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Glucose Modulates Human Ventral Tegmental Activity in Response to Sexual Stimuli

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ABSTRACT

Background: Attribution of salience to sexual stimuli is mediated by the dopaminergic midbrain, including the ventral tegmental area (VTA). The existence of glucose-sensing neurons in the VTA, as suggested by animal studies, offers the opportunity to modulate aberrant salience coding involved in sexual disorders such as sexual addiction. Recent neuroimaging work supported that VTA activity in humans can be modulated by intravenously infusing a small bolus of glucose. However, that study used appetitive food stimuli, leaving the possibility that glucose modulation of VTA-mediated salience coding might be bound to this class of stimuli.

Aim: To test whether glucose-modulatory effects generalize to food-unrelated stimuli despite being in the class of primary reinforcers.

Methods: During functional imaging, 37 healthy men were exposed to images showing nude or clothed female upper bodies. At the end of the 1st quarter (~6 minutes) of the experiment, 18 participants received a small amount of intravenously infused glucose.

Results: Before glucose administration, VTA activity was higher for nude than for clothed female stimuli. After infusion of glucose, this pattern reversed such that VTA activity was higher for clothed than for nude female stimuli. The effect was at its maximum approximately 7 to 12 minutes after glucose infusion, changing back during the experiment's 4th phase. In another 19 participants not treated with glucose, VTA activity was consistently higher for nude than for clothed female stimuli throughout the experiment.

Conclusion: The present findings show that glucose modulates VTA-mediated salience coding of sexual stimuli. These results suggest that glucose might affect salience coding in a stimulus-general way. However, future studies are necessary to address the question of whether glucose modulation also affects the VTA's salience coding of secondary reinforcers. **Ulrich M, Stauβ P, Grön G. Glucose Modulates Human Ventral Tegmental Activity in Response to Sexual Stimuli. J Sex Med 2018;15:20–28.**

Key Words: Functional Magnetic Resonance Imaging; Ventral Tegmental Area; Hypothalamus; Glucose Infusion; Modulation; Salience Coding; Addiction; Reward

INTRODUCTION

Modern society is surrounded by an overabundance of "superficially seductive"[1] environmental cues that can lead to maladaptive addictive behaviors with negative long-term consequences for health or well-being. For instance, hedonic eating, the consumption of palatable high-fat, high-carbohydrate food beyond saturation, can culminate in obesity. Another example is "out-of-control sexual behavior," also called "sex addiction" among other names, which has been estimated to affect approximately 3% to 6% of the general adult population.[2,3] Food and sex are primary reinforcers that elicit neural activity in the so-called mesolimbic system, parts of which attribute salience to external and internal stimuli.[4,5] At the heart of this system lies the ventral tegmental area (VTA), a midbrain region rich in dopaminergic neurons. Interestingly, decades ago it was shown that glucose suppresses activity of dopaminergic neurons in the substantia nigra and VTA in experimental animals.[6–10] Thus, glucose might be used as a means of correcting aberrant salience coding of superficially seductive, rewarding stimuli such as palatable food,[11] sexual stimuli (ie, pornography), or other cues involved in addictive behaviors.

In preparation of translating the above-cited rat findings to humans, we recently began to explore glucose-induced effects on VTA activity in healthy male participants using functional

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magnetic resonance imaging (fMRI).[11] In that study, pictures of high- and low-caloric food cues and non-food stimuli were presented to participants who had to decide whether the stimulus depicted food or non-food. The experiment consisted of 4 approximately 6-minute phases, and brain activity was continuously measured during the entire experiment. Importantly, a small 10-g bolus of glucose was intravenously infused after phase 1. Focusing on the VTA and hypothalamus, the blood oxygen level-dependent (BOLD) signal difference of high- minus low-caloric food stimuli changed: The initially positive BOLD difference during phase 1 decreased and even reversed significantly during phase 3, an effect that was absent in a control group of untreated participants. This suggests that, in situations with 2 stimulus alternatives, glucose decreases salience of the stimulus carrying higher baseline salience, whereas the stimulus with lower baseline salience becomes more salient under the influence of glucose. Based on that interpretation, we were curious to test whether salience of other stimulus classes also would be affected by glucose. In the present investigation, we chose sex-related cues because sex, like food, is a primary reinforcer and therefore should engage the brain's reward system, including the VTA.[12–19] In a male-only sample, we used fMRI to compare VTA activity in response to images depicting nude vs clothed female torsos. After a baseline period, a bolus of glucose was intravenously applied. Directly derived from our previous work using food cues, we predicted robustly higher VTA activity for stimuli of nude vs clothed women under unmodulated baseline conditions, and this effect was hypothesized to decrease or even reverse under the influence of administered glucose. For a second group of participants not receiving any infusion treatment, we expected higher VTA activity for the more salient stimulus class throughout the experiment.

