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Dietary sugars and non-caloric sweeteners elicit different homeostatic and hedonic responses in the brain

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ABSTRACT

Objective: The brain is essential in regulating intake of food and beverages by balancing energy homeostasis, which is regulated by the hypothalamus, with reward perception, which is regulated by the ventral tegmental area (VTA). The aim of this study was to investigate the effects of ingestion of glucose, fructose, sucrose, and sucralose (a non-caloric artificial sweetener) on the magnitude and trajectory of the hypothalamic and the VTA blood oxygen level–dependent (BOLD) responses.

Method: In five visits, 16 healthy men between 18 to 25 y of age with a body mass index between 20 and 23 kg/m^2 drank five interventions in a randomized order while a functional magnetic resonance imaging scan was taken. The interventions consisted of 50 g of glucose, fructose, or sucrose, or 0.33 g of sucralose dissolved in 300 mL tap water. The control condition consisted of 300 mL of plain tap water. BOLD signals were determined in the hypothalamus and the VTA within a manually drawn region of interest. Differences in changes in BOLD signal between stimuli were analyzed using mixed models.

Results: Compared with the control condition, a decrease in BOLD signal in the hypothalamus was found after ingestion of glucose ($P = 0.0003$), and a lesser but delayed BOLD response was found after ingestion of sucrose ($P = 0.006$) and fructose ($P = 0.003$). Sucralose led to a smaller and transient response from the hypothalamus ($P = 0.026$). In the VTA, sucralose led to a very similar response to the water control condition, leading to an increase in VTA BOLD activity that continued over the measured time period. The natural sugars appeared to only lead to a transient increase in VTA activity.

Conclusions: Glucose induces a deactivation in the hypothalamus immediately after ingestion and continued over the next 12 min, which is correlated with satiety signaling by the brain. Fructose and sucrose are both associated with a delayed and lesser response from the hypothalamus, likely because the sugars first have to be metabolized by the body. Sucralose leads to the smallest and most transient decrease in BOLD in the hypothalamus and leads to a similar response as plain water in the VTA, which indicates that sucralose might not have a similar satiating effect on the brain as the natural sugars.

Introduction

The human brain is essential in regulating the intake of food and beverages by balancing energy homeostasis with reward perception [1]. The hypothalamus is an important structure that regulates energy homeostasis by integrating information from glucose and insulin trajectories with varying levels of hormones and peptides from the gut and stomach [2–5]. The mesolimbic pathway, in conjunction with homeostatic regulation, is responsible for the hedonic response to food. The ventral tegmental area (VTA) and

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other areas of the limbic system (amygdala, nucleus accumbens) are important parts of the mesolimbic pathway involved in this hedonic response [6]. The VTA is the origin of dopaminergic neurons and dopamine signaling in the mesolimbic system, which is a key substrate for reward prediction and response [7]. The VTA is anatomically and functionally connected to the hypothalamus and integrates homeostatic signals with reward responses [8–10]. Both homeostatic and mesolimbic pathways respond to glucose, which is the natural and preferred source of energy for the body and brain [11,12]. Glucose concentration in the blood is kept under tight homeostatic control, partly mediated by glucose-sensing neurons in the brain [12]. Glucose intake leads to changes in hypothalamic blood oxygen level–dependent (BOLD) levels, which have been interpreted as a sign of satiety [4,13]. However, little VTA data are available [14], and further investigation into the VTA may be essential in the understanding of the integration of homeostatic and hedonic responses regulation feeding behavior [6].

In many foods and beverages, monosaccharides and disaccharides or artificial sweeteners are used as sweeteners [15]. It has been suggested that increased consumption of these sugars and sweeteners in the modern diet plays a role in pathophysiology of obesity, decreased vascular health, metabolic syndrome, and type 2 diabetes [15–18]. High fructose consumption also has been hypothesized to have detrimental health effects, is associated with fatty liver disease, and has been shown to have greater adverse effects on metabolism and vascular health than glucose in several animal studies [19,20]. Fructose is used as a sweeter alternative to glucose, allowing for the use of smaller amounts, but the metabolism of both sugars is very different. In contrast to glucose, fructose cannot be used directly as a source of energy [21]. Fructose, which is a naturally occurring saccharide in fruits and vegetables, has to be metabolized by the liver before it can be made available as a source of energy [22]. Fructose can be consumed in its free form as a monosaccharide in fruits and high-fructose corn syrup but also in the form of sucrose, which is a glucose–fructose disaccharide. In addition to the use of added natural sugars, non-caloric artificial sweeteners are increasingly being used to sweeten foods and beverages. The use of non-caloric sweeteners could be expected to decrease total caloric intake and might therefore be useful to control obesity [23]. However, some epidemiologic studies suggest that non-caloric sweeteners might have the opposite effect and might actually lead to increased energy intake [5,24,25]. Although these results are not conclusive and the effects of non-caloric sweeteners remain a subject of debate, these results do indicate that these sweeteners could have unexpected effects in the brain. Currently, the homeostatic and mesolimbic effects in the brain of these sweeteners and other common dietary sugars are unknown. The differences in how various sugars are metabolized and made available as energy, and because of the decoupling of sweetness and energy in non-caloric sweeteners, each could lead to different metabolic and physiological responses in the brain [26–29].

