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ORIGINAL PAPER

Berberine chloride improved synaptic plasticity in STZ induced diabetic rats

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Abstract Previous studies indicated that diabetes affects synaptic transmission in the hippocampus, leading to impairments of synaptic plasticity and defects in learning and memory. Although berberine treatment ameliorates memory impairment and improves synaptic plasticity in streptozotocin (STZ) induced diabetic rats, it is not clear if the effects are pre- or post-synaptic or both. The aim of this study was to evaluate the effects of berberine chloride on short-term plasticity in inhibitory interneurons in the dentate gyrus of STZ-induced diabetic rats. Experimental groups included: The control, control berberine treated (100 mg/kg), diabetic and diabetic berberine treated (50,100 mg/kg/day for 12 weeks) groups. The paired pulse paradigm was used to stimulate the perforant pathway and field excitatory post-synaptic potentials (fEPSP) were recorded in dentate gyrus (DG). In comparison with control, paired pulse facilitation in the diabetic group was significantly increased ($P<0.01$) and this effect prevented by chronic berberine treatment (50,100 mg/kg). However, there were no differences between responses of the control berberine 100 mg/kg treated and diabetes berberine treated (50 and 100 mg/kg) groups as compared to the control group. The present results suggest that the pre-synaptic component of synaptic plasticity in the dentate gyrus is affected under diabetic conditions and that berberine prevents this effect.

Keywords Berberine · Diabetes · Synaptic plasticity

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Introduction

Behavioral and electrophysiological experiments have shown that diabetes induces impairment of synaptic plasticity or learning and memory defects (Biessels et al. 1996) by affecting the hippocampus gradually from 8 weeks after the induction of diabetes (Biessels et al. 2002). However, the mechanism of these impairments in diabetes has not been well understood. Diabetes affects synaptic transmission, by influencing both pre-synaptic (Baptista et al. 2011; Kamal et al. 2006) and post-synaptic (Reisi et al. 2010) components at cellular level. The streptozotocin induced diabetes alters the synaptic terminal structure in the hippocampus, including the rearrangement of vesicles (Magarinos et al. 1997), depletion of synaptic vesicles and retraction and simplification of apical dendrites of hippocampal neurons (Magarinos and McEwen 2000). In addition, these deficits were partially reversed by the use of insulin (Biessels et al. 1998). However, it is still not clear if the improvement in synaptic plasticity in the hippocampus due to berberine treatment are pre- or postsynaptic or both (Bhutada et al. 2011). Berberine, an isoquinoline alkaloid, has a wide range of clinical applications in both Iranian and Chinese medicine (Imanshahidi and Hosseinzadeh 2008). Although pharmacological investigations of berberine have been reported by many in the past, there is renewed interest in berberine because of its reported beneficial effect in various neurodegenerative and

