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Research Article

Pentylenetetrazol-induced seizures strength in diabetic and normal serum glucose elevated male mice

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ABSTRACT

Background: Epilepsy is one of the most important neurological disorders, afflicting both genders during their lifetime. Metabolic disturbances, including hyperglycemia and hypoglycemia, are one of the main reasons of seizures in which frequently have been seen in diabetes mellitus. A large body of literature has investigated correlation between hyperglycemia, hypoglycemia and seizure. However, a definitive conclusion has not been taken, yet. Hence, we developed a rodent model of PTZ-induced seizure in order to investigate about relation between PTZ-induced seizures and glycemic changes, including diabetic and non-diabetic hyperglycemia and hypoglycemia.
Methods: We chose 50 naive, adult male inbred mice of the Balb/c strain (aged 8–10 weeks, weighted 25-35 grams) and divided them into 5 groups, randomly (n=10 in each groups): 1. Control (received saline and citrate buffer). 2. Diabetic group (received STZ 140 mg/kg I.P). 3. Diabetic+Glibenclamide group (received STZ 140 mg/kg I.P and treated with Glibenclamide 1 mg/kg I.P daily). 4. Non-diabetic hyperglycemic group (received glucose "D-dextrose" 2 g/kg I.P 30 min before PTZ administration. 5. Hypoglycemic group (the animals were fasted one day other days during experimental period). Chemical kindling was induced by PTZ injection (35 mg/kg, I.P), every other days (11 periods that lasted 22 days).
Results: Our data shown non-diabetic hyperglycemic mice that had elevated blood glucose levels, were more resistant to seizures compared to control group ($p<0.05$). Threshold and duration of the second phase of the seizures in non-diabetic hyperglycemic mice were increased ($p<0.001$). Moreover, threshold of the phase 5 was enhanced ($p<0.001$). Again, hypoglycemic mice had statistically significant decrease in threshold of phase 5 compared to control group ($p<0.05$).
Conclusions: We found that acute non-diabetic hyperglycemia not only have had no aggravating effects on seizure susceptibility but also have shown anticonvulsive effects. As well, we found that hypoglycemia has decreased threshold of phase 5 in challenge dose, i.e. onset of the most severe phase of the seizures was accelerated.

Keywords: PTZ, Diabetic, Seizure, Glucose mice

INTRODUCTION

Epilepsy is one of the most important neurological disorders, afflicting both genders during their lifetime. It affects 0.5-1% of world's population, i.e. about 45-50 million of people worldwide.[1,2] In North America, overall epilepsy prevalence is 5 to 10 cases per 1000 persons, i.e. 3 million people are involved in epilepsy.[3] Seizure control is now a standard treatment for epilepsy, but no effective treatments exist to avoid neural damage after the seizure. Generally, seizure is the abnormal synchronized discharge of the cortical neurons.[4,5] Indeed, seizure occurs by imbalance between stimulatory and inhibitory factors, for the benefit of stimulating factors, that are in competition on cortical neuronal networks.[4] There are many causes for occurrence of Seizure, including head trauma, prenatal and postnatal injuries, brain tumors, alcohol and drug withdrawal syndromes, infections,

genetic factors and finally, metabolic disturbance specially hyperglycemia and hypoglycemia.[4,6,7]

Hyperglycemia and hypoglycemia are two main causes of seizures in which frequently have been seen in diabetes mellitus.[8,9] Epileptic seizure has been reported as the first symptom in 6% diabetic patients and about 19-25% of these patients had periods of seizure in their life.[10] A large body of literature has investigated correlation between hyperglycemia, hypoglycemia and seizure. However, a definitive conclusion has not been taken, yet. Some papers have stated that hyperglycemia aggravated seizure susceptibility, and hypoglycemia probably had anticonvulsant effects.[8,10-13] However, other investigations have underlined the correlation between hypoglycemia and elevated occurance of epileptic seizures, and report hyperglycemia may has some neurological protective effects.[9,14,15] It is specified that epileptic diabetic patients have had better outcomes if their blood glucose status had been brought under control.[16] Again, there are many clinical evidences that reveal hypoglycemic events lead to seizures. Anyway, the mechanisms of aforesaid mentioned were remained unclear, yet.