To gain a better understanding of the different homeostatic and hedonic responses after ingestion of caloric and non-caloric sweeteners, we investigated the effects of glucose, fructose, sucrose, and sucralose (an artificial non-caloric sweetener) on the trajectory and magnitude of BOLD response of the hypothalamus and VTA in young men of normal weight.

Methods

Participants

Sixteen healthy men 18 to 25 y of age were recruited by advertisements around Leiden University. Inclusion criteria were body mass index (BMI) between 20 and 23 kg/m^2 and height between 170 and 190 cm. Exclusion criteria were presence of diabetes or a history of disturbances of glucose metabolism; genetic or psychiatric disease affecting the brain; renal or hepatic disease; any chronic disease; weight changes >3 kg within the previous 3 mo or attempts to lose weight; smoking (within the previous 6 mo); alcohol consumption >21 units/wk; use of recreational drugs (within the previous 12 mo); recent blood donation; recent participation in other biomedical research projects, and contraindications for magnetic resonance imaging scanning. Informed consent was obtained from all participants and the study was approved by the local institutional review board and registered at Clinicaltrails.gov. Participant characteristics are presented in Table 1.

Study design

In this randomized, double-blind, crossover study, the participants received five different conditions, one per occasion with a 1-wk interval. Participants were asked to fast for a minimum of 10 h overnight (except for drinking water), while scans were obtained the next morning. Participants received one of the five conditions on each occasion in a randomized order. The interventions consisted of 50 g of glucose in 300 mL tap water; 50 g of fructose in 300 mL tap water; 50 g of sucrose in 300 mL tap water; 0.33 g of sucralose (matched for sweetness with the glucose solution) in 300 mL tap water; and 300 mL plain tap water as a control condition. No additional flavoring was added to the stimuli. The 50 g of sugar in the study stimuli is comparable to sugar amounts found in several high-energy beverages and was chosen to provide a strong blood glucose and insulin response. The glucose, sucrose, and fructose solutions all contained 200 kcal, the sucralose-sweetened solution was 0 kcal. All stimuli were ingested at room temperature. Drinking was performed through an oral tube, lying supine in the scanner during the functional MRI (fMRI) scan while the participants were monitored by the investigators. Five minutes after the start of the scan, the men were instructed to steadily and continuously drink the total amount. Scanning was continued during and after the start of the ingestion for 16 min, making for a total scan time of 21 min with 5 min before ingestion, 4 min during ingestion, and 12 min after ingestion.

Blood samples and visual analog scales

Before and after the scanning procedure, 5 mL blood samples were taken by venipuncture in an antecubital vein. Insulin and glucose levels before and 30 min after ingestion of the study stimuli were determined by the laboratory for Clinical Chemistry at Leiden University Medical Centre. Plasma glucose was measured using a fully automated Hitachi 704/911 system. Plasma insulin was measured by a radioimmunoassay (Medgenix, Fleurus, Belgium).

Participants were asked to rate their feelings of hunger in advance of and after the scanning procedure using a visual analog scale (VAS), which consisted of a 10 cm line, with *not hungry* and *extremely hungry* as anchors. Participants were asked to indicate their score on the line; higher scores indicated feeling more hungry. In addition, 30 min after ingestion after finishing the MRI procedure, pleasantness and sweetness of the drink were rated using a similar VAS with *disgusting* to *very tasty* and *not sweet* to *extremely sweet* as anchors.

