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Article

Insulin replacement prevents the acquisition but not the expression of morphine-induced conditioned place preference in streptozotocin-induced diabetic rats

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Insulin receptors have distributed in all brain regions, including the nucleus Accumbens (NAc), and where is implicated in the reward properties of drugs. It is well known that insulin signaling can regulate dopamine release. Therefore, in the present study, we tried to examine the effect of insulin replacement on the acquisition and expression of morphine-induced conditioned place preference (CPP) in diabetic rats. Forty-eight male Wistar rats were divided into two non-diabetic (Naïve) and diabetic groups rendered by a single injection of streptozotocin (STZ). These groups separately received insulin (10U/kg) or saline (1 ml/kg) one hour prior to morphine administration (5mg/kg;s.c.) during conditioning days (acquisition phase) or post-conditioning day (expression phase) in the CPP paradigm. In this paradigm, conditioning score (CS) and locomotion activity were recorded by Ethovision. The STZ-induced diabetic rats displayed higher CS compared to naïve rats ($P<0.05$). This effect was abolished in all diabetic rats that received insulin during conditioning days but not the expression phase. This study has provided evidence that insulin plays a modulatory role in morphine-induced CPP, and insulin replacement during the acquisition phase could reduce the rewarding properties of morphine in diabetes conditions through a possible modulating effect on dopamine release in the NAc region.

Keywords: Reward. Diabetes. Insulin replacement. Morphine. Conditioned place preference. Rat.

INTRODUCTION

Diabetes mellitus is a metabolic disease with a high prevalence that leads to metabolic complications such as hyperglycemia, results from a lack of insulin production and secretion (insulin-dependent diabetes mellitus) and/or a decreased action of insulin at receptors (non-insulin dependent diabetes mellitus) is highly considered (Cruz *et al.*, 2019; Eccles *et al.*, 2011). Insulin, a peptide hormone, is produced by beta cells of the pancreas (Lauretta *et al.*, 2014). To date, the physiological role of insulin signaling in the central nervous system (CNS) and its mode of action to regulate energy homeostasis and glucose metabolism remains a matter of debate (Vogt, Brüning, 2013). Although it appears that CNS is not generally considered to be an insulin-dependent tissue, there is evidence showing that insulin can, in fact, cross the blood brain barrier (Margolis, Altszuler, 1967; Woods, Porte, 1977) via a saturable

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transport system (Schwartz *et al*., 1990) and interact with insulin receptors that are densely concentrated in cerebral neurons such as striatal dopaminergic neurons (Figlewicz, 2003; Schulingkamp *et al*., 2000). Therefore, insulin can regulate neuronal function in different regions of the CNS. The previous studies found that insulin receptors are widely distributed in the CNS of the rat (Havrankova, Roth, Brownstein, 1978)including nucleus Accumbens (NAc) and ventral tegmental area (VTA) (Ferrario, Reagan, 2017) which are considered as reward pathway. On the other hand, chronic hyperglycemia in diabetes leads to long-term damage and malfunction of different organs especially the CNS (American-Diabetes-Association, 2014; Baluchnejadmojarad, Roghani, 2011). Hence, insulin cooperates in the regulation of neuronal function, especially in reward circuits (Bayat, Haghparast, 2015; Bruijnzeel *et al*., 2011; Davis, Choi, Benoit, 2010; Daws *et al*., 2011; O'Dell, Nazarian, 2016; Plum, Schubert, Brüning, 2005). Nevertheless, the concise role of these signals on the cerebral reward circuits still not well understood.

Several lines of evidence revealed that the reward is induced by addictive drugs (ex., morphine) depends on their ability to increase dopamine (DA) in the synapses of VTA neurons in the midbrain on NAc (Koob, Bloom, 1988; Wise, Bozarth, 1987), which was located in the ventral striatum, particularly inside the shell and core part of NAc (Klawonn, Malenka, 2019; Pontieri, Tanda, Di Chiara, 1995). Dopamine transporter (DAT) is a primary mechanism for terminating DA neurotransmission (Giros *et al*., 1996). Insulin influences reward pathways via interaction with DAT (Samandari *et al*., 2013). Furthermore, insulin can modulate this critical transporter's intracellular redistribution from the plasma membrane to the cytoplasm. (Owens *et al*., 2005). Thus, it impacts any agent's ability that targets the dopaminergic neurons and therefore exerts their neurobehavioral and neurochemical effects (Samandari *et al*., 2013). Moreover, suppression of downstream molecules or enzymes signaling the insulin pathway also conspicuously reduces the DAT expression and DA clearance in the synaptic membrane (Daws *et al*., 2011). Thus, considering the reviewed evident in above and this finding that there is an insulin modulation of the reward-associated opioidergic system of the brain as a result of the complex connections between the opioidergic and dopaminergic system in the ventral striatum (Castro, Berridge, 2014; Tuominen *et al*., 2015).

