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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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that STZ-treatment increased the rewarding effects of nicotine. This work is significant, as it suggests that strong reinforcing effects of nicotine may contribute to greater tobacco use in persons with diabetes.

A subsequent study examined whether insulin resistance, produced by a HFD regimen, enhances the rewarding effects of nicotine, as measured by the conditioned place preference (CPP) paradigm (Richardson et al., 2014). Rats were placed on either a regular diet (RD) or an HFD for 5 weeks, after which they were assessed for insulin resistance via blood glucose measurements after an insulin challenge. The results revealed that an HFD regimen produced insulin-resistant and non-insulin-resistant animals. Interestingly, the magnitude of nicotine CPP was larger in insulin-resistant rats versus RD rats. Nicotine CPP was absent in rats that were placed on an HFD regimen, but did not display insulin resistance. The increase in body weight was the same in all HFD-fed rats. The major finding was that the rewarding effects of nicotine were uniquely exacerbated in rats that received the HFD and also displayed insulin resistance, suggesting an enhancement in nicotine reward via a disruption of insulin signaling. Moreover, HFD-fed rats that remained insulin sensitive displayed a lack of nicotine reward.

A previous study of high relevance to our work revealed that mice placed on a HFD regimen did not display nicotine CPP (Blendy et al., 2005). These findings are consistent with our results showing that rats given a HFD do not exhibit nicotine CPP. Importantly, the latter effect was only observed in rats that were not insulin resistant. Thus, when comparing the Blendy report with ours, one possibility is that the mice in the Blendy study may not have been insulin resistant. Alternatively, the discrepancies in these reports may also be related to metabolic differences between rats and mice and/or different doses of nicotine and routes of administration that were used. Taken together, our CPP findings of HFD insulin-resistant animals suggest direct effects of insulin resistance and lack of insulin signaling, rather than the effects of the diet and increased body weight per se.

The rewarding effects of drugs of abuse other than nicotine have been examined in diabetic rats. For example, STZ-treated rats display a decrease in the locomotor activating effects of amphetamine, as well as a decrease in amphetamine intake(Galici et al., 2003b; Sevak et al., 2008), although no change in amphetamine CPP was shown (Sevak et al., 2008). Also, diabetic rats do not display changes in cocaine intake (Galici et al., 2003a) but show a decrease in cocaine-induced CPP (Kamei and Ohsawa, 1997). Although diabetic rats display an increase in CPP produced by methamphetamine (Bayat and Haghparast, 2015; Kamei and Ohsawa, 1996) and morphine (Kamei et al., 1997; Samandari et al., 2013). The disparate findings in these studies are unclear despite a consistent alteration in dopamine function.

5. Interaction between insulin and dopamine systems

Insulin is a 51-amino acid long peptide hormone that is synthesized and released from pancreatic beta islet cells. Insulin receptors are tyrosine kinase receptors that consist of an extracellular alpha subunit and a transmembrane beta subunit. Food consumption increases blood glucose levels and triggers the release of insulin into the blood. The presence of insulin activates insulin receptors and leads to the peripheral uptake of glucose, which plays a vital role in the overall metabolism of carbohydrates and fats. Insulin is transported from the periphery into the brain via a receptor-mediated transport process through the blood brain barrier (Israel et al., 1993; King and Johnson, 1985; Schwartz et al., 1990; Woods et al., 2003a). Insulin acts on insulin receptors found throughout the brain. Most notably, there are insulin receptors within brain regions of the limbic system (Figlewicz et al., 2003; Havrankova et al., 1978; Unger et al., 1991; Werther et al., 1987). These include the dopaminergic cell bodies of the ventral tegmental area (VTA), as well as terminal regions such as the nucleus accumbens (NAc) and amygdala that play a central role in modulating nicotine reward processing (Mansvelder et al., 2003, 2009).

Insulin is an important element of the diabetes process that modulates feeding, reward processing, learning and memory, mood regulation, synaptic plasticity and neurodegenerative disorders. The action of insulin on natural hedonic processing has been well established and reviewed elsewhere (Figlewicz and Sipols, 2010; Stice et al., 2012). Direct effects of insulin on reward processing of foods indicate insulin to possess anorexigenic properties. For example, intra-cerebroventricular (ICV) administration of insulin reduces sucrose self-administration (Figlewicz et al., 2006; Sipols et al., 2000) and CPP produced by palatable food (Figlewicz et al., 2004). Also, ICV and intra-VTA infusions of insulin produce a decrease in brain reward function (Bruijnzeel et al., 2011; Carr et al., 2000). These findings suggest that insulin plays a modulatory role in the processing of natural rewards via homeostatic regulation of the mesolimbic circuitry.