MRI data acquisition

MRI was performed using a 3 Tesla Achieva whole-body MRI scanner (Philips Healthcare, Best, The Netherlands) equipped with a 32-channel head coil. The protocol for structural MRI comprised a scout view for planning, a high resolution three-dimensional T_1-weighted sequence for registration purposes and a mid-sagittal high-resolution single slice for accurate hypothalamus and VTA localization (repetition time 550 ms, echo time 10 ms, field of view 208 × 208 mm, voxel size = 0.52 × 0.52 × 14 mm). Mid-sagittal fMRI was performed for 21 min in total, by a T_2-weighted, gradient echo-planar imaging sequence mid-sagittal single slice that renders BOLD contrast (repetition time 120 ms; echo time 30 ms; flip angle 30 degrees; field of view 208 × 208 mm; voxel size = 0.81 × 0.90 × 14 mm; scanning time of one dynamic image 2.52s for a total of 500 data points). A slice thickness of 14 mm was chosen to encompass the hypothalamus in the left to right direction and a single slice technique was used for sufficient signal-to-noise ratio.

Table 1
Participant characteristics

	Mean ± SD (N = 16)
Age (y)	22.4 ± 1.3
Height (m)	1.82 ± 0.06
Weight (kg)	73 ± 7.1
BMI (kg/m^2)	22 ± 1.2

BMI, body mass index.

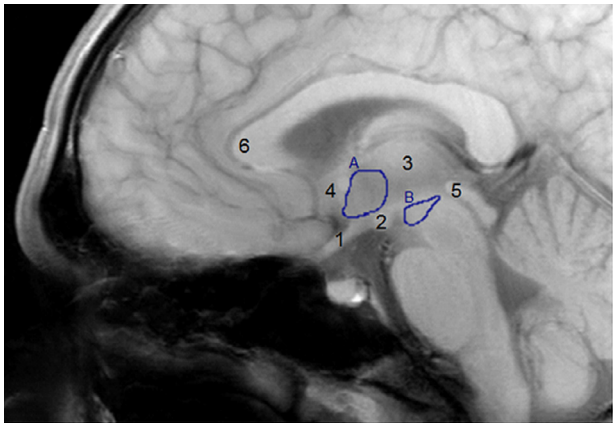

Fig. 1. A representative sagittal view with the hypothalamus (**A**) and the ventral tegmental area (VTA) (**B**) regions of interest (ROIs). For the hypothalamus ROI (**A**), the optic chiasm (1), the mammillary bodies (2), the thalamus (3), and the anterior commissure (4) were used as landmarks. For the VTA ROI (**B**), the top of the cerebral aqueduct (5) and the mammillary bodies (2) were used as landmarks. The reference ROI was drawn superior of the genu to the corpus callosum (6) in the grey matter.

fMRI processing

Imaging data were preprocessed and analyzed using fMRI from the Brain Software Library (FSL) version 5.0.8. [30]. The mid-sagittal fMRI was preprocessed as described previously [31]. In short, all 500 dynamic images were motion-corrected by registration to the image that was acquired halfway through the fMRI period (scan 250) by means of multimodality image registration using information theory (oftware in FSL by maximization of mutual information [32]. The complex data were averaged for each set of four subsequent volumes, after which 125 images were rendered. Regions of interest (ROIs) were drawn manually using subject-specific T_1-weighted images as a visual aid to define anatomic borders. Three ROIs were drawn: the hypothalamus, the VTA, and a reference area. The ROI for the hypothalamus was drawn as described earlier using the optic chiasm, mammillary bodies, thalamus, and anterior commissure as anatomic landmarks [31]. Using literature describing the VTA region [33,34], we defined the ROI for the VTA in the midbrain with half the volume of the hypothalamus. The top of the cerebral aqueduct and the mammillary bodies were used as anatomic landmarks (Fig. 1). To correct for scanner drift, a third internal reference ROI half the volume of the hypothalamus ROI was selected in the gyrus superior to the genu of the corpus callosum in the gray matter. Hypothalamic and VTA BOLD signals were adjusted linearly to the BOLD signal of this internal reference ROI. Subsequently, to investigate the individual BOLD response after study intervention on the hypothalamus and VTA, the BOLD responses after ingestion were all normalized to the BOLD responses before ingestion, that is, the mean BOLD signal before ingestion; the average BOLD signal of the first 4 min of the fMRI scan can be seen in Figure 2.