So far, there were little experiments that investigated hypoglycemic and hyperglycemic mice in a PTZ-kindling model, hence, we developed a rodent model of PTZ-induced seizure in order to investigate about relation between PTZ-induced seizures and glycemic changes, including diabetic and non-diabetic hyperglycemia and hypoglycemia.

METHODS

Animal model and experimental protocol

All experiments were conducted in accordance with the specifications of the ethical committee of Shahed University. Procedures for animal experimentation were reviewed and approved by the Institutional Animal Care and Use committee. The animals were housed under standard laboratory conditions, 12 h cycles (lights on at 6:00 am), temperature (25±1°C) and 55-65% humidity. The mice were given free access to food and water (except hypoglycemic group that fasted once every second days).

Animal groups

As a first step, we chose 50 naive, adult male inbred mice of the Balb/c strain (aged 8–10 weeks, weighted 25-35 grams) and divided them into 5 groups, randomly (n= 10 in each groups):

- Group 1: Control (received saline and citrate buffer).
- Group 2: Diabetic group (received STZ 140 mg/kg I.P).
- Group 3: Diabetic + glybenclamide group (received STZ 140 mg/kg I.P and treated with Glibenclamide 1 mg/kg I.P daily).
- Group 4: Non-diabetic hyperglycemic group (received glucose "D-dextrose" 2 g/kg I.P 30 min before PTZ administration.
- Group 5: Hypoglycemic group (the animals were fasted one day other days during experimental period).

Chemicals

Drugs used were as follows: streptozocin (STZ; Sigma, St. Louis, MO, USA), pentylenetetrazole (Sigma, Bristol, UK), Glibenclamide (Pursina, Tehran, Iran), dextrose 20%. Glibenclamide was dissolved in DMSO. STZ was dissolved in 5 mM citrate buffer (pH 4.0).

Measuring of the weights and blood glucose concentrations

All animals were weighted on a digital scale and their blood glucose was measured on days 1, 8, 16, 24. We snipped the tip of each mice's tail and collected a small drop of blood (5 µl) on a test strip, which was inserted into the glucose meter (MediSmart Sapphire, Switzerland). The blood glucose level was ready in a few seconds and reported in mg/dl.

PTZ-induced (kindling) seizures

Chemical kindling was induced by PTZ injection (35 mg/kg, I.P), every other days (11 periods that lasted 22 days).[17] At final injection (named challenge dose, twelfth periods or day 24th), PTZ was injected at dose 75 mg/kg to the animals. The animals were followed for convulsion scores (0-5) during thirty minutes after PTZ injection. The intensity of convulsions was registered according to a six-point scale:

0. No response
1. Ear and facial twitching
2. Myoclonic jerks without rearing
3. Myoclonic jerks, rearing
4. Turn over into side position, clonic–tonic seizures
5. Turn over into back position, generalized clonic –tonic seizures

STZ-induced diabetes

The mice were made insulin-dependent diabetic (type I) by I.P injection of 140 mg/kg STZ, which was dissolved in 5 mM citrate buffer (pH 4.0).[18,19] Control animals only received citrate buffer. After one week following STZ administration, blood samples were taken from tail vein and hyperglycemia was confirmed by measuring blood glucose levels, using a blood glucose meter. Moreover, diabetic+Glibenclamide mice received Glibenclamid 1 mg/kg I.P as a treatment.[20,21]

Non-diabetic hyperglycemia

Acute hyperglycemia was induced by I.P injection of dextrose (2 g/kg body weight) 30 min prior to PTZ injection and seizure induction.[22]

Hypoglycemia

We used fasting model to induce hypoglycemia. The animals had access to food and water ad libitum, for 24 hours, but they didn't access to any food in next day, before seizure test, although they had free access to tap water.[8]

Statistical analysis

Statistical analyses were performed using the Sigma Stat software (SystatSofware, Inc., Point Richmond, CA, USA). A significance level of $P<0.05$ was used for differences between groups. Data are presented in the text and in all figures as means±SEM. The repeated measure ANOVA followed by Dunn post hoc test was used to analyze the seizure threshold and duration's data. Kruskal–Wallis test was used for statistical analysis of the other data.

RESULTS

Effects of blood glucose changes on body weights

All animals were weighted on a digital scale in days 1, 8, 16, 24. As shown in Table 1, statistical analysis has not shown significant correlation between data.

