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Original Article

Proof of concept: Effect of GLP-1 agonist on food hedonic responses and taste sensitivity in poor controlled type 2 diabetic patients

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ABSTRACT

Aims: GLP-1 analogues decrease food intake and have great promise for the fight against obesity. Little is known about their effects on food hedonic sensations and taste perception in poor controlled patients with type 2 diabetes (T2D).
Materials and methods: Eighteen T2D patients with BMI $\geq$25 kg/m^2 and poor controlled glycemia were studied before and after 3 months of treatment with Liraglutide. Detection thresholds for salty, sweet and bitter tastes, optimal preferences, olfactory liking, wanting and recalled liking for several food items were assessed. Subjects also answered questionnaires to measure their attitudes to food.
Results: T2D patients had a significant decrease in bodyweight and HbA1c after treatment with Liraglutide. Liraglutide improved gustative detection threshold of sweet flavors, and decreased wanting for sweet foods and recalled liking for fatty foods. It also led to a decrease in feelings of hunger.
Conclusions: Liraglutide increases sensitivity to sweet tastes and decreases pleasure responses for fatty foods in poor controlled T2D patients, and is of particular interest in the understanding of the mechanisms of weight loss.
Clinical trial: NCT02674893.

1. Introduction

Glucagon like peptide-1 (GLP-1) analogues are currently used in the treatment of type 2 diabetes (T2D). In addition to their beneficial glucose lowering effects [1] (stimulates meal-related insulin secretions, inhibits glucagon release and delays gastric emptying), GLP-1 analogues have been shown to increase satiety [2]. These compounds have also been shown to reduce food intake and body weight in rodents and humans [2–4].

GLP-1 receptors (GLP-1Rs) are expressed in the periphery and in several brain areas involved in appetite regulation [5,6], and the stimulation of both central nervous and peripheral GLP-1Rs result in a decrease in food intake. The peripheral anorectic effects of GLP-1 have been shown to involve humoral and vagal afferent signalling from the gut to the brain [7]. The combined effects of GLP-1, that is to say satiation and weight loss, have great potential for the treatment of overweight or obese individuals with T2D.

Little is known about the effect of GLP-1 analogues on eating behavior. Eating habits are driven by homeostatic, pleasure and sensory perception systems which are closely related. In rats, 12 weeks of GLP-1 analogue therapy shifted food preferences towards an increase in the consumption of a chow diet and a decrease in candy intake [4]. Furthermore, Shin et al. [8] have shown that GLP-1

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is produced in mouse taste cells, and GLP-1 receptors are expressed on the adjacent intragemmal afferent nerve fibres. In addition, behavioural tests showed that GLP-1 receptor knockout mice had a strong decrease in taste responses to sweeteners, suggesting that GLP-1 maintains or enhances sensitivity to sweet tastes [8]. These results suggest a novel paracrine mechanism for the regulation of taste function with GLP-1. In obese type 2 diabetic individuals, a study [9] used functional MRI to demonstrate that GLP-1 induces increased central nervous system response to the ingestion of palatable foods. A recent study with Semaglutide [10] has shown in non-diabetic patients less appetite and food cravings, better control of eating and lower relative preference for fatty, energy-dense foods.

The objective of the present study was to evaluate the impact of liraglutide on taste sensitivity as well as on liking and wanting components of the food reward system in individuals with poor controlled type 2 diabetes yet treated with several antidiabetic drugs and for whom liraglutide treatment seemed well appropriate.

2. Subjects and materials and methods

2.1. Subjects

Eighteen T2D patients (6 men, 12 women) were recruited by the department of Endocrinology and Diabetology of the Dijon University Hospital. Liraglutide (NovoNordisk, Puteaux, France) therapy was indicated and prescribed in these patients because they had a body mass index (BMI) $\geq 25\ kg/m^2$ and difficulty regulating their blood glycaemia despite previous anti-diabetic treatment.

The patients were between 18 and 80 years old. Exclusion criteria were: impaired kidney function (creatinine clearance < 50 ml/min), pregnancy, congestive heart failure, acute and chronic infection, active cancer, cirrhosis, ongoing antibiotic treatment, smoking (more than 5 cig/day), alcohol consumption (more than 20 g/day), aversion to the foods eaten or smelled during the study, or impaired comprehension for cognitive tasks. Each patient signed a written consent form.

