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Effects of liraglutide on depressive behavior in a mouse depression model and cognition in the probe trial of Morris water maze test

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ABSTRACT

Background: We investigated the effects of liraglutide, a glucagon-like peptide-1 (GLP-1) agonist, on a depression-like phenotype in mice exposed to chronic unpredictable stress (CUS). Learning and memory were also assessed using the Morris water maze (MWM) test.
Methods: Liraglutide (0.3 mg/kg/day for 21 days) was administered to mice with or without exposure to CUS. After 21 days of CUS, the forced swim test (FST) was performed to assess its antidepressant effect. To evaluate cognitive function, liraglutide was administered to mice under stress-free conditions for 21 days, and then the MWM test was performed on 6 consecutive days.
Results: Chronic liraglutide treatment reduced FST immobility in mice with and without CUS. In the probe trial of the Morris water maze test, the search error rate was reduced and the time spent and path length in the target quadrant and the number of platform crossings were increased.
Limitation: Additional animal model experiments and molecular level studies are needed to support the results obtained in this study.
Conclusions: Liraglutide appears to exert antidepressant effects and could improve cognitive function. Based on these results, GLP-1 agonists could have potential as novel antidepressants.

1. Introduction

Depression is a chronic and relapsing psychiatric illness characterized by symptoms such as depressed mood, loss of interest, cognitive impairment, and sleep disturbance (Otte et al., 2016). It also causes a decline in social functioning and can even lead to suicide (Hawton et al., 2013; Woodhead et al., 2020). Currently, there are about 246 million people with depression worldwide, which imposes a tremendous economic and social burden (Gbd, 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018).

Pharmacotherapy and psychological treatments are both commonly used for depression, although antidepressants are currently the most widespread treatment (Hofmann, 2020). However, the therapeutic response to antidepressants is often unsatisfactory; in pooled analyses of double-blind antidepressant trials, the remission rate for depression was 30–45 % (Carvalho et al., 2007; Rafeyan et al., 2020). In particular, symptoms such as cognitive impairment persist even in patients whose depression improves after antidepressant treatment, where cognitive impairment decreases functioning and quality of life (Sonnenberg et al., 2008; McIntyre et al., 2013, 2015; Perini et al., 2019). In clinical studies

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of adults aged over 50 years, taking antidepressants for 6 years did not prevent changes in cognitive function, while in a randomized longitudinal study taking antidepressants for 8 weeks improved depressive symptoms, but not higher-order cognitive functions or information processing (Saczynski et al., 2015; Shilyansky et al., 2016). Given the negative effects of cognitive impairment on depressed patients, it is necessary to develop new treatments to improve cognition and restore the patient's social functioning (Bortolato et al., 2016).

Agents with novel mechanisms of action capable of modulating neuroplasticity and neurogenesis could be used as antidepressants (Massart et al., 2012; Pilar-Cúellar et al., 2014; Duman et al., 2016). In particular, studies have demonstrated changes in neuroplasticity and neural connectivity in response to antidepressant treatment, attributed to changes in mechanistic target of rapamycin complex 1 (mTORC1) signaling (Duman, 2014; Yang et al., 2019). Li et al. (2010) reported that ketamine, a glutamate *N*-methyl-D-aspartic acid (NMDA) receptor antagonist, administered to the prefrontal cortex of rats, rapidly activated the mechanistic target of rapamycin (mTOR) pathway, thereby promoting the production of new spines and synaptogenesis. Moreover, immobility time in the forced swim test (FST) was reduced.

Ketamine has also shown efficacy for treatment-resistant depression in clinical studies, while esketamine, an enantiomer of ketamine, has been developed as a prescription drug and is currently being used in clinical settings (Wan et al., 2015; Daly et al., 2019; McIntyre et al., 2021a). In addition to the antidepressant effects of ketamine, a small number of studies have indicated that it may improve cognitive function. In a systematic review, Gill et al. (2021) reported that intravenous (IV) ketamine had procognitive effects in treatment-resistant depression patients through its action in brain regions related to visual learning and working memory. Moreover, McIntyre et al. (2021b) reported that IV ketamine showed rapid procognitive effects in patients with treatment-refractory depression.

