Glucagon-Like Peptide-1 and Psychiatric Disorder

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The glucagon-like peptide-1 (GLP-1) is an incretin hormone with a peptide structure that can be synthesized in a variety of locations all through the body and performs a variety of functions.[1] GLP-1 produced mainly by L cells in small intestine distal ileum[2] and colon, with a very small amount produced by alpha cells found in the pancreas.[1]

Glucagon-like peptide-1 receptor agonists (GLP-1RA) activate the GLP-1 receptors (GLP-1Rs) in the body, which is attached to essential amino acids, fatty acids, or glucose that convert into post-nutrient intake basic components,[3] enabling multiple intracellular pathways to work, including cAMP/PKA/CREB and PI3K/Akt.[4] GLP-1R activation occurs when nutrients are consumed orally, but not when nutrients are consumed intravenously (İV).[5]

Dipeptidyl Peptidase-4 (DPP-4) is a serine protease that separates dipeptides from polypeptides' amino-terminal. CD56 is another term for the same subject.[6] Due to proteolytic enzyme DPP-4's rapid inhibition, the half-life of GLP-1 in circulation is less than 2 minutes.[7] DPP-4 inhibitors (DPP4-I) are a new variant of oral hypoglycemic agent that increases GLP-1 levels

ABSTRACT

GLP-1 (Glucagon-like peptide-1) receptor agonists have incretin, cardioprotective and neuroprotective effects. Liraglutide, a GLP-1 receptor agonist, is used to treat comorbid diseases such as obesity and diabetes through its incretin and cardioprotective effects. The therapeutic targets of Exenatide on neurodegenerative diseases have recently been concentrated, particularly after the discovery of GLP-1's neuroprotective effects. Mood disorders and metabolic comorbidities are the two groups of diseases that have the greatest global impact on mortality. There is also a significant correlation between patients with mood disorders and patients with obesity and T2DM (Type 2 diabetes mellitus), according to epidemiological data. GLP-1 receptor agonists are exceedingly being used to treat psychological disorders. According to the results of preclinical studies, Liraglutide can prevent cognitive function regression and develop normal functions. This condition suggests that GLP-1 receptor agonists could be useful in the treatment of psychiatric disorders in the future. This review examined the relationship between GLP-1 Receptor Agonists and Psychiatric diseases.

Keywords: Bipolar spectrum disorder, GLP-1, liraglutide, mood disorders, neuroprotection, obesity, schizophrenia.

in the bloodstream and are used to treatment of diabetes.[8]

GLUCAGON-LIKE PEPTIDE-1 RECEPTORS

In addition to the ability to produce GLP-1, the brain contains many GLP-1Rs. GLP-1Rs are produced predominantly in neurons, astrocytes and microglia in the brain.[9] Cardiovascular functions are controlled by GLP-1Rs found in Nucleus tractus solitarius (NTS) connected with area postrema (AP). In a study of dogs, it was observed that glp-1 infusion stimulates cardiac flow and improves hemodynamics of the left heart in dilate cardiomyopathy caused by fast pacing.[10] Increased cardiovascular function is independent of catecholamines during the iv infusion of GLP-1.[11]

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Glucagon-like peptide-1 receptors are also located in reward areas of the brain, where flavor or drug consumption affects elevated dopamine levels and glutaminergic neuron transmission. GLP1-R agonists act by inhibiting pentagastrin, which has gastrin-like effect, and gastrin, which is stimulated by food and prevents stomach emptying.[12] So, food consumption and substance use gradually decline, and weight loss results.[13]

EFFECTS OF GLUCAGON-LIKE PEPTIDE-1

The incretin effect on pancreatic beta cells is one of the functions that makes GLP-1 so famous today. The release of insulin, which is stimulated following glucose intake into the bloodstream, causes the incretin effect in glucose metabolism.[14] GLP-1 is secreted by the Leptin, which is a hormone synthesized from L-cells in distal ileum.

