ARTICLE IN PRESS

Brain, Behavior, and Immunity xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

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

Review Article

Can neuroimmune mechanisms explain the link between ultraviolet light (UV) exposure and addictive behavior?

Krystal Iacopetta[a], Lyndsey E. Collins-Praino[a], Femke T.A. Buisman-Pijlman[a], Mark R. Hutchinson[a,b,*]

[a] Adelaide Centre for Neuroscience Research, Adelaide Medical School, University of Adelaide, SA, Australia
[b] Australian Research Council Centre of Excellence for Nanoscale BioPhotonics, University of Adelaide, Adelaide, SA, Australia

ARTICLE INFO

Keywords:
Alarmins
Tanning addiction
Neuroimmunology
Dopamine
Inflammation

ABSTRACT

High ultraviolet (UV) light exposure on the skin acts as a reinforcing stimulus, increasing sun-seeking behavior and even addiction-like sun seeking behavior. However, the physiological mechanisms that underlie this process remain to be defined. Here, we propose a novel hypothesis that neuroimmune signaling, arising from inflammatory responses in UV-damaged skin cells, causes potentiated signaling within the cortico-mesolimbic pathway, leading to increased sun-seeking behaviors. This hypothesized UV-induced, skin-to-brain signaling depends upon cell stress signals, termed alarmins, reaching the circulation, thereby triggering the activation of innate immune receptors, such as toll-like receptors (TLRs). This innate immune response is hypothesized to occur both peripherally and centrally, with the downstream signaling from TLR activation affecting both the endogenous opioid system and the mesolimbic dopamine pathway. As both neurotransmitter systems play a key role in the development of addiction behaviors through their actions at key brain regions, such as the nucleus accumbens (NAc), we hypothesize a novel connection between UV-induced inflammation and the activation of pathways that contribute to the development of addiction. This paper is a review of the existing literature to examine the evidence which suggests that chronic sun tanning resembles a behavioral addiction and proposes a novel pathway by which persistent sun-seeking behavior could affect brain neurochemistry in a manner similar to that of repeated drug use.

1. Introduction

Since the mid 20th century, it has become socially desirable and acceptable in many cultures to have the “healthy tan” that comes with sun exposure (Hunt et al., 2012). A tan develops as ultraviolet radiation (UVR) triggers keratinocyte release of α-melanocyte stimulating hormone (α-MHS) through p53-mediated transcriptional induction of the proopiomelanocortin (POMC) gene, which results in increased synthesis of the pigment melanin (Cui et al., 2007; Videira et al., 2013). Melanin forms a protective barrier to absorb UVR, preventing DNA damage and consequently causing the skin to darken (Bergenmar and Brandberg, 2001). While this may lead to the desired “healthy tan” effect, prolonged and repeated exposure to UV is a public health concern due to its causal relationship to the development of skin cancer (Young, 2009).

The incidence of skin cancer continues to rise in many Westernized nations including the United States, Canada, Australia, New Zealand and numerous countries in Europe (Lucas et al., 2006). The increase of skin cancer has been attributed to a multitude of factors, some of which fall outside the locus of control of the individual, such as effects of pollution damaging the ozone layer, increasing the amount of ambient UVR (Diffey, 2003; Leary and Jones, 1993). However, the single biggest risk factor continues to be behavioral: the willingness to be exposed to UVR for the aesthetic purposes of achieving a tanned appearance (Diffey, 2003; Leary and Jones, 1993). These behavioral choices can include increased voluntary UVR exposure through sunbathing, an increased amount of time spent outdoors participating in leisure activities, and changes in clothing styles exposing more skin (Diffey, 2003; Leary and Jones, 1993).

