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Effect of insulin deficiency on the rewarding properties of methamphetamine in streptozotocin-induced diabetic rats

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ABSTRACT

The reward is a positive behavioural response to the pleasant stimuli that can be induced by drugs, such as psychostimulants. Furthermore, diabetes mellitus is a chronic disease that many people throughout the world suffer from. Methamphetamine (METH), as a psychostimulant, engages the dopaminergic system in the reward circuitry and the synapses of dopaminergic terminals can be modified by insulin. In this study, in order to assess the effect of insulin deficiency on reward, streptozotocin (STZ)-induced diabetic animals were used as an appropriate model. One hundred and thirty-two adult male rats were divided into nine groups (three non-diabetic and six diabetic groups) to determine the most effective dose of METH (0.25, 0.5, 1 and 2 mg/kg ip), and insulin replacement (10 U/kg; ip) during the acquisition period in a conditioned place preference (CPP) paradigm. The diabetes model was induced by a single injection of STZ (60 mg/kg; ip). The conditioning score was considered to be the difference in time spent in drug- and saline-paired compartments. The results demonstrated that the most effective doses of METH were 1 and 2 mg/kg in non-diabetic animals. Although the place preference was not shown in non-diabetic animals at the dose of 0.5 mg/kg, this dose significantly induced place preference to METH in STZ-diabetic rats. Additionally, insulin replacement could reverse the METH-induced CPP in diabetic animals. Our findings suggest that the positive effect of insulin deficiency on METH rewarding properties is dependent on insulin level in part, and the replacement of the insulin in diabetic rats as a treatment can improve the rewarding properties of METH.

1. Introduction

Several lines of evidence have indicated that methamphetamine (METH) is a widely-abused and highly-addictive psychostimulant that markedly interferes with reward (Mizoguchi et al., 2004). A large body of work, including transgenic, pharmacological and lesion studies, has established that the rewarding properties of addictive drugs depend on their ability to increase dopamine in the synapses by midbrain ventral tegmental area neurons on the nucleus accumbens (NAc) (Koob and Bloom, 1988; Wise and Bozarth, 1987), which occupies the ventral striatum, especially within the NAc shell region (Pontieri et al., 1995).

The dopamine transporter (DAT) is the METH substrate localized exclusively to dopaminergic neurons and is the primary mechanism for terminating dopamine (DA) neurotransmission (Giros et al., 1996). METH has a stronger effect on DAT-mediated cell physiology than AMPH, which may contribute to the euphoric and addictive characteristics of METH compared to amphetamine (AMPH) (Goodwin et al., 2009). In the brain, METH elevates the levels of extracellular monoamine neurotransmitters, especially DA, by interfering with their reuptake and promoting their release at the neural terminals (Fleckenstein et al., 2007; Sulzer et al., 2005), which is thought to be the main mechanism through which METH exerts its psychostimulant effect (Xie and Miller, 2009). In addition to its ability to compete with other neurotransmitters for reuptake at the transport sites (Rothman and Baumann, 2003), METH also causes modulatory effects on the monoamine transporters that include phosphorylation, down-regulation of the transporters and transport reversal (Cervinski et al., 2005; Johnson et al., 2005); however, mechanisms by which METH triggers these effects are not known.

Diabetes mellitus (DM) is a chronic illness with high prevalence (Eccles et al., 2011). It has been associated with hyperglycaemia, a decrease in insulin (type I), and is well-known for its influence on the central nervous system (CNS) (Baluchnejad-mojarad and Roghani, 2011). Insulin can move across the blood–brain barrier and interact with receptors that are densely concentrated in cerebral areas enriched with DA neural cell bodies and receptors (Figlewicz et al., 2003; Schulingkamp et al., 2000). Anatomical proximity and overlap between the dopaminergic system and insulin has a great functional significance; for instance, DAT mRNA increases dramatically in the substantia nigra in hyperinsulinaemic rats (Zuckerfa/fa) and in those chronically treated with insulin (Figlewicz et al., 1994). In contrast, DAT activity decreases in rats with low blood insulin levels (Owens et al., 2005; Patterson et al., 1998). DAT is the major site of action for drugs such as METH

