4.804, p = .006) and maximum digit span forward (F[3,35] = 3.889, p = .017)) following 6 months of exenatide administration (Mullins et al., 2019). Additionally, exenatide administration was associated with significant decreases in $A\beta_{42}$ in comparison to participants administered with placebos (F[1,16.3] = 4.71, p = 0.045), but not other CSF biomarkers (i.e. tau, p181- tau, plasma $A\beta_{40}$) (Mullins et al., 2019). Taken together, these findings suggest that exenatide may reduce the risk of AD, wherein further research must be conducted to further elucidate this effect.

3.3.1.3. Effects of Liraglutide on Alzheimer's Disease in Humans. In the pharmacovigilance study by Akimoto et al. (2020), the effects of liraglutide on AD was also examined. Similar to previous GLP-1 RAs, liraglutide administration was associated with significantly lowered risk of AD in all populations (ROR = 0.36, 95 % CI [0.19, 0.62], p < 0.001, n = 2083) (Akimoto et al., 2020). These findings were replicated in both female (ROR = 0.38, 95 % CI [0.16, 0.75], p = 0.013, n = 1163) and male (ROR = 0.34, 95 % CI [0.12, 0.75], p = 0.018, n = 950) populations (Akimoto et al., 2020). Consistent with Akimoto et al. (2020), a randomized clinical trial by Gejl et al. (2016) (n = 34) suggests that liraglutide may be involved in modulating protective effects against AD. Specifically, daily administration of liraglutide over 26 weeks has been associated with attenuating impairments in the orientation test of the Wechsler Memory Scale (WMS-IV), but the effect was not significant between groups (p = 0.085) (Gejl et al., 2016). Notwithstanding, no significant changes in cognitive score were observed from baseline (Gejl et al., 2016).

Additionally, participants administered with liraglutide exhibited significant increases in [^{11}C] binding in the temporal (P = 0.04, 0.056, 95 % CI [0.0017, 0.11]) and occipital (P = 0.04, 0.048, 95 % CI [0.0013, 0.094]) lobes, and insignificantly in the cingulate (P = 0.09, 0.088, 95 % CI [−0.017, 0.19]) and cerebral (P = 0.09, 0.055, 95 % CI [−0.0099, 0.12]) cortices, whilst a significant decrease was observed in the cerebellum (P = 0.09, 0.010, 95 % CI [0.023, −0.0019]) (Gejl et al., 2016).

It was further observed that participants administered with placebo exhibited significantly increased [^{11}C] binding in the temporal lobe (P = 0.04, 0.036, 95 % CI [0.0012, 0.070]), and insignificantly in the occipital lobe (P = 0.09, 0.023, 95 % CI [−0.0043; 0.050]) (Akimoto et al., 2020). These results suggest that even though liraglutide may attenuate cognitive deficits associated with AD, retention of amyloid beta in humans may not be affected. Notwithstanding, these findings support the notion that liraglutide may reduce the risk of AD, and may ameliorate cognitive deficits associated with AD.

3.3.2. Effects of GLP-1 and GLP-1 RAs on Parkinson's Disease in Humans

To examine the effects of GLP-1 on Parkinson's Disease in humans, we have identified 4 studies (Rozani et al., 2024; Athauda et al., 2017; Aviles-Olmos et al., 2013; Meissner et al., 2024).

3.3.2.1. Effects of GLP-1 on Parkinson's Disease in Humans. In a retrospective cohort study by Rozani et al. (2024) (n = 86,229), administration of GLP-1 was associated with reducing risk of PD (HR = 0.54, 95 % CI [0.39, 0.73], p < 0.001). Evidently, further research is required to further examine the role of GLP-1 on PD in humans (Rozani et al., 2024).

3.3.2.2. Effects of Exenatide on Parkinson's Disease in Humans. Extant literature supports the notion that exenatide may attenuate and improve cognitive symptoms of PD. In a randomized control trial by Athauda et al. (2017) (n = 62), patients administered with exenatide for 48 weeks exhibited significant improvements in PD symptoms, as evidenced by lower scores on the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Patients administered with exenatide exhibited significantly reduction in scores (-2.3, 95 % CI [-4.1, 0.7]) in comparison to placebo (1.7, 95 % CI [-0.6, 4.0]), wherein the adjusted difference between groups was significant (-4.3, 95 % CI [-7.1, −1.6], p = 0.0026) (Athauda et al., 2017). These results were replicated 12 weeks post-exenatide treatment as patients administered with exenatide continued to exhibit significant improvements in PD symptoms (-1.0, 95 % CI [-2.6, 0.7]) in comparison to placebo controls (2.1, 95 % CI [-0.6, 4.8]), wherein the adjusted difference between groups was significant (-3.5, 95 % CI [-6.7, −0.3], p = 0.0318) (Athauda et al., 2017).

A separate clinical study by Aviles-Olmos et al. (2013) (n = 44) further supported these results, wherein administration of exenatide for 12 months significantly reduced MDS-UPDRS scores (-2.7 ± 7.7) in comparison to placebo controls (2.2 ± 7.3), with a significant adjusted difference between groups (4.9, 95 % CI [0.3, 9.4], p = 0.037). The aforementioned observation persisted for 2 months after exenatide treatment, wherein improvements in PD symptoms persisted (-1.7 ± 7.4) in comparison to controls (2.8 ± 6.7), with a significant adjusted difference between groups (4.4, 95 % CI [0.2, 8.7], p = 0.042) (Athauda et al., 2017; Aviles-Olmos et al., 2013). No significant differences between groups were observed in the Montgomery-Asberg Depression Rating Scale, Unified Dyskinesia Rating Scale, NonMotor Symptoms Severity Scale, Parkinson's Disease Questionnaire summary index, or EuroQol Five Dimensions Questionnaire in both studies (Athauda et al., 2017; Aviles-Olmos et al., 2013). Taken together, these studies demonstrate that exenatide treatment may attenuate cognitive symptoms in PD.

3.3.2.3. Effects of Lixisenatide on Parkinson's Disease in Humans. A randomized control trial by Meissner et al. (2024) (n = 156) investigated the effects of lixisenatide on participants with PD. Results indicate that participants administered with lixisenatide exhibited significant reductions in MDS-UPDRS scores (-0.04, 95 % CI [-1.62, 1.54]) in comparison to placebo controls (3.04, 95 % CI [1.46, 4.62]), wherein the differences between groups are significant (p = 0.007) (Meissner et al., 2024). Although these findings suggest that lixisenatide may ameliorate cognitive deficits associated with PD, further research is required to understand the mechanistic role of lixisenatide in modulating neuroprotective effects in PD.

3.4. Cognitive Effects of GLP-1 and GLP-1 RAs in animal models

3.4.1. Cognitive Effects of GLP-1 and GLP-1 RAs on Alzheimer's disease in animals

To highlight the specific changes in cognition associated with disparate GLP-1 RAs, we identified 37 studies (Table 3). Among these

Table 2
Study characteristics investigating effect of GLP-1 agonists on neurodegenerative diseases in human models.

Author(s)	Study Type	Sample Size	Diagnoses	Mean Age	Measurement Tools	Outcome(s) of Interest
Exenatide						
Athauda et al. (2017)	Randomized Control Trial	62 total participants 32 participants administered with exenatide 30 placebo controls	PD	**Exenatide:** 61.6 ± 8.2 years **Placebo:** 57.8 ± 8.0 years	Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)	Patients were administered weekly with 2 mg exenatide for 48 weeks. At 48 weeks, participants administered with exenatide exhibited improvements in PD symptoms based on scores on the MDS-UPDRS (-2.3, 95 % CI [-4.1, 0.7]). In contrast, participants administered with placebo exhibited worsening of PD symptoms (1.7, 95 % CI [-0.6, 4.0]), wherein the adjusted difference between groups was significant (-4.3, 95 % CI [-7.1, −1.6], p = 0.0026). At 60 weeks, participants administered with exenatide exhibited improvements in PD symptoms based on scores on the MDS-UPDRS (-1.0, 95 % CI [-2.6, 0.7]). In contrast, participants administered with placebo exhibited worsening of PD symptoms (2.1, 95 % CI [-0.6, 4.8]), wherein the adjusted difference between groups was significant (-3.5, 95 % CI [-6.7, −0.3], p = 0.0318). No differences between groups were observed on the Mattis Dementia Rating Scale, Montgomery-Asberg Depression Rating Scale, Unified Dyskinesia Rating Scale, NonMotor Symptoms Severity Scale, Parkinson's Disease Questionnaire summary index, or EuroQol Five Dimensions Questionnaire, nor in results on timed motor tests or Hauser diaries.
Aviles-Olmos et al. (2013)	Randomized Control Trial	44 total participants 20 participants administered with exenatide 24 placebo controls	PD	**Exenatide:** 61.4 ± 6.0 years **Placebo:** 59.4 ± 8.4 years	Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Mattis dementia rating scale–2 (Mattis DRS−2)	Patients were administered bidaily with 5 μg exenatide for 1 month, ramping up to 10 μg exenatide for 11 months. Administration of exenatide was associated with improvements of PD symptoms based on MDS-UPDRS scores (−2.7, SD = 7.7). Contrastingly, participants administered with placebo exhibited worsening of PD symptoms (2.2, SD = 7.3), wherein the adjusted difference between groups was significant (4.9, 95 % CI [0.3, 9.4], p = 0.037) This trend was replicated at 14 months, wherein administration of exenatide was associated with improvements of PD symptoms based on MDS-UPDRS scores (−1.7, SD = 7.4). Contrastingly, participants administered with placebo exhibited worsening of PD symptoms (2.8, SD = 6.7), wherein the adjusted difference between groups was significant (4.4, 95 % CI [0.2, 8.7], p = 0.042) At 14 months, exenatide administration was associated with improvements on the Mattis DRS−2 scale (2.8), wherein deterioration was observed in participants administered with placebo (3.5). A significant difference was observed between groups (6.3 points, 95 % CI [2.7, 9.9], p = 0.001). No significant differences between group were observed in Montgomery-Asberg depression rating scale (MADRS) scores or Parkinson Disease Questionnaire–39 (PDQ39) summary index scores.
Mullins et al. (2019)	Randomized Control Trial	21 total participants 11 participants administered with exenatide 10 placebo controls	AD	Exenatide: 71.7 ± 6.9 years Placebo: 74.0 ± 6.4 years	Clinical Dementia Rating (CDR) Mini-Mental State Exam (MMSE) 70-point Alzheimer's Disease Assessment Scale cognitive subscale (ADASCog) Frontal Assessment Battery (FAB) Verbal Fluency California Verbal Learning Task (CVLT) Boston Naming Test	Participants were administered with 5 μg exenatide twice a day, increased to 10 μg twice a day for 18 months. Administration of exenatide did not significantly improve group differences in within-subject differences with the exception of Digit-Span forward total score (F[3,36.2] = 4.804, p = .006) and maximum digit span forward (F [3,35] = 3.889, p = .017)) scores at 6 months. Significant changes in cognition were observed over time in both groups, including decreases the MMSE (F [3,52.0] = 3.738, p = 0.017), verbal fluency (F[3,52.1] = 3.008, p = 0.038),

(*continued on next page*)

Table 2 (*continued*)

Author(s)	Study Type	Sample Size	Diagnoses	Mean Age	Measurement Tools	Outcome(s) of Interest
Exenatide						
Athauda et al. (2017)	Randomized Control Trial	62 total participants 32 participants administered with exenatide 30 placebo controls	PD	**Exenatide:** 61.6 ± 8.2 years **Placebo:** 57.8 ± 8.0 years	Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)	Patients were administered weekly with 2 mg exenatide for 48 weeks. At 48 weeks, participants administered with exenatide exhibited improvements in PD symptoms based on scores on the MDS-UPDRS (-2.3, 95 % CI [-4.1, 0.7]). In contrast, participants administered with placebo exhibited worsening of PD symptoms (1.7, 95 % CI [-0.6, 4.0]), wherein the adjusted difference between groups was significant (-4.3, 95 % CI [-7.1, −1.6], p = 0.0026). At 60 weeks, participants administered with exenatide exhibited improvements in PD symptoms based on scores on the MDS-UPDRS (-1.0, 95 % CI [-2.6, 0.7]). In contrast, participants administered with placebo exhibited worsening of PD symptoms (2.1, 95 % CI [-0.6, 4.8]), wherein the adjusted difference between groups was significant (-3.5, 95 % CI [-6.7, −0.3], p = 0.0318). No differences between groups were observed on the Mattis Dementia Rating Scale, Montgomery-Asberg Depression Rating Scale, Unified Dyskinesia Rating Scale, NonMotor Symptoms Severity Scale, Parkinson's Disease Questionnaire summary index, or EuroQol Five Dimensions Questionnaire, nor in results on timed motor tests or Hauser diaries.
					Wechsler Memory Scale Logical Memory Subtest Trail-making Test Parts A & B American National Adult Reading Test (ANART) Clock drawing Wechsler Adult Intelligence Scale Digit-Symbol and Digit Span Forward & Backward Subtests Benton Visual Retention Task (BVRT) University of Pennsylvania Smell Identification Test (UPSIT)	Boston naming correct after stimulus cue, (F [3,53.0] = 3.973, p = 0.013), and Digit-symbol total (F[3,45.0] = 2.918, p = 0.044). Contrastingly, increases were also observed over time in Trails-making test B time (F[3,49.4] = 3.023, p = 0.038), ADCS (F[3,49.7] = 5.47, p = 0.003), and digit-symbol total (F[3,45.0] = 2.918, p = 0.044). Participants administered with exenatide exhibited significant reductions in Aβ42 in comparison to participants administered with placebos (F[1,16.3] = 4.71, p = 0.045), but not in other CSF biomarkers (i.e. tau, p181- tau, plasma Aβ40).
Liraglutide						
Gejl et al. (2016)	Randomized Control Trial	34 total participants 14 participants administered with liraglutide 20 placebo controls	AD	**Liraglutide:** 63.1 years **Placebo:** 66.6 years	Wechsler Memory Scale (WMS)	Participants were administered with either placebo or liraglutide daily for 26 weeks, ramping up from 0.6 mg daily for a week, to 1.2 mg daily, to the final amount of 1.8 mg daily. **[^{11}C] RIB Retention:** Participants administered with placebo exhibited significant increases in [^{11}C] binding by the following mean ratios in the temporal lobe (P = 0.04, 0.036, 95 % CI [0.0012, 0.070]), and insignificantly in the occipital lobe (P = 0.09, 0.023, 95 % CI [−0.0043; 0.050]). Similarly, participants administered with liraglutide exhibited significant increases in [^{11}C] binding by the following mean ratios in the temporal (P = 0.04, 0.056, 95 % CI [0.0017, 0.11]) and occipital (P = 0.04, 0.048, 95 % CI [0.0013, 0.094]) lobes, and insignificantly in the cingulate (P = 0.09, 0.088, 95 % CI [−0.017, 0.19]) and cerebral (P = 0.09, 0.055, 95 % CI [−0.0099, 0.12]) cortices. Contrastingly, a nonsignificant decrease was observed in the cerebellum (P = 0.09, 0.010, 95 % CI [0.023, −0.0019]). **Cerebral Blood Flow:** Participants administered with placebo exhibited significant increases in cerebral blood flow in the frontal, (P = 0.04, 3.56 ml/hg/min, 95 % CI [0.17, 6.94], parietal (P = 0.04, 3.27 ml/hg/min, 95 % CI [0.10; 6.45], and

(*continued on next page*)

Table 2 (*continued*)

Author(s)	Study Type	Sample Size	Diagnoses	Mean Age	Measurement Tools	Outcome(s) of Interest
Exenatide						
Athauda et al. (2017)	Randomized Control Trial	62 total participants 32 participants administered with exenatide 30 placebo controls	PD	**Exenatide:** 61.6 ± 8.2 years **Placebo:** 57.8 ± 8.0 years	Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)	Patients were administered weekly with 2 mg exenatide for 48 weeks. At 48 weeks, participants administered with exenatide exhibited improvements in PD symptoms based on scores on the MDS-UPDRS (-2.3, 95 % CI [-4.1, 0.7]). In contrast, participants administered with placebo exhibited worsening of PD symptoms (1.7, 95 % CI [-0.6, 4.0]), wherein the adjusted difference between groups was significant (-4.3, 95 % CI [-7.1, −1.6], p = 0.0026). At 60 weeks, participants administered with exenatide exhibited improvements in PD symptoms based on scores on the MDS-UPDRS (-1.0, 95 % CI [-2.6, 0.7]). In contrast, participants administered with placebo exhibited worsening of PD symptoms (2.1, 95 % CI [-0.6, 4.8]), wherein the adjusted difference between groups was significant (-3.5, 95 % CI [-6.7, −0.3], p = 0.0318). No differences between groups were observed on the Mattis Dementia Rating Scale, Montgomery-Asberg Depression Rating Scale, Unified Dyskinesia Rating Scale, NonMotor Symptoms Severity Scale, Parkinson's Disease Questionnaire summary index, or EuroQol Five Dimensions Questionnaire, nor in results on timed motor tests or Hauser diaries.
						occipital (P = 0.02, 3.27 ml/hg/min, 95 % CI [0.10; 6.45]) lobes, the cerebellum (P = 0.009, 4.47 ml/hg/min, 95 % CI [1.28, 7.65]), and in the cortex as a whole (P = 0.03, 3.61 ml/hg/min, 95 % CI [0.41, 6.81]). No significant increases in cerebral blood flow (P ≥ 0.41) were observed in the liraglutide treatment group. Similarly, no differences in ratios were observed between the groups (P ≥ 0.13). **Cerebral Glucose Metabolism:** Participants administered with placebo exhibited significant decreases in cerebral glucose metabolism in the precuneus (P = 0.009, 3.2 μmol/hg/min, 95 % CI [5.45, 0.92]), and in the parietal (P = 0.04, 2.1 μmol/hg/min, 95 % CI [4.21, 0.081]), temporal (P = 0.046, 1.54 μmol/hg/min, 95 % CI [3.05, 0.030]), and occipital (P = 0.009, 2.10 μmol/hg/min, 95 % CI: [3.61, 0.59]) lobes, and in the cerebellum (P = 0.04, 1.54 μmol/hg/min, 95 % CI [3.01, 0.064]). In contrast, participants administered with liraglutide exhibited increased non-significant increases in cerebral glucose metabolism (P ≥ 0.49). **Cognitive Impairment:** Significant impairments were observed in participants administered with the placebo during the orientation test (p = 0.041), but not participants administered with liraglutide. No significant differences, however, were observed between the two groups.
Lixisenatide						
Meissner et al. (2024)	Randomized Control Trial	156 total participants 78 participants administered with lixisenatide 78 placebo controls	PD	**Lixisenatide:** 59.5 ± 8.1 years **Placebo:** 59.9 ± 8.4 years	Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS)	Experimental groups were initially administered with 10 μg lixisenatide for 14 days, ramping up to 20 μg/day for the remainder of the 12-month period. Participants administered with lixisenatide exhibited improvements in PD symptoms based on scores on the MDS-UPDRS (−0.04, 95 % CI [−1.62, 1.54]). In contrast, administration of placebo was associated with increases in MDS-UPDRS mean score (3.04, 95 % CI [1.46, 4.62]), wherein the difference between groups was

(*continued on next page*)

Table 2 (*continued*)

Author(s)	Study Type	Sample Size	Diagnoses	Mean Age	Measurement Tools	Outcome(s) of Interest
Exenatide						
Athauda et al. (2017)	Randomized Control Trial	62 total participants 32 participants administered with exenatide 30 placebo controls	PD	**Exenatide:** 61.6 ± 8.2 years **Placebo:** 57.8 ± 8.0 years	Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)	Patients were administered weekly with 2 mg exenatide for 48 weeks. At 48 weeks, participants administered with exenatide exhibited improvements in PD symptoms based on scores on the MDS-UPDRS (-2.3, 95 % CI [-4.1, 0.7]). In contrast, participants administered with placebo exhibited worsening of PD symptoms (1.7, 95 % CI [-0.6, 4.0]), wherein the adjusted difference between groups was significant (-4.3, 95 % CI [-7.1, −1.6], p = 0.0026). At 60 weeks, participants administered with exenatide exhibited improvements in PD symptoms based on scores on the MDS-UPDRS (-1.0, 95 % CI [-2.6, 0.7]). In contrast, participants administered with placebo exhibited worsening of PD symptoms (2.1, 95 % CI [-0.6, 4.8]), wherein the adjusted difference between groups was significant (-3.5, 95 % CI [-6.7, −0.3], p = 0.0318). No differences between groups were observed on the Mattis Dementia Rating Scale, Montgomery-Asberg Depression Rating Scale, Unified Dyskinesia Rating Scale, NonMotor Symptoms Severity Scale, Parkinson's Disease Questionnaire summary index, or EuroQol Five Dimensions Questionnaire, nor in results on timed motor tests or Hauser diaries.
						significant (p = 0.007). Both groups were administered with similar mean doses of levodopa.
Glucagon-Like Peptide−1 Receptor Agonists						
Akimoto et al. (2020)	Pharmacovigilance Study	66,086 total participants 961 participants administered with dulaglutide 3158 participants administered with exenatide 2083 participants administered with liraglutide	AD	N/A	N/A	Significantly lower risk of AD was associated with exenatide (ROR = 0.22, 95 % CI [0.11, 0.37], p < 0.001, n = 3158), liraglutide (ROR = 0.36, 95 % CI [0.19, 0.62], p < 0.001, n = 2083), dulaglutide (ROR = 0.39, 95 % CI [0.17, 0.77], p = 0.014, n = 961). Significantly lower risk of AD was associated with exenatide (ROR = 0.25, 95 % CI [0.09, 0.55], p = 0.002, n = 1254) and liraglutide (ROR = 0.34, 95 % CI [0.12, 0.75], p = 0.018, n = 950) in men, but not significantly in dulaglutide (ROR = 0.41, 95 % CI [0.10, 1.10], p = 0.131, n = 401). Significantly lower risk of AD was associated with exenatide (ROR = 0.20, 95 % CI [0.08, 0.40], p < 0.001, n = 1904), liraglutide (ROR = 0.38, 95 % CI [0.16, 0.75], p = 0.013, n = 1163), dulaglutide (ROR = 0.40, 95 % CI [0.12, 0.98], p = 0.048, n = 560) in women.
Rozani et al. (2024)	Retrospective Cohort Study	86,229 total participants	PD	60.0 ± 11.0 years	N/A	Significant lower risk of PD was associated with the administration of GLP−1 receptor agonists (HR = 0.54, 95 % CI [0.39, 0.73], p < 0.001).

