MOLECULAR
METABOLISM

Dissociation of GLP-1 and insulin association with food processing in the brain: GLP-1 sensitivity despite insulin resistance in obese humans

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ABSTRACT

Objective: Glucagon-like peptide-1 (GLP-1) is released into the bloodstream after food intake. In addition to stimulating insulin release, it causes satiety and contributes to the termination of food intake. In this study, we investigated whether endogenous GLP-1 affects food-related brain activity and hunger.

Methods: Twenty-four volunteers (12 lean; 12 obese) underwent a 75 g oral glucose tolerance test that promotes GLP-1 secretion. Food cue-induced brain activity was assessed by functional magnetic resonance imaging and GLP-1 concentrations were measured before, 30, and 120 min after glucose intake.

Results: The significant increase in GLP-1 levels negatively correlated with a change in the food cue-induced brain activity in the orbitofrontal cortex, a major reward area. This association was independent of simultaneous alterations in insulin and glucose concentrations. The association was present in lean and overweight participants. By contrast, postprandial insulin changes were associated with orbitofrontal activations in lean individuals only.

Conclusions: The postprandial release of GLP-1 might alter reward processes in the orbitofrontal cortex and might thereby support the termination of food intake and reduce hunger. While obese persons showed brain insulin resistance, no GLP-1 resistance was observed. Our study provides novel insight into the central regulation of food intake by the incretin hormone GLP-1.

1. INTRODUCTION

After food intake, humoral and neural signals from the periphery reach the brain to cause satiety, terminate food intake, and induce brain-derived regulation of whole-body metabolism.

One important endocrine signal is glucagon-like peptide-1 (GLP-1), a peptide hormone released from intestinal L-cells after food intake [1,2]. GLP-1 based therapies are used for the treatment of type 2 diabetes either by enhancing GLP-1 concentrations due to inhibition of the degrading enzyme or by administering long-lasting analogues [1]. While the main therapeutic effect of these therapies was initially thought to be the promotion of endogenous insulin secretion, it is now clear that pleiotropic effects are present in a large number of other organs [2,3]. Unlike many other diabetes drugs, GLP-1 analogues substantially reduce body weight [1,4] by reducing appetite and enhancing satiety, thereby decreasing food intake [1,5]. Since, this effect on eating behavior is not limited to specific drugs, it can also be induced by native GLP-1 administration [5,6]. Many other satiety signals are impaired in obesity, but activation of the GLP-1 receptor by GLP-1 analogues can also reduce body weight in obese persons [1,5]. Activation of the GLP-1 receptor in the periphery transmits signals to the brain via the vagus nerve [7,8]. The brain might also be directly activated due to widely expressed GLP-1 receptors in the central nervous system [5]. The importance of the latter mechanism is underscored by the recent report that intranasal GLP-1 administration introduced beneficially metabolic effects in patients with type 2 diabetes [9]. The authors suggest that a number of the effects observed are due to absorption of GLP-1 directly into the brain [9]. Moreover, a

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recent study established that treatment with a GLP-1 receptor agonist influenced food-related activity in different appetite- and reward-related brain areas [10].

Given GLP-1's benefits for weight management and glycemic control [1,2,5], it is vital to further elucidate the specific brain areas that respond to endogenous GLP-1. On the basis of our recent publication on food-related brain activity after oral glucose intake [11], we now investigated whether endogenous GLP-1 correlates with food cue-induced brain response independently of insulin in lean and obese individuals.

2. MATERIAL AND METHODS

2.1. Participants

Twelve lean (23 $\pm$ 2 years; body mass index [BMI] 21.2 $\pm$ 1.1 kg/m^2; six women) and twelve obese (age 25 $\pm$ 2 years; BMI 30.5 $\pm$ 1.8 kg/m^2; six women) healthy volunteers participated in this study. More details on patient characteristics can be found in [11]. Informed written consent was obtained and the local ethics committee approved the protocol.

2.2. Experimental setup and fMRI data analysis

All subjects underwent a 75 g oral glucose tolerance test. Whole-brain fMRI data were obtained using a 3.0T scanner (Siemens TimTrio, Erlangen, Germany). Brain response to food pictures was recorded directly before, 30 and 120 min after glucose intake as already described [11]. Pre-processing and statistical analysis of the fMRI data were performed with SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK). To estimate brain activation changes to food cues in this study, individual contrasts were computed after oral glucose intake and compared to the baseline recording. The resulting contrasts were used to evaluate the association between GLP-1 and the postprandial response to food using a multiple regression analysis in SPM8 ($p < 0.05$, whole-brain family-wise-error (FWE) correction for multiple comparisons). BOLD response of regions showing significant association with GLP-1 was extracted for further statistical analyses.