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and is critical into regulating DA neurotransmission by the high-affinity uptake of DA released into the synaptic space. Insulin can also exert regulatory control on DAT activity. It seems that insulin plays a more prominent role in regulating the dopaminergic reward pathways in the brain than previously (Owens et al., 2005; Daws et al., 2011). This hormone has different influences on brain function and its role has been verified by the identification of receptors and a transport system for insulin in the CNS (Figlewicz, 2003).

Studies on the effects of insulin on the brain reward circuit indicate that it can interact directly with the limbic system to diminish the reward value of experimental and natural stimuli (Figlewicz, 2003; Figlewicz et al., 2008). It appears that decreasing insulin in DM (type I) can affect the brain reward system (Samandari et al., 2013). It has also been proven that insulin signalling regulates DA neurotransmission, affects the ability of psychostimulants in the DA system and facilitates their neurochemical and behavioural outcomes. Schoffelmeer et al. (2011) demonstrated that insulin can presynaptically enhance the function of cocaine sensitive monoamine transporters, including DAT, and may decrease impulsive behaviours in rat NAc (Dawset al., 2011). This suggests that insulin receptors may modulate the cocaine-sensitive inhibitory response control by intensifying the monoamine transporter function (Schoffelmeer et al., 2011). In fact, insulin shows CNS specificity in its effects on monoamine transporter function and may provide a novel therapeutic target for inhibitory control of disorders, such as drug addiction and obesity (Daws et al., 2011).

Streptozotocin (STZ)-induced hypoinsulinaemia depresses the DA-releasing action of AMPH by suppressing downstream signalling of insulin receptors, which further decreases the surface expression and function of DAT in the neural system (Schoffelmeer et al., 2011). Given the fact that psychostimulants target the dopaminergic system, clarifying how DA and other brain reward systems are regulated by insulin may create opportunities to develop new treatments for drug and food addiction (Davis et al., 2010). The present study investigated the effect of diabetes and insulin replacement in STZ-diabetic rats on the development of METH-induced conditioned place preference.

2. Materials & methods

2.1. Animals

One hundred and thirty-two adult male albino Wistar rats (Neuroscience Research Center, Tehran, Iran) weighing between 200–230 g (7–8 weeks old at the beginning of the experiments) were used in this study. The number of animals per group was 7–10 varying upon the specific experiment and the group. They were housed in a 12/12 hour light/dark cycle (lights on at 07:00) with free access to laboratory chow and tap water. Rats were handled for ten days before the experimental procedures. All experiments were executed according to the guidelines for the care and use of laboratory animals (National Institutes of Health Publication No. 80-23, revised 1996) and were approved by the Research Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran. All behavioural tests were performed during the light schedule between 9 a.m. and 4 p.m., with each rat tested/conditioned at the same hour on each day.

2.2. Drugs

In the present study, the following agents were used: Methamphetamine Hydrochloride (Sigma-Aldrich, USA) that was freshly diluted in normal saline and was given subcutaneously (sc). Streptozotocin (Sigma-Aldrich, USA) was dissolved in cold normal saline and was administrated intraperitoneally (ip). All drugs mentioned above were prepared immediately before use. Moreover, insulin regular (Ronak Darou, Save, Iran) was injected sc in insulin replacement groups. Furthermore, in separate groups, control animals received normal saline (0.9%) as a vehicle.