The T2D patients included in the study were first hospitalized in the department of Endocrinology and Diabetology for medical analyses, observations, experimental tests and treatment during 2.5 days. Once the initial tests were carried out, Liraglutide treatment was started. The initial dose was 0.6 mg/day subcutaneously during five days, which was then up-titrated to a daily dose of 1.2 mg. After three months of daily treatment, the patients returned to the hospital for a diabetes checkup and to undergo the same experimental tests during half a day, in external consultation.

2.2. Materials and Methods

The experimental tests were carried out in the morning. Blood samples were collected between 8:30 and 9:00 a.m. in patients who had fasted overnight. HbA1c levels were measured immediately after blood sampling by High Performance Liquid Chromatography (Variant, Tosoh Bioscience, Tokyo, Japan). Plasma ghrelin and leptin levels were measured (immediately separated after drawing and stored at −80 °C), using ELISA kits (Millipore, Billerica, USA for ghrelin; R&D systems, Abingdon, UK for leptin).

Taste detection thresholds were measured for salty, sweet and bitter tastes using the three-alternative forced-choice procedure (3-AFC) [10]. The 3-AFC consists in presenting three opaque plastic cups to the participants. Two of them contain 10 ml of water (Evian) and the other one contains 10 ml of the stimulus (sapid compounds diluted in Evian water). The participant had to taste the three samples and identify which one was different from the other two. The 3-AFCs were presented in ascending order of concentration until the participant correctly identified the stimulus. In this case, the same concentration was given to the participant twice more. If he correctly identified the stimuli, the test was stopped and the detection threshold was designated as the concentration at which the participant made three consecutive correct identifications. If the participant failed to identify the stimulus, the following concentration was presented, and so on [11]. The aqueous solutions containing the stimuli were as follows: 13 saccharose solutions (Cooper, Melun, France), for sweet detection thresholds and 13 sodium chloride solutions (Cooper, Melun, France) for salt detection thresholds with concentrations ranging from 0.001 to 1.0 M (dilutions increasing by increments of 0.25 log units); 13 quinine chlorhydrate solutions (Cooper, Melun, France) with a concentration ranging from 0.0001 to 0.1 mM (dilutions increasing by increments of 0.25 log units) for bitter taste detection thresholds.

Optimal taste preferences [12] were evaluated for cakes, cottage cheese and stewed fruit which were produced in five versions with different fat contents (cakes and cottage cheese) or sugar contents (other cakes and stewed fruit). For each variant of the food item, patients tasted the food and evaluated their experience using a 10-cm visual analog scale with the statements “not pleasant at all” (0) or “very pleasant” (+10) at each extremity.

Olfactory liking and wanting were then evaluated [13]. Olfactory liking was evaluated for food items rich in fat or carbohydrates. Each food was presented separately in a transparent 40 ml cup. The subjects had to sniff the food orthonasally and answer the following question: “When you smell this food, how pleasant would it be to eat a mouthful of this food now?” Olfactory liking was evaluated using 10-cm visual analog scales anchored at each end by the statements “not pleasant at all” (0) and “very pleasant” (+10). To measure wanting, the subjects were shown pictures of foods, some of which were fatty or carbohydrate-rich. The subjects had to look at each picture and to answer the question “How much do you want to eat some of this food now?”. Wanting was evaluated using 10-cm visual analog scales with the statements “I do not want any at all” (0) or “I very much want to eat some” (+10) at each extremity.

Then, patients were asked to complete two questionnaires. The objective of the first questionnaire, called PrefQuest, was to measure a subject's recalled liking for fatty-salty, fatty-sweet and sweet (non-fatty) tastes [14]. Contrary to olfactory or flavor liking and optimal preferences, which evaluate pleasure that is experienced concomitantly, PrefQuest collects recalled preferences which are therefore influenced by a different set of external factors. This questionnaire includes different types of items: liking for sweet, fatty-sweet and fatty-salty foods, preferences in the level of seasoning (with sweeteners or fat) and overall questions about sweet- and fat-related behavior.