Streptozotocin (STZ) is an antibiotic with the ability to induce diabetes isolated from Streptomyces achromogenes in 1960 (Furman, 2015). Because of the selective destruction of β- cells islet of the pancreas (Junod *et al*., 1967), this agent is frequently used to induce diabetic model in laboratory rodent (Furman, 2015).

Morphine induced-conditioned place preference (CPP) is a standard behavioral model that is suitable to assess reward properties of drugs in an experimental animal such as the rat, and the present study was designed to shed light on the critical role of the insulin shortage on acquisition and expression of morphine induced-CPP to make clear some behavioral aspects of insulin function in the rewarding circuits of CNS.

MATERIAL AND METHODS

Note that all methods described in this part were based on our prior studies (Bayat, Haghparast, 2015; Fatahi, Zibaii, Haghparast, 2017; Samandari *et al*., 2013).

Subjects

Forty-eight male adult albino Wistar rats (Pasteur Institute, Tehran, Iran) weighing 210-280 g were used in these experiments. All rats were housed in groups of 2-3 per cage, in humidity (65%) and temperature (20-22°C) controlled room. Rats were maintained on a 12-h light/dark cycle (lights OFF at 6:00 PM and ON at 6:00 AM) and had ad-libitum access to standard rodent water and diet in their home cage. All experiments were done in accordance with the Guide for the Care and Use of Laboratory Animals published by the United States National Institutes of Health (NIH Publication No. 80-23, revised 1996) and was approved by the Research and Ethics Committee of Shahid Beheshti University

of Medical Sciences (IR.SBMU.PHNS.REC. 1397.108), Tehran, Iran.

Drugs

In this study, the following agents were used: STZ (Sigma–Aldrich, USA) and morphine sulfate (TEMAD co., Tehran, Iran). Morphine was dissolved in 0.9% saline (pH 7.4), and STZ was dissolved in a sodium citrate buffer solution (pH 4.5). All drugs mentioned above were prepared immediately before use. Moreover, insulin regular (Ronak Daroo, Saveh, Iran) was injected subcutaneously (SC) in insulin replacement groups. Furthermore, in separate groups, control animals received normal saline (0.9%) as a vehicle.

STZ diabetes induction

In this report, the animals were randomly assigned to diabetic and non-diabetic groups. The rats were rendered diabetic by a single intraperitoneal injection of 45 mg/kg STZ (Cruz *et al*., 2019; Íbias, O›Dell, Nazarian, 2018). Furthermore, ten 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 ≥ 250 mg/dl were considered diabetic (Baluchnejadmojarad, Roghani, 2011). Also, diabetes was verified by the presence of polyphagia, hyperglycemia, polyuria, polydipsia, and weight loss in the rats (Figure 1). The average glucose level in the naïve and diabetic groups was 101 ± 7.3 and 320.3 ± 26.8 mg/dl. Moreover, their weights were also measured ten days after STZ or saline (as a vehicle) injection in the diabetic (159.5 ± 14 g) and naïve (264.7 ± 13 g) groups, respectively. Furthermore, the diabetic rats were then separated into two groups that received insulin or saline.