neuropsychiatric disorders including Alzheimer's, cerebral ischemia, mental depression, schizophrenia and anxiety (Kulkarni and Dhir 2010; Ye et al. 2009). Moreover the alkaloid is reported to modulate neurotransmitters and their receptor systems in the brain (Peng et al. 2007; Kulkarni and Dhir 2008). In previous studies we have shown that chronic oral administration of berberine could improve cognitive performance and long term potentiation (LTP) induction and maintenance in dentate gyrus of streptozotocin induced diabetes rats (Kalalian-Moghaddam et al. 2013) When the perforant path is stimulated by two closely paired stimuli, a series of temporal changes occurs in granule cell excitation to the second pulse. Usually, granule cell response to the second stimulus is more than that to the first evoked response at inter-pulse interval (IPI) 40–200 ms because of facilitation of pre-synaptic Ca^{2+} influx that leads to paired-pulse facilitation (PPF)(Dobrunz and Stevens 1997) When the second stimulus is less than that to the first evoked response at inter-pulse interval 10–40 ms because of recurrent inhibition induced, the paired-pulse depression (PPD) occurs (Brucato et al. 1992; Tuff et al. 1983)The phenomena of PPF well known as short-term forms of synaptic plasticity and generally accepted as a model for evaluation of the pre-synaptic component of the synaptic plasticity (Craig and Commins 2005; Sokolov et al. 1998; Chen et al. 1996). PPF is an enhancement in the amplitude of the EPSP evoked by a second stimulus that follows the first one in the paired pulse paradigm with a short inter stimulus interval (Reisi et al. 2008). Facilitation is the result of an increase in probability of neurotransmitter release that is mainly attributed to residual Ca^{2+} in the nerve terminals after the first stimulus (Collin et al. 2005). Short-term synaptic plasticity lasting from a few milliseconds to a few minutes serves as a flexible mechanism for temporal information processing in higher cortical integration. (Schulz et al. 1995; Santschi and Stanton 2003; Pan et al. 2004; Gerges et al. 2003; Craig and Commins 2005). The purpose of this electrophysiological study was to investigate the effects of chronic oral administration of berberine, using paired pulse stimulation and field potential recordings method, on short-term pre-synaptic plasticity in the dentate gyrus of streptozotocin induced diabetic rats.

Materials and methods

Animals

Male albino Wistar rats weighing 225–285 g were housed in an air conditioned colony room on a light/dark cycle (21–23 ◦C and a humidity of 30–40%) and supplied with standard pelleted diet and tap water ad libitum. Procedures involving animals and their care were conducted in conformity with the NIH guidelines for the care and use of laboratory animals.

Experimental procedure

The rats (n=30) were randomly allocated and similarly grouped into five groups: control, control berberine treated (100 mg/kg), diabetic and diabetic berberine treated (50 and 100 mg/kg) groups. Berberine hydrochloride and streptozotocin (Sigma–Aldrich Co, St. Louis, MO) were used in the present study. All the drugs were dissolved in doubled distilled water except STZ, which was dissolved in citrate buffer (pH =4.4). Drug solutions were prepared fresh and their doses are expressed in terms of their free bases. Diabetes was induced in rats by using an earlier reported method. In brief, STZ was dissolved in 0.1 M sodium citrate buffer, pH 4.4 and administered at the dose of 55 mg/kg through I.P. route. Streptozotocin-treated rats received 5% of glucose solution instead of water for 24 h after injection of STZ in order to reduce death due to hypoglycemic shock. Blood samples were taken from the tail vein 72 h after STZ injection to measure blood glucose levels. Control animals received an injection of an equivalent volume of normal saline. Three days after STZ injection, overnight fasting blood samples were collected and serum glucose concentrations were measured using glucose oxidation method (Zistshimi Co, Tehran). Only the animals with a fasting serum glucose level higher than 250 mg/dl were selected as diabetic for the following experiments. The day on which hyperglycemia had been confirmed was designated as day 0 and berberine chloride was administered P.O. at doses of 50 and 100 mg/kg/day for 12 weeks.

Electrophysiological recordings and PP induction

Dentate gyrus LTP was recorded under anesthesia. Twelve weeks after diabetes induction, the rats were anesthetized with urethane (1.5 g/kg) and placed in a stereotaxic apparatus and their heads were fixed in a stereotaxic head-holder.

The rectal temperature was monitored and maintained at 37±0.5 °C with an automatic heating pad. The skull was exposed and two small holes were drilled at the positions of the stimulating and recording electrodes. The exposed cortex was kept moist by the application of paraffin oil. Bipolar stimulating and recording electrodes were made of stainless steel wire (0.125 mm diameter, Advent, UK). It was positioned stereotaxically so as to selectively stimulate the medial perforant path while recording in the dentate gyrus. The electrode stimulating the medial perforant path was implanted 4.2 mm lateral to the true lambda. A recording electrode was implanted ipsilaterally 3.8 mm posterior and 2.2 mm lateral to the bregma. The electrical signals from the DG were amplified 1000-fold, digitized at 10 kHz, and band-pass filtered at 0.1 Hz–10 kHz using a DAM80 differential amplifier (WPI, USA). Signals were passed through an analogue to digital interface (Power lab/4SP, AD Instruments, Australia) to a computer, and data were analyzed using Biochart software.