Abbreviations: T2DM = Type 2 Diabetes Mellitus, AD = Alzheimer's Disease, PD = Parkinson's Disease, MWM = Morris Water Maze, Ex-4 = Exendin-4, i.p. = Intraperitoneal, i.c.v. = Intracerebroventricular, APP = Amyloid Precursor Protein, ROS = Reactive Oxygen Species, N/A = Not Available

studies, McClean and Hölscher (2014a) examined the effect of liraglutide and lixisenatide on AD.

3.4.1.1. Cognitive Effects of GLP-1 on Alzheimer's Disease in Animals. The role of GLP-1 in modulating cognitive deficits in AD has yielded mixed results. Findings from Ma et al. (2012) identified that GLP-1 $(9-36)^{amide}$ - a cleavage product of GLP-1 - attenuated AD-induced memory and learning deficits. This was evidenced by significant reductions in escape latency during Morris Water Maze (MWM) tasks (p = 0.0001) and increased target quadrant occupation during probe trial tests (p < 0.05) (Ma et al., 2012). In addition, a study by Li et al. (2012) (n = 30) reported that administration of 50 μM (Val8)GLP-1 was associated with significant reductions in escape latency and distance in the MWM task (p < 0.05) (Li et al., 2012). In contrast, a separate study indicated that administration of Val^8(GLP-1) in rats did not exhibit changes in mean escape latency (p > 0.05) or time spent in target quadrant in comparison to controls (p > 0.05) (Wang et al., 2010). These findings suggest that GLP-1 administration may ameliorate cognitive effects associated with AD, although further research is required to examine this interaction.

3.4.1.2. Cognitive Effects of Dulaglutide on Alzheimer's Disease in Animals. There is insufficient information on the effects of dulaglutide. Zhou et al. (2019) examined the cognitive effects of dulaglutide in AD mice models. Results indicate that dulaglutide administration was associated with non-significant decreased escape latency during MWM

Table 3
Study characteristics investigating effect of GLP-1 agonists on neurodegenerative diseases in animal models.

Author(s)	Study Type	Sample Size	Diagnoses	Measurement Tool(s)	Outcome(s) of Interest
GLP−1					
Bergkvist et al. (2021)	Animal Study	C57/B6 mice	PD	N/A	Mice treated with α-syn preformed fibrils (PFF) and injected with 0.24 mg/kg long-lasting GLP−1 analogue exhibited no changes in pSer129 α-syn reactivity at 5 weeks post-GLP−1 injection, but 74.5 % increase 13 weeks post-injection in comparison to controls ($p = 0.005$).
Gault and Hölscher (2008)	Animal Study	Male Wistar rats	AD	N/A	GLP−1, GLP−1(9−36), and (Val^8)GLP−1 had no significant changes on LTP in absence of beta-amyloid (25–35). Injection of (Val^8)GLP−1 (15 nmol in 5 μl i.c.v.) simultaneously with beta-amyloid (25–35) did not significantly revert the impairing effect of LTP of beta-amyloid (100 nmol in 5 μl i.c.v.). Similarly, no significant effect was observed when (Val^8)GLP−1 was injected 15 minutes prior to beta-amyloid. Notwithstanding, complete reversal of amyloid-induced impairing of LTP was observed when (Val^8)GLP−1 was injected 30 minutes prior to beta-amyloid injection.
Gengler et al. (2012)	Animal Study	APP/PS−21 C57BL/6 mice	AD	N/A	**Cellular Changes:** No differences in microglial load was observed after 25 nmol/kg (Val^8) GLP−1 administration for 3 weeks in comparison to saline control. **Molecular Changes:** 9-month old mice administered with 25 nmol/kg (Val^8)GLP−1 for 3 weeks exhibited significantly stronger increases LTP in the CA1 region of the hippocampus in comparison to saline control ($n = 15$, $F = 4.35$, $df = 1$, $p < 0.05$). This trend was replicated in 18-month old mice ($n = 11$, $F = 4.7$, $df = 1$, $p < 0.05$), wherein no enhanced LTP was observed after saline injection. No differences in beta-amyloid plaque load was observed after 25 nmol/kg (Val^8)GLP−1 administration for 3 weeks in comparison to saline control.
Li et al. (2012)	Animal Study	30 male Wistar rats	AD	Morris Water Maze (MWM) task	AD mice models were induced via administration of streptozotocin (STZ). **Cognitive Changes:** Mice administered with 50 μM (Val8)GLP−1 exhibited significant reductions in escape latency and distance in the MWM task in comparison to no GLP−1 administration ($p < 0.05$). **Molecular Changes:** Administration of 50 μM (Val8)GLP−1 was associated with significant decreases in phosphorylated tau / tau ratio ($p < 0.05$), simultaneously attenuating STZ-induced increases in tau expression in comparison to controls.
Ma et al. (2012)	Animal Study	APP/PS1 mice	AD	Morris Water Maze (MWM) task Probe Trial Tests	Mice were administered with 500 μg / kg GLP−1(9−36)^{amide} over a period of two weeks. **Cognitive Changes:** Administration of GLP−1(9−36)^{amide} was associated with attenuation of AD-induced learning and memory deficits, exemplified by significant decreases in escape latency during MWM tasks ($p = 0.0001$) and increases in target quadrant occupation during probe trial tests ($p < 0.05$). **Molecular Changes:** GLP−1(9−36)^{amide} was not associated with significant changes in APP or Aβ levels when compared to mice administered with vehicle control ($p > 0.05$). Mice administered with GLP−1(9−36)^{amide} attenuated AD-induced increases in mitochondrial superoxide and AD-induced activation of GSK3β in comparison to vehicle control. No significant changes in Akt was observed ($p > 0.05$), whereas a non-significant decrease in caspase−3 was observed ($p = 0.35$) in comparison to vehicle control.
Wang et al. (2010)	Animal Study	Male Wistar rats	AD	Morris Water Maze (MWM) test	Rats were administered with 5 μL, 0.05pmol / 5 μL Val^8-GLP−1(7−36) *i.c.v.* **Cognitive Changes:** Rats administered with GLP−1 did not exhibit significant changes in mean escape latency and mean escape distances ($p > 0.05$) in the MWM test. These results were replicated in the probe task, wherein no significant changes in time spent in target quadrant was observed ($p > 0.05$) in comparison to controls.
Dulaglutide					
Khalaf et al. (2023)	Animal Study	24 male Wistar rats	PD	N/A	Mice were continuously injected with a low dose (0.05 mg/kg) or high dose (0.1 mg/kg) of liraglutide every week. **Molecular Changes:** Mice administered with low weekly doses of dulaglutide attenuated rotenone-associated oxidative stress, characterized by significant increases in glutathione (GSH) content (70.14 %, $p \leq 0.05$), superoxide dismutase (SOD) activity (32.46 %, $p \leq 0.05$), and significant decreases in oxidative stress markers malondialdehyde (MDA) (30 %, $p \leq 0.05$) and nitric oxide (NO) (26.14 %, $p \leq 0.05$). Mice administered with high weekly doses of dulaglutide attenuated rotenone-associated oxidative stress, characterized by significant increases in GSH content (143 %, $p \leq 0.05$), SOD activity (96.25 %, $p \leq 0.05$), and significant decreases in oxidative stress markers MDA (82.65 %, $p \leq 0.05$)

(*continued on next page*)

Table 3 (*continued*)

					and NO (45.44 %, $p \leq 0.05$). Mice administered with dulaglutide significantly attenuated rotenone-induced hyperactivity of monoaminoxidase-B (MAO-B) in low dulaglutide dose (38.71 %; $p \leq 0.05$) and high dulaglutide dose (57.60 %; $p \leq 0.05$) when compared to the rotenone group. Mice administered with low doses of dulaglutide exhibited significant reductions in rotenone-induced hyperactivity of pro-inflammatory cytokines IL−1β (62 %, $p \leq 0.05$), TNF-α (31.79 %, $p \leq 0.05$) and IL−6 (62 %, $p \leq 0.05$). This trend was replicated in mice administered with high doses of dulaglutide, wherein significant decreases in IL−1β (88.28 %, $p \leq 0.05$), TNF-α (83.41 %, $p \leq 0.05$) and IL−6 (79.07 %, $p \leq 0.05$) were observed in comparison to the rotenone group. Administration of low doses of liraglutide significantly attenuated rotenone-induced decreases in various neurotransmitters, leading to significant increases in dopamine (DA) (93.53 %, $p \leq 0.05$), 3,4-dihydroxyphenylacetic acid (DOPAC) (159.78 %, $p \leq 0.05$), and homovanillic acid (HVA) (44.70 %, $p \leq 0.05$) in comparison to rotenone treatment. Similarly, high dose liraglutide administration was associated with significant increases in DA (222.35 %, $p \leq 0.05$), DOPAC (224.91 %, $p \leq 0.05$), and HVA (137.88 %, $p \leq 0.05$).
Zhou et al. (2019)	Animal Study	C57BL/6 mice	AD	Morris Water Maze (MWM) test	**Cognitive Changes:** Weekly administration of 0.6 mg/kg dulaglutide over 3 weeks in STZ-induced AD models decreased escape latency during MWM tests and increased time spent in target quadrants during probe tasks. **Molecular Changes:** Dulaglutide was associated with decreased levels of phosphorylated Tau and neurofibrillary tangles, whilst upregulating the expression of pPI3K, pAkt, and pGSK3 ($p < 0.01$).
Exenatide					
An et al. (2019)	Animal Study	48 5xFAD mice	AD	N/A	**Cellular Changes:** Exenatide administered at 100 μg/kg subcutaneously twice daily was associated with significant increases in specific surface area of mitochondria ($p < 0.05$), indicative of the degree of swelling in mitochondria. **Molecular Changes:** Exenatide administered at 100 μg/kg subcutaneously twice daily was associated with decreased area of amyloid plaques in the hippocampal CA1 region ($p < 0.05$). Exenatide administered at 100 μg/kg subcutaneously twice daily was associated with significantly increased levels of postsynaptic marker PSD95 ($p < 0.001$) and presynaptic marker Syn ($p < 0.01$). Exenatide administered at 100 μg/kg subcutaneously twice daily was associated with significantly decreased levels of malondialdehyde (MDA) ($p < 0.05$), but increased superoxide dismutase (SOD) activity within the hippocampus ($p < 0.05$), suggesting that it alleviates cellular damage.
Bomba et al. (2013)	Animal Study	47 total mice 15 female 3xTg-AD mice 20 male 3xTg-AD mice 5 female PS1-KI mice 7 male PS1-KI mice	AD	Morris Water Maze (MWM) test	Mice were administered with saline or 500 mg/kg exenatide daily, 5 days a week over 9 months. **Cognitive Changes:** Administration of exenatide did not significantly improve MWM test performance and target quadrant occupancy in 3xTg-AD mice in comparison to saline. **Molecular Changes:** Administration of exenatide in 3xTg-AD mice did not significantly decrease h-tau immunoreactivity ($p = 0.337$) or intraneuronal Aβ levels in the hippocampus ($p = 0.552$).
Bomba et al. (2019)	Animal Study	46 3xTg-AD mice	AD	Morris Water Maze (MWM) test Object Recognition Test (ORT)	**Cognitive Changes:** Exenatide administration at a dosage of 500 μg/kg, delivered i.p. five days a week, had no effect on cognitive performances in the MWM test and Objection Recognition tests ($p > 0.05$). **Molecular Changes:** Exenatide administered at 500 μg/kg i.p. five days per week did not significantly affect Aβ and tau levels in comparison to injection of vehicles. Exenatide administration at a dosage of 500 μg/kg, delivered i.p. five days a week was associated with enhanced BDNF signaling ($p < 0.001$), and significantly reduced proBDNF signaling ($p < 0.05$).
Bu et al. (2021)	Animal Study	Female Sprague-Dawley rats	PD	Rotarod Test Cylinder Test	**Cognitive Changes:** Ex−4 injections at a dosage of 5 μg/kg/day, administered i.p. twice daily, rescued predominant motor deficits in mice injected with AAV-A53T-α-syn, characterized by reduced asymmetric forepaw touches during the cylinder test 6 weeks post-injection ($p = 0.0092$). **Cellular Changes:** Ex−4 injections at 5 μg/kg/day, administered i.p. twice daily, attenuated loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) in comparison to vehicle injection at 6 weeks post-injection (−39 % vs. −42 %) and significantly at 10 weeks post-injection (−37 % vs −61 %; $p = 0.0005$). These trends were mirrored in the striatum at 6 weeks post-

(*continued on next page*)

Table 3 (*continued*)

					injection (−31.98 % vs −37.65 %) and significantly 10 weeks post-injection (−27.93 % vs. −49.01 %; $p = 0.0151$).
Chen et al. (2012)	Animal Study	30 male Wistar rats	AD	Morris Water Maze (MWM) test	**Cognitive Changes:** Ex−4 administration at a dosage of 10 μg/kg, delivered subcutaneously twice daily for 14 days, significantly reverted STZ-induced increases in escape latencies and distances moved during the MWM test ($p < 0.05$). Similarly, Ex−4 administration reverted STZ-decreases in time spent in target quadrant in the probe task ($p < 0.05$). **Molecular Changes:** Ex−4 administered at 10 μg/kg subcutaneously twice daily for 14 days significantly reduced STZ-induced hyperphosphorylation of tau at Ser396 ($p < 0.05$), Thr181 ($p < 0.01$) in comparison to controls.
Garabadu and Verma (2019)	Animal Study	36 male Wistar rats	AD	Morris Water Maze (MWM) test Y-maze test	**Cognitive Changes:** Ex−4 administered at a dosage of 5 μg/kg i.p. daily for 14 days, reverted Aβ-induced memory deficits in the MWM test, significantly reducing escape latency ($p < 0.05$). Similarly, Ex−4 reverted Aβ-induced decrease in spontaneous alteration behavior (SAB) in the Y-maze test ($p < 0.05$). **Molecular Changes:** Ex−4 at 5 μg/kg i.p. daily for 14 days significantly reduced Aβ-induced increases in Aβ levels in the rat hippocampus and prefrontal cortex ($p < 0.05$). Similarly, Ex−4 ameliorates Aβ-induced decreases in Akt phosphorylation ($p < 0.05$).
Jia et al. (2016)	Animal Study	Adult male Sprague-Dawley rats	AD	Morris Water Maze (MWM) test Probe Trial test	**Cognitive Changes:** Administration of 0.02 nmol Ex−4 i.c.v. in mice did not revert Aβ1–42-induced increases in the average escape latency and distance to hidden platform during the MWM task ($n = 10$, $p > 0.05$). These results were replicated in the probe task, wherein Ex−4 administration was not significantly associated with changes in total time elapsed and time spent within the target quadrants ($p > 0.05$). In contrast, administration of 0.2 nmol Ex−4 ($n = 10$) and 2 nmol Ex−4 ($n = 10$) i.c.v reverted Aβ1–42-induced increases in escape latency ($p < 0.05$) and swim distance to hidden platforms ($p < 0.05$) during the MWM task. These results were replicated in time spent in target quadrants during the probe task ($p < 0.05$). **Molecular Changes:** Ex−4 administration significantly reverted Aβ1–42-induced decreases in *Bcl−2* expression ($p < 0.01$), increases in *Bax* expression ($p < 0.01$), and upregulation of Caspase−3 ($p < 0.01$).
Li et al. (2010)	Animal Study	30 3xTg AD mice	AD	N/A	**Molecular Changes:** Administration of Ex−4 significantly reverted STZ-induced increases in Aβ levels ($p < 0.05$). Similarly, administration of Ex−4 was associated with non-significant decreases in Aβ levels (25 %, $p > 0.05$) in absence of STZ. Female mice administered with Ex−4 did not exhibit significant changes in tau levels ($p > 0.05$).
Robinson et al. (2019)	Animal Study	Tg2576 mice Wild-type C57BL/6 mice	AD	Morris Water Maze (MWM) test Probe Trial test	**Cognitive Changes:** AD mice administered with exenatide exhibited significantly reduced latencies in the MWM task ($p = 0.011$) in comparison to saline controls. **Molecular Changes:** Administration of exenatide did not have a significant impact on Aβ42 levels ($n = 9$, $p > 0.05$).
Song et al. (2022)	Animal Study	Wild-type *Caenorhabditis elegans* CL4176 *C. elegans* CL2006 *C. elegans* CL1553 *C. elegans*.	AD	N/A	Significant delays in paralysis progression in AD worms were observed after administration of Ex−4 at 0.3 mg/ml ($p = 0.0157$), 0.5 mg/ml ($p < 0.0001$), and 1.2 mg/ml ($p < 0.0001$). **Molecular Changes:** Administration of 0.5 mg/ml Ex−4 was associated with significant reductions in Aβ levels (39.78 %, $p < 0.001$). 0.5 mg/ml Ex−4 significantly decreased reactive oxygen species (ROS) levels in CL4176 (13.57 %, $p < 0.01$) and CL2006 (17.22 %, $p < 0.05$).
Wang et al. (2016)	Animal Study	C57BL/6 mice	AD	Wheel-Running Activity Morris Water Maze (MWM) test	Mice were administered with either 0.05 nmol or 0.5 nmol Ex−4 via internasal treatment. **Cognitive Changes:** Administration of Ex−4 was associated with attenuating Aβ31–35-induced increases in escape latency on days 2–5 of the MWM test ($p < 0.05$), but not on day 1 ($p > 0.05$). Similarly, Ex−4 administration attenuated Aβ31–35-induced decreases in time spent in the target quadrant during the probe task ($p < 0.05$). Administration of Ex−4 was associated with attenuating Aβ31–35-induced decreases in locomotor activity ($p < 0.05$).
Wang et al. (2018)	Animal Study	APP/PS1 mice Wild-type C57BL/6 mice	AD	Morris Water Maze (MWM) test Probe trial test	Experimental mice were administered twice daily with 25 nmol/kg Ex−4 for four weeks. **Cognitive Changes:** APP/PS1 mice administered with Ex−4 exhibited significant decreases in escape latency ($p < 0.01$) during the MWM task and increases in time spent in target quadrant in the probe task ($p < 0.01$) in comparison to controls. **Molecular Changes:** APP/PS1 mice administered with Ex−4 exhibited reduced levels of Aβ and hyperphosphorylated tau levels in the hippocampus and cortex.

