climate change. Responsible solutions to the problem of pervasive PFAS uses require acknowledging both immediate and long-term impacts through life cycle analysis frameworks. A strategy that takes into account both timescales ensures that PFAS-free alternatives will avoid unintended issues while meeting essential needs.

For alternatives to PFAS, setting realistic expectations is important. Not all substitutes may immediately match the performance of well-established chemicals that have been optimized over decades of use (*14*). However, these differences do not outweigh the enormity of risks posed by PFAS and the large cost of remediating widespread contamination. Transitioning away from PFAS requires some trade-offs, at least temporarily, until alternative solutions can be further refined. Giving appropriate weight to health, safety, and environmental stewardship means that such compromises are necessary. With collaborative research and development, performance gaps will narrow over time, just as they have for many other regulated chemicals. Meanwhile, uses where adequate substitutes already exist should transition rapidly. Remaining applications can buy time through risk-reduction measures while innovation occurs. Continuing the widespread use of PFAS can no longer be justified given the consequences. Moving forward will take open-minded problem-solving and willingness to accept a diversity of different solutions (*15*). ■

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MEDICINE

The benefits of GLP-1 drugs beyond obesity

Glucagon-like peptide–1–based medicines have weight loss–independent actions

By **Daniel J. Drucker**

Glucagon-like peptide–1 (GLP-1) is secreted from gut endocrine cells in response to food ingestion and acts as an incretin hormone to potentiate glucose-dependent insulin secretion. Pharmacological GLP-1 receptor (GLP-1R) activation reduced glucagon secretion (which raises blood glucose) and gastric emptying, leading to the development of GLP-1 therapies for the treatment of type 2 diabetes (T2D). GLP-1R is expressed on several pancreatic islet cell types and within multiple regions of the central nervous system. Subsequent studies revealed that exogenous GLP-1 administration inhibited food intake through brain GLP-1R activation in animals and humans, leading to weight loss. The decades-long use of GLP-1 medicines, principally acylated peptides such as liraglutide and semaglutide, for the treatment of obesity and T2D (*1*) has revealed that they also exert pleiotropic actions beyond glucose and weight control, such as reduction of heart and kidney diseases. There are several potential mechanisms underlying these benefits, such as reducing systemic inflammation (*2*), which have implications for future clinical applications and drug development.

The first approved GLP-1 medicines, such as exenatide and liraglutide, required once- or twice-daily administration and were followed by longer-acting versions such as dulaglutide, exenatide once weekly, semaglutide, and tirzepatide [a glucose-dependent insulinotropic polypeptide receptor (GIPR) and GLP-1R coagonist] that are suitable for once-weekly administration. A major nonmetabolic benefit of GLP-1 therapies became evident in the cardiovascular system. A series of preclinical studies demonstrated that GLP-1R agonists protect ischemic myocardium and preserve cardiac function after ischemic cardiac injury, actions that are independent of glucose control or weight loss (*1*). GLP-1 medicines were studied in eight distinct cardiovascular outcome trials in people with T2D, and one trial in people with obesity. Long-acting GLP-1 medicines that are continuously present in the circulation reduced rates of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death in people with T2D and/or obesity. Subsequent trials demonstrated a benefit for semaglutide in people with heart failure with preserved injection fraction, with or without T2D (NCT04788511).

How might this happen? Indirect roles for the cardiovascular benefit of GLP-1 drugs include reduction of blood pressure and attenuation of atherogenic lipoproteins secreted from the gut, better control of blood glucose, and weight loss. However, preclinical studies demonstrate that GLP-1 protects the ischemic heart in normotensive nondiabetic animals to a greater extent than achieved with weight loss. Furthermore, a long-acting GLP-1 therapy, albiglutide, withdrawn from the market owing to modest efficacy for reduction of glucose and body weight in people with T2D, reduced the rates of major adverse cardiovascular events by 22% (NCT02465515).