Recording of field potentials was started at least 15 min after placing the stimulation and recording electrodes. All the stimuli were biphasic square wave pulses (200 ms width) and their intensities for base liner recording were set at the current that evoked 40% of the maximum population spike amplitude (PSA). Test stimuli (0.1 Hz) were delivered at 10s intervals to monitor field excitatory post synaptic potentials (fEPSP) and population spike (PS). The strength of a field potential was evaluated from the slope of the EPSP and amplitude of the PS. The maximal EPSP slope was obtained on the first positive deflection of the field potential. The PS amplitude was measured by averaging the distance from the negative peak to the preceding peak and the following positive peak

After stable baseline recording for at least 30 min, the response to paired-pulse stimulation was subsequently recorded, delivered at 40%-maximal stimulus intensity with an inter stimulus interval of 10, 20, 30, and 50 ms). For each time-point, 15 consecutive evoked responses were averaged at 10 s stimulus interval. The population spike amplitude ratio [second population spike amplitude/first population spike amplitude at percent; PS2/PS1%, paired pulse index (PPI)] and the fEPSP slope ratio [second fEPSP slope/first fEPSP slope at percent; fEPSP2/fEPSP1%] were measured at different inter stimulus intervals and compared to the control group.

Input/output functions

At the beginning of the experiments, to determine the stimulus intensity that evoked 40% maximal field responses, Stimulus–response or input/output (I/O) curve was constructed, that comprised 10 stimulus intensities (interval of 10s) ranging from100 μA to maximal response, to evaluate synaptic potency. The strength of a field potential was evaluated from the slope of the EPSP and amplitude of the population spike (PS). The maximal EPSP slope was obtained on the first positive deflection of the field potential. The PS amplitude was measured by averaging the distance from the negative peak to the preceding peak and following positive peak.

Data analysis

For electrophysiological comparison, data was analyzed using a repeated measure two-way ANOVA, with bonferroni post-hoc test to compare replicate means between groups. Body weight and blood glucose data were analyzed by repeated measure one-way ANOVA followed by Tukey's post-hoc test (PRISM, Graph Pad software Inc, USA). In all calculations, an appropriate statistically significant level was set at $P_{value}<0.05$. Results are expressed as means±S.E.M.

Results

General considerations

Two week after STZ injection, 2 rats from berberine treated groups were excluded from the study due to side effect of gavage being dead. The weight of the diabetic control rats at 4th week was found to be significantly decreased as compared to control rats ($P_{value}<0.05$). Moreover, at 8th week after STZ injection, chronic treatment with berberine (50 and 100 mg/kg) significantly increased body weights in diabetic rats ($P_{value}<0.05$ and 0.01, respectively) (Fig. 1). In addition, diabetic rats had also an elevated serum glucose level over those of control rats ($P_{value}<0.001$) and treatment of diabetic rats with berberine at both doses of 50 and 100 mg/kg for 12 weeks caused a significant decrease in the serum glucose ($P_{value}<0.01$) as compared to diabetic control group. Moreover, control berberine treated (100 mg/kg) rats had also a reduced in the weight (Fig. 1) and serum glucose level over those of control (Fig. 2).