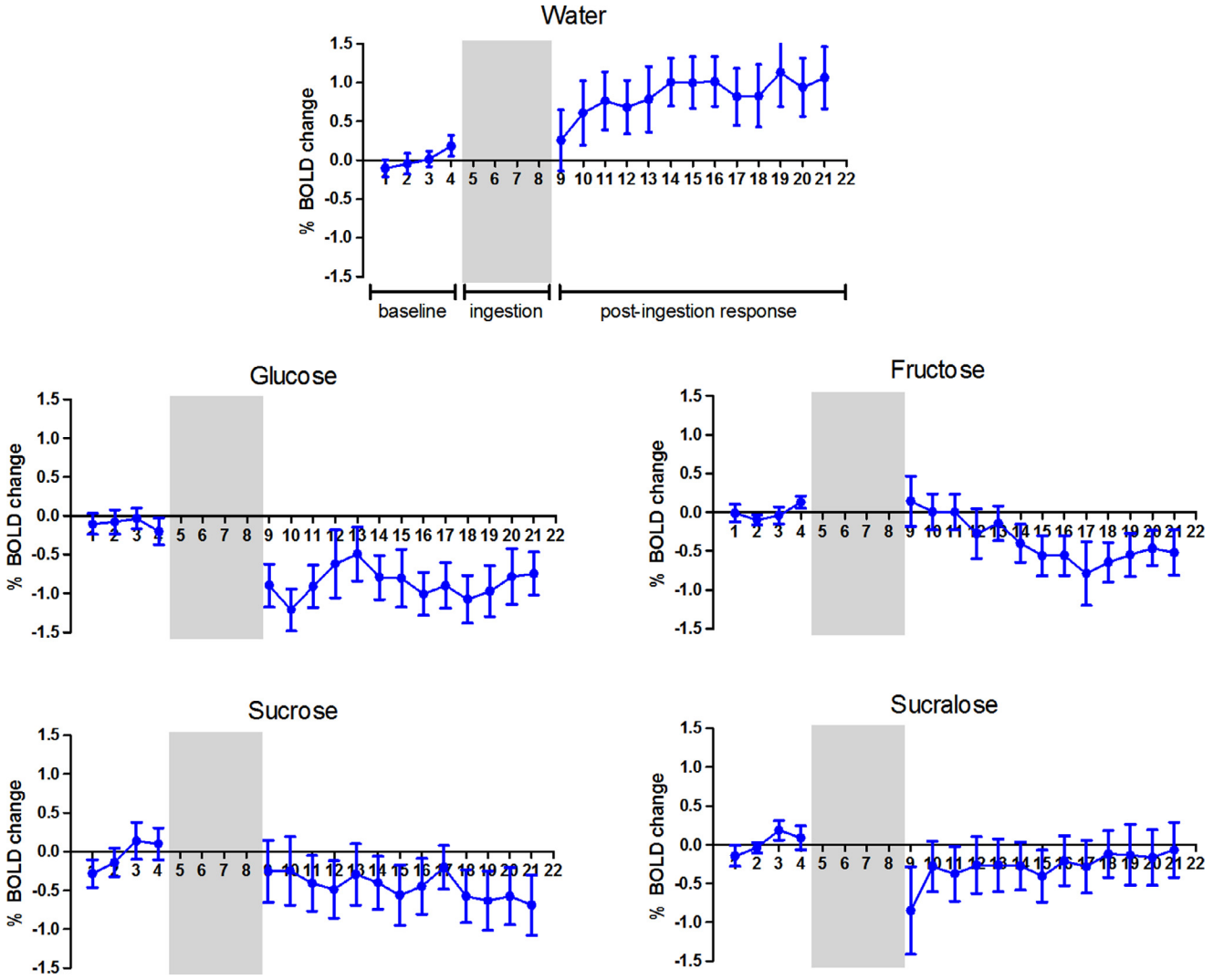

Fig. 2. Normalized BOLD response (% change) in the hypothalamus after ingestion of water (control condition), glucose, fructose, sucrose, and sucralose stimuli. Data presented as mean response for all participants (N = 16) per minute with SE. Postingestion response was calibrated to the baseline period. Grey bar represents ingestion period, data recorded during this period was excluded from analysis. BOLD, blood oxygen level–dependent; SE, standard error.