Table 1: Body weights of animals on days 1, 8, 16 and 24 (in grams).

Days / Groups	Day 1	Day 8	Day 16	Day 24
Control	28.83±2.58	27.08±1.8	26.41±1.3	26.67±1.02
Hypoglycemia	25.35±1.88	24.66±2.8	24.72±2.13	25.12±2.13
Non-diabetic hyperglycemia	29.82±1.8	27.21±1.19	27.81±1.08	28.3±1.14
Diabetic	27.13±1.75	27.07±1.9	27.37±2.14	27.31±2.2
Diabetic+Glibenclamide	31.9±1.89	26.77±2.08	27.2±2.35	28.04±2.45

Data are expressed as mean±SEM. Each group consisted of 10 animals.

Table 2: Animals blood glucose values on days 1, 8, 16 and 24 (mg/dl).

Days / Groups	Day 1	Day 8	Day 16	Day 24
Control	146.77±5.4	138.5±9.53	136.5±9.53	134.25±4.5
Hypoglycemia	133.5±4.71	98.14±6.52*	99.87±6.52*	86.87±6.98*
Non-diabetic hyperglycemia	141.77±4.94	250.14±23.59*	270.14±22.59*	368.14±49.03*
Diabetic	145±10.27	165.43±13.74	188.75±11.74*	193.25±8.33*
Diabetic+Glibenclamide	133±4.58	140.85±8.98	130.85±8.8#	149.6±19.15#

Data are expressed as mean±SEM. Each group consisted of 10 animals. * and # represent differences, with $P<0.05$, in the same days compared to corresponding control and diabetic groups, respectively.

Blood glucose changes

Animals did not show significant differences in the first day of experiment, but significant statistical differences appeared on day 8 in hypoglycemic and non-diabetic hyperglycemic mice compared to control group ($p<0.05$). On day 16 and 24, diabetic mice found elevated blood glucose levels and statistically significant differences compared to control group ($p<0.05$). Diabetic mice that had received Glibenclamid shown significant statistical difference compared to diabetic animals, in days 16 and 24. It should be mentioned that despite the STZ dose and injection protocol were consistent with reliable literatures, and despite the fact that statistically significant blood glucose elevation was seen in diabetic mice, the elevations were not above 250 mg/dl.

Effects of blood glucose changes on the progress of phases of seizure

As shown in Figure 1, non-diabetic hyperglycemic mice that had elevated blood glucose levels, were more resistant to seizures compared to control group ($p<0.05$).

Effects of blood glucose changes on seizure severity

As shown in Figure 2, non-diabetic hyperglycemic mice have shown statistically significant differences, in terms of seizures severity, compared to control group ($p<0.05$), in the sense that non-diabetic hyperglycemic mice were more resistant against seizure occurrence in periods 5 to 11 of injections.

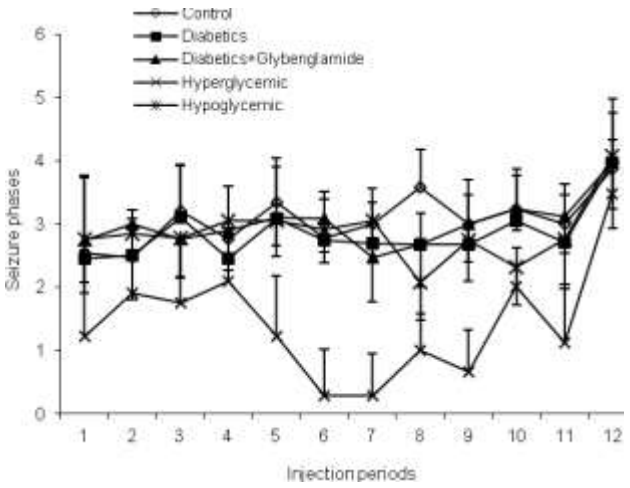

Figure 1: Effects of blood glucose changes on the progress of phases of seizure, in periods 1 to 12 of the experiment and points represent mean±SEM.

