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RESEARCH ARTICLE

Induction of anxiolytic, antidepressant and analgesic effects by Shiff base of (*E*)-3-(1*H*-imidazol-4-yl)-2-((2-oxoindolin-3-ylidene)amino) propanoic acid derivatives in diabetic rats

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Abstract

Diabetes mellitus is a metabolic disorder with several psychological problems such as anxiety, depression, and pain sense. This study aimed to evaluate the effect of Schiff base on the modulation of anxiety, depression, and pain behaviors in diabetic rats. Anxiety, depression, and pain behaviors were evaluated by elevated plus maze (EPM), forced swim test (FST), and hot-plate test, respectively. The results indicated that induction of diabetes decreased time spent in open arms (OAT) in the EPM whereas injection of insulin (1 ml/kg), glibenclamide (5 mg/kg), and Schiff base II (100 mg/kg) increased OAT in the EPM. So, induction of diabetes in rats caused an anxiogenic effect that this effect reversed by drug treatment. Interestingly, co-treatment of insulin and glibenclamide along with an ineffective dose of Schiff base II potentiated anxiolytic behavior in diabetic rats. Furthermore, induction of diabetes increased immobility time in the FST but administration of insulin (1 ml/kg), glibenclamide (5 mg/kg), and Schiff base II (25, 50, and 100 mg/kg) decreased immobility time in the FST which indicated depressant effect in diabetic rats without drug-treatment and antidepressant effect in diabetic rats with drug-treatment. Additionally, induction of diabetes decreased latency in the hot-plate test while injection of insulin (1 ml/kg), glibenclamide (5 mg/kg), Schiff base I (50 mg/kg), and Schiff base II (25, 50, and 100 mg/kg) enhanced latency in the hot-plate test which revealed hyperalgesic effect in diabetic rats without drug-treatment and analgesic effect in diabetic rats with drug-treatment. Consequently, induction of diabetes-induced anxiogenic, depressant, and hyperalgesia effects that administration of insulin, glibenclamide, Schiff bases I, and II reversed these effects.

Keywords Diabetes · Schiff bases · Depression · Anxiety · Pain · Rat

Introduction

Diabetes mellitus is a complex chronic disease that is the main source of ill health worldwide in which an individual has a high blood sugar level, either because the pancreas does not secrete sufficient insulin, or cells do not react to the insulin which is secreted. This metabolic disease is recognized primarily by hyperglycemia and disorders in the metabolism of carbohydrate, fat, and protein, secondary to an absolute or comparative lack of the hormone insulin [1–4]. The chronic hyperglycemia of diabetes is related to long-term injury, dysfunction, and failure of various organs, particularly the eyes, kidneys, nerves, heart, and blood vessels [5]. Besides hyperglycemia, numerous other factors such as dyslipidemia or hyperlipidemia participate in the development of micro- and macro-vascular problems of diabetes which are chief reasons for morbidity and death metabolisms, secondary to an absolute or comparative lack of the hormone insulin [6].

Diabetes mellitus is not only an organic disease, it is a disorder with psychiatric and psychosocial dimensions [7]. The most common psychiatric disorders related to

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diabetes mellitus are anxiety and depression. In patients with diabetes, depression and anxiety are seen at a higher rate than in the general population [8–13]. Furthermore, diabetic peripheral neuropathic pain is a common problem of diabetes [14–16]. The pain related to diabetic peripheral neuropathy may be due to failure of the endogenous analgesic mechanisms in the descending spinal pathways which modulate pain transmission to the brain [17, 18].

Schiff bases are some of the most broadly used organic compounds which use in the pharmaceutical and biological field [19–22]. Schiff bases of isatin exhibit anticonvulsant, anti-influenza virus, antimicrobial, anti-HIV, and anti-inflammatory activities [23–26].

Insulin and oral hypoglycemic drugs similar glibenclamide, sulphonylureas and biguanides are still the agents of choice and as these drugs are to be used throughout the life and reduction of response after long use and induce side effects [27]. Because of the drawbacks of the existing drugs, there is continually a need to find novel anti-diabetic drugs. In this aspect, the current research was undertaken to assess the anti-diabetic effect of Schiff bases on the modulation of anxiety, depression, and pain behaviors in diabetic rats.

Materials and methods

Synthesis of Schiff bases

Schiff bases I and II were synthesized by the condensation of isatin (3.50 mmole), 5-chloroisatin (3.50 mmole), with the histidine (3.50 mmole) in 1: 1 molar ratio using ethanol (30 mL) as the reaction medium, and then it was refluxed for 4–5 h. The mixture of reactions was filtered and washed with hot ethanol (75%) to give remarkably pure powders of the products (Fig. 1). In all experimental groups, the LD50 value of the applied Schiff's base was less than 5%.

Animals

Animals were adult male Wistar rats weighing 220–250 g obtained from the Shahid Beheshti University (Tehran, Iran). The rats were kept 4 per Plexiglas cage in a room with controlled temperature (22 ± 2 °C) under 12/12 h light/dark cycles (lights on 07:00 a.m.). The rats had free access to food and water. Eight rats were used in each experimental group and each rat was only tested once. Behavioral tests were performed during the light phase of the light/dark cycle. All procedures in this research were conducted under the institutional guidelines for animal care and use.