Leptin tolerance and a reduction in GLP-1 levels are seen in people who eat a high-fat diet and become obese.[15] GLP-1RA and DPP-4 inhibitors are also successful in the treatment of type 2 diabetes mellitus (T2DM) though breaking down the leptin resistance.[3] In particular, Liraglutide and Exenatide are powerful T2DM receptor agonists in the treatment of GLP-1.[16]

CARDIOPROTECTIVE EFFECTS

Despite the fact that GLP-1RAs have cardioprotective effects, DPP-4 inhibitors are ineffective in patients with cardiovascular disease.[17] GLP-1 receptors reduce left ventricular functions in the isolated rat heart, thus reducing ischemia and infarction sizes.[18] In a retrospective study, it was reported with the LEADER study that the risk of cardiovascular disease in diabetic patients who had been given Liraglutide had decreased with the placebo group. But no obvious cardiovascular changes were reported compared to placebo if Lixisenatide which was also GLP-1RA in another study, was administered to diabetic patients with acute coronary syndrome (ACS).[19]

In the high-risk population for ACS, a comparable analysis was not performed in non-diabetic patients. As a result, it's unknown if GLP-1 RA has therapeutic efficacy in non-diabetic patients with ACS.[20] Furthermore, clinical trials in T2DM patients have shown that GLP-1RA[20,21] is more effective than DPP-4 inhibitors[22,23] in preventing the development of cardiovascular risks.

NEUROPROTECTIVE EFFECTS

There are many cases where GLP-1 and GLP-1RAs active in the brain. GLP-1 and GLP-1RAs block apoptosis induced by hypoxia or methylglyoxal (MG), a product of chronic hyperglycemia, by regulating glucose levels in the brain.[24-26] It also shows a neuroprotective effect by minimizing amyloid precursor protein (APP) accumulation in the brain[27] and attempting to control neuronal damage that occurs after ischemia.[28,29]

The mouse brain has been observed to reduce chronic inflammation following radiation exposure with Liraglutide application.[30] Furthermore, it is also reported that GLP-1R agonists are increasing the progenitor cell proliferation in dentate gyrus and the antagonists are decreasing the progenitor cell proliferation and have a positive effect on synaptic plasticity.[31,32]

Liraglutide, a long-acting GLP-1RA, can penetrate circumventricular organs (CVOs) and hypothalamic neurons by crossing the blood brain barrier.[33,34] Likewise, DPP-4 inhibitors are also thought to be capable of crossing the intact blood brain barrier.[35]

In a study of T2DM mice, findings of a high degree of learning and memory impairment were observed through tests of mEPM (modified elevated plus maze) and PA (passive avoidance). Exenatide is thought to be a drug to reduce the effects of cognitive diseases in later periods due to improving cognitive ability and stimulating the molecular mechanisms of memory storage in mice.[36]

GLUCAGON-LIKE PEPTIDE-1 EFFECTS ON NEURODEGENERATIVE DISEASES

Many *in vivo* and in vitro studies have shown that GLP-1RAs have protective effects in neurodegenerative diseases such as Alzheimer's (AD) and Parkinson's disease (PD),[37] raising the possibility that GLP-1RAs may be used to treat these diseases.[38]

GLP-1 AND ALZHEIMER'S DISEASE (AD)

Alzheimer's disease is a deadly neurodegenerative disease characterized by dementia and decreased cognitive functions (such as language and thought disorders) that result in the progression of memory loss. Today, AD is the most common among neurodegenerative diseases. Although the etiology of AD has not been conclusively determined, the common pathological

properties that patients have are characterized by the accumulation of non-neuron beta-amyloid (Aβ) plaques and neurofibrillary tangles of intra-neuron hyperphosphorylene tau proteins.[39] Today, no therapies that affect the progression of the disease have been developed, and patients are only given symptomatic care.[40]

The preclinical models studied showed reduced amyloid accumulation and neuroinflammation with Liraglutide application,[41,42] improved cognitive outcomes with increased brain glucose metabolism,[43] and increased proliferation of neuronal progenitor cells.[44]

GLP-1 AND PARKINSON'S DISEASE (PD)

Parkinson's disease is characterized by the death of dopaminergic neurons in the substantia nigra, central nervous system, which appears tremor and rigidity symptoms.[45] It is the most common second neurodegenerative disease after AD.[46]

The coexistence of dopaminergic neurons and insulin receptors in Substantia nigra makes the association between T2DM and Parkinson's even stronger. Dopamine depletion in the striatum and reduced insulin signaling in basal ganglia are also associated with the issue. Previous studies have confirmed that patients with insulin resistance and T2DM are in the high risk group for PD as a result of the high rate of abnormal glucose tolerance seen in Parkinson's patients.[47] It is therefore thought that antidiabetic agents such as peroxisome proliferator activated receptor-γ, GLP-1, and DPP-4 may be important therapeutic targets in the pathophysiological mechanism of PD.[47-50]