The desire to tan has largely been attributed to appearance factors acting as the primary reinforcement; that is, people believe they look and feel better with a tan (Dennis et al., 2009). However, an increasing body of literature is emerging indicating that UVR itself is a reinforcing stimulus, acting to increase UV-seeking behaviors (Feldman et al., 2004; Fell et al., 2014; Harrington et al., 2011a). Despite increasing efforts to alter perceptions of tanning and increase awareness of the damaging effects of UVR, frequent tanners are not deterred from

* Corresponding author at: Australian Research Council Centre of Excellence for Nanoscale BioPhotonics, University of Adelaide, Adelaide, Australia.
E-mail address: mark.hutchinson@adelaide.edu.au (M.R. Hutchinson).

https://doi.org/10.1016/j.bbi.2018.07.008
Received 17 May 2017; Received in revised form 3 July 2018; Accepted 12 July 2018
0889-1591/

Please cite this article as: Iacopetta, K., Brain, Behavior, and Immunity (2018), https://doi.org/10.1016/j.bbi.2018.07.008

engaging in tanning behaviour (Montague et al., 2001), particularly among adolescents and young adults (Cokkinides et al., 2006; Guy et al., 2015; Livingston et al., 2003). In fact, although public knowledge regarding the dangers of sun exposure greatly increased between 1986 and 1996, sun burning and regular use of tanning beds also increased (Robinson et al., 1997).

Remarkably, survey studies have revealed that frequent tanners are well informed, often displaying higher levels of knowledge regarding the risk of UVR than their non-tanning peers (Poorsattar and Hornung, 2007). An overwhelming majority, more than 90% of past and current tanners surveyed, revealed that they believed that skin cancer was a possible consequence of tanning. The same study also identified that 81% of past tanners and 53% of current tanners did not believe that tanning beds were safe (Knight et al., 2002), indicating that tanners know the dangers of tanning. Frequent tanners are more likely to be informed about UV-induced skin damage but are also more likely to believe that tanned skin improves appearance and protects against subsequent UV damage (Grange et al., 2015). Even having a hereditary risk of cancer was not enough to prevent the use of tanning beds in a sub-population of young adults (Bergenmar and Brandberg, 2001).

Therefore, despite a growing awareness of the danger associated with overexposure to UVR and the increased risk of skin cancer or having watched a family member face a deadly cancer, frequent tanners are not deterred from engaging in tanning behavior. In this way, continuing to tan resembles behaviors associated with substance use or gambling disorder when there is a loss of control of a behaviour despite being aware of the potential dangers. The person is not able to change the behavior even when adverse consequences arise that are clearly aggravated by the use (American Psychiatric Association, 2013; Kourosh et al., 2010; Nolan and Feldman, 2009).

While the exact mechanisms that may lead to tanning dependence are still unknown, this paper reviews the evidence that chronic UV exposure has physiologically reinforcing effects comparable to addiction and proposes a novel hypothesis by which UV light could affect brain neurochemistry via cutaneous-brain inflammatory signaling.

2. Evidence to suggest that tanning is comparable to behavioral addictions

People who tan frequently can exhibit signs of psychological and physical dependence that parallel those seen in other addictive disorders suggesting a form of behavior addiction (Poorsattar and Hornung, 2007; Stapleton et al., 2017). For example, using diagnostic screening tests, such as the CAGE questionnaire (Ewing, 1984), originally developed for alcohol dependence, as well as criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) adapted for tanning behavior, it was discovered that approximately 70% of both frequent outdoor (Warthan et al., 2005) and indoor (Harrington et al., 2011b) tanners met the modified criteria for addictive disorders or dependence. Specifically, frequent tanners continued to tan despite attempts to stop, showed persistent tanning in the presence of adverse consequences and neglected other responsibilities to maintain a tan (Harrington et al., 2011b; Warthan et al., 2005). Collectively, these behaviors show significant resemblance to the characteristics that define addictions such as gambling disorder (American Psychiatric Association, 2013). In support of this, a survey of 325 American college students, using the Structured Interview for Tanning Abuse and Dependence (SITAD), discovered that 10.8% and 5.4% of this population met criteria for tanning abuse and dependence, respectively. These rates are comparable to those reported for alcohol (5.8%) and alcohol or any illicit drug dependence (7.7%) in this age group (Hillhouse et al., 2012).