Induction of diabetes

Diabetes was induced by a single intraperitoneal (i.p.) administration of streptozotocin (50 mg/kg of body weight) which dissolved in physiological serum [5, 28]. Diabetes was confirmed after the third day of streptozotocin injection by estimating serum glucose using a glucose peroxidase kit (Pars Azmoon Co., Tehran, Iran). Rats that developed serum glucose levels of more than 200 mg/dl were considered diabetic and were used for the research.

Materials

Streptozotocin was purchased from the Sigma Chemical Company (St Louis, USA). Insulin and glibenclamide were purchased from the Exir Company and Minoo Company (Tehran, Iran) respectively.

Experimental design

The rats were randomly divided into 10 groups with 8 rats each. Group 1, Normal control group treated with saline (1 ml/kg); Group 2, Diabetic rats treated with saline (1 ml/kg); Group 3, Diabetic rats treated with insulin (1 ml/kg); Group 4, Diabetic rats treated with glibenclamide

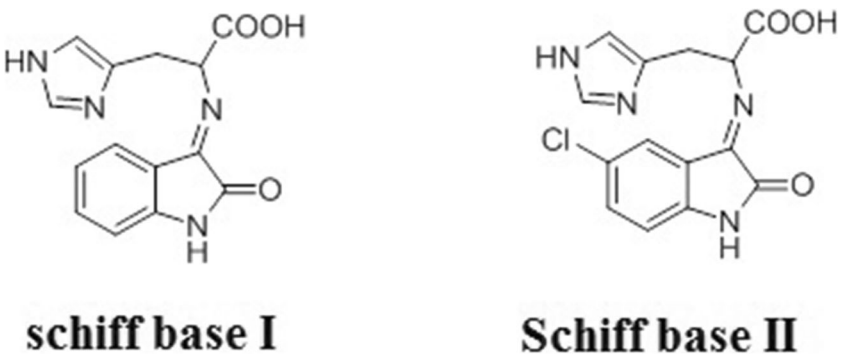

Fig. 1 Schematic structure of Schiff bases I and II

(5 mg/kg); Group 5: Diabetic rats treated with Schiff base I (50 mg/kg); Group 6: Diabetic rats treated with Schiff base II (25 mg/kg); Group 7: Diabetic rats treated with Schiff base II (50 mg/kg); Group 8: Diabetic rats treated with Schiff base II (100 mg/kg); Group 9: Diabetic rats treated with Schiff base II (25 mg/kg) along with insulin (1 ml/kg); Group 10: Diabetic rats treated with Schiff base II (25 mg/kg) along with glibenclamide (5 mg/kg). The diabetes induction day was determined as Day 0. Days 1–3 were considered for confirmation of diabetes induction. Drug treatment was carried out intraperitoneally (i.p.) at a period of 14 days (from Day 4, after confirmation of diabetes induction, to Day 17). On Day 17, 30 min after drug treatment, behavioral tests (Elevated plus maze (EPM) test, Forced swim test (FST), and Hot-plate) were carried out. All experiments were done by someone blind to the responses and statistical analysis. The experimental groups were clarified in Table 1.

Behavioral tests

Elevated plus maze (EPM) test

The apparatus made of four arms two of which had no side or end walls (open arms; 50 × 10 cm). The other two arms had side walls and end walls, but were open on the top (closed arms; 50 × 10 × 40 cm). Where the four arms crossed, there was a square platform of 10 × 10 cm. Rats were located in the experimental room at least 1 h before the test. Rats were individually located in the center of the apparatus facing a closed arm and allowed 5 min of free exploration. The number of entries into the open arms, the number of entries into the closed arms, the total time spent in the open arms, and the total time spent in the closed arms were recorded via a video camera through a monitor and a computer recording system were installed in a next room. The test room was illuminated via two 60-