(*continued on next page*)

Table 3 (*continued*)

					Administration of Ex−4 was associated with significant increases in β-catenin ($p < 0.01$), pAkt ($p < 0.01$), and pGSK3β ($p < 0.01$).
Zhang et al. (2021)	Animal Study	40 adult male Sprague-Dawley rats	PD	Open Field test Apomorphine Rotational test	**Cognitive Changes:** 6-OHDA-induced PD rats administered daily with 10 nmol/kg *i.p.* Ex−4 for 30 days exhibited significant increases in distance traveled in the open-field test ($p < 0.05$). **Cellular Changes:** Ex−4 administration significantly ameliorated PD-associated loss of dopamine neurons in the striatum ($p < 0.01$). Contrastingly, Ex−4 treatment significantly attenuated PD-associated activation of GFAP-marked astrocytes ($p < 0.05$). **Molecular Changes:** Administration of Ex−4 was associated with significant reductions in PD-associated α-syn expression in the substantia nigra ($p < 0.05$), IL−1β ($p < 0.05$), and TNF-α ($p < 0.05$) in the striatum.
Zhang et al. (2022a)	Animal Study	5xFAD mice	AD	N/A	Mice were administered bidaily with 100 μg/kg exenatide for 16 weeks. **Cellular Changes:** Administration of exenatide in transgenic 5xFAD was non-significantly associated with reductions in GFAP-marked astrocytes. **Molecular Changes:** Exenatide administration in transgenic 5xFAD was associated with significant reductions in TNF-α ($p < 0.05$), IL−1β ($p < 0.05$), NLRP2 ($p < 0.05$) expression, and a non-significant reduction of ROS (30 %, $p > 0.05$) and $A\beta_{1-42}$ deposition.
Liraglutide					
Bakhshwin et al. (2024)	Animal Study	25 adult male Wistar rats	AD	Morris Water Maze (MWM) test	AD rat models were induced via administration of aluminum chloride (AlCl3) and D-galactose (D-GAL). Rats were administered with subcutaneous injection of liraglutide 300 μg/kg/twice daily. **Cognitive Changes:** Rats administered with liraglutide exhibited significantly reduced escape latency in the MWM test (5.40 %; $p < 0.01$). **Molecular Changes:** Administration of liraglutide was associated with attenuating AD-associated decreases in catalase (CAT) and superoxide dismutase (SOD) activity ($p < 0.01$).
Batista et al. (2018)	Animal Study	Male Swiss mice Adult Cynomolgus Macaques	AD	Novel Object Recognition (NOR) test Contextual Fear Conditioning (CFC) test	**Cognitive Changes:** Liraglutide administered at a dosage of 25 nmol/kg i.p. daily for seven days, was associated with the prevention of cognitive deficits, notably in the novel object recognition tasks ($p < 0.05$), contextual fear conditioning tests ($p < 0.05$) and object location memory tests ($p < 0.05$). **Molecular Changes:** Liraglutide administration at 25 nmol/kg was associated with attenuation of abnormal tau hyperphosphorylation in the non-human primate brains, but only modest attenuation of AβO-induced synaptic loss in the frontal cortex ($p = 0.1480$).
Carranza-Naval et al. (2021)	Animal Study	APP/PS1 mice	AD T2DM	Morris Water Maze (MWM) test	Liraglutide administration was increased incrementally 500 μg/kg/day daily for 20 weeks **Cognitive Changes:** Administration of liraglutide significantly reduced acquisition phase performance during the MWM test in mice with T2DM and AD ($p < 0.01$). This trend was replicated, wherein mice administered with liraglutide were associated with time spent in the target quadrant ($p = 0.002$). **Cellular Changes:** Administration of liraglutide was associated with significant reduction in microglial burden in APP/PS1 mice ($p < 0.01$). **Molecular Changes:** Administration of liraglutide significantly reduced amyloid plaque burden in APP/PS1 mice ($p < 0.001$).
Chen et al. (2017)	Animal Study	3xTg-AD mice	AD	Morris Water Maze (MWM) test	**Cognitive Changes:** MWM performance was increased in AD mice after administration of liraglutide at a dosage of 300 μg/kg daily via subcutaneous injection for 8 weeks. This improvement was characterized by a significant decrease in path length ($p < 0.05$) and significant increases in target quadrant preferences during the probe trial test ($p < 0.05$). **Molecular Changes:** Liraglutide administration at 300 μg/kg daily via subcutaneous injection for 8 weeks was associated with attenuation of tau hyperphosphorylation ($p < 0.05$) and neurofilaments ($p < 0.05$) in AD mice. Similarly, liraglutide rescued JNK and ERK signaling in AD mice ($p < 0.05$).
Dong et al. (2022)	Animal Study	5xFAD mice	AD	Morris Water Maze (MWM) test	**Cognitive Changes:** Administration of 200 μg/kg liraglutide daily in AD mice was associated with reductions in escape latency on day 5 of the MWM test ($p < 0.05$), but not between training days 1–4.
Duarte et al. (2020)	Animal Study	3xTG-AD mice	AD	Morris Water Maze (MWM) test Y-maze test	**Cognitive Changes:** AD mice treated with liraglutide at a dosage of 28 mg/kg daily for 28 days did not exhibit significant improvements in the open field test, Y-maze test,

(*continued on next page*)

Table 3 (*continued*)

					and MWM test ($p > 0.05$). **Molecular Changes:** Liraglutide administration at 0.2 mg/kg daily for 28 days reduced brain $A\beta_{1-42}$ levels significantly $F(2,14) = 15.206$; $p < 0.0001$. AD mice treated with liraglutide at a dosage of 28 mg/kg daily for 28 days exhibited normalized levels of proinflammatory markers IL−10 ($Z = -0.319$, $p = 0.805$) and IL−1β ($Z = -2.00$, $p = 0.051$) in comparison to wild-type mice. Liraglutide administration non-significantly reduced oxidative stress marker 8-OHdG ($p > 0.05$).
Han et al. (2013)	Animal Study	Male Sprague-Dawley Rats	AD	Morris Water Maze (MWM) test	**Cognitive Changes:** Administration of liraglutide at a dosage of 0.05 nmol did not attenuate Aβ25–35-induced increases in escape latency during the MWM test ($p > 0.05$), but attenuated increases in escape latency at dosages of 0.5 nmol ($p < 0.05$) and 5 nmol ($p < 0.05$). Liraglutide administration was associated with significant increases time spent in target quadrants at 0.5 nmol (38.01 ± 1.67 % vs. 24.85 ± 0.89 %; $p < 0.05$) and 5 nmol (43.22 ± 0.93 % vs. 24.85 ± 0.89 %; $p < 0.05$) in comparison to no liraglutide administration.
Hansen et al. (2015)	Animal Study	SAMP8 mice	AD	Novel Object Recognition (NOR) test T-maze test	**Cognitive Changes:** Liraglutide mice were either treated with 100 μg/kg or 500 μg/kg daily over 4 months. Liraglutide-treated mice required significantly fewer tests to complete the memory retention test in comparison to 10-month-old vehicle-dosed mice ($p < 0.001$). **Cellular Changes:** Mice treated with 100 μg/kg liraglutide exhibited significantly higher levels of CA1 pyramidal neurons in comparison to vehicle-dosed mice (14.3 ± 0.3 %, $p < 0.01$). However, mice treated with 500 μg/kg liraglutide had no significant effect on pyramidal neuron levels ($p > 0.05$).
Hansen et al. (2016a)	Animal Study	Female transgenic $hAPP_{Lon}/PS1_{A246E}$ mice Female transgenic $hAPP/PS1_{\Delta E9}$ mice Wild-type FVB/N x C57Bl/6 J control mice	AD	Morris Water Maze (MWM) test Novel Object Recognition (NOR) test T-maze test	No significant changes in survival were associated with liraglutide. **Cognitive Changes:** Transgenic mice administered with 100 ng/kg/day liraglutide for 3 months exhibited no differences in MWM task performance, notably within the time required to reach the platform and time spent in target quadrant ($p < 0.05$) in comparison to control mice. This trend was not replicated in mice administered with 500 ng/kg/day liraglutide daily for 3 months. Mice treated with liraglutide exhibited no significant differences in latency to platform, time spent in target quadrant, and latency time required to reach the platform during the probe task ($p > 0.05$). **Molecular Changes:** No significant differences in β-amyloid plaque volumes were observed between mice injected with liraglutide or saline in both mice populations ($p > 0.05$).
Hansen et al. (2016b)	Animal Study	53 total mice 36 female hTauP301L FVB/N mice 17 female wild-type mice	AD Tauopathies	Clasping Behavior Stereological Analysis	**Cognitive Changes:** Daily 500 mg/kg liraglutide was administered for 22 weeks, wherein mice administered with liraglutide exhibited significant reductions in hind limb motor impairment, characterized by reduced clasping behavior in comparison with vehicle injection ($p = 0.003$, $\chi^2 = 13.67$, $df = 3$). Similarly, survival rates were significantly increased ($p = 0.003$, $\chi^2 = 8.655$, $df = 1$). **Molecular Changes:** Liraglutide administration was associated with significant reductions in neuronal phospho-tau volumes in comparison to vehicle injection ($p < 0.0001$, $F(2140) = 42.06$). Specifically, significant reductions were observed in the ventral pons (0.053 ± 0.014 mm^3; 69.4 ± 7.9 % reduction, $p < 0.001$), dorsal pons (0.043 ± 0.010 mm^3; 59.5 ± 12.9 % reduction, $p < 0.05$) medulla (0.046 ± 0.012 mm^3; 61.0 ± 8.6 % reduction, $p < 0.01$), and non-significantly in the diencephalon (0.034 ± 0.015 mm^3; 50.7 ± 22.5 % reduction, $p < 0.05$). A significant, positive linear correlation was observed between neuronal phospho-tau load and severity of clasping behavior ($r^2 = 0.8829$, $p < 0.001$)
Hao et al. (2024)	Animal Study	APP/PS1 male mice	AD	Morris Water Maze (MWM) test Open Field task Y-Maze test	**Cognitive Changes:** Administration of liraglutide significantly shortened the escape latency of APP/PS1 in comparison to controls on day 4 ($p < 0.05$) and day 5 ($p < 0.01$). Liraglutide administration was associated with significant increases in rearing numbers during the open field task in comparison to controls ($p < 0.05$). Liraglutide administration was associated with significant increases in spontaneous alterations of the Y-maze test in comparison to controls ($p < 0.01$). **Molecular Changes:** Administration of liraglutide significantly decreased the density of Aβ1–42 in comparison to no liraglutide administration ($p < 0.01$).
Holubová et al. (2019)	Animal Study	APP/PS1 male mice C57BL/6 male mice	AD	N/A	**Cellular Changes:** Administration of liraglutide was associated with a non-significant

(*continued on next page*)

Table 3 (*continued*)

					reduction in dentate gyrus microgliosis ($p = 0.3484$), but was associated with significant reductions in astrocytosis in the cortex ($p = 0.0348$) **Molecular Changes:** Mice administered daily with 0.2 mg/kg liraglutide over two months exhibited significant decreases in the number and size of Aβ plaques in the CA1 area of the hippocampus [$F(2, 25) = 4.410$, $p = 0.0229$ (one-way ANOVA); $p = 0.0303$.
Long-Smith et al. (2013)	Animal Study	$APP_{SWE}/PS1_{\Delta E9}$ mice Wild-type C57BL/6 mice	AD	N/A	Mice were administered with 25 nm/kg liraglutide *i.p.* biweekly over 6 months. **Cellular Changes:** Administration of liraglutide in AD mice was associated with significant decreases in astrocytic activation ($p < 0.01$) and Iba1-tagged microglia ($p < 0.05$) in comparison to saline injection. **Molecular Changes:** Liraglutide administration in AD mice was significantly associated with decreases in β-amyloid levels (31.5 %, $p < 0.0001$) in comparison to saline injection.
Maskery et al. (2020)	Animal Study	Male $APP_{SWE}/PS1_{\Delta E9}$ mice	AD	Morris Water Maze (MWM) test	**Cognitive Changes:** AD mice administered with 10 nmol/kg liraglutide were associated with significant decreases in acquisition phase time in ($p < 0.01$) in comparison to saline injections, indicating improvements in spatial learning. Administration of liraglutide in AD mice was not significantly associated with significant increases in time spent in target quadrant in comparison to saline administration ($p > 0.05$) during the probe test. **Molecular Changes:** AD mice administered with liraglutide exhibited a non-significant decrease in beta-amyloid plaque load in the neocortex ($p > 0.05$). Similarly, non-significant decreases in proinflammatory cytokines IL−1β ($p > 0.05$) and TNF-α ($p > 0.05$) were observed in comparison to saline administration.
McClean and Hölscher (2014b)	Animal Study	$APP_{SWE}/PS1_{\Delta E9}$ mice Wild-type C57BL/6 mice	AD	Morris Water Maze (MWM) test	**Cognitive Changes** 25 nm/kg bw, i.p. liraglutide daily for 8 weeks was associated with significantly reduced escape latency during MWM tasks in wild-type ($p < 0.05$) and AD mice ($p < 0.01$). Similarly, significant increases in time spent in target quadrants during the probe task was observed in AD mice in comparison to saline treatment ($p < 0.05$). **Molecular Changes:** Administration of liraglutide in AD mice was associated with significant decreases in β-amyloid load ($p = 0.0007$), soluble amyloid oligomer levels ($p = 0.0355$), and total APP levels ($p = 0.0423$).
McClean et al. (2011)	Animal Study	$APP_{SWE}/PS1_{\Delta E9}$ mice Wild-type C57BL/6 mice	AD	Morris Water Maze (MWM) test Object Recognition Task	**Cognitive Changes:** AD mice administered with saline and liraglutide 30 minutes prior to open-field behavior tests yielded no significant results. AD mice administered daily with 25 nm/kg bw, i.p. liraglutide for 8 weeks exhibited significant improvements in recognition memory ($p = 0.0013$). Administration of liraglutide in wild-type mice was associated with significant reductions in escape latencies during the MWM test ($p < 0.01$) in comparison to saline treatment. **Cellular Changes:** Administration of liraglutide in AD mice resulted in a significant reduction of activated microglia in the cortex (50 %, $p < 0.001$) in comparison to saline administration. **Molecular Changes:** Administration of liraglutide in AD mice resulted in significant reductions in β-amyloid plaque formation in the cortex (50 %, $p < 0.001$) and brain APP levels ($p = 0.0272$) in comparison to saline administration.
McClean et al. (2015)	Animal Study	$APP_{SWE}/PS1_{\Delta E9}$ mice Wild-type C57BL/6 mice	AD	Morris Water Maze (MWM) test Object Recognition Task	**Cognitive Changes:** Both wild-type mice and AD mice administered daily with 25 nm/kg liraglutide for 8 months exhibited no significant changes in open field tests. AD mice administered with liraglutide exhibited significantly higher preference for novel objects during object recognition memory tasks in comparison to saline treatment ($p < 0.05$). Liraglutide significantly reduced escape latency during MWM tests ($F = 53.5$, $p < 0.0001$) and significantly increased time spent in target quadrants during the probe task ($p < 0.05$) in comparison to saline treatment. **Cellular Changes:** Administration of liraglutide was associated with significant decreases in Iba1-marked microglia (50 %, $p < 0.0001$) in the cortex and the CA1 region of the hippocampus (47 %, $p < 0.0001$) in comparison to saline treatment. **Molecular Changes:** Administration of liraglutide was associated with significant decreases in beta-amyloid plaque load in the cortex (40 %, $p < 0.001$) and CA1 region of the hippocampus (45 %, $p < 0.001$) in comparison to saline treatment.
Paladugu et al. (2021)	Animal Study	48 total mice 24 5xFAD mice	AD	Passive Avoidance (PA) task Open Field task	**Cognitive Changes:** No significant differences in behavioral measures were observed after liraglutide treatment in passive avoidance, open-field, and novel object-

(*continued on next page*)

Table 3 (*continued*)

		24 age-matched wild-type mice		Novel Object Recognition (NOR) task	recognition tasks ($p > 0.05$). **Cellular Changes:** 5xFAD mice administered daily with 25 nM/kg liraglutide for 30 days exhibited significantly reduced activation of GFAP-immunoreactive astrocytes in the CA1 region of the hippocampus ($p < 0.01$) when compared to vehicle administration. In contrast, no significant changes in Iba1-positive microglial cells were observed following liraglutide treatment in comparison to vehicle controls ($p > 0.05$). **Molecular Changes:** Liraglutide administration in 5xFAD mice was associated with significant decreases in hippocampal Aβ levels in comparison to vehicle injection ($p < 0.001$). Similarly, liraglutide was associated with significant reductions in phosphorylated Akt in the cortex ($p < 0.01$) and significant increases in pGSK3β in the hippocampus in comparison to vehicle controls ($p < 0.01$).
Qi et al. (2016)	Animal Study	C57BL/6 mice	AD	Morris Water Maze (MWM) test Y-maze test	**Cognitive Changes:** Daily subcutaneous injections of 25 nmol/kg liraglutide over 8 weeks was associated with significant reversal of $A\beta_{1-42}$-induced decline in Y maze performance ($p < 0.05$). Similarly, liraglutide was associated with significant reductions in escape latency during the MWM test ($p < 0.05$) and increases in time spent in target quadrant during the probe task ($p < 0.05$) in mice injected with $A\beta_{1-42}$. **Molecular Changes:** Administration of liraglutide significant reversed $A\beta_{1-42}$-induced tau hyperphosphorylation ($p < 0.05$), and reversed $A\beta_{1-42}$-induced decreases in pAkt ($p < 0.05$) and pGSK3β ($p < 0.05$).
Salles et al. (2018)	Animal Study	Female APP/PS1 mice	AD	N/A	**Cellular Changes:** Administration of liraglutide was associated with increases in DCX-positive neuroblasts in the subventricular zone of APP/PS1 mice ($p < 0.01$), but not astrocyte numbers ($p > 0.05$) in comparison to saline treatment. **Molecular Changes:** Administration of liraglutide was associated with significant reductions in Aβ plaque load in the cortex ($p < 0.0001$), CA1 region of the HPC ($p < 0.01$), and the dentate gyrus (DG) ($p < 0.0001$) in comparison to saline.
Salles et al. (2020)	Animal Study	APP/PS1 mice Wild-type C557BL/6 mice	AD	N/A	**Cellular Changes:** AD mice administered daily with 25 nmol/kg liraglutide for 4 weeks exhibited significant increases in newborn neurons ($p < 0.01$) in comparison to saline injection. Additionally, liraglutide administration significantly reduces Iba1-marked microglia ($p < 0.0001$) and hippocampal GFAP-marked astrocytes ($p < 0.01$). **Molecular Changes:** Administration of liraglutide significantly reduced Aβ plaque load in the CA1 region of the HPC ($p < 0.001$), cortex ($p < 0.0001$), and dentate gyrus ($p < 0.001$).
Xie et al. (2021)	Animal Study	5x FAD mice	AD	N/A	Mice were administered with 25 nmol/kg liraglutide daily for 8 weeks. **Cellular Changes:** Administration of liraglutide was associated with significant attenuation of AD-associated neuronal loss in the cortex ($p < 0.05$), and non-significantly in the hippocampus ($p > 0.05$) **Molecular Changes:** Administration of liraglutide was associated with increased activation of the cAMP / PKA pathway ($p < 0.05$), simultaneously attenuating overproduction of ROS ($p < 0.05$), and enhancing production of ATP ($p < 0.05$).
Xiong et al. (2013)	Animal Study	24 male Kunming mice	AD	Morris Water Maze (MWM) test	**Cognitive Changes:** Mice administered with 300 μg/kg daily over 14 days in conjunction with 30 days of daily 3 mg/kg STZ administration exhibited significant reductions in escape latency during MWM tests ($p < 0.05$) and significant increase in time spent in target quadrant during probe trials ($p < 0.05$) in comparison to STZ and saline administration. **Molecular Changes:** Liraglutide administration was associated with significant decreases in tau phosphorylation ($p < 0.05$) in the cerebrum.
Zhang et al. (2023)	Animal Study	36 A53T transgenic mice	PD	Rotarod Test Pole Test Open Field test	**Cognitive Changes:** Liraglutide administration at a dosage of 50 nmol/kg daily via i.p. for 14 consecutive days was associated with significant improvements in the Rotarod Motor Assessment in comparison to saline groups ($p < 0.05$). Liraglutide administration at a dosage of 50 nmol/kg daily via i.p. for 14 consecutive days was associated with significant improvements in the Pole Test in comparison to saline groups ($p < 0.01$). Liraglutide administration at a dosage of 50 nmol/kg daily via i.p. injection for 14 consecutive days was associated with significant improvements in the Open Field Test in comparison to saline groups ($p < 0.05$). **Molecular Changes:** Administration of liraglutide at a dosage of 50 nmol/kg daily via i.p. injection for 14 consecutive days resulted in significant reductions in α-Syn