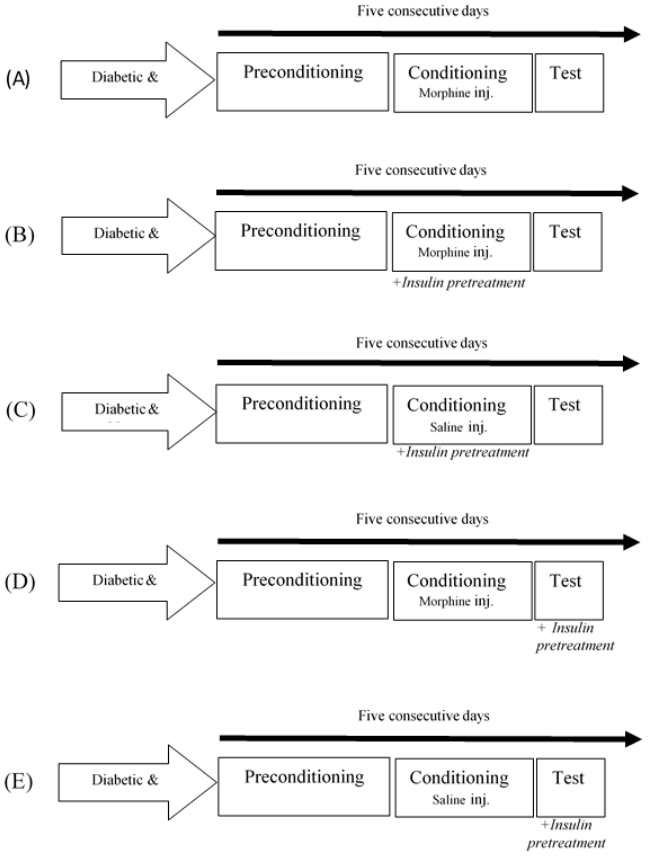

FIGURE 1 - Graphical scheme of CPP protocols in experimental groups (diabetic and naïve) of the present study. Both groups are divided into three subgroups, that these subgroupings are demonstrated in this figure. ***(A)*** CPP protocol in diabetic and naïve to determine CS induced by morphine without insulin pretreatment (first subgroup). ***(B)*** and ***(C)*** CPP protocol to determine CS induced by morphine and saline in addition to insulin pretreatment in three consecutive conditioning days (second subgroup). ***(D)*** and ***(E)*** CPP protocol to determine CS induced by morphine and saline with insulin pretreatment in test day (third subgroup).

Conditioning place preference paradigm

Apparatus

A three-compartment CPP apparatus was used in this study (Samandari *et al*., 2013). The apparatus was made of Plexiglas that two compartments were identical in size (30 cm×30 cm×40 cm) but differed in shading and texture. Compartment A was white with black horizontal stripes 2 cm wide on walls and a textured floor. Compartment B was black with vertical white stripes 2 cm wide and also with a smooth floor. The

third compartment (C) was a red tunnel (30 cm×15 cm×40 cm). It protruded from the rear of the two large compartments and connected the entrances of them. In this apparatus, rats showed no consistent preference for either compartment, supporting our unbiased conditioned place preference paradigm. Conditioned place preference consisted of a 5-day schedule with three distinct phases: pre-conditioning, conditioning, and post-conditioning.

Conditioning place preference protocol

The CPP is a standard method to study the motivational properties such as rewarding effects of morphine in animals (Karimi-Haghighi, Haghparast, 2018; Sahafzadeh *et al*., 2018).

Pre-conditioning (pre-test) phase. During this phase (day 1), each animal was placed separately into the apparatus to allow access to all compartments for 10 min. Each animal's displacement was recorded using a 3CCD camera (Panasonic Inc., Japan) placed 2 meters above the CPP boxes by Ethovision software (Version 3.1), a video tracking system for automation of behavioral experiments (Noldus Information Technology, the Netherlands). In the experimental setup used in this study, the subjects did not show any preference for either of the compartments. Animals were randomly assigned to one of the two compartments for place conditioning, and 6–8 animals were used for each subsequent experiment. Also, in diabetic subjects, the day on which hyperglycemia was confirmed was considered as the pre-conditioning day in CPP.

Conditioning (acquisition) phase. This phase started one day after the pre-conditioning phase. It consisted of six 30 min sessions in a 3-day schedule. These sessions were conducted twice each day (from day 2 to day 4) with 6 hours' intervals. On each day, separate groups of animals received conditioning sessions with morphine and another with saline. During the conditioning phase, the animals were injected with saline (5 ml/kg, SC) or morphine (5 mg/kg, s.c.) (Edalat *et al*., 2018; Samandari *et al*., 2013) and were immediately placed in one side of the conditioning chamber for 30 min. Based on our recent experiments, one dose of morphine (5 mg/kg; s.c.) was selected as the effective dose for the rest of the experiments. During the 30-min interval sessions for morphine/ saline, the animals were confined to one compartment by closing the removable wall. The treatment compartment and the order of presentation of morphine/saline were counterbalanced for either group.