Liraglutide, a glucagon-like peptide-1 receptor (GLP-1R) agonist, was initially developed to control body weight and blood sugar levels (in conjunction with dietary and exercise interventions) in adult type 2 diabetic patients, and has been approved by the US Food and Drug Administration (Gross, 2013). In addition to its antidiabetic action, it has neuroprotective and procognitive effects by promoting neuroplasticity. Li et al. (2015) observed that liraglutide stimulated the proliferation of SH-SY5Y cells in a dose-dependent manner, and that pretreatment prevented SH-SY5Y cell death by modulating oxidative stress and glutamate toxicity. Zhu et al. (2016) reported neuroprotective effects via activation of the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) and mitogen-activated protein kinase (MAPK) pathways, as well as suppression of reactive oxygen species (ROS); these actions prevented ischemia-induced apoptosis. In another study, liraglutide prevented diabetes-induced hippocampal neuronal injury and cognitive impairment by activating autophagy through the monophosphate-activated protein kinase (AMPK)/mTOR pathway (Kong et al., 2018).

Based on the results discussed above, liraglutide could help alleviate the symptoms of depression and cognitive decline in depressed patients. To investigate its mechanisms of action underlying the antidepressant and procognitive effect, we used an animal model of depression induced by chronic unpredictable stress (CUS) (Wu et al., 2016). Changes in the depressive phenotype were evaluated using the FST, and the effect of liraglutide on cognitive function was investigated using the Morris water maze (MWM) test (Morris et al., 1982; Can et al., 2012; Song et al., 2016).

2. Materials and methods

2.1. Animals

All animal experiments were approved by the Committee for Animal Experimentation and Institutional Animal Review Board of Inje Medical College (approval no. 2016-044). Male C57BL/6 J mice (body weight: 21.5 ± 1.5 g; 7 weeks old) were purchased from Orient Bio (Seongnam, Korea) and acclimatized for 1 week. Mice remained undisturbed, except for necessary procedures such as routine cage cleaning, during acclimatization. After acclimatization, the mice (23.5 ± 1.5 g; 8 weeks old) were randomly assigned to experimental groups based on their body weights. All animals were maintained under standard laboratory conditions (21 °C, 12/12 h light/dark cycle, food and water ad libitum). After behavioral tests, the mice were euthanized using carbon dioxide gas.

2.2. Drug administration and experimental groups

Liraglutide powder (GL Biochem Ltd., Shanghai, China) was dissolved in distilled water (vehicle) and injected subcutaneously into the loose skin over the neck at a dose of 0.3 mg/kg/day for 3 weeks. This dose was selected based on a report showing that it has protective effects against hippocampal neurodegeneration via activation of the mTOR signaling pathway in rats (Palleria et al., 2017). Liraglutide was administered once daily (between 09:00 and 10:00), 1 h prior to stress treatment, for 21 days. No adverse effects of chronic liraglutide treatment were observed. For the FST, mice were assigned randomly to one of the following groups: the control group (non-stressed mice that received vehicle; n = 7), liraglutide group (non-stressed mice that received liraglutide; n = 7), CUS group (stressed mice that received vehicle; n = 6), or CUS plus liraglutide group (stressed mice that received liraglutide; n = 8) (Fig. 1A). For the MWM test, mice were assigned to a control (n = 5) or liraglutide (n = 8) group (Fig. 1B).

2.3. Chronic unpredictable stress

The CUS procedure was modified from that previously described in mice (Wu et al., 2016). Mice were exposed to various stressors for 3 weeks (Fig. 1C), including an empty cage (24 h), restraint stress (4 h), cage tilted at 45° (4 h), 4 °C cold swimming test (5 min), tail nip 1 cm from the tip of the tail (1 min), food and water deprivation (24 h), and wet bedding (sawdust soaked with 100 mL water; 24 h). One stressor was applied daily, and the order of administration was randomized over 1 week. The stressors were applied for 3 weeks in total.

2.4. Forced swim test

The antidepressant-like effects of liraglutide were assessed using the FST, with minor modifications of the protocol described by Can et al. (2012). The control, liraglutide, CUS, and CUS plus liraglutide groups (n = 7–8 animals/group) were subjected to the FST 24 h after the last CUS. Briefly, mice were placed in transparent plastic cylinders (10 cm in diameter, 25 cm in height) filled with water (23–25 °C) for 7 min. The behavior of each mouse was videotaped and subsequently scored. Immobility time was measured during the last 5 min of the test by three trained experimenters who were blinded to the groups and not involved in the behavioral tests.