2.3. Induction of STZ-diabetes

In the present study, the animals were randomly assigned to diabetic and non-diabetic groups. Rats were rendered diabetic by a single ip injection of 60 mg/kg STZ, freshly dissolved in cold normal saline (Sedaghat et al., 2011). Furthermore, 10 days after STZ injection, blood samples were collected and serum glucose concentrations were spectrophotometrically measured using the glucose oxidation method. Only those rats with serum glucose higher than 250 mg/dl were considered diabetic (Baluchnejad-mojarad and Roghani, 2011). Diabetes was verified by the presence of hyperglycaemia, polyphagia, polydipsia, polyuria, and weight loss. The day on which hyperglycaemia was confirmed is considered as the pre-test day in the conditioned place preference (CPP) paradigm. The mean of glucose levels in the naïve and diabetic groups were 100 ± 7.8 and 309.3 ± 26.9 mg/dl, respectively. Moreover, their weights were also measured 10 days after single injection of the STZ or saline (as a vehicle) in the diabetic (163.9 ± 15 g) and naïve (234.9 ± 13.3 g) groups, respectively (Electronic Supplementary Fig. 1).

2.4. Conditioning place preference paradigm

CPP is a commonly used method to evaluate preferences for environmental stimuli associated with a reward (Flaisher-Grinberg and Einat, 2011; Taslimi et al., 2011).

2.4.1. Apparatus

A three-compartment CPP apparatus ($30 \times 30 \times 40$ cm) was used in these experiments. Place conditioning was conducted using an unbiased procedure (Taslimi et al., 2011; Azizi et al., 2009). The apparatus was divided into two equal size compartments with the third section being the null section which connected the two equal size sections ($30 \times 15 \times 40$ cm) by a black Plexiglas removable wall. Both compartments had white backgrounds with black stripes in different orientations (vertical vs. horizontal). To provide the tactile difference between the two major compartments, black coloured-stainless steel floors, one of them smooth and another net, were used. In this apparatus, rats showed no consistent preference for either compartment during the pre-conditioning phase, an observation that supports our unbiased conditioned place preference paradigm. All compartments and bottom trays were deodorized by a thorough cleaning with an isopropyl alcohol (70%)-rinsed paper towel followed by a drying process before each trial of training and testing.

2.4.2. Conditioning place preference protocol

CPP paradigm, took place over seven consecutive days consisting of three distinct phases including pre-conditioning, conditioning and post-conditioning. For all of these phases, the animals were tested in a unique room and during the same time period each day. Moreover, a semi-dark illumination was used to improve contrast for recording by the camera (ElectronicSupplementary Fig. 2).

2.4.2.1. Pre-conditioning phase. During the pre-conditioning phase, i.e., the first day, each rat was placed separately into the apparatus to be allowed into all compartments. Each animal's displacement was recorded using a 3CCD camera (Panasonic Inc., Japan) placed two metres above the CPP boxes by Ethovision software (Version 3.1), and a video-tracking system was used for the automation of behavioural experiments (Noldus Information Technology, the Netherlands). As with the experimental setup used in this study, the animals did not show any preference for either of the compartments. Animals were then randomly assigned to one of the two compartments for place conditioning and 7–8 animals were used for each subsequent experiment.

2.4.2.2. Conditioning phase. The conditioning phase started one day after the latest pre-conditioning session. It consisted of ten 45-minute

sessions (five with saline and five as drug pairing) during a five-day schedule (Zakharovaet al., 2009). These sessions were conducted twice each day (from day 1 to day 6) within six-hour intervals. On every conditioning session, separate groups of animals received conditioning sessions with METH and saline. Four doses of METH (0.25, 0.5, 1 and 2 mg/kg; ip) were administered to accomplish the experiments. During the 45-min interval sessions for METH/saline administration, the animals were confined to one compartment by closing the removable wall. The treatment compartment and the order of presentation of METH/saline were randomly counterbalanced for each group.

2.4.2.3. Post-conditioning phase. On day 7, i.e., the test day, the partitioning wall was removed so that the rats could access the entire apparatus for 10 min. The mean time spent for each rat in both compartments was recorded by Ethovision software. Conditioning score (CS), as a preference index, was then calculated as the time spent in the drug-paired compartment minus the time spent in the saline-paired compartment. Each animal's CS was calculated in both control and experimental groups.