Post-conditioning (expression) phase. On the fifth day of the expression phase, the partition was removed, and the rats could access the entire apparatus. The mean time spent for each rat in both compartments was recorded by Ethovision software. Conditioning score (CS) represents the time spent in the drug-paired compartment minus the time spent in the saline-paired compartment during a 10 min period.

EXPERIMENTAL DESIGN

All rats were randomly divided into two naïve and diabetic groups. As mentioned above, the subjects were rendered diabetic by STZ. The day on which hyperglycemia had been confirmed was designated as the pre-conditioning day in the CPP paradigm. Control animals did not receive any injections. Both groups were separated into three subgroups. In the first diabetic and naïve subgroups (Figure 2A), it assessed conditioning score CS (differences between the times spent in the drug- and saline-paired compartments) in rats without any insulin replacement to clarify the pure effect of STZ induced diabetes on morphine CS. In the second and third diabetic and naïve subgroups (Figure 2B, C, D & E), insulin replacement was performed in conditioning days (acquisition phase) or post-conditioning day (expression phase), simultaneously.

It should be noted that each diabetic or naïve subgroup has a separate control group. The second and third diabetic and naive subgroups received morphine with or without insulin pretreatment in conditioning or post-conditioning sessions. CPP test was performed on the naïve and diabetic groups as described before.

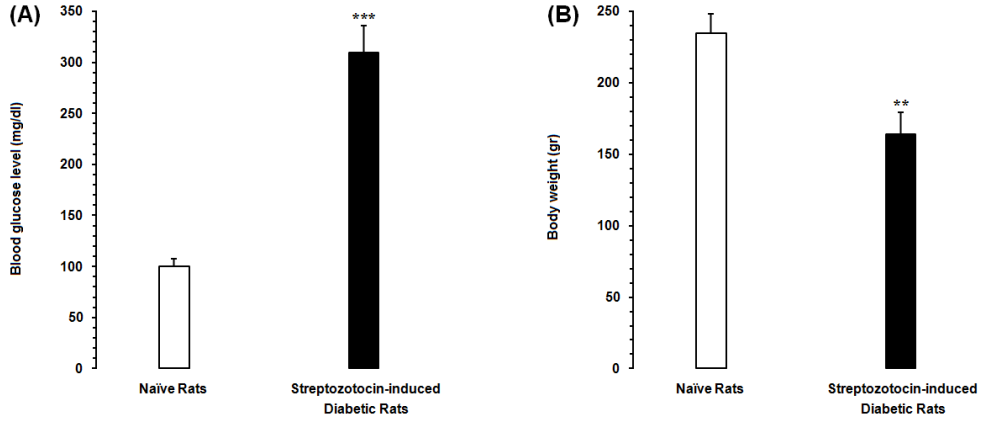

FIGURE 2 - One week after STZ injection, diabetes was verified by measuring ***(A)*** fast blood glucose level (mg/dl) and ***(B)*** body weight (gr). As depicted here, there is a significant difference in both variables in naïve and diabetic rats (as a result of STZ induced diabetes mellitus) simultaneously. Each point shows the mean ± SEM for 8 rats.

** $P < 0.01$ and *** $P < 0.001$ different from the naive rats

STATISTICAL ANALYSIS

In the statistical analysis of data, the two CS and distance traveled parameters are expressed as MEAN ± SEM. All data were analyzed by GraphPad Prism® (Version 5.0) software. To compare the CS and the distance traveled in the diabetic and control groups, one-way analysis of variance (ANOVA) followed by post hoc analysis (Dunnett's or Newman–Keuls test) was used, as appropriate. Also, *P*-values less than 0.05 ($P < 0.05$) were considered to be significant, statistically.

