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Dopamine efflux in response to ultraviolet radiation in addicted sunbed users

Pamela M. Aubert [a], John P. Seibyl [b], Julianne L. Price [c], Thomas S. Harris [d], Francesca M. Filbey [e], Heidi Jacobe [a], Michael D. Devous Sr. [d,f], Bryon Adinoff [c,g,*]

[a] Department of Dermatology, University of Texas Southwestern, Dallas, TX, USA
[b] Institute for Neurodegenerative Disorders, Molecular Neuroimaging, LLC, and Yale University, New Haven, MA, USA
[c] Department of Psychiatry, University of Texas Southwestern, Dallas, TX, USA
[d] Department of Neurology, University of Texas Southwestern, Dallas, TX, USA
[e] Center for Brain Health, University of Texas Dallas, Dallas, TX, USA
[f] Avid Radiopharmaceuticals, Inc, Philadelphia, PA, USA
[g] VA North Texas Health Care System, Dallas, TX, USA

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ABSTRACT

Compulsive tanning despite awareness of ultraviolet radiation (UVR) carcinogenicity may represent an "addictive" behavior. Many addictive disorders are associated with alterations in dopamine (D2/D3) receptor binding and dopamine reactivity in the brain's reward pathway. To determine if compulsive tanners exhibited neurobiologic responses similar to other addictive disorders, this study assessed basal striatal D2/D3 binding and UVR-induced striatal dopamine efflux in ten addicted and ten infrequent tanners. In a double-blind crossover trial, UVR or sham UVR was administered in separate sessions during brain imaging with single photon emission computerized tomography (SPECT). Basal D2/D3 receptor density and UVR-induced dopamine efflux in the caudate were assessed using ^{123}I-iodobenzamide (^{123}I-IBZM) binding potential non-displaceable (BPnd). Basal BPnd did not significantly differ between addicted and infrequent tanners. Whereas neither UVR nor sham UVR induced significant changes in bilateral caudate BPnd in either group, post-hoc analyses revealed left caudate BPnd significantly decreased (reflecting increased dopamine efflux) in the addicted tanners – but not the infrequent tanners – during the UVR session only. Bilateral ΔBPnd correlated with tanning severity only in the addicted tanners. These preliminary findings are consistent with a stronger neural rewarding response to UVR in addicted tanners, supporting a cutaneous-neural connection driving excessive sunbed use.

1. Introduction

Almost 30 million Americans visit indoor tanning salons each year (Kwon et al., 2002) including over 40% of college students and 10% of teens (Wehner et al., 2014). This younger age group is particularly vulnerable to development of melanoma (Bleyer et al., 2006), an often fatal and increasingly common disease in adolescents and young adults. In recognition of these risks, ultraviolet radiation (UVR) has recently been classified as a known human carcinogen by the United States Department of Health and Human Services and the World Health Organization International Agency has elevated the UVA/UVB rays utilized in tanning devices to Group 1 (i.e. "carcinogenic to humans") (El Ghissassi et al., 2009).

Persistent tanning despite perceived and experienced consequences suggests tanning has "addictive" properties (Nolan and Feldman, 2009). Approximately 40% of frequently sunbathers (Harrington et al., 2011; Mosher and Danoff-Burg, 2010; Poorsattar and Hornung, 2007; Warthan et al., 2005) report behaviors consistent with an addictive disorder, including an inability to decrease tanning frequency and continued tanning despite adverse consequences. Awareness of UVR toxicity, including warning labels on tanning beds, has not altered tanning activity (Knight et al., 2002; Monfrecola et al., 2000; Zeller et al., 2006). UVR may therefore have physiologically reinforcing properties distinct from any psychosocial benefits of having a tan (Feldman et al., 2004; Harrington et al., 2011). A neurocutaneous pathway mediated by β-endorphin has been posited to produce physiologic dependence to UVR and potentially affect reward and addiction-related neurobiological systems (Fell et al., 2014; Kaur et al., 2005).

The mesostriatal dopamine pathway plays a key role in both reward and uncontrolled compulsive behaviors defining the

Abbreviations: ^{123}I-IBZM, ^{123}I-Iodobenzamide; BPnd, Striatal binding potential

* Corresponding author at: Department of Psychiatry, University of Texas Southwestern, 5323 Harry Hines Blvd, Dallas TX 75390-8564, USA.
E-mail address: bryon.adinoff@utsouthwestern.edu (B. Adinoff).

