Psychiatry Research: Neuroimaging 252 (2016) 19–25

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Amphetamine alters neural response to sucrose in healthy women

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ARTICLE INFO

Article history:
Received 17 June 2015
Received in revised form
29 April 2016
Accepted 29 April 2016
Available online 4 May 2016

Keywords:
Taste
Hunger
FMRI
Amphetamine
Sucrose
Water
Insula
Dorsal ACC

ABSTRACT

Amphetamine, likely via action on the brain's dopaminergic systems, induces anorectic eating behavior and blunts dopaminergic midbrain activation to rewards. Past work has hypothesized that this blunted reward responsivity is a result of increasing tonic over phasic DA activity. We sought to extend past findings to sweet taste during fMRI following single-blind administration of dextroamphetamine and placebo in 11 healthy women. We hypothesized that neural response in both limbic and cognitive sweet taste circuits would mirror past work with monetary rewards by effectively blunting sweet taste reward, and 'equalizing' it's rewarding taste with receipt of water. Behavioral results showed that amphetamine reduced self-reported hunger (supporting the existence of amphetamine anorexia) and increased self-report euphoria. In addition, region of Interest analysis revealed significant treatment by taste interactions in the middle insula and dorsal anterior cingulate confirming the 'equalizing' hypothesis in the cingulate, but unlike monetary reinforcers, the insula actually evinced enhanced separation between tastes on the amphetamine day. These results suggest a divergence from prior research using monetary reinforcers when extended to primary reinforcers, and may hint that altering dopaminergic signaling in the insula and anterior cingulate may be a target for pharmacological manipulation of appetite, and the treatment of obesity.

1. Introduction

In both children and adults, obesity has had a steadily increasing prevalence for the past several decades and has become one of the largest public health issues in modern society. Successful pharmacological treatment of obesity has remained highly elusive, which likely has limited the impact of drug-based interventions in preventing obesity related health problems. In comparison, amphetamine is one of the most successful classes of anorectic drugs currently in existence. Although chronic use of amphetamines as a pharmacological treatment for obesity is clearly problematic, a better understanding of the underlying mechanisms enabling such successful appetite suppression could provide a pathway to develop more effective medications without amphetamine's adverse side effects. The current work is the first to the author's knowledge to investigate amphetamine's effects on neural response to a rewarding sweet taste in humans, which we believe may be a useful starting point in translating animal research on amphetamine's potent appetite suppression effects to human subjects.

Dextroamphetamine sulfate (dAMPH) is the dextro-isomer of the compound d,l-amphetamine sulfate, a sympathomimetic amine of the amphetamine group. dAMPH is considered a very successful anorectic agent (Foltin et al., 1995), and is thought to fundamentally affect reward discrimination (Schultz, 2011), a factor which may relate to it's poorly understood anorectic effects. Positron Emission Tomography (PET) studies with dAMPH during [18F]fallypride scans indicate increased dopamine concentrations in both striatal and extrastriatal regions of the brain including medial orbital frontal cortex (OFC), cingulate, precuneus, amygdala, and hippocampus (Dropley et al., 2008; Riccardi et al., 2006). Moreover, PET studies implicate gender-specific effects following dAMPH administration (Riccardi et al., 2011), highlighting the importance of careful control of potential gender differences when experimentally administering dAMPH.

To our knowledge, no studies have used fMRI to investigate the

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http://dx.doi.org/10.1016/j.pscychresns.2016.04.017
0925-4927/

effects of dAMPH on reward responsivity to primary reinforcers in humans. Because food reward is complex, we used the response to a sweet taste as a simplified model of one aspect of eating behavior that aligns nicely with prior work done with monetary rewards (Knutson et al., 2004). As described in Kaye et al., (Kaye et al., 2009), sweet taste perception starts with the tongue, and is carried to the nucleus of the solitary tract by cranial nerves 7, 9, and 10, with some projections directly leading to the thalamus (Small, 2010). From the thalamus, taste processing is thought to flow through both a ventral (limbic) network of regions including the amygdala, insula, ventral striatum, ventral anterior cingulate cortex (vACC), and orbital frontal cortex (OFC), as well as a dorsal (cognitive) network that includes the hippocampus, dorsal ACC (dACC), dlPFC, and parietal cortex. This ventral network is thought to play an important role in determining the rewarding aspects of homeostatic appetitive needs, whereas the dorsal network is thought to mediate cognitive functioning such as planning and inhibition.