Electrophysiological experiments

Input/output (I/O) function

In the recordings of the DG area of the hippocampus, amplitude of PS and slope of EPSP obtained from input/output curve, 30 min basic recording, and paired-pulse10-20-30-50 ms were analyzed in order to evaluate synaptic potency between the groups. Stimulant pulses were delivered at 0.1 Hz, and a total of 10 responses at each current level were averaged. As it is shown in Fig. 3a, a repeated measure ANOVA indicated that, a significant difference in PS amplitude in stimulus intensity from 100 to 1,000 μA between the control group and diabetic group in all currents and between control berberine treated (100 mg/kg) and diabetic group ($P_{value}<0.01$). In addition no significant difference in PS amplitude was observed between control and berberine treated (50,100 mg/kg) groups. There was also no significant difference in EPSP slope in stimulus intensity from 100 to 1,000 μA between the all groups (Fig. 3b).

The effect of berberine on paired-pulse plasticity

A repeated measure ANOVA revealed that in the diabetic group compared to the control, the population spike ratio at inter stimulus intervals 10, 20 and 30 ms increased the paired-pulse facilitation (PPF) (control versus diabetic in pp10, $P_{value}<0.001$, control versus diabetic in pp20, $P_{value}<0.01$ and control versus diabetic in pp30 $P_{value}<0.05$) (Figs. 4a and 5). Under chronic berberine post-treatment (50 and 100 mg), the rate of the paired-pulse response at 10, 20 and

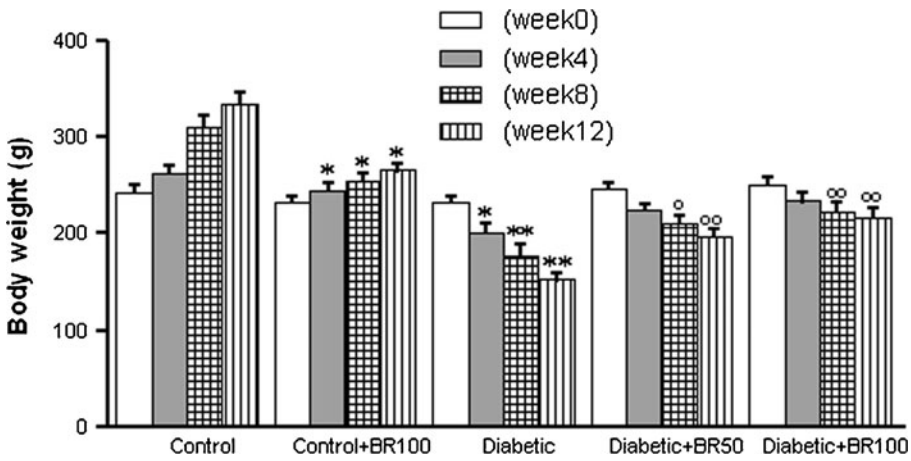

Fig. 1 Effect of Berberine on body Weight in different weeks (means ± S.E.M.).* $P<0.05$ ** $P<0.01$ vs. the control group, ○ $P<0.05$, ○○ $P<0.001$ vs. the diabetic group, as compared in the same week

30 inter-pulse intervals was significantly reduced. There was no significant difference between the control berberine treated (100 mg/kg) group as compared to control group. Paired pulse facilitation induced in the EPSP slope ratio were significant at inter-stimulus intervals of 10, 20 and 30 ms in the diabetic group compared to the control; (control versus diabetic in pp10, $P_{value}<0.01$, control versus diabetic in pp20 and in pp30, $P_{value}<0.05$) and at inter-stimulus intervals of 10, 20 and 30 ms in the diabetic group as compared to the diabetic berberine treated (100 mg/kg) groups (Figs. 4b and 5).