2.5. Morris water maze

Spatial learning and memory were assessed using the MWM test, according to a procedure described in earlier studies (Morris et al., 1982; Song et al., 2016). The control and liraglutide groups (n = 5–8 animals/group) were tested 24 h after the last liraglutide treatment. A circular pool (150 cm in diameter, 50 cm in height) was filled with cloudy water (white tempera paint; OfficeMax, Auckland, New Zealand) to a depth of 35 cm (26 ± 2 °C) to render the platform invisible. The pool was divided into four quadrants (E, east; W, west; S, south; N, north) and a circular escape platform (12 cm in diameter) was placed 1 cm below the water surface in the middle of the SE quadrant. Data were recorded by a digital camera placed in the ceiling and connected to an image tracking system (HVS Image, Hampton, UK). Each mouse performed four trials per day

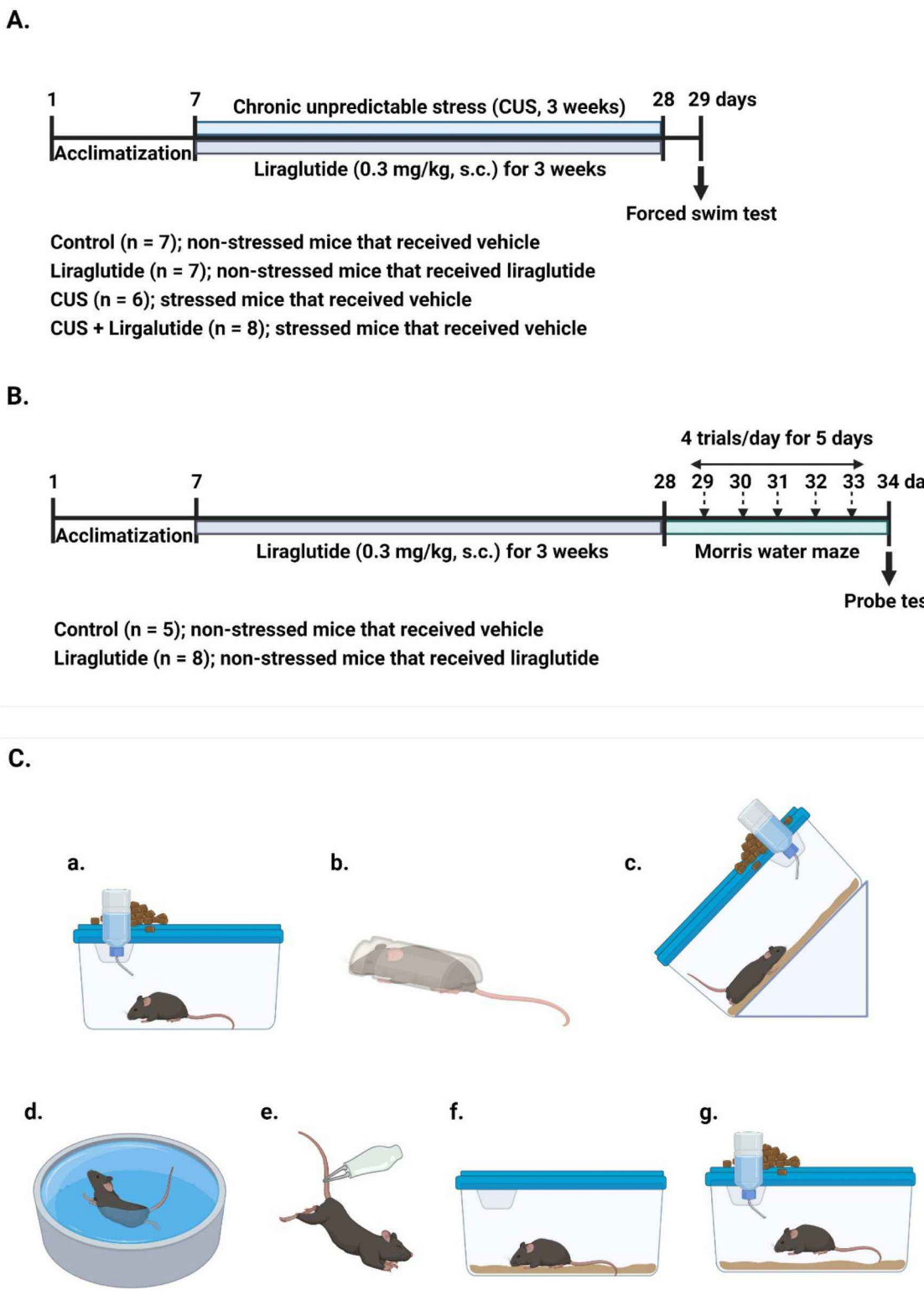


Fig. 1. Schematic representation of the experimental design and chronic unpredictable stress procedures.
(A) Experimental design of the FST. The mice were subjected to chronic unpredictable stress (CUS) daily for 3 weeks, followed by chronic liraglutide (0.3 mg/kg) or vehicle (1 mL/kg, distilled water) treatment (n = 7–8 animals/group). The immobility time was measured 24 h after the last CUS session. (B) Experimental design for the MWM. The mice received liraglutide (0.3 mg/kg) or vehicle (1 mL/kg, distilled water) for 3 weeks (n = 5–8 animals/group). At 24 h after the last injection, escape latency and swimming speed were measured in four trials performed daily for 5 consecutive days. On day 6, the probe trial was measured. (C) a. Empty cage: mice were placed in a sawdust-free cage for 24 h. b. Restraint stress: mice were fully restrained for 4 h in a plastic restraint tube (10 cm in height, 3 cm in diameter). c. Cage tilt: the cage was tilted at 45°, with food and water available at the top of the slope for 4 h. d. Cold swimming: mice were placed in transparent plastic cylinders filled with 4 °C water for 5 min. e. Tail pinch: the tail was nipped 1 cm from the tip over 1 min. f. Food and water deprivation: mice were kept in a cage without food or water for 24 h. g. Wet bedding: mice were kept in a cage having sawdust soaked with 100 mL of water for 24 h. One stressor was applied daily, and the order of administration was randomized over a 1-week period. The stressors were applied for 3 weeks in total. Original illustration created by MK Seo using BioRender (biorender.com).