2.4.3. Locomotion tracking apparatus

The locomotor activity of each animal was recorded using locomotion tracking apparatus by a video tracking system (Ethovision software). In these experiments, the total distance travelled (in centimetre) for each animal was measured in pre- and post-tests for the naïve and diabetic groups.

2.5. Experimental design

2.5.1. Dose–response effects of METH on CPP paradigm in naïve and diabetic rats

In this study, a dose–response relationship for METH on the CPP paradigm was established. Different doses of METH (0.25, 0.5, 1 and 2 mg/ml/kg) were tested (ip) for induction of CPP during five days of conditioning in the naïve and STZ-diabetic animals. In STZ-diabetic groups, after verification of diabetes (as mentioned above in Section 2.3), a dose–response relationship for METH in different doses (0.25–2 mg/ml/kg) on the CPP paradigm was also established. In the vehicle group, animals received saline (1 ml/kg; ip) instead of METH during the conditioning phase and then the two parameters CS and distance travelled were calculated for each rat.

2.5.2. Effects of insulin replacement on the dose–response relationship of METH on the CPP paradigm in diabetic rats

After determining the most effective dose of METH in STZ-diabetic and naïve rats, insulin regular (10 mU/kg) (Lowy et al., 1980; Balagura and Hobel, 1967; Kuhad et al., 2009), was injected 30 min before METH (0.25, 0.5, 1 and 2 mg/kg) in each conditioning session. Indeed, in this section of the study, the effect of insulin replacement was considered to clarify the difference of rewarding properties of METH between STZ-diabetic and naïve animals. In this study, different doses of METH (0.25, 0.5, 1 and 2 mg/kg) were tested (ip) for the induction of CPP over five days of conditioning in STZ-diabetic rats. All animals received insulin regular before each METH injection during conditioning phase. In the vehicle group, however, the animals concurrently received insulin regular (10 mU/kg; ip) and saline (1 ml/kg; ip) instead of METH during the conditioning phase. In the saline-treated group, the animals received only saline during the conditioning phase after which CS and distance travelled were calculated for each rat.

2.6. Statistical analysis

In the following statistical analysis of data, the two parameters of conditioning score and distance travelled are expressed as MEAN ± SEM. All Data were analysed by GraphPad Prism® (Version 5.0) software. In order to compare the values of CS and distance travelled in the naïve and/or diabetic animals between drug and vehicle-treated groups, and two-way and/or one-way analysis of variance (ANOVA) followed by post-hoc analysis were performed, respectively. The unpaired Student *t*-test was also used to compare the blood glucose level and body weight in the naïve and STZ-diabetic rats. *P*-values less than 0.05 ($P < 0.05$) were considered to be statistically significant.

3. Results

3.1. Dose–response effects of METH on the CPP paradigm in naïve and STZ-diabetic rats

In the first set of experiments, a dose–response effect of systematic administration of METH (0.25, 0.5, 1 and 2 mg/kg, ip) on the CPP paradigm was examined in the naïve group of animals. As shown in Fig. 1, two-way ANOVA followed by the Bonferroni test [treatment factor (naive rats vs. diabetic rats): $F(1,70) = 3.832$, $P = 0.0054$; dose factor: $F(4,70) = 9.37$, $P < 0.0001$; and interaction: $F(4,70) = 19.32$, $P < 0.0001$] revealed that there is a significant difference in methamphetamine-induced place preference between naïve and STZ-diabetic rats. On the other hand, in naïve animals, one-way ANOVA followed by Newman–Keuls's multiple comparison test showed that there are significant differences in the values of parameter CS amongst the experimental (different doses of METH) and vehicle (saline) groups [$F(5,43) = 21.24$, $P < 0.0001$; Fig. 1, left panel]. Thereby, the effective doses of METH were identified to be 1 and 2 mg/kg in naïve animals. However, there isn't any significant difference in place preference (conditioning score) between these two high doses of METH in the naïve rats. Moreover, in STZ-diabetic rats, the Newman–Keuls's multiple comparison test indicated that in STZ-diabetic animals there are significant differences in CS between the experimental and vehicle (saline) groups [$F(5,51) = 8.625$, $P < 0.0001$; Fig. 1, right panel]. The most effective dose of METH was identified to be 0.5 mg/kg ($P < 0.001$) in STZ-diabetic animals.

