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Enhanced vulnerability to tobacco use in persons with diabetes: A behavioral and neurobiological framework

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ABSTRACT

Tobacco use significantly magnifies the negative health complications associated with diabetes. Although tobacco use is strongly discouraged in persons with diabetes, clinical evidence suggests that they often continue to smoke and have more difficulty quitting despite serious contraindications. Here, we suggest that a potential reason for enhanced vulnerability to tobacco use in persons with diabetes is greater rewarding effects of nicotine. This review summarizes pre-clinical evidence indicating that the rewarding effects of nicotine are enhanced in rodent models of type 1 and type 2 diabetes. We also provide a framework of neurobiological mechanisms that are posited to promote tobacco use in persons with diabetes. This framework suggests that diabetes induces a disruption in insulin signaling that leads to a suppression of dopamine systems in the mesolimbic reward pathway. Lastly, we consider the clinical implications of enhanced rewarding effects of nicotine that may promote tobacco use in persons with diabetes. The clinical efficacy of smoking cessation medications that enhance dopamine are important to consider, given that persons with diabetes may display disrupted dopaminergic mechanisms. Future work is needed to better understand the complex interaction of dopamine and insulin in order to develop better smoking cessation medications for persons with diabetes.

1. Introduction

Diabetes is a complex metabolic disorder that causes a multiplicity of negative health outcomes. These include an array of both physical problems, such as pain and circulatory issues, as well as hunger, stress, depression, and cognitive problems (Holt et al., 2010). The management of diabetes and its complications requires intensive pharmacological interventions that target an array of biological systems. As the disease progresses, persons with diabetes need to learn how to apply various pharmacological tools in an optimal manner to manage different negative health consequences. These health effects may increase vulnerability to experiment with, and ultimately abuse, an array of addictive substances, such as alcohol, opioid analgesics, and sedatives.

Tobacco products are particularly appealing for persons with diabetes for several reasons. It has been argued that tobacco use among persons with diabetes is due in large part to control appetite and as a tool to cope with stress. Tobacco products have also been shown to improve cognitive processes that may be compromised by chronic diabetes. Although over 4,800 chemical compounds have been identified in tobacco, its addictive nature has been largely attributed to nicotine, a major alkaloid component of tobacco (Goodwin et al., 2015; Stolerman and Jarvis, 1995). Following chronic tobacco use, periods of smoking abstinence produce nicotine withdrawal which elicits an array of negative symptoms that are believed to motivate relapse behavior. Therefore, the majority of pre-clinical studies have focused on the unique contribution of nicotine as the primary motivating factor in promoting tobacco use.

Diabetes and tobacco abuse are complex problems involving an array of transmitter, hormone, and other biological processes. There have been comprehensive review papers that address the role of insulin signaling (Daws et al., 2011; Figlewicz and Sipols, 2010) and dopamine systems (Baladi et al., 2012) in the context of drug addiction and reward processing. There have also been comprehensive review papers on the compounded negative health outcomes of smoking and diabetes (Eliasson, 2003; Tonstad, 2009), as well as the effects of nicotine and smoking on endocrine function and energy regulation (Tweed et al., 2012; Zoli and Picciotto, 2012). This review paper extends prior work by presenting a neurobiological hypothesis that diabetes enhances nicotine reward via a disruption in insulin signaling that suppresses dopamine systems. This hypothesis was developed from pre-clinical work showing that the rewarding effects of nicotine are enhanced in rodent models of type 1 (O'Dell et al., 2014) and type 2 (Richardson et al.,

Abbreviations: STZ, Streptozotocin; HFD, High-fat diet; CPP, Conditioned place preference; RD, Regular diet; NAc, Nucleus accumbens; ICV, intra-cerebroventricular; VTA, Ventral tegmental area; DAT, Dopamine transporter; DARPP-32, dopamine- and cAMP-regulated neuronal phosphoprotein; PI3K, phosphatidylinositide 3-kinase; AKT, Thymoma viral proto-oncogene; GLUT4, Glucose transporter-4.

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2014) diabetes. Below, we summarize studies that relate to our hypothesis regarding tobacco use in persons with diabetes.

2. Problem of tobacco use in persons with diabetes

Persons with diabetes that use tobacco products are twice as likely to experience mortality and various negative health outcomes versus non-smokers (Scemama et al., 2006; Tonstad, 2009). The health-care costs associated with treating diabetes in persons that smoke are 300% higher than the cost of treating diabetes complications in non-smokers (Gilmer et al., 2005). Given the compounded health consequences of diabetes and smoking, a critical question is whether people with diabetes are more vulnerable to tobacco use.

Clinical evidence suggests that persons with diabetes may be more vulnerable to tobacco use. Given that adolescence is the period where tobacco use is initiated (Moolchan et al., 2003), adolescents displaying diabetes may be particularly attracted to tobacco products. Indeed, smoking rates in adolescents with type 1 diabetes have been reported to be significantly higher compared to healthy controls (47% vs 38%; Scaramuzza et al., 2010). The latter study also reported higher rates of illicit drug use and risky sexual behavior in young persons with diabetes. Also, anti-smoking efforts have little effect in young persons with type 1 or type 2 diabetes (Ardron et al., 1988; Ismail et al., 2000; Masson et al., 1992). A survey study also revealed that 68% of young persons with type 1 diabetes habitually use street drugs more than once a month, and 72% of them are unaware of the adverse effects of drug use on diabetes (Ng et al., 2004). Feltbower et al. (2008) also reported that among 108 young persons that died from complications associated with type 1 diabetes, 11 of them were accounted for by misuse of prescription and non-prescription opiates. Thus, the possibility exists that young persons with diabetes experience enhanced rewarding effects of nicotine.