Mechanistically, the distribution of GLP-1R expression differs in the mouse versus the human heart, challenging the utility of preclinical studies for inferring underlying mechanisms in humans. GLP-1 therapies also reduce the development of atherosclerosis in sensitized mouse models, and clinical trials are underway in people with peripheral artery disease (NCT04560998). The mechanisms linking GLP-1R activation to the reduction of atherosclerosis and/or improved blood flow are not well understood but may be independent of weight loss and are instead associated with reduced inflammation. Interestingly, the cardioprotective effect of semaglutide observed in people with obesity developed within months of drug initiation, well before meaningful weight loss had been achieved in most trial participants. Furthermore, in the SELECT cardiovascular outcome trial (NCT03574597) studying semaglutide in people with obesity, the extent of weight loss did not correlate with the effects of the drug to reduce heart attacks, stroke, and cardiovascular death. Whether GLP-1 medicines might be cardioprotective in people with type 1 diabetes, or nondiabetic individuals at

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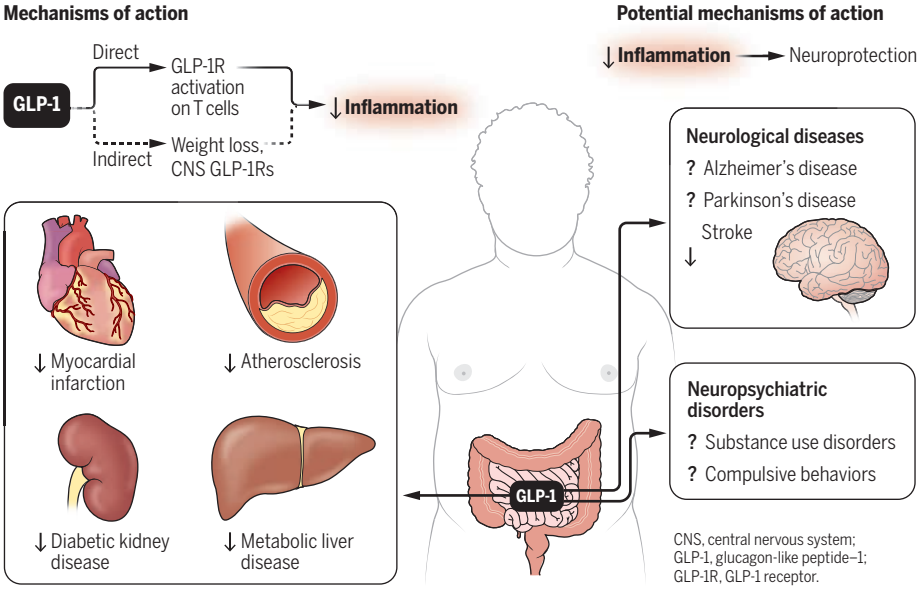
The actions of GLP-1 medicines

GLP-1 exerts direct and indirect actions to reduce glucose and body weight. GLP-1 attenuates inflammation indirectly through weight loss and neuronal GLP-1R activation and directly through GLP-1R activation on T cells, while reducing complications by targeting GLP-1R in multiple organs. Originally shown to reduce blood glucose and body weight, subsequent trials demonstrated that GLP-1 medicines reduce the cardiorenal complications of metabolic disease. GLP-1 medicines are currently being explored in a wide range of neurological and psychiatric disorders.



high risk for stroke or myocardial infarction, has not been studied.

Clinical trials and animal studies also support a role for GLP-1 medicines in the treatment of people with metabolic liver disease, and a phase 3 trial is underway with semaglutide (NCT04822181). GLP-1R is not expressed by hepatocytes, challenging the understanding of how GLP-1 improves liver health. Although weight loss is associated with a reduction of hepatic steatosis and inflammation, preclinical experiments implicate rare populations of intrahepatic GLP-1R–expressing cells, largely endothelial cells and T cells (*3*), as contributing to the therapeutic benefits of GLP-1 in metabolic liver disease. Intriguingly, semaglutide reduces the rate of kidney disease and cardiovascular death by 24% in people with T2D (NCT03819153), and gain and loss of GLP-1R signaling improves or deteriorates kidney function, respectively, in animal models of renal injury (*4*). The understanding of the renal mechanisms of GLP-1 action is incomplete. Although sustained GLP-1R agonism reverses diabetes-induced dysregulation of gene expression in multiple renal cell types, GLP-1R expression in the kidney is localized to a subset of vascular smooth muscle cells, but not glomerular epithelial or tubular cells, in the rodent and human kidney (*5*). Hence, whether the effects of GLP-1 medicines on the kidney reflect direct renal effects or indirect contributions from extrarenal GLP-1R$^+$ cell populations remains uncertain.