Insulin has been shown to have different modulatory effects on dopamine in healthy versus diabetic subjects. Within the dopamine cell body region, insulin has been shown to decrease dopamine function in healthy rats. Particularly, insulin administered into the VTA decreases somatodendritic dopamine release (Mebel et al., 2012). This effect is likely due to an insulin-induced long-term depression of glutamatergic terminals known to stimulate dopaminergic neuronal activity in the VTA (Labouèbe et al., 2013). These findings reflect insulin suppressive actions on reward processing and dopamine modulation under healthy/basal conditions. However, if insulin signaling is eliminated via genetic deletion of insulin receptors from dopaminergic neurons of the VTA, animals exhibit an increase in the rewarding effects of palatable foods and a trend towards an increase in the rewarding effects of cocaine (Könner et al., 2011). Likewise, hypoinsulinemia induced by STZ administration increases brain reward function (Carr et al., 2000). These findings show that in healthy animals, the effect of insulin is to suppress dopamine systems and reduce reward processing, whereas in diabetic subjects, it appears that a reduction in insulin signaling suppresses dopamine systems in a manner that enhances reward processing. The latter effect is believed to promote the rewarding effects of nicotine.

Previous work has examined changes in the dopamine system in the NAc following STZ administration (O'Dell et al., 2014). This study revealed that STZ-treated rats display an increase in dopamine transporter (DAT) and a decrease in dopamine D1 receptors levels. Also, STZ-treated animals exhibit a decrease in basal and nicotine-evoked dopamine release in the NAc. A similar decrease in dopamine release has also been demonstrated in the dorsal striatum of STZ-treated rats (Lim et al., 1994; Murzi et al., 1996; Owens et al., 2005; Saller, 1984; Williams et al., 2007). Several mechanisms may contribute to a hypodopaminergic state in the NAc of diabetic rats. First, hyperglycemia found in diabetic animals has been shown to reduce dopamine neuronal firing rates, which could decrease dopamine release in the NAc (Saller and Chiodo, 1980). Second, in STZ-treated rats, hypothalamic opioid circuitry reduces VTA dopamine function, which may lower dopamine activity in the NAc (Berman et al., 1995; Carr, 1994; Wolinsky et al., 1996). Third, an increase in DAT density and/or an increase in DAT function may decrease dopamine levels in the NAc. Indeed, our findings demonstrate an increase in DAT levels in the NAc, which can increase dopamine clearance and thus, lead to a decrease in synaptic levels of dopamine.

In contrast to our finding that DAT levels increase in the NAc of STZ-treated rats, a decrease in DAT levels and function have been reported in the dorsal striatum of STZ-treated rats (Owens et al., 2005, 2012; Sevak et al., 2007b; Williams et al., 2007). These region-dependent differences might be expected, given previous work showing differences in DAT levels and function between the NAc and striatum (Nirenberg et al., 1997; Siciliano et al., 2014). Furthermore, neuronal activity in response to amphetamine administration is also different within the NAc and striatum (Williams et al., 2007).

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6. Dopamine receptor subtypes in nicotine reward

Dopamine receptors can be widely distributed into two families: D1 and D2, which are coupled to inhibitory (D1) or excitatory (D2) G-proteins (Brunton et al., 2011). Examination of D1 receptors in rodent models of diabetes have found a decrease in receptor levels in various brain regions, including the striatum and the NAc (O'Dell et al., 2014; Saitoh et al., 1998; Sumiyoshi et al., 1997). Systemic administration of D1 receptor antagonists decreases the rewarding effects of nicotine as assessed by CPP and self-administration procedures in rats (Corrigall and Coen, 1991; Spina et al., 2006). In the core region of the NAc, a reduction in dopamine transmission or blockade of D1 receptors promotes the rewarding effects of nicotine by shifting aversive doses of nicotine to doses that produce CPP (Laviolette and van der Kooy, 2003; Laviolette et al., 2008). In humans, D1 receptors are reduced in the NAc of nicotine-dependent smokers (Dagher et al., 2001). Thus, the possibility exists that reduced dopamine D1 receptor signaling in the NAc may promote the rewarding effects of nicotine.