RESULTS

Investigation of the acquisition of morphine-induced CPP in diabetic and non-diabetic rats

In this set of experiments, we examine the effect of STZ-induced diabetes on the acquisition of morphine-induced CPP. As shown in Figure 3, one-way ANOVA showed that in both diabetic and non-diabetic group morphine (5 mg/kg) can induce CPP. In diabetic group CS significantly increased as compared with non-diabetic subjects ($P < 0.05$). Furthermore, there were significant differences in CS between the vehicle (saline control) and experimental (naïve and diabetic) groups ($P < 0.01$ and $P < 0.001$, respectively).

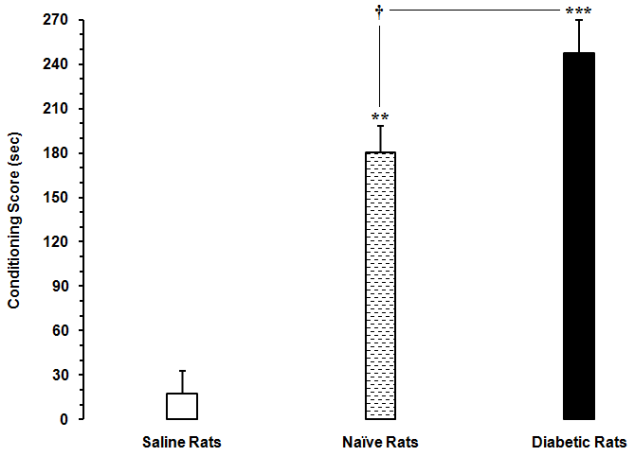

FIGURE 3 - Effect of STZ-induced diabetes on the acquisition of morphine-induced place preference (relevant to Figure 1A). Animals received saline (1 ml/kg) or morphine (5 mg/kg) during the three consecutive conditioning days in the CPP protocol. In the diabetic group, animals received a single injection of STZ (45 mg/kg) ten days prior to the conditioned place preference paradigm. Each point shows the mean ± SEM for 8 rats.

** $P < 0.01$ and *** $P < 0.001$ different from the saline control group

† $P < 0.05$ different from the naive group

The effect of insulin on the acquisition of morphine-induced CPP in diabetic and non-diabetic rats

In this experiment, to examine the effect of insulin on the acquisition of reward, it was injected one-hour

prior to administration of morphine during the 3-day conditioning phase. As illustrated in Figure 4, one-way ANOVA followed by Newman-Keuls multiple comparison tests showed that in the non-diabetic group, insulin does not affect the reward properties of morphine relative to non-diabetic that not received insulin. In the diabetic rats, insulin injection significantly reduced CS compared with the diabetic group with no insulin pretreatment ($P < 0.05$).