To compare GLP-1 and insulin associations with orbitofrontal activity, we additionally extracted BOLD response for the previously described [11] insulin-responsive cluster in this brain region for 30 min.

2.3. Hormone measurements

We measured total GLP-1 before, 30 and 120 min after glucose ingestion and ascertained that GLP-1 levels increased rapidly after glucose ingestion and remained high for a considerable period of time, as described by others (e.g. [12]). For 120 min post glucose, samples were available from only 21 of 24 subjects. After drawing blood, samples were immediately placed on ice and stored at $-80\ ^{\circ}$C until analysis. Total GLP-1 was quantified by a specific commercial ELISA (Millipore, Watford, UK) which had been selected on the basis of its reliability in a recent comparison of GLP-1 assays [13].

Details on measurements of plasma insulin and glucose can be found in [11].

2.4. Calculations and statistical analyses

Changes from before to after glucose ingestion were calculated by subtracting the measurement "after" from the measurement "before". We used the software package JMP 10 (SAS, Cary, USA) for all statistical analysis. Correlations and adjustments were calculated by multiple linear regression analyses. Results with values of $p < 0.05$ were considered statistically significant. Data are given as means $\pm$ SE.

3. RESULTS

3.1. Plasma GLP-1 levels

From baseline levels of 3.4 $\pm$ 1.1 pmol/l, GLP-1 plasma levels significantly increased after glucose intake to 49.8 $\pm$ 2.9 pmol/l at 30 min and remained high at 51.1 $\pm$ 2.5 pmol/l at 120 min (both time points vs basal $p < 0.0001$). There were no differences in GLP-1 levels between lean and overweight participants (all $p > 0.2$, Supplementary Table 1).

The increase in GLP-1 at 30 min positively correlated with the concurrent increase in insulin levels ($p = 0.0024$).

3.2. Brain activity

To investigate the effects of GLP-1 on brain processing of food cues, we analyzed the relationship between the increase in GLP-1 and changes in food-related brain activity. This was carried out on a whole-brain level, i.e. in a hypothesis-free approach testing all regions within the brain.

We found a significant, negative correlation between GLP-1 changes and food cue-induced orbitofrontal activity from before to 120 min after glucose intake ($p < 0.0001$, Figure 1, MNI-coordinates: +/$-$3, 45, -18). This association remained significant after adjustment for the possible confounders gender and BMI ($p < 0.0001$) as well as for gender, BMI, and age ($p = 0.0001$). Furthermore, this association remained significant after adjustment for the concurrent change in insulin and glucose concentrations ($p < 0.0001$).

In addition, an association between change in GLP-1 and brain activity from before to 30 min after glucose intake was observed at the trend level ($p = 0.06$, $r^2 = 0.2$).

The relationship between the change in plasma GLP-1 and change in orbitofrontal response from before to 120 min post glucose intake did not interact with BMI (ANCOVA $p = 0.7$). The negative association was therefore present in both lean and obese persons ($p = 0.0317$ and $p = 0.0007$, respectively; Figure 2B,D).

As previously shown [11,14], the orbitofrontal cortex is also influenced by insulin. We therefore specifically compared associations of insulin and GLP-1 with regional brain activity in this area (Figure 2). The insulin-responsive cluster in the orbitofrontal cortex (MNI-coordinates: 24, 42, -12) was based on our recent publication, in which we detected significant associations at 120 min [11]. Unlike GLP-1 (Figure 2B,D), divergent results for both weight groups were detected for insulin: The steep increase in plasma insulin from baseline to 30 min post glucose load was significantly associated with the concomitant change in food-induced orbitofrontal activity in lean participants only ($p = 0.0348$, Figure 2A). In obese participants, no significant correlation was detected ($p = 0.2$, Figure 2C).

4. DISCUSSION

In the current study, the increase in endogenous GLP-1 after an oral glucose load was associated with the postprandial processing of food cues in the orbitofrontal cortex. Food response in the orbitofrontal cortex was associated with plasma insulin in lean persons only, whereas the association with GLP-1 was present in both lean and obese participants.

