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Pathophysiology and biochemical alterations associated with hyperthyroidism-induced renal impairment and the renal ameliorative role of GLP-1 agonists: comprehensive review

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Abstract: Background: Hyperthyroidism is a medical condition characterized by the overproduction and release of thyroid hormone by the thyroid gland Hyperthyroidism can manifest as either overt or subclinical. Overt hyperthyroidism is defined by abnormally low levels of thyroid-stimulating hormone (TSH) in the blood and elevated levels of thyroid hormones, specifically thyroxine (T4), triiodothyronine (T3), or both Thyroid hormones (TH) are necessary for the kidney to grow and develop to the proper extent. However, hyperthyroidism induces kidney injury and impairment since the kidney serves as both a target organ for some of the activities of iodothyronines and an organ for the metabolism and excretion of TH. Significant alterations in glomerular and tubular functioning, as well as electrolyte and water homeostasis, are brought on by thyroid disease. Glucagon-like peptide-1 agonists (GPL-1) therapy displayed a promising role in retrieving hyperthyroidism-induced renal impairment via modulating several molecular pathways which are orchestrated via glucagon-like hormone and its receptors in this review we summarized the pathophysiology of the hyperthyroidism-induced renal impairment and the ameliorative role of the GLP-1 agonist

Keywords: *Hyperthyroidism _thyroid stimulating hormone (TSH)_ kidney impairment_ Glucagon Like peptide GLP-1*

Introduction

The thyroid gland's normal or increased uptake of radioactive iodine causes either thyrotoxicosis with hyperthyroidism or true hyperthyroidism, which is the condition's hallmark**.** When thyroid hormone is created outside of the thyroid gland or when pre-existing thyroid hormones are released into the bloodstream with a limited thyroid absorption of radioactive iodine, thyrotoxicosis without hyperthyroidism results **(1)**

The most common cause of hyperthyroidism in areas with sufficient iodine is Graves' disease. The occurrence of Graves' disease in Sweden is on the rise, with a yearly rate of 15-30 new cases per 100,000 individuals in the 2000s. This condition is believed to have multiple causes, resulting from the breakdown of immune tolerance and the production of autoantibodies that activate thyroid follicular cells by attaching to the TSH receptor **(2)**

Relationship between kidney and thyroid gland

Thyroid and kidney function are related, according to clinical and translational studies, and the thyroid gland affects metabolic processes in the body **(3)**

Thyroid hormones (TH) are necessary for the kidney to grow and develop properly. On the other hand, the kidney serves as both a target organ for some of the activities of iodothyronines and an organ for the metabolism and excretion of TH. Significant alterations in glomerular and tubular functioning, as well as electrolyte and water homeostasis, are brought on by thyroid disease The kidney's physiology, growth, and development are significantly influenced by TH. It is established that hyperthyroidism raises the kidney-to-body weight ratio by a process that is still poorly understood **(4).**
So there is effect of thyroid hormone on the kidney in figure 1**(5)**