(*continued on next page*)

Table 3 (*continued*)

					levels in the substantia nigra in comparison to saline ($p < 0.05$). Administration of liraglutide at a dosage of 50 nmol/kg daily via i.p. injection for 14 consecutive days resulted in significant reductions on TNF-α ($p < 0.001$) and IL−1β ($p < 0.01$) levels in the substantia nigra comparison to control. Administration of liraglutide at a dosage of 50 nmol/kg daily via i.p. injection for 14 consecutive days resulted in significant reductions on TNF-α ($p < 0.05$) but not IL−1β ($p > 0.05$) levels in the striatum comparison to control. In contradistinction, liraglutide administration was associated with significant increases on IL−10 levels in the striatum ($p < 0.001$).
Lixisenatide					
Cai et al. (2014)	Animal Study	Adult male Sprague-Dawley rats	AD	Morris Water Maze (MWM) test	**Cognitive Changes:** Lixisenatide injections, administered bilaterally into the hippocampi at a concentration of 5 nmol/μL (total volume of 2 μL per side), significantly reverted Aβ25–35-induced spatial learning disabilities in the MWM test, characterized by significant decreases in escape latency ($p < 0.001$; $n = 10$). Lixisenatide injection significantly reverted Aβ25–35-induced spatial-memory deficits in the probe trial during the MWM test, characterized by reversion of Aβ25–35-induced decreases in swimming time in target quadrants ($p < 0.001$; $n = 10$). **Molecular Changes:** Lixisenatide, injected bilaterally into the hippocampi at 5 nmol/μL (2 μL per side), significantly reversed Aβ25–35-induced decreases in pGSK3β (S9) ($p < 0.05$; $n = 6$) and increases in pGSK3β (Y216) ($p < 0.05$; $n = 6$).
Cai et al. (2017)	Animal Study	Adult male Sprague-Dawley rats	AD	Morris Water Maze (MWM) test Y-Maze test	**Cognitive Changes:** Lixisenatide, administered intrahippocampally at a dosage of 5 nmol/μl with an injection rate of 0.2 μl/min, showed a significantly reduced Aβ25–35-induced spatial working memory during the Y-maze working memory test ($p < 0.001$; $n = 10$). **Cellular Changes:** Lixisenatide, administered intrahippocampally at 5 nmol/μl with a 0.2 μl/min injection rate, significantly reduced Aβ25–35-induced cytotoxicity in hippocampal neurons ($p < 0.001$; $n = 10$). **Molecular Changes:** Lixisenatide, at an intrahippocampal dosage of 5 nmol/μl administered at 0.2 μl/min, significantly reversed Aβ25–35-induced decreases in pAkt and MEK1/2 ($p < 0.05$; $n = 10$).
Cai et al. (2018)	Animal Study	3xTg-AD mice	AD	N/A	**Cellular Changes:** Lixisenatide at 10 nmol/kg daily significantly reduced the percentage of p-tau positive cells in the hippocampi of APP/PS1/tau mice in comparison to saline injections (62.30 % ± 4.90 % vs. 89.20 % ± 6.20 %; $p = 0.037$) Lixisenatide at 10 nmol/kg daily significantly decreased neuroinflammation in the hippocampi of APP/PS1/tau mice, characterized by changes in microglia marked by percentage of Iba1 + cells. Significant decreases were noted, wherein mice injected with lixisenatide exhibited significantly reduced levels of Iba1 + cells in comparison to saline (7.41 % ± 0.90 % vs. 16.85 % ± 1.90 %; $p = 0.037$). **Molecular Changes:** Lixisenatide, administered at a dosage of 10 nmol/kg i.p. daily for 60 days, significantly reduced the percentage of Aβ-area in the hippocampi of APP/PS1/tau mice in comparison to saline injections (5.87 % ± 0.70 % vs. 9.48 % ± 1.20 %; $p = 0.04$). Lixisenatide at 10 nmol/kg daily administration significantly reduced percentage of p-tau area in the hippocampi of APP/PS1/tau mice in comparison to saline injections (14.99 % ± 1.40 %% vs. 32.58 % ± 3.90 %; $p = 0.043$) The 10 nmol/kg dosage of lixisenatide reverted the suppression of the PKA signaling ($p = 0.039$) and CREB signaling ($p = 0.042$) in the hippocampi of APP/PS1/tau mice. In contrast, lixisenatide significantly inhibited activation of the p38-MAPK pathway ($p = 0.038$).
Semaglutide					
Forny Germano et al. (2024)	Animal Study	5xFAD mice APP/PS1 mice	AD	Morris Water Maze (MWM) test Open Field test Novel Object Recognition (NOR) test	Mice were administered initially with 10 nmol/kg semaglutide or 2.5 nmol/kg tirzepatide, ramping up to 17 nmol/kg semaglutide or 5 nmol/kg tirzepatide after one week, and 25 nmol/kg semaglutide or 10 nmol/kg tirzepatide after two weeks. **Cognitive Changes:** Semaglutide treatment was associated with increased time spent in the center area in female 5xFAD ($p < 0.05$) and decreased time spent in the center area in APP/PS1 mice ($p < 0.05$). These trends were not replicated in male 5xFAD ($p > 0.05$) and APP/PS1 mice ($p > 0.05$). Additionally, semaglutide treatment was not associated with improvements in exploration time during the NOR test in both 5xFAD and APP/PS1 mice ($p > 0.05$). Similarly, semaglutide was not associated with significant changes in escape latency ($p > 0.05$) and number of target quadrant crossings ($p > 0.05$) during the MWM test. Tirzepatide was associated with increasing exploration times and

(*continued on next page*)

Table 3 (*continued*)

					discrimination indices for the novel object in male 5xFAD mice ($p < 0.05$). Notwithstanding, these trends were not replicated in female 5xFAD mice ($p > 0.05$). Additionally, tirzepatide was not associated with increases in time spent in the center area during the open field test in 5xFAD mice ($p > 0.05$). Finally, tirzepatide was not associated with significant changes in escape latency ($p > 0.05$) and number of target quadrant crossings ($p > 0.05$) during the MWM test. **Cellular Changes:** Administration of semaglutide was not associated with reductions in Iba1-positive microglia and GFAP-positive astrocytes in both 5xFAD and APP/PS1 mice ($p > 0.05$). Tirzepatide did not significantly alter Iba1-positive microglia or GFAP-positive astrocyte cell density in 5xFAD mice. **Molecular Changes:** Administration of semaglutide was associated with reductions in Aβ plaque in the hippocampus of female APP/PS1 mice ($p < 0.05$). This was not consistently replicated in the cerebral cortex, hippocampus, and subiculum of both 5xFAD and APP/PS1 mice ($p > 0.05$). Administration of tirzepatide was not associated with reductions in Aβ plaque in the cerebral cortex, hippocampus, and subiculum of both 5xFAD and APP/PS1 mice ($p > 0.05$).
Wang et al. (2023)	Animal Study	100 total mice 50 3xTg APP/PS1/Tau mice 50 C57B6/129 wild-type mice	AD	Open Field test Novel Object Recognition (NOR) test Y-maze test	**Cognitive Changes:** Mice administered with bidiurnal 0.1 mg/kg semaglutide *i.p.* for 30 days exhibited significant increases in novel object recognition ($p < 0.05$, $n = 10$). **Molecular Changes:** Semaglutide administration ameliorated AD-associated decreases in SIRT1 ($p < 0.01$) and GLUT4 ($p < 0.01$). Injection of semaglutide was associated with significant decreases in tau levels in the hippocampus of 3xTg mice ($p < 0.01$).
Zhang et al. (2022b)	Animal Study	40 male Sprague-Dawley rats	PD	N/A	**Cellular Changes:** Bidiurnal administration of 25 nmol/kg semaglutide for 31 days significantly protected against PD-associated dopaminergic neurons in the substantia nigra ($n = 6$, $p < 0.005$) in comparison to saline controls. **Molecular Changes:** Semaglutide was not significantly associated with changes in striatal dopamine levels in comparison to controls ($p > 0.05$). Contrastingly, semaglutide administration significantly reverted PD-associated increases in TNF-α ($n = 5$, $p \leq 0.005$) and IL−1β ($n = 5$, $p < 0.0002$). Similarly, semaglutide was associated with decreased α-syn monomer levels in comparison to saline control ($n = 5$, $p < 0.01$).
Tirzepatide					
Yang et al. (2024)	Animal Study	APP/PS1 mice	AD	N/A	**Cellular Changes:** Mice administered with weekly 10 nmol/kg tirzepatide *i.p.* for 8 weeks exhibited significant reduction in astrocyte activation in comparison to saline control ($p < 0.01$). **Molecular Changes:** Tirzepatide was associated with significant decreases in Aβ-plaques in the cortex ($p < 0.001$), but not hippocampus of mice in comparison to saline control. Tirzepatide administration reverted Aβ-induced production of ROS ($p < 0.001$).
Glucagon-Like Peptide−1 Receptor Agonists					
McClean and Hölscher (2014a)	Animal Study	$APP_{SWE}/PS1_{\Delta E9}$ mice Wild-type C57BL/6 mice	AD	Object Recognition Task	**Cognitive Changes:** No significant effect in the object recognition task were observed in AD mice following administration of 1 nmol/kg lixisenatide ($n = 12$, $p = 0.1674$), 10 nmol/kg lixisenatide ($n = 12$, $p = 0.1192$), 2.5 nmol/kg liraglutide ($n = 12$, $p = 0.2338$), and 25 nmol/kg liraglutide ($n = 12$, $p = 0.2594$) in comparison to saline treatment 30 minutes prior to the task. Notwithstanding, a significant increase in recognition index in the object recognition task was observed following daily administration of 1 nmol/kg lixisenatide ($n = 12$, $p = 0.0336$), 10 nmol/kg lixisenatide ($n = 12$, $p = 0.0456$), and 25 nmol/kg liraglutide ($n = 12$, $p = 0.0318$), but not 2.5 nmol/kg liraglutide ($n = 12$, $p = 0.0690$) in comparison to saline treatment over 66 days. Daily administration of lixisenatide and liraglutide at all doses did not have a significant effect on open field behavior in both wild-type and AD mice treated with 1 nmol/kg lixisenatide, 10 nmol/kg lixisenatide, 2.5 nmol/kg liraglutide, and 25 nmol/kg liraglutide over 65 days. **Cellular Changes:** Significant reductions in activation of Iba1-marked microglia was observed in AD mice administered daily with 1 nmol/kg lixisenatide (47 %, $p < 0.001$, $n = 11$), 10 nmol/kg lixisenatide (43 %, $p < 0.001$, $n = 11$), 2.5 nmol/kg liraglutide (48 %, $p < 0.001$, $n = 11$), and 25 nmol/kg liraglutide (49 %, $p < 0.001$, $n = 11$) over 10 weeks in comparison to saline administration. **Molecular Changes:**

(*continued on next page*)

Table 3 (*continued*)

					Significant reductions in beta amyloid plaques in the cortex was observed in AD mice administered daily with 1 nmol/kg lixisenatide (49 %, $p < 0.05$, $n = 11$), 10 nmol/kg lixisenatide (43 %, $p < 0.05$, $n = 11$), 2.5 nmol/kg liraglutide (46 %, $p < 0.01$, $n = 11$), and 25 nmol/kg liraglutide (45 %, $p < 0.01$, $n = 11$) over 10 weeks in comparison to saline administration.
Zhang et al. (2019)	Animal Study	72 C57BL/6 mice	PD	Open Field test Rotarod test	**Cognitive Changes:** Bidiurnal administration of 25 nmol/kg *i.p.* semaglutide over 30 days in MPTP-induced PD models was significantly associated with increases in distance traveled during the open field test ($n = 12$, $p < 0.001$), time spent on rotating rod during rotarod tests ($n = 12$, $p < 0.001$), and grip strength ($n = 12$, $p < 0.001$). Daily administration 25 nmol/kg *i.p.* Liraglutide over 30 days in MPTP-induced PD models was significantly associated with increases in distance traveled during the open field test ($n = 12$, $p < 0.01$), time spent on rotating rod during rotarod tests ($n = 12$, $p < 0.001$), and grip strength ($n = 12$, $p < 0.001$). **Cellular Changes:** Administration of semaglutide in MPTP-induced PD mice was associated with significant attenuation in dopaminergic neuronal loss in the substantia nigra ($p < 0.001$), and was significantly more efficient than liraglutide ($p < 0.05$). Contrastingly, administration of semaglutide was associated with significant reductions in striatal activation of astrocytes ($n = 6$, $p < 0.001$) and microglia ($n = 6$, $p < 0.001$), wherein semaglutide was significantly more efficacious in reducing astrocyte activation in comparison to liraglutide ($p < 0.05$). Administration of liraglutide in MPTP-induced PD mice was associated with significant attenuation of dopaminergic neuronal loss in the substantia nigra ($p < 0.01$). Contrastingly, administration of liraglutide was associated with significant reductions in striatal activation of astrocytes ($n = 6$, $p < 0.001$) and microglia ($n = 6$, $p < 0.001$). **Molecular Changes:** Semaglutide was associated with significant decreases in striatal liquid peroxidation ($n = 6$, $p < 0.001$) and α-Syn levels in the substantia nigra ($n = 4$, $p < 0.001$). Semaglutide was significantly more effective than liraglutide ($p < 0.05$). Liraglutide was associated with significant decreases in striatal liquid peroxidation ($n = 6$, $p < 0.001$) and α-Syn levels in the substantia nigra ($n = 4$, $p < 0.01$).

Abbreviations: T2DM = Type 2 Diabetes Mellitus, AD = Alzheimer's Disease, PD = Parkinson's Disease, MWM = Morris Water Maze, Ex-4 = Exendin-4, i.p. = Intraperitoneal, i.c.v. = Intracerebroventricular, APP = Amyloid Precursor Protein, ROS = Reactive Oxygen Species, N/A = Not Available

tests and time spent in target quadrant during probe tasks (Zhou et al., 2019). Due to the limited data, a comprehensive evaluation of GLP-1's cognitive effects cannot be made.

3.4.1.3. Cognitive Effects of Exenatide on Alzheimer's Disease in Animals. We identified 9 studies examining the cognitive effects of exenatide on AD in animal models (Bomba et al., 2013, 2019; Chen et al., 2012; Garabadu and Verma, 2019; Jia et al., 2016; Robinson et al., 2019; Song et al., 2022; Wang et al., 2016, 2018).

Results from Song et al. (2022) identified that Ex-4 attenuated progression of paralysis in *Caenorhabditis elegans* following administration of Ex-4 at 0.3 mg/ml ($p = 0.0157$), 0.5 mg/ml ($p < 0.0001$), and 1.2 mg/ml ($p < 0.0001$). Additionally, findings from Garabadu and Verma (2019) reported that Ex-4 administration ameliorated Aβ-induced memory deficits in rats, reverting decreases in spontaneous alternation behavior in the Y-maze test ($p < 0.05$), and significantly reducing escape latency during the MWM test ($p < 0.05$). These trends were replicated in a study by Chen et al. (2012) ($n = 30$), wherein Ex-4 administration in rats significantly reverted streptozotocin (STZ)-induced increases in escape latencies ($p < 0.05$) and STZ-induced decreases in target quadrant time during the probe task ($p < 0.05$). Findings from Jia et al. (2016) further supported these results, wherein administration of 0.2 nmol Ex-4 ($n = 10$) and 2 nmol Ex-4 ($n = 10$) reverted $A\beta_{1-42}$ induced increases in escape latency ($p < 0.05$), swim distances to hidden platforms ($p > 0.05$) during the MWM task, simultaneously increasing time spent in target quadrants during the probe task ($p > 0.05$).

In accordance with the aforementioned results, Robinson et al. (2019) reported that Ex-4 administration in AD mice models significantly reduced escape latencies during the MWM task ($p = 0.011$). These findings were supported by Wang et al. (2018), wherein Ex-4 administration in APP/PS1 mice significantly decreased escape latencies ($p < 0.01$) and increased time spent in target quadrants during probe tasks ($p < 0.01$) in comparison to controls. Similarly, findings by Wang et al. (2016) reported that Ex-4 attenuated Aβ31–35-induced increases in escape latency on days 2–5 of the MWM test ($p < 0.05$), whilst attenuating decreases in time spent in target quadrants during the probe task ($p < 0.05$). Interestingly, Ex-4 was also associated with attenuating Aβ31–35-induced decreases in locomotor activity ($p < 0.05$) (Wang et al., 2018). However, two disparate studies by Bomba et al. (2013) ($n = 47$) and Bomba et al. (2019) ($n = 46$) indicate that exenatide administration in 3x-Tg AD mice had no significant effect on results in the MWM tests and object recognition tests ($p > 0.05$). Taken together, these results indicate that exenatide is likely to exert an overall protective effect against AD-associated cognitive deficits.

3.4.1.4. Cognitive Effects of Liraglutide on Alzheimer's Disease in Animals. We identified 19 studies that evaluated the cognitive effects of liraglutide on animal models of AD (Table 3). Animal studies by Duarte et al. (2020) and McClean et al. (2011) reported no significant changes in open field test performance following liraglutide administration in 3xTg ADand $APP_{SWE}/PS1_{\Delta E9}$ mice, respectively. Additionally, studies by McClean and Hölscher (2014a) and Paladugu et al. (2021) reported no significant changes in open field test performance and novel object recognition tasks. Notwithstanding, findings from Batista et al. (2018) identified an association between liraglutide administration improved novel object recognition ($p < 0.05$) and object location memory test

performances ($p < 0.05$) in mice. Similarly, McClean et al. (2015) reported no significant changes in open field test performances ($p > 0.05$), but identified significant improvements in novel object recognition tasks ($p < 0.05$).

