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Dopamine and food reward: Effects of acute tyrosine/phenylalanine depletion on appetite

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ABSTRACT

It has been suggested that obese individuals over-eat in order to compensate for deficits in the dopaminergic reward system. The current study used acute tyrosine/phenylalanine depletion (ATPD) to investigate the effect of reduced dopamine function on appetite and the reward value of food in healthy volunteers. The compensatory-eating hypothesis would predict an increase in the reward value and consumption of food following depletion by this method. In a double-blind, counterbalanced, crossover study, 17 male participants (mean age = 29.2 (*SEM* = 2.7) years; mean body mass index = 24.4 (*SEM* = 0.6) kg/m^2) were administered with a tyrosine/phenylalanine-free mixture (TYR/PHE-free; depletion condition) and a balanced amino acid mixture (BAL; control). Plasma amino acid levels were measured at baseline and peak depletion (300 min). Appetite, willingness to pay for food, liking, desired portion size and ad libitum food intake were also assessed. The TYR/PHE-free mixture was associated with significant decreases in tyrosine, phenylalanine, and the ratio of tyrosine + phenylalanine to the other large neutral amino acids (all $p < .001$). There were no effects on our measures of willingness to pay for food or liking. However, in the TYR/PHE-free condition, participants reported significantly lower levels of hunger following a fixed-test meal relative to the BAL condition. In conclusion, we found no evidence for compensatory eating following ATPD. Our results also provide support for the role of dopamine in motivational components of eating.

1. Introduction

Dopamine is known to be important for the control of food intake. Animal studies indicate that eating rate and meal size are under dopaminergic control, and dopamine is believed to underlie mechanisms that permit switching from feeding to other classes of behaviour [1]. In addition, the role of dopamine in mediating food reward has been extensively documented [2–4]. It therefore seems plausible that abnormalities in the dopaminergic system contribute to over-eating and obesity. However, findings to date appear inconsistent and the extent to which obesity may be explained by over-active or, alternatively, under-active reward circuitry remains to be determined [5].

In support of the theory that dopamine function is under-active, there is evidence that obese humans have lower availability of striatal dopamine D_2 receptors relative to lean controls [6,7]. Subsequent research showed a 'blunted' striatal response to receipt of a palatable food in obese individuals, the extent of which was predictive of weight gain over a 6- to 12-month period [8,9]. These authors and others [10] suggest that obese individuals may over-eat and hence gain weight in order to compensate for deficits in the dopaminergic system. The effect of this, it is suggested, is to further attenuate the responsivity of rewards circuitries which exacerbates over-eating in a 'feed forward' process of vulnerability [11]. Importantly, drug addiction is also associated with marked decreases in both dopamine D_2 receptors and dopamine release [12]. This commonality has lead to the idea that individuals may become addicted to highly-palatable food in much the same way as being addicted to illicit drugs [13,14].

The prospect that downregulated dopaminergic function leads to over-eating merits scrutiny in an experimental setting. In this respect, a promising approach is to use acute tyrosine/phenylalanine depletion (ATPD). This neurobiological challenge depletes global levels of dopamine by limiting the availability of its amino acid precursor, tyrosine (via administration of an amino acid mixture that lacks both tyrosine and its precursor, phenylalanine). This reduces tyrosine availability in the brain through increased protein synthesis (lowering plasma tyrosine levels) and increased competition for transport across the blood–brain barrier [15,16]. The tyrosine-free mixture reduces central levels of tyrosine and DOPA, and attenuates the amphetamine-induced release of dopamine in rats [17]. Human studies have shown increased prolactin levels [18] and enhanced [^{11}C]raclopride binding (indicating decreased extracellular dopamine levels) [19,20] as a result of the depletion. Importantly, levels of noradrenaline do not appear to be affected by the ATPD challenge [17].

ATPD is increasingly being recognised as a valuable paradigm for examining the effects of reduced dopamine function on addictive behaviours. Indeed, in smokers it has been shown to increase the

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reward value of cigarettes, subjective craving, and the intensity of smoking [21,22]. Such findings are entirely consistent with the notion that deficits in the reward system (i.e., reduced dopaminergic function) may drive compensatory reward-seeking behaviours. There is great potential for ATPD to be used as an acute experimental model of the hypo-dopaminergic state that is found in obesity. To our knowledge, however, no studies have applied ATPD to the study of human ingestive behaviour. The aim of the current study was therefore to establish the effect of ATPD on appetite, food reward, and consumption in healthy volunteers. The research outlined above would predict an increase in the reward value and intake of food as a result of the depletion. We also included a comparable measure of the reward value of alcohol to determine the extent to which potential effects were food-specific or relevant to reward systems in general.

2. Material and methods

2.1. Participants

Eighteen male volunteers were recruited via an online database drawn from the University of Bristol and the wider community. The following exclusion criteria were applied: regular smoking; illicit drug use; current or past psychiatric disorder; history of neurological illness; current or recent use of psychotropic medications; phenylketonuria; uncorrected impaired vision or colour blindness. All participants were consumers of alcohol. Ethical approval was granted by the Faculty of Science Research Ethics Committee, University of Bristol. Participants provided written informed consent prior to participation. They were reimbursed £100 upon completion of the study.