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addicted state (Adinoff, 2004; Koob and Volkow, 2010). Increases in dopamine efflux follow the administration of cocaine (Mach et al., 1997), amphetamine (Drevets et al., 2001; Martinez et al., 2003), alcohol (Boileau et al., 2003), and nicotine (Fehr et al., 2008) and are associated with substance-induced euphoria (Barrett et al., 2004; Brody et al., 2004; Drevets et al., 2001; Yoder et al., 2005). Basal striatal post-synaptic D2/D3 receptors are decreased in a number of substance use disorders, presumably due to either premorbid risk and/or down-regulation due to persistent substance-induced dopaminergic stimulation (Fehr et al., 2008; Martinez et al., 2007; Volkow et al., 2002). Additionally, in cocaine-addicted subjects, a blunted dopaminergic efflux in response to a rewarding substance has been shown to predict greater drug craving (Martinez et al., 2007).

Our group previously explored the central nervous system (CNS) effects of UVR by exposing addicted tanners to UVR in a commercial tanning bed with one of two filters in place (Feldman et al., 2004). One filter removed UVR ("sham UVR") whereas the other filter did not ("active UVR"). Using single photon emission computerized tomography (SPECT) to measure brain perfusion, addicted indoor tanners exposed to UVR, relative to sham UVR, showed increased regional cerebral blood flow (rCBF) in the striatum (Harrington et al., 2012). UVR may therefore have centrally active properties driving tanning over and above cosmetic benefit.

The goal of this study was to determine if UVR induces striatal dopaminergic efflux and if basal D2/D3 receptors and UVR-induced dopamine efflux was altered in addicted sunbed tanners relative to infrequent tanners. Basal D2/D3 receptors and UVR-induced dopamine efflux were assessed using ^{123}I-iodobenzamide (^{123}I-IBZM) striatal binding potential (BPnd) and SPECT. We hypothesized (1) striatal D2/D3 would be lower in addicted relative to infrequent tanners, (2) striatal dopamine efflux, as reflected by decreases in ^{123}I-IBZM BPnd, would increase in response to active UVR but not sham UVR, and (3) striatal dopamine efflux would be blunted in the addicted relative to infrequent tanners. Region of interest was limited to the dorsal striatum (i.e., bilateral caudate) given the previously observed increased in rCBF (Harrington et al., 2012). Secondary aims included exploring the relationship between striatal D2/D3 BPnd and dopaminergic efflux with measures of tanning severity.

2. Methods

2.1. Study population

The study was approved by the University of Texas Southwestern Institutional Review Board (clinicaltrials.gov identifier NCT01761032). Participants were recruited through flyers and Internet advertisements. Initial screening information was collected using Research Electronic Data Capture (REDCap), a biomedical informatics tool (Harris et al., 2009). Subjects were 18-45 years old Caucasian or Hispanic men and women with Fitzpatrick skin phototype II-IV. Addicted sunbed users must have reported using a sunbed at least two times weekly over the previous year and met previously validated criteria for "tanning dependence" (Hillhouse et al., 2012), including an inability to cut down or stop tanning. Sex-, age-, ethnicity-, and skin phototype-matched infrequent tanners were included as a comparison group Inclusion criteria included a minimum of 10 lifetime episodes of sunbed use, no more than 4 indoor tanning episodes in the previous 90 days, and failure to meet criteria for tanning abuse or dependence. Familiarity with salon tanning without the addictive behaviors offered a more appropriate comparison group than a tanning-naïve group due to their lack of having formed an addiction to tanning despite adequate sunbed exposure. All subjects were right-handed. Exclusion criteria for all participants included pregnancy, use of medications with CNS properties (e.g., psychotropic medication), medical disorders that might interfere with normal brain functioning, any lifetime history of Diagnostic Statistical Manual (DSM)-IV Substance Dependence, Seasonal Affective, or Body Dysmorphic Disorder, or any active mood, psychotic or anxiety disorder.

2.2. Assessments

Assessments included the Structured Interview for Tanning Abuse and Dependence (SITAD) (Hillhouse et al., 2012), Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 2002), Body Dysmorphic Disorder modification of the Yale-Brown Obsessive-Compulsive Scale (Phillips et al., 1997), Beck Depression Scale (Beck et al., 1979), Speilberger State Anxiety Inventory (Speilberger, 1971), Fitzpatrick Skin Phototype (Fitzpatrick, 1988), routine laboratory chemistry and complete blood count, and urine drug screen. To quantitate tanning addiction severity, lifetime history of sunbed tanning episodes was obtained using the Time Line Follow Back (TLFB) (Fals-Stewart et al., 2000). The TLFB uses significant life events as chronological anchor points to accurately recall temporal patterns of tanning episodes.