Moreover, when we consider individual difference in behavior it appears that factors such as age of initiation and frequency of the tanning behavior correlate with difficulty to cease tanning among adolescents (Zeller et al., 2006), similar to what we see in drug dependence. Those who were 14–15 years old at the time of the initiation were more likely to report difficulty in stopping the behavior compared to 16–17 year olds (Zeller et al., 2006). This parallels other high-risk activities, such as gambling, smoking and alcohol abuse, in which age of initiation is inversely correlated with success of quitting (Abdolahinia et al., 2012; Guttmannova et al., 2011; Khuder et al., 1999; Rahman et al., 2012).

Mechanistically, it is important to consider whether there are similarities in the biological basis of the effects of UVR exposure and the development of compulsive tanning with that of behavioral addictions. Frequent tanners indicated that besides aesthetic appeal (90%), tanners wanted to feel good (69%) and relax (56%) (Harrington et al., 2011b). Although the perception of a good appearance may be reinforcing, the latter two responses are comparable to what is reported by those with substance use disorders as reasons for drug or alcohol use (Titus et al., 2007). But are the tanners addicted to UVR exposure, or mainly the relaxing nature of the activity? A study by Feldman et al. (2004) highlighted that frequent tanners show a preference for UV tanning beds compared to identical non-UV beds, based solely on subjective feeling (Feldman et al., 2004). This suggests that the UV light may have physiologically reinforcing effects separate from aesthetic motivation alone.

However, is there any evidence that there is similar engagement of the mesolimbic dopamine or opioid system in frequent tanning, as is seen with other forms of addiction? Dopamine efflux follows administration of amphetamines (Di Chiara and Imperato, 1988), alcohol (Melendez and Rodd-Henricks, 2002) and cannabinoids (Jianping et al., 1990). Increased synaptic dopamine is also implicated in multiple behaviors that can become addictions, such as overeating (Avena et al., 2009), gambling (Bergh et al., 1997) and sexual behavior (Balfour et al., 2004). Aubert et al. (2016) showed an increase in dopamine efflux in addicted tanners in response to UVR compared to sham UVR, while such changes were not seen in infrequent tanners (Aubert et al., 2016). Interestingly, a pilot study using SPECT (single photon emission computed tomography) imaging to measure regional cerebral blood flow (rCBF) during a (blinded) session with either UVR or sham UVR in frequent tanners demonstrated that during the UVR session, tanners had a significant increase in rCBF in the left striatum, indicating activation of this dopamine rich region (Harrington et al., 2011a). These changes were accompanied by a decrease in the subjective desire to tan. Similarly, emerging evidence suggests that the reinforcing effects of UVR may be mediated by the opioid system, specifically through β-endorphin (Fell et al., 2014; Kaur et al., 2005, 2006). β-Endorphin is an endogenous opioid peptide with high affinity for the mu-opioid receptor (Volkow and McLellan, 2016), the same receptor responsible for producing the analgesic and euphoric properties from exogenous opioid derivatives, including drugs of abuse (Akil et al., 1998). UVR exposure in rodents, as well as cultured human cells, triggers release of β-endorphin as a by-product of the physiological processes that contribute to tanning (Fell et al., 2014). Daily exposure to UVR for a period of 6 weeks was associated with elevated plasma levels of β-endorphin in rodents. This was accompanied by increases in pain related thresholds, an effect that could be reversed with systemic administration of opioid antagonist naloxone and was abated in β-endorphin null mice. Administration of naloxone following chronic daily UV exposure resulted in numerous sign of opioid withdrawal in mice under experimental conditions. This included increased wet dog shake, paw tremor, teeth chatter and rearing. Furthermore, chronically UV-irradiated mice conditioned with naloxone in a black box developed condition place aversion for the black box during the postconditioning preference testing. Conversely, naloxone conditioning in the black box had no effect on mock UV-irradiated mice, demonstrating that chronic UV exposure imparts an opioid-like physical dependence sufficient enough to guide behavior. Finally, cross tolerance between UV-exposure and morphine developed, as evidenced by the fact that higher doses of morphine were required to produce comparable analgesia between