Discussion

Our study demonstrates that chronic berberine treatment significantly improved synaptic plasticity in DG. This conclusion is supported by recovery of population spike component of basal evoked potential and increased paired pulse facilitation in DG neurons of diabetic rats. Moreover no significant effects ($P<0.01$) were observed in healthy rats. LTP is considered as a major synaptic mechanism for evaluating long-term synaptic plasticity and previous results showed that fEPSP-LTP and PS-LTP decreased in diabetic group and berberine treatment prevents the destructive changes induced by diabetes in LTP induction and synaptic plasticity in DG. Moreover chronic treatment with berberine significantly decreased diabetes induced behavioral changes as compared to diabetic rats (Kalalian-Moghaddam et al. 2013). Short term synaptic plasticity in the hippocampus is postulated to be a cellular substrate for memory and learning and DG neurons, serves as a gateway to the hippocampus (Wiesner et al. 1987; Valjakka et al. 1991). Moreover paired-pulse stimulation is a standard technique for evaluating short-term synaptic plasticity in rodents (Aoyagi et al. 1998; Katsuta et al. 2003). Our study showed that in diabetic rats, the I/O curve significantly shifted to the right, indicating changes in releasing of neurotransmitters by pre-synaptic components and decreases basal synaptic transmission. This reduction of basal synaptic transmission and synaptic plasticity may be caused by impairment of synaptic functions, as reported by other researchers (Aoyagi et al. 1998). Moreover paired-pulse tests with high intensity have been used to evaluate the recurrent and feed forward inhibition, mediated by GABAergic interneurons in the dentate gyrus of rodents. GABAergic neurons regulate post-synaptic action potential firing and neuronal excitability of granular and pyramidal cells in the hippocampus (Austin et al. 1992; Steffensen and Henriksen 1991). When GABAergic inhibitory interneurons in the dentate gyrus receive excitatory inputs from the granule

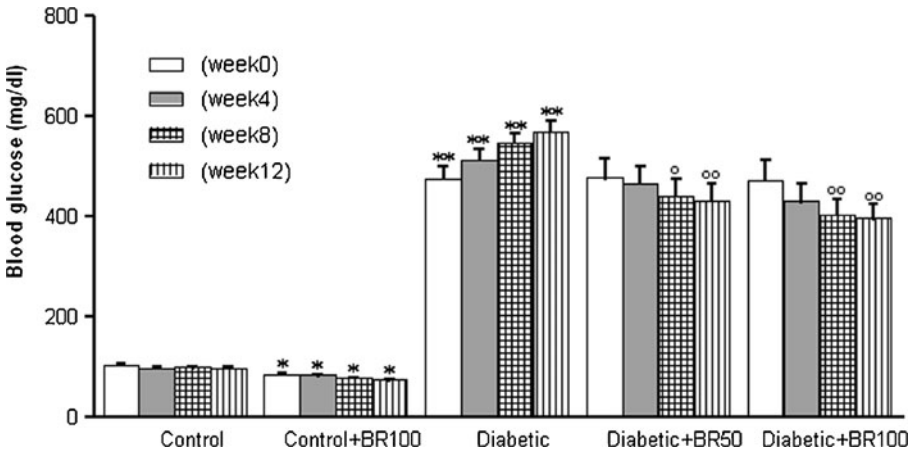

Fig. 2 Effect of Berberine on blood glucose in different weeks (means ± S.E.M.). *$P<0.05$, ** $P<0.001$ vs. the control group and ○ $P<0.05$, ○○ $P<0.01$ vs. the diabetic group, as compared in the same week