Studies examining D2 receptor densities in humans have reported a negative correlation between D2 receptor levels in the NAc and insulin sensitivity (Caravaggio et al., 2015; Dunn et al., 2012; Guo et al., 2014). Mixed findings have been reported in animals, with some reports showing an increase in D2 receptors (Anitha et al., 2012; Lim et al., 1994; Lozovsky et al., 1981; Sharma and Fulton, 2013), while others report no differences in D2 receptor levels (O'Dell et al., 2014; Sumiyoshi et al., 1997) in STZ-treated rats. A decrease in the potency of D2 selective agonists and antagonists in yawning and catalepsy behavior has been reported in STZ-treated rats (Sevak et al., 2005, 2007a), which may reflect a decrease in D2 receptor levels. Activation of D2 receptors increases blood glucose via centrally mediated mechanisms (Arnerić et al., 1984; Saller and Kreamer, 1991). However, not all D2 receptor agonists produce a similar response, as bromocriptine, a D2 preferring agonist (Corrodi et al., 1973; Rascol, 1999; Vance et al., 1984), improves insulin resistance and reduces free fatty acid and triglyceride levels (Cincotta and Meier, 1996; Cincotta et al., 1991, 1993; Meier et al., 1992; Pijl et al., 2000). Importantly, bromocriptine decreases tobacco use in humans (Caskey et al., 1999, 2002; Jarvik et al., 2000; Murphy et al., 2002). In fact, bromocriptine (Cycloset) has recently been approved by the U.S. Food and Drug Administration for the treatment of type 2 diabetes. Thus, it is important to study the role of D2 receptors in nicotine reward processing and diabetes, as this work may reveal important cellular interactions that modulate tobacco use in persons with diabetes. Fig. 1 summarizes our results with regard to the effects of STZ-induced diabetes on dopamine neurotransmission at the synaptic level.

7. Convergent signaling of insulin and dopamine receptors

Recent evidence suggests that dopamine and insulin receptors activate common downstream signal transduction pathways, as depicted in Fig. 2. Activation of dopamine and insulin receptors leads to phosphorylation of downstream signaling molecules that are critically involved in reward processing. For instance, dopamine D1 receptors are positively coupled to cAMP, which upon receptor activation leads to the phosphorylation of dopamine- and cAMP-regulated neuronal phosphoprotein (DARPP-32). Phosphorylation of DARPP-32 at the Thr-34 site is involved in the enhancement of nicotine reward processing (Abdolahi et al., 2010; Svenningsson et al., 2005). Aside from modifying nicotine-reward processing, DARPP-32 is also known to modulate insulin signaling (Brady et al., 1997). Also, D2 receptors are negatively coupled to cAMP, but in addition, they are also coupled to phosphatidylinositide 3-kinase (PI3K), which upon receptor activation leads to the phosphorylation of the serine/threonine protein kinase (AKT).

A recent goal has been to examine changes in downstream signal transduction mechanisms that are common to dopamine and insulin receptors in diabetic rats. Specifically, the effect of STZ-treatment on insulin and dopamine receptor signaling was compared in the NAc, as depicted in Fig. 3 (unpublished data). The results revealed that STZ-treatment decreased phosphorylation of IRS-2, which indicates compromised insulin-receptor signaling. Basal phosphorylation levels of DARPP-32 at the Thr-34 site were also increased in STZ-treated rats. This increase is likely a compensatory response to the downregulation of D1 receptors. A similar D1 receptor downregulation and an increase in DARPP-32 phosphorylation have been observed in rats that were exposed to a HFD regimen (Carlin et al., 2013; Sharma and Fulton, 2013). Lastly, STZ-treated rats display a higher level of basal phosphorylation of