for 5 consecutive days, where the goal was to locate the hidden platform. On each day, the mice were placed facing the wall of the circular pool, starting at the E, S, W, or N point. A maximum of 60 s were allowed to locate the platform. After reaching the platform, the mice were allowed to stay on it for 20 s. Mice failing to find the platform within 60 s were placed on it for 60 s. The time to reach the platform was recorded. Swimming speed was also analyzed, as an index of motor ability. A single 60 s probe trial was performed without the hidden platform on day 6, and the following were recorded to evaluate reference memory: search error, time spent in the target quadrant, path length in the target quadrant, and the number of platform crossings.

2.6. Statistical analysis

All statistical analyses were performed using GraphPad Prism software (ver. 9.3.1; GraphPad Software, Inc., La Jolla, CA, USA). To determine the main and interactive effects of CUS and liraglutide on immobility time in the FST, a two-way analysis of variance (ANOVA) of the control, liraglutide, CUS, and CUS plus liraglutide groups was performed. Tukey's post hoc multiple comparison test was applied as appropriate. Data from the first 5 days of the MWM test were compared between the control and liraglutide groups using repeated-measures ANOVA, followed by Tukey's test. Data for the probe trial were analyzed using the unpaired *t*-test. *P*-values <0.05 were considered statistically significant.

3. Results

3.1. Effects of liraglutide on CUS-induced depressive-like behavior

Fig. 2 shows the effect of chronic liraglutide (0.3 mg/kg) on the immobility induced by CUS in the FST. Two-way ANOVA revealed significant main effects of CUS ($F_{[1,25]} = 22.75$, $p < 0.001$) and liraglutide ($F_{[1,25]} = 34.85$, $p < 0.001$), but there was no significant CUS × liraglutide interaction effect ($F_{[1,25]} = 0.11$, $p = 0.742$). CUS increased immobility, indicating that a depression-like phenotype had been induced by chronic stress (control group vs. CUS group: 69.90 vs. 131.78 s, $p = 0.002$). Liraglutide prevented the increase in immobility time induced by CUS (CUS group vs. CUS plus liraglutide group: 131.78 s vs. 82.50 s, $p = 0.009$). In addition, it significantly reduced the immobility time compared to the control group (13.25 s vs. 69.90 s, $p = 0.004$). These results indicate that chronic liraglutide treatment has an antidepressant-like effect.