Table 1 The table explained experimental groups

Experiments	Fig.	Drug injection (Intraperitoneally)	Effect on anxiety	Effect on depression	Effect on pain
1	A	Saline 1 ml/kg, Insulin 1 ml/kg, Glibenclamide 5 mg/kg, Schiff base I 50 mg/kg, Schiff base II 25, 50, 100 mg/kg	Diabetes(anxiogenic) Drugs (anxiolytic)	-	-
	B	Saline 1 ml/kg, Insulin 1 ml/kg, Glibenclamide 5 mg/kg, Schiff base I 50 mg/kg, Schiff base II 25, 50, 100 mg/kg	No effect	-	-
	C	Saline 1 ml/kg, Insulin 1 ml/kg, Glibenclamide 5 mg/kg, Schiff base I 50 mg/kg, Schiff base II 25, 50, 100 mg/kg	No effect	-	-
2	A	Saline 1 ml/kg, Insulin 1 ml/kg, Glibenclamide 5 mg/kg, Schiff base II 25, Schiff base II 25 mg/kg + Insulin 1 ml/kg, Schiff base II 25 mg/kg + Glibenclamide 5 mg/kg	No effect	-	-
	B	Saline 1 ml/kg, Insulin 1 ml/kg, Glibenclamide 5 mg/kg, Schiff base II 25, Schiff base II 25 mg/kg + Insulin 1 ml/kg, Schiff base II 25 mg/kg + Glibenclamide 5 mg/kg	Anxiolytic	-	-
	C	Saline 1 ml/kg, Insulin 1 ml/kg, Glibenclamide 5 mg/kg, Schiff base II 25, Schiff base II 25 mg/kg + Insulin 1 ml/kg, Schiff base II 25 mg/kg + Glibenclamide 5 mg/kg	No effect	-	-
3	A	Saline 1 ml/kg, Insulin 1 ml/kg, Glibenclamide 5 mg/kg, Schiff base I 50 mg/kg, Schiff base II 25, 50, 100 mg/kg	-	Diabetes(depressant) Drugs(antidepressant)	-
	B	Saline 1 ml/kg, Insulin 1 ml/kg, Glibenclamide 5 mg/kg, Schiff base II 25, Schiff base II 25 mg/kg + Insulin 1 ml/kg, Schiff base II 25 mg/kg + Glibenclamide 5 mg/kg	-	No effect	-
4	A	Saline 1 ml/kg, Insulin 1 ml/kg, Glibenclamide 5 mg/kg, Schiff base I 50 mg/kg, Schiff base II 25, 50, 100 mg/kg	-	-	Diabetes(hyperalgesia) Drugs (analgesia)
	B	Saline 1 ml/kg, Insulin 1 ml/kg, Glibenclamide 5 mg/kg, Schiff base II 25, Schiff base II 25 mg/kg + Insulin 1 ml/kg, Schiff base II 25 mg/kg + Glibenclamide 5 mg/kg	-	-	No effect

W bulbs placed 1.5 m above the apparatus. Raw data were used to manually evaluate the anxiety-like behaviors. Entry was considered as putting all four paws in the arms and calculated via a hand counter. The time spent in open arms (OAT) and the numbers of entry to the open arms (OAE) was recorded as an amount for anxiety. Moreover, the number of total arm entries was measured as an amount for locomotor activity. Drugs that act on anxiety-like behavior may either enhance or reduce OAT and OAE showing anxiolytic-like or anxiogenic like behaviors respectively [29].

Forced swim test (FST)

FST is commonly used to assess depressant like behaviors in rodents. FST is upon the hypothesis that when a rat is located in a container filled with water; it will first attempt to escape. Nonetheless, the rat finally will show immobility which may be determined as a measure of behavioral despair. Rats were subjected to the FST apparatus which made of a cylindrical glass container (height = 30 cm and diameter = 20 cm) filled with water (25 °C). Each rat was individually located in the apparatus for 6 min. Because great agitation is usually perceived during the first 2 min, only the immobility times observing during the last 4 min were recorded. A rat was detected immobile when it stopped its swimming tries and sustained floating motionless in the water, making only those movements necessary to keep its head above water [30].

Hot plate test

The hot plate test is an assessment of pain behavior in rodents which is alike to the tail-flick test. The hot plate test is performed to evaluate the pain threshold and to examine the effectiveness of the analgesic by detecting the response to the heat produced pain. Eddy and Leimbach suggested the hot plate test in 1953 [31]. In this protocol, behaviors including jumping are induced after a noxious thermal stimulus. Jumping determines a more elaborated response, with latency, and contains an emotional component of escaping. The plate was surrounded by four Plexiglas walls. Consequently, the rat could not escape. The rat was removed from the plate rapidly after jumping or no response within 50 s.

Statistical analysis

The results were statistically assessed by the one-way variance analysis (ANOVA) followed by Tukey's multiple comparisons to analyze drug action, and two-way variance analysis ANOVA was used to analyze the interactions between the drug combination in comparison to the individual treatment groups. Mean ± SD indicates the possible different outcomes among the experimental groups and their corresponding controls. Following a significant F value, Post-hoc analysis (Tukey test) was performed to assess differences between groups. P-value was less than 0.05 showing statistical significance.

Results

Effects of insulin, glibenclamide and Schiff bases on anxiety behavior in diabetic rats

Figure 2 indicated the effects of i.p. administrations of insulin, glibenclamide, Schiff base I, and Schiff base II on anxiety behavior in male diabetic rats. One-way ANOVA and post hoc analysis exhibited that i.p. administration of saline (1 ml/kg), insulin (1 ml/kg), glibenclamide (5 mg/kg), Schiff base I (50 mg/kg), Schiff base II (25, 50, 100 mg/kg) changed OAT [$F(7, 56) = 2.726$, $P = 0.017$; Fig. 2a] but did not alter OAE [$F(7, 56) = 0.525$, $P = 0.812$; Fig. 2b] and locomotor activity [$F(7, 56) = 0.210$, $P = 0.982$; Fig. 2c] in comparison with the saline group. Post-hoc analysis displayed that induction of diabetes decreased OAT while administration of insulin (1 ml/kg), glibenclamide (5 mg/kg), and Schiff base II (100 mg/kg) increased OAT in the EPM in comparison with saline group, presenting anxiogenic effect in diabetic rats without drug treatment and anxiolytic effect in diabetic rats with drug treatment.