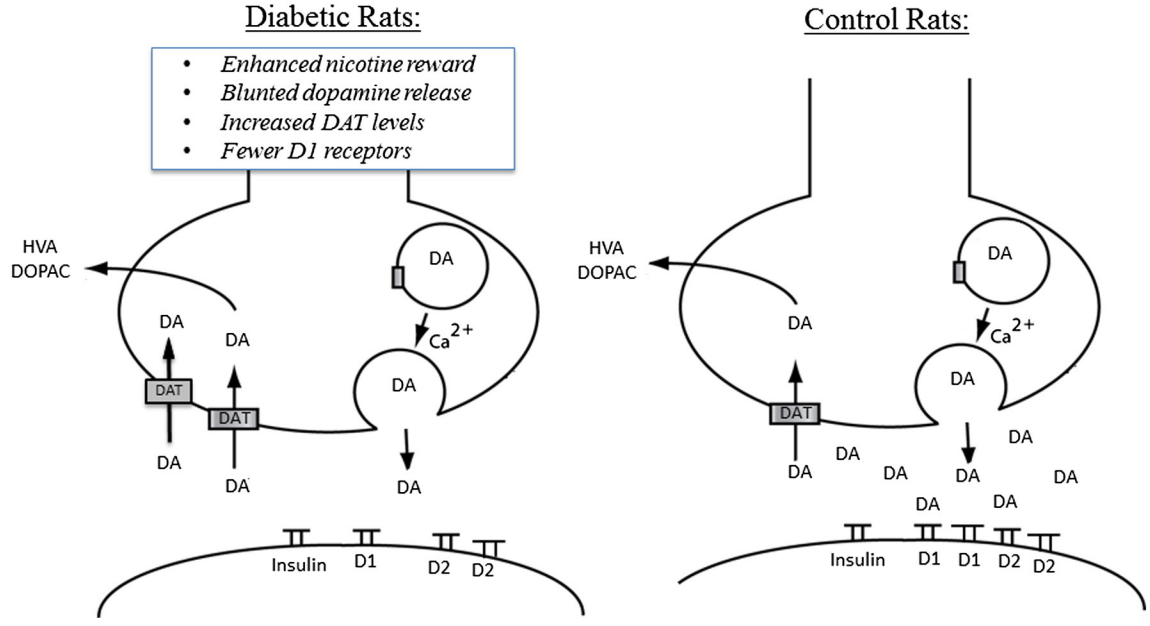

Fig. 1. Graphical summary of the effects of STZ-treatment on pre- and post-synaptic changes in dopamine systems in the NAc. STZ administration produces a suppression of dopamine systems in the NAc. This is evident as 1) an increase in nicotine intake, 2) reduced D1 receptors, 3) increased DAT levels, and 4) blunted basal dopamine release and in response to nicotine administration (O'Dell et al., 2014). These measures were taken in the NAc following a 2-week period after STZ or vehicle administration. When considered together, our findings reflect a hypodopaminergic state produced by diabetes.

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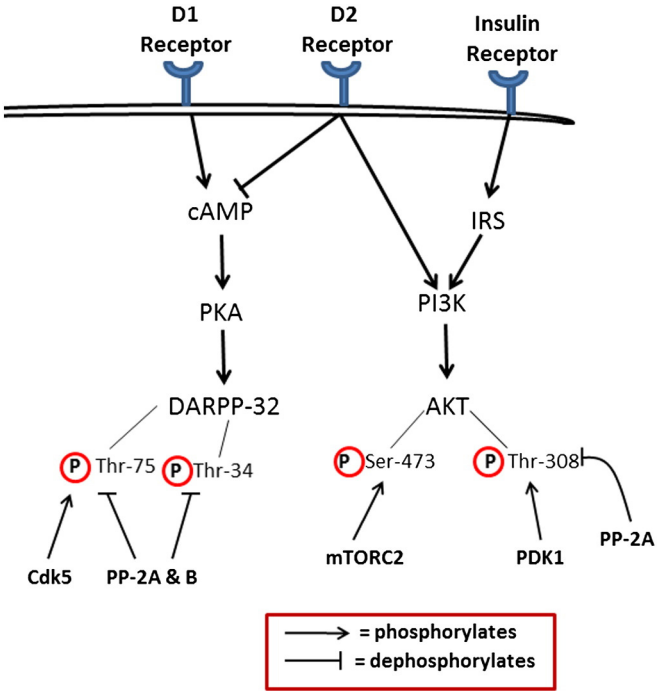

Fig. 2. Graphical representation of the convergent signaling pathways for dopamine and insulin receptors. Intracellular pathways that are common between dopamine and insulin receptors are demonstrated. Dopamine D1 receptors signal primarily through cAMP and PKA leading to activation of DARPP-32. D2 receptors inhibit cAMP and enhance AKT activity via activation of PI3K insulin receptors activate IRS leading to activation of PI3K and AKT.