Then the Three-Factor Eating Questionnaire (TFEQ) was administered to evaluate attitude to food, dietary restraint, disinhibition (tendency to lose self-control when eating) and hunger [15].

2.3. Statistical analysis

To evaluate changes before and after the initiation of liraglutide therapy in T2D patients, the non-parametric Wilcoxon test was used for anthropometric data, treatment modifications, and biological parameters. Correlations between quantitative parameters were calculated by the non-parametric Pearson test. Analyses were conducted using R software 2.14.0, with the level of statistical significance set at $\alpha = 0.05$. The statistical analyses for tests evaluating food behavior and preferences were done with SAS 9.4 software. Differences were considered significant when $p \leq 0.05$. For each

food product from PrefQuest tests, a comparison of the expected normal distribution of the pleasure ratings and the observed distribution for all participants was assessed with a kappa coefficient. The expected distribution was as follows: 10%, 20%, 40%, 20%, and 10%. For the remaining evaluations (wanting, liking, optimal preferences, and taste detection thresholds) a paired T-test was done.

3. Results

At inclusion, the age of our subjects was 56.5 ± 8.8 (mean ± SD) years and their BMI was 39.2 ± 6.4 kg/m^2. Mean duration of diabetes was 10.6 ± 9.1 years. Mean HbA1c was 8.6% ± 1.7. All of the patients taking antidiabetic drugs: 6/18 (33.3%) were using insulin, 8/18 (44.4%) sulphonylurea, 2/18 (11.1%) glinides, 15/18 (83.3%) biguanides, and 2/18 (11.1%) DDP-IV inhibitors (Dipeptidyl peptidase-IV).

After three months of treatment with liraglutide, three of the 6 patients on insulin were able to stop the injections. DPP-IV inhibitors were stopped with the introduction of liraglutide. There were no significant modifications in other oral anti-diabetic treatment (Table 1).

Three months after the initiation of liraglutide ($p = 0.0013$), overall weight loss averaged 4.3 ± 4.2 kg and a significant improvement in BMI was observed (from 39.2 ± 6.4 kg/m^2 to 37.6 ± 6.7 kg/m^2) ($p = 0.0011$).

Blood sugar levels were also better controlled, with a decrease in HbA1c (from 8.6% to 7.0%, $p = 0.0003$). There was no significant difference in levels of plasma leptin and ghrelin before and after liraglutide treatment (Table 1).

A specific decrease in the detection threshold for sweet and bitter tastes ($p = 0.009$ and 0.04 respectively) was observed after three months of liraglutide treatment, which indicates enhanced perception of these tastes. Thresholds for salty, however, remained unchanged (Fig. 1).

Optimal preferences for fat decreased at the limit of significance for fat cakes near the end of the treatment ($p = 0.051$), whereas no significant modifications for fat in cottage cheese or sugar in sweet cakes or stewed fruit were observed (Fig. 2a). Results of PrefQuest test show that the recalled liking for fatty-salty and fatty-sweet tastes decreased after liraglutide ($p = 0.02$ and 0.04 respectively) whereas there was no change for sweet foods (Fig. 2b).

Wanting for sweet food decreased significantly with liraglutide treatment ($p = 0.004$) (Fig. 3). No significant modification was observed for wanting for fatty food. Olfactory liking for fatty and sweet foods decreased with liraglutide treatment, but not significantly even if there is a visible trend ($p = 0.08$ and $p = 0.06$, respectively).

The restraint score, as measured by the TFEQ, was not modified by the liraglutide treatment. In contrast, the hunger and disinhibition scores decreased after three months of treatment ($p = 0.009$ and 0.003 respectively) (Fig. 4).

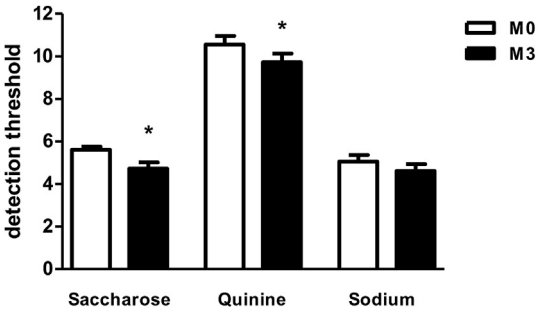

Fig. 1. Changes in detection thresholds for sweet (saccharose; mol/l), bitter tastes (quinine; mol/l), and salt (sodium; mmol/l) after three months of treatment with Liraglutide. *P ≤ 0.05 when comparing M0 and M3.