Effects of co-treatment of insulin and glibenclamide along with Schiff bases II on anxiety behavior in diabetic rats

In Fig. 3 are seen the effects of co-administrations of insulin and glibenclamide along with ineffective dose of Schiff base II on anxiety behavior in male diabetic rats. Two-way ANOVA showed a significant difference between diabetic rats without drug treatment in comparison to drug treatment in OAE [treatment effect: $F(1,42) = 23.548$, $P = 0.000$, dose effect: $F(2,42) = 12.590$, $P = 0.000$, treatment–dose interaction: $F(2,42) = 4.424$, $P = 0.018$; Fig. 3b] but not for OAT [treatment effect: $F(1,42) = 2.022$, $P = 0.162$, dose effect: $F(2,42) = 1.554$, $P = 0.223$, treatment–dose interaction: $F(2,42) = 0.697$, $P = 0.504$; Fig. 3a] and locomotor activity [treatment effect: $F(1,42) = 0.176$, $P = 0.677$, dose effect: $F(2,42) = 0.591$, $P = 0.558$, treatment–dose interaction: $F(2,42) = 0.103$, $P = 0.903$; Fig. 3c]. Thus, co-administration of insulin and glibenclamide along with not-effective dose of Schiff base II increased anxiolytic behavior in diabetic rats.

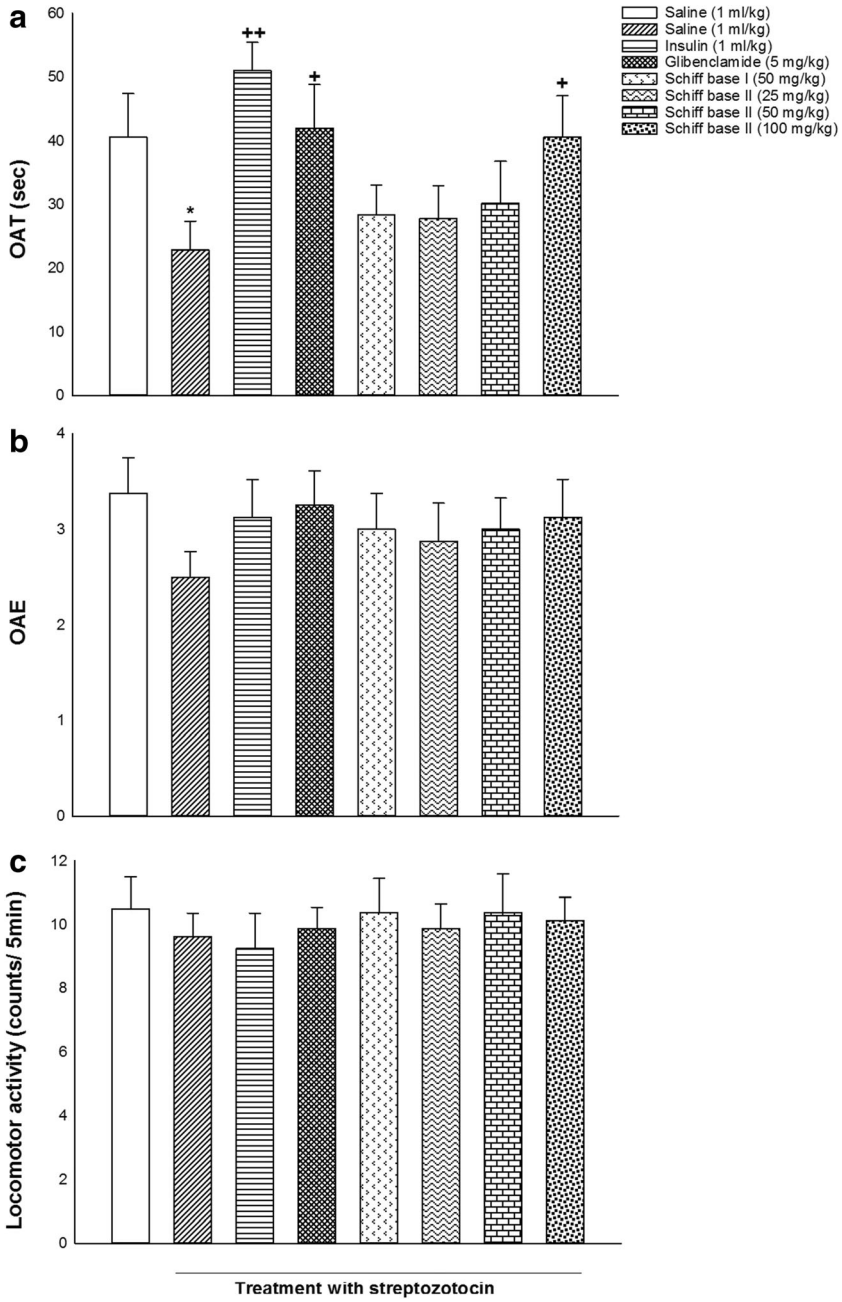

Fig. 2 The effects of insulin, glibenclamide, Schiff base I, and Schiff base II on behavioral despair in the OAT (**a**), OAE (**b**), and locomotor activity (**c**). Values are expressed as mean ± S.E.M. from 8 rats and were analyzed by one-way ANOVA followed by Tukey's post hoc test. * $p < 0.05$ in comparison to the saline group. ++ $p < 0.01$ and + $p < 0.05$ in compared with the saline/ streptozotocin group