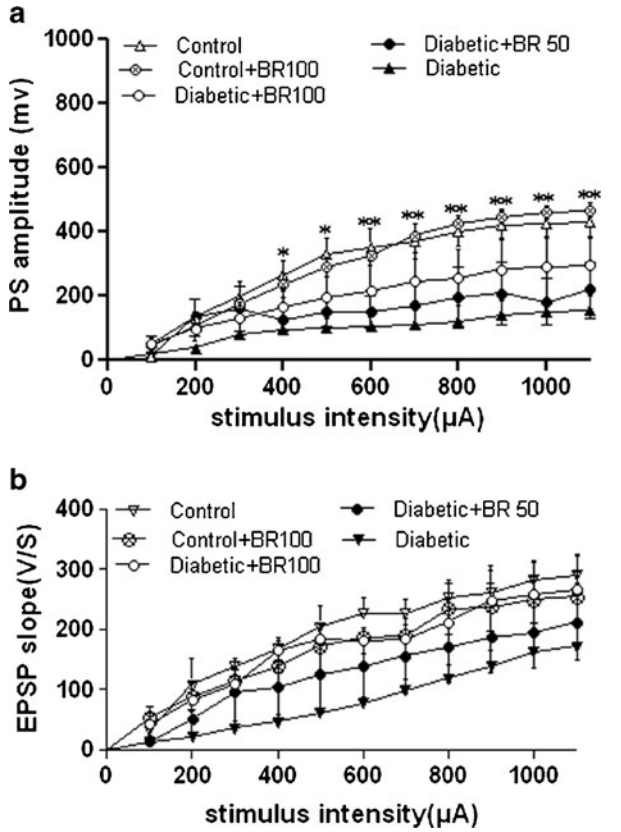

Fig. 3 Input–output curves (mean ± S.E.M) of **a** The PS amplitude and **b** The EPSP slope in the dentate gyrus region of the hippocampus (*p<0.01 and **p<0.001 with respect to the control group. n=6 for each experimental group)

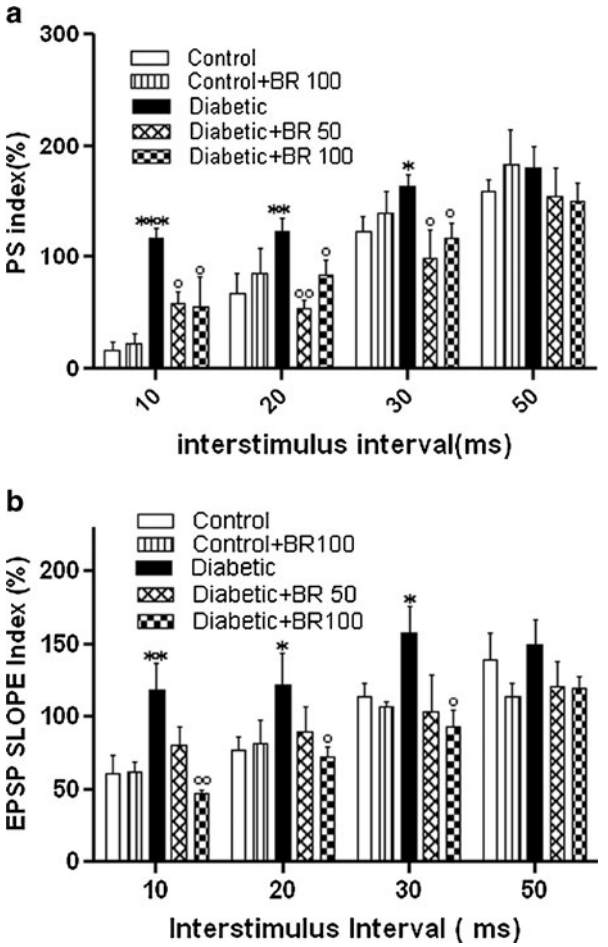

Fig. 4 The effect of berberine on recurrent inhibition in the dentate gyrus of the hippocampus at A: the population spike amplitude ratio, (percentage of mean PS2/PS1±E.M), and B: EPSP slope ratio (percentage of mean EPSP2/EPSP1±S.E.M.). * P<0.05, ** P<0.01, *** P<0.001 vs. the control group and ○ P<0.05, ○○ P<0.01 vs.) with respect to the diabetic group (n=6 for each experimental group)

