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OZEMPIC (SEMAGLUTIDE): A NEW WEIGHT LOSS DRUG FOR CHRONIC WEIGHT MANAGEMENT

Khalid Abdullah Alsefri[1]*, Mohammed Ayed Alsefri[2], Morad Ayed Alsefri[3] and Abdullah Salem Alharbi[4]

[1*]Pharmacist, Kaalsefri@moh.gov.sa , Alazizyah Children Hospital - Jeddah
[2]Pharmacy Technician, maalsefri@moh.gov.sa, King Abdullah Medical Complex - Jeddah
[3]Pharmacy Technician, moradaa@moh.gov.sa, East Jeddah Hospital-Jeddah
[4]Pharmacist, Aalharbi561@moh.gov.sa, East Jeddah Hospital - Jeddah

***Corresponding Author:** Khalid Abdullah Alsefri
Email: Kaalsefri@moh.gov.sa

Abstract

Background: Obesity is a chronic, relapsing disease that imposes significant costs on individuals, society, and the economy. Semaglutide is thought to cause weight loss by improving appetite control and, as a result, reducing energy intake through effects in the hypothalamus and the area postrema of the brain

Methodology: A numbers of 9 mice were subjected to semaglutide uptake, in King Abdulaziz medical city research laboratory، Riyadh, KSA.Data were analysed with statistical package of social sciences (SPSS).

Results: The results showed BW decreased by 22% at the highest dose tested (mean ± SEM, 100 nmol/kg from 43.6 ± 1.6 g to 34.8 ± 1.4 g) and 10% at the lowest dose tested (mean ± SEM, 1 nmol/kg, from 42.5 ± 1.3 g to 38.2 ± 1.3 g)

Conclusion: Fluorescently labelled semaglutide was detected in regions traditionally associated with GLP-1R-mediated food intake regulation, such as the hypothalamic ARH in the brainstem. The ARH mediates liraglutide-regulated food intake and weight loss through direct activation.

Keywords: Ozempic, Semaglutide, Weight Management new drug, A New Weight Loss Drug, Obesity new drug

1. Introduction

Obesity is a chronic, relapsing disease that imposes significant costs on individuals, society, and the economy. Maintaining long-term weight loss is difficult due to metabolic adaptation and the difficulty of adhering to lifestyle interventions3, with weight regain common after weight loss.[1]

Sustained weight loss of 5% to 15% is recommended to improve many conditions associated with overweight/obesity, with adjunctive pharmacotherapy used to aid in this goal.However, approved antiobesity medications have only moderate efficacy (a 3%-8% reduction in body weight over lifestyle intervention alone). Short-term treatment (3-6 months) does not produce long-term health benefits, and several agents raise safety concerns. Well-tolerated new therapies that can produce significant, sustained weight loss when used over time are therefore required.[2]

Semaglutide, a glucagon-like peptide 1 (GLP-1) receptor agonist, is approved for the treatment of type 2 diabetes at doses of 1.0 mg or less once weekly. Semaglutide is thought to cause weight loss

by improving appetite control and, as a result, reducing energy intake through effects in the hypothalamus and the area postrema of the brain. In the global phase, once-weekly subcutaneous semaglutide (2.4 mg) is being studied for the treatment of overweight/obesity. Semaglutide Treatment Effect in People With Obesity (STEP) Programme.[3]

Semaglutide accessed the brainstem, septal nucleus, and hypothalamus but did not cross the blood-brain barrier; instead, it interacted with the brain via the circumventricular organs and a few select sites adjacent to the ventricles. Semaglutide activated central c-Fos in ten brain areas, including those directly targeted by semaglutide and secondary areas without direct GLP-1R interaction, such as the lateral parabrachial nucleus. Automated analysis of semaglutide access, c-Fos activity, GLP-1R distribution, and brain connectivity revealed that activation may involve meal termination mediated by neurons in the lateral parabrachial nucleus. [4]

2. Literature review

Patients with obesity are more likely to develop comorbidities such as hypertension, type 2 diabetes, hyperlipidemia, stroke, and even certain cancers. As a result, they are at a higher risk of dying from cardiovascular complications, which are the leading cause of death in obese patients.[5]

Lifestyle changes can reduce the risk of developing cardiovascular complications, but patients often struggle to maintain any weight loss they have achieved. If lifestyle changes do not produce significant results, the addition of pharmacotherapeutics may help to promote weight loss.[6]

There are four FDA-approved weight loss medications on the market: phentermine-topiramate (Qsymia), orlistat (Xenical), naltrexone-bupropion (Contrave), and liraglutide (Saxenda), a glucagon-like peptide-1 receptor agonist (GLP-1).[7]

Lorcaserin (Belviq) was previously approved by the FDA, but it was recalled in early 2020 due to an increased risk of malignancy. Ozempic (semaglutide), the GLP-1 RA, received FDA approval in 2021.[8]

GLP-1 receptor agonists have repeatedly demonstrated promising results in weight loss in obese patients with and without diabetes.3489 They are also effective at improving glycemic control by increasing insulin secretion and decreasing glucagon secretion without causing hypoglycemia. Although their weight-loss effects are well known, the mechanism underlying them is still unclear. The majority of studies into the underlying mechanisms of GLP-1 on appetite and weight loss have focused on liraglutide.[9]

The most well-known mechanisms involve the central and peripheral nervous systems, with direct activation of the hypothalamus and hindbrain or indirect activation via the vagus nerve resulting in reduced appetite and food intake. GLP-1 can influence reward and motivation reactions to food through projections from the nucleus tractus solitarius in the hindbrain to the ventral tegmental area and the nucleus accumbens, lowering overall palatability. GLP-1 RAs have also been shown to delay gastric emptying, but the effect on overall weight loss appears to be minimal. Overall, it appears that the mechanisms affect energy intake rather than resting metabolic rate.[10]