3.2. Effects of liraglutide on learning and memory

To evaluate the effect of liraglutide on cognitive function, the MWM test was used. The MWM is commonly employed to assess the effects of drugs on learning and memory. Although there was a trend toward a faster learning rate in the liraglutide group on days 2, 4, and 5 compared to the control group, repeated-measures ANOVA revealed no significant difference among the groups; both the control and liraglutide groups performed the test effectively (Fig. 3A). Liraglutide did not affect swimming speed (Fig. 3B). To assess memory retention, a probe trial was performed without the platform 24 h after the final training session. Search error, time spent in the target quadrant, path length in the target quadrant, and the number of platform crossings were significantly affected by liraglutide treatment. Compared to the control, the liraglutide group exhibited a significantly lower search error rate (51.95 vs. 33.96 m; $p = 0.003$, Fig. 3C), greater proportion of time spent in the target quadrant (10.44 % vs. 31.09 %, $p = 0.009$, Fig. 3D), longer target quadrant path length (11.770 % vs. 29.86 %, $p = 0.007$, Fig. 3E), and more platform crossings (0.20 vs. 2.50, $p < 0.001$, Fig. 3F). These results indicate that liraglutide treatment improved memory performance.

4. Discussion

In this study, chronic administration of liraglutide reduced the immobility time in the FST in mice with CUS-induced depressive behavior, including under non-stress conditions. Chronic liraglutide administration improved memory performance in the MMW probe test.

The FST is widely used to evaluate the effects of behavioral and neurobiological manipulations on experimental animals, and the antidepressant effects of experimental drugs (Can et al., 2012). CUS is an experimental method to measure the effect of stress in animal models, and is mainly achieved by subjecting rodents to repetitive and unpredictable stress (Monteiro et al., 2015).

In our study, liraglutide administration (0.3 mg/kg for 3 weeks) in CUS-treated mice significantly reduced immobility in the FST. The immobility time in the FST is considered a proxy for behavioral despair in depressed patients, and reduced immobility time following drug administration indicates an antidepressant effect (Kulkarni and Dhir, 2007; Yankelevitch-Yahav et al., 2015). Liraglutide reduced immobility in the FST in rats who underwent long-term treatment with the antipsychotic drug olanzapine (Sharma et al., 2015). Kamble et al. (2016) reported no change in immobility in FST when 200 μg/kg of liraglutide was administered to rats. However, in their study, the CUS-induced depressive behavior model was not used, and 200 μg/kg of liraglutide was administered only once. Our study was the first to verify the antidepressant effects of liraglutide in an animal model of CUS-induced

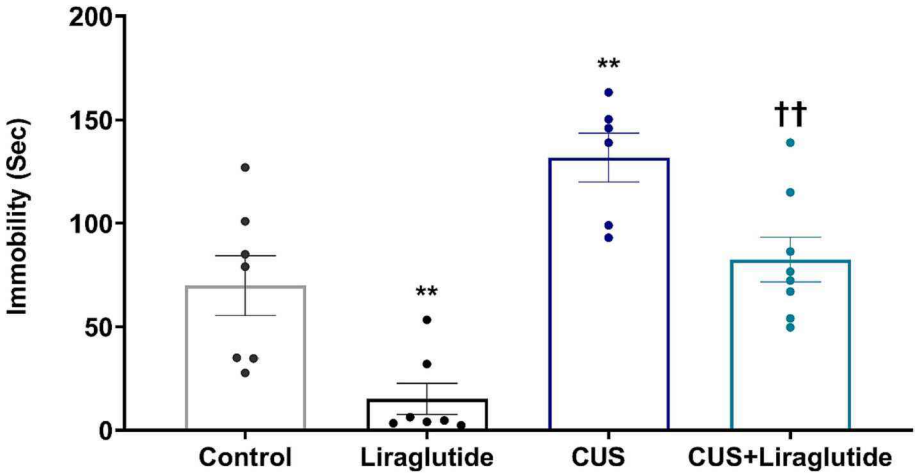
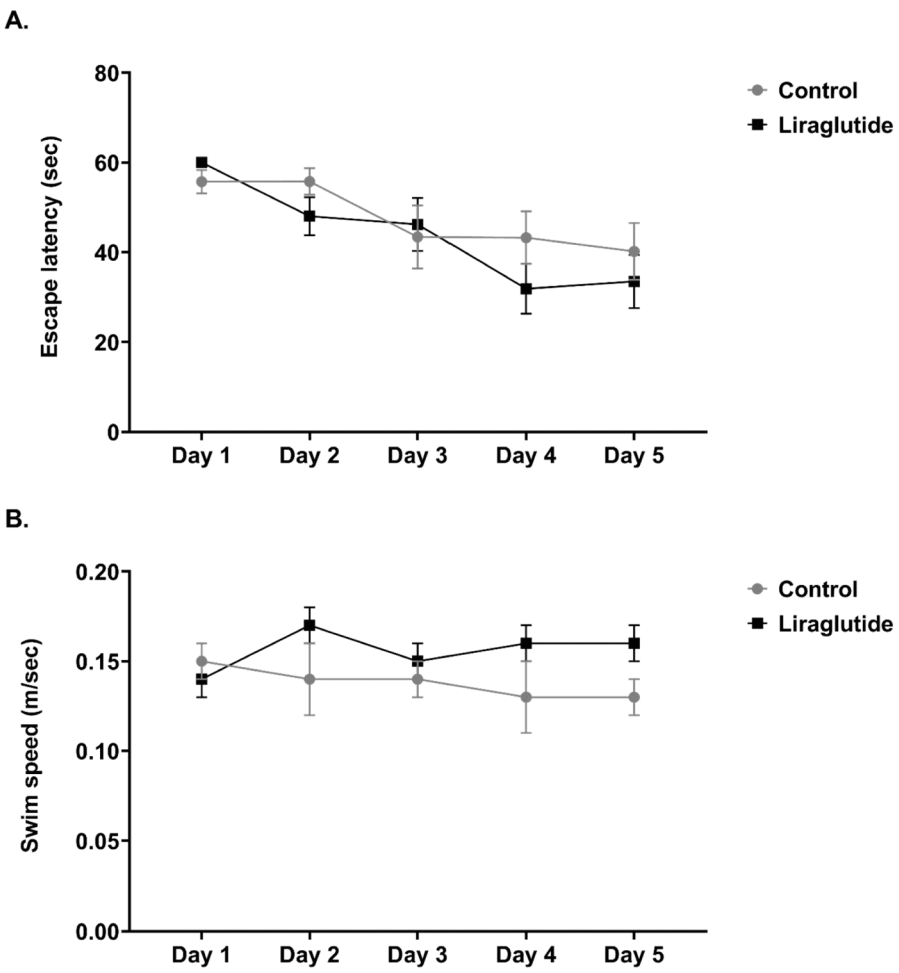