As a result of this paper being the first of it's kind, we turned to both animal research on dAMPHs effects on reward responsivity, and past work combining fMRI, dAMPH, and responsivity to monetary rewards to form our hypothesis. Research in baboons has hinted towards a potential sensitization towards sweet reward following amphetamine consumption (Foltin, 2011), which may contribute to the decreased eating durations and resultant anorexia. In addition, there is evidence that dAMPH may encourage alterations in eating behavior specifically via the D1 subtype of dopamine (Gilbert and Cooper, 1985), which has high cortical and subcortical concentrations in both the cognitive and limbic taste pathways (Hurd et al., 2001). Amphetamine administration has been shown to have both an inhibitory and excitatory effect on reward thresholds depending on the specifics of the experiment, and seems to be dependent on dopaminergic systems despite dAMPH acting on both noradrenergic and dopaminergic systems (Coelle et al., 1988). Self-stimulation of the lateral hypothalamus in the rat only follows administration of the d-amphetamine isomer (which acts on both dopaminergic and noradrenergic systems) and not l-amphetamine isomer (which acts only on noradrenergic systems), and is most potently modulated when directly infused into the nucleus accumbens which is a primary afferent of dopaminergic cell bodies in the ventral tegmental area (Coelle et al., 1988). In humans, dAMPH has been shown to reduce reward *anti*cipation activation in the nucleus accumbens, and serves to essentially 'equalize' reward and punishment anticipation (Knutson et al., 2004). We reasoned that neural response in both limbic and cognitive sweet taste circuits would mirror past work with monetary rewards by effectively blunting sweet taste reward, and 'equalizing' it's rewarding taste with receipt of water.

2. Methods

2.1. Participants

Eleven right-handed, healthy women with normal or corrected to normal visual acuity aged 22–40 were recruited through local and national advertisements or via previous study participation. Exclusion criteria included: past history of alcohol or drug abuse or dependence 3 months prior to the study; any medical or neurologic concerns; and any conditions contraindicative to magnetic resonance imaging. All participants underwent diagnostic and clinical assessments by a board-certified psychiatrist or psychologist using the Mini International Neuropsychiatric Interview (Sheehan et al., 1998) to ensure the absence of any Axis I diagnosis. No participants had any history of past or current drug abuse or dependence, and all participants had no use of either psychoactive medication or tobacco 3 months prior to the study. Participants additionally were required to have had a stable body weight (between 90% and 120% of ideal body weight defined as 45.5 kg +2.3 kg for each inch over 5 feet) since puberty to further establish the absence of any eating related disorder. Based on previous work showing that menstrual phase can affect response to amphetamine (Justice and de Wit, 1999), we attempted to schedule all participants to complete their fMRI sessions within the first 10 days of the follicular phase of the menstrual cycle, however, two participants were in the final one or two days of the luteal phase when the first scan took place due to slight unforeseeable cycle variations. Participants had a mean age of 26.5 (4.9SD), were all right handed, had a current BMI in the normal range (mean 22.03; 1.3SD), and ranged in educational level between 12 and 19 years (mean education 15.8; 1.9SD). The study was conducted according to the institutional review board regulations of the University of California, San Diego, and all participants gave informed consent. All eleven recruited participants completed the study, and were included in analysis.

2.2. Experimental Design

Participants performed a taste task developed at UCSD (Frank et al., 2003; Oberndorfer et al., 2013; Wagner et al., 2008) during fMRI scanning on two visits 24 h apart. Participants were informed that they would receive a dose of either dextroamphetamine sulfate (dAMPH) or a placebo (PLAC) on day one of the study, and that they would receive the dose they had not yet received on day two. In keeping with a single blind format, PLAC was always administered on day one of the study, whereas, dAMPH was administered on day two. All participants had completed prior scans at the UCSD neuroimaging center so as to reduce any confounding anxiogenic effects of undergoing scanning that may change between sessions. Scans were held on consecutive days due to many participants travelling to participate, as a result, PLAC was always administered on the first day to ensure that there was not a carry-over effect of dAMPH due to the close succession of drug conditions. Upon arrival 3 h prior to scanning each day, participants consumed a standardized breakfast and ingested either dAMPH or PLAC, this timing was employed to ensure peak response to the orally ingested AMPH (typically between 2.5 and 3.5 h) would occur while the participant was in the scanner (Asghar et al., 2003). During the course of the study, participant's heart rate, blood pressure and behavior (via several self-report measures) were measured periodically throughout the day to ensure no negative reactions to the drug, though blood glucose in response to the meal was not measured so variations in this cannot be ruled out as a confound.

2.3. Oral amphetamine administration

Dextroamphetamine sulfate was ordered and dispensed by the UCSD pharmacy. Subjects received dAMPH doses based on their individual weight, approximately 0.5 mg/kg (in 2.5 mg increments). This dAMPH dose was chosen based off prior neuroimaging work with dAMPH finding this to be an ideal dose for enhanced effects of the drug, while maintaining as little side effects as possible (Agrist and Sanfilipo, 2001).

2.4. Taste solution delivery

During the taste task, subjects were presented with two different stimuli: a 10% sucrose solution (Fisher Scientific, USA), and distilled water (Evian). Past literature has described these solutions as pleasant and neutral, respectively (Drewnowski et al., 1987). Participants received 1-mL of either the sucrose solution or the distilled water from a semi-automatic programmable