Review Article

Inflammation: The Mother of All Diseases Meets the Mother of All Therapies

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Article Info

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Abstract

Introduction: Incretins are small peptides secreted by the gastrointestinal tract. These peptides exert their action by binding to G-protein-coupled receptors that are widely distributed in the pancreas, throughout the gastrointestinal tract, and the brain. The physiological role of incretins (such as GLP-1) is to regulate glucose levels by increasing insulin secretion, delaying gastric emptying, and decreasing appetite, leading to weight loss.

Method: In this review, we aimed to report the effects of inflammation on human health and how GLP-1 and GLP-1 receptor agonists, which are now being used as first-line agents to control obesity, can have a broader effect on human diseases.

Results: The literature shows the benefits of these drugs in diseases other than obesity, including in diseases of many organs such as heart, kidneys, liver, blood vessels, and in neurodegenerative and psychiatric conditions. These diverse beneficial effects are attributed to the anti-inflammatory activities of these new drugs.

Conclusions: The physiological actions of incretins have recently been better understood. The surprisingly diverse therapeutic activities of this class of new drugs suggest that they will likely play central roles not only in the management of type-2 diabetes but for the treatment of obesity and a wide spectrum of diseases for which inflammation is a major factor.

Introduction

Inflammation is an immune response to harmful stimuli, such as pathogens, damaged cells, or irritants. Normally, it is a protective mechanism that aims to eliminate the cause of injury, clear out dead cells, and initiate tissue repair [1–3]. However, when acute inflammation becomes chronic, it can cause severe organ dysfunction. Inflammation has been known to humans for about 2 millennia through basic observation; some of the most frequent signs and symptoms (such as pain, heat, redness, and swelling) are usually visible on the skin [1].

Among the 10 leading causes of death of US citizens, 9 of them are associated with chronic inflammation [2]. Chronic inflammation is also responsible for significant patient morbidity, due to malfunction or loss of function of vital organs. Table 1 summarizes the 10 most common causes of death in the US [2]. All these diseases have been previously linked to chronic inflammation (accidents are not related to inflammation or disease).

Table 1: Leading causes of death of US citizens. Modified from Ahmad et al., 2023.

Cause of death in the US in Year 2022	Number of deaths annually 2022
Heart disease	702,880
Cancer	608,371
Accidents (unintentional injury)	227,039
COVID-19	186,552
Stroke (cerebrovascular disease)	165,393
Chronic lower respiratory disease	147,382
Alzheimer's disease	120,122
Diabetes	101,209
Nephritis and related diseases	57,937
Chronic liver disease and cirrhosis	54,803

During an injury of any cause to the body, an immediate response takes place that involves immune cells, blood vessels, and molecular mediators. Key immune cells include neutrophils and macrophages, and small molecules include cytokines (e.g. TNF-alpha, IL-1, IL-6), chemokines (e.g. CXCL-8), prostaglandins, leukotrienes, and histamine [3]. Among the most important cells in inflammation are macrophages, whose role in the tissues is to clean up debris and produce growth factors under physiological conditions [3]. During tissue inflammation, tissue-resident macrophages secrete cytokines and chemokines and recruit other cells, such as monocytes, from the general circulation. More details on the pathobiology of inflammation can be found in these reviews [3–5].

The prototype of known and extensively studied chronic inflammatory diseases are autoimmune diseases. These are conditions where the immune system mistakenly attacks the body's own tissues, leading to multi-organ symptoms [6]. Some of the best-known chronic inflammatory diseases are shown in Table 2.

Table 2: Examples of chronic inflammatory diseases due to autoimmunity.

Autoimmune Disease	Cardinal Features	Inflammatory markers/autoantibodies
Rheumatoid Arthritis	Chronic inflammation of the joints leading to pain, swelling, and eventual joint destruction.	Rheumatoid factor, Anti-citrullinated protein antibodies, anti-carbamylated protein antibodies [7].
Systemic Lupus Erythematosus	A multisystem disease with symptoms affecting the skin, joints, kidneys, and other organs.	Anti-double-stranded DNA antibodies, anti-Smith antibodies, anti-ribonucleoprotein, anti-Ro/SSA, anti-La/SSB, antinuclear antibodies [8].
Multiple Sclerosis	Involves inflammation and damage to the myelin sheath of nerve fibers.	Increased Immunoglobulin G antibodies, pro-inflammatory cytokines [9].
Inflammatory Bowel Diseases	These are chronic inflammatory conditions of the gastrointestinal tract such as Crohn's Disease which can affect any part of the gastrointestinal tract causing deep ulcers and inflammation. Ulcerative Colitis primarily affects the colon and rectum, leading to superficial inflammation and ulcers.	Perinuclear anti-neutrophil cytoplasmic antibodies,anti-*Saccharomyces cerevisiae antibodies*, anti-chitobioside carbohydrate antibodies, pancreatic antibodies, anti-glycan antibodies etc. [10].
Vascular inflammatory disease	These are associated with inflammation affecting blood vessels such as Vasculitis. The latter causes inflammation of blood vessels that can lead to organ damage.	Anti-neutrophil cytoplasmic antibodies, anti-proteinase-3 antibodies, C-reactive protein, interleukin-6, white blood cell count, erythrocyte sedimentation rate etc. [11,12].