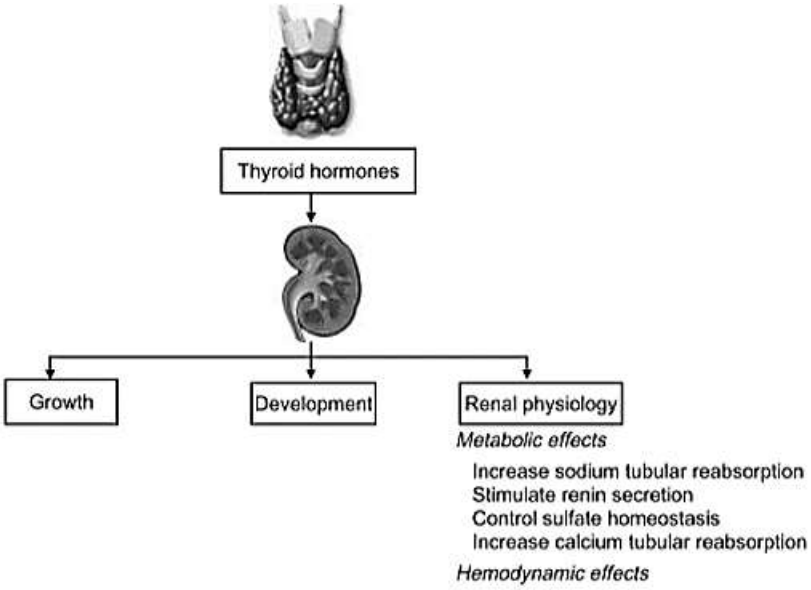
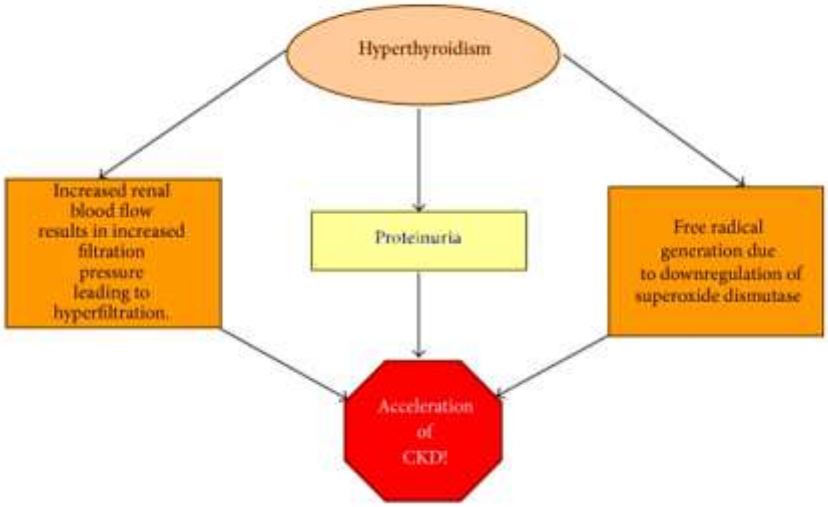


Figure 1 Effects of thyroid hormones on the kidney.

Hyperthyroidism with kidney impairment
People with reduced renal function are getting more and more common with chronic kidney disease (CKD), which is becoming a severe health issue. The advancement of chronic kidney disease (CKD) is linked to other problems, such as thyroid dysfunction **(6)** chronic kidney disease (CKD) can be caused by or accelerated by hyperthyroidism through several processes. First, intra-glomerular hypertension is caused by hyperthyroidism (higher filtering pressure) and the ensuing hyperfiltration. Second, hyperthyroidism increases the risk of proteinuria, which has been directly
linked to kidney damage Thirdly, elevated mitochondria produced by hyperthyroidism energy metabolism in addition to the suppression of Superoxide dismutase plays a role in the elevated levels of free radical production and the ensuing damage to the kidneys Deteriorating. Stress plays a role in hypertension in hyperthyroidism as well.
which accelerates the course of CKD **(7).**
Mechanism of action of kidney impairment due to hyperthyroidism
It is true that hyperthyroidism can hasten CKD. These systems consist of the following: (i) Hyperthyroidism's increased renal blood flow causes intraglomerular hypertension, which in turn raises filtration pressure and causes hyperfiltration. It is well known that proteinuria, which is present in hyperthyroidism, directly damages the kidneys; (ii) enhanced mitochondrial energy metabolism and downregulated superoxide dismutase, both present in hyperthyroidism, promote the formation of free radicals that damage the kidneys; (iii) Oxidative

stress also has a role in hypertension associated with hyperthyroidism, which advances chronic kidney disease **(8)**
And this will be shown below in figure 2 **(8)**



When FT4 or T4 quartile levels climbed and FT3 or T3 quartile levels decreased, the frequency of renal problems increased (all $P < 0.05$). Following complete adjustment, linear regression demonstrated a negative correlation between urinary albumin to creatinine ratio (UACR) levels and FT3 and T3 ($P < 0.001$). Furthermore, TSH, FT4 levels, thyroglobulin antibody (TgAb), positivity, and estimated glomerular filtration rate (eGFR) were all negatively correlated with one another and favorably correlated with FT3 and T3 (all $P < 0.05$). Higher TSH and FT4 and lower **(9)** FT3 and T3 were linked to renal diseases by binary logistic regression. One can have overt or subclinical hyperthyroidism. Low blood thyroid-stimulating hormone (TSH) and increased serum thyroxine (T4), triiodothyronine (T3), or both are indicative of overt hyperthyroidism. On the other hand, low blood TSH levels along with normal serum levels of T3 and T4 are indicative of subclinical hyperthyroidism (SCH). Patients with Subclinical hyperthyroidism SCH displayed a decrease in vascular resistance. Changes in blood pressure and thyroid hormones may be the main causes of the renal function changes in SCH patients **(10)**