On the other hand, as illustrated in Fig. 2, two-way ANOVA indicated that all different doses of METH (0.25–2 mg/kg; ip) in naïve and STZ-diabetic rats did not affect the locomotor activity during a 10-minute test period in comparison with that of saline and/or vehicle control groups [Group factor (naive vs. STZ-diabetic rats): $F(1,70) = 0.17502$, $P = 0.7850$; dose factor: $F(4,70) = 0.7133$, $P = 0.5856$; and interaction:

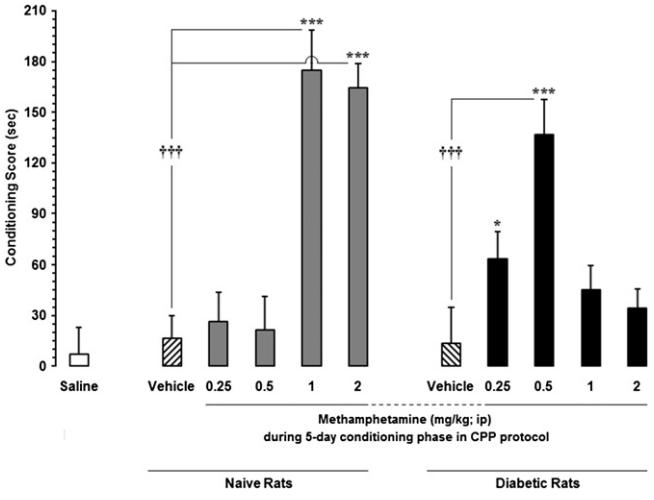

Fig. 1. Dose–response effects of METH on (A) CPP paradigm and (B) locomotor activity in naïve (*left*) and diabetic (*right*) animals. The diabetic animals received a single dose of STZ (60 mg/kg) ten days prior to the CPP test. Each point shows the mean ± S.E.M. for 7–8 and 7–10 in naïve and diabetic rats, respectively. CPP, conditioning place preference; METH, methamphetamine. * $P < 0.05$, *** $P < 0.001$ different from the saline control group. ††† $P < 0.001$ different from the respective vehicle group.

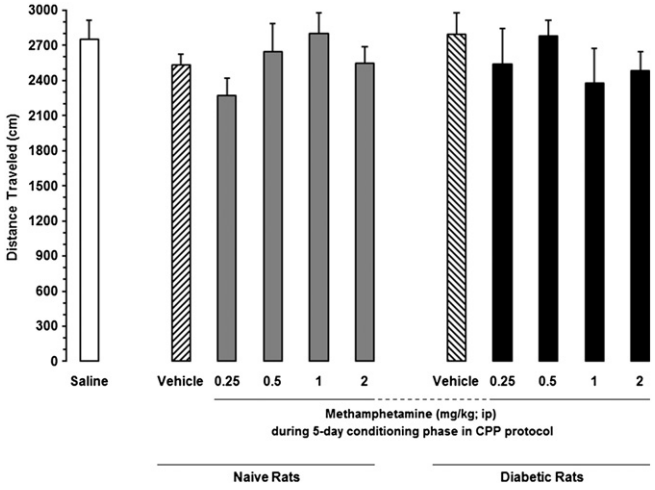

Fig. 2. Effects of different doses of METH on the locomotion in naïve (*left*) and diabetic (*right*) rats. As verified by one-way ANOVA, there were no significant differences in the distance travelled between the diabetic and non-diabetic groups. Locomotor activities for all of these groups were tested 24 h after the last conditioning session on the test day for 10-min period. Each point shows the mean ± S.E.M. for 7–10. METH, methamphetamine.