METHODS

Participants

Participants were 37 heterosexual healthy male medical students from the University of Ulm (Ulm, Germany), with a mean age of 23.9 years (SD = 2.1 years) and body weight of 79.5 kg (SD = 8.6 kg). Mean body mass index (BMI) was 23.6 kg/m^2 (SD = 1.9 kg/m^2). The pool of participants was randomly split into 2 experimental groups (glucose group, n = 18; control group, n = 19 participants). Groups did not significantly differ in age, weight, or BMI* ($t_{35} < 1.56$, $P > .129$ for all comparisons). There were no contraindications regarding the infusion of glucose (eg, disturbed glucose tolerance) or the fMRI procedure, and there were no self-reports of psychiatric or neurologic disorders. The study was approved by the local ethics committee at the University of Ulm and was in accordance with the Declaration of Helsinki. Written informed consent was obtained from each subject before the investigation.

Experimental Task During fMRI

Images depicting the upper body of nude and clothed women and men were presented. Participants were asked to decide as quickly and as accurately as possible whether the depicted person was a woman or a man and to indicate their decision using 1 of 2 predefined buttons (right index finger for woman; right middle finger for man). The original images, derived from various freely available internet resources using Google search, were cropped so that they resembled half-length portraits, featuring the upper body (with the most inferior part approximately 2 inches below the navel), head, and arms. The depicted person was clothed (ie, sweatshirts, T-shirts, jackets, and business dress) or nude. If nude, only breasts as secondary sex characteristics were visible due to cropping; pubic hair or the woman's sexual organ was never shown. All pictures were scaled to fit a height of 400 pixels. The depicted persons were estimated to be not older than 30 years, and their facial expression was neutral.

Each stimulus category (♀$_{clothed}$, ♀$_{nude}$, ♂$_{clothed}$, ♂$_{nude}$) consisted of 60 different pictures. Unbeknown to participants, the experiment, which had a total duration of 25.6 minutes, was subdivided into 4 phases of equal length (6.4 minutes per phase). After initial randomization, 15 stimuli of each stimulus category were presented during each phase, in accord with a prespecified trial sequence provided by the program Optseq2[26] (http://surfer.nmr.mgh.harvard.edu/optseq/). Each stimulus was presented only once per participant. It appeared centered in front of white background and lasted 2.5 seconds. During the intertrial period of variable length (mean = 3.8 seconds, SD = 3.7 seconds, maximum = 25.0 seconds), participants were asked to fixate on a black cross that was shown in the center of the screen. Presentation 14.8 (Neurobehavioral Systems Inc, San Francisco, CA, USA) was used for stimulus delivery on a 32-inch liquid-crystal display (NordicNeuroLab AS, Bergen, Norway) at a resolution of 1,280 × 720 pixels projected to participants' eyes by a mirror.

Procedure

Participants arrived at the laboratory from 8:00 to 9:00 AM after an overnight fast, which was tested by measuring the concentration of blood glucose (ACCU-CHEK Inform II; Roche Diagnostics GmbH, Mannheim, Germany). In the scanner, a T1-weighted anatomic image was acquired, followed by a practice run of the task. During the subsequent experiment, the BOLD signal was measured to estimate subjects' brain activation. Participants of the glucose group received 20% glucose solution 50 mL (B. Braun Melsungen AG, Melsungen, Germany), approximately 6.4 minutes after the start of the experiment, infused into the antecubital vein of the left arm using an MRI-compatible infusion pump (ACCUTRON MR; MEDTRON AG, Saarbrücken, Germany). The glucose bolus was given within a period of 30 seconds (flow rate ~ 1.7 mL/second). Before and after the

* Increased body weight, reflected by a higher BMI, is associated with a higher level of circulating leptin,[20] and there is evidence that leptin modulates neuronal activity in the hypothalamus and the VTA.[21–25] Thus, if the mean BMI significantly differed between the experimental groups, the putative effects of treatment-induced modulation of brain activity might be confounded by the influence of leptin.