Fig. 2. Effect of liraglutide on chronic unpredictable stress (CUS)-induced depressive-like behavior in the forced swim test.
The mice were subjected to CUS daily for 3 weeks, followed by chronic liraglutide (0.3 mg/kg) or vehicle (1 mL/kg, distilled water) treatment (n = 7–8 animals/group). The immobility time was measured 24 h after the last CUS session. Control, non-stressed mice that received vehicle; Liraglutide, non-stressed mice that received liraglutide; CUS, stressed mice that received vehicle; CUS plus Liraglutide, stressed mice that received liraglutide. Values are expressed as mean ± SEM. $^{**}p < 0.01$ vs. control group; $^{††}p < 0.01$ vs. CUS group.



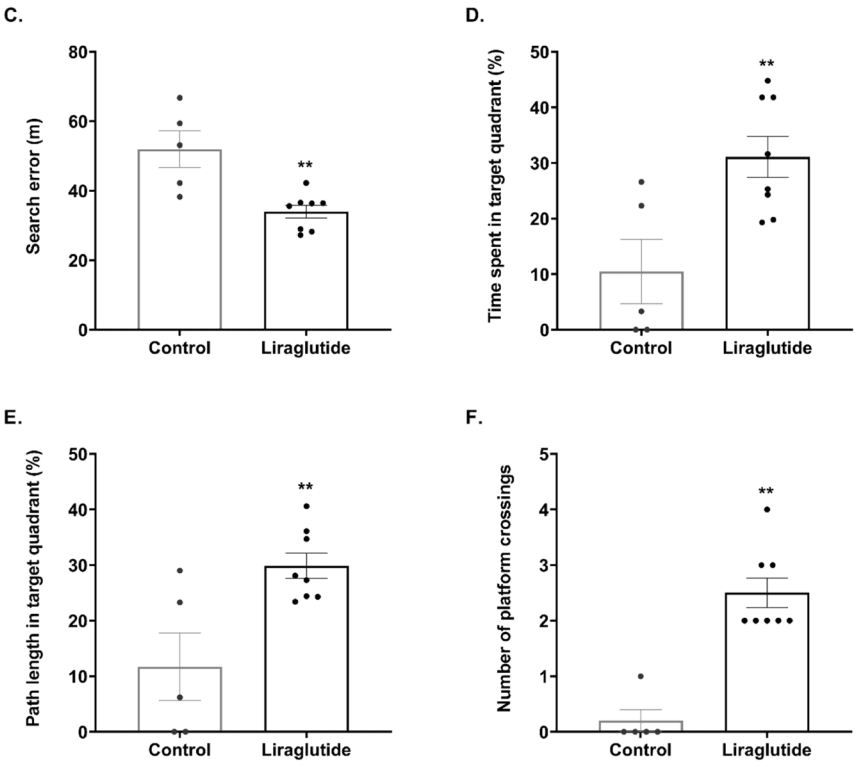


Fig. 3. Effect of liraglutide on cognition: results of the Morris water maze test.
The mice received liraglutide (0.3 mg/kg) or vehicle (1 mL/kg, distilled water) for 3 weeks (n = 5–8 animals/group). Escape latency (A) and swimming speed (B) were assessed over 5 days (4 trials/day) after the final treatment. The search error rate (C), time spent in the target quadrant (D), path length in the target quadrant (E), and number of platform crossings (F) were evaluated on day 6 in the absence of the platform. Control, non-stressed mice that received vehicle; Liraglutide, non-stressed mice that received liraglutide. Values are expressed as mean ± SEM. $^{**}p < 0.01$ vs. control group.

depression.

In addition to its antidepressant effects, we also found that liraglutide improved cognitive function in mice, reflected in improved MWM performance. The MWM test is used to evaluate spatial memory (i.e., the ability to locate a submerged escape platform) in rodents, and is a robust and reliable test of hippocampal synaptic plasticity and NMDA receptor function (Vorhees and Williams, 2006; Bromley-Brits et al., 2011). In our study, liraglutide treatment did not affect the swimming speed of mice in the MWM test. However, the search error, time spent in the target quadrant, path length in the target quadrant, and number of platform crossings all significantly improved compared to the control group. Chen et al. (2017) reported that liraglutide reduced escape latency and increased the number of platform crossings in the MWM test in a transgenic mouse model of Alzheimer's disease. In another transgenic mouse model of Alzheimer's disease, liraglutide improved spatial cognition in the MWM test (Zheng et al., 2021). Similarly, in diabetic rats, liraglutide induced a dose-dependent reduction in escape latency in the MWM test and increased the time spent on the target platform (Sedky, 2021). Taken together, the evidence suggests that liraglutide may improve cognitive function in animal models of cognitive impairment, as measured by MWM performance.

