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REVIEW

Treating cognitive impairment in schizophrenia with GLP-1RAs: an overview of their therapeutic potential

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ABSTRACT

Introduction: Schizophrenia is a neuropsychiatric disorder that affects approximately 1% of individuals worldwide. There are no available medications to treat cognitive impairment in this patient population currently. Preclinical evidence suggests that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) improve cognitive function. There is a need to evaluate how GLP-1 RAs alter specific domains of cognition and whether they will be of therapeutic benefit in individuals with schizophrenia.

Areas covered: This paper summarizes the effects of GLP-1 RAs on metabolic processes in the brain and how these mechanisms relate to improved cognitive function. We provide an overview of preclinical studies that demonstrate GLP-1 RAs improve cognition and comment on their potential therapeutic benefit in individuals with schizophrenia.

Expert Opinion: To understand the benefits of GLP-1 RAs in individuals with schizophrenia, further preclinical research with rodent models relevant to schizophrenia symptomology are needed. Moreover, preclinical studies must focus on using a wider range of behavioral assays to understand whether important aspects of cognition such as executive function, attention, and goal-directed behavior are improved using GLP-1 RAs. Further research into the specific mechanisms of how GLP-1 RAs affect cognitive function and their interactions with antipsychotic medication commonly prescribed is necessary.

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1. Introduction

The treatment of schizophrenia remains a monumental challenge within medicine as current medications fail to address core symptoms within the disorder. On average, individuals with schizophrenia experience a 14.5-year decrease in life expectancy [1]. In large part this is driven by an increased vulnerability toward cardiovascular disease, diabetes, and obesity [2]. Even at the onset of schizophrenia diagnosis, impaired glucose homeostasis and insulin resistance are present [3]. Crucially, in a population vulnerable to metabolic disturbances [4], antipsychotics only worsen metabolic dysregulation [5–7].

Metabolic dysregulation may also exacerbate cognitive dysfunction in schizophrenia. Metabolic syndrome and diabetes are both associated with cognitive impairment, a core disabling feature of the disease that reduces individuals' functional outcome and quality of life [8–10]. Individuals with schizophrenia exhibit marked deficits in many domains of cognition including executive function, working memory, processing speed, attention, and visual/verbal learning [11]. These cognitive deficits persist despite antipsychotic medications successfully treating positive symptoms within the disorder [12] This makes the identification of novel treatments for cognitive impairment within schizophrenia vital.

Given the potential relationship between altered metabolic function and cognition, numerous therapies have been investigated in the hopes of improving central nervous system insulin action and cognition. Glucagon-like peptide-1 is an endogenous hormone that exerts action over insulin-signaling pathways and mediates insulin and glucose levels [13]. Mounting evidence shows glucagon-like peptide-1 receptor agonists (GLP-1 RAs) regulate cellular pathways involved in neuroinflammation, neuroplasticity, and neurotransmission. GLP-1 RAs are effective in reducing weight [14], improving glycemic regulation [15], and their potential in exerting neuroprotective effects is of relevance in schizophrenia and other neuropsychiatric disorders where brain insulin dysregulation occurs [16,17]. Here we will provide an overview of the importance of insulin signaling in cognition in addition to the potential mechanisms by which GLP-1 RAs may improve cognition. Finally, we will explore the existing preclinical evidence that GLP-1 RAs improve cognition and comment on their potential as an adjunctive treatment for schizophrenia.

2. Methods

In this narrative review, we included publications containing preclinical studies examining GLP-1 RAs and their effects on cognition in animal models relevant to metabolic dysregulation and neuropsychiatric disease. For a study to be included, one or more aspects of cognition had to be measured within

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Article Highlights

- Individuals with schizophrenia experience an increased incidence of metabolic dysfunction that co-occurs with cognitive impairment.
- GLP-1RAs are currently used to reduce metabolic side-effects caused by antipsychotics. However, further investigation is required to assess whether they can improve cognition in individuals with schizophrenia.
- Preclinical testing of GLP-1RAs in animal models that recapitulate key cognitive deficits in schizophrenia is needed. We suggest that future studies should utilize translational rodent assays such as touch-screen testing to investigate the effects of GLP-1RAs on executive function, attention, and working memory.
- Adjunctive treatment with other antipsychotic medication may offer an effective strategy to counter weight-gain and improve cognitive status in individuals with schizophrenia. Further research is required to understand whether newer GLP-1RAs are effective in reducing weight and improving cognition.

the study and include the use of a GLP-1 RA as a treatment group. We used the guidelines outlined by the Joanna Briggs Institute (JBI) for narrative reviews [18]. Searches included studies in both English and non-English. We searched the databases of PubMed, Google Scholar, SCOPUS, Web of science, and PsycInfo from inception until March 1 2021. Our search strategy on PubMed was ((GLP-1 RA*) OR (GLP-1 agonist*) OR liraglutide OR exenatide) AND ((metabolism) AND (cognition)) AND (((schizophrenia) OR (animal) OR (diabetes) OR (Alzheimer's disease) OR (bipolar disorder) OR (neuropsychiatric disease))) and subsequently adapted to the requirements of other databases searched.

3. Cognitive and metabolic dysfunction in schizophrenia

Alongside positive and negative symptoms, cognitive impairment is considered a cardinal feature of schizophrenia [19]. More than 80% of individuals with schizophrenia exhibit cognitive impairment [8]. Although its presentation varies between individuals, cognitive impairment contributes to the long-term burden associated with the disease and leads to reduced quality of life [20]. Numerous cognitive domains are impaired in schizophrenia including verbal learning and memory, visual learning and memory, reasoning and problem solving, attention, and processing speed [21]. While a number of treatments for cognitive impairment have been investigated, therapeutic options remain limited [22]. Furthermore, first- and second-generation antipsychotics appear to have limited efficacy in improving cognition [23] and appear to exacerbate metabolic dysfunction [6,24].