Effects of alone and co-injection of insulin, glibenclamide and Schiff bases on depression behavior in diabetic rats

Figure 4 showed the effects of alone and co-injection of insulin, glibenclamide, Schiff base I, and Schiff base II on depression behavior in diabetic rats. One-way ANOVA and post hoc analysis indicated that alone injection of saline (1 ml/kg), insulin (1 ml/kg), glibenclamide (5 mg/kg), Schiff base I (50 mg/kg), Schiff base II (25, 50, 100 mg/kg) modified immobility time in the FST [F (7, 56) = 2.739, P = 0.016; Fig. 4a]. Post-hoc analysis revealed that induction of diabetes enhanced immobility time whereas injection of insulin (1 ml/kg), glibenclamide (5 mg/kg), and different doses of Schiff base II (25, 50, and 100 mg/kg) decreased immobility time in the FST in comparison with saline group, indicating depressant response in diabetic rats without drug treatment and antidepressant response in diabetic rats with drug treatment.

Moreover, two-way ANOVA showed no significant effect of drugs co-injection in immobility time of the FST [treatment effect: F (1,42) = 5.627, P = 0.022, dose effect: F (2,42) =

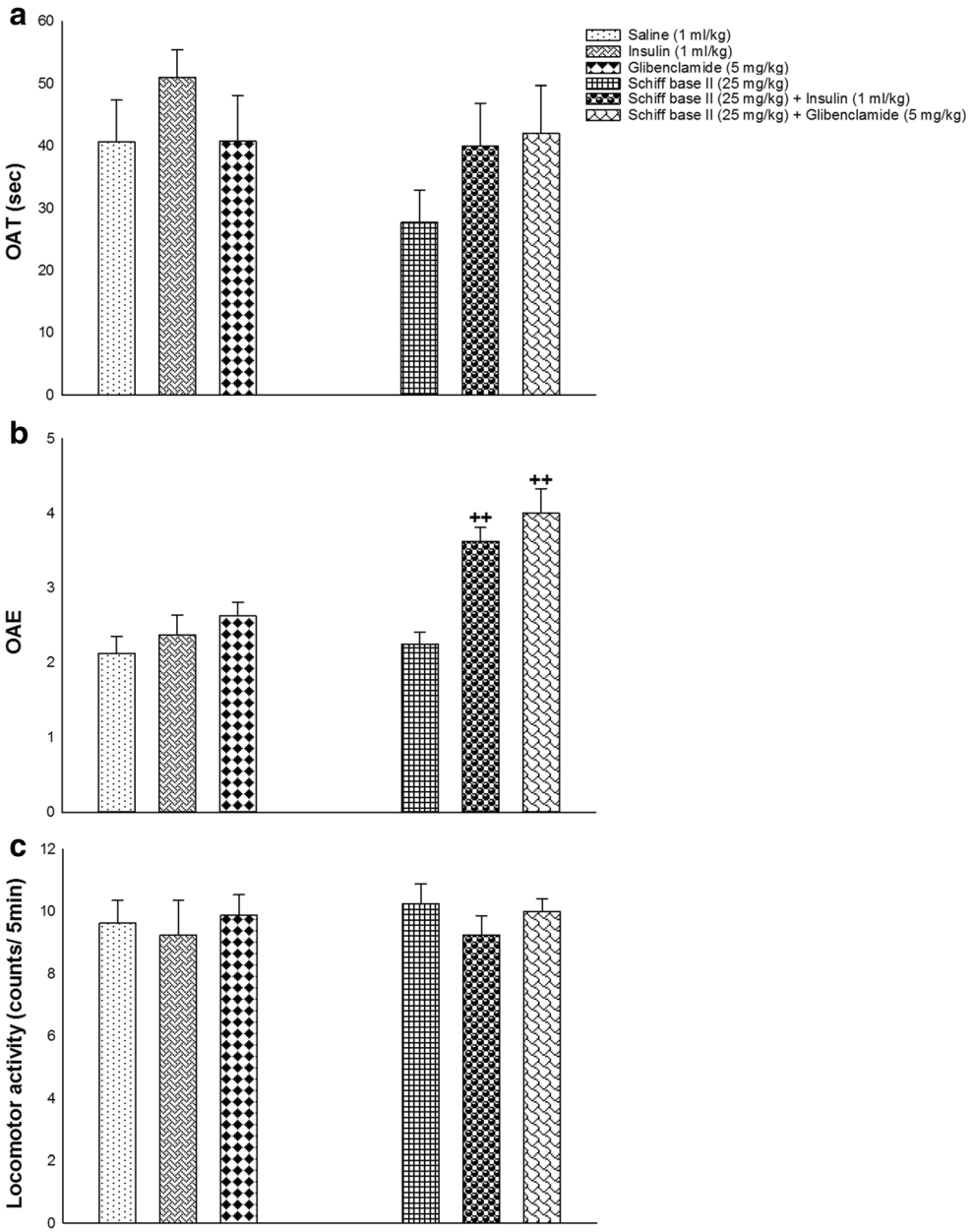

Fig. 3 The co-administrations of insulin and glibenclamide along with a not-effective dose of Schiff base II on behavioral despair in the OAT (**a**), OAE (**b**), and locomotor activity (**c**). Values are indicated as mean ± S.E.M. from 8 rats and were analyzed by two-way ANOVA followed by Tukey's post hoc test. ++ $p < 0.01$ in compared with respective group

7.975, P = 0.001, treatment–dose interaction: F (2,42) = 0.821, P = 0.447; Fig. 4b].