Diagnosis of inflammatory diseases involves a combination of clinical evaluation, laboratory tests (e.g. C-reactive protein, acute-phase reactants, erythrocyte sedimentation rate, white cell counts), and more recently, imaging studies (e.g., MRI, CT scans), and sometimes tissue biopsies. Acute inflammation (lasting hours or days) is usually managed with anti-inflammatory medications (e.g., NSAIDs, (nonsteroidal anti-inflammatory drugs such as ibuprofen), antibiotics for infections, and other supportive measures).

The treatment of chronic inflammation (lasting weeks to years) focuses on controlling inflammation and its underlying causes with medications such as corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and more recently with an ever-expanding list of biologics such as monoclonal antibodies against TNF (e.g. https://www.humira.com/) and cytokines. Lifestyle changes and physical therapy may also be recommended. Among the lifestyle and preventive measures are anti-inflammatory diets rich in omega-3 fatty acids, antioxidants, and fiber. Additional measures include exercise, stress management, and avoidance of irritants such as environmental toxins, and smoking cessation. Managing chronic infections can help mitigate inflammation.
The most common human organs that are affected by inflammation include the heart, pancreas, liver, kidney, lung, brain, intestinal tract, and the reproductive system [13]. If the chronic inflammation persists for long periods, the afflicted organs are damaged and eventually become non-functional.

Neuroinflammation

For many years it was believed that the brain is immune-privileged [14]. When the brain is challenged by non-self antigens or other stimuli, its response is attenuated. It has now been realized that the central nervous system (CNS) does show local inflammation in response to various stimuli, including infections, neurodegeneration, trauma, environmental toxins, and metabolic disturbances [15]. Neuroinflammation is a complex biological response of the CNS to various forms of injury, infection, or disease. It involves the activation of glial cells, (microglia and astrocytes), which play critical roles in maintaining homeostasis and responding to pathological changes, as well as leukocytes [16,17]. While neuroinflammation is a protective mechanism, chronic or excessive inflammation can lead to detrimental effects on neuronal function and health, contributing to a range of neurological and psychiatric disorders [18,19]. The consequences of prolonged neuroinflammation include neuronal damage, Blood-Brain Barrier disruption and cognitive decline, potentially through mechanisms such as synaptic loss, neuronal death and altered neurotransmitter signaling [17].

Therapeutic Implications

Given the role of neuroinflammation in many harmful processes, targeting neuroinflammatory pathways presents a potential therapeutic strategy. Approaches include anti-inflammatory agents, immunomodulation (representing therapies that modulate the immune response, such as monoclonal antibodies targeting specific cytokines and receptors, including agonists

and blockers), neuroprotective agents such as neurotropic factors, and lifestyle interventions such as exercise and stress management.

Our motivation for preparing this review originated from the development of a relatively new class of therapeutics, generally known as incretins, and their analogs, which were initially intended to treat type-2 diabetes (T2D) [20]. It was quickly realized that these drugs cause marked reduction in body weight and were thus also deployed for weight loss. Clinical trials worldwide suggest that these drugs can show efficacy in a surprisingly long list of seemingly unrelated diseases (see Table 3). These small peptides interact with receptors that are found throughout the body, including the brain, suggesting that they could target diverse tissues, promoting, among other activities, glycemic control, loss of appetite, and slow gastric emptying [21]. It has been speculated that the pleiotropic activities of these therapeutics are due to their ability to decrease inflammation [20]. While the pathophysiological aspects of these drugs are undoubtedly very interesting, we will briefly describe below a long list of diseases that seem to phenomenologically respond favorably and at various degrees, to these agents. These drugs may represent a new class of compounds with potent anti-inflammatory action, by extrapolation, this could be beneficial in diseases where chronic inflammation is a key characteristic.

Table 3: List of human diseases that have been studied for potential treatment using incretins as therapeutic agents.