$F(4,70) = 0.9426$, $P = 0.4446$]. Therefore, the effects of different doses of METH on place preference were not due to the alteration of locomotor activity in rats.

3.2. Effects of insulin replacement on dose–response relationship of METH on the CPP paradigm in STZ-diabetic rats

To find out the effect of insulin replacement on rewarding properties of METH in STZ-diabetic rats, all groups received insulin regular (10 mU/kg) before each METH injection during the conditioning phase. Following this procedure, both tests of one-way ANOVA and Newman–Keuls's multiple comparison were performed, which indicated significant differences in CS values among the experimental and vehicle groups [$F(5,43) = 13.05$, $P < 0.0001$; Fig. 3A].

The acquired data showed a significant increase in CS values of two highest doses of METH (1 and 2 mg/kg; $P < 0.001$) in the STZ-diabetic groups. On the other hand, Fig. 3B indicates that concurrent administration of insulin regular and different doses of METH (0.25–2 mg/kg; ip) did not significantly affect the locomotor activity [$F(5,43) = 0.602$, $P = 0.6984$] during 10-min test period in post-conditioning phase.

4. Discussion

The present study developed METH-induced CPP in diabetic rats and compared the results to those for naïve animals. The study assessed the effect of hypoinsulinaemics on the acquisition of conditioning with METH. The major findings are: (i) METH induced place preference in naïve rats in a dose response manner; (ii) METH-induced place preference in diabetic rats required a different dose than that for naïve animals; (iii) insulin replacement during the acquisition phase significantly improved CS in the STZ-diabetic animals.

The study supported the results of previous studies and focused on understanding how the CNS communicates with peripheral tissues. Previous studies have made clear that the main regulator of DA homeostasis is DAT, a specialized and exclusive transporter that terminates DA activity. This transporter controls the strength and life span of DA in the CNS (Patterson et al., 1998; Daws et al., 2011; Batchelor and Schenk, 1998; Doolen and Zahniser, 2001; Galici et al., 2003; Kahlig and Galli, 2003). Any modulation in DAT function can influence psychostimulant activity. Comparison of the diabetic and non-diabetic groups indicates that STZ-diabetes could shift the dose response of METH and that insulin replacement could improve the values to be