The heart, blood vessels, liver, and kidney contain populations of GLP-1R$^+$ cells that might contribute to organ protection (*5*). Another potentially unifying mechanism of action for GLP-1R agonism is the reduction of inflammation (see the figure). The enteroendocrine L cells within the mucosa of the small and large intestine function as pathogen sensors, secreting GLP-1 in response to infection or sterile tissue injury (*6*). GLP-1 in turn acutely reduces gut and systemic inflammation in animals and humans. Populations of intestinal intraepithelial lymphocytes (IELs) and some exhausted T cells are the predominant cellular sites of GLP-1R expression in the immune system (*7*). The IEL GLP-1R is required for transducing the local and systemic anti-inflammatory actions of GLP-1 when inflammation is induced through activation of T cells, for example, using antibodies targeting the T cell coreceptor CD3 (*8*). Nevertheless, the IEL GLP-1R is dispensable for the anti-inflammatory actions of GLP-1 when inflammation is induced by multiple toll-like receptor (TLR) ligands, exemplified by lipopolysaccharide (LPS) (*2, 8*). Unexpectedly, the systemic anti-inflammatory actions of GLP-1 that attenuate TLR-activated inflammation require GLP-1R signaling in the brain, within neurons (*2*). Moreover, α_1-adrenergic and δ-and κ-opioid receptor signaling are critical for transduction of the systemic anti-inflammatory actions of GLP-1 medicines. Brain GLP-1R is also required for the actions of GLP-1 medicines to attenuate systemic inflammation in the lungs and myeloid cells of mice with polymicrobial sepsis (*2*).

Gain and loss of GLP-1R signaling attenuates or exacerbates, respectively, the extent of neurodegeneration and neuroinflammation in experimental mouse models of brain injury, stroke, or neurodegeneration (*9, 10*). Several clinical trials have examined the therapeutic potential of exenatide in people with Parkinson's disease, with mixed results. A larger phase 3 trial is examining the potential efficacy of once-weekly exenatide in Parkinson's disease (NCT04232969). Interrogation of real-world health care databases and clinical trial data link the use of GLP-1 medicines to reduced rates of cognitive dysfunction in people with T2D, and two phase 3 trials, EVOKE (NCT04777396) and EVOKE Plus (NCT04777409), are assessing the impact of oral semaglutide in individuals at risk for progressive cognitive dysfunction (*10*).

The expanding use of more potent GLP-1 medicines such as semaglutide and tirzepatide that produce greater reductions in blood glucose and more weight loss in people with T2D or obesity has fostered scrutiny of whether these medicines might modify the outcomes of multiple central nervous system disorders, including depression, compulsive behaviors, excessive use of alcohol or narcotics, and suicidal ideation. Reports of psychiatric disorders in the SELECT cardiovascular outcome trial were not different over more than 3 years of exposure in people with overweight or obesity and a history of cardiovascular disease randomized to semaglutide (n = 8803) versus placebo (n = 8801) (*11*). Analysis of rates of new or recurrent suicidal ideation in two different real world cohorts within large health care databases of people with overweight or obesity, with or without T2D, revealed lower rates of suicidal ideation in those receiving semaglutide, compared to users of other glucose-lowering or weight loss agents. Hazard ratios (which quantify the relative chance of an event occurring) were 0.27 and 0.44 for new or recurrent reports of suicidal ideation, reflecting reduced rates in semaglutide-treated individuals (*12*). Moreover, analysis of electronic health records in the TriNetx network revealed lower rates of new or recurrent cannabinoid use disorder, in people with T2D and or overweight or obesity, relative to use of non–GLP-1 glucose-lowering or weight-reducing medicines, respectively (*13*).

Although anecdotal reports of reduced alcohol use with GLP-1 medicines are common, the results of randomized trials are inconclusive. Individuals treated with du-

laglutide for 12 weeks with the primary goal to examine smoking cessation reported reduced alcohol consumption (*14*), whereas people with alcohol use disorder randomized to exenatide once weekly for 26 weeks did not reduce the overall number of heavy-drinking days, despite exhibiting attenuated alcohol cue reactivity in the septal and ventral striatum regions of the brain, as determined by functional magnetic resonance imaging (*15*). Anecdotal reports of improvements in a wide range of dependence-related behaviors have prompted initiation of multiple randomized controlled trials to determine whether GLP-1 medicines might have therapeutic utility in these disorders.