Condition	Incretin-like drug (dose, mode, participants)	Study name, Duration	Findings
Obesity	Semaglutide (2.4mg/w[1], SC[3], n=803) Liraglutide (3mg/d[2], SC, n=338) Tirzepatide (10mg or 15mg/w, SC, n=670)	STEP 4 (20w), STEP 8 (68w), SURMOUNT-4 (36w + 52w),	Reduction of weight [22–24]
Obstructive sleep apnea	Tirzepatide (10mg or 15mg/w, SC, n=469)	SURMOUNT-OSA (52w)	Reduced severity, improved sleep-related outcomes [25]
Adverse cardiovascular outcomes	Semaglutide (3mg, 7mg, 14mg/d [0-4w, 4-8w, 9-82w], oral, n=3183)	PIONEER 6 (82w)	Reduced risk of cardiovascular outcomes [26]
Non-alcoholic streatohepatitis	Semaglutide (0.1, 0.2 or 0.4mg/d, SC, n=320) Tirzepatide (5mg, 10mg or 15mg/w, SC, n=190)	NCT02970942 (72w) SYNERGY-NASH (52w)	Disease resolution [27,28]
Liver cirrhosis	Exenatide, Dulaglutide, Liraglutide, Semaglutide (variable doses, unknown, n=16058)	In silico study, data: VHA database (2006-2022)	Reduced risk of cirrhosis [29]
Myocardial infarction	Semaglutide (2.4mg/w, SC, n= 17604)	SELECT (240w)	Reduced risk of death from disease [30]
Opioid use disorder	Semaglutide (variable doses, unknown, n=33006)	In silico study, data: TriNetX Analytics Platform (49w)	Reduced craving and opioid overdose [31]
Depression	Exenatide (2mg/w, SC, n=491)	DURATION-2(26w)	Reduced feelings of depression [32]
Stroke	Semaglutide (2.4mg/w, SC, n= 17604)	SELECT (240w)	Reduced risk of death from stroke [30,33]
Atherosclerosis	Tirzepatide (5mg,10mg or 15mg/w, SC, n=2539)	SURMOUNT-1 (72w)	Reduced risk of disease [34]
Addiction (alcohol, smoking)	Semaglutide (variable doses, unknown, n=222942) Exenatide (2mg/w, SC, n=127)	In silico study (2017-2023) NCT03232112 (26w)	Reduced risk of addiction, improved abstinence [33,35,36]

Condition	Incretin-like drug (dose, mode, participants)	Study name, Duration	Findings
Suicidal tendencies	Semaglutide (variable doses, oral & SC, n=65176)	In silico study, data: TriNetX US Collaborative Network (2017-2021)	Reduced risk of suicidal ideation [33]
Alzheimer's disease	Liraglutide (1.8mg/d, SC, n=206) Semaglutide (14mg/d, oral, n=1840)	ELAD (52w) EVOKE (173w)- Ongoing	Slowed cognitive decline, reduced brain shrinkage [37,38]
Dementia	Semaglutide (variable doses, oral & SC, n=65176)	In silico study, data: TriNetX US Collaborative Network (2017-2021)	Reduced risk of dementia [33]
Parkinson's disease	Exenatide (2mg/w, SC, n=62)	NCT01971242 (48w)	Improved motor function [39]
Kidney disease	Semaglutide (1mg/w, SC, n=3533)	FLOW (156w or 265w)	Reduced risk of disease [40]
Polycystic ovary syndrome	Exenatide (Varying amounts, unknown, n=785)	Meta-analysis (12w-25w)	Increased pregnancy rate [41]
Female infertility	Exenatide (Varying amounts, unknown, n=785)	Meta-analysis (12w-25w)	Improved measurements [41]
Male infertility	Liraglutide (1.20-1.80mg/kg, SC, n=42)	Non-human study (42 days)	Improved sperm characteristics (mice) [42]

[1] per week

[2] per day

[3] subcutaneous

Incretins and Their Therapeutic Potential

Incretins are a group of hormones released by the gut in response to food intake. They play a vital role in regulating glucose metabolism by enhancing insulin secretion, inhibiting glucagon release, and promoting satiety [21]. The two primary incretin hormones are glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP). Understanding the physiological roles of incretins has led to significant advancements in diabetes treatment and weight management. Details about the structure of incretins can be found elsewhere [6].