AKT at the Thr-308 site. Given the attenuation of insulin signaling, it is possible that the enhanced AKT phosphorylation is a result of D2 receptor activation by dopamine, especially since D2 receptors remained unchanged in STZ-treated rats. This finding suggests that a regulatory process that traffics the activation of AKT between D2 and insulin receptors has shifted such that D2 receptors have a greater influence on AKT activity following STZ treatment. This hypothesized mechanism is based on a similar shift in the modulatory role of D1 versus D2 receptors following chronic cocaine administration (Edwards et al., 2007). Since an increase in phosphorylation of DARPP-32 and AKT proteins promotes drug-reward processing, our finding that STZ enhanced the activity of these second messengers in the NAc suggests that changes in these signaling pathways are an important part of the larger mechanism that promotes nicotine reward in a diabetic state.

In peripheral tissues, an increase in AKT phosphorylation leads to increased glucose uptake and improved glucose homeostasis. The latter effect occurs via modulation of glucose transporters, such as the insulin-responsive glucose transporter-4 (GLUT4; Farese et al., 2005; Ramm et al., 2006; Roach et al., 2007; Fayard et al., 2010; Lee et al., 2012). Presumably, the phosphorylation of AKT by nicotine increases insulin signaling and improves the diabetic state. However, the effects of nicotine on AKT phosphorylation in peripheral tissue appears to be opposite to that of the brain. Recent work has shown that nicotine administration decreases AKT phosphorylation and impairs the translocation of GLUT4 to the plasma membrane in peripheral tissue (Tatebe and Morita, 2011). The actions of nicotine in the periphery and the brain likely work in concert to promote the rewarding effects of nicotine. Namely, nicotine reduces AKT phosphorylation in the periphery, which decreases insulin sensitivity. At the same time, nicotine increases AKT phosphorylation in the brain, which may promote the rewarding effects of nicotine. We suggest that nicotine modulates an array of downstream signaling processes in the brain and periphery that provide a network of biological changes that promote nicotine use in persons with diabetes.

8. Hypothesis of tobacco use vulnerability in persons with diabetes

The mesolimbic reward system modulates feelings of wanting, wellbeing, and a reduction of stress. Although our physiology is motivationally programmed to experience pleasurable stimuli, recent theories suggest that deficits in the brain circuitry of dopamine weaken inhibitory control of excessive pleasure seeking (George et al., 2011). Thus, compulsive behaviors are believed to overcompensate for a reward deficiency syndrome that is rooted in suppressed dopaminergic functioning (Blum et al., 2000; Fineberg et al., 2010). There is clinical evidence to suggest that long-term activation of dopaminergic reward circuitry reduces compulsive drug- and food-seeking (Blum et al., 2008). Furthermore, individuals that are predisposed to compulsive disorders display genetic polymorphisms involving fewer dopamine receptors and an increased rate of synaptic dopamine catabolism (Blum et al., 2007, 2009). Taken together, these studies suggest that individuals with dopamine deficits may self-medicate with substances that activate dopamine, such as nicotine in tobacco products. Accordingly, it is hypothesized that diabetic subjects display increased nicotine intake to compensate for suppressed dopamine signaling. We suggest that diabetes is another condition by which dopamine systems are suppressed and this reward deficiency syndrome leads to enhanced susceptibility to compulsive tobacco use to facilitate dopamine transmission. Taken together, it is suggested that individuals with dopamine deficits self-medicate with substances that activate dopamine, such as nicotine in tobacco products.

