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Food can lift mood by affecting mood-regulating neurocircuits via a serotonergic mechanism

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ABSTRACT

It is commonly assumed that food can affect mood. One prevalent notion is that food containing tryptophan increases serotonin levels in the brain and alters neural processing in mood-regulating neurocircuits. However, tryptophan competes with other long-neutral-amino-acids (LNAA) for transport across the blood–brain-barrier, a limitation that can be mitigated by increasing the tryptophan/LNAA ratio. We therefore tested in a double-blind, placebo-controlled crossover study (N = 32) whether a drink with a favourable tryptophan/LNAA ratio improves mood and modulates specific brain processes as assessed by functional magnetic resonance imaging (fMRI). We show that one serving of this drink increases the tryptophan/LNAA ratio in blood plasma, lifts mood in healthy young women and alters task-specific and resting-state processing in brain regions implicated in mood regulation. Specifically, Test-drink consumption reduced neural responses of the dorsal caudate nucleus during reward anticipation, increased neural responses in the dorsal cingulate cortex during fear processing, and increased ventromedial prefrontal–lateral prefrontal connectivity under resting-state conditions. Our results suggest that increasing tryptophan/LNAA ratios can lift mood by affecting mood-regulating neurocircuits.

Introduction

Primarily, food is required to meet basic nutritional requirements, and energetic needs. However, in societies where these requirements appear safely met, attention has shifted towards healthy diets including biologically active components potentially reducing disease risks and optimizing physical as well as mental well-being (Hamer et al., 2005). Stress-resilience and good, stable mood are essential to both health and well-being (WHO, 2011), and amongst the general public a common assumption exists which holds that food can improve mood. However, this link is poorly investigated empirically in humans and evidence for a mechanism that can explain how food affects mood directly is lacking. Food could potentially affect mood in many ways. For example, food consumption may increase feelings of satiety and vigour through systems regulating energy homeostasis such as glucose, insulin, leptin, and ghrelin, but may also affect hedonic experiences through opioid and dopamine release (Saper et al., 2002). More directly, biologically active nutritional ingredients could affect neural processes in brain regions central to mood regulation like the prefrontal cortex, cingulate cortex, amygdala, hippocampus and striatum (Price and Drevets, 2009; Ressler and Mayberg, 2007). Mood disturbances and attenuations in this neural network have been associated with altered serotonin levels (Canli et al., 2008; Cools et al., 2011; Macoveanu et al., 2012; Markus, 2008; Roiser et al., 2007; Tanaka et al., 2009). Therefore, it has been proposed, based on pharmacological research, that food containing the serotonin precursor tryptophan (Trp) increases serotonin levels in the brain, and modulates processing in the neurocircuit regulating mood in a way that is beneficial for mood (Markus, 2008).

In line with this hypothesis, reducing serotonin through tryptophan depletion is well-known to affect mood negatively (Cools et al., 2011; Markus, 2008; Tanaka et al., 2009). However, the results of such drug studies do not simply generalize to food. Food is a product or substance that can reasonably be expected to be ingested by humans and normally occurs in the existing food chain (Regulation (EC) No 178/2002). Moreover, attempting to lift mood by ingesting food with high tryptophan levels is not as straightforward. Tryptophan competes with other long-neutral-amino-acids (LNAA) for a transport molecule that allows entry into the brain (Wurtman et al., 1980), thus limiting the possibility of food to increase brain tryptophan levels and lift mood. Although dietary effects on plasma Trp/LNAA ratio have been reported, these, and the resulting behavioural changes, have been modest (Markus, 2008). However, the ingestion of food with optimized Trp/LNAA ratio

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produced by a hydrolyzed egg protein can result in substantial increases in plasma Trp/LNAA ratio. Preliminary data indicate that such nutrition may improve mood and motor control, and reduce cortisol responses to stress (Markus, 2008), yet the neurobiological mechanisms underlying these effects are currently unknown.

We therefore tested whether a food with a Trp/LNAA ratio favourable to Trp uptake into the brain leads to mood improvements and changes in a set of neural processes implicated in mood regulation. Given the networks implicated in mood disturbances, of specific interest here are the ventromedial prefrontal cortex (vMPFC), cingulate cortex, striatum, and amygdala, which determined our task selection. Briefly, in a double-blind cross-over design thirty-two female participants consumed a Test-drink with an increased Trp/LNAA ratio or a Control-drink on two separate visits to the lab aimed at modulating the serotonergic system through food intake. On both occasions blood plasma Trp/LNAA levels and mood were measured to assess whether food consumption indeed affected the serotonergic system and mood. In addition, neural activity during reward anticipation (Knutson et al., 2001), threat of shock (Kumari et al., 2007), and emotional processing tasks (Hariri et al., 2002), as well as resting state connectivity with the vMPFC were investigated with Blood Oxygenation Level Dependent functional Magnetic Resonance Imaging (BOLD-fMRI) to determine whether food that affects the serotonergic system and mood, is associated with changes in a set of neural processes implicated in mood regulation. Considering recent suggestions on the functional interaction of serotonin and dopamine (Cools et al., 2011), we predicted that increasing tonic serotonin levels by heightened availability augments neural responses in areas exhibiting cognitive control over negative affect, down-scales striatal activity related to response-priming during reward anticipation, and reduces emotion related responses in the amygdala. Such a set of functional changes is assumed to result in mood improvements through inhibition of negative thoughts or, in other words, a general cognitive bias towards positive and away from negative emotions.