The trial previous study looked at the primary causes of weight loss in patients taking semaglutide (Ozempic), a relatively new GLP-1 RA that is only available as an antidiabetic in injectable and oral tablet form. Lower energy intake was thought to be the primary cause of weight loss.[11] The Semaglutide Treatment Effect in People with Obesity (STEP) programme is a phase III clinical trial aimed at obtaining approval for semaglutide as a weight loss medication in obese patients. This programme included five trials that compared 2.4 mg, once-weekly, subcutaneous semaglutide to placebo treatment. This trial programme did not compare semaglutide to other antiobesity medications currently available on the market. Results have shown that 2.4 mg semaglutide, when used in combination with lifestyle modifications, shows clinically significant weight loss in patients with obesity compared with placebo.[12]

3. Methodology

A numbers of 9 mice were subjected to semaglutide uptake, in King Abdulaziz medical city research laboratory، Riyadh, KSA.

Mice received VivoTag750-S-labeled semaglutide (semaglutideVT750) and were compared to mice injected with vehicle.
Animals were subjected to a 12-hour light/12-hour darkness cycle. RER is an abbreviation for respiratory exchange ratio, and sema stands for semaglutide. A three-week on DIO mice, semaglutide reduced BW and suppressed food intake. Semaglutide targets GLP-1R-positive brain areas after peripheral administration.[13]
Data were analysed with statistical package of social sciences (SPSS).

4. Results

The results showed BW decreased by 22% at the highest dose tested (mean ± SEM, 100 nmol/kg from 43.6 ± 1.6 g to 34.8 ± 1.4 g) and 10% at the lowest dose tested (mean ± SEM, 1 nmol/kg, from 42.5 ± 1.3 g to 38.2 ± 1.3 g) (Figure 1, A & B). In addition to the changes in BW, reductions in fat mass were seen.
In contrast, the effect on lean mass was minor and insignificant in relation to vehicle control. The highest dose of semaglutide (mean ± SEM, 100 nmol/kg) resulted in the greatest reduction in food intake within the first 5 days, with a reduction of 68.2% ± 4.3% compared to the vehicle. In DIO rats, a similar pattern of body weight loss and transient food intake suppression was observed.

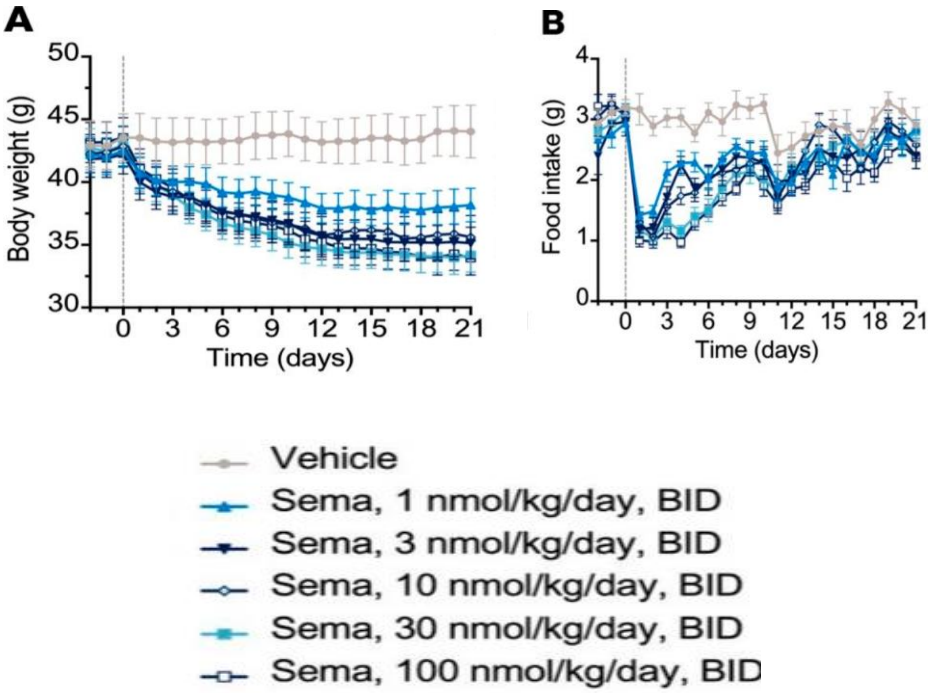

Figure 1 (A and B) shows BW and food intake in DIO mice treated with semaglutide twice daily (n = 9).
Semaglutide treatment resulted in a significant and dose-dependent reduction in body weight (Figure 1I, $P < 0.05$ for 0.3 nmol/kg semaglutide; $P < 0.001$ for 1 nmol/kg semaglutide) compared to controls.

5. Discussion

Semaglutide causes weight loss, reduces food intake, and alters food preferences in diet-induced obese rodents. Diet-induced obese (DIO) mice and rats fed a high-fat diet received semaglutide subchronically, and the effects on food intake and body weight were evaluated.
The mechanism of action of semaglutide in obese patients is similar to that of liraglutide primarily energy intake reduction but semaglutide has also been shown to improve control of eating and food cravings, as well as reduce preference for fatty, energy-dense foods, implying that semaglutide may affect food intake via both hedonic and homeostatic pathways.

Characterization of GLP-1R neuron phenotypes in areas directly targeted by semaglutide revealed that proteins involved in appetite regulation coexpress with GLP-1R.[14]

6. Conclusions

Fluorescently labelled semaglutide was detected in regions traditionally associated with GLP-1R-mediated food intake regulation, such as the hypothalamic ARH in the brainstem. The ARH mediates liraglutide-regulated food intake and weight loss through direct activation.

7. References

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