Table 2
Blood glucose and insulin levels

	Glucose	Fructose	Sucrose	Sucralose	Water
Preingestion glucose	5 ± 0.7	4.9 ± 0.4	4.8 ± 0.3	5.2 ± 1.6	4.7 ± 0.9
Postingestion glucose	7 ± 1.1*	5.4 ± 0.7	7 ± 0.7*	4.7 ± 0.8	4.6 ± 0.9
Delta glucose	2 ± 1.4	0.5 ± 0.9	2.3 ± 0.8	−0.5 ± 1.7	−0.1 ± 0.5
Preingestion insulin	6.4 ± 4.7	6.5 ± 4	7.5 ± 6	6.5 ± 5.3	8 ± 5.4
Postingestion insulin	32.5 ± 20.3*	12.3 ± 5.9*	26.5 ± 18.9*	5.3 ± 4.6*	6.6 ± 5.1
Delta insulin	26 ± 18.5	5.8 ± 3.9	19 ± 15	−1.6 ± 1.6	−1.5 ± 3.6

All values in mean ± SD.
Glucose levels in mmol/L, insulin levels in mU/L.
*Significantly different between pre- and postingestion at $P < 0.05$.

Statistical analysis

Statistical testing of hypothalamus and VTA activations was performed using SPSS version 23 (IBM, Armonk, NY, USA). Differences in VAS scores and blood values between pre- and postingestion and between conditions were tested using repeated measures analysis of variance. To test for differences in the postingestion BOLD responses between sugars and sweeteners and the water control, a mixed model approach was used, with intervention and study visit number as fixed effects and time point as a covariate and a random effect for subject × study visit number. To determine the time effects in the BOLD response the entire 12-min post-ingestion response was divided into four arbitrary 3-min time blocks. Mixed-model analysis for comparison between sugars and sweeteners and the water control was performed per time block. Significances are presented uncorrected. Pearson correlations were used to determine the association between BOLD response and blood levels and VAS scores.

Results

Blood glucose and insulin levels

Blood glucose and insulin level measurements for all participants are shown in Table 2. All participants demonstrated normal fasting glucose levels and the average fasting glucose did not differ between conditions. As expected, glucose and sucrose ingestion led to significant increases in both blood glucose and insulin levels. Fructose had no significant effect on blood glucose levels but led to a small significant increase in blood insulin levels. Sucralose had no significant effect on blood glucose levels but led to a small yet significant decrease in insulin levels.

VAS for hunger and subjective rating of the study stimuli

VAS scores for hunger and subjective rating of the stimuli for all participants per study stimulus are shown in Table 3. No significant differences were found between the stimuli in hunger score before ingestion. After ingestion of water, the VAS score and delta VAS score for hunger was significantly increased compared with the other or stimuli. The taste of sucralose and water was rated significantly less pleasant than the fructose and sucrose and, as expected, the water condition was rated significantly less sweet than the sugars and sweetener. All other study stimuli were rated similarly for sweetness.

Hypothalamic BOLD response

Figure 2 shows the mean normalized hypothalamic BOLD response curves after ingestion of the five study stimuli. Table 4 shows the corresponding BOLD effect sizes and statistical differences relative to the control condition, both for the entire response curve and the 3-min response intervals. Ingestion of plain water led to an increase in BOLD signal, whereas all sugars and sucralose led to a decrease in BOLD signal. Compared with the control condition, glucose led to an immediate and continuous decrease in BOLD response (mean difference 1.8%; $P = 0.0003$). Fructose and sucrose also led to a significant average decrease compared with the water control condition (mean difference 1.2%; $P = 0.006$ and mean difference 1.3%, $P = 0.003$, respectively). However, the response in the first 3 min after ingestion of both fructose and sucrose did not significantly differ from water, indicating a delayed response to these stimuli. The response to sucralose compared to water was significantly lower (mean difference 0.9%, $P = 0.026$), but this difference did not increase over time as was the case with the other sugars.

VTA BOLD response

Figure 3 shows the mean normalized BOLD response for all participants in the VTA over time after ingestion of the study stimuli. In the VTA, all conditions led to an increase in BOLD response after ingestion. Table 5 shows the mean effect sizes and statistical differences relative to the control condition over the entire 12-min post-ingestion period and during the four 3-min time blocks. Ingestion of plain water led to an increase in BOLD signal; comparatively, all sugars led to a smaller increase in BOLD signal (mean difference 0.4%). However, when comparing the response to the sugars with the response to plain water, no significant differences were found. The response to sucralose showed a close resemblance to the response to water, as indicated by the smallest mean difference between the water and sucralose response (mean difference 0.1%). The response to sucralose, and also to water, remained elevated over the entire 12-min postingestion time period, whereas the response to the natural sugars appeared transient. In addition, glucose ingestion was the only stimulus that led to an initial decrease in VTA BOLD response in the first 3 min after ingestion.