Individuals with schizophrenia experience severe dysregulation in metabolic functioning even prior to the onset of illness [25]. Metabolic syndrome refers to a cluster of cardiovascular risk factors, including insulin resistance, obesity, atherogenic dyslipidemia, and hypertension [26]. The incidence of metabolic syndrome is approximately 33.5% in schizophrenia [27]. A range of lifestyle, biological, and genetic factors associated with schizophrenia contribute to this elevated risk. Greater sedentary lifestyle and poorer diet choices are common in schizophrenia [28,29]. Additionally, genes related to insulin signaling [30], glucose metabolism [31], and inflammation [32] are altered in schizophrenia. Crucially, antipsychotics that are used to treat positive symptoms increase the prevalence of diabetes and metabolic syndrome in individuals with schizophrenia.

Convergent evidence suggests that there is an overlap between cognitive impairment and metabolic abnormalities in schizophrenia. As reviewed by MacKenzie and colleagues [6], several genes such as the methylenetetrahydrofolate reductase gene and serotonin receptor gene 5HT2A are associated with an increased risk of metabolic abnormalities and deficits in cognitive flexibility, attention, and verbal recall [33]. Clinical studies show that individuals with schizophrenia and co-morbid diabetes show lower global cognitive function [34]. Specifically, deficits in attention, processing speed, memory, and reasoning are more severe in those with schizophrenia with co-morbid metabolic syndrome compared to those with schizophrenia alone [8,35]. This is consistent with evidence that cognitive impairment is associated with metabolic abnormalities independent of schizophrenia. Overall, metabolic syndrome, obesity, and diabetes are all associated with impairments in cognitive functioning [36–38].

3.1. Insulin signaling as a common pathway to cognitive impairment in schizophrenia

Even before the widespread use of antipsychotic treatment, a unique vulnerability toward impaired insulin action was observed in schizophrenia [39]. Insulin resistance is defined as a state where there is failure of exogenous and endogenous insulin to increase glucose uptake and utilization [40]. Around 15% of antipsychotic drug naïve patients with schizophrenia show insulin resistance [41]. Critically, antipsychotics contribute to increased insulin resistance [42]. Reduced insulin receptor signaling in the dorsolateral prefrontal cortex has been found in postmortem samples of individuals with schizophrenia [43]. Magnetic resonance spectroscopy shows brain insulin resistance is associated with impairments in verbal memory in individuals with schizophrenia [44]. Additionally, research using animal models shows that insulin resistance induced by high-fat diets is associated with impairments in learning and memory [45].

Insulin receptors are widely distributed in the brain [46,47] and insulin readily crosses the blood–brain barrier [48]. Insulin receptor signaling has a regulatory role in cerebral glucose metabolism, hedonic, and non-hedonic aspects of feeding, and levels of midbrain dopamine and glutamate transmission [5]. Single-cell digital polymerase-chain reaction in the rat cerebral cortex shows insulin is also expressed in gamma-aminobutyric acid (GABA)-ergic neurogliaform cells [49]. This local insulin secretion is thought to support the synaptic function necessary for normal excitatory and inhibitory function. Indeed insulin also plays a role in regulating synaptic plasticity by recruiting $GABA_A$ receptors to postsynaptic membranes within the central nervous system [50]. Insulin has neurotrophic functions within the brain that regulate neuronal proliferation [51] and neurite growth [52]. Insulin also plays a neuroprotective role in the brain in a dose-dependent manner, preventing cell death [53] and protecting against

oxidative stress in cortical neurons [54]. All these function to support aspects of cognitive functioning that are known to be impaired in individuals with schizophrenia.

One of the primary signaling pathways of insulin is the via the AKT1/GSK3 signaling pathway. This pathway has been implicated in the pathogenesis of schizophrenia through several genetic linkage studies that show a significant association between an AKT1 haplotype and development of the disease [55]. AKT1 is reduced in the hippocampus and frontal cortex of those with schizophrenia compared to healthy subjects [55]. Efforts to link alterations in these pathways have looked at the association between AKT1 single nucleotide polymorphisms (SNPs) and specific domains of cognition. For example, Tan and colleagues [56] found that variants in AKT1 SNPs were associated with deficits in cognition such as executive functioning and processing speed. Abnormal GSK3 signaling has also been reported in schizophrenia patients. Examination of postmortem brain tissue from patients with schizophrenia has revealed decreased phosphorylation levels and GSK-3B protein levels in the frontal cortex, and decreased GSK-3B mRNA levels in the dorsolateral prefrontal cortex [55,57,58]. N-methyl-D-aspartate (NMDA) receptor hypofunction also plays a key role in the cognitive dysfunction seen in schizophrenia and is important for learning and memory [59]. Several studies have also demonstrated that GSK3 influences cell trafficking and cell surface expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors [60,61]. Additionally, the AKT/GSK3 signaling pathway directly regulates synaptic plasticity and down regulates neuroinflammation [62,63].

In summary, cognitive dysfunction is a core feature of schizophrenia and contributes to a lower quality of life [20]. No effective interventions exist to improve cognitive deficits in individuals with schizophrenia [64] and current antipsychotics exacerbate metabolic dysregulation already present before the onset of the disease [6]. Insulin resistance and aberrant insulin signaling features in diabetes and metabolic syndrome and is also present in individuals with schizophrenia. Taken together, the evidence from these studies indicates that therapeutic interventions that improve insulin signaling and metabolic function may also have a beneficial impact on cognition within the brain.