Material and methods

A brief description of the methods and materials is presented in this section. For a full and detailed description, please refer to the Supplementary material.

Participants

Thirty-two healthy young women (age-range: 18–39 yr, mean: 22.387, SD: 3.955) were included in the study, and were tested during the second week of their menstrual cycle, i.e. the second week after discontinuation of noticeable menstruation, to avoid possible interactions with menstrual cycle effects. We chose to only include women to reduce group variance, and because women have higher prevalence rates of mood disturbances relative to men (Waraich et al., 2004). The study was approved by the institutional ethics committee (CMO Regio Arnhem-Nijmegen, The Netherlands) and all subjects provided written informed consent.

Food

Subjects consumed drinks (300 mL) containing an equal amount of basis protein, but differential tryptophan and LNAA (long-neutral-amino-acids; valine, isoleucine, leucine, tyrosine, and phenylalanine) concentrations. The Control-drink contained 11.97 g casein protein hydrolysate with 0.12 g Trp. The Test-drink (LumiVida™: DSM Nutritional Product, Switzerland) contained a hydrolyzed enzymatic digest of egg white with 0.66 g Trp. The Control-drink and Test-drink are identical in content with the exception of the Trp/LNAA ratio and provide the same caloric intake (see Table 1).

Table 1
Specification Test- and Control-drinks.

	Test-drink	Control-drink
Casein protein hydrolysate	0 g	11.97 g
Lysozyme protein hydrolysate	12 g	0 g
Sweetener (sucralose)	0.063 g	0.063 g
Sweetener (acesulfame-k)	0.027 g	0.027 g
Citric acid	0.72 g	0.72 g
Lemon lime flavour	0.45 g	0.45 g
Content:		
Tryptophan (Trp)	5.5% (0.66 g)	~1% (0.12 g)
Trp/LNAA ratio (LNAA; valine, isoleucine, leucine, tyrosine, and phenylalanine)	0.19	~0.02
Chemical/physical data		
pH in 1% solution	4.3	4.6
Ash	7.97%	<5%
Microbiological data		
Total plate count	<10 cfu/g	<10 cfu/g
Yeast & moulds	<10 cfu/g	<10 cfu/g
Bacillus cereus	<10 cfu/g	<10 cfu/g
Salmonella	Negative in 25 g	Negative in 25 g
Staphylococcus aureus	Negative in 1 g	Negative in 1 g
Listeria monocytogenes	Negative in 25 g	Negative in 25 g

Behavioural tasks

Participants were subjected to three behavioural tasks while BOLD fMRI data was acquired. The reward anticipation task (Fig. S1) is a modified version of the monetary incentive delay task (Knutson et al., 2001) in which cues are presented that signal trials that are either potentially rewarding or non-rewarding. Subjects respond to the appearance of a target by pressing a button, and if pressed fast enough receive a euro on reward trials, but not on non-reward trials. The threat-of-shock task (Fig. S2) was based on a previous fear-potentiated startle paradigm (Kumari et al., 2007). In the task, cues were presented that either signalled periods during which an electrical shock might be received or signalled periods of safety. A mild electrical shock was delivered only once in the first session. In the Emotion processing paradigm (Fig. S3) subjects were presented with blocks of trials consisting of angry and fearful stimuli in Emotion blocks, or ellipses (that consisted of scrambles of the same face stimuli) in visuo-motor Control blocks (Hariri et al., 2002). Subjects indicated which of the two images presented at the bottom of the screen matched a target at the top of the screen in terms of orientation (Control trial) or emotional expression (Emotion trial). The Baseline checkerboard paradigm (Fig. S4) constituted interleaved presentation of Fixation blocks and blocks of visual stimulation by a rapidly alternating checkerboard pattern.

Blood plasma Trp/LNAA ratio analyses

Blood samples were collected in duplicates of 5 mL vacutainer tubes containing sodium heparine and centrifuged at 1550 *g* for 5 min at 4 °C. The supernatant lithium heparine plasma (750 μL) was mixed with 120 μL sulfasalicyl acid in duplo and stored at −80 °C until analysis. Plasma amino acid analysis was conducted with high-pressure liquid chromatography (HPLC), making use of a 2- to 3-μm Bischof Spherisorb ODS II column. The plasma tryptophan to LNAA ratio was calculated by dividing the plasma tryptophan concentration (in μmol/L) by the sum of the other long neutral amino acids, i.e. valine, isoleucine, leucine, tyrosine, and phenylalanine, and averaging over the two samples.

Mood questionnaires

The short-form Profile of Mood States questionnaire (POMS-SF) measures mood along 5 dimensions: fatigue, tension, depression, anger, and vigour (Shacham, 1983). Total negative mood was calculated