At the end of a 2020 meta-analysis, Exenatide use was reported to have prevented cognitive impairment and extended lifetime by improving quality of life by increasing in UPRDS (Unified Parkinson's Disease Rating Scale) scores with a cognitive test score in Parkinson's patients.[51-53] A study with Exenatide in patients with Parkinson's supported that Exenatide can be used for motor dysfunction diseases' treatment[54] causing decreases non-motor symptoms and motor complications.[50]

GLP-1 AND ISCHEMIC STROKE

Ischemia is one of the major causes of death in the world.[55] An ischemic stroke can be performed 4-6 hours after a thrombolysis or thrombectomy when the patient's body is suitable for the procedure.

However, only a small percentage of patients are eligible for the treatment.[56]

Although animal studies on the treatment of GLP-1 in stroke are extremely high, clinical studies on humans have recently begun to increase.[24] The immediate use of GLP-1RA following a stroke shows a good therapeutic window of up to 3 hours in mice, compared to approximately 36 hours in a human. This suggests that using GLP-1RA to treat ischemic stroke is a favorable treatment option.[57] According to tissue plasminogen activators (tPA) whose therapeutic window is 4.5 hours, GLP-1RAs have been shown to have a much longer effect and have a potential to be used in acute stroke.[17]

MOOD DISORDERS AND SCHIZOPHRENIA

Mood disorders and schizophrenia are the most common and severe observed chronic mental disorders.[58]

GLP-1R gene expression has a large difference between the healthy group and patients with mood disorders when factors such as age, sex, ethnicity are kept stable.[58] It has been reported through animal studies that declining numbers of GLP-1 positive cells in the brain is associated with obesity and metabolic syndrome.[59] In 2018, association between Body Mass Index (BMI) and GLP-1R expression over the brain tissues of death psychiatric patients was investigated. Excess GLP-1R and GLP-2R expression was detected in the postmortem brains of people with mental conditions as a result of this research.[58]

In a meta-analysis study, it was reported that GLP-1RAs may be effective at blocking the weight increase observed as a side effect in patients on Clozapine/Olanzapine, medications prescribed for treating schizophrenia and similar mood disorders.[60,61] Another study of patients using Clozapine found that after adding liraglutide to the treatment of schizophrenia patients, their HbA1c levels decreased from 10.0% to 6.5%, and as much as 8.7% of their body weight was lost.

As a result of epidemiological studies on humans, correlation is observed between mood disorders and metabolic comorbidities such as obesity, and T2DM.[62-65] While the increased prevalence of depression is observed in T2DM people, depression is also considered to be a risk factor for the development of diabetes.[66,67] A study reported that diseases such as obesity, T2DM and metabolic syndrome were observed 2 times more frequently

in patients with mood disorder compared to the general population[68] One of the common factors underlying the link between obesity/diabetes and mood disorders is hypothalamic-pituitary-adrenal (HPA) axis dysfunction.[69] The co-observation of these diseases also reveals conditions that negatively affect the pathology of two diseases, such as obesity, the rapid rise of insulin resistance, increased suicide attempts, resistance to treatment.[70-72]

For non-diabetic individuals with mood disorders, GLP-1R agonists are safe and well tolerable agents. It is also thought that it may have beneficial effects that can alleviate metabolic disorders.[73]

Due to Preclinical studies, although the potential impact of Liraglutide on individuals with mood disorder was reported,[73] no noticeable effects have been found in trials with Exenatide in patients with schizophrenia.[74]

EATING DISORDERS

Eating disorders are serious psychiatric illnesses characterized by overeating and weight control, which can result in death by progressing if left untreated.[75] Eating behavior is inhibited by GLP-1 receptor activation found at the CA1 site in the ventral hippocampal area.[76] GLP-1 receptor agonists such as Liraglutide are thought to be effective in treating overeating by affecting this region.[77]

Emotional eating status has an activation-reducing effect in the insula region of the brain in T2DM patients and in the amygdala in obese patients. Glucose intake reduces food consumption in the succeeding period, increasing the feeling of satiety, but GLP-1 receptor antagonists disappear these changes.[78] Levels of GLP-1 in obese people have not changed if the meal, which is not tasty or tasty, is eaten.[79]

