GLP-1RA – LIJEKOVI KOJI SU PROMIJENILI PRIČU O PRETILOSTI

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Agonisti receptora glukagonu sličnog peptida-1 (GLP-1RA) predstavljaju značajnu klasu lijekova u modernoj terapiji. Ovi lijekovi su sintetske verzije prirodnog ljudskog hormona i prilagođeni su radi bolje stabilnosti i učinkovitosti. Ovaj sažetak pruža detaljan pregled GLP-1RA, pokrivajući njihov mehanizam djelovanja, kliničku primjenu, dokazanu učinkovitost u kontroli tjelesne težine i njihov složeni sigurnosni profil. Agonisti GLP-1 receptora su sintetski analozi ljudskog inkretinskog hormona GLP-1. Ključna značajka dizajna je njihova otpornost na proteolizu (razgradnju) enzimom dipeptidilpeptidaza-4 (DPP-4). Ova otpornost im omogućuje da dulje ostanu u tijelu, što rezultira višim koncentracijama u plazmi i značajno poboljšanim farmakološkim učincima u usporedbi s izvornim hormonom. Terapijske koristi ove klase lijekova proizlaze iz njihovog višestrukog utjecaja na metaboličke procese u tijelu. Primarni učinci uključuju stimulaciju lučenja inzulina, smanjenje apetita i usporavanje pražnjenja želuca. GLP-1RA djeluju na β-stanice gušterače kako bi potaknule oslobađanje inzulina na način ovisan o glukozi, što pomaže u regulaciji razine glukoze u krvi. GLP-1RA djeluju na receptore u mozgu kako bi povećali osjećaj sitosti i smanjili apetit. Usporavanjem brzine kojom hrana napušta želudac, GLP-1RA doprinose produljenom osjećaju sitosti nakon obroka, dodatno pomažući u kontroli apetita. GLP-1RA se mogu grubo podijeliti u dvije skupine na temelju učestalosti aplikacije i trajanju učinka: kratkodjelujuće i dugodjelujuće formulacije. Kako bi se smanjile nuspojave i poboljšala suradljivost pacijenata, jednom tjedno dugodjelujući pripravci postali su preferirani izbor, pojednostavljujući režim liječenja za pacijente. Što se tiče primjene, gotovo svi lijekovi u ovoj kategoriji primjenjuju se potkožnom injekcijom. Najčešće prijavljene nuspojave su gastrointestinalne prirode. Pacijenti koji započinju ili titriraju terapiju GLP-1RA mogu osjetiti mučninu, povraćanje i proljev, koji su najčešći na početku terapije i postupno nestaju. Učinkovitost GLP-1RA u poticanju gubitka težine snažno je potkrijepljena kliničkim podacima. U kliničkim ispitivanjima, pacijenti s pretilošću ili prekomjernom težinom koji su uzimali 2,4 mg semaglutida tjedno doživjeli su prosječno smanjenje tjelesne težine od 14,9% do 17,3% tijekom 68 tjedana u usporedbi s 2,4% u placebo skupini. Nedavni razvoj dvostrukih agonista koji ciljaju i GLP-1 i GIP receptore ima za cilj sinergijski pojačati njihove učinke. Tirzepatid predstavlja značajan napredak u metaboličkoj terapiji, konstruiran kao jednomolekularni ili unimolekularni dvostruki agonist. Ovaj peptid od 39 aminokiselina istovremeno cilja dva ključna inkretinska

hormonska receptora: receptor glukagonu sličan peptid-1 (GLP-1) i receptor glukozno ovisnog inzulinotropnog polipeptida (GIP). Aktiviranjem oba puta, tirzepatid nudi višestruki pristup kontroli glikemije i upravljanju težinom, što ga razlikuje od terapija koje ciljaju samo GLP-1 receptor. Terapijska učinkovitost tirzepatida ukorijenjena je u njegovoj jedinstvenoj interakciji s GIP i GLP-1 receptorima. Razumijevanje različitih i komplementarnih uloga ova dva nativna hormona ključno je za razumijevanje mehanizma lijeka. GIP snažno pojačava glukozom stimuliranu sekreciju inzulina iz beta stanica gušterače, pomažući u upravljanju porastima glukoze u krvi nakon obroka i povećanog protoka krvi u masno tkivo. GIP također doprinosi boljoj kvaliteti kosti zbog utjecaja na smanjenje njene resorpcije. Kod hipoglikemije, GIP stimulira oslobađanje glukagona, što pomaže u sprječavanju opasno niskih razina glukoze. Molekula tirzepatida pokazuje nijansirani afinitet vezanja za svoje ciljne receptore. Njegov afinitet za GIP receptor usporediv je s afinitetom nativne molekule GIP-a, što mu omogućuje robusno oponašanje prirodnih učinaka GIP-a. Nasuprot tome, njegov afinitet vezanja za GLP-1 receptor približno je pet puta niži od afiniteta nativnog GLP-1. Ovaj „neuravnoteženi" agonizam, s jakom preferencijom za GIP receptor, definirajuća je karakteristika lijeka i smatra se ključnim za njegove snažne učinke i na glukozu i na težinu. Tirzepatid se primjenjuje potkožnom injekcijom jednom tjedno. Najčešće prijavljene nuspojave su gastrointestinalne prirode. Među njima su mučnina i proljev najčešći. Ove nuspojave su karakteristično ovisne o dozi i najizraženije su na početku. U kliničkim ispitivanjima, sudionici s pretilošću i bez dijabetesa tipa 2 koji su uzimali najveću dozu (15 mg) izgubili su u prosjeku 20,9% tjelesne težine, pri čemu je 91% tih sudionika postiglo više od 5% smanjenja težine.