We did not observe a significant correlation between weight loss or HbA1c reduction and taste detection thresholds for sweetness ($p = 0.894$ and $p = 0.270$, respectively) or bitter ($p = 0.822$ and $p = 0.630$, respectively). It was the same with changes in optimal preferences for fat cakes ($p = 0.069$ and $p = 0.753$); changes in recalled liking for fatty-salty ($p = 0.537$ and $p = 0.210$) and fatty-sweet tastes ($p = 0.065$ and $p = 0.210$); wanting for sweet food ($p = 0.117$ and $p = 0.210$) and hunger ($p = 0.082$ and $p = 0.210$). We found a significant correlation between disinhibition and weight loss ($p = 0.047$) but not with HbA1c improvement ($p = 0.515$).

4. Discussion

The present study provides a detailed analysis of pleasure and taste perceptions in overweight or obese poor controlled type 2 diabetes patients requiring treatment with Liraglutide. Parts of these results corroborate with those observed with non-diabetic patients under Semaglutide in an experimental test [10].

The strength of our study is that happened in real life, with poor controlled T2D patients, in whom, Liraglutide was expected as a good treatment according to the profile of our patients (overweight and obese patients with part of resistance to insulin). That is why, our ethics committee refused the use of placebo in such unstable diabetic population. That is why too, we had to change therapeutics in our patients according to the introduction of Liraglutide. Indeed we had to stop DPP-IV inhibitors according to the rules following Liraglutide prescription [16]. However, it is known that DPP-IV inhibitors do not influence weight, suggesting no effect on food behavior [17]. And to avoid hypoglycemia with association Liraglutide-insulin, we had to reduce insulin units. So, we cannot exclude impact of therapy modification on these results (less

Table 1
Changes in antidiabetic treatment, anthropometric parameters (weight and BMI), glycemic control (HbA1c) and leptin and ghrelin hormones before (M0) and after 3 months of treatment (M3) with Liraglutide.

	M0	M3	p
Insulin treatment	6/18	3/18	P = 0.08
Sulfamides treatment	8/18	4/18	P = 0.10
Glinides treatment	2/18	3/18	P = 0.32
Biguanides treatment	15/18	17/18	P = 0.15
DPPIV inhibitors treatment	2/18	0/18	
Weight (kg)	106.0 ± 19.2	101.6 ± 19.7	P = 0.0013*
BMI (kg/m^2)	39.2 ± 6.4	37.6 ± 6.7	P = 0.0011*
HBA1c (%)	8.6 ± 1.7	7.0 ± 0.8	P = 0.0003*
Leptin concentration (ng/ml)	38.1 ± 20.6	43.2 ± 28.2	P = 0.23
Ghrelin concentration (pg/ml)	5131.8 ± 2075.3	5501.5 ± 2178.5	P = 0.42

*p is significant when ≤0.05.