Treatment of hyperthyroidism

Patients with hyperthyroidism have three alternatives for treatment: radioactive iodine ablation, surgery, and antithyroid drugs (ATDs). For those with Graves' illness, all three of the available therapy choices are successful. However, as these patients rarely experience remission, those with toxic adenoma or toxic multinodular goiter should get either radioactive iodine therapy or surgery**. (11)** ATDs are usually used to treat toxic nodular goiter before receiving final therapy with radioactive iodine or surgery and return thyroid function to normal. Unless the patient has a poor life expectancy or the other two therapies are inappropriate, ATDs are rarely employed as a long-term treatment. Geographical location affects the choice of Graves' disease treatment **(12).**

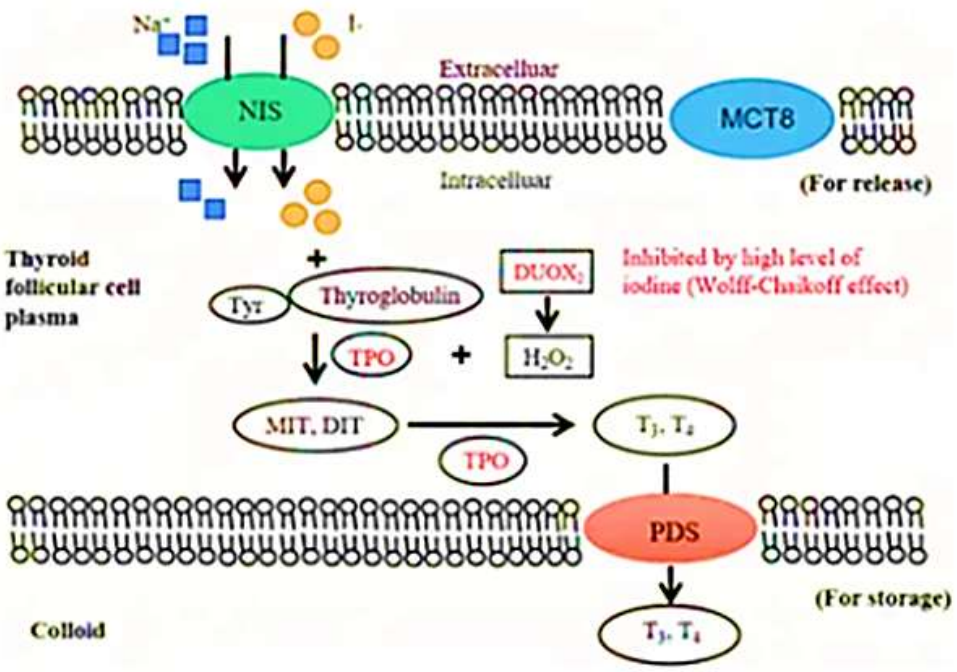
Thyroid hormone production is inhibited by antithyroid thioamide medications such as carbimazole, thiamazole, and propylthiouracil. Every material is aggressively carried into the thyroid gland, where it inhibits the enzyme thyroid peroxidase, preventing iodide oxidation and organocation. Additionally, this inhibition stops iodothyronine from coupling, which is required to produce the thyroid hormones T4 and T3**(13).** For Graves' hyperthyroidism, thioamide antithyroid (ATD) are the

recommended course of treatment. The primary disadvantage of 1-2 years of ATD treatment is that around 50% of patients experience a return of hyperthyroidism. Recent research has demonstrated that most patients receiving ATD treatment for longer than five years' experience long-term remission without experiencing any extra serious side effects in either adults or children. When compared to radioactive iodine therapy, long-term ATD yields better benefits **(14).**

Carbimazole is converted into its active form, thiamazole, which is like thiamazole in properties. High doses of propylthiouracil inhibit peripheral tissues' outer ring deiodinase of T4, which lowers the amount of T4 that is converted to T3. Conversely, thiamazole doesn't have this effect. These drugs may also have immunosuppressive and anti-inflammatory qualities **(15).**

Application of oral inorganic iodine in the treatment of Graves' disease.