cells, they elicit impulses and these cells then give raise to a recurrent inhibition of the granule cells. For this reason, the response induced by the second pulse to the perforant path is depressed due to this recurrent inhibition at inter stimulus intervals of 10–40 ms and there is facilitation at inter stimulus intervals of 50–150 ms (Ruan et al. 1998). The results shows at inter stimulus intervals of 10, 20 and 30 ms a shift from paired pulse depression toward paired pulse facilitation, demonstrates that recurrent inhibition decreased in diabetes. These findings suggest that impairment in recurrent inhibition was possibly due to functional alterations in GABAergic pre-synaptic terminals on DG neurons and are consistent with studies have been shown that GABA homeostasis alters in diabetes and also extracellular GABA levels in the brain are decreased (Gomez et al. 2003; Guyot et al. 2001b). Reduction of extracellular GABA levels in the brain and GABA release cause a post-synaptic depolarization of neurons and resulting in PPF (Abel and McCandless 1992). Interestingly, GABAergic neuron play an important role in convolution and berberine is reported to exhibit anticonvulsant like activity in various animal models, so we suppose that further studies are needed to show the protective effect of berberine in GABAergic neuron and memory impairment (Bhutada et al. 2010).

Berberine has been used by oral administration as an unprescribed drug in China, and the safety and efficacy of berberine by this administration mode have been generally accepted (Vuddanda et al. 2010). Moreover, in this study, we choose the dose 50 and 100 mg/kg, because this dose and administration mode is more close to the clinical practice than veno-injection or intraperitoneal administration (Zhu and Qian 2006; Kulkarni and Dhir 2010; Imanshahidi and Hosseinzadeh 2008). Further, chronic treatment with berberine (50 and 100 mg/kg) reduced blood glucose levels and increased body weights in diabetic rats which is well in accordance of earlier studies (Bhutada et al. 2011; Lee et al. 2006; Leng et al. 2004; Tang et al. 2006; Zhang et al. 2008; Zhou et al. 2009). Berberine easily cross the blood brain barrier and also rapidly transport and accumulate into the hippocampus neurons (Wang et al. 2005) and extensive research demonstrates that berberine treatment has neuroprotective effects (Imanshahidi and Hosseinzadeh 2008). Berberine decreases lipid peroxidation,