4. GLP-1RA therapeutic mechanisms of action: insulin signaling, neurotransmission, neuroprotection, neuroinflammation, synaptic plasticity

GLP-1 is an incretin hormone that exerts action over insulin-signaling pathways and mediates insulin and glucose levels [13]. GLP-1Rs are widely distributed throughout the human and rodent brain with GLP-1R binding found within the cerebral cortex, thalamus, hypothalamus, substantia nigra, circumventricular organ, hippocampus, cerebellum, and brainstem nucleus [65–67]. GLP-1RAs are currently used to treat obesity and insulin resistance in diabetes [68]. Additionally, preliminary clinical and preclinical studies suggest GLP-1RAs have therapeutic efficacy in improving cognition and preventing cognitive decline in neuropsychiatric disorders [69].

GLP-1RAs have direct modulatory effects on insulin signaling pathways that may benefit cognition. In preclinical animal models of Alzheimer's disease, GLP-1RAs reduces brain insulin resistance [70] and amplifies insulin signaling [71]. GLP-1R agonism also activates cyclic adenosine monophosphate (cAMP) [72]. This in turn promotes neuronal development, neuroprotection, attenuate oxidative stress, and neuroinflammation independent of insulin signaling [73–75]. By reducing cellular damage that accumulates over time, GLP-1R agonism may mitigate the consequences of aberrant insulin signaling and alleviate cognitive impairment.

GLP-1RAs may also act to restore alterations in neurotransmitter function which may benefit cognition. Alterations in glutamate and GABA have long been thought to contribute to the neuropathology of schizophrenia [76,77]. One of the most influential hypotheses is that NMDA receptor hypofunction may disrupt excitatory and inhibitory neurotransmission in the brain, contributing to cognitive impairment in schizophrenia [71]. NMDA receptors are a subtype of the ionotropic glutamate receptor family and play a crucial role in regulating synaptic development, neuroplasticity, and differentiation [71]. Postmortem brain tissues from individuals with schizophrenia shows hypofunction of NMDA receptor subunits [78]. Importantly, ketamine administration has been broadly shown to induce cognitive impairments in animals and healthy human individuals that are similar to those seen in schizophrenia [79]. Additionally, levels of GluN1 are decreased in the hippocampus of postmortem tissue samples from individuals with schizophrenia [80]. Furthermore, elevated glutamate levels, due to reduced glutamate uptake, have been demonstrated in H-MRS studies in individuals with schizophrenia during their first episode of psychosis [81]. The GLP-1RA exendin-4 reversed decreases in glutamate uptake and increased GluN1 content in an animal model of diabetes mellitus, and increased glutamate uptake in astrocyte cell cultures and hippocampal slices in vitro [82]. NMDA function is also important for regulating neuroplasticity in the brain including synaptic plasticity, the ability of a synapse between two neurons to change in strength over time, and non-synaptic plasticity which itself is a modification of the intrinsic excitability of the neuron mediated through changes in structures, such as the soma, axon, or dendrites [83].

Inhibitory neurotransmission within the prefrontal cortex is critical for maintaining normal cognitive function, and postmortem studies of brain tissue from those with schizophrenia have shown that there is a decrease in GAD67, the synthesizing enzyme for GABA, which subsequently alters inhibitory neurotransmission and contributes to cognitive dysfunction [84]. It has been demonstrated that GLP-1R analogues act to enhance GABA signaling within the hippocampus [85] and to upregulate $GABA_A$ receptors in the prefrontal cortex. This make sense given GLP-1RAs activate similar downstream signaling cascades as insulin receptors that have also been demonstrated to restore GABA function [86,87].

GLP-1RAs may also normalize insulin signaling within the brain, stimulating neuroplasticity. GLP-1R analogues have

been shown to increase long-term plasticity in the CA1 of the hippocampus [88] and prevent apoptosis occurring due to excessive glutamate release [89], a phenomenon that occurs in schizophrenia [90]. GLP-1RAs may also act to stimulate the release of brain-derived neurotrophic factor (BDNF), a growth factor that regulates activity-dependent neuroplasticity, important for learning and memory and low levels of which have been linked to poorer cognitive performance in individuals with schizophrenia [91].

Another potential mechanism by which GLP-1RAs may improve cognitive function is by reducing neuroinflammation. Schizophrenia is characterized by significant structural changes that include gray and white matter volume loss that are progressive over the course of the illness [92]. Neuroinflammation has been proposed as a potential pathophysiological mechanism by which these structural abnormalities may arise and worsen cognition in the disorder. Specifically, changes in inflammatory cytokines including interleukins 1 and 6 (IL-1, IL-6) and tumor necrosis factor alpha (TNF-α) are associated with a deterioration of cognitive function [93]. At the onset of illness, individuals with first-episode psychosis display a consistent co-occurrence of metabolic and inflammatory changes [94,95]. A recent study investigating changes in biomarkers in those with first-episode psychosis identified an increase in inflammatory markers MIP-1b/CCL4, VEGF, IL-6, and PAI-1, while IL-17 and metabolic regulators ghrelin, glucagon, and GLP-1R were decreased in these individuals [94]. Given the evidence that the 2–5 year period after first-episode psychosis is crucial in the evolution and long-term prognosis of the disease [96], the pro-inflammatory actions of incretin mimetics may represent a potential ameliorative effect in the long-term prognosis of the disorder on inflammatory, metabolic, and cognitive processes. One pathway by which GLP-1RAs may decrease neuroinflammation is supressing TNF – α as has been demonstrated in vitro [97]. Furthermore, in a rat model of Alzheimer's disease where intracerebroventricular streptozotocin was infused to induce hyperglycemia with concomitant intraperitoneal exenatide injections over 2 weeks, TNF-α levels remained stable in animals administered a GLP-1R agonist compared to rats that did not receive it. While the relationship between immune function disruption and glucose homeostasis is still being uncovered in schizophrenia, it is important to note many of the inflammatory cytokines exert pleiotropic effects within the body and undergo changes after antipsychotic administration. IL-1 and IL-6 for example are key mediators of the anti-obesity effects of GLP-1R [98], yet their elevation at the onset of schizophrenia has been linked with disturbances in glucose utilization [32]. IL-6 also shows decreased levels after antipsychotic administration in schizophrenia individuals [99] which may be a consequence of weight gain, suggesting the importance of intervening at the onset of illness to mitigate long-term metabolic dysregulation and subsequent cognitive impairment. Given the evidence that peripheral immune changes within schizophrenia can modulate brain function and behavior, GLP-1RAs have therapeutic potential as an adjunctive therapy, especially at the onset of illness.