Dietary and therapeutic iodine are two types of oral inorganic iodine that are directly related to thyroid metabolism and immunity. The hallmarks of Graves' disease (GD), also called diffuse toxic goiter, include hyperthyroidism and elevated iodine metabolism. In clinical settings, individuals with GD are frequently advised to restrict or eliminate iodine in their diets. Recent studies have shown that there may be an overestimation of the impact that dietary iodine has with the therapy of antithyroid medications (ATDs). Furthermore, inorganic iodine has demonstrated promising outcomes when administered as a drug for the treatment of GD in individuals with mild hyperthyroidism, low thyroid autoantibody concentration, small thyroid volume, high iodine diet, and other related conditions. As a backup, inorganic iodine can also be utilized by patients who encounter **Figure 3 (16).**



Treatment with thyroidectomy

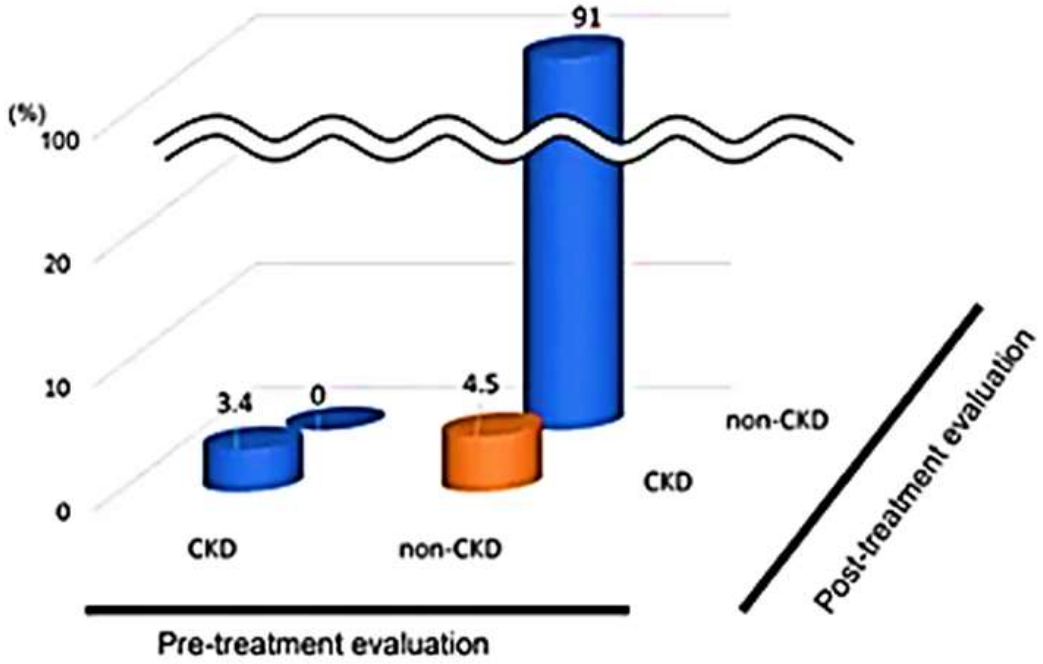
The best course of treatment for Graves' hyperthyroidism is thyroidectomy, which comes highly recommended. Because whole thyroidectomies have much greater success rates and the incidence of complications is the same, they are favored over partial thyroidectomies. Patients with big goiters, low radioactive iodine uptake, suspected or proven thyroid cancer, moderate-to-severe ophthalmopathy, or a predilection for surgery are especially advised to have thyroidectomies **(17).**

The following surgical procedures are recommended for GD: bilateral subtotal thyroidectomy, which aims to remove all thyroid tissue; hemithyroidectomy + contralateral subtotal thyroidectomy, commonly referred to

as the Dunhill technique; or total thyroidectomy **(18).** Over the past six years, our institution has seen an increase in the rate of thyroidectomy. Patients were primarily referred because they presented with obstructive symptoms, were resistant to or intolerable to antithyroid drugs, or preferred surgery **(19)**

Treatment with radioactive iodine (RAI).