Correlation of hypothalamic and VTA BOLD response with VAS and blood levels

A significant negative correlation was found between the rating of perceived sweetness and the hypothalamic BOLD response ($r = -0.350$; $P = 0.002$). This indicates that a sweeter rated stimulus leads to a stronger decrease in hypothalamic response. We found no significant correlations between blood glucose and insulin levels and the BOLD responses of neither the hypothalamus nor the VTA.

Discussion

Data from the present study found that the hypothalamus and VTA demonstrate different BOLD responses to glucose, fructose, sucrose, and sucralose ingestion. In contrast to glucose, which has a direct and effect on the hypothalamus, fructose and sucrose ingestion resulted in delayed and smaller hypothalamic BOLD responses. Sucralose ingestion led to a transient response in the hypothalamus. In the VTA, sucralose ingestion led to the same effect as the ingestion of plain water, being a prolonged activation

Table 3
VAS scores for hunger, pleasantness, and sweetness

	Glucose	Fructose	Sucrose	Sucralose	Water
Preingestion VAS hunger	5.3 ± 2.5	5.7 ± 1.9	4.8 ± 2.1	5.3 ± 1.9	5.2 ± 1.9
Postingestion VAS hunger	5.1 ± 2.4	5.5 ± 1.9	5.0 ± 1.8	5.3 ± 2.3	5.8 ± 2.3*
Delta VAS hunger	−0.2 ± 1.5	−0.2 ± 2.3	0.3 ± 1.8	0.0 ± 1.2	0.6 ± 0.9*
VAS pleasantness	5.9 ± 1.7	6.8 ± 1.8	6.4 ± 1.9	5.3 ± 2.1*	5.1 ± 1.1*
VAS sweetness	5.4 ± 2.1	6.4 ± 1.4	6.9 ± 1.4	5.6 ± 2.2	0.8 ± 1.6*

VAS, visual analog scale.
All values in mean ± SD.
*Significantly different from other study conditions at $P < 0.05$.

Table 4
Mean difference in postingestion hypothalamic BOLD responses to the study stimuli and the water control condition

	Average response	Response min 9–11	Response min 12–14	Response min 15–17	Response min 18–21
Glucose	−1.9 ± 0.4*	−1.4 ± 0.5*	−1.5 ± 0.4*	−1.9 ± 0.5*	−2 ± 0.5*
Fructose	−1.2 ± 0.4*	−0.5 ± 0.5	−1.2 ± 0.4*	−1.6 ± 0.5*	−1.5 ± 0.5*
Sucrose	−1.3 ± 0.4*	−0.9 ± 0.5	−1.3 ± 0.5*	−1.3 ± 0.5*	−1.6 ± 0.5*
Sucralose	−0.9 ± 0.4*	−0.9 ± 0.5*	−1.2 ± 0.4*	−1.2 ± 0.4*	−0.9 ± 0.5*

BOLD, blood oxygen level–dependent.
Mean difference in BOLD response indicated in mean % change ± SE.
*Significantly different from the water control condition at $P < 0.05$.

over the measured time period. On the contrary, the natural sugars glucose, fructose, and sucrose elicited a smaller VTA activation compared with plain water ingestion.

The results are in line with earlier studies showing hypothalamic deactivation, which has been associated with satiety signaling, after ingestion of the natural occurring energy-containing sugar glucose [3,4]. The hypothalamus is important in the homeostatic system's ability to regulate energy balance [3,4], and thus a response to glucose was expected as it is an important energy source for the body and the brain [11]. This is reflected in the results of the present study by the almost immediate reaction to glucose, which is almost directly metabolically available and recognized by the brain [11]. We found that the hypothalamic response to fructose and sucrose was delayed after ingestion, which might be related to the fact that the sucrose dimer has to be broken down and that fructose has to be metabolized by the liver before it can be detected by energy-sensing neurons in the brain [35].

The sweet taste of the study stimuli could be the prediction of the imminent reward of energy content, as sweet taste is deemed a predictor of the postingestive consequences of food [6,36]. The initial response found immediately after ingestion in the hypothalamus and VTA might therefore be a response to the sweet taste, which creates an expectation of an energetic reward, rather than to gut hormones or energy content and increases in blood glucose levels [37,38]. This is in line with our finding that the artificial sweetener sucralose elicits an initial decrease in BOLD signal in the hypothalamus but does not result in a longer hypothalamic response like the ingestion of natural sugars, possibly because of the absence of energetic content.