The success of GLP-1 medicines for T2D and obesity has fostered interest in developing next-generation therapies that are even more effective and produce greater weight loss than current GLP-1R agonists. Tirzepatide simultaneously targets GIPR and GLP-1R, resulting in unprecedented glycemic control and weight loss (*1*). Like GLP-1, GIP is also a gut peptide that is important for physiological control of blood glucose, and pharmacological activation of GIPR with a long-acting GIPR agonist also produces weight loss in humans (NCT04586907). As GIP and GLP-1 exert complementary actions through distinct receptors, simultaneous activation of both receptors provides an opportunity to maximize metabolic benefits beyond targeting only one receptor. Additional GLP-1 medicines under clinical development include those that are combined with GIPR antagonists, glucagon receptor or GLP-2R agonists, or amylin receptor agonists. The goal is to achieve greater weight loss while preserving or ideally enhancing the cardiorenal and hepatic actions of current GLP-1R agonists. These new medicines are most often designed as peptides for parenteral administration, and in some cases, developed as small molecules or peptides formulated for oral administration.

How might these emerging combinations improve outcomes in people with T2D or obesity, at risk for developing cardiovascular, kidney, liver, or neurodegenerative disease? The receptors for glucagon, GIP, and amylin are all expressed within the central nervous system, but much less is known about their potential for neuroprotection, relative to GLP-1R agonism. These receptors are not highly expressed in the human heart, and their likelihood of modifying GLP-1–mediated cardioprotection has not been carefully scrutinized. Glucagon receptors are expressed in hepatocytes and kidney cells, and the available data suggest that glucagon receptor activation may confer additional benefits, perhaps reducing rates of metabolic liver disease and diabetic kidney disease beyond that possible with GLP-1 alone. Although a short-acting amylin analog, pramlintide, has been approved for the treatment of diabetes in the United States for 19 years, amylin receptors are expressed predominantly in the nervous system, and there are no definitive studies examining whether amylin receptor agonism improves long-term health outcomes. A GLP-2 analog, teduglutide, has been used for more than a decade to treat intestinal failure, and GLP-2R agonism may improve gut barrier function and reduce liver inflammation. However, clinical experience with GLP-2R agonists in people with T2D or obesity, alone or in combination with GLP-1R agonists, is limited.

The initial chapter of GLP-1 innovation focused on glucose control, and later, weight loss. Subsequent waves seem likely to improve health outcomes in people with a range of chronic disorders. Dozens of new molecules are being interrogated in the clinic, with some likely to target new mechanisms and achieve greater benefits in multiple disorders beyond simply more effective glucose control and weight loss. A wide range of clinical trials is underway, with results likely to support expansion of the range of clinical indications benefiting from GLP-1 therapies. Hence, after almost two decades of the clinical use of GLP-1 for T2D and 10 years after the first GLP-1 medicine, liraglutide, was approved for weight loss in people with obesity, the next decade may bring even greater progress, introducing more powerful GLP-1 medicines while expanding the utility of GLP-1 therapeutics beyond currently established cardiometabolic disorders. ■

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ECOLOGY

A hard fruit to swallow

Foraging niches become more specialized toward bird range limits

By **Anna L. Hargreaves**[1] *and* **Jake M. Alexander**[2]

Children are often taught about the natural world through facts about species, such as what a toucan eats. Yet species are not homogeneous, and different populations within a species vary in how they use their environment. Gaining a better understanding of this variation is a key challenge in ecology. One idea is that niche variation should be particularly apparent toward the edges of species' geographic distributions, where the amount or quality of habitat declines (*1*). However, there is little theory that predicts which niche components will vary toward range edges and remarkably few compelling examples from nature. On page 331 of this issue, Martins *et al.* (*2*) offer both, combining optimal foraging theory and observed foraging patterns to predict and demonstrate that fruit-eating (frugivorous) birds have narrower diet niches toward the edges of their geographic ranges. Accounting for such heterogeneity in resource use will be important for accurately predicting species' responses to environmental change (*3*, *4*).

Optimal foraging theory predicts that for a given set of environmental constraints, a population will evolve a foraging strategy (where, when, and what to eat) that maximizes fitness (*5*, *6*). Martins *et al.* argued that under environmentally stressful conditions, such as the edges of species' ranges, birds face more stringent energetic constraints and predicted that the optimal foraging strategy for frugivorous birds would be to eat the biggest fruits they can fit in their beaks. Combining large datasets on species traits, interactions, and geographic distributions, they showed that frugivorous birds do indeed maximize the match between fruit size and beak size more closely at their range edges than in their range center, resulting in a narrower

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