A high-resolution T1-weighted magnetic resonance imaging (MRI) [3-T Phillips Achieva MR scanner; 3D magnetization prepared rapid gradient-echo (MPRAGE) sequence] was acquired in all subjects to assure the absence of cerebral anatomic pathology.

2.3. Scanning procedure

UVR was administered using a Sunquest 3000S canopy while participants were undergoing active SPECT imaging. One of two visually identical plastic/acrylic filters (Polycast UF3, Sterling Industries, Shawnee, Kansas) (Kucenic et al., 2002) was placed under the canopy (Feldman et al., 2004; Harrington et al., 2012). One filter was transparent to UVR (irradiance for UVA and UVB was 0.1 W/cm^2 and 0.047 W/cm^2); the other blocked UVR (0.001 W/cm^2 and 0.0 W/cm^2). Both filters were transparent to visible light. The estimated dose delivered for the UVR transparent filter was 6 J/cm^2 UVA and 0.282 J/cm^2 UVB; for the UVR blocked filter 0.06 J/cm^2 UVA and 0 J/cm^2 UVB. The tanning bed canopy was placed 8 in. above the participants' abdomen. On two separate visits, participants were imaged via SPECT while exposed to either UVR or sham UVR. Sessions were approximately seven days apart (addicted tanners: 8.4 $\pm$ 3.6 days, range 5–17; infrequent tanners: 7.9 $\pm$ 3.7, 4–17 days). Scan order (active or sham) was balanced across groups. Exposure to active UVR and sham UVR was presented in a double-blind design; all study staff having contact with the participant were blinded to filter placement. Prior to each session, participants were instructed to refrain from tanning for at least 48 hours so that tanners were in an unsatiated state. Upon arrival for the session, TLFB was obtained from participants since their last visit to confirm tanning had not occurred in the previous 48 h. One hour following iodoral administration (to limit thyroid exposure) a 10 mCi bolus of ^{123}I-IBZM was administered (Anazao Health, Tampa, Florida, IND 115555). Just prior to imaging, participants changed into their tanning attire (typically a bathing suit, with torso exposed) and placed in the scanning bed. Participants were asked to rate "How much do you feel like tanning right now?" from 1 ("Not at all") to 10 ("More than I ever have."). To avoid overexposure in infrequent tanners, UVR exposure was determined based upon the Sunquest 3000 manufacturer recommendation ranging from 4 min (skin type II) to 8 min (skin type IV) (Table 1). To provide a physiologically relevant UVR dose, addicted tanners received 10 min of UVR exposure [consistent with Feldman et al. (2004), Harrington et al. (2012) and Kaur et al. (2006)]. The first three addicted tanners, however, received between 4 and 6 min of UVR exposure. Fifteen minutes after the initiation of UVR exposure, participants rated their enjoyment and expectations of UVR administration ["How much did you enjoy the tanning session?" from "not at all" (1) to "the most ever" (5); "How good of a tan do you expect to get from this session?" from "no tan" (1) to "the perfect tan" (5); "Do you think you received active or non-active tanning light?"]. In the second session, participants were also asked, "Did you prefer the first or second tanning session or have no preference?" To maintain blinding, upon completion of the first scan participants covered exposed body areas with a sunless tanning lotion prior to leaving the sunbed. A thermometer at the participant's side recorded temperature during UVR. As the scanning room was chilly, blankets were placed on the participants prior to and following light exposure.

2.4. Image acquisition

SPECT scans were obtained at Zale Lipshy University Hospital Nuclear Medicine department. To limit thyroid exposure to ^{123}I-iodobenzamide (^{123}I-IBZM), 100 mg iodoral (IOD-50) was administered one hour prior to ^{123}I-IBZM administration. One hour following iodoral, a 10 mCi bolus of ^{123}I-IBZM was administered (Anazao Health, Tampa, Florida, IND 114748). Upon session completion, participants were provided with iodoral and instructed to take two tablets every 12 h for the next 48 h (4 doses). Scanning began 120 min after ^{123}I-IBZM.

SPECT images were acquired on a dual-headed Siemens Ecam SPECT camera using ultra high-resolution fan-beam collimators (reconstructed resolution of 10–15 mm) in a 128 $\times$ 128 matrix into a 15% symmetric energy window centered on 159 keV. Reconstructed data from SPECT scans were filtered with a 3D Butterworth filter with order of 8 and cutoff of 0.42 and attenuation corrected using the Chang method. As a modest signal was anticipated, region of interest (ROI) analyses was limited to the caudate head as it is relatively resistant to partial volume sampling