2.2. Amino acid mixtures

As in previous studies [21–23], we used the 90 g tyrosine/phenylalanine-free (TYR/PHE-free) mixture that was developed by McTavish and colleagues [17]. Its composition is shown in Table 1. The balanced (BAL) mixture additionally contained tyrosine and phenylalanine. In previous studies, the BAL mixture contained 12.5 g each of phenylalanine and tyrosine resulting in a total weight of 115 g. In our study, however, it was important to ensure that the mixtures were equivalent in weight (i.e., 90 g). We therefore used a BAL mixture of 90 g in which the quantities of all amino acids were reduced while maintaining equivalent proportions with respect to the TYR/PHE-free mixture (see Table 1). We used the method of May and Hill [24] to confirm that the amino acid mixtures were of equivalent metabolisable energy content (TYR/PHE-free = 480 kcal; BAL = 487 kcal). The mixtures were prepared by suspending the amino acids in tap water. A 4 g sachet of flavouring (Vitaflo, Liverpool, UK; kcal = 13) was added to disguise the unpleasant taste. Pilot testing indicated that there was no discernible difference in taste between the two mixtures.

Table 1
Composition of the TYR/PHE-free and balanced (BAL) amino acid drinks.

	TYR/PHE-free	BAL
Isoleucine	15 g	11.5 g
Leucine	22.5 g	17.5 g
Lysine	17.5 g	13.5 g
Methionine	5 g	4 g
Valine	17.5 g	13.5 g
Threonine	10 g	8 g
Tryptophan	2.5 g	1.5 g
Tyrosine	–	10 g
Phenylalanine	–	10 g
Total	*90 g*	*90 g*

2.3. Experimental sessions

Candidates who expressed an interest in the study were invited to an initial screening session, during which their eligibility to participate in the study was verified. Measures of height and weight were taken at this point, and the Dutch Eating Behaviour Questionnaire (DEBQ) [25] was completed. A dummy-run of all experimental tasks was also undertaken. Eligible participants then completed the two 7-h test sessions conducted within our laboratory.

Participants were administered with the TYR/PHE-free mixture and the BAL mixture in a double-blind, counterbalanced, crossover design, with 1 week separating the two challenge conditions. For 24 h prior to each test session, participants followed a low-protein diet (total protein content less than 20 g) and they abstained from eating from midnight. The low-protein diet was necessary in order to standardise the levels of amino acids from diet across participants. All participants confirmed their compliance with the low-protein diet at the start of each test session. To minimize the possibility of caffeine withdrawal, participants who were regular consumers were instructed to have their usual morning amount.

Participants were tested individually with each test session beginning at 0900 h. Participants provided a baseline blood sample and completed ratings of mood, physical sensations and appetite. They then consumed either the TYR/PHE-free or the BAL amino acid mixture. Following consumption of the drink, participants remained in the laboratory and were given access to DVDs and light reading material. Ratings of mood, physical sensations (including nausea) and appetite were taken at 60-, 120-, 180-, 240-, and 300-min post-consumption. At 300-min (approximate time of peak depletion, [18]), a second blood sample for amino acid analysis was obtained. Participants then completed a series of computerised tasks, in the following order (i.) desired portion size of food, (ii.) willingness to pay for food, (iii.) expected liking for food, and (iv.) willingness to pay for alcohol. Upon completion of these tasks participants were provided with a fixed meal of pasta (beef cannelloni, Sainsburys plc, London, UK; per 400 g serving, kcal = 498, protein = 23.7 g, carbohydrate = 41.9 g, fat = 26.2 g). They were asked to consume the meal in its entirety and all participants complied with this request. Ratings of appetite and nausea were taken pre- and post-consumption of the meal. Finally, participants remained in the laboratory for a further 10 min and were given ad libitum access to 500 g of biscuits presented in a large bowl (chocolate chip cookies, Sainsburys plc, London, UK; per 100 g, kcal = 496, protein = 5.9 g, carbohydrate = 64.3 g, fat = 23.9 g). Biscuits were broken into pieces so that participants could not easily monitor the amount consumed (following the method of Higgs and Woodward [26]). Intake was determined by weighing the biscuits pre- and post-consumption. Our rationale for including the biscuit intake measure was twofold. In the first instance, we wished to avoid potential ceiling effects that may have been apparent if we had simply used consumption of the pasta meal as the variable of interest (given that participants had not eaten for several hours). We therefore followed the savoury meal with the sweet biscuits in order to mimic a dessert course. Secondly, the presentation of biscuits in this way enabled us to obtain a measure of incidental snacking, which is similar to that used by other studies in the literature (e.g., 'eating in the absence of hunger' tests, see [27]).

2.4. Measures

2.4.1. Willingness to pay for food

In this task, participants indicted the amount of money that they would be prepared to spend on food. This technique has been used in previous research [28]. It was chosen because a clear relationship exists between the incentive value of food and of money [29].