In addition to the aforementioned findings, liraglutide administration was associated with significant reductions in escape latency during MWM tests ($F = 53.5$, $p < 0.0001$) and significant increases in time spent in target quadrants during the probe task ($p < 0.05$). Similar to McClean et al. (2015), a disparate study also identified significant decreases in path lengths during MWM tests ($p < 0.05$) and significant increases in time spent in target quadrant during probe tasks ($p < 0.05$) following liraglutide administration in transgenic AD mice (Chen et al., 2017). Additionally, a study by Bakhshwin et al. (2024) ($n = 25$) reported that liraglutide administration was associated with significant reductions in escape latency (5.40 %; $p < 0.01$). Similarly, administration of liraglutide significantly reduced escape latency during MWM tasks ($p < 0.05$) and increases in time spent in target quadrant during probe tasks ($p < 0.05$) in both wild-type and $APP_{SWE}/PS1_{\Delta E9}$ mice (McClean and Hölscher, 2014b). These trends in the MWM and probe tasks were similarly replicated in STZ-models of AD mice, transgenic $APP_{Lon}PS1_{A246E}$ mice, $A\beta_{1-42}$-induced AD models of C57BL/6 mice, APP/PS1 transgenic mice, and 5xFAD mice (Carranza-Naval et al., 2021; Dong et al., 2022; Hansen et al., 2016a; Qi et al., 2016; Xiong et al., 2013) (Table 3).

These trends were further replicated in an Aβ25–35-induced AD rat model by Han et al. (2013), wherein Aβ25–35-induced increases in escape latency was attenuated following 0.5 nmol liraglutide ($p < 0.05$) and 5 nmol liraglutide administration ($p < 0.05$), but not 0.05 nmol liraglutide administration ($p > 0.05$). Additionally, liraglutide was associated with significant increases time spent in target quadrants at 0.5 nmol (38.01 ± 1.67 % vs. 24.85 ± 0.89 %; $p < 0.05$) and 5 nmol (43.22 ± 0.93 % vs. 24.85 ± 0.89 %; $p < 0.05$) in comparison to no liraglutide administration (Han et al., 2013). In a disparate study by Hao et al. (2024), wherein administration of liraglutide was associated with significant increases in rearing numbers during the open field tasks ($p < 0.05$) and spontaneous alterations of the Y-maze task ($p < 0.01$) in comparison to controls. Notwithstanding, however, two separate studies identified no significant changes in probe tests and MWM tests, respectively (Duarte et al., 2020; Maskery et al., 2020).

Interestingly, results from Duarte et al. (2020) also identified no significant changes in the Y-maze test ($p > 0.05$). Contrastingly, a separate study reported that liraglutide significantly reverted $A\beta_{1-42}$-induced decline in Y-maze performances ($p < 0.05$) (Qi et al., 2016). In addition, liraglutide administration in SAMP8 mice was also associated with significant improvements in memory retention tests ($p < 0.001$) (Hansen et al., 2015). Furthermore, a study by Hansen et al. (2016b) identified significant increases in survival rates associated with liraglutide administration ($p = 0.003$, $\chi^2 = 8.655$, $df = 1$). Taken together, these results indicate that liraglutide may improve motor function and cognitive memory in AD models of mice.

3.4.1.5. Cognitive Effects of Lixisenatide on Alzheimer's Disease in Animals. We identified 3 studies examining the cognitive effects on AD in animal models (McClean and Hölscher, 2014a; Cai et al., 2014, 2017). In an animal study by Cai et al. (2014), lixisenatide injection in rats significantly reverted Aβ25–35-induced increases in escape latency in WMW tests ($p < 0.001$; $n = 10$) and Aβ-25–35-induced decreases in time spent in target quadrants ($p < 0.0001$; $n = 10$). These cognitive benefits were also observed during Y-maze working memory tests in rats ($p < 0.001$; $n = 10$) in a separate study by Cai et al. (2017). Additionally, findings from McClean and Hölscher (2014a) reported significant increases in recognition index in the object recognition task following daily administration of 1 nmol/kg lixisenatide ($n = 12$, $p = 0.0336$) and 10 nmol/kg lixisenatide ($n = 12$, $p = 0.0456$) for 66 days in $APP_{SWE}/PS1_{\Delta E9}$ mice. These results suggest a positive association between lixisenatide administration and amelioration of AD-like symptoms.

3.4.1.6. Cognitive Effects of Semaglutide on Alzheimer's Disease in Animals. There is currently insufficient information examining the effects of semaglutide on cognitive effects of AD in animals. Notwithstanding, findings from Wang et al. (2023) identified significant improvements in novel object recognition ($p < 0.05$, $n = 10$) in mice. In contrast, findings from Forny Germano et al. (2024) reported that semaglutide administration was not associated with improvements in exploration time during the novel object recognition test in both 5xFAD and APP/PS1 mice ($p > 0.05$). Simultaneously, semaglutide was not associated with changes in escape latency ($p > 0.05$) and number of target quadrant crossings ($p > 0.05$) during the MWM test (Forny Germano et al., 2024). Notwithstanding, semaglutide treatment in female 5x FAD mice was associated with increased time spent in the center area during the open field tests ($p < 0.05$) and decreased time spent in center area in female APP/PS1 mice ($p < 0.05$) (Forny Germano et al., 2024). These trends were not replicated in male 5x FAD and APP/PS1 mice, wherein no significant effect was observed ($p > 0.05$) (Forny Germano et al., 2024). Due to the limited data available, a comprehensive evaluation of semaglutide's effect on cognitive changes in AD cannot be made.

3.4.1.7. Cognitive Effects of Tirzepatide on Alzehimer's Disease in Animals. In addition to examining changes in cognition following semaglutide administration, Forny Germano et al. (2024) also examined the cognitive effects of tirzepatide in mice. Results indicated that tirzepatide was associated with increasing exploration times and discrimination indices for the novel object in male 5xFAD mice ($p < 0.05$), but not in female 5xFAD mice ($p > 0.05$) (Forny Germano et al., 2024). In contrast, tirzepatide was not significantly associated with increases in time spent in the center area during the open field test in 5xFAD mice ($p > 0.05$), escape latency during MWM test ($p > 0.05$), and number of target quadrant crossings during the MWM test ($p > 0.05$) (Forny Germano et al., 2024). Evidently, further research is required to examine the role of tirzepatide on cognitive changes in AD.

3.4.2. Cognitive Effects of GLP-1 and GLP-1 RAs on Parkinson's Disease in Animals

To examine the roles of disparate GLP-1 RAs on PD, we examined four studies (Zhang et al., 2019; Bu et al., 2021; Zhang et al., 2021, 2023). Of which, Zhang et al. (2019) investigates the cognitive effect of both semaglutide and liraglutide on AD.

3.4.2.1. Cognitive Effects of Exenatide on Parkinson's Disease in Animals. Bu et al. (2021) identified that administration of Ex-4 rescued motor deficits during the cylinder test in rats ($p = 0.0092$). In addition, an animal study by Zhang et al. (2021) ($n = 40$) reported that administration of exenatide significantly increased distances traveled by rats during open field tests ($p < 0.05$). Taken together, these results suggest that exenatide may provide benefits in ameliorating motor effects associated with PD.

3.4.2.2. Cognitive Effects of Liraglutide on Parkinson's Disease in Animals. In an animal study by Zhang et al. (2023) ($n = 36$), administration of liraglutide was associated with significant improvements in rotarod motor assessment ($p < 0.05$), pole test ($p < 0.01$), and open field test ($p < 0.05$) in comparison to saline groups. Additionally, administration of liraglutide in MPTP-induced PD models was significantly associated with increased distance traveled in the open field test ($n = 12$, $p < 0.001$), extended time on the rotating rod in rotarod tests ($n = 12$, $p < 0.001$), and enhanced grip strength ($n = 12$, $p < 0.001$) (Zhang et al., 2019). This suggests that liraglutide may be able to alleviate motor impairments associated with PD.

3.4.2.3. Cognitive Effects of Semaglutide on Parkinson's Disease in Animals. There is currently insufficient information to evaluate the cognitive effects of semaglutide. Notwithstanding, an animal study reported that semaglutide administration was associated with significant increases in distance traveled during the open field test ($n = 12$, $p < 0.001$), time spent on the rotating rod in rotarod tests ($n = 12$, $p < 0.001$), and grip strength ($n = 12$, $p < 0.001$) (Zhang et al., 2019). Evidently, further research is required to investigate the association between semaglutide and cognition in PD.

3.5. Cellular Effects of GLP-1 and GLP-1 RAs in Animal Models

3.5.1. Cellular Effects of GLP-1 and GLP-1 RAs on Alzheimer's Disease in Animal Models

We identified 18 studies examining the effects of GLP-1 and GLP-1 RAs on neuronal populations and subsets in AD (Table 3). Of which, McClean and Hölscher (2014a) examines changes in neuronal populations associated with liraglutide and lixisenatide administration. Additionally, Forny Germano et al. (2024) examines changes in neuronal populations associated with semaglutide and tirzepatide administration.

3.5.1.1. Cellular Effects of GLP-1 on Alzheimer's Disease in Animal Models. There is currently insufficient information on the cellular effects of GLP-1 on AD. Nonetheless, an animal study by Gengler et al. (2012) reported no significant changes in microglial load following administration of Val^8(GLP-1) for three weeks in comparison to saline control. Given the lack of data available, further research is required to identify the role of GLP-1 on the cellular effects of AD.

3.5.1.2. Cellular Effects of Exenatide on Alzheimer's Disease in Animal Models. To investigate the effect of exenatide on changes in neuronal populations in AD, we identified twostudies (An et al., 2019; Zhang et al., 2022a). An et al. (2019) ($n = 48$) reported that exenatide administration was associated with significant increases in specific surface area of mitochondria ($p < 0.05$). Furthermore, findings from Zhang et al. (2022a) indicate that exenatide was non-significantly associated with reductions in GFAP-marked astrocytes ($p > 0.05$). These findings indicate that exenatide may mediate changes in various neuronal populations, though the extent to which exenatide modulates these changes remains to be elucidated.

3.5.1.3. Cellular Effects of Liraglutide on Alzheimer's Disease in Animal Models. We identified 10 studies examining the cellular effects of liraglutide on AD (Long-Smith et al., 2013; McClean et al., 2011; McClean and Hölscher, 2014a; Paladugu et al., 2021; McClean et al., 2015; Carranza-Naval et al., 2021; Holubová et al., 2019; Salles et al., 2020, 2018; Xie et al., 2021). Results from Holubová et al. (2019) identifies that liraglutide administration in $APP_{SWE}/PS1_{\Delta E9}$ mice was associated with significant reductions in astrocytosis in the cortex ($p = 0.0348$) and a non-significant reduction in microgliosis in the dentate gyrus (DG) ($p = 0.3484$). Similarly, a separate study by Paladugu et al. (2021) ($n = 48$) supports these findings, wherein administration of liraglutide in 5x FAD mice reduced activation of astrocytes in the CA1 region of the hippocampus (HPC) ($p < 0.01$), but not microglial cells ($p > 0.05$) in comparison to vehicle controls. Contrastingly, findings by Long-Smith et al. (2013) identified significant decreases in astrocytic ($p < 0.01$) and microglial activation ($p < 0.05$) in comparison to saline injections. These trends were reinforced by Salles et al. (2020), wherein liraglutide administration was associated with significant decreases in microglia ($p < 0.0001$) and astrocytes ($p < 0.01$), whilst significantly increasing newborn neurons ($p < 0.01$) in comparison to saline injection. Similarly, a separate study by Salles et al. (2018) reported that liraglutide administration increased DCX-positive neuroblasts in the subventricular zone (SVZ), but not astrocyte numbers ($p > 0.05$) in comparison to saline treatment.

Consistent with aforementioned trends, liraglutide was associated with decreases in microglial populations in $APP_{SWE}/PS1_{\Delta E9}$ mice following daily administration of 2.5 nmol/kg liraglutide (48 %, $n = 11$, $p < 0.001$) and 25 nmol/kg liraglutide (49 %, $n = 11$, $p < 0.01$) over 10 weeks (McClean and Hölscher, 2014a). Similarly, a separate study by McClean et al. (2011) reported that administration of liraglutide significantly reduced activation of microglia in the cortex (50 %, $p < 0.001$). These findings were supported by a later study, wherein administration of liraglutide reduced activation of microglia in the cortex (50 %, $p < 0.0001$) and the CA1 region of the HPC (47 %, $p < 0.0001$) in comparison to saline treatment (McClean et al., 2015). Similarly, a study by Carranza-Naval et al. (2021) reported that liraglutide was associated with significant reductions in microglial burden ($p < 0.01$).

Interestingly, a study by Xie et al. (2021) identified that liraglutide attenuated AD-associated neuronal loss in the cortex ($p < 0.05$), and non-significantly in the HPC ($p > 0.05$). Taken together, these results suggest that liraglutide reduces neuroinflammation through the attenuation of immune hyperactivity in the HPC, providing mechanistic insight on how liraglutide may modulate neuroprotective effects.

3.5.1.4. Cellular Effects of Lixisenatide on Alzheimer's Disease in Animal Models. To examine the effects of lixisenatide on neuronal populations in AD, we identified 3 studies (McClean and Hölscher, 2014a; Cai et al., 2017, 2018). Cai et al. (2017) reported a significant decrease in $A\beta_{25–35}$ induced cytotoxicity in HPC neurons ($n = 10$, $p < 0.001$) in rats following lixisenatide administration. In addition, lixisenatide also significantly reduced percentage of pTau-positive neurons (62.30 % ± 4.90 % vs. 89.20 % ± 6.20 %; $p = 0.037$) and microglia (7.41 % ± 0.90 % vs. 16.85 % ± 1.90 %; $p = 0.037$) in comparison to saline injections (Cai et al., 2018). These results were reinforced by McClean and Hölscher (2014a), wherein significant reductions in microglial activation were observed following daily administration of 1 nmol lixisenatide (47 %, $n = 11$, $p < 0.001$) and 10 nmol/kg lixisenatide (43 %, $n = 11$, $p < 0.001$) over 10 weeks in comparison to saline administration. These findings indicate that lixisenatide may also have anti-inflammatory properties, providing a mechanistic explanation into potential neuroprotective effects in AD.

3.5.1.5. Cellular Effects of Semaglutide on Alzheimer's Disease in Animal Models. There is currently insufficient information regarding the role of tirzepatide on neuronal populations in AD. Notwithstanding, an animal study by Forny Germano et al. (2024) reported that semaglutide was not associated with reductions in microglia and astrocyte numbers in 5xFAD and APP/PS1 mice ($p > 0.05$).

3.5.1.6. Cellular Effects of Tirzepatide on Alzheimer's Disease in Animal Models. An animal study by Yang et al. (2024) reported that tirzepatide administration in APP/PS1 mice significantly reduced astrocyte activation in comparison to saline controls ($p < 0.01$). In contrast, findings from Forny Germano et al. (2024) reported that tirzepatide administration was not associated with reductions in microglia and astrocyte numbers in 5xFAD and APP/PS1 mice ($p > 0.05$). Evidently, further research is required to further elucidate the role of semaglutide on various neuronal populations in AD.

3.5.2. Cellular Effects of GLP-1 and GLP-1 RAs on Parkinson's Disease in Animal Models

To examine the cellular effects of GLP-1 and GLP-1 RAs in PD, we identified 4 studies (Zhang et al., 2019; Bu et al., 2021; Zhang et al., 2021, 2022b). Of which, Zhang et al. (2019) examines the effects of liraglutide and semaglutide on neuronal populations.

3.5.2.1. Cellular Effects of Exenatide on Parkinson's Disease in Animal Models. Findings by Bu et al. (2021) report that administration of exenatide attenuated loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc) in comparison to vehicle controls 6 weeks post-injection (-39 % vs. −42 %) and significantly 10 weeks post-injections (-37 % vs. −61 %, $p = 0.0005$). This trend was replicated in the striatum at 6 weeks post-injection (-31.98 % vs. −37.65 %) and significantly 10 weeks post-injections (-27.93 % vs. −49.01 %, $p = 0.0151$) (Bu et al., 2021). In a separate study by Zhang et al. (2021), administration of Ex-4 significantly ameliorated PD-induced loss of DA neurons in the striatum ($p < 0.01$), whilst significantly attenuating astrocyte activation ($p < 0.05$). Taken together, these results suggest that exenatide may have neuroprotective properties for DA neurons, whilst potentially modulating neuroinflammatory responses in PD.

3.5.2.2. Cellular Effects of Liraglutide on Parkinson's Disease in Animal Models. Zhang et al. (2019) ($n = 72$) reports that administration of liraglutide in MPTP-induced PD mice significantly attenuated DA neuronal loss in the substantia nigra (SN) ($p < 0.01$), simultaneously reducing striatal activation of astrocytes ($n = 6$, $p < 0.001$) and microglia ($n = 6$, $p < 0.001$). Notwithstanding, further research is required to elucidate the role of liraglutide on various neuronal populations in PD.

3.5.2.3. Cellular Effects of Semaglutide on Parkinson's Disease in Animal Models. In addition to the aforementioned findings, Zhang et al. (2019) identifies that semaglutide administration also attenuates DA neuronal loss in the SN ($p < 0.001$), simultaneously reducing striatal activation of astrocytes ($n = 6$, $p < 0.001$) and microglia ($n = 6$, $p < 0.001$). Additionally, semaglutide administration was significantly more efficacious in reducing astrocyte activation ($p < 0.05$) and microglial activation ($p < 0.05$) than liraglutide (Zhang et al., 2019). A separate study by Zhang et al. (2022b) reinforces these results, reporting that semaglutide administration significantly protected against PD-associated DA neuronal loss in the SN ($n = 6$, $p < 0.005$) (Zhang et al., 2022b). Similarly to exenatide, these findings suggest that semaglutide may exert neuroprotective effects for DA neurons, whilst simultaneously modulating neuroinflammatory responses in PD. Notwithstanding, further research is required to examine the anti-inflammatory effect of semaglutide.

3.6. Molecular Effects of GLP-1 and GLP-1 RAs in animal models

3.6.1. Molecular Effects of GLP-1 and GLP-1 RAs on Alzheimer's disease in animal models

To investigate the effects of GLP-1 and GLP-1 RAs on signaling molecules, pathways, and protein expression, we identified 41 studies (Table 3). Of which, McClean and Hölscher (2014a) examines the molecular effect of liraglutide and lixisenatide on AD.

3.6.1.1. Molecular Effects of GLP-1 on Alzheimer's disease in animal models. We identified 4 studies examining the molecular effects of GLP-1 in AD (Ma et al., 2012; Li et al., 2012; Gengler et al., 2012; Gault and Hölscher, 2008). In an animal study by Li et al. (2012) reported that administration of 50 μM (Val8)GLP-1 was associated with decreases in phosphorylated tau / tau ratio ($p < 0.05$), whilst attenuating STZ-induced increases in tau expression in comparison to controls. Similarly, Gengler et al. (2012), administration of Val^8(GLP-1) in APP/PS-21 mice did not result in changes in Aβ-plaque load in comparison to controls. These trends are supported by Ma et al. (2012), wherein GLP-$1(9-36)^{amide}$ was not associated with changes in amyloid-beta (Aβ) precursor protein (APP) and Aβ levels in comparison to vehicle controls. Notwithstanding, administration of GLP-$1(9-36)^{amide}$ attenuated AD-induced increases in mitochondrial superoxide and activation of GSK3β, whilst simultaneously modulating a non-significant decrease in Caspase-3 ($p = 0.35$) (Ma et al., 2012). No effect was observed on Akt levels ($p > 0.05$) (Ma et al., 2012). Additionally, administration of (Val^8)GLP-1 did not revert amyloid-induced impairments of LTP signals (Gault and Hölscher, 2008). Taken together, these results suggest that GLP-1 may be associated with modulating proliferative pathways. Notwithstanding, further research is required to understand the role of GLP-1 on signaling molecules and pathways that subserve AD pathology.

3.6.1.2. Molecular Effects of Dulaglutide on Alzheimer's Disease in Animal Models. We identified a study by Zhou et al. (2019) reporting that dulaglutide administration in STZ-induced AD models reduced levels of phosphorylated Tau ($p < 0.01$) and neurofibrillary tangles ($p < 0.05$), whilst upregulating the expression of pPI3K, pAkt, and pGSK3β ($p < 0.01$). These findings suggest that dulaglutide may attenuate development of AD through the modulation of proliferative pathways, whilst regulating levels of tau. Due to the limited data, however, a comprehensive analysis of dulaglutide's molecular effects cannot be conducted.