5. GLP-1RA effects on cognition in preclinical research

GLP-1RA analogues have been used in a variety of animal disease models to examine their efficacy in improving cognition. In addition to treating altered metabolic functioning in diseases such as diabetes, GLP-1RAs have the potential to improve cognition in neuropsychiatric diseases that share underlying pathophysiology with diseases of metabolic dysregulation. Preclinical studies demonstrate GLP-1RAs exert beneficial effects on several cognitive domains, such as executive function, spatial learning and memory, and recognition memory. Models of diabetes that recapitulate metabolic abnormalities such as impaired glucose homeostasis, obesity, and impaired insulin sensitivity have all shown that GLP-1RAs can improve glucose homeostasis and improve memory [100–104]. Yang and colleagues [104] recently showed that in Goto Kakizaki (GK) rats with disrupted glucose homeostasis, liraglutide improves spatial learning and memory on the Morris water maze. Alterations in signaling cascade pathways related to insulin such as PI3K, Akt, AMPK, and mTOR were reversed in the treatment group compared to controls. In a model of juvenile diabetes mellitus, Iwai, and colleagues [105] showed GLP-1 improved learning and memory on a Y-maze test. This was confirmed by Palleria and colleagues [102] also showing liraglutide lead to improvements in spatial learning and memory on the Morris water maze and passive avoidance in a model of juvenile diabetes mellitus. Liraglutide also lead to reduced hippocampal neuronal cell death and a reduction of alterations in the insulin signaling cascade in this study, suggesting targeting the metabolic alterations present in the model is central to its procognitive effects.

Alzheimer's disease is a neurodegenerative disorder whereby patients also exhibit altered glucose regulation from hyperinsulinemia and insulin resistance [106,107]. Within transgenic models of Alzheimer's disease, GLP-1RAs also appear to be effective in alleviating memory deficits that are apparent in animal models and human patients [108,109]. Chen and colleagues [110] used an APP/PS1/Tau triple transgenic model while administering liraglutide for 8 weeks. It was found that liraglutide treatment alleviated deficits in escape latency and time to find the platform in the Morris water maze. Alterations to JNK and ERK signaling were also normalized, suggesting improvement of cellular metabolism. Similarly, Long-Smith and colleagues [111] found that in APP/PS1 mice, 8 weeks of treatment with liraglutide was effective in improving spatial learning and memory on the Morris water maze. This improvement was also seen in a reversal phase of the task. Interestingly, improved recall was associated with significantly better long-term potentiation in the CA1 area of these mice. The findings from Mclean and Hölscher [112] also demonstrated liraglutide increased long-term potentiation in the hippocampus, and Hansen and colleagues [113] have demonstrated that liraglutide increases CA1 pyramidal neuron number. Research by Tai and colleagues [114] also confirms that liraglutide increases spatial learning and memory in models of Alzheimer's disease, but also decreases markers of neuroinflammation and increases neurogenesis within the hippocampus.

Limited research exists demonstrating GLP-1RAs improve cognition in animal models of schizophrenia, depression, or bipolar disorder. Filho and colleagues [115] recently investigated whether liraglutide could reverse memory deficits in an amphetamine-induced model of bipolar disorder. The effect of liraglutide was observed in monotherapy or combined with lithium to observe its effectiveness against amphetamine-induced mania-like symptoms of bipolar disorder. They found liraglutide on its own showed efficacy in reversing deficits in amphetamine-induced hyperlocomotion, executive function and spatial learning and memory deficits, but did not reverse risk-taking behavior and fear learning impairments. When combined with lithium, liraglutide was effective in reversing most behavioral changes and successfully reversed the pro-oxidative measures associated with the model. To examine potential effects of liraglutide in a rodent model relevant to depression, Kamble and colleagues [116] administered liraglutide in rats and mice to see whether antidepressive and anti-anxiolytic effects could be observed. Performance was examined on the elevated plus maze, Morris water maze, forced swim test, and T-maze test. Memory deficits were induced by scopolamine or pentylenetetrazole and administration of liraglutide prior to testing showed an improvement of performance on the Morris water maze.

Liraglutide has also been found to improve spatial learning and memory impairments when metabolic dysregulation is present. Babic and colleagues [117] showed liraglutide reduced olanzapine-induced weight gain and glucose intolerance in a cohort of rats that received liraglutide co-administered with either olanzapine or clozapine. Importantly, liraglutide prevented working memory deficits on the T-maze test when liraglutide was administered alongside olanzapine in rats. Within schizophrenia there is a complex interplay of preexisting metabolic dysfunction and the metabolic side-effects induced by antipsychotics that worsen these symptoms. This study suggests that liraglutide may be effective at improving measures of cognition related to memory when metabolic dysregulation is present, however, further human studies are needed to confirm whether GLP-1RAs can improve cognition from the onset of illness.