Effects of alone and co-administration of insulin, glibenclamide and Schiff bases on pain behavior in diabetic rats

The effects of alone and co-administration of insulin, glibenclamide, Schiff base I, and Schiff base II on pain behavior in diabetic rats are illustrated in Fig. 5. The results determined using one-way ANOVA displayed that alone administration of saline (1 ml/kg), insulin (1 ml/kg), glibenclamide (5 mg/kg), Schiff base I (50 mg/kg), Schiff base II (25, 50, 100 mg/kg) significantly altered latency in the hot-plate test [F (7, 56) = 5.399, P = 0.000; Fig. 5a]. Post-hoc analysis displayed that induction of diabetes decreased threshold of latency but the injection of insulin (1 ml/kg), glibenclamide (5 mg/kg), Schiff base I (50 mg/kg), and diverse doses of Schiff base II (25, 50, and 100 mg/kg) increased threshold of latency in the hot-plate test in comparison with saline group, suggesting hyperalgesic effect in diabetic rats without drug treatment and analgesic effect in diabetic rats with drug treatment.

Furthermore, two-way ANOVA exhibited no meaningful effect of drugs co-administration in latency of the hot-plate

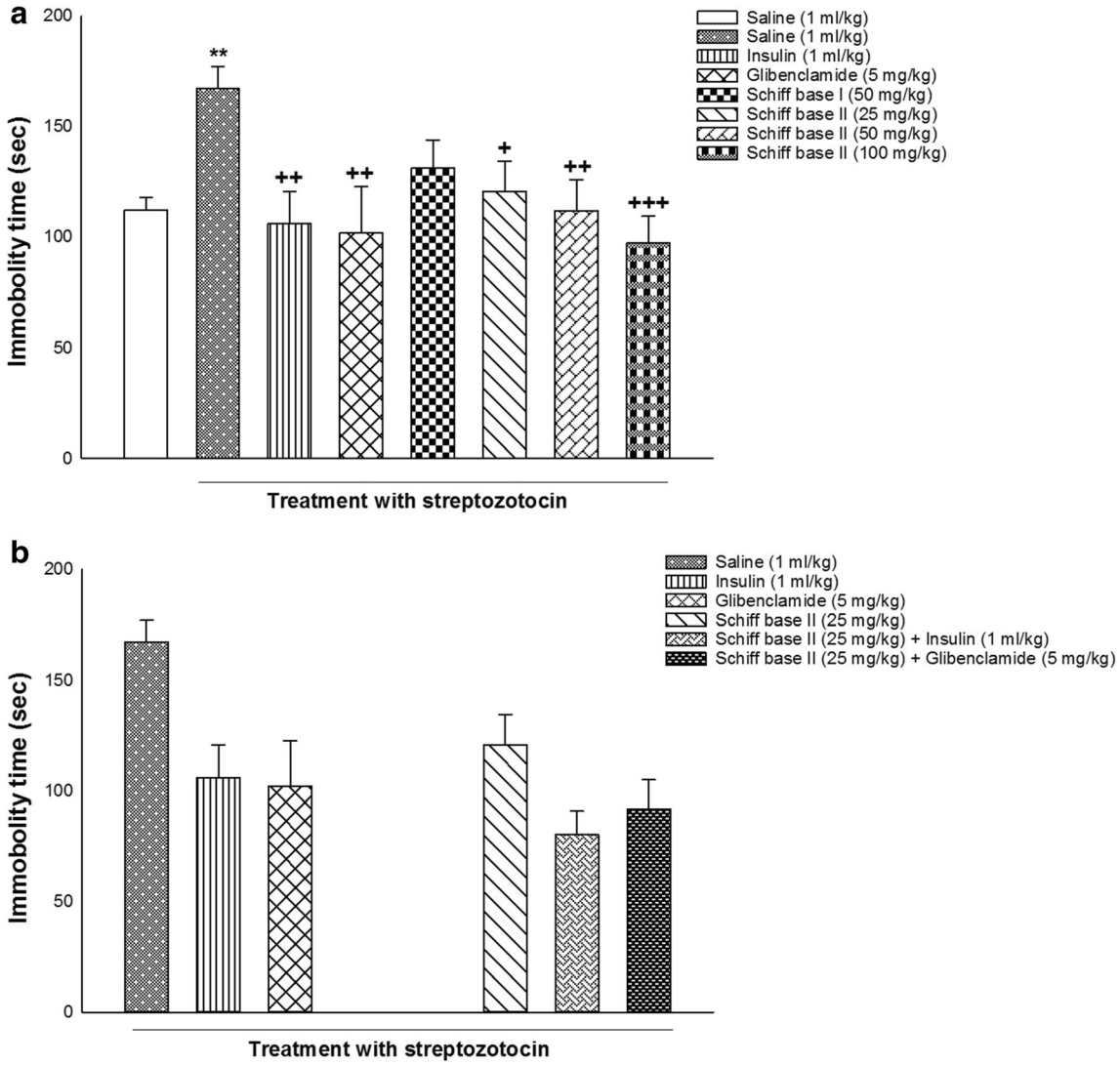

Fig. 4 The effects of alone and co-administration of insulin, glibenclamide, Schiff base I, and Schiff base II on behavioral despair in the immobility time in the FST (**a** and **b**). Values are presented as mean ± S.E.M. from 8 rats and were analyzed by one- and two-way ANOVA followed by Tukey's post hoc test. ** $p < 0.01$ in comparison to saline group. +++ $p < 0.001$, ++ $p < 0.01$ and + $p < 0.05$ in compared with the saline/streptozotocin group

test [treatment effect: F (1,42) = 8.336, P = 0.005, dose effect: F (2,42) = 5.294, P = 0.009, treatment–dose interaction: F (2,42) = 2.689, P = 0.080; Fig. 5b].

Discussion

In the present research, diabetes mellitus was induced in rats via a streptozotocin injection which destroys the β-cells of Langerhans islets, as reported by many researchers [2, 32, 33]. In addition to the problems of type 2 diabetes, some psychological syndromes are also very common in these patients [7]. The results of the present research indicated that the induction of type 2 diabetes mellitus produced anxiogenic, depressant, and hyperalgesia effects in male rats. The association between anxiety and depression with diabetes has been extensively analyzed [34]. Anxiety and depression are usual disorders in patients suffering from type 2 diabetes [7, 35, 36]. Evidence revealed that symptoms of anxiety and depression often remain unrecognized in diabetes diseases. As diabetes has enhanced worldwide recently, it is essential to decrease the prevalence of factors which are related to anxiety and depression in diabetes patients [35]. Our results support early detection of anxiety and depression in patients with diabetes. The occurrence of anxiety and depressive diseases can be as high as two-fold greater in individuals suffering from type 2 diabetes [8–11, 13]. Evidence demonstrated a bidirectional correlation between diabetes mellitus, and anxiety and depressive disorders. So that patients with anxiety symptoms may be at enhanced risk of developing type 2 diabetes and vice versa [37]. Also, there are many controlled researches indicating