Incretins exert their effects primarily through the following mechanisms [21]:

1. Insulin secretion: In response to meals, GLP-1 and GIP stimulate pancreatic beta cells to release insulin. This response is glucose-dependent, which means that insulin secretion is enhanced when blood glucose levels are elevated.
2. Glucagon suppression: GLP-1 inhibits glucagon secretion from pancreatic alpha cells, which helps lower blood glucose levels by reducing hepatic glucose production.
3. Gastric emptying: Incretins slow gastric emptying, leading to a more gradual release of glucose into the bloodstream, which helps prevent spikes in blood glucose levels.
4. Satiety and weight management: GLP-1 promotes feelings of fullness, reducing appetite and caloric intake, characteristics that are beneficial for weight management.

Therapeutic Applications of Incretin-Like Peptides

The unique properties of incretins have led to the development of several therapeutic agents, primarily for the treatment of T2D and obesity [25]. The diverse therapeutic benefits of incretins are attributed to their anti-inflammatory actions, in addition to optimal management of diabetes and weight loss [21]. The GLP-1 receptor is a G protein-coupled receptor (GPCR) found in beta cells of the pancreas, neurons, stomach, duodenum, lung, and hypothalamus [21].

GLP-1 receptor agonists are synthetic analogs of GLP-1 that mimic its effects and have already been successfully used in the treatment of T2D [26]. Notable examples of GLP-1 agonists include liraglutide (used for both diabetes and weight loss management), and semaglutide (marketed as Ozempic) which demonstrates significant weight reduction and glycemic control, with some formulations approved specifically for weight management (e.g. Wegovy) [23].

Dipeptidyl Peptidase-4 (DPP-4) is an enzyme that inactivates GLP-1-like peptides, thus decreasing their long-term efficacy [20]. DPP-4 inhibitors (e.g., sitagliptin, saxagliptin) enhance endogenous incretin activity, by inhibiting the enzyme that breaks down GLP-1 and GIP [43]. These medications help improve glycemic control with a lower risk of hypoglycemia compared to traditional therapies.

Recent studies are also exploring the broader therapeutic potential of incretin-based therapies. Several combination therapies (more than one incretin peptide; with or without other

diabetes drugs) are now in clinical trials [44]. Ongoing research continues to uncover the full therapeutic potential of incretins, offering hope for improved treatment strategies in metabolic disorders and beyond [45].

Any list of candidate diseases that could benefit from these agents is bound to be incomplete, given the extraordinary number of ongoing clinical trials and the possibility of combining the new agents together or other conventional therapeutics. Additionally, the already reported efficacies and side effects need to be independently verified to avoid false discovery and false hopes, especially for serious diseases that currently do not have effective therapies (such as neurodegeneration).

To recognize the importance of these new agents as therapeutics, the prestigious 2024 Lasker-DeBakey Clinical Medical Research Award has been presented to Svetlana Mojsov, PhD, Joel Habener, MD, and Lotte Bjerre Knudsen, DMSc, for the discovery of GLP-1 for the treatment of obesity [46]. The Lasker Award is considered a reliable prodromal to the Nobel Prize.

Future Directions

The incretins as pharmacological agents have been highly successful for the treatment of diabetes and weight control. Preliminary evidence from small clinical trials suggests a much broader therapeutic benefit, for diseases that did not seem to be related to the pathogenesis of diabetes or obesity. A hypothesis that could explain this surprising finding evolves around the central role of inflammation in a myriad of diseases and the ability of incretins to reduce it.

The future of GLP-1 and related molecules is undoubtedly very bright. New derivatives and combinations will likely lead to even more effective and safer formulations that will have more lasting effects. This is currently an important limitation since it has been shown that drug withdrawal leads to regaining most of the lost weight, and sustained therapy interventions are needed to maintain benefits [47]. Long-term trials have also reported dropout rates, often due to adverse effects and tolerability issue; guidelines to minimize occurrence and severity have been suggested, as well as ways to mitigate the adverse effects after they have appeared [48]. The expected decrease in production costs will catalyze their even more widespread use for diseases that currently have no treatments. The completion of large, multicenter placebo-controlled prospective clinical trials will shed more light on the optimal use of these agents.

Declarations

Authors' disclosures

The authors have no conflicts to report.

Authors' contributions

MKC drafted and edited the manuscript and prepared Tables 2 and 3. EPD conceptualized, drafted the manuscript, and prepared Table 1.

Ethical approval and human subject authorization

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Non-standard abbreviations

CNS, central nervous system; DPP-4, Dipeptidyl Peptidase-4; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; GPCR, G protein-coupled receptor; NSAIDs, nonsteroidal anti-inflammatory drugs; DMARDs, disease-modifying antirheumatic drugs; T2D, Type-2 diabetes; VHA, Veterans Health Administration.

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