The hypothalamus is functionally and anatomically connected to the VTA and influences the dopamine reward system via several pathways [6,8–10]. During fasting or while in a hungry state, an activated lateral hypothalamus has been shown to send signals to the VTA that promote reward-seeking behavior in mice [39]. Overstimulation of this hypothalamus–VTA axis by a continuously high hypothalamic activity has been shown to lead to compulsive sucrose seeking in mice [39]. The present results show that the hypothalamus becomes deactivated when it senses glucose or energy content of the ingested sweetener, which could then influence the magnitude of the VTA response through the proposed connection between the hypothalamus and the VTA. The present results show that sucralose appears to lead to a prolonged activation of the VTA, coinciding with a more transient response from the hypothalamus compared with the natural sugars, thus indicating that because the lack of energy content elicits a deactivation of the hypothalamus, a prolonged activation of the VTA may occur. This suggests that non-caloric sweeteners do not lead to the same homeostatic and hedonic effects in the brain as energy-containing natural sugars, potentially caused by the dissociation between sweet taste and energy content [27].

A limitation of the present study was generalizability. We investigated a relatively small sample of men, and it can be expected that sex differences are present because it is known that there are several sex-specific differences in energy metabolism [40]. In addition, we only investigated lean men, and earlier studies have shown different hypothalamic function in obesity [41]. This decreases the generalizability of our findings to the general population. A further limitation is the fact that the sugars in this study were dissolved in water and not part of a broader food matrix. This also could limit the generalizability of our findings to more general, marketable products. On the other hand, by comparing the effect of sugars and sweeteners only, the results are not contaminated by spurious influences of other ingredients of the test products. A further limitation of the experimental design is that it was not representative of normal ingestive behavior of sugar-sweetened beverages because these are not usually ingested in a fasted state in the morning or in a supine position. In addition, because we only found few significant results, owing to a relatively large variation in VTA responses between participants, an increase in sample size would be preferable to be able to better determine the VTA response and the difference in response between stimuli. Furthermore, more extensive VAS scoring of hunger immediately after ingestion, instead of after 30 min, and monitoring of energy intake during the rest of the day could provide better insight into the immediate and longer-term effects on hunger and satiation caused by the study stimuli.

A strength of the present study was the measurements of the hypothalamic and VTA response over time, which allowed us to determine the dynamics of these responses to differently metabolized sugars.

Taken together, the results of the present study demonstrated that ingestion of glucose elicits a prolonged decrease in