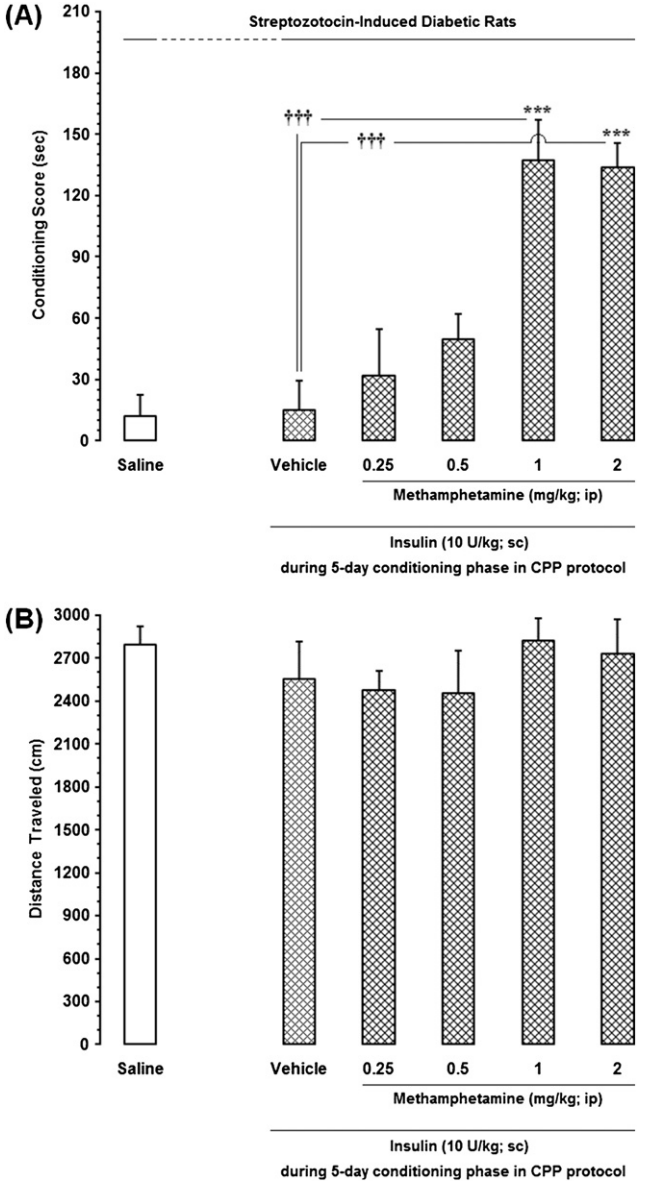

Fig. 3. Effects of insulin replacement on dose–response effects of METH on (A) conditioning place preference (CPP) paradigm and (B) locomotor activity in diabetic rats. For induction of STZ-Diabetes, animals received a single injection of STZ (60 mg/kg) 10 days prior to the CPP test. Each point indicates the mean ± S.E.M. for 7–10 rats. Locomotion did not change in experimental groups compare to control significantly. *** $P < 0.001$ different from the saline control group. ††† $P < 0.001$ different from the respective vehicle group. METH, methamphetamine; STZ, streptozotocin.

similar to the naïve rat group. This means that restoring the insulin in STZ-diabetic rats returned place preference to the normal state. On the other hand, we showed that METH (1 and 2 mg/kg) is effective to induce reward in the naïve rats, but an earlier study demonstrate that METH at the dose of 3 mg/kg produce conditioned aversion in naïve rats (Martin and Ellinwood, 1974).

Despite molecular and cellular evidence for the effect of insulin and insulin receptors on regulation of DAT in the brain, this change in effective dosage to induce a conditioning response cannot be easily interpreted. There is a lack of studies that concentrate on the behavioural aspects of METH under hypoinsulinaemic conditions. It is important to note that most studies on the role of insulin in modulating the reward system do not suggest an influence of STZ-diabetes on the dose response of METH administration in the reward process. But a recent study showed that insulin action in the VTA may decrease the salience of food-associated contexts or cues (Labouèbe et al., 2013). So, there is

a novel mechanism by which insulin reduces excitatory synaptic efficacy onto VTA dopaminergic neurons. Labouèbe et al. (2013) demonstrated that a sweetened high fat meal, which elevates plasma insulin, transiently weakens excitatory synaptic transmission onto dopamine neurons. This attenuation in VTA synaptic efficacy may lead to variation in the response of the naïve and STZ-diabetic subjects in different doses of METH. In another word, the shift of the dose–response curve of the METH in STZ-diabetic animals compared to naïve rats may be a result of changes in VTA synaptic efficacy. Therefore, it may be such that a mechanism recovers the dose–response shift in STZ-diabetic subjects after insulin replacement. As a matter of fact, reward is considered to be an introduction to addiction and almost all major classes of abused drugs share an ability to potentiate DA transmission throughout the cerebral reward circuit. DAT is the main transporter for clearing DA from the extracellular space of dopaminergic nerves, especially within the striatal region.