Current preclinical evidence suggests that GLP-1RAs such as liraglutide and exenatide are effective at improving spatial learning and memory, recognition memory, episodic memory, and recognition memory. When used in conjunction with psychiatric medications such as lithium, clozapine, and olanzapine, it is effective in reducing metabolic dysregulation and preventing cognitive impairment in rodent models of schizophrenia, depression, and bipolar disorder. The evidence that GLP-1RAs improve executive function is limited and other domains of cognition such as processing speed and goal-directed behavior require further investigation. In addition, variations in treatment administration method, duration of administration, and differences in dosing regimens make it difficult to directly compare studies. Furthermore, a causal mechanism of how GLP-1RAs exert their procognitive effect is still needed. However, it is important to highlight that GLP-1RAs improve cognition in models of diabetes as well as neurodegenerative diseases such as Alzheimer's disease suggesting that the improvements in cognition function are not dependent on glucose normalization. GLP-1RAs appear to have a multifunctional throughout the brain by influencing important metabolic processes that are neuroprotective. GLP-1RAs increase long-term potentiation within the hippocampus, improve alterations in insulin signaling. Furthermore they act to decrease neuroinflammation, oxidative stress, and apoptosis within the brain.

6. GLP-1RAs effects on cognition in clinical research

Current clinical research shows mixed evidence regarding the efficacy of GLP-1RAs to improve cognition in individuals with schizophrenia. Ishøy and colleagues [118] investigated whether exenatide-enhanced cognitive performance on the Brief Assessment of Cognition in Schizophrenia test but found no improvement in measures of verbal memory and learning, working memory, motor function, verbal fluency, and executive function. As has been noted previously by Agarwal and colleagues [5], individuals also did not lose weight in this study, suggesting there could be a confounding factor such as duration of treatment or dose that explains the negative findings. In contrast, liraglutide has been shown to improve executive function and memory in individuals with major depressive disorder and bipolar [119] and improve memory in obese individuals with prediabetes or early type 2 diabetes [120]. However, further clinical trials are needed to establish these benefits in individuals with schizophrenia.

7. Conclusion

While antipsychotic treatment for schizophrenia primarily targets dopamine neurotransmitter systems within the brain to effectively alleviate positive symptoms, it has shown limited ability to improve cognitive deficits in schizophrenia. Current preclinical evidence shows that GLP-1RAs improve metabolic dysregulation and may also exert beneficial effects on cognitive function. GLP-1RAs clearly exert neuroprotective effects within the brain through influencing neurogenesis and synaptic plasticity, neuroinflammation, neurotransmission, insulin signaling transduction, neuroapoptosis, and reducing oxidative damage [121] and may also be useful in attenuating metabolic dysregulation found in antipsychotic naïve individuals and those who are undertaking antipsychotic treatment. Although the molecular pathways by which GLP-1RAs signal through have been identified, the direct mechanism by which incretin mimetics may improve cognitive processes are yet to be elucidated and require further research. Current clinical research has also demonstrated partial evidence that GLP-1R agonism may improve cognitive performance yet further research is required to validate a plausible mechanism by which GLP-1RAs improve cognition. A bias in the literature exists toward focusing primarily on models of diabetes and Alzheimer's disease to observe the potentially beneficial effects of GLP-1RAs on cognition. Consequently, further studies are needed on the effects of GLP-1RAs in models of schizophrenia in order to demonstrate

predictive validity of the drug for this patient population. Given the range of pathophysiological mechanisms that may be responsible for cognitive impairment, modeling combined metabolic and schizophrenia-related cognitive dysfunction using animal models to increase the translational relevance of the findings is essential.

8. Expert opinion

Impaired insulin signaling has been identified as a feature of schizophrenia, diabetes, and numerous neuropsychiatric diseases. Given the important role insulin has in cognitive function, the identification of novel therapies to normalize insulin signaling within the brain represents an important therapeutic target. GLP-1RAs are a promising therapeutic candidate and preclinical research shows they protect neuronal function through improvement of insulin signaling, neurotransmission, neuroinflammation, and synaptic plasticity. However, further research is still needed to elucidate the direct mechanism by which GLP-1RAs improve cognition and whether this effect translates to humans.

Despite promising preclinical evidence of GLP-1RAs improving memory, other domains of cognition have not yet been thoroughly investigated. To address this, future researchers may consider using cognitive assays in rodents that have translational relevance in humans. Initiatives such as the RDoC matrix [122] have highlighted that research into cognitive-enhancing drugs should become more focused on cognitive domain-based testing. The development of technology such as touchscreen cognitive testing [123] means we are now capable of standardizing tasks across species in a high through-put manner. This technology allows researchers to probe the effects of GLP-1RAs in preclinical models of neuropsychiatric diseases across multiple cognitive domains, such as attention, cognitive flexibility, and goal-directed action. Human behavioral and neurobiological phenotypes applied to preclinical animal research may be of use in assessing the efficacy of GLP-1RAs on metabolic and cognitive processes, an approach highlighted by Sarnyai and colleagues [124]. For example, GLP-1RAs have been shown to increase BDNF (see Table 1) and recent evidence shows that variants of the CACNA1C gene found in individuals with schizophrenia results in lower BDNF expression in the prefrontal cortex and impaired reversal learning [125,126]. GLP-1RA administration may be tested in a knockout model to observe whether cognitive performance is improved to gain insight into a specific mechanism of action through which GLP-1RAs improve cognition. Additionally, future researchers may consider using pharmacological approaches, such as the sub-chronic ketamine model, to recapitulate alterations in NMDA function as well as deficits in cognitive flexibility seen in schizophrenia [127]. Using models that recapitulate key molecular, genetic, and phenotypic alterations found in individuals with schizophrenia will best inform the clinical use of GLP-1RAs such as liraglutide. Furthermore, testing the administration of GLP-1RAs in animals of different ages and sex will be important in producing findings that are translatable to human clinical populations. Indeed, the administration of GLP-1RAs before the progression of disrupted insulin signaling and metabolic disruption may be key to preventing cognitive decline in schizophrenia and other neuropsychiatric diseases.