3.6.1.3. Molecular Effects of Exenatide on Alzheimer's Disease in Animal Models. To examine the molecular effects of exenatide on AD, we identified 11 studies (Table 3). In an animal study by Jia et al. (2016), Ex-4 administration significantly reverted $A\beta_{1-42}$-induced decreases in *Bcl-2* expression ($p < 0.01$), Aβ-induced increases in *Bax* expression ($p < 0.01$) and upregulation of Caspase-3 ($p < 0.01$). In a separate study by An et al. (2019), exenatide administration significantly decreased levels of malondialdehyde (MDA) ($p < 0.05$), simultaneously increasing superoxide dismutase (SOD) activity within the HPC ($p < 0.05$). Additionally, exenatide significantly increased levels of postsynaptic marker PSD95 ($p < 0.001$) and presynaptic marker Syn ($p < 0.01$), whilst significantly decreasing area of amyloid plaques in the HPC CA1 region ($p < 0.05$) (An et al., 2019). In a separate study by Song et al. (2022), administration of Ex-4 significantly decreased ROS levels in CL4176 *C. elegans* (13.57 %, $p < 0.01$), CL2006 *C. elegans* (17.22 %, $p < 0.05$). Furthermore, Ex-4 significantly reduced Aβ levels (39.78 %, $p < 0.001$) (Song et al., 2022).

In comport with previous studies, a study on 3xAD mice ($n = 30$) reported that Ex-4 significantly reverted STZ-induced increase in Aβ levels ($p < 0.05$), and non-significant decreases in Aβ levels (25 %, $p > 0.05$) in absence of STZ (Li et al., 2010b). These findings are reinforced by Garabadu and Verma (2019) ($n = 36$), wherein Ex-4 administration significantly reduced Aβ-induced increases in Aβ in the rat HPC and prefrontal cortex (PFC) ($p < 0.05$), simultaneously ameliorating Aβ-induced decreases in Akt phosphorylation ($p < 0.05$). These trends were replicated by Wang et al. (2018) and Zhang et al. (2022a), wherein administration of Ex-4 in APP/PS1 mice reduced levels of Aβ and hyperphosphorylated tau levels in the HPC and cortex. Contrastingly, however, Robinson et al. (2019) reports that exenatide administration did not have a significant impact on $A\beta_{1-42}$ levels ($n = 9$, $p < 0.05$). Similarly, a separate study identified no significant effect on Aβ and tau levels following exenatide administration in comparison to vehicle controls (Bomba et al., 2019). Notwithstanding, exenatide administration was also associated with enhanced BDNF signaling ($p < 0.001$) and reduced proBDNF signaling ($p < 0.05$) (Bomba et al., 2019). In addition to the aforementioned effects, Ex-4 administration has been associated with reducing STZ-induced hyperphosphorylation of tau at Ser396 ($p < 0.05$) and Thr181 ($p < 0.01$) in comparison to controls (Chen et al., 2012). In contrast, a separate study by Bomba et al. (2013) reported that exenatide did not significantly decrease h-tau immunoreactivity ($p = 0.337$) or intraneuronal Aβ levels in the HPC ($p = 0.552$).

In addition to examining Aβ and tau, Wang et al. (2018) reports significant increases in β-catenin ($p < 0.01$), pAkt ($p < 0.01$) and pGSK3β ($p < 0.01$) levels in APP/PS1 mice following exenatide administration. Similarly, Zhang et al. (2022a) reports changes in levels of various components of the immune system in addition to changes on

Aβ levels. Specifically, exenatide administration in 5xFAD mice was associated with significant reductions in TNF-α ($p < 0.05$), IL-β ($p < 0.05$), NLRP2 ($p < 0.05$) expression, and a non-significant reduction of ROS (30 %, $p > 0.05$) (Zhang et al., 2022a). Taken together, these findings suggest that exenatide modulates changes in AD through multifaceted processes. Namingly, exenatide may alleviate oxidative stress, amyloidopathies, and neuroinflammation.

3.6.1.4. Molecular Effects of Liraglutide on Alzheimer's Disease in Animal Models. To examine the molecular effects of liraglutide on AD, we identified 21 studies (Table 3). Results from Chen et al. (2017) identified attenuation of tau hyperphosphorylation ($p < 0.05$) and neurofilaments ($p < 0.05$) following liraglutide administration in 3xTg-AD mice, simultaneously rescuing ERK and JNK signaling ($p < 0.05$). In a separate study, liraglutide significantly reversed $A\beta_{1-42}$-induced tau hyperphosphorylation ($p < 0.05$), whilst reverting $A\beta_{1-42}$-induced decreases in pAkt ($p < 0.05$) and pGSK3β ($p < 0.05$) (Qi et al., 2016). These results were supported by Paladugu et al. (2021), wherein administration of liraglutide in 5xFAD mice was associated with significant decreases in HPC Aβ levels ($p < 0.001$), phosphorylated Akt in the cortex ($p < 0.01$), and significant increases in pGSK3β in the HPC ($p < 0.01$) in comparison to vehicle controls.

In addition to the aforementioned changes, liraglutide has been shown to protect against oxidative stress, whilst reducing neuroinflammation. Specifically, administration of liraglutide in 3xTg-AD mice has been associated with normalization of proinflammatory markers IL-10 ($Z = -0.319$, $p = 0.805$) and IL-1β ($Z = -2.00$, $p = 0.051$) in comparison to wild-type mice, whilst non-significantly reducing oxidative stress marker 8-OHdG ($p > 0.05$) (Duarte et al., 2020). These trends were somewhat supported by Maskery et al. (2020), wherein administration of liraglutide non-significantly decreased levels of proinflammatory cytokine IL-1β ($p > 0.05$) and TNF-α ($p > 0.05$), with a non-significant decrease in Aβ plaque load in the neocortex ($p > 0.05$). Additionally, liraglutide was associated with attenuating AD-associated decreases in catalase (CAT) and SOD activity ($p < 0.01$) (Bakhshwin et al., 2024). Moreover, liraglutide increased the activation of the cAMP / PKA pathway ($p < 0.05$), production of ATP ($p < 0.05$), whilst attenuating overproduction of ROS ($p < 0.05$) (Bakhshwin et al., 2024). These findings indicate that liraglutide may reduce neuroinflammatory effects, reducing oxidative stress.

Findings by McClean and Hölscher (2014b) reported that liraglutide administration in $APP_{SWE}/PS1_{\Delta E9}$ mice significantly decreased Aβ load ($p = 0.0007$), soluble amyloid oligomer levels ($p = 0.0355$), and total APP levels (0.0423). A separate study by McClean and Hölscher (2014a) further supported these results, wherein reductions in cortical Aβ plaques were significantly reduced following administration of 2.5 nmol/kg liraglutide (46 %, $n = 11$, $p < 0.01$) and 25 nmol/kg liraglutide (45 %, $n = 11$, $p < 0.01$). Consistent with the aforementioned results, results from McClean et al. (2011) report that liraglutide administration reduced formation of cortical Aβ plaques (50 %, $p < 0.001$), simultaneously reducing brain APP levels ($p = 0.0272$) in comparison to saline administration. Similarly, liraglutide was associated with significant decreases in cortical Aβ load in the cortex (40 %, $p < 0.001$) and CA1 region of the HPC (45 %, $p < 0.001$) in comparison to saline treatment (McClean et al., 2015). These trends were further reinforced by Long-Smith et al. (2013), wherein liraglutide significantly decreased Aβ levels in $APP_{SWE}/PS1_{\Delta E9}$ (31.5 %, $p < 0.0001$). Results from Holubová et al. (2019) further supported these trends, wherein liraglutide administration was associated with significant decreases in the number and size of Aβ plaques in the CA1 region of the HPC [$F(2,25) = 4.410$, $p = 0.0229$ (one-way ANOVA); $p = 0.0303$]. In addition to the aforementioned trends, Salles et al. (2020) report significant decreases in the DG ($p < 0.001$) in addition to the CA1 region of the HPC ($p < 0.001$) and the cortex ($p < 0.0001$). Furthermore, Salles et al. (2018) also report decreases in the cortex ($p < 0.0001$), in addition to the CA1 region of the HPC ($p < 0.01$) and DG ($p < 0.0001$) in comparison to saline. These trends were further supported by studies in APP/PS1 mice, wherein liraglutide administration was associated with reducing amyloid plaque burden (Carranza-Naval et al., 2021; Hao et al., 2024). Contrastingly, an animal study by Hansen et al. (2016a) reported no significant differences in Aβ plaque volume between AD mice models administered with liraglutide and saline ($p > 0.05$).

In addition to changes in Aβ, liraglutide attenuated abnormal tau-hyperphosphorylation in cynomolgus macaques, and only modest changes in Aβ-induced synaptic loss in the frontal cortex ($p = 0.1480$) (Batista et al., 2018). Notwithstanding, liraglutide administration was associated with significant reductions in phospho-tau volumes in the ventral pons (0.053 ± 0.014 mm^3; 69.4 ± 7.9 % reduction, $p < 0.001$), dorsal pons (0.043 ± 0.010 mm^3; 59.5 ± 12.9 % reduction, $p < 0.05$) medulla (0.046 ± 0.012 mm^3; 61.0 ± 8.6 % reduction, $p < 0.01$), and non-significantly in the diencephalon (0.034 ± 0.015 mm^3; 50.7 ± 22.5 % reduction, $p > 0.05$) (Hansen et al., 2016b). In a separate study by Xiong et al. (2013) ($n = 24$), liraglutide also decreased tau phosphorylation in the cerebrum ($p < 0.05$). These results suggest that liraglutide may ameliorate cognitive effects of AD through the dose-independent attenuation of Aβ plaque formation and tau phosphorylation, in addition to modulating neuroinflammation and proliferation.

3.6.1.5. Molecular Effects of Lixisenatide on Alzheimer's Disease in Animal Models. To examine the molecular effects of lixisenatide on AD, we identified four studies (McClean and Hölscher, 2014a; Cai et al., 2014, 2017, 2018). Findings by Cai et al. (2014) reported that lixisenatide administration reverted Aβ-induced decreases in pGSK3β(S9) ($n = 6$, $p < 0.05$) and pGSK3β(Y216) ($n = 6$, $p < 0.05$). In a separate study by Cai et al. (2017), administration of lixisenatide significantly reversed $A\beta_{25-35}$ induced decreases in pAkt and MEK1/2 levels ($n = 10$, $p < 0.05$). Moreover, lixisenatide has also been associated with ameliorating AD-induced PKA signaling ($p = 0.039$) and CREB signaling ($p = 0.042$) in the hippocampi of 3xTg-AD mice, whilst simultaneously inhibition activation of the p38-MAPK pathway ($p = 0.038$) (Cai et al., 2018).

In addition to the aforementioned findings, Cai et al. (2018) also reported that lixisenatide significantly reduced percentage of Aβ-area in the HPC in comparison to saline injections ($5.87\ \% \pm 0.70\ \%$ vs. $9.48\ \% \pm 1.20\ \%$; $p = 0.04$). Similarly, lixisenatide reduced the percentage of p-tau area in the HPC ($14.99\ \% \pm 1.40\ \%\%$ vs. $32.58\ \% \pm 3.90\ \%$; $p = 0.043$) (Cai et al., 2018). These results were supported by McClean and Hölscher (2014a), wherein reductions in Aβ plaques in the cortex was observed following daily administration of 1 nmol/kg lixisenatide (49 %, $p < 0.05$, $n = 11$) and 10 nmol/kg lixisenatide (43 %, $p < 0.05$, $n = 11$) over 10 weeks. Taken together, these results suggest that lixisenatide may reduce levels of protein associated with AD manifestation, whilst acting on various cellular survival and proliferative pathways.

3.6.1.6. Molecular Effects of Semaglutide on Alzheimer's Disease in Animal Models. There is currently insufficient information regarding the molecular effects of semaglutide on AD. In concordance with other results, injection of semaglutide was associated with significant decreases in HPC tau levels of 3xTg mice ($p < 0.01$) (Wang et al., 2023). Additionally, semaglutide ameliorated AD-induces in sirtuin 1 (SIRT1) ($p < 0.01$) and glucose transporter type 4 (GLUT4) ($p < 0.01$).66 Furthermore, semaglutide was associated with reductions in Aβ plaque in the HPC of female APP/PS1 mice ($p < 0.05$) (Forny Germano et al., 2024). Notwithstanding, this was not consistently replicated in the cerebral cortex, HPC, and subiculum of both 5xFAD and male APP/PS1 mice ($p > 0.05$) (Forny Germano et al., 2024). Despite the need for further research, preliminary evidence suggests that semaglutide may ameliorate cognitive symptoms of AD through the modulation of Tau, and may have further effects in protein transcription and gene

activations.

3.6.1.7. Molecular Effects of Tirzepatide on Alzheimer's Disease in Animal Models. Regarding the molecular effects of tirzepatide on AD, there is currently insufficient information. Notwithstanding, an animal study by Forny Germano et al. (2024) reported that tirzepatide was not associated with reductions in Aβ plaque in the cerebral cortex, HPC, and subiculum of both 5xFAD and APP/PS1 mice ($p > 0.05$). In contrast, Yang et al. (2024) identified that tirzepatide was significantly associated with decreases in Aβ-plaques in the cortex ($p < 0.001$), but not in the HPC ($p > 0.05$) of APP/PS1 mice in comparison to saline controls. Furthermore, tirzepatide administration reverted Aβ-induced production of ROS ($p < 0.001$) (Yang et al., 2024). These findings suggest that tirzepatide may have the potential to ameliorate AD-like symptoms through the modulation of abnormal Aβ plaques in the cortex and reducing oxidative stress. Notwithstanding, further research is required to explore the cognitive effects of tirzepatide in AD.

3.6.2. Molecular Effects of GLP-1 and GLP-1 RAs on Parkinson's Disease in Animal Models

To examine changes in molecular pathways, signaling molecules, and protein products associated with GLP-1 and GLP-1 RA administration in PD, we identified 6 studies (Table 3). Of which, Zhang et al. (2019) examines the effects of liraglutide and semaglutide.

3.6.2.1. Molecular Effects of GLP-1 on Parkinson's Disease in Animal Models. There is currently insufficient information regarding the molecular effects of GLP-1 on PD. Nonetheless, findings from a mouse model of PD reported no significant changes in pSer129 α-syn reactivity 5 weeks post-GLP-1 analogue administration, but a 74.5 % increase 13 weeks following administration ($p = 0.005$) in comparison to controls (Bergkvist et al., 2021). Evidently, further research is required to elucidate the role of GLP-1 on PD.

3.6.2.2. Molecular Effects of Dulaglutide in Parkinson's Disease in Animal Models. Khalaf et al. (2023) examines the effect of dulaglutide on multiple molecular markers in rotenone-induced PD models of rats. Their findings indicate that low doses of dulaglutide (0.05 mg/kg) administered weekly in Wistar rats attenuated rotenone-induced oxidative stress, characterized by increases in glutathione (GSH) (70.14 %, $p \leq 0.05$), superoxide dismutase (SOD) activity (32.46 %, $p \leq 0.05$), simultaneously decreasing malondialdehyde (MDA) (30 %, $p \leq 0.05$) and nitric oxide (NO) (26.14 %, $p \leq 0.05$) (Khalaf et al., 2023). These trends were replicated following weekly administration of dulaglutide at high doses (0.1 mg/kg), characterized by increases in GSH content (143 %, $p \leq 0.05$), SOD activity (96.25 %, $p \leq 0.05$), whilst decreasing MDA levels (82.65 %, $p \leq 0.05$) and NO (45.44 %, $p \leq 0.05$) (Khalaf et al., 2023). Additionally, dulaglutide also attenuated rotenone-induced hyperactivity of monoaminoxidase-B (MAO-B) at low doses (38.71 %, $p \leq 0.05$) and high doses (57.60 %, $p \leq 0.05$) of dulaglutide (Khalaf et al., 2023).

In addition to the aforementioned results, Khalaf et al. (2023) also examines the anti-inflammatory properties of dulaglutide. Findings indicate that low doses of dulaglutide significantly reduced hyperactivity of pro-inflammatory cytokines IL-1β (62 %, $p \leq 0.05$), TNF-α (31.79 %, $p \leq 0.05$), and IL-6 (62 %, $p \leq 0.05$) (Khalaf et al., 2023). These trends were replicated at high doses of dulaglutide administration, wherein reduced hyperactivity of pro-inflammatory cytokines IL-1β (88.28 %, $p \leq 0.05$), TNF-α (83.41 %, $p \leq 0.05$), and IL-6 (79.07 %, $p \leq 0.05$) was observed in comparison to the rotenone group (Khalaf et al., 2023).

Results further indicate that low doses of dulaglutide significantly increased DA levels (93.53 %, $p \leq 0.05$), 3,4-dihydroxyphenylacetic acid (DOPAC) (159.78 % $p \leq 0.05$), and homovanillic acid (HVA) (44.70 %, $p \leq 0.05$) in comparison to rotenone treatment (Khalaf et al., 2023). Consistent with aforementioned trends, these effects were observed following high doses of dulaglutide, significantly increasing DA levels (222.35 %, $p \leq 0.05$), DOPAC (224.91 %, $p \leq 0.05$), and HVA (137.88 %, $p \leq 0.05$) (Khalaf et al., 2023). Taken together, these findings suggest that dulaglutide may exert protective properties against oxidative stress, simultaneously attenuating neuroinflammation and regulate neurotransmitter levels.

3.6.2.3. Molecular Effects of Exenatide in Parkinson's Disease in Animal Models. There is currently insufficient information regarding the role of exenatide in modulating molecular pathways in PD. Notwithstanding, results from Zhang et al. (2021) indicate that Ex-4 administration significantly reduced PD-associated α-syn expression in the SN ($p < 0.05$), and IL-1β ($p < 0.05$) and TNF-α ($p < 0.05$) in the striatum. These findings support the overarching trend wherein GLP-1 RAs may attenuate inflammation in the brain. However, research is required to further elucidate the molecular effects of exenatide in PD.

3.6.2.4. Molecular Effects of Liraglutide in Parkinson's Disease in Animal Models. To examine the effects of liraglutide on molecular changes in PD, we identified two studies (Zhang et al., 2019, 2023). In an animal study by Zhang et al. (2019) administration of liraglutide significantly decreased striatal liquid peroxidation ($n = 6$, $p < 0.001$) and α-syn levels in the SN ($n = 4$, $p < 0.01$). Findings from Zhang et al. (2023) supported these results, wherein liraglutide administration in A53T transgenic mice significantly reduced levels of α-syn in the SN ($p < 0.05$). Simultaneously, liraglutide significantly reduced levels of TNF-α ($p < 0.001$), IL-1β ($p < 0.01$) in the SN (Zhang et al., 2023). Furthermore, liraglutide significantly reduced levels of TNF-α ($p < 0.05$) and increased levels of IL-10 ($p < 0.001$) in the striatum, but not in IL-1β ($p > 0.05$) (Zhang et al., 2023). In comport with other GLP-1 RAs, evidence suggests that liraglutide may protect against synucleinopathies, whilst likely exerting an anti-inflammatory effect.

3.6.2.5. Molecular Effects of Semaglutide in Parkinson's Disease in Animal Models. Consistent with other GLP-1 RAs, Zhang et al. (2019) reported that semaglutide administration was associated with significant decreases in striatal liquid peroxidation ($n = 6$, $p < 0.001$) and α-syn levels in the SN ($n = 4$, $p < 0.001$), wherein semaglutide was significantly more effective than liraglutide ($p > 0.05$). In a separate study by Zhang et al. (2022b) ($n = 40$), semaglutide significantly reverted PD-associated increases in TNF-α ($n = 5$, $p \leq 0.005$), IL-1β ($n = 5$, $p < 0.0002$), α-syn monomer levels in comparison to saline controls ($n = 5$, $p < 0.01$). Surprisingly, semaglutide was not significantly associated with changes in striatal DA levels ($p > 0.05$) (Zhang et al., 2022b). Notwithstanding, these results suggest that semaglutide may also exert neuroprotective and anti-inflammatory effects.