Ključne riječi

debljina, glp-1, farmakodinamika, farmakokinetika, učinkovitost, nuspojave

GLP-1RA – DRUGS THAT CHANGED THE STORY OF OBESITY

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Glucagon-like peptide-1 receptor agonists (GLP-1RA) represent a significant class of medications in modern therapeutics. These drugs are synthetic versions of a naturally occurring human hormone and have been engineered for enhanced stability and efficacy. This abstract provides a detailed examination of GLP-1RAs, covering their mechanism of action, clinical applications, demonstrated efficacy in weight management, and their complex safety profile. GLP-1 receptor agonists are synthetic analogs of the human incretin hormone GLP-1. A key design feature is their resistance to proteolysis (breakdown) by the enzyme dipeptidyl peptidase 4 (DPP-4). This resistance allows them to persist in the body for longer periods, resulting in higher plasma concentrations and significantly enhanced pharmacological effects compared to the native hormone. The therapeutic benefits of this class of medications stem from their multi-faceted impact on the body's metabolic processes. The primary effects include stimulation of insulin secretion, appetite reduction and

slowing of gastric emptying. GLP-1RAs act on the β-cells of the pancreas to promote the release of insulin in a glucose-dependent manner, which helps regulate blood sugar levels. GLP-1Ras act on receptors in the brain to increase feelings of satiety and reduce appetite. By delaying the rate at which food leaves the stomach, GLP-1RAs contribute to a prolonged sense of fullness after meals, further aiding in appetite control. GLP-1RAs can be broadly categorized into two groups based on their injection frequency and duration of effect: short-acting and long-acting formulations. To minimize side effects and to improve patient compliance once-weekly long-acting preparations, have become the preferred choice, simplifying the treatment regimen for patients. Regarding administration, nearly all drugs in this category are administered via subcutaneous injection. The most frequently reported adverse events are gastrointestinal in nature. Patients initiating or titrating GLP-1RA therapy may experience nausea, vomiting, and diarrhea which are most common at the beginning of therapy and gradually disappear. The effectiveness of GLP-1RAs in promoting weight loss is robustly supported by clinical data. In clinical trials, patients with obesity or overweight taking 2.4 mg of weekly semaglutide experienced an average body weight reduction of 14.9% to 17.3% over 68 weeks compared to 2.4% in the placebo group. Recent development in dual agonists targeting both GLP- 1 and GIP receptors aim to enhance their effects synergistically. Tirzepatide represents a significant advancement in metabolic therapy, engineered as a single-molecule, or unimolecular, dual agonist. This 39-amino acid peptide simultaneously targets two key incretin hormone receptors: the glucagon-like peptide-1 (GLP-1) receptor and the glucose-dependent insulinotropic polypeptide (GIP) receptor. By engaging both pathways, tirzepatide offers a multi-faceted approach to glycemic control and weight management, distinguishing it from therapies that target only the GLP-1 receptor. The therapeutic efficacy of tirzepatide is rooted in its unique interaction with both GIP and GLP-1 receptors. Understanding the distinct and complementary roles of these two native hormones is crucial to appreciating the drug's mechanism. GIP potently boosts glucose-stimulated insulin secretion from pancreatic beta-cells, helping to manage post-meal blood sugar spikes and increases blood flow to adipose tissue. GIP also contributes to bone health by reducing bone resorption. In hypoglycemia GIP stimulates the release of glucagon thereby helping to prevent dangerously low glucose levels. Tirzepatide's design exhibits a nuanced binding affinity for its target receptors. Its affinity for the GIP receptor is comparable to that of the native GIP molecule, allowing it to robustly mimic GIP's natural effects. In contrast, its binding affinity for the GLP-1 receptor is approximately five times lower than that of native GLP-1. This "imbalanced" agonism, with a strong preference for the GIP receptor, is a defining characteristic of the drug and is thought to be key to its potent effects on both glucose and weight. Tirzepatide is administered via subcutaneous injection once a week. The most commonly reported adverse effects are gastrointestinal in nature. Among these, nausea and diarrhea are the most frequent. These side effects are characteristically dose-dependent and most pronounced at initiation. In clinical trials, participants with obesity

and without type 2 diabetes taking the highest dose (15 mg) lost an average of 20.9% of their body weight, with 91% of those participants achieving more than 5% of weight reduction.

Keywords

obesity, glp-1, pharmacodynamics, pharmacokinetics, efficacy, side-effects

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