In humans, there is evidence that the orbitofrontal cortex reacts to the hormone insulin [14,15], which is released in response to GLP-1 and is also tightly correlated to GLP-1 in our study. We had already detected associations of plasma insulin and orbitofrontal activity at 120 min, with significance at the whole-brain level [11], in a cluster directly adjacent to the cluster currently found to correlate with GLP-1. We now
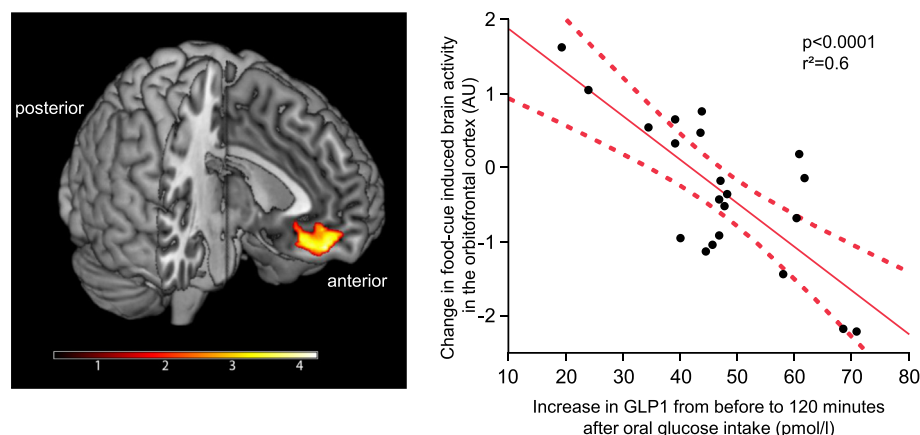
Figure 1: Increase in GLP-1 after oral glucose is associated with change in food cue-induced orbitofrontal activity. The **left panel** shows a color-coded F-value map with significant associations of increase in GLP-1 concentration from baseline to 120 min post glucose load with the concomitant change in orbitofrontal activity. In the **right panel**, increase in GLP-1 concentration from baseline to 120 min post glucose load is plotted against change in food picture-induced orbitofrontal activity. Line represents fit line $\pm$ confidence intervals from an unadjusted model. N = 24.

also confirmed this correlation for 30 min post glucose load for lean participants. This finding is underscored by interventional studies that also detected insulin effects in prefrontal areas in lean persons [14—16]. However, the associations of GLP-1 with orbitofrontal activity were independent of insulin in our current study. Thus, insulin and GLP-1 might both decrease activity in the orbitofrontal cortex and might synergistically contribute to the regulation of regional brain activity in the postprandial state.

It is worth mentioning that our GLP-1 results showed no differences between lean and obese persons. By contrast, postprandial insulin was associated with the orbitofrontal response in lean individuals only, but not in obese persons, an observation pointing towards brain insulin resistance. It is known that obesity results in the brain becoming resistant to a number of satiety-inducing peptide hormones including insulin [17,18] and leptin [19]. Our current results indicate, however, that the brain could still be sensitive to endogenous GLP-1. This tallies well with the clinical observation that GLP-1 agonists evolve their weight-reducing effect in obese patients also [1,5]. Therapeutic approaches addressing central GLP-1 pathways therefore seem appropriate when treating obese patients.

The orbitofrontal cortex is modulated by feeding with reduced activity after eating [20,21]. Besides its well-characterized function for the integration of multiple sensory systems, the orbitofrontal cortex is one major reward center [22,23]. This area is very important in the evaluation of food-related stimuli [24—26]. Pictures of highly caloric food activate this area in hungry individuals [25]. However, the exact mechanism underlying the modulation of reward in this area are still under investigation [22,24]. The GLP-1 receptor is expressed in prefrontal areas ([27] via BioGPS [28]). Accordingly, exogenous administration of GLP-1 together with the peptide hormone PYY reduced orbitofrontal activity [29] and a current study identified pharmacological levels of a GLP-1 receptor agonist to modulate orbitofrontal activity [10] and reward [30]. Furthermore, cerebral glucose metabolism in this area was modulated by a GLP-1 receptor agonist in a study with lean men [31]. Our current results suggest that endogenous GLP-1 may contribute to food-related reward processes in the orbitofrontal cortex. Beyond reward, recent data indicate that orbitofrontal activity might also contribute to the regulation of whole-body glucose metabolism [16], which is indeed modulated by GLP-1 via the brain in rodents [32,33]. It remains to be investigated whether orbitofrontal GLP-1

action is involved in such homeostatic outputs and if other brain regions such as the hypothalamus also play a role [32]. One previous study using positron emission tomography showed that increases of endogenous GLP-1 levels after a liquid formula meal were associated with increases of cerebral blood flow in the prefrontal cortex and the hypothalamus [34]. Due to different experimental protocols, nutritional stimuli, GLP-1 assays with much lower stimulation of GLP-1 levels and different imaging techniques [34], it is difficult to draw comparisons between the two studies.

The postprandial response to GLP-1 in the orbitofrontal cortex suggested by our current data could contribute to the immediate termination of food intake and may also prevent further excessive food intake. These findings can, at least in part, explain how incretin-mimetic drugs reduce food intake and decrease body weight [1,2].

Additional brain areas detected in pharmacological studies [10,35] might also be involved. Due to our sample size of 24 participants and the stringent correction for multiple comparisons, smaller effects in other areas may have been overlooked. Unfortunately, no appropriate material was available for measurement of active GLP-1 in this study. Furthermore, besides insulin and glucose, there are many other hormones and metabolites that change in response to glucose intake. For example, circulating PYY is also increased that has been demonstrated to affect orbitofrontal brain activity as well [29,36]. Therefore, we cannot exclude that further factors contribute to the change in orbitofrontal activity detected in this study.