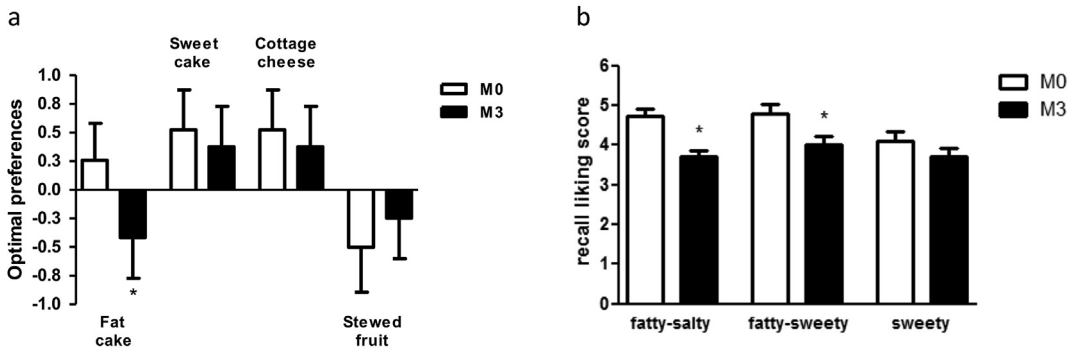

Fig. 2. Changes in optimal taste preferences for fatty food (fat cake, cottage cheese), and sweet food (sweet cake and stewed fruit) (2a) and in recalled liking (prefquest test) for fatty-salty, fatty-sweet and sweet foods (2b) after three months of treatment with Liraglutide *P ≤ 0.05 when comparing M0 and M3.

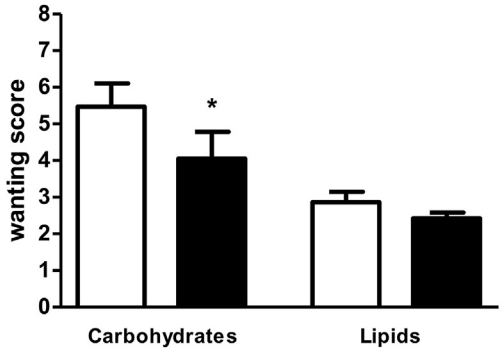

Fig. 3. Changes in wanting for carbohydrate and lipid foods after three months of treatment with Liraglutide. *p ≤ 0.05 when comparing M0 and M3.

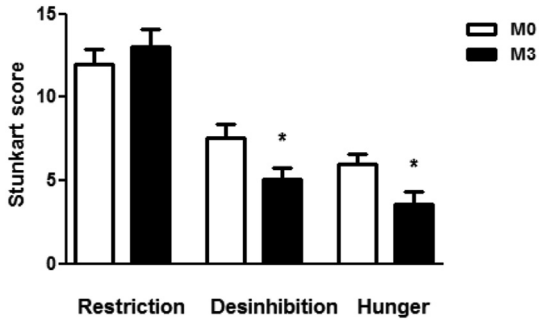

Fig. 4. Changes in the three-factor-eating questionnaire score (Stunkard) before (M0) and after a three months of treatment with Liraglutide (M3). *p ≤ 0.05 when comparing M0 and M3.

insulin, modification with oral antidiabetic drugs). However, parts of our results are similar to those observed in others studies [8,10] were subjects or animal models treated with GLP-1 analogue were without other treatment for T2D.

We demonstrate that Liraglutide leads to a decrease in the detection threshold for sweet tastes, meaning that patients are more sensitive to sweet flavors during treatment. This result corroborates the significant reduction in response to sweeteners described in GLP-1 receptor knockout mice during behavioural tests [8]. Both results suggest that GLP-1 and its analogue enhance sensitivity to sweet tastes. GLP-1 was shown to be produced in mouse taste cells and GLP-1 receptors were shown to be expressed on adjacent intragemmal afferent nerve fibers of mouse taste cells [8]. GLP-1 analogues seem to restore this threshold for sweet taste by resisting DPP-IV inhibition. One study suggested that the detection threshold for sweet tastes is positively correlated with plasma leptin in humans [18], but leptin levels were not modified by Liraglutide therapy in our study, suggesting that the link with leptin variations does not exist in T2D.

Moreover, we demonstrate that Liraglutide induces a decrease in the detection threshold for bitter tastes, which is a novel observation. In Takai and al [19], for example, only sweet tastes were modified by GLP-1. A few studies have shown that the activation of bitter taste receptor pathways induces GLP-1 secretion [20,21], but no study had shown the impact of GLP-1 on the bitter taste threshold.