Another way to assess tobacco use vulnerability is to compare smoking rates in the general population with those found in persons with diabetes. Although smoking exacerbates the complications associated with diabetes, it is surprising that the rates of current smoking are 17–40% among patients with type 1 or type 2 diabetes (Gill et al., 2005; Jenssen et al., 2008; Reynolds et al., 2011). Few studies have directly compared smoking rates in persons with and without diabetes. A recent examination of cigarette smoking trends from 2001 to 2010 revealed that smoking rates are generally similar in persons with and without diabetes (Fan et al., 2013). Importantly, the latter survey also found that the decline in smoking rates over this period is lower in persons with diabetes, indicating a sustained use of tobacco in persons with diabetes. Bishop et al. (2009) found that persons with type 1 diabetes report higher rates of current smoking (12.3%) as compared to non-diabetic subjects (8.6%). With regard to tobacco cessation rates, there is evidence that quit rates are lower in persons with diabetes. For example, persons with type 2 diabetes display lower tobacco cessation rates and express greater concern about weight gain if they quit as compared to smokers without diabetes (Gill et al., 2005). Persons with type 1 diabetes that are current smokers also display higher levels of stress, negative effect, and depressive clinical symptoms than non-smokers (Haire-Joshu et al., 1994; Spangler et al., 2001). Interestingly, 34–50% of persons with diabetes have never heard of nicotine replacement or pharmacological therapies and consider these interventions to be unsafe given their diabetes status (Gill et al., 2005). Persons with diabetes also report poorer health outcomes and display lower readiness to quit smoking as compared to non-diabetic persons (Solberg et al., 2004). These clinical studies indicate that a person with diabetes who smokes copes with a milieu of complex physical and emotional symptoms that may serve as an obstacle for smoking cessation and proper diabetes management.

Another aspect of vulnerability to consider is that smoking increases the risk of developing diabetes (Eliasson et al., 1997; Tonstad, 2009). Indeed, tobacco use has been strongly associated with an exacerbation of insulin resistance (Chiolero et al., 2008; Eliasson et al., 1997; Thiering et al., 2011) and visceral adiposity (Berlin, 2008). Smoking significantly worsens insulin resistance to a greater extent in persons with diabetes as compared to healthy controls (Axelsson et al., 2001; Targher et al., 1997). The latter findings appear to be related to a direct effect of nicotine given that administration of this drug reduces insulin sensitivity via activation of alpha-7 subunit containing nicotinic acetylcholine receptors (Lakhan and Kirchgessner, 2011; Wang et al., 2011; Xu et al., 2012).

There are several challenges with regard to fully understanding the bi-directional vulnerabilities between diabetes and smoking behavior. Clinical evidence suggests that persons with diabetes may be more likely to engage in tobacco use and have a harder time quitting. There is also strong evidence suggesting that tobacco use increases the risk of developing diabetes and worsening an existing metabolic syndrome. Future studies are needed to better understand the complex mechanisms by which diabetes enhances vulnerability to tobacco use. It is important to study the mechanisms by which these complex diseases overlap in order to reduce health disparities associated with these co-morbid conditions.

3. Rodent models of diabetes used to study nicotine reward

There are various rodent models of diabetes. Two of the most commonly used models involve either streptozotocin (STZ) administration or a chronic high-fat diet regimen (Artinano and Castro, 2009; Buettner et al., 2007; Lee et al., 2010). STZ is a drug that is taken up via glucose (type 2) transporters that are concentrated on the insulin-producing beta cells of the pancreas. STZ is toxic to these cells and, as a result, produces a decrease in insulin (hypoinsulinemia) and a concomitant increase in blood glucose (hyperglycemia). The STZ model generally represents the etiology of type 1 diabetes or advanced stages of type 2 diabetes (Bell Jr. and Hye, 1983). The STZ model has been extensively studied and used to assess the complications of type 1 diabetes (Badalzadeh et al., 2015; Piculo et al., 2014), learning and memory (Bellush and Rowland, 1989; Flood et al., 1990), natural hedonic processing and drug reward (Carr, 1994; Carr et al., 2000; Galici et al., 2003b; O'Dell et al., 2014). Thus, the STZ model represents a common method of inducing diabetes via disruptions in insulin signaling. The high-fat diet (HFD) model of diabetes resembles the etiology of type 2 diabetes as animals develop insulin resistance and hyperglycemia (Baladi et al., 2011; Woods et al., 2003b). The percent of fat in the diet and the duration of time on the diet regimen impact the development of insulin resistance. The HFD regimen has been employed using various parameters, including diets consisting of 30% and above in fat content by weight and different durations of exposure ranging from 4 weeks to 20 weeks (Baladi et al., 2011; Buettner et al., 2007). The length of diet exposure has been shown to predict whether the HFD regimen produces insulin resistance in rodents (Buettner et al., 2007). Below we focus on pre-clinical studies that have employed the STZ and HFD-induced models to study the behavioral effects of nicotine. Both models of diabetes ultimately lead to a lack of insulin signaling. In the high-fat diet model, insulin receptors are insensitive to the effects of insulin, whereas in the STZ model, insulin receptors are not activated by insulin.

4. Enhanced nicotine reward in rodent models of diabetes

Previous work has compared the rewarding effects of nicotine in STZ- and vehicle-treated rats. To study nicotine reward, a model involving 23-hour access to intravenous self-administration of nicotine was used (O'Dell et al., 2014). The latter study also compared nicotine metabolism and dose-dependent effects of nicotine self-administration across groups. STZ-treated rats exhibited a consistent enhancement in nicotine intake across escalating doses of nicotine infusion. Moreover, STZ-treatment did not change nicotine metabolism, as cotinine levels were similar across diabetic and control rats. These findings suggest

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