A particular approach that will be of future interest is in evaluating the effects of dual and triple receptor agonists in animal models of schizophrenia. Dual agonists such as DA_5-CH and DA-JC_4 that activate GLP-1 and gastric inhibitory polypeptide (GIP) have been demonstrated to increase working memory and long-term spatial memory in animal models of Alzheimer's disease [142]. Indeed these dual agonists have shown superior ability to reduce markers of inflammation when compared to the GLP-1RA liraglutide [143]. Novel triple receptor agonists that target glucagon receptors as well as GIP and GLP-1 have demonstrated neuroprotective properties in animal models of Alzheimer's disease [114]. The application of these dual and triple receptor agonists may be of great interest to individuals with schizophrenia with cognitive impairment, especially if they demonstrate superior efficacy when compared to preexisting GLP-1RAs.

Further preclinical and clinical studies will investigate the effects of GLP-1RAs on cognition to determine whether they are effective in terms of treatment outcome, cost-effectiveness, and are tolerable as an adjunctive treatment in individuals with schizophrenia. In preclinical research, future studies will probe the underlying mechanisms of how GLP-1RAs improve cognition in animal models of schizophrenia that recapitulate key alterations in insulin signaling, neurotransmitter balance, and cognitive dysfunction. Furthermore, preclinical evidence will elucidate whether new dual and triple receptor agonists are superior in terms of their neuroprotective effects and subsequently whether they will be more effective in clinical populations for treating cognitive impairment.

Converging preclinical evidence demonstrating mechanism of action and large clinical trials demonstrating GLP-1RAs have measurable benefits for cognition in individuals with schizophrenia will be required to weigh potential side-effects of the drug versus the benefits in this clinical population. GLP-1RAs such as liraglutide have common adverse effects such as nausea and vomiting and must be injected once per day [144]. This presents a barrier to the uptake of GLP-1RAs as an adjunctive treatment for schizophrenia. Newly developed GLP-1RAs such as semaglutide have been developed as a once-weekly injection [144]. However, research comparing their efficacy to liraglutide as well as their long-term cost-effectiveness is still required. Long-term, further clinical trials are needed to assess the benefit of current GLP-1RAs on cognition in individuals with schizophrenia. Clinical trials will assess the effects of these drugs over a longer duration in patients, observe whether there is an effect of dose on cognitive enhancement and whether these drugs improve cognition independent of their effects on weight-loss. Future research will also assess how GLP-1RAs interact with antipsychotic medications that may differ in terms of their effect on metabolic dysregulation.

Table 1. Preclinical studies using GLP-1RAs to enhance cognition.

Model	Drug	Dose	Route	Duration	Age of treatment	Species, strain, sex	Cognitive domains tested	Behavioral changes	Neurobiological changes	Effect on Metabolism	References
AD	Liraglutide	Once daily, 100 or 500 µg/kg/day	s.c.	4 months	6 months old	Mice, SAMP8, male	Spatial learning and memory, working memory	↑ recall on active avoidance t-maze	↑ CA1 pyramidal neuron number	Not tested	[113]
AD	GLP-1R/GIP/ Glucagon triple receptor agonist	Once daily, 10 nmol/ kg	i.p.	2 months	6 months old	Mice, APP/PS1, not stated	Spatial learning and memory	↓ deficits on Morris water maze	↓ mitochondrial pro-apoptotic signaling, β-amyloid, neuroinflammation, and oxidative stress in the cortex and hippocampus ↑ levels of growth factors Bcl-2, BDNF, and synaptophysin ↑ neurogenesis in the dentate gyrus	Not tested	[114]
AD	GLP-1R/GIP/ Glucagon triple receptor agonist	Once daily, 10 nmol/ kg	i.p.	1 month	7 months old	Mice, 3xTg-AD, males and females	Spatial learning and memory	↑ performance on open field and Y-maze	↑ LTP in CA1 region of the hippocampus ↓ Amyloid plaque levels and phosphorylated tau aggregates ↑ expression of ^{S133}p-CREB, ^{T286}p-CAMKII and ^{S9}p-GSK3β	Not tested	[128]
AD	GLP-1R/GIP/ Glucagon triple receptor agonist	Once daily, 10 nmol/ kg	i.p.	1 month	7 months old	Mice, 3xTg-AD, males and females	Spatial learning and memory	↑ performance on radial arm maze	↑spontaneous excitatory synaptic activity in pyramidal neurons in hippocampal slices Normalized voltage and chemically gated Ca^{2+}flux	Not tested	[129]
AD	Liraglutide or Lixisenatide	Liraglutide (2.5 or 25 nmol/kg), Lixisenatide (1 or 10 nmol/kg)	i.p.	Once daily for 10 weeks	7 months old	Mice, APP/PS1, males	Recognition memory	↑ performance on novel object recognition task	↑ LTP in hippocampus ↓ Amyloid plaque levels ↓ Microglial activation (changes seen in all treatment groups)	Not tested	[112]

(*Continued*)

Table 1. (Continued).