4. Discussion

To our knowledge, this systematic review is the first to comprehensively examine the cognitive, cellular, and molecular changes in neurodegenerative disease associated with GLP-1 and GLP-1 RAs administration. Extant literature reports that GLP-1 and GLP-1 RAs are associated with an overall neuroprotective effect, wherein changes within inflammatory cell populations and neuronal proliferation pathways may subserve these effects.

Overall, our results suggest that GLP-1 and GLP-1 RA administration is associated with an overarching improvement in motor symptoms and amelioration of cognitive impairments associated with neurodegenerative diseases. Notably, administration of dulaglutide, exenatide, and liraglutide were able to reduce the risk of AD in humans, wherein exenatide and lixisenatide were associated with attenuation of cognitive decline in patients with PD. Additionally, administration of GLP-1, dulaglutide, exenatide, liraglutide, lixisenatide, and semaglutide

improved memory and learning in animal models of AD, whilst liraglutide administration also improved motor function. Similarly, administration of exenatide, liraglutide, and semaglutide improved motor function in PD models in animals. Notwithstanding, clinical data examining the ability of GLP-1 and GLP-1 RAs on improving motor and cognitive symptoms remain limited, wherein some mixed results have been reported with regards to GLP-1 modulation of motor and cognition. Notably, a novel phase III clinical trial by Vijiaratnam et al. (2025) reported that GLP-1 RA administration (exenatide) had no impact on cognitive and motor symptoms in participants with PD. As such, further research is required to ascertain the effects of GLP-1 receptor agonism on motor and cognition in persons with neurodegenerative conditions (Vijiaratnam et al., 2025).

In addition to modulating cognitive symptoms, our results indicate that GLP-1 and GLP-1 RA administration is associated with modulating astrocyte, microglia, dopaminergic, and tau-positive neurons. Specifically, exenatide administration reduced astrocytic activation and attenuated loss of dopaminergic neurons in the striatum in both AD and PD animal models. Similarly, liraglutide and semaglutide administration reduced astrocytic and microglial activity, whilst attenuating loss of DA neurons in animal models.

Simultaneously, GLP-1 and GLP-1 RAs administration is also associated with downregulation of various molecular markers, with notably decreases in inflammatory cytokines, oxidative stress, and changes in proliferative pathways. Notably, the decreases in ROS, NO, and other oxidative molecules in conjunction with reduced levels of inflammatory cytokines IL-1β, TNF-α, IL-6 from the attenuation of astrocytic and microglial activity may partially subserve the mechanism wherein GLP-1 and GLP-1 RAs exert neuroprotective effects (Hurley and Tizabi, 2013). In addition, GLP-1 and GLP-1 RA-induced rescue of GSK3β, ERK, and *Bcl-2* may promote neuronal proliferation and neurogenesis, which may subserve the mechanism wherein GLP-1 and GLP-1 RAs attenuate cognitive deficit in AD and PD (Hur and Zhou, 2010; Lei et al., 2012; Jiang et al., 2015).

GLP-1 and GLP-1 RAs may serve an effective option for weight management in persons with neurodegenerative conditions (Chen et al., 2023). By understanding the association between GLP-1 and GLP-1 RAs on changes in various molecular pathways, we are able to examine the mechanisms and interactions wherein these agents ameliorate cognitive deficits associated with neurodegenerative diseases (Holst et al., 2011). For instance, reduced levels of oxidative stress, as well as aSyn and Aβ act synergistically to attenuate neuronal death in neurodegenerative conditions (Fig. 2) (Hajieva et al., 2014; Pluta et al., 2020). Furthermore, activation of anti-inflammatory pathways and cytokines (i.e. IL-10) following GLP-1 administration reduces neuronal injury and further attenuates neuronal cell death (Hogan et al., 2014; Fricker et al., 2018). These effects act synergistically with neurogenesis properties associated with GLP-1 receptor agonism, subsequently increasing neuronal proliferation and modulating loss of dopaminergic neurons (Li et al., 2010a; Au et al., 2025). Notably, this increase in neurogenesis may also be attributed to other observed molecular effects of GLP-1 receptor agonism, such as increased activation of signal molecules involved in proliferative pathways (e.g. pPI3K, pAkt, and pGSK3β) (Li et al., 2010a). Given that motor and cognitive deficits associated with neurodegenerative conditions can be attributed to dopaminergic neuronal loss and neurotransmitter imbalance, the molecular effects (i.e. reducing oxidative stress) of GLP-1 receptor agonism may subserve improvements in cognition and motor coordination in individuals with

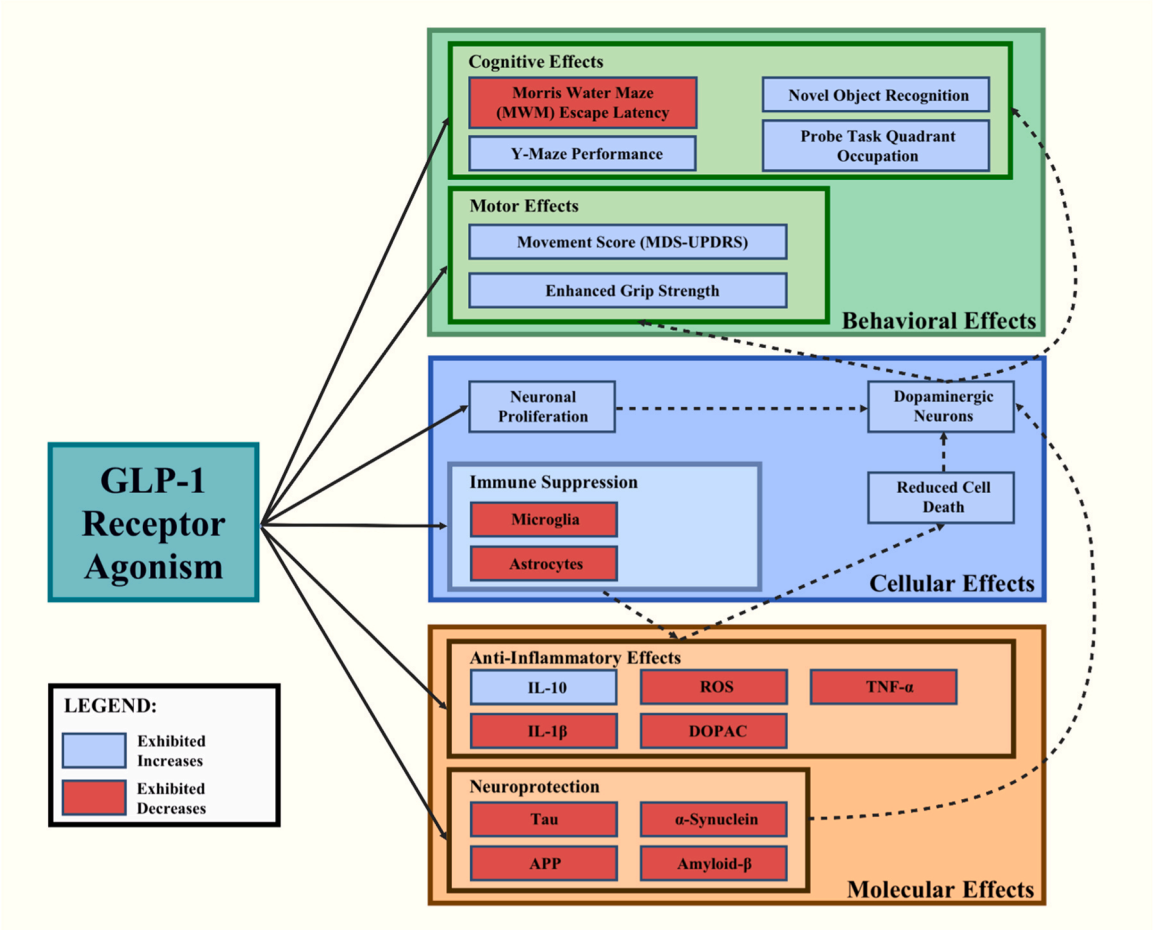

Fig. 2. Potential interactions between the molecular, cellular, and cognitive effects of GLP-1 agonism on neurodegenerative conditions.

neurodegenerative conditions (Yang et al., 2023). Notably, changes in inflammation can be examined in humans via examination of CSF cytokine levels, wherein changes in microglial populations can be also be investigated using neuroimaging modalities such as positron emission tomography (Llano et al., 2012; Edison et al., 2008). These techniques open the possibility of using various biomarkers to examine the neuroprotective effect of GLP-1 receptor agonism on a cellular and molecular level.

Several methodological limitations may impact interpretations and inferences of our systematic review. Firstly, assessed animal models vary in species, which may confound the interpretation of our results. Specifically, the physiology between various animal models of AD and humans vary greatly, which may limit the ability for some results to be translated to humans. Additionally, treatment dosages varied greatly across disparate studies, which may further affect the interpretation of our findings. Notwithstanding, future research vistas should be directed to further elucidate the interactions between cognitive, cellular, and molecular effects induced by GLP-1 and GLP-1 RA administration in neurodegenerative diseases.

5. Conclusion

A replicated finding is that GLP-1 and GLP-1 RAs are associated with neuroprotective effects, which may be a direct and/or indirect effect via attenuation of neuroinflammation and rescue of proliferative pathways. These findings provide a summary of the association between GLP-1 and GLP-1 RAs on cognitive changes, cellular changes, and molecular changes in neurodegenerative diseases, providing a proof of mechanism basis for developing GLP-1 RAs as a treatment strategy for neurodegenerative diseases.

Declaration of Competing Interest

Dr. Roger S. McIntyre has received research grant support from CIHR/GACD/National Natural Science Foundation of China (NSFC) and the Milken Institute; speaker/consultation fees from Lundbeck, Janssen, Alkermes, Neumora Therapeutics, Boehringer Ingelheim, Sage, Biogen, Mitsubishi Tanabe, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Sunovion, Bausch Health, Axsome, Novo Nordisk, Kris, Sanofi, Eisai, IntraCellular, NewBridge Pharmaceuticals, Viatris, Abbvie, Atai Life Sciences. Hezekiah C.T. Au, Pak Ho Lam, and Dr. Poh Khuen Lim have no conflicts to declare.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2025.106159.

References

Akimoto, H., Negishi, A., Oshima, S., et al., 2020. Antidiabetic Drugs for the Risk of Alzheimer Disease in Patients With Type 2 DM Using FAERS. Am. J. Alzheimer'S. Dis. Other Dement. ® 35, 1533317519899546. https://doi.org/10.1177/1533317519899546.

An, J., Zhou, Y., Zhang, M., et al., 2019. Exenatide alleviates mitochondrial dysfunction and cognitive impairment in the 5×FAD mouse model of Alzheimer's disease. Behav. Brain Res. 370, 111932. https://doi.org/10.1016/j.bbr.2019.111932.

Athauda, D., Maclagan, K., Skene, S.S., et al., 2017. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet 390 (10103), 1664–1675. https://doi.org/10.1016/S0140-6736(17)31585-4.

Au, H.C.T., Zheng, Y.J., Le, G.H., et al., 2025. Association of Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) and Neurogenesis: A Systematic Review. Acta Neuropsychiatr. 1–25. https://doi.org/10.1017/neu.2025.4.

Aviles-Olmos, I., Dickson, J., Kefalopoulou, Z., et al., 2013. Exenatide and the treatment of patients with Parkinson's disease. J. Clin. Investig. 123 (6), 2730–2736. https://doi.org/10.1172/JCI68295.

Bak, A.M., Egefjord, L., Gejl, M., et al., 2011. Targeting amyloid-beta by glucagon-like peptide -1 (GLP-1) in Alzheimer's disease and diabetes. Expert Opin. Ther. Targets 15 (10), 1153–1162. https://doi.org/10.1517/14728222.2011.600691.

Bakhshwin, D.M., Alhalabi, F.W., Barasheed, M.O., et al., 2024. Neuroprotective effect of liraglutide and memantine in a rat model of Alzheimer's disease. Asian Pac. J. Trop. Biomed. 14 (5). https://doi.org/10.4103/apjtb.apjtb_937_23.

Baquero, M., Martín, N., 2015. Depressive symptoms in neurodegenerative diseases. World J. Clin. Cases 3 (8), 682–693. https://doi.org/10.12998/wjcc.v3.i8.682.

Batista, A.F., Forny-Germano, L., Clarke, J.R., et al., 2018. The diabetes drug liraglutide reverses cognitive impairment in mice and attenuates insulin receptor and synaptic pathology in a non-human primate model of Alzheimer's disease. J. Pathol. 245 (1), 85–100. https://doi.org/10.1002/path.5056.

Bergkvist, L., Johnson, M.E., Mercado, G., et al., 2021. An extended release GLP-1 analogue increases α-synuclein accumulation in a mouse model of prodromal Parkinson's disease. Exp. Neurol. 341, 113693. https://doi.org/10.1016/j.expneurol.2021.113693.

Bomba, M., Ciavardelli, D., Silvestri, E., et al., 2013. Exenatide promotes cognitive enhancement and positive brain metabolic changes in PS1-KI mice but has no effects in 3xTg-AD animals. e612 Cell Death Dis. 4 (5), e612. https://doi.org/10.1038/cddis.2013.139.

Bomba, M., Granzotto, A., Castelli, V., et al., 2019. Exenatide Reverts the High-Fat-Diet-Induced Impairment of BDNF Signaling and Inflammatory Response in an Animal Model of Alzheimer's Disease. J. Alzheimer'S. Dis. 70 (3), 793–810. https://doi.org/10.3233/jad-190237.

Bu, L.-L., Liu, Y.-Q., Shen, Y., et al., 2021. Neuroprotection of Exendin-4 by Enhanced Autophagy in a Parkinsonian Rat Model of α-Synucleinopathy. Neurotherapeutics 18 (2), 962–978. https://doi.org/10.1007/s13311-021-01018-5.

Cai, H.Y., Hölscher, C., Yue, X.H., et al., 2014. Lixisenatide rescues spatial memory and synaptic plasticity from amyloid β protein-induced impairments in rats. Neuroscience 277, 6–13. https://doi.org/10.1016/j.neuroscience.2014.02.022.

Cai, H.-Y., Wang, Z.-J., Hölscher, C., et al., 2017. Lixisenatide attenuates the detrimental effects of amyloid β protein on spatial working memory and hippocampal neurons in rats. Behav. Brain Res. 318, 28–35. https://doi.org/10.1016/j.bbr.2016.10.033.

Cai, H.-Y., Yang, J.-T., Wang, Z.-J., et al., 2018. Lixisenatide reduces amyloid plaques, neurofibrillary tangles and neuroinflammation in an APP/PS1/tau mouse model of Alzheimer's disease. Biochem. Biophys. Res. Commun. 495 (1), 1034–1040. https://doi.org/10.1016/j.bbrc.2017.11.114.

Carranza-Naval, M.J., del Marco, A., Hierro-Bujalance, C., et al., 2021. Liraglutide Reduces Vascular Damage, Neuronal Loss, and Cognitive Impairment in a Mixed Murine Model of Alzheimer's Disease and Type 2 Diabetes. Orig. Res. *Front. Aging Neurosci.* 13. https://doi.org/10.3389/fnagi.2021.741923.

Chen, S., Liu, A.-r, An, F.-m, Yao, W.-b, Gao, X.-d, 2012. Amelioration of neurodegenerative changes in cellular and rat models of diabetes-related Alzheimer's disease by exendin-4. AGE 34 (5), 1211–1224. https://doi.org/10.1007/s11357-011-9303-8.

Chen, S., Sun, J., Zhao, G., et al., 2017. Liraglutide Improves Water Maze Learning and Memory Performance While Reduces Hyperphosphorylation of Tau and Neurofilaments in APP/PS1/Tau Triple Transgenic Mice. Neurochem. Res. 42 (8), 2326–2335. https://doi.org/10.1007/s11064-017-2250-8.

Chen, S.-D., Chuang, Y.-C., Lin, T.-K., Yang, J.-L., 2023. Alternative role of glucagon-like Peptide-1 receptor agonists in neurodegenerative diseases. Eur. J. Pharmacol. 938, 175439. https://doi.org/10.1016/j.ejphar.2022.175439.

Covidence. September 27, 2024. Accessed November 11, 2024. ⟨https://www.covidence.org/⟩.

Dong, Y., Cheng, L., Zhao, Y., 2022. Resetting the circadian clock of Alzheimer's mice via GLP-1 injection combined with time-restricted feeding. Orig. Res. *Front. Physiol.* 13. https://doi.org/10.3389/fphys.2022.911437.

Duarte, A.I., Candeias, E., Alves, I.N., et al., 2020. Liraglutide Protects Against Brain Amyloid-β1–42 Accumulation in Female Mice with Early Alzheimer's Disease-Like Pathology by Partially Rescuing Oxidative/Nitrosative Stress and Inflammation. Int. J. Mol. Sci. 21 (5), 1746.

Dugger, B.N., Dickson, D.W., 2017. Pathology of Neurodegenerative Diseases. Cold Spring Harb. Perspect. Biol. 9 (7). https://doi.org/10.1101/cshperspect.a028035.

Edison, P., Archer, H.A., Gerhard, A., et al., 2008. Microglia, amyloid, and cognition in Alzheimer's disease: An [11C](R)PK11195-PET and [11C]PIB-PET study. /12/01/ 2008 Neurobiol. Dis. 32 (3), 412–419. https://doi.org/10.1016/j.nbd.2008.08.001.

Forny Germano, L., Koehler, J.A., Baggio, L.L., et al., 2024. The GLP-1 medicines semaglutide and tirzepatide do not alter disease-related pathology, behaviour or cognitive function in 5XFAD and APP/PS1 mice. /11/01/ 2024 Mol. Metab. 89, 102019. https://doi.org/10.1016/j.molmet.2024.102019.

Fricker, M., Tolkovsky, A.M., Borutaite, V., Coleman, M., Brown, G.C., 2018. Neuronal Cell Death. Physiol. Rev. 98 (2), 813–880. https://doi.org/10.1152/physrev.00011.2017.

Garabadu, D., Verma, J., 2019. Exendin-4 attenuates brain mitochondrial toxicity through PI3K/Akt-dependent pathway in amyloid beta (1–42)-induced cognitive deficit rats. Neurochem. Int. 128, 39–49. https://doi.org/10.1016/j.neuint.2019.04.006.

Gault, V.A., Hölscher, C., 2008. GLP-1 agonists facilitate hippocampal LTP and reverse the impairment of LTP induced by beta-amyloid. Eur. J. Pharmacol. 587 (1), 112–117. https://doi.org/10.1016/j.ejphar.2008.03.025.

Gejl, M., Gjedde, A., Egefjord, L., et al., 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. https://doi.org/10.3389/fnagi.2016.00108.

Gengler, S., McClean, P.L., McCurtin, R., Gault, V.A., Hölscher, C., 2012. Val(8)GLP-1 rescues synaptic plasticity and reduces dense core plaques in APP/PS1 mice. Neurobiol. Aging 33 (2), 265–276. https://doi.org/10.1016/j.neurobiolaging.2010.02.014.

Hajieva, P., Bayatti, N., Granold, M., Behl, C., 2014. Membrane protein oxidation determines neuronal degeneration. J. Neurochem. 133. https://doi.org/10.1111/jnc.12987.

Han, W.-N., Hölscher, C., Yuan, L., et al., 2013. Liraglutide protects against amyloid-β protein-induced impairment of spatial learning and memory in rats. Neurobiol. Aging 34 (2), 576–588. https://doi.org/10.1016/j.neurobiolaging.2012.04.009.

Hansen, H.H., Fabricius, K., Barkholt, P., et al., 2015. The GLP-1 Receptor Agonist Liraglutide Improves Memory Function and Increases Hippocampal CA1 Neuronal Numbers in a Senescence-Accelerated Mouse Model of Alzheimer's Disease. J. Alzheimer'S. Dis. 46 (4), 877–888. https://doi.org/10.3233/jad-143090.

Hansen, H.H., Fabricius, K., Barkholt, P., et al., 2016a. Long-Term Treatment with Liraglutide, a Glucagon-Like Peptide-1 (GLP-1) Receptor Agonist, Has No Effect on β-Amyloid Plaque Load in Two Transgenic APP/PS1 Mouse Models of Alzheimer's Disease. PLOS ONE 11 (7), e0158205. https://doi.org/10.1371/journal.pone.0158205.