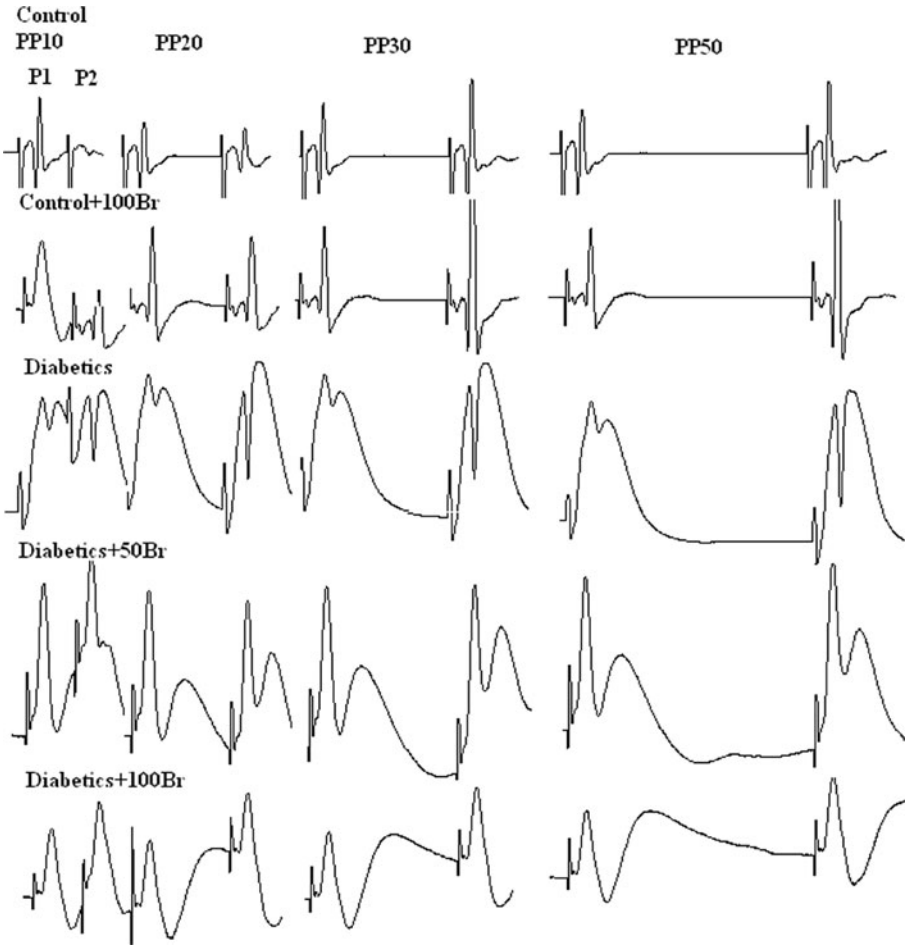

Fig. 5 Single traces recorded at inter-stimulus interval 10,20, 30 and 50ms were shown in. n=6 for each experimental group

acting as a free radical scavenger, prevents accumulation of reactive oxygen species, balances NO system, inhibits acetylcholine esterase enzyme activity and also plays an important role in memory impairment in Alzheimer disease (AD) (Yoo et al. 2008; Zhu and Qian 2006; Dhir et al. 2007). In our study, an improvement of paired-pulse response at inter-pulse intervals 10, 20 and 30, as an indicator of short-term plasticity was observed following berberine (50 and 100 mg) treatment in diabetic rats, indicating that both doses of berberine have had an improving effect regarding short-term memory. A possible explanation for the results as mentioned before is the neuroprotective effect of berberine on GABAergic interneurons. Indeed, cell proliferation in the DG is suppressed (Kim et al. 2002) in diabetic animals and berberine treatment may experimentally modified these conditions. The protective effect of berberine could partly mediate by its anti-apoptosis activity, which might result from inhibiting mitochondrial apoptotic pathway. Moreover, Berberine blocks potassium channels of hippocampus CA1 neurons, leads to the suppression of apoptosis and a substantial increase in the rate of cell survival . Thus the increment in potassium currents in CA1 neurons may contribute not only to excitability changes but also to cell death (Hu et al. 2012; Lee et al. 2010). Moreover, GLP-1 receptor has growth factor-like properties and plays imperative role in diabetes (Drucker 2003; Gengler et al. 2012), cognitive dysfunction, learning and neuroprotection (During et al. 2003; Abbas et al. 2009; Mc Clean et al. 2009). Interestingly, Lu, Yu et al., reported that berberine enhances GLP-1 release and biosynthesis, so berberine ameliorated pathologies of diabetes-induced cognitive dysfunction may involve GLP-1 receptor modulation (Yu et al. 2010; Lu et al. 2009). Moreover extracellular levels of glutamate extensively increased in diabetes and in early phase of diabetes induced by STZ, brain extracellular concentration of glutamate is high, which has neurotoxin effects (Guyot et al. 2001a). Berberine has been identified to reverse NMDA-induced excitotoxicity when tested in hippocampal neurons. Interestingly, reported that berberine exhibits NMDA antagonist like activity and is capable of protecting neuronal cells in the brain from ischemic episodes (Cui et al. 2009). In one study, it has been demonstrated that berberine reduced NMDA receptor bindings and inhibit NMDA receptor channel current in brain (Yoo et al. 2006; Imanshahidi and Hosseinzadeh 2008), therefore neuroprotective effect of berberine may be partly due to mentioned mechanism which further could be investigated. In conclusion, we have shown that pre-synaptic component of synaptic plasticity is affected in diabetic rats and restoring paired pulse response was probably one of the mechanisms by which berberine treatment improves

learning and memory capacities impaired by diabetes which could find clinical use in treating cognitive and neural function in diabetics. Further studies are warranted to investigate involve mechanisms in detail.

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