Our results demonstrated liraglutide's efficacy for mitigating depression-like behavior in an animal model of depression, and provided preliminary evidence supporting its pro-cognitive effects in the absence of CUS exposure.

Preclinical and clinical studies have demonstrated antidepressant and pro-cognitive effects of liraglutide. As stated previously, liraglutide, a GLP-1R agonist with 97 % homology to human GLP-1, is approved for the treatment of type 2 diabetes and obesity (Bode, 2011; Gross, 2013). In addition to its antidiabetic action and therapeutic effects in obesity, it has a neuroprotective effect by promoting neuroplasticity, and also affects cognitive function. Weina et al. (2018) reported that depressive- and anxiety-like behavior decreased when liraglutide was administered in a corticosteroid-induced depression mouse model. In our previous study, we found that liraglutide affected synaptogenesis and neuroplasticity, promoted mTORC1 signaling, and activated AMPAR activity in the primary hippocampal neurons of rats under dexamethasone-induced toxicity. It also increases dendritic outgrowth, spine density, and synaptic protein expression (post-synaptic density-95 [PSD-95], synapsin I, and AMPA receptor subunit GluR1 [GluA1]) (Park et al., 2018, Fig. 4). In addition to these preclinical studies, clinical studies have shown that liraglutide shows antidepressant effects and improves cognitive function in patients with depression. Mansur et al. (2017a) observed clinically significant weight loss and improved cognitive function in depressed patients prescribed liraglutide (1.8 mg/day for 4 weeks) in addition to their regular medication; they also reported a volumetric increase in frontal and striatal regions of the brain (Mansur et al., 2017a). In another study, the standard score on the Trail Making Test B and composite *Z*-score for multiple cognitive tests significantly increased in subjects with mood disorders after liraglutide treatment for 4 weeks (Mansur et al., 2017b). Kahal et al. (2019) reported that body weight, depressive symptoms, and quality of life improved when liraglutide (1.8 mg/day for 6 months) was administered to obese polycystic ovarian syndrome patients with depressive symptoms. Taken together, the results of these preclinical and clinical studies indicate that liraglutide has antidepressant and procognitive effects. Based on the results of this study, we suggest that modulation of the GLP-1 receptor is a potential target for antidepressant drugs with a new mechanism of action, and the ability to simultaneously exert antidepressant and pro-cognitive effects.