Overeating is defined as consuming an abnormally large amount of food in a short period of time, with a subjective sense of loss of control.[80] In T2DM patients with an eating disorder, the GLP-1 effect has been observed to be low.[81,82]

A study involving normal weight and obese adults using Liraglutide examined the weight status of individuals with mood disorders. According to the findings of the study, Liraglutide improved metabolic parameters in non-diabetic individuals with mood disorders, and after treatment, subcortical structure and frontal gray matter

volumes associated with weight loss increased. This increase has been associated with improvement in cognitive functions.[83]

A study of Bulimia nervosa patients found that reduced GLP-1 levels caused overeating episodes.[84] Although the relationship between bulimia and GLP-1 could not be explained clearly[85] GLP-1RA Liraglutide was suggested that there would be safe and effective treatments in Bulimia nervosa and overeating disorders.[86]

ANHEDONIA AND DEPRESSION

Depression is a psychiatric disease associated with extreme blood-brain barrier permeability, neuroinflammation and synaptic dysfunction,[87,88] adversely affecting the lives of the patient and his family.[89] In the severity and incidence of depression, the gene pool and environmental stressors that one and their family have are thought to be effective.[90]

Anhedonia is a reduction in the ability to motivate or enjoy and manifests in many psychiatric disorders.[91] Although many antidepressants are available for anhedonia and depression, 30% of diagnosed patients do not have the required therapeutic effect in these treatments.[92]

In the study among patients diagnosed with 100 control and 164 schizophrenia/bipolar spectrum disorders, GLP-1R polymorphisms' Anhedonia's laboratory-based measurement method as a probabilistic reward learning task response bias was observed in Anhedonia and depression phenotypes.[93]

Another study in rats reported that depression and metabolic abnormalities that develop as a result of prolonged use of atypical antipsychotics with Liraglutide could be blocked.[94]

MAJOR DEPRESSIVE DISORDER

Major Depressive disorder is a neuropsychiatric disorder common in society, characterized by the observation of emotion condition changes such as irritability or state of sadness to the extent that it affects one's work and family life, lasting at least 2 weeks. These mood changes can be cited as examples of anorexia, sexual reluctance, inability to enjoy, crying, suicidal ideation, slowing down in speech and actions.[95] Major depressive disorder (MDB) can be observed with comorbid conditions and obesity.[96]

BIPOLAR SPECTRUM DISORDER

Bipolar disorder (BD) is a chronic psychiatric disease that repeats itself manically and depressively in two extreme phases with certain periods.[97,98] Diagnosis is easier to make during the manic period when symptoms are more observable. Most bipolar patients may not get an accurate diagnosis during the early periods of the disease, as the cycle begins with a period of depression.[99]

To diagnose Bipolar Disorder type 1, at least one manic episode is needed.[100] These patients also experience depressive periods, but the presence of manic periods for diagnosis is distinctive.[101]

In bipolar disorder type 2, no manic periods are observed. It is replaced by one or more hypomanic periods and one or more major depressive periods that are not as severe as the manic period.[100]

A study of patients with BD and a control group found that the level of GLP-1 was significantly lower in patients with BD but it was also noted that GLP-1 levels were not enough to stage the disease.[102]

As a result of the study of 57 Bipolar patients, 24 of type 1, 33 of type 2, the low levels of GLP-1, glucagon and Ghrelin and high levels of the Gastric inhibitor polypeptide (GIP) are common qualifications in all patients and can have a role in the pathogenesis and diagnosis of BD, particularly in the depressive phase.[103]

Patients with BD have three times higher incidence of T2DM. At the same time, severe BD is extremely likely to occur in comorbid T2DM patients, and these patients are extremely resistant to treatment. T2DM and Bipolar patients have higher cardiovascular morbidity and mortality. These two disorders may be related from common pathophysiological origins, such as LHPA (limbic-hypothalamic-pituitary-adrenal) or mitochondrial dysfunction, or from common genetic connections or epigenetic interactions. It is thought that these drugs could be used to treat T2DM after studies have shown that the drugs used for bipolar spectrum disorder facilitate glycemic control.[104]