One affordable alternative for treating Graves' illness is radioiodine. It is customarily saved for patients in the UK who relapse following initial thionamide therapy. The new guidelines from the National Institute for Health and Care Excellence (NICE) suggest that radioiodine be used as the first line therapy for Graves' disease, which is a departure from existing practice. On the other hand, there has recently been a discussion on the safety of radioiodine about the risk of long-term mortality. The evidence from hyperthyroidism treatment-related mortality studies is analyzed in this analysis, and its implications for future Graves' disease treatment techniques are discussed **(20).** For over 70 years, the treatment of hyperthyroidism has involved the use of radioactive iodine (RAI). As one of the three main treatments (i.e., RAI, antithyroid medications, and thyroidectomy) for patients with overt Graves hyperthyroidism, the American Thyroid Association guidelines highly recommend RAI therapy with moderate-quality evidence. When the need for lifelong thyroid hormone replacement and the quick resolution of hyperthyroidism are viewed as less important than the definitive control of hyperthyroidism, avoiding surgery, and the possible side effects of antithyroid medications, RAI treatment is the better option **(21).** Around the world, ATDs are the first-line treatment. They are generally safe, usually administered for 18 to 24 months, and prolonged treatment may reduce relapses. RAI is risk-free; however, it has a minimal risk of GO development, especially in smokers. Thyroidectomies need highly experienced and proficient surgeons. In a shared decision-making process, patients are central to the therapeutic decision-making process. The outcomes of targeted treatments that influence distinct phases of the autoimmune process, such as ATX-GD-59, rituximab, inhibiting TSHR-Ab, and small compounds that function as TSHR antagonists, are in the early stages of research and development but show promise over the medium to long term **(22).** Following therapy for a thyroid condition, which may reflect the patient's true kidney function, these patients were classified as having "masked" chronic kidney disease (CKD) under hyperthyroidism. As a result, we divided the subjects into kidney function groups for both the pre-and post-treatment periods of hyperthyroidism **figure 4 (23).**

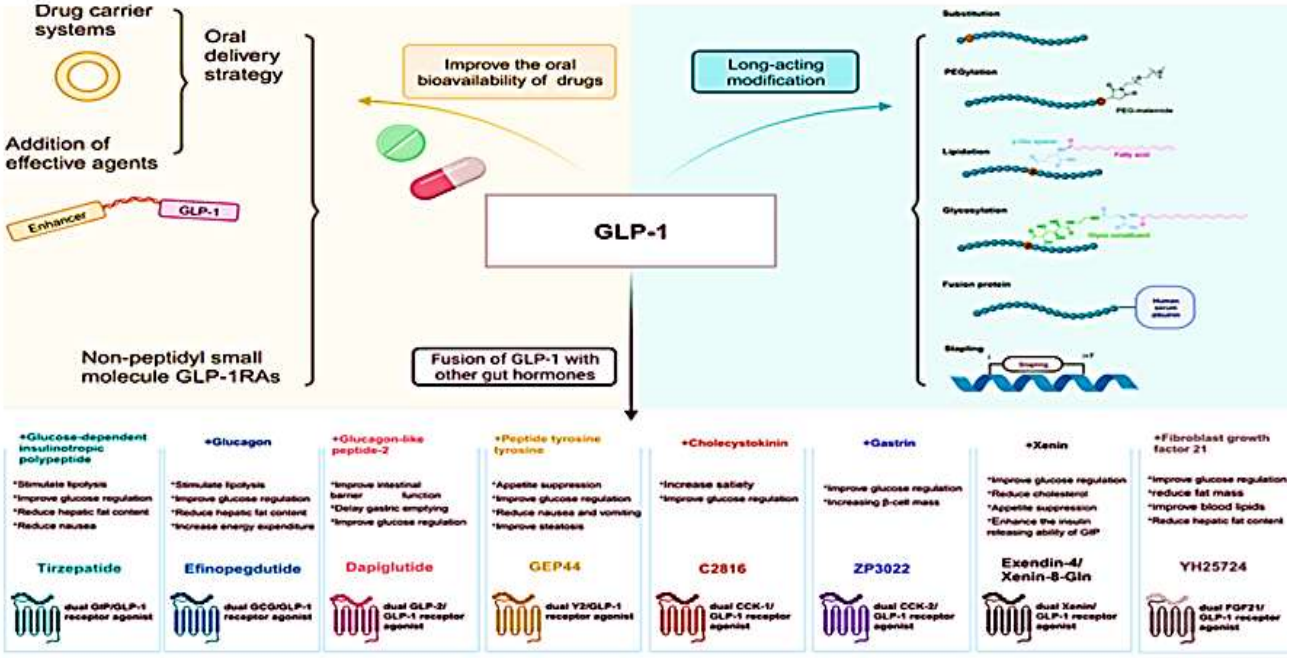


Glucagon Like peptide GLP-1

Glucagon-like peptide-1 (GLP-1), a peptide hormone derived from the digestive system, regulates insulin secretion, food intake, and gut motility to effectively maintain postprandial glucose homeostasis. Many of the medications used today to treat type 2 diabetes, obesity, and other conditions are based on GLP-1, as are other novel compounds that are in the development stage **(24).**