Although our positive findings have been validated, the results should be interpreted in light of certain methodological limitations. First, the antidepressant effect was indexed only by reduced immobility time in the FST. To comprehensively evaluate the antidepressant effects of liraglutide, additional behavioral evaluations are needed, such as a sucrose consumption test (Scheggi et al., 2018). Second, changes in neuroplasticity induced by liraglutide should be assessed based on mTORC1 signaling and the expression of synaptic proteins. Third, liraglutide did not significantly improve cognitive function in our animal model of CUS-induced depression, except in the probe trial. Therefore, further well-designed studies are needed to confirm that liraglutide can improve cognitive function in animal models of depression.

5. Conclusion

In this study, we demonstrated that chronic liraglutide administration could exert antidepressant effects and improve cognitive function. These results show that GLP-1 agonists could be repurposed as antidepressants and/or pro-cognitive agents for individuals with mental disorders.

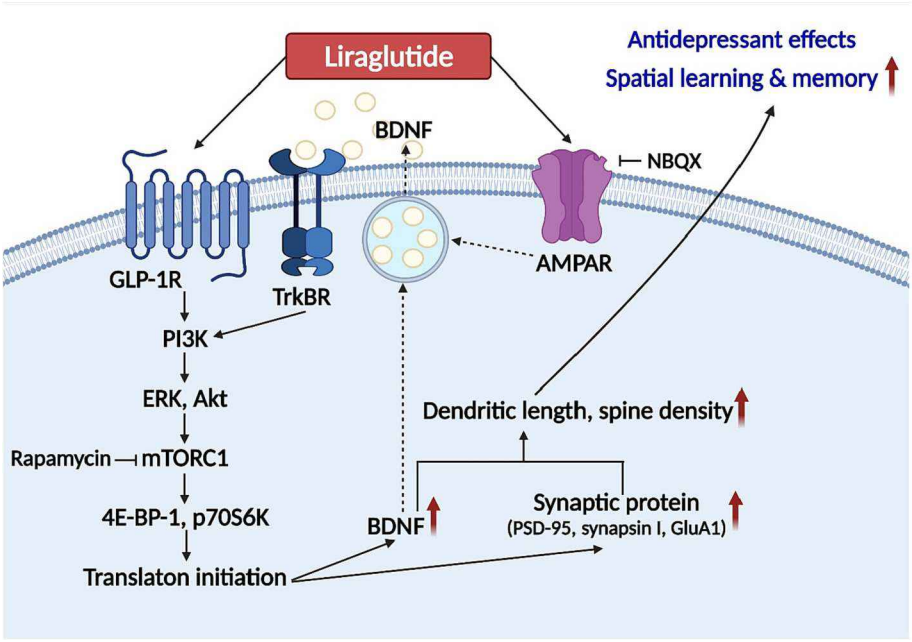


Fig. 4. Molecular mechanisms underlying the effects of liraglutide on synaptogenesis and neuroplasticity. Akt, protein kinase B; AMPAR, a-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor; BDNF, brain-derived neurotrophic factor; ERK, extracellular signal-regulated kinase; GLP-1R, glucagon-like peptide-1 receptor; GluA1, AMPA receptor subunit GluR1; mTORC1, mammalian target of rapamycin complex 1; NBQX, 2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[*f*]quinoxaline-7-sulfonamide; p70S6K, P70S6 kinase; PI3K, phosphoinositide 3-kinase; PSD-95, post-synaptic density-95; TrKBR, tropomyosin receptor kinase B receptor; 4E-BP-1, eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1. Original illustration created by MK Seo using BioRender (biorender.com).

CRediT authorship contribution statement

RS Mc McIntyre, SW Park, and JG Lee designed the study. MK Seo, SW Park, and JA Lee performed the experiment of this study. MK Seo, SW Park, JH Lee, and Y Lee wrote the protocol and undertook the statistical analysis. RS Mc McIntyre, S Jeong, and DH Seog contributed the methods and analysis tools. JG Lee, SW Park and MK Seo wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

Dr. Roger McIntyre has received research grant support from CIHR/GACD/National Natural Science Foundation of China (NSFC); speaker/consultation fees from Lundbeck, Janssen, Alkermes, Mitsubishi Tanabe, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Sunovion, Bausch Health, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals, Abbvie, Atai Life Sciences. Dr. Roger McIntyre is a CEO of Braxia Scientific Corp.

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