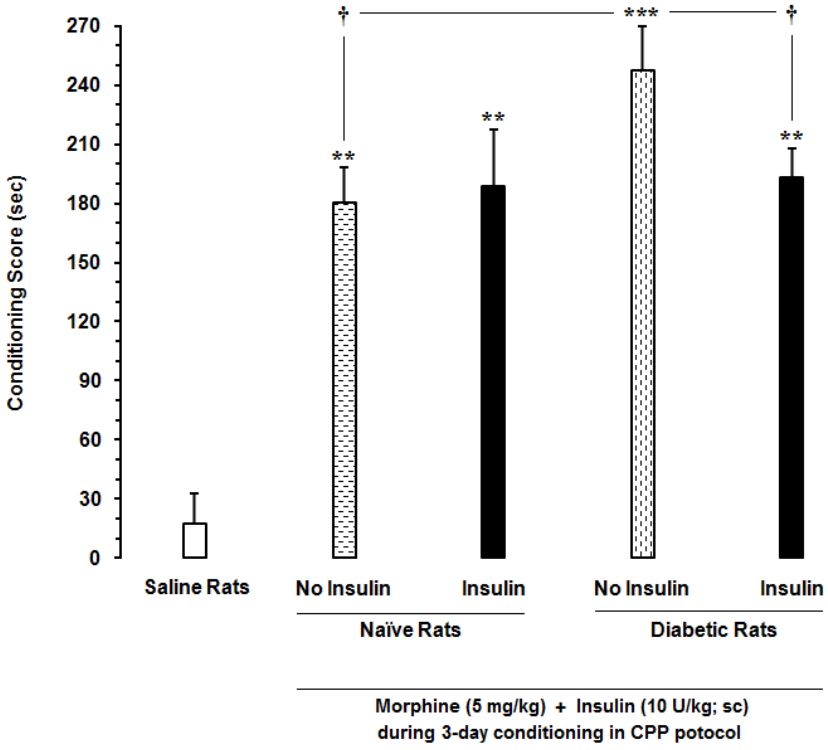

FIGURE 4 - Effect of insulin on the acquisition of morphine-induced place preference (relevant to Figures 1B and C). Animals received insulin (10 U/kg) 30 minutes' prior administration of morphine (5 mg/kg; SC) during the three consecutive conditioning days in the CPP protocol. As depicted here, insulin pretreatment reduced CS in diabetic rats. Each point shows the mean ± SEM for eight rats.

** $P < 0.01$ and *** $P < 0.001$ different from the saline control group

† $P < 0.05$ different from the naive group

The effect of insulin on the expression of morphine-induced CPP in diabetic and non-diabetic rats

Following the CPP conditioning days, insulin (10 U/kg) was injected in the expression phase (the post-conditioning day of CPP). As shown in Figure 5, one-way ANOVA followed by Newman-Keuls multiple comparison tests showed that in both groups (diabetic and naïve), insulin failed to modulate the reward properties of morphine compared to groups that did not receive insulin.

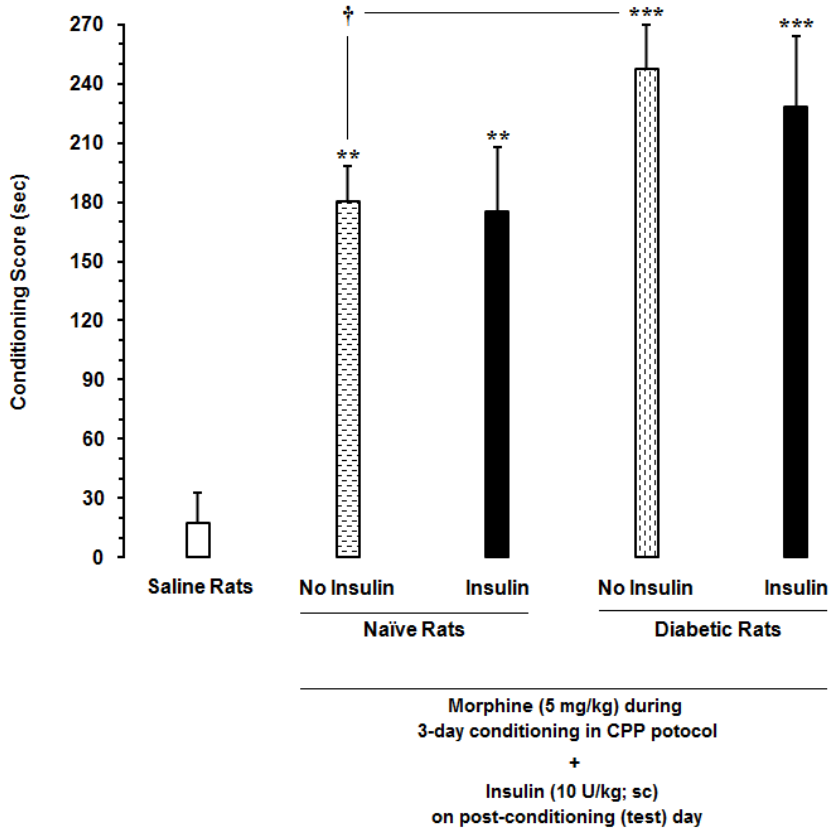

FIGURE 5 - Effect of insulin replacement on the expression of morphine-induced conditioned place preference (relevant to Figures 1D and E). Animals received insulin (10 U/kg) 30 min before starting the CPP protocol. Each point shows the mean ± SEM for 8 rats.