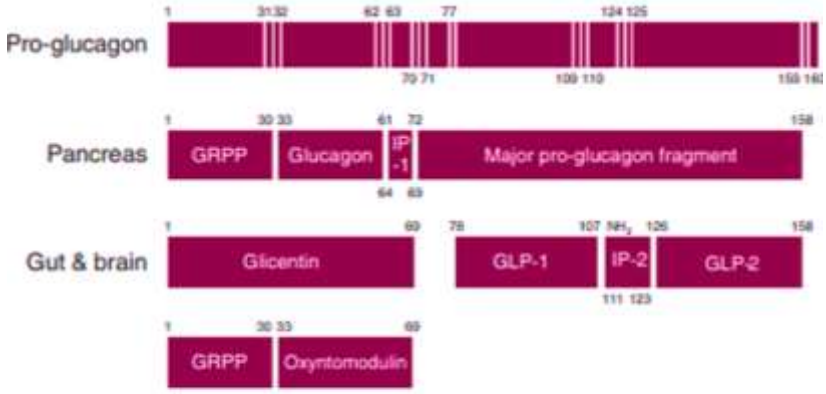
When nutrients are consumed, intestinal-derived incretin hormones are released. These hormones are secreted at low levels during the basal state and decrease postprandial hyperglycemia by increasing the amount of insulin secreted in response to meals **(25).** The first known incretin, glucose-dependent insulinotropic polypeptide (GIP), was obtained by biochemical purification and functional characterization in the 1970 **(26).**

In the 1980s, the sequence of mammalian GLP-1 was found by cloning and sequencing complementary DNAs and genes of proglucagon (GCG) **(27).** GLP-1(7-36) and N-terminally shortened GLP-1(7-37) The gut's enteroendocrine L cells release NH2, which are the bioactive forms. The gut is where the majority of GLP-1 is found. When fasting or in the inter-prandial state, GLP-1 is continually released at low basal levels, and its levels in the blood rise two to three times after eating **(28).** GLP-1 is also produced in the brain stem and sent to various parts of the central nervous system (CNS) via axonal routes. While GLP-1 can be synthesized by the wounded pancreas and islets ex vivo, normal mouse and human pancreas have incredibly low pancreatic levels of intact bioactive GLP-1 **(29).** Dipeptidyl peptidase-4 (DPP-4), a highly expressed serine protease, rapidly cleaves bioactive GLP-1**(30)** accountable for the short half-life of physiologically active GLP-1 in the circulation (t1/2 = <2 minutes), together with renal clearance. At physiological quantities, DPP-4 activity produces GLP-1 and GLP-1NH2, GLP-1 metabolites that do not activate the canonical GLP-1r, **figure 5 (31, 32).**



Biological role of GLP

Glucagon-like peptide-1 (GLP-1) is an incretin belonging to the pro-glucagon family that is involved in hunger and fullness regulation**(33).** GLP-1 functions via GLP-1 receptor (GLP-1R), a member of the G protein-coupled receptor (GPCR) superfamily of 463 amino acids**(34).** GLP-17–37 and GLP-17–36 amide are the two equipotent molecular forms of bioactive GLP-1. DP IV quickly cleaves GLP-1, generating the mostly inactive molecular forms GLP-17-37 and GLP-19-36 amide.With DP IV expressed in the capillary surrounding gut L cells, most GLP-1 exiting the intestinal venous circulation has already been cleaved, giving intact GLP-1 in vivo an estimated half-life (**35).** Many tissues, including the brain, pancreas, colon, lung, stomach, and kidney, contain the GLP-1 receptor. GLP-1's actions seem to be both insulinotropic and insulinomimetic, contingent on the level of glucose in the surrounding environment. GLP-1 is a new insulinotropic peptide that is heavily researched in type 2 diabetes. Its activities are dependent on the surrounding blood glucose level. GLP-1's ability to trigger the release of pancreatic insulin is diminished when the concentration of glucose falls below 4 mmolar. Furthermore, GLP-1 inhibits the secretion of glucagon, gastric emptying, and gastric acid while decreasing food intake following both intracerebroventricular and peripheral injection. These activities are independent of the release of insulin, figure 6 **(36, 37).**