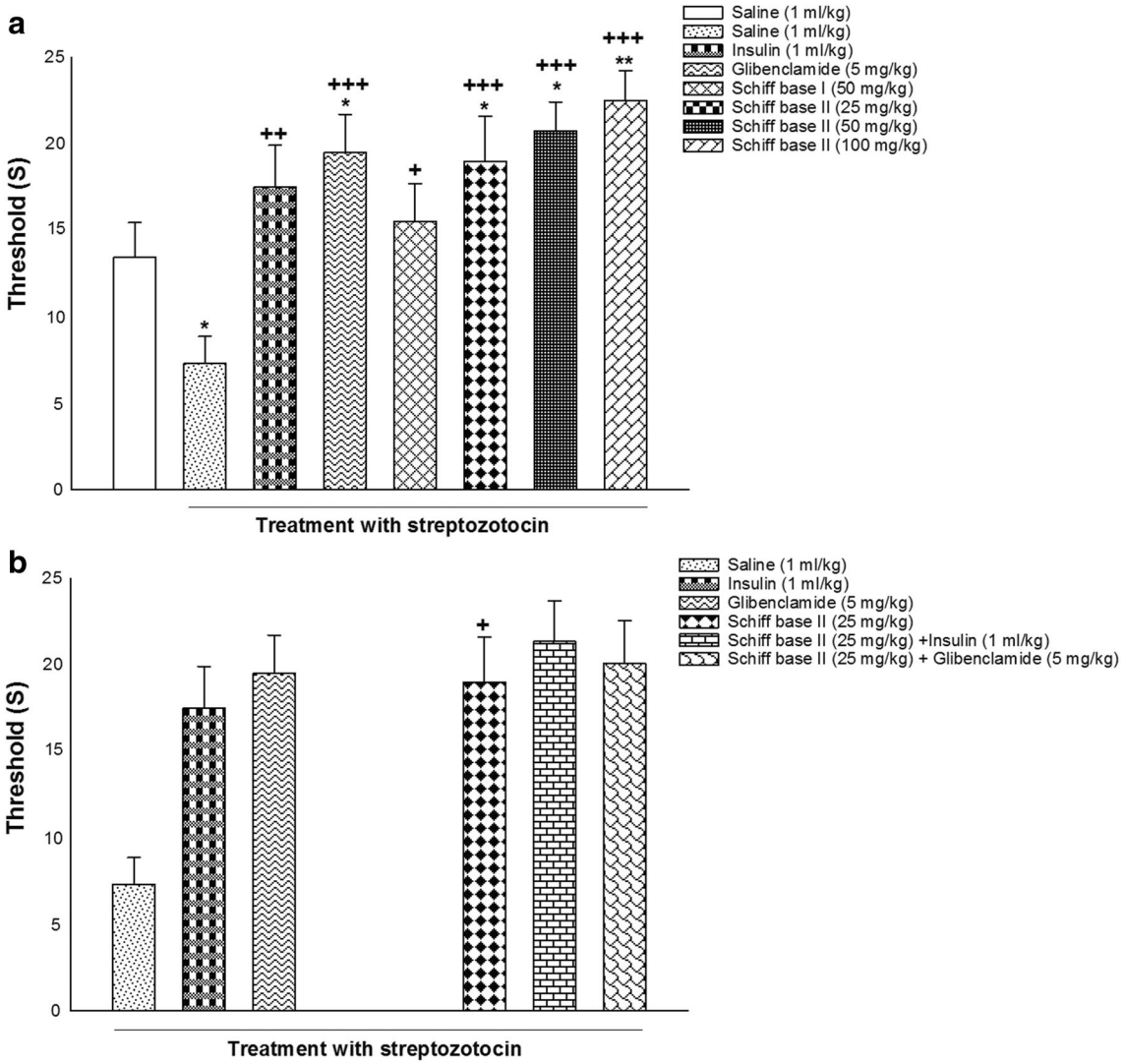

Fig. 5 The effects of alone and co-injection of insulin, glibenclamide, Schiff base I, and Schiff base II on behavioral despair in the latency of the hot-plate test (**a** and **b**). Values are displayed as mean ± S.E.M. from 8 rats and were analyzed by one- and two-way ANOVA followed by Tukey's post hoc test. ** $p < 0.01$ and * $p < 0.05$ in comparison to saline group. +++ $p < 0.001$, ++ $p < 0.01$ and + $p < 0.05$ in compared with the saline/streptozotocin group

the enhanced prevalence of depression in patients with type 2 diabetes mellitus [34]. Indeed, there are many biological reasons why diabetes and anxiety/depression enhance each other's prevalence [14]. Studies revealed that inflammatory markers-related to diabetes increased in diabetes diseases which along with hyperglycemia and maybe hyperinsulinemia caused a net pro-inflammatory state in numerous tissues. Access of pro-inflammatory markers to the brain may then lead to activation of the processes leading to the progress of psychological disorders such as anxiety and depression. Moreover, type 2 diabetes mellitus is linked with decreased size of the brain area such as the hippocampus and amygdala, providing evidence for the proposition that type 2 diabetes mellitus provide a biological risk factor for anxiety and depression [38]. Additionally, microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (cardiovascular and cerebrovascular) problems are common in type 2 diabetes mellitus [16, 39–41] which is possible due to failure of the endogenous analgesic system in the descending spinal pathway [17, 18].

Furthermore, our results indicated that the administration of insulin, glibenclamide, Schiff bases I, and Schiff base II induced anxiolytic, antidepressant, and analgesic effects in diabetic rats. Previous researches have revealed that events of psychological nature are key factors interfering with insulin secretion causing poor diabetic stability. According to reports, the relationship between these conditions is bi-directional. It is reported that patients with anxiety, depression, and diabetes, compared to diabetic patients alone, have been linked with more diabetes complications. The incidence of anxiety and depression in persons with diabetes appears to be linked with physical activity, socioeconomic status, family status, obesity, and smoking habits [8, 42]. As the disease's additional progress and complications of diabetes ensue,