In our study, optimal preferences for fat cakes, and recalled liking for fatty-salty and fatty-sweet tastes decreased significantly after treatment with Liraglutide. Here, both tasting and recalled liking, of fatty foods were reduced show a decrease pleasure for fat food. As it is currently accepted that overconsumption of fatty foods increases the risk of cardiovascular diseases [22], the Liraglutide-induced reduction in recalled liking for fat-rich foods may help in lowering cardiovascular risk in the high-risk population of overweight or obese patients with T2D [23]. This can be added to the significant positive cardiovascular effects of GLP-1 analog described in recent studies [24–26]. Similarly, reduced preference for fatty, energy-dense foods has been observed after Semaglutide treatment, without an increase in energy expenditure [10]. The mechanisms responsible for the drop in cravings for fat-rich foods induced by Liraglutide could be related to the intrinsic properties of GLP-1 analogues. Indeed, a reduction in preference for and intake of fat has been observed in rats after bariatric surgery [27] which is known to increase postprandial GLP-1 levels [28,29]. Bariatric surgery has also been shown to lower the proportion of dietary fat in humans [27].

We did not observe a variation in ghrelin or leptin under Liraglutide treatment, though several studies have reported a decrease in plasma ghrelin under the same conditions [30,31]. Nonogaki and Suzuki [32] found that Liraglutide-induced suppression of plasma ghrelin was not related to increased plasma levels of active GLP-1 in fasted mice, but to the suppression of efferent vagus nerve-mediated ghrelin secretions. However, another study did not report changes in ghrelin levels or in other gut hormones like PYY, but reported changes in leptin and GIP levels [33].

Our data indicate that there is no modification in dietary restriction, but both disinhibition and hunger scores decreased under treatment. These points are relevant to patients' well-being, as GLP-1 analogues increase satiety and decrease food intake without inducing feelings of restriction, and could help patients stick to diets designed for weight loss.

The fact that changes in the thresholds for sweet or bitter tastes, in optimal preferences for fat cakes, in recalled liking for fatty-salty or fatty-sweet tastes, in wanting for sweet foods and in hunger after Liraglutide treatment were not correlated with weight loss and HbA1c improvement indicates that the effect of Liraglutide on food enjoyment and taste perception is likely to be direct.

We are aware that our study has limitations. Firstly, we lacked a diabetic placebo group (placebo of GLP-1 analog) which would have been tested at 0 and 3 months to confirm the absence of a placebo effect. Studies using placebo included patients with no history past of diabetes and HbA1c criteria <6.5% [10] or T2D patients with HbA1c around 6.5% [33]. In our study, mean HbA1c was 8.6% ± 1.7, and our ethics committee refused the use of placebo in an unstable diabetic population. The number of patients is small in our study, but interesting results have been observed in others studies with few patients too and mixed gender [10]. Included patients were hospitalized for medical test, education and treatment adaptation with Liraglutide implementation. The different tests for the study were done just at admission, before medical care or other exams. So, hospital environment was the same that for M3, when they came back. So we do not think that hospital admission could influence the results at M0. We cannot exclude Hawthorne effect and social desirability of our patients; however, our results concerning fatty foods are similar to those recently described by Blundell et al. [10]. We included non-smokers or mild smokers patients (less than 5 cigarettes per day) who had not smoked since the day before tests. Heavy smokers were not included. As shown in previous data, only heavy smoking (20 + cig/day) alters gustatory pathways [34]. Concerning smell impairment, it is shown a dose response with increasing number of daily smoked cigarettes [34], others studies do not find impact of smoking habits (data collected in Thomas −Danguin et al., 2003 [35]). Five or less cigarettes per day can be considered as having few impact on smell capacity. Moreover, patients were their own witnesses, and did not change their smoking habits, during the period of the study. To finish, it is well known that diabetic patients suffer from oral troubles as xerostomia or hyposalivation and these lead to taste disorders and impairment [36]. We cannot exclude that better control of glycemia improve the neuropathy of the taste sensing nerves. Nevertheless our results are concordant with other studies in human or animal models in which there was no diabetes [8,10]

5. Conclusion

In conclusion, the present proof of concept study conducted on a population of T2D patients with BMI $\geq 25\ kg/m^2$ and poor controlled glycemia with several antidiabetic drugs found that liraglutide treatment led to changes in the perceptions of pleasure when eating and the tastes of certain foods. These results corroborate others results conducted in non-diabetic population, or in non real life conditions. Liraglutide treatment led to decreased cravings for fat foods and an enhanced sensitivity to sweet and bitter tastes without affecting the pleasure in eating. These properties are of particular interest in the nutritional care of overweight or obese patients with T2D.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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