Model	Drug	Dose	Route	Duration	Age of treatment	Species, strain, sex	Cognitive domains tested	Behavioral changes	Neurobiological changes	Effect on Metabolism	References
AD	Liraglutide	300 µg/kg	s.c.	Once daily for 8 weeks	7 months old	Mice, App/PS1/3xTg-AD, males	Spatial learning and memory	↑ performance on the Morris water maze	↓ phosphorylated tau aggregates ↑ ERK phosphorylation ↓ JNK phosphorylation ↓ Degenerative neurons in the hippocampus and cortex	No change in body weight or fasting blood glucose	[110]
AD	Dual receptor agonist DA5-CH GLP-1R/GIP	Once daily, 10 nmol/kg	i.p.	1 month	9 months old	Mice, APP/PS1, males and females	Spatial learning and memory, working memory	↑ performance Y-maze and Morris water maze	↓ hippocampal amyloid senile plaques and phosphorylated tau protein levels ↑ PI3K/Akt signaling	Not Tested	[130]
AD	Exenatide	Twice daily, 100 µg/kg	s.c.	4 months	5 months old	Mice, 5 x FAD, males	Spatial learning and memory	↑performance on the Morris water maze	↓ Amyloid deposits Improved hippocampal mitochondrial morphology and dynamics ↓oxidative damage	Not tested	[131]
AD	Lixisenatide	5 nmol/µl	Micropump infusion	Single bilateral injection	Adults	Rats, Sprague-Dawley, males injected with Aβ25–35 in hippocampus	Spatial learning and memory	↑performance on the Morris water maze	Lixisenatide Improved Aβ25–35 induced impairment in spatial learning and Aβ25–35 induced block of LTP in the hippocampus Inhibited Aβ25–35 induced activation of GSK3β	Not tested	[132]
AD	Exendin-4	Twice daily, 25 nmol/kg	s.c.	4 weeks	6 months	Mice, APP/PS1, males	Spatial learning and memory	↑performance on the Morris water maze	↓ aberrant neuronal expression of GnT-III and bisecting GlcNAc N-glycans in vitro	Not tested	[133]
T2DM/AD	Exendin-4	Daily, 10 µg/kg	s.c.	4 months	6–8 weeks old	Mice, C57BL/6 J, male	Spatial learning and memory	↑performance on the Morris water maze in treatment groups	Improved hyperglycemia	Not tested	[134]

(*Continued*)

Table 1. (Continued).

Model	Drug	Dose	Route	Duration	Age of treatment	Species, strain, sex	Cognitive domains tested	Behavioral changes	Neurobiological changes	Effect on Metabolism	References
T2DM	Liraglutide	Gradually dosed from 37.5 to 75 µg/kg in low dose group and from 37.5 to 200 µg/kg in the high dose group over the first 4 days	s.c.	Once daily for 28 days	32 weeks old	Rats, GK Wistar, males	Spatial learning and memory	↑ performance on the Morris water maze	↓ apoptosis and increased autophagy ↑ beclin-1, LC-3 II, AMPK and PI3K/Akt signaling	Improved glucose levels in STZ-induced diabetic rats	[104]
T2DM	Liraglutide	200 µg/kg	s.c. (in vivo) and i.c.v. (in vitro)	Twice daily for 28 days	6–8 weeks old	Mice, Swiss (high-fat diet), males	Recognition memory, spatial learning and memory	↑ performance on the novel object recognition test	↑ LTP in CA1 of the hippocampus	Reduced fasting glucose, normalized OGTT results	[103]
T2DM	Lixisenatide	50 nmol/kg	i.p.	Twice daily injections for 40 days	6 months old	Mice, Swiss (high-fat diet), males	Recognition memory	↑ performance on the novel object recognition test	↑ hippocampal cell proliferation ↑ neuronal autophagy	Reduced fasting glucose, normalized OGTT results	[101]
T2DM	Liraglutide	300 µg/kg	s.c.	Once daily for 4 or 6 weeks	6 weeks old	Rats, Wistar (Either i.c.v. or i.p. STZ-induced diabetes)	Spatial learning and meory	↑ learning and memory on Morris water maze, passive avoidance test, forced swim test	↓ hippocampal neuronal death ↓ phosphorylation of AKT and P70S6K	Not tested	[102]
T2DM	Liraglutide	200 µg/kg	i.p.	Once daily for 8 weeks	6 weeks old	Mice, C57BL/6 (STZ-induced diabetes), males	Spatial learning and memory	↑ learning and memory on Morris water maze,	↑ beclin-1, LC-3 II, AMPK ↓ p-mTOR and p62 degradation	Not tested	[100]
T2DM	Liraglutide	240 µg/kg	s.c.	Once daily for 16 weeks	7 weeks old	Mice, db/db and db/m	Spatial learning and memory	↑ learning and memory on Morris water maze,	↓ RAGE activity in db/db mice in in vitro ↑ neuronal cell survival in CA1, CA3, and DG	Not tested	[135]
T2DM	Dual agonist – N-ac(d-Ala^2) GIP/GLP-1-exe	25 nmol/kg	i.p.	Twice daily for 28 days	12–14 weeks old	Mice, Swiss (high-fat diet), sex not stated	Recognition memory	↑ performance on object recognition on the object recognition task	↑ hippocampal neurogenesis, synapse formation ↓neuronal oxidative stress	Improved body weight, HbA_{1C}, glucose tolerance, and insulin sensitivity	[136]
T2DM	Exenatide and/or Pioglitazone	Pioglitazone (10 mg/kg) and/or Exenatide (10 or 20 µg/kg)	Orally s.c.	7 weeks Daily 7 weeks	8 weeks old	Rats, Wistar (high fructose diet), males	Spatial learning and memory	↑ performance on eight-arm radial maze in (all treatment groups)	↓hippocampal degeneration ↓hippocampal microglia expression and beta amyloid oligomer deposition	↓blood glucose level, insulin level, and insulin resistance in treatment groups	[137]

(*Continued*)

Table 1. (Continued).