Key: GLP = glucagon-like peptide; GRPP = glicentin-related pancreatic peptide; IP = intervening peptide
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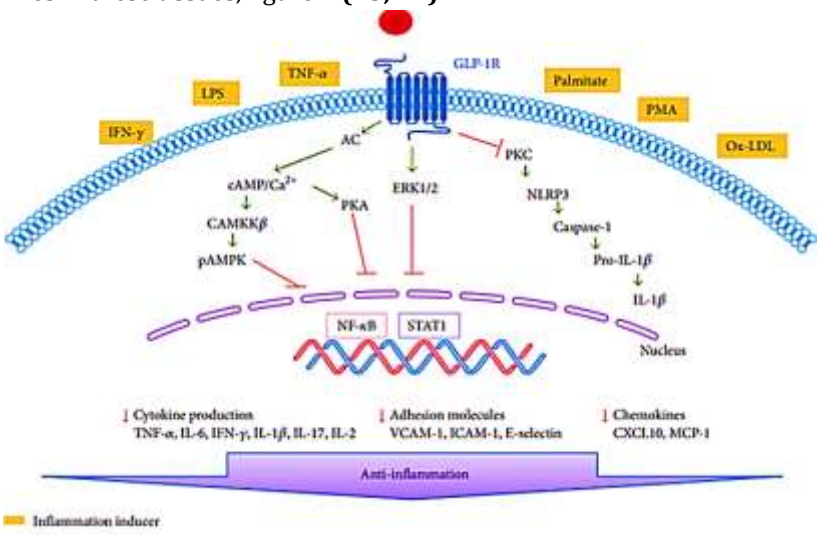
Therapeutic approaches forGLP-1

Research on natural GLP-1 and GLP-1-based medications in type 2 diabetes (T2D) patients or animal models has also revealed their potent anti-inflammatory properties **(38, 39).** Numerous tissues and organs, such as the kidney, lung, heart, hypothalamus, endothelial cells, neurons, astrocytes, microglia, and pancreatic beta-cells, have been shown to express the GLP-1 receptor **(40)**. Indicating that GLP-1 may have functions beyond reducing blood sugar. Studies have shown that GLP-1 reduces inflammation in adipose tissue and pancreatic islets, which helps lower blood sugar levels in diabetics **(41)**. Emerging evidence also suggests that GLP1-based therapies have anti-inflammatory effects on the brain, kidney, lung, testis, liver, vascular system, including the aorta and vein endothelial cells, and skin by lowering the infiltration of immune cells and the production of inflammatory cytokines in these tissues, figure 7 **(43, 42).**



Some Examples for GLP DRUGS

Semaglutide is a next-generation GLP-1 RA based on liraglutide that was authorized by the FDA in December 2017 under the brand name Ozempic®. To evade degradation by DPP-4, semaglutide features an extra amino acid substitution in the 8th position from Ala to α-aminobutyric acid (AIB) compared to liraglutide. Semaglutide was created with a longer stearic (C18) di-acid fatty chain, whereas liraglutide contains a C16 fatty acid chain. Compared to liraglutide, semaglutide exhibits a higher affinity for binding albumin, which could be attributed

to the latter's longer fatty acid side chain **(46).** Liraglutide is the most effective example of an acylated GLP-1; it was approved by the FDA in 2010 and marketed under the Victoza® brand. Derived from natural GLP-1, ligandulose contains a 16-C fatty acid connected to Lys26 via a γ-Glu spacer, with Arg replacing Lys at position 34 **(47).**

Table active ingredients of GLP with it is drug (44, 45)

Drug name	Brand name	Administration	Dosage	FDA Approval	Company
Liraglutide	Victoza®	Once a day (SQ)	Initiate at 0.6 mg/dose (equivalent to 0.16 µmol GLP-1 RA per dose) for one week then increase to 1.2 mg/dose (0.32 µmol/dose). Dose can be increased to 1.8 mg/dose for additional glycemic control (0.48 µmol/dose).	Jan 2010	Novo Nordisk
Semaglutide	Ozempic®	Once weekly (SQ)	Initiate at 0.25 mg/dose (equivalent to 0.061 µmol GLP-1 RA per dose), increase up to 1 mg/dose (0.24 µmol/dose) after 4 weeks.	Dec 2017	Novo Nordisk

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