Some studies suggest a critical role for signalling pathways, such as insulin and insulin-like growth factors in DA clearance (e.g., insulin growth factor-1) (Owens et al., 2005; Galici et al., 2003; Carvelli et al., 2002; Garcia et al., 2005). Inappropriate activity of dopaminergic neurotransmission plays a role in neuropsychiatric disorders such as Parkinson's disease and stimulant abuse (Carvelli et al., 2002; Giros and Caron, 1993). At least one earlier study has demonstrated that, in diabetic animals, both AMPH self-administration and DA uptake in the striatum decrease (Galici et al., 2003). The interaction between insulin and drug-induced increase of extracellular DA levels may well contribute to the high coincidence of eating disorders and drug abuse. For example, the caloric restrictions and food deprivation of anorexia and bulimia may decrease insulin and potentiate reward-related behaviours (Daws et al., 2011; Davis et al., 2010).

Since insulin and PI3K (Phosphoinositol 3-kinase) signalling have been found to fine-regulate DAT membrane expression (Garcia et al., 2005; Wei et al., 2007), it is possible that inhibition of PI3K signalling in vivo by decreasing DAT plasma membrane expression inhibits AMPH-induced DA efflux and its behavioural effects. Insulin depletion can effect PI3K signalling in the brain. In addition, DAT cell surface expression and the DAT-mediated behavioural effects of AMPH could possibly decrease following STZ pre-treatment (Williams et al., 2007). Hypoinsulinaemic conditions and the selective pharmacological inhibition/activation of PI3K regulate the ability of AMPH to evoke DAT-mediated DA release in the striatal areas of the brain (Williams et al., 2007). Taken together, in vitro studies support the novel concept that insulin signalling – perhaps by means of PI3K – plays a critical role in DA homeostasis by regulating DA clearance and increasing extracellular DA induced by AMPH-like psychostimulants. Although the PI3K/protein kinase B signalling pathway is heavily engaged in development (acquisition), progression and maintenance of drug dependence (Izzo et al., 2002; Pandey, 1998; Russo et al., 2007), the exact interaction between the insulin signalling pathway and DAT plasma membrane expression remains unknown.

Some studies indicate that STZ-treated hypoinsulinaemic rats show a decrease in striatal DA clearance over controls animals (Owens et al., 2005; Daws et al., 2011) and are resistant to the behavioural effects of AMPH (Galici et al., 2003; Marshall, 1978; Uhart and Wand, 2009; Saitoh et al., 1998). Galici et al. (2003) demonstrated that there is a selective reduction in AMPH self-administration in hypoinsulinaemic rats from the decrease in dopamine uptake in hypoinsulinaemic rats (Owens et al., 2005). Given that the striatum is highly enriched in insulin (Schulingkamp et al., 2000; Banks and Kastin, 1998), insulin receptors (Schulingkamp et al., 2000; Hill et al., 1986), and DAT (Nirenberg et al., 1996; Figlewicz, 2003; Cass et al., 1992), these studies support the prominent role of neuronal PI3K pathways in regulating DAT activity, extracellular DA levels and the METH activity. Although prolonged exposure to METH increases cell membrane DAT, brief exposure is found to produce the opposite effect (Zahniser and Sorkin, 2009). Insulin opposes amphetamine-induced DAT internalization and protein kinase B is required for this effect (Garcia et al., 2005). PKC inhibitors block METH-induced reductions in DAT activity in striatal synaptosomes and AMPH-induced reductions in DAT activity in hDAT-oocytes (Sandoval et al., 2001).

Further pharmacological and electrophysiological investigations are needed to elucidate the hypothesis of the role of STZ-diabetes and insulin replacement in acquisition for METH-induced CPP in rats and mechanisms modulating the exact role of insulin deficiency caused by STZ-induced diabetes on CPP scores. The present study confirms the significance of insulin in the brain for regulating the reward circuit and can be considered a novel therapeutic approach to deal with drug abuse. There is no doubt that more in vivo/vitro studies are necessary to explain the unknown aspects of insulin involvement in psychostimulant activity of reward circuit in the brain.

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