Hansen, H.H., Barkholt, P., Fabricius, K., et al., 2016b. The GLP-1 receptor agonist liraglutide reduces pathology-specific tau phosphorylation and improves motor function in a transgenic hTauP301L mouse model of tauopathy. Brain Res. 1634, 158–170. https://doi.org/10.1016/j.brainres.2015.12.052.

Hao, L., Shi, M., Ma, J., et al., 2024. A Cholecystokinin Analogue Ameliorates Cognitive Deficits and Regulates Mitochondrial Dynamics via the AMPK/Drp1 Pathway in APP/PS1 Mice. J. Prev. Alzheimer'S. Dis. 11 (2), 382–401.

Hogan, A.E., Gaoatswe, G., Lynch, L., et al., 2014. Glucagon-like peptide 1 analogue therapy directly modulates innate immune-mediated inflammation in individuals with type 2 diabetes mellitus. /04/01 2014 Diabetologia 57 (4), 781–784. https://doi.org/10.1007/s00125-013-3145-0.

Holst, J.J., Burcelin, R., Nathanson, E., 2011. Neuroprotective properties of GLP-1: theoretical and practical applications. Curr. Med. Res. Opin. 27 (3), 547–558. https://doi.org/10.1185/03007995.2010.549466.

Holubová, M., Hrubá, L., Popelová, A., et al., 2019. Liraglutide and a lipidized analog of prolactin-releasing peptide show neuroprotective effects in a mouse model of β-amyloid pathology. Neuropharmacology 144, 377–387. https://doi.org/10.1016/j.neuropharm.2018.11.002.

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 (1), 43. https://doi.org/10.1186/1471-2288-14-43.

Hur, E.-M., Zhou, F.-Q., 2010. GSK3 signalling in neural development. Nat. Rev. Neurosci. 11 (8), 539–551. https://doi.org/10.1038/nrn2870.

Hurley, L.L., Tizabi, Y., 2013. Neuroinflammation, Neurodegeneration, and Depression. Neurotox. Res. 23 (2), 131–144. https://doi.org/10.1007/s12640-012-9348-1.

Jia, X.-T., Ye, T., Yuan, L., et al., 2016. Exendin-4, a glucagon-like peptide 1 receptor agonist, protects against amyloid-β peptide-induced impairment of spatial learning and memory in rats. Physiol. Behav. 159, 72–79. https://doi.org/10.1016/j.physbeh.2016.03.016.

Jiang, P., Zhu, T., Xia, Z., et al., 2015. Inhibition of MAPK/ERK signaling blocks hippocampal neurogenesis and impairs cognitive performance in prenatally infected neonatal rats. Eur. Arch. Psychiatry Clin. Neurosci. 265 (6), 497–509. https://doi.org/10.1007/s00406-015-0588-y.

Khalaf, M.M., El-Sayed, M.M., Kandeil, M.A., Ahmed, S., 2023. A novel protective modality against rotenone-induced Parkinson's disease: A pre-clinical study with dulaglutide. Int. Immunopharmacol. 119, 110170. https://doi.org/10.1016/j.intimp.2023.110170.

Kopp, K.O., Glotfelty, E.J., Li, Y., Greig, N.H., 2022. Glucagon-like peptide-1 (GLP-1) receptor agonists and neuroinflammation: Implications for neurodegenerative disease treatment. Pharmacol. Res. 186, 106550. https://doi.org/10.1016/j.phrs.2022.106550.

Lee, S., Lee, D.Y., 2017. Glucagon-like peptide-1 and glucagon-like peptide-1 receptor agonists in the treatment of type 2 diabetes. Ann. Pedia Endocrinol. Metab. 22 (1), 15–26. https://doi.org/10.6065/apem.2017.22.1.15.

Lei, Z.-N., Liu, F., Zhang, L.-M., Huang, Y.-L., Sun, F.-Y., 2012. Bcl-2 increases stroke-induced striatal neurogenesis in adult brains by inhibiting BMP-4 function via activation of β-catenin signaling. Neurochem. Int. 61 (1), 34–42. https://doi.org/10.1016/j.neuint.2012.04.004.

Li, L., Zhang, Z.-F., Holscher, C., Gao, C., Jiang, Y.-H., Liu, Y.-Z., 2012. Val8) glucagon-like peptide-1 prevents tau hyperphosphorylation, impairment of spatial learning and ultra-structural cellular damage induced by streptozotocin in rat brains. Eur. J. Pharmacol. 674 (2), 280–286. https://doi.org/10.1016/j.ejphar.2011.11.005.

Li, Y., Tweedie, D., Mattson, M.P., Holloway, H.W., Greig, N.H., 2010a. Enhancing the GLP-1 receptor signaling pathway leads to proliferation and neuroprotection in human neuroblastoma cells. J. Neurochem. 113 (6), 1621–1631. https://doi.org/10.1111/j.1471-4159.2010.06731.x.

Li, Y., Duffy, K.B., Ottinger, M.A., et al., 2010b. GLP-1 Receptor Stimulation Reduces Amyloid-β Peptide Accumulation and Cytotoxicity in Cellular and Animal Models of Alzheimer's Disease. J. Alzheimer'S. Dis. 19 (4), 1205–1219. https://doi.org/10.3233/jad-2010-1314.

Llano, D.A., Li, J., Waring, J.F., et al., 2012. Cerebrospinal Fluid Cytokine Dynamics Differ Between Alzheimer Disease Patients and Elderly Controls. Alzheimer Dis. Assoc. Disord. 26 (4).

Long-Smith, C.M., Manning, S., McClean, P.L., et al., 2013. The Diabetes Drug Liraglutide Ameliorates Aberrant Insulin Receptor Localisation and Signalling in Parallel with Decreasing Both Amyloid-β Plaque and Glial Pathology in a Mouse Model of Alzheimer's Disease. NeuroMolecular Med. 15 (1), 102–114. https://doi.org/10.1007/s12017-012-8199-5.

Lopez-Ferreras, L., Asker, M., Krieger, J.-P., Skibicka, K.P., 2023. Sex-divergent effects of hindbrain GLP-1-producing neuron activation in rats. Orig. Res. *Front. Neurosci.* 17. https://doi.org/10.3389/fnins.2023.1265080.

Lutz, T.A., Osto, E., 2016. Glucagon-like peptide-1, glucagon-like peptide-2, and lipid metabolism. Curr. Opin. Lipidol. 27 (3), 257–263. https://doi.org/10.1097/mol.0000000000000293.

Ma, L.-L., Wang, Y.-Y., Yang, Z.-H., Huang, D., Weng, H., Zeng, X.-T., 2020. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better? Mil. Med. Res. 7 (1), 7. https://doi.org/10.1186/s40779-020-00238-8.

Ma, T., Du, X., Pick, J.E., Sui, G., Brownlee, M., Klann, E., 2012. Glucagon-Like Peptide-1 Cleavage Product GLP-1(9-36) Amide Rescues Synaptic Plasticity and Memory Deficits in Alzheimer's Disease Model Mice. J. Neurosci. 32 (40), 13701–13708. https://doi.org/10.1523/jneurosci.2107-12.2012.

Maskery, M., Goulding, E.M., Gengler, S., Melchiorsen, J.U., Rosenkilde, M.M., Hölscher, C., 2020. The Dual GLP-1/GIP Receptor Agonist DA4-JC Shows Superior Protective Properties Compared to the GLP-1 Analogue Liraglutide in the APP/PS1 Mouse Model of Alzheimer's Disease. Am. J. Alzheimer'S. Dis. Other Dement. 35, 1533317520953041. https://doi.org/10.1177/1533317520953041.

McClean, P.L., Hölscher, C., 2014b. Liraglutide can reverse memory impairment, synaptic loss and reduce plaque load in aged APP/PS1 mice, a model of Alzheimer's disease. Neuropharmacology 76, 57–67. https://doi.org/10.1016/j.neuropharm.2013.08.005.

McClean, P.L., Hölscher, C., 2014a. Lixisenatide, a drug developed to treat type 2 diabetes, shows neuroprotective effects in a mouse model of Alzheimer's disease. Neuropharmacology 86, 241–258. https://doi.org/10.1016/j.neuropharm.2014.07.015.

McClean, P.L., Parthsarathy, V., Faivre, E., Hölscher, C., 2011. The Diabetes Drug Liraglutide Prevents Degenerative Processes in a Mouse Model of Alzheimer's Disease. J. Neurosci. 31 (17), 6587–6594. https://doi.org/10.1523/jneurosci.0529-11.2011.

McClean, P.L., Jalewa, J., Hölscher, C., 2015. Prophylactic liraglutide treatment prevents amyloid plaque deposition, chronic inflammation and memory impairment in APP/PS1 mice. Behav. Brain Res. 293, 96–106. https://doi.org/10.1016/j.bbr.2015.07.024.

McIntyre, R.S., Powell, A.M., Kaidanovich-Beilin, O., et al., 2013. The neuroprotective effects of GLP-1: Possible treatments for cognitive deficits in individuals with mood disorders. Behav. Brain Res. 237, 164–171. https://doi.org/10.1016/j.bbr.2012.09.021.

McIntyre, R.S., Rasgon, N., Goldberg, J.F., et al., 2025. The Effect of Glucagon-Like Peptide-1 and Glucose Dependent Insulinotropic Polypeptide Receptor Agonists on Neurogenesis, Differentiation and Plasticity: Potential Mechanistically-Informed Therapeutics in the Treatment and Prevention of Mental Disorders. CNS Spectr. 1–25. https://doi.org/10.1017/S1092852925000124.

Meissner, W.G., Remy, P., Giordana, C., et al., 2024. Trial of Lixisenatide in Early Parkinson's Disease. N. Engl. J. Med. 390 (13), 1176–1185. https://doi.org/10.1056/NEJMoa2312323.

Mullins, R.J., Mustapic, M., Chia, C.W., et al., 2019. A Pilot Study of Exenatide Actions in Alzheimer's Disease. Curr. Alzheimer Res. 16 (8), 741–752. https://doi.org/10.2174/1567205016666190913155950.

Muscogiuri, G., DeFronzo, R.A., Gastaldelli, A., Holst, J.J., 2017. Glucagon-like Peptide-1 and the Central/Peripheral Nervous System: Crosstalk in Diabetes. Trends Endocrinol. Metab. 28 (2), 88–103. https://doi.org/10.1016/j.tem.2016.10.001.

Page, M.J., Moher, D., Bossuyt, P.M., et al., 2021. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 372, n160. https://doi.org/10.1136/bmj.n160.

Paladugu, L., Gharaibeh, A., Kolli, N., et al., 2021. Liraglutide Has Anti-Inflammatory and Anti-Amyloid Properties in Streptozotocin-Induced and 5xFAD Mouse Models of Alzheimer's Disease. Int. J. Mol. Sci. 22 (2), 860.

Perry, T., Lahiri, D.K., Sambamurti, K., et al., 2003. Glucagon-like peptide-1 decreases endogenous amyloid-β peptide (Aβ) levels and protects hippocampal neurons from death induced by Aβ and iron. J. Neurosci. Res. 72 (5), 603–612. https://doi.org/10.1002/jnr.10611.

Pluta, R., Ułamek-Kozioł, M., Januszewski, S., Czuczwar, S.J., 2020. Participation of Amyloid and Tau Protein in Neuronal Death and Neurodegeneration after Brain Ischemia. Int. J. Mol. Sci. 21 (13), 4599.

Qi, L., Ke, L., Liu, X., et al., 2016. Subcutaneous administration of liraglutide ameliorates learning and memory impairment by modulating tau hyperphosphorylation via the glycogen synthase kinase-3β pathway in an amyloid β protein induced alzheimer disease mouse model. Eur. J. Pharmacol. 783, 23–32. https://doi.org/10.1016/j.ejphar.2016.04.052.

Robinson, A., Lubitz, I., Atrakchi-Baranes, D., et al., 2019. Combination of Insulin with a GLP1 Agonist Is Associated with Better Memory and Normal Expression of Insulin Receptor Pathway Genes in a Mouse Model of Alzheimer's Disease. J. Mol. Neurosci. 67 (4), 504–510. https://doi.org/10.1007/s12031-019-1257-9.

Rozani, V., Bezimianski, M.G., Azuri, J., Bitan, M., Peretz, C., 2024. Anti-diabetic drug use and reduced risk of Parkinson's disease: A community-based cohort study. Park. Relat. Disord. 128. https://doi.org/10.1016/j.parkreldis.2024.107132.

Salles, G.N., Calió, M.L., Afewerki, S., et al., 2018. Prolonged Drug-Releasing Fibers Attenuate Alzheimer's Disease-like Pathogenesis. ACS Appl. Mater. Interfaces 10 (43), 36693–36702. https://doi.org/10.1021/acsami.8b12649.

Salles, G.N., Calió, M.L., Hölscher, C., Pacheco-Soares, C., Porcionatto, M., Lobo, A.O., 2020. Neuroprotective and restorative properties of the GLP-1/GIP dual agonist DA-JC1 compared with a GLP-1 single agonist in Alzheimer's disease. Neuropharmacology 162, 107813. https://doi.org/10.1016/j.neuropharm.2019.107813.

Sengupta, U., Kayed, R., 2022. Amyloid β, Tau, and α-Synuclein aggregates in the pathogenesis, prognosis, and therapeutics for neurodegenerative diseases. Prog. Neurobiol. 214, 102270. https://doi.org/10.1016/j.pneurobio.2022.102270.

Shu, X., Zhang, Y., Li, M., et al., 2019. Topical ocular administration of the GLP-1 receptor agonist liraglutide arrests hyperphosphorylated tau-triggered diabetic retinal neurodegeneration via activation of GLP-1R/Akt/GSK3β signaling. Neuropharmacology 153, 1–12. https://doi.org/10.1016/j.neuropharm.2019.04.018.

Song, X., Sun, Y., Wang, Z., Su, Y., Wang, Y., Wang, X., 2022. Exendin-4 alleviates β-Amyloid peptide toxicity via DAF-16 in a Caenorhabditis elegans model of Alzheimer's disease. Orig. Res. Front. Aging Neurosci. 14. https://doi.org/10.3389/fnagi.2022.955113.

Study Quality Assessment Tools. National Heart Lung and Blood Institute. Accessed November 11, 2024. ⟨http://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools⟩.

Teleanu, D.M., Niculescu, A.-G., Lungu, I.I., et al., 2022. An Overview of Oxidative Stress, Neuroinflammation, and Neurodegenerative Diseases. Int. J. Mol. Sci. 23 (11), 5938. https://doi.org/10.3390/ijms23115938.

Velmurugan, K., Bouchard, R., Mahaffey, G., Pugazhenthi, S., 2012. Neuroprotective actions of Glucagon-like peptide-1 in differentiated human neuroprogenitor cells. J. Neurochem. 123 (6), 919–931. https://doi.org/10.1111/jnc.12036.

Vijiaratnam, N., Girges, C., Auld, G., et al., 2025. Exenatide once a week versus placebo as a potential disease-modifying treatment for people with Parkinson's disease in the UK: a phase 3, multicentre, double-blind, parallel-group, randomised, placebo-controlled trial. Lancet 405 (10479), 627–636. https://doi.org/10.1016/S0140-6736(24)02808-3.

Wang, X., Wang, L., Xu, Y., Yu, Q., Li, L., Guo, Y., 2016. Intranasal administration of Exendin-4 antagonizes Aβ31–35-induced disruption of circadian rhythm and impairment of learning and memory. Aging Clin. Exp. Res. 28 (6), 1259–1266. https://doi.org/10.1007/s40520-016-0548-z.

Wang, X.H., Li, L., Hölscher, C., Pan, Y.F., Chen, X.R., Qi, J.S., 2010. Val8-glucagon-like peptide-1 protects against Aβ1-40-induced impairment of hippocampal late-phase long-term potentiation and spatial learning in rats. Neuroscience 170 (4), 1239–1248. https://doi.org/10.1016/j.neuroscience.2010.08.028.

Wang, Y., Chen, S., Xu, Z., Chen, S., Yao, W., Gao, X., 2018. GLP-1 receptor agonists downregulate aberrant GnT-III expression in Alzheimer's disease models through the Akt/GSK-3β/β-catenin signaling. Neuropharmacology 131, 190–199. https://doi.org/10.1016/j.neuropharm.2017.11.048.

Wang, Z.-J., Li, X.-R., Chai, S.-F., et al., 2023. Semaglutide ameliorates cognition and glucose metabolism dysfunction in the 3xTg mouse model of Alzheimer's disease via the GLP-1R/SIRT1/GLUT4 pathway. Neuropharmacology 240, 109716. https://doi.org/10.1016/j.neuropharm.2023.109716.

Xie, Y., Zheng, J., Li, S., et al., 2021. GLP-1 improves the neuronal supportive ability of astrocytes in Alzheimer's disease by regulating mitochondrial dysfunction via the cAMP/PKA pathway. Biochem. Pharmacol. 188, 114578. https://doi.org/10.1016/j.bcp.2021.114578.

Xiong, H., Gong, C., Alonso, A., et al., 2013. The Neuroprotection of Liraglutide on Alzheimer-Like Learning and Memory Impairment by Modulating the Hyperphosphorylation of Tau and Neurofilament Proteins and Insulin Signaling Pathways in Mice. J. Alzheimer'S. Dis. 37 (3), 623–635. https://doi.org/10.3233/jad-130584.

Yang, S., Zhao, X., Zhang, Y., et al., 2024. Tirzepatide shows neuroprotective effects via regulating brain glucose metabolism in APP/PS1 mice. Peptides 179, 171271. https://doi.org/10.1016/j.peptides.2024.171271.

Yang, Z., Zou, Y., Wang, L., 2023. Neurotransmitters in Prevention and Treatment of Alzheimer's Disease. Int. J. Mol. Sci. 24 (4), 3841.

Zhang, L., Zhang, L., Li, L., Hölscher, C., 2019. Semaglutide is Neuroprotective and Reduces α-Synuclein Levels in the Chronic MPTP Mouse Model of Parkinson's Disease. J. Park. Dis. 9 (1), 157–171. https://doi.org/10.3233/jpd-181503.

Zhang, L., Li, C., Zhang, Z., et al., 2022b. DA5-CH and Semaglutide Protect against Neurodegeneration and Reduce α-Synuclein Levels in the 6-OHDA Parkinson's Disease Rat Model. Park. 'S. Dis. 2022 (1), 1428817. https://doi.org/10.1155/2022/1428817.

Zhang, L.-Y., Jin, Q.-Q., Hölscher, C., Li, L., 2021. Glucagon-like peptide-1/glucose-dependent insulinotropic polypeptide dual receptor agonist DA-CH5 is superior to exendin-4 in protecting neurons in the 6-hydroxydopamine rat Parkinson model. Neural Regen. Res. 16 (8), 1660–1670. https://doi.org/10.4103/1673-5374.303045.

Zhang, M., Wu, Y., Gao, R., Chen, X., Chen, R., Chen, Z., 2022a. Glucagon-like peptide-1 analogs mitigate neuroinflammation in Alzheimer's disease by suppressing NLRP2 activation in astrocytes. Mol. Cell. Endocrinol. 542, 111529. https://doi.org/10.1016/j.mce.2021.111529.

Zhang, Z., Shi, M., Li, Z., et al., 2023. A Dual GLP-1/GIP Receptor Agonist Is More Effective than Liraglutide in the A53T Mouse Model of Parkinson's Disease. Park. 'S. Dis. 2023 (1), 7427136. https://doi.org/10.1155/2023/7427136.

Zhou, M., Chen, S., Peng, P., et al., 2019. Dulaglutide ameliorates STZ induced AD-like impairment of learning and memory ability by modulating hyperphosphorylation of tau and NFs through GSK3β. Biochem. Biophys. Res. Commun. 511 (1), 154–160. https://doi.org/10.1016/j.bbrc.2019.01.103.