DEPRESSION AND ANXIETY

GLP-1RA can have significant effects on psychological stress responses as well as mood disorders.[105] Liraglutide has the mitigating effect of symptoms on depressive and anxiety behaviors caused by corticosteroids and regulates the endocrine system by normalizing Adrenocorticotropic hormone (ACTH) levels after stress treatment. As a consequence it is conceivable that it could be used as an antidepressant drug in the long term.[106]

In a pilot study with 19 volunteers, daily use of 1.8 mg of Liraglutide proved safe and well tolerable for non-diabetics with mood disorder.[83]

SUBSTANCE ABUSE

GLP-1 Rs are located in areas important for the brain's reward mechanism. GLP-1 R's are helping reduce delicious food intake and cocaine, amphetamine, opioid, nicotine and alcohol use by significantly altering dopamine levels and glutamatergic neurotransmission following food or drug intake.[13]

A study in those with cocaine addict people found that following cocaine injection, GLP-1 levels were significantly reduced, thus triggering more cocaine intake and subjective anxiety in the person.[107] Exenatide-4 supplementation decreased cocaine-induced preference for the conditioned location and dopamine release.[108]

Exenatide-4 (2.4 g/kg) decreased abnormal amphetamine mobility, conditional location preference, and accumulated accumbal dopamine release without disturbing the drug's spontaneous locomotor activity in amphetamine users.[108]

Exenatide reduced the locomotor behavior induced by nicotine in mice and blocked locomotor sensitivity. It also reduced the release of accumulated dopamine and the preference for nicotine-derived conditioned places.[108]

Ethanol intake and spontaneous locomotor activity decreased depending on dose with Exenatide-4 in rats.[109] Alcohol addicts received a significant decrease in alcohol intake and alcohol-seeking behaviors as a result of receiving Exenatide-4 treatment for 8 months.[108]

A study in alcohol-dependent mice observed significantly reduced ethanol intake with AC3174, an Exenatide analogue.[110] Another agonist, Liraglutide, also eased the rise in alcohol-related dopamine and conditional location preference, preventing alcohol abstinence-related drinking.[111]

Another trial in monkeys showed that Liraglutide and Exenatide decreased alcohol consumption without causing adverse effects including dehydration or nausea/vomiting.[112]

SUICIDE

The inhibitory effect of Sitagliptin, a very powerful inhibitor of DPP-4, stops at plateau stage 93%. High levels of Sitagliptin causes levels of the increasing hormones and contributes to preventing hypoglycemia after overdose due to the fact that the activity of the incretin is dependent on glucose.[113]

Depression prevalence is high in patients with diabetes, and depression is a strong risk factor for suicide.[8] Sitagliptin is recommended for treating diabetes in the elderly and patients with suicidal psychiatric disorders.[8] Although nocturnal hypoglycemia could not be completely ruled out in the Japanese woman patient who attempted suicide by taking 1700 mg Sitagliptin aged 86, apparent hypoglycemia was observed later and as a result of this condition, Sitagliptin is defined as a low-risk oral hypoglycemic agent.

CONCLUSION-RESULTS

When we examined the studies done on GLP-1, it was concluded that receptor agonists improve cognitive functions and inhibit reduction in functions due to their antidiabetic effects, as well as their neuroprotective effects. The number of clinical trials studying its use in treating neurodegenerative disorders such as AD and PD is continuously rising, with promising therapeutic findings in the near term. However, the number of studies on neuroprotection should be increased even further, and not only cognitive properties as well as their effects on social behaviors should be investigated.

Larger randomized controlled studies should be conducted on the topic, and studies should be translated and expanded into more languages so that studies to accelerate around the world and include more scientists. Psychiatric disorders that can be observed along with metabolic abnormalities such as diabetes mellitus should certainly not be overlooked, but follow-up and treatment should be done in consultation with psychiatry-endocrinology.

Likewise, reducing mortality in patients with bipolar spectrum disorder, reducing cardiovascular risk factors as much as possible and treating metabolic disorders that have the potential to develop to improving patients' quality of life are also extremely critical for physicians.

It is also thought that GLP-1RAs can be used to treat substance abuse through a significant reduction in addiction and similar behaviors for cocaine, amphetamines, alcohol and nicotine.

GLP-1RAs are seen as an effective agent for potential mortality in patients with metabolic comorbidity and emotion condition disorder due to their beneficial impact on both weight control and cognitive functions.

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