particularly neuropathy, nephropathy, and sexual dysfunction, the incidence of depression in the patient further increases [43–45]. Insulin and glibenclamide as hypoglycemic drugs are still the drugs of choice. These drugs are used throughout life that reduction of response after long use may produce side effects [27]. Therefore, finding new anti-diabetic drugs that potentiate the anti-diabetic effects of low-dose of insulin and/or glibenclamide will be a good achievement in the medicine for diabetes management. In this respect, Schiff bases are some of the most generally used organic compounds that indicated anti-diabetic activity [22]. In keeping with our findings, Khan and colleagues (2009) reported that Schiff bases of isatin indicated a variety of biological activities including antidepressant, anti-inflammatory, antimicrobial, and effects on the central nervous system [46]. Schiff bases of isatin are capable of crossing the blood–brain-barrier. Also, isatins induce antiglycation activity [46]. So that numerous Schiff bases show α-glucosidase inhibitory properties [19–21]. α-Glucosidase is a membrane-bound enzyme that hydrolyzes terminal non-reducing 1–4 connected α-glucose residues to release monomeric glucose molecules that is principally responsible to induce hyperglycemia [47, 48]. Blocking of α-glucosidase action can delay carbohydrate absorption and used as one of the therapeutic procedures for the treatment of diabetes [48, 49]. It has been reported that Schiff bases of isatins possessed antiglycation activity [46, 50] and can restore insulin signaling in the muscle, liver, and fat cells [50, 51]. Schiff bases I and II via inhibition of α-glucosidase function likely blocked problems induced by diabetes for example anxiogenic, depressant, and hyperalgesia effects. Interestingly, our data indicated that co-administration of Schiff base II and insulin or glibenclamide induced anxiolytic effect in diabetic rats, suggesting an interaction between these drugs on the modulation of anxiety behavior. However, further studies are needed to determine Schiff base II therapeutic potential against diabetes complications.

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Compliance with ethical standards

The study was carried out under ethical standards in all aspects.

Conflict of interest No financial or other conflicts of interest are declared.

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