In summary, our current data support a model in which GLP-1 is secreted after food intake, and subsequently reaches the brain where it regulates food-related activity of the orbitofrontal cortex, independently of insulin. While obese persons seem to be insulin-resistant in this brain area, they might remain sensitive to GLP-1. The orbitofrontal GLP-1 response might regulate reward and reduce hunger, which could help individuals to stop eating and prevent further food intake. Our study provides novel insights into the regulation of food intake, metabolism, and body weight by GLP-1 in the postprandial state.
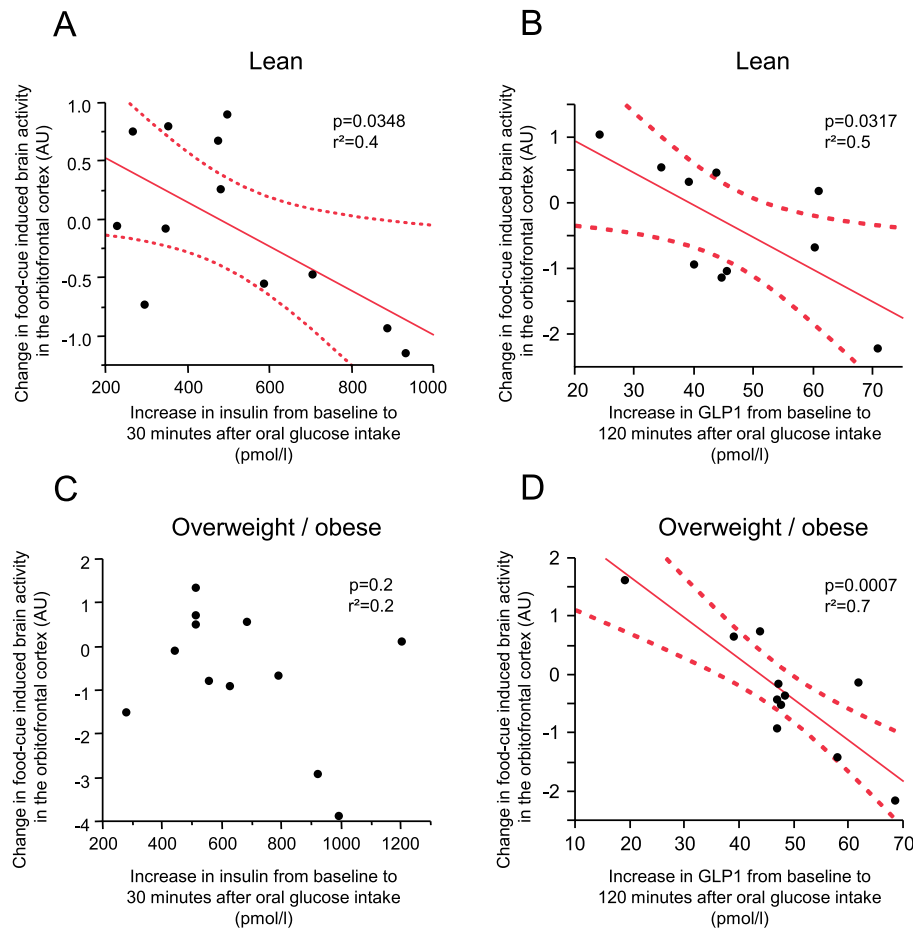
Figure 2: Divergent associations of glucose-induced increase in insulin and GLP-1 and change in food cue orbitofrontal activity between lean and obese persons. Increase in plasma insulin concentration from baseline to 30 min post glucose load is significantly associated with concomitant change in orbitofrontal activity in lean **(A)** but not in obese persons **(C)**. By contrast, increase in GLP-1 from baseline to 120 min post load is significantly associated with change in orbitofrontal activity between baseline and 120 min post load in both lean **(B)** and obese participants **(D)**. Line represents fit line ± confidence intervals from an unadjusted model. N = 24 for A and C; N = 21 for B and D.

AUTHOR CONTRIBUTIONS

MH designed the study, performed experiments, analyzed results and wrote the manuscript. SK performed brain imaging, analyzed results and discussed the paper. HUH and BG discussed the analyses and the discussed the paper. HP and AF designed the study, supervised the project and discussed the paper. AF is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

Baptist Gallwitz has served as a member of advisory boards for AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Novartis, Novo Nordisk, MSD, Roche and Sanofi, and has also received honoraria from these companies for giving lectures.

All other authors declare that they have no conflicts of interest that are directly relevant to the content of this study.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.molmet.2015.09.007.

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