Model	Drug	Dose	Route	Duration	Age of treatment	Species, strain, sex	Cognitive domains tested	Behavioral changes	Neurobiological changes	Effect on Metabolism	References
T2DM	Exenatide	240 µg/kg Exenatide	s.c.	Twice daily for 2 weeks	Not stated	Mice, BALB/c (STZ-induced diabetes), males	Spatial learning and memory	↑ performance on modified elevated plus maze	↑ CREB and BDNF expression	Improved glucose homeostasis in treatment group	[138]
T2DM	Liraglutide	100 µg/kg and 300 µg/kg	s.c.	Daily for 4 weeks	Not stated	Rats, Wistar (i.p. STZ-induced diabetes with high fat diet), males	Spatial learning and memory	↑ learning and memory on Morris water maze in diabetic rats treated with liraglutide	Liraglutide treated diabetic rats showed increased osteocalcin and serum BDNF and glutathione levels	Improved glucose homeostasis and lipid metabolism in diabetic rats with both doses of Liraglutide	[139]
Metabolic memory-induced neurotoxicity	Metformin, exendin-4, Lixisenatide	Metformin (200 mg/kg) Exendin-4 (25 nmol/kg) + Met Lixisenatide (10 nmol/kg) + Met	i.g. s.c. s.c.	Twice daily, 6 weeks Twice daily, 6 weeks Once daily, 6 weeks	8 weeks old	Mice, C57BL/6JNju and db/db mice, male	Spatial learning and memory	↑ performance on the Morriss water maze in GLP-1RA + metformin treatment groups	↓neuronal cell injury in high glucose treated cells in all treatment groups	↓blood glucose level in db/db mice in treatment groups	[140]
Juvenile Diabetes	Liraglutide	5 µl (behavioral testing) 100 nM (electrophysiology)	i.c.v. i.c.v.	Infused before Y-maze sessions	17 days old	Rats, Wistar (STZ-induced hyperglycemia), males and females	Spatial learning and memory	↑ performance on Y-maze	↑ LTP in CA1 of the hippocampus	Blood glucose of treatment condition not measured	[105]
Antipsychotic-induced metabolic dysregulation	Liraglutide	0.2 mg/kg	s.c.	Twice daily for 6 weeks	Not stated	Rats, Sprague-Dawley	Recognition memory, Spatial learning and memory, episodic memory	↑ performance on novel object recognition test (clozapine and olanzapine) ↑ performance on T-maze caused by Olanzapine-induced deficits	Not tested	↓ reduced olanzapine-induced weight gain and adiposity ↓ reduced clozapine-induced glucose tolerance	[117]
BPD	Liraglutide	120 or 240 µg/kg	i.p.	Once daily for 14 days	Postnatal Day 70	Mice, Swiss (AMPH-induced mania), males	Recognition memory, spatial learning and memory, working memory	↓ AMPH-induced hyperlocomotion, ↑ performance on the novel object recognition task	↑ BDNF levels ↑ GSH levels ↓ lipid peroxidation	Prevented lithium-induced weight-gain	[115]

(*Continued*)

Table 1. (Continued).

Model	Drug	Dose	Route	Duration	Age of treatment	Species, strain, sex	Cognitive domains tested	Behavioral changes	Neurobiological changes	Effect on Metabolism	References
Anxiety and depression-like behavior	Liraglutide	100 µg/kg, 200 µg/kg	i.p.	30 minutes prior to testing	Not stated	Rats, Wistar, males Or Mice, Swiss, males	Recognition memory, spatial learning and memory	Prevented deficits on EPM from PTZ and scopolamine Prevented scopolamine-induced deficits on Morris water maze ↑ performance on the elevated plus maze	Not tested	Not tested	[116]
Depression	Exendin-4	0.1 µg/kg	i.p.	Twice daily for two weeks	Not stated	Rats, Sprague-Dawley, males	Reference memory Stress coping	Improved performance on radial arm maze Reduced immobility on forced swim test	↑bromodeoxyuridine and doublecortin in hippocampal dentate gyrus	Not tested	[141]

AD, Alzheimer's disease; AKT, a serine/threonine-specific protein kinase; AMPH, amphetamine; AMPK, 5′ adenosine monophosphate-activated protein kinase; APP/PS1, amyloid precursor protein/presenilin 1; Bcl-2, B-cell lymphoma 2; BAX, bcl-associated X; BDNF, Brain-derived neurotrophic factor; CA1, hippocampal cornu ammonis; DG, dentate gyrus; ERK, extracellular signal-regulated kinase; GK, Goto Kakizaki; GLP-1RR, glucagon-like peptide-1 receptor; GSH, glutathione; i.c.v., intracerebroventricular; i.g., intra-gastric; i.p., intraperitoneal; JNK, c-Jun N-terminal kinase; LC3-II, light chain 3-II; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; LTP, long-term potentiation; OGTT, oral glucose tolerance test; pCREB, phosphorylated CREB; ^{T286}p-CAMKII, P70S6K, protein 70S6 kinase; PTZ, pentylenetetrazole; RAGE, receptor of advanced glycation end products; SAMP8, senescence-accelerated mouse prone 8; STZ, streptozotocin; s.c., subcutaneous; ^{S133}CREB, S133 Cyclic adenosine 3,5-monophosphate response element binding protein; T2DM, type 2 diabetes mellitus T286 phosphorylated Calcium/calmodulin-dependent protein kinase type II; 3xTg-AD, triple transgenic mouse model of Alzheimer's Disease; ^{S9}p-GSK3β, phosphorylated Glycogen synthase kinase 3 beta

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