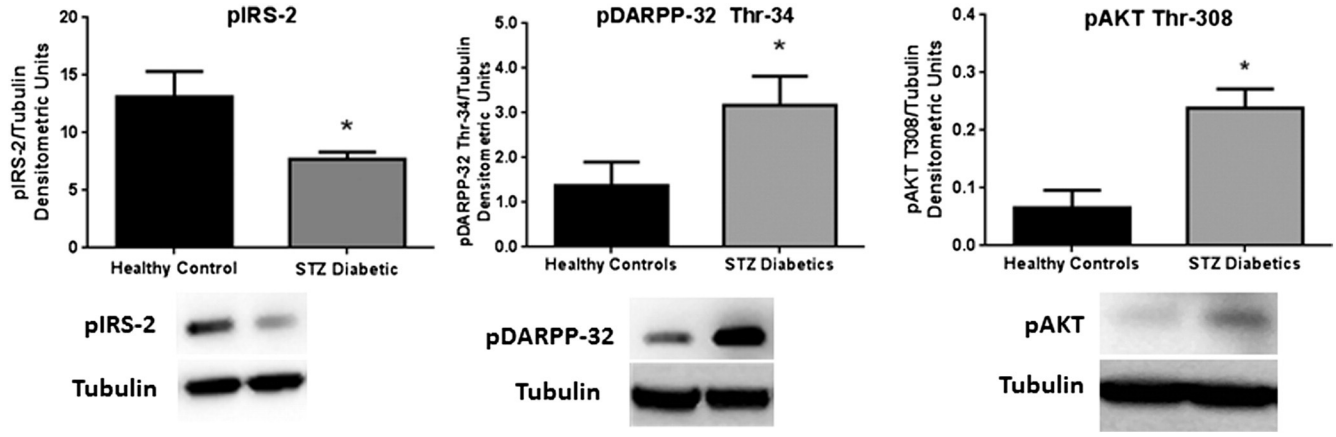

Fig. 3. Graphical representation of the effects of STZ on phosphorylation of IRS-2, DARPP-32, and AKT in the NAc. A decrease in phosphorylation of IRS-2 was detected in STZ-treated rats, indicative of a reduced insulin signaling. Meanwhile, an increase in DARPP-32 Thr-34 and AKT Thr-308 phosphorylation was detected in STZ-treated rats. These results reflect STZ-induced changes in common signaling mechanisms for dopamine and insulin receptors.

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Our hypothesis is based on work that has revealed that STZ-treatment produces an increase in nicotine-reward processing. At the synaptic level, diabetic rats display a reduction in dopamine release. Our understanding of dopamine pharmacology might have predicted a compensatory increase in the dopamine receptor subtypes as a result of lower synaptic levels of dopamine. However, our data suggest that the dopamine systems of diabetic subjects do not compensate in an expected manner, as indicated by reduced D1 receptors and a lack of changes in D2 receptors in the NAc (see Fig. 1). At the intracellular level, phosphorylation of DARPP-32 and AKT are increased in diabetic rats (see Fig. 3). The enhanced activation of these signals may reflect a potential mechanism by which the effects of nicotine are greater in a diabetic animal. Future studies are needed to carefully assess the mechanisms that promote nicotine-reward processing in diabetic subjects at different levels of cellular processing.

9. Clinical implications and remaining questions

Given the epidemic increase in diabetic cases, it is critical to determine whether patients with diabetes display changes in their brain reward pathways that may increase their susceptibility to tobacco use. Smoking in persons with diabetes is a concern because tobacco use compounds health complications associated with metabolic disorders, such as diabetes. In this review, pre-clinical evidence was presented showing that the rewarding effects of nicotine are enhanced in diabetic rats. An important implication of this work is that persons with diabetes may also experience strong rewarding effects of nicotine that put them at a greater risk for tobacco use and relapse during smoking abstinence. Another implication of pre-clinical studies is that proper insulin regulation is an integral part of smoking cessation approaches.

Studies examining the effects of diabetes on dopamine systems speak to the potential clinical efficacy of pharmacotherapies that target dopamine. More specifically, the finding that dopamine systems are suppressed in diabetic subjects suggests that the efficacy of dopaminergic medications may be compromised in persons with diabetes. This is important given that smoking cessation medications, such as bupropion (Wellbutrin), enhances dopamine neurotransmission. Future studies are needed to compare the efficacy of these medications in diabetic versus healthy persons who smoke. As one example, the dopamine agonist bromocriptine (Cycloset) is used to treat insulin resistance. The application of this drug in humans attests to the importance of research focused on understanding the role of dopamine in diabetes and co-morbid conditions such as tobacco addiction. Future research is needed to understand the complex interaction between dopamine and insulin in nicotine-reward processing. Elucidating the brain substrates that mediate vulnerability to tobacco use will help guide the development of specialized and more effective cessation treatments for persons with diabetes.

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