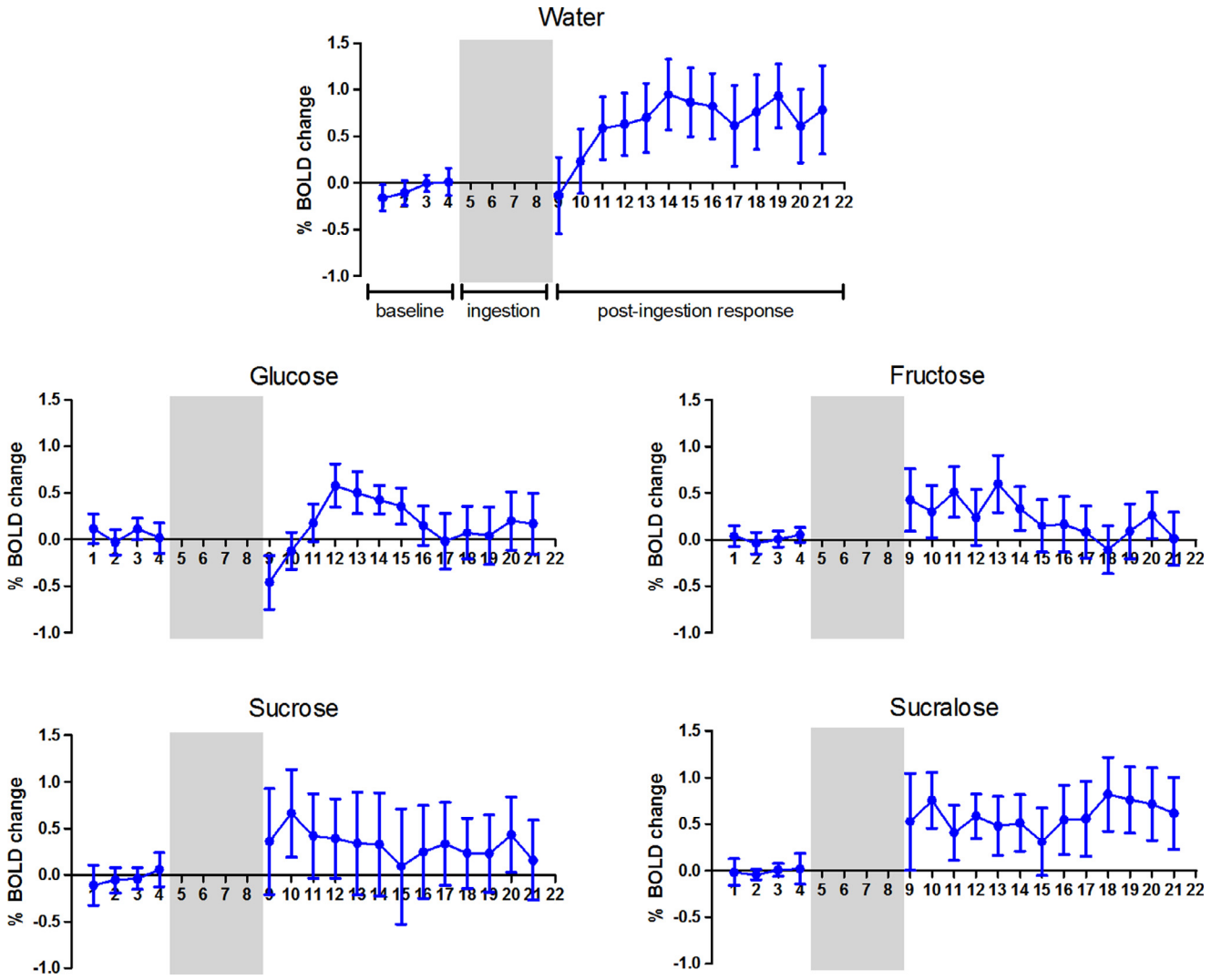

Fig. 3. Normalized BOLD response (% change) in the ventral tegmental area after ingestion of water (control condition), glucose, fructose, sucrose, and sucralose stimuli. Data presented as mean response for all participants (N = 16) per minute with SE. Postingestion was calibrated to the baseline period. Grey bar represents ingestion period, data recorded during this period was excluded from analysis. BOLD, blood oxygen level–dependent; SE, standard error.

Table 5
Mean difference in post-ingestion VTA BOLD responses to the study stimuli and the water control condition

	Average response	Response min 9–12	Response min 13–16	Response min 17–21	Response min 17–21
Glucose	−0.4 ± 0.4	−0.3 ± 0.5	−0.2 ± 0.5	−0.5 ± 0.5	−0.6 ± 0.5
Fructose	−0.4 ± 0.4	+0.2 ± 0.4	−0.4 ± 0.5	−0.6 ± 0.5	−0.6 ± 0.5
Sucrose	−0.4 ± 0.4	+0.2 ± 0.5	−0.5 ± 0.5	−0.5 ± 0.5	−0.5 ± 0.5
Sucralose	−0.1 ± 0.4	+0.3 ± 0.4	−0.3 ± 0.4	−0.2 ± 0.5	−0.1 ± 0.4

BOLD, blood oxygen level–dependent; VTA, ventral tegmental area.
Mean difference in BOLD response indicated in mean % change ± SE.

hypothalamus activity with a possible transient response from the VTA, which could be associated with satiety signaling. Sucrose and fructose lead to a delayed hypothalamic response and a small response from the VTA, if any response at all. The present data indicated that the brain responds directly and readily to glucose as the preferred source of energy of the brain, but might not respond as efficiently to other sugars. Ingestion of the non-caloric sweetener sucralose, however, appears to lead to a more transient deactivation from the hypothalamus and led to the same response from the VTA as plain water ingestion. This could reflect a lack of satiety signaling by the hypothalamus and a different hedonic response to non-caloric sweetener ingestion owing to a lack of caloric content. The present findings indicated that the responses by the hypothalamus and VTA are mainly driven by sweet taste coupled with caloric content and that sweet taste without caloric content does not seem to elicit a lasting response from these brain areas.

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