** $P < 0.01$ and *** $P < 0.001$ different from the saline control group

† $P < 0.05$ different from the no insulin group

DISCUSSION

The main findings of the present study include the following: ***(i)*** Morphine could induce conditioned place preference in both diabetic and naïve rats ***(ii)*** In the diabetic group; CS significantly increased compared with non-diabetic rats ***(iii)*** Insulin administration/replacement during 3-day conditioning phase significantly decreased CS compared with STZ-induced diabetic group. However, ***(iv)*** Insulin administration in the non-diabetic group did not have a significant effect on the reward properties of morphine compared with non-diabetic that not received insulin ***(v)*** Pretreatment with insulin in the expression phase of CPP revealed that in both diabetic and non-diabetic groups, insulin did not have any significant effect on the properties of reward.

Generally, the present study showed that diabetes could affect morphine-induced conditioning place preference. So, it displayed that diabetic rats were more sensitive to morphine. It is possible the lower doses of morphine-induced place preference in diabetic rats. Our study supported previous studies' results (Bayat, Haghparast, 2015; Samandari *et al.*, 2013; Sevak *et al.*, 2007). Furthermore, diabetes may change the concentration of monoamine involved in the reward pathway. Previous studies showed a major regulator of DA homeostasis is the DAT, and the DAT regulates the strength and duration of DA neurotransmission in CNS, especially in reward centers in the ventral striatum (Daws *et al.*, 2011; Doolen, Zahniser, 2001; Galici *et al.*, 2003; Kahlig, Galli, 2003). A recent study revealed that insulin in the VTA might decrease the salience of food-associated cues or contexts (Labouèbe

et al., 2013). Labouèbe et al. (2013) also demonstrated that a sweetened high-fat meal, which elevates plasma insulin, weakens excitatory synaptic transmission onto dopaminergic neurons in CNS (Labouèbe *et al*., 2013). This attenuation in VTA synaptic efficacy may lead to variation in the naïve and STZ-diabetic subjects' responses. Chronic hypoinsulinemia may alter synaptic DA signaling by alleviating the availability of cell membrane DAT (Carvelli *et al*., 2002). Former studies have demonstrated that DAT expression in the cell membrane is modulated by the insulin signaling pathway (Garcia *et al*., 2005). Besides, it is shown that the ablation of pancreatic β cells by a single administration of STZ in rats would diminish DAT expression in the plasma membrane and maybe DAT-mediated behavioral effects of amphetamine and cell membrane levels and functions of DAT reduce in STZ-induced diabetes dramatically (Williams *et al*., 2007).

As mention previously, we indicated that insulin injection decreased CS. This change in CS might result from dopaminergic terminal modulation in neuronal circuits of the ventral striatum. The prior investigations showed that direct administration of insulin into the VTA (Labouèbe *et al*., 2013; Mebel *et al*., 2012) and in the NAc (Stouffer *et al*., 2015) influence the DA release. Insulin-induced depression of somatodendritic DA has been attributed to the upregulation of the number or function of DAT in the VTA (Mebel *et al*., 2012). Also, insulin administration decreases glutamatergic neurotransmission onto DA neurons of VTA, which may decrease DA release in the mesocorticolimbic area of the brain (Labouèbe *et al*., 2013). Therefore, it appears that insulin-mediated reduction in DA activity in the VTA might ablate the salience of morphine reward via diminished DA release in the NAc.

Moreover, this finding that insulin can affect morphine-induced reward in the acquisition phase of condition protocol indicates the importance of insulin to create the condition memory for morphine reward. Therefore, the acquisition of morphine-induced CPP is shown to be enhanced by the systematic application of insulin. It also must be noted that the VTA is one of the important players in morphine preference. Furthermore, it should focus on the role of other neural structures such as the extended amygdala (Fadel, Deutch, 2002) and mesocorticolimbic system (Baldo *et al*., 2003) in the evaluation of reward. In conclusion, insulin has a critical role in modulating morphine-induced reward. So, consistent with the previous investigation, insulin could be a proper candidate to use as a therapeutic agent in opiate addiction.

CONFLICTS OF INTEREST

The authors of the manuscript have no conflicts of interest to declare

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CONTRIBUTORS

Substantial contributions to conception and design: Abbas Haghparast; Acquisition data: Rezvan Hassanpour and Atieh Chizari; Analysis, interpretation of data and drafting the article: Amir-Hossein Bayat, Ronak Azizbeigi and Zahra Mousavi; Final approval of the version to be published: Abbas Haghparast. All authors critically reviewed content and approved the final version for publication.

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