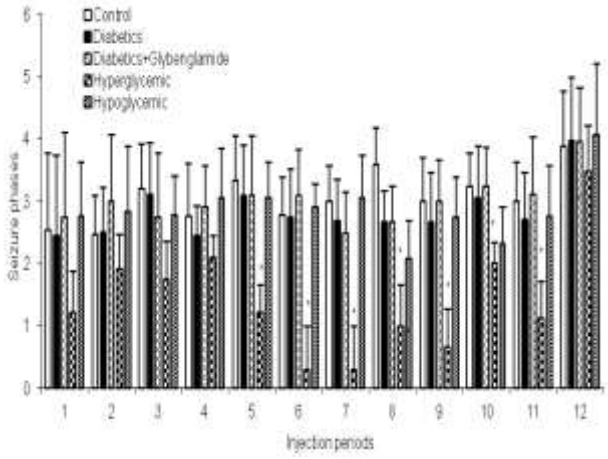

Figure 2: Effects of blood glucose changes on seizures severity, in periods 1 to 12 of the experiment and columns represent mean±SEM.

Table 3: Effects of blood glucose changes on thresholds and durations of phase 2 and phase 5 (seconds)

Groups \ Times	phase 2 threshold	phase 2 duration	phase 5 threshold	phase 5 duration
Control	137.93±12.65	16.19±3.33	150.36±14.45	8.85±0.96
Hypoglycemia	106.66±6.47	12.15±3.52	112.95±9.76	7.21±0.54
Non-diabetic hyperglycemia	197.72±23.37***	89.41±13.82***	292.08±45.39***	6.17±0.75
Diabetic	116.03±5.75	12.92±2.02	124.26±10.8	7.35±0.63
Diabetic+Glibenclamide	115.91±5.58	11.83±2.92	163.56±13.78	10.61±2.06

Data are expressed as mean±SEM. Each group consisted of 10 animals. *** represents difference, with p<0.05, compared to control group.

Table 4: Effects of blood glucose changes on threshold and duration of the phase 5 and animals mortality in challenge dose (seconds).

Groups \ Times	phase 5 threshold	phase 5 duration	mortality percentage
Control	126.01±23.12	7.41±2.37	70%
Hypoglycemia	57.36±6.95	4.33±0.88	80%
Non-diabetic hyperglycemia	296.67±70.50**	11.60±1.80	20%
Diabetic	90.71±11.33	7.00±0.78	70%
Diabetic+Glibenclamide	109.23±22.81	34.28±15.57	50%

Data are **e**xpressed as mean±SEM. Each group consisted of 10 animals. ** represents difference, with P<0.05, compared to control group.

Effects of blood glucose changes on thresholds and durations of the phase 2 and phase 5 of the seizures in periods 1 to 11 of injections

As shown in table 3, threshold and duration of the second phase of the seizures in non-diabetic hyperglycemic mice, were increased and have shown statistically difference compared to control group (p<0.001). Moreover, threshold of the phase 5 has been enhanced, too (p<0.001).

Effects of blood glucose changes on threshold and duration of the phase 5 and animals mortality in challenge dose (12th period of injection)

Phase 5 is the most severe phase of the seizures. As shown in table 4, hypoglycemic mice had statistically significant decrease in threshold of phase 5 compared to control group (p<0.05), whereas, non-diabetic hyperglycemic animals had raised threshold (p<0.01).

Again, mortality percentage was decreased in non-diabetic hyperglycemic mice (20% compared to 70% in control group).

DISCUSSION

Despite some literatures have demonstrated that high blood glucose levels aggravate and make animals more susceptible to seizure, surprisingly, we found that acute non-diabetic hyperglycemia not only have had no aggravating effects on seizure susceptibility but also have shown anticonvulsive effects.[8] As well, we found that hypoglycemia has decreased threshold of phase 5 in challenge dose, i.e. onset of the most severe phase of the seizures was accelerated. The latter finding was in consistent with results of the other literatures.[18,23]

The anticonvulsive effect of hyperglycemia, more or less, is a new finding, and recently, have reported in a handful of literatures.[15] Indeed over the years, hyperglycemia were known as unfavorable factor that have increased seizures, but we showed that acute non-diabetic hyperglycemia, by itself, makes animals more resistant against seizure onset, and prevents them to go to more intense phases of the seizures. Moreover, non-diabetic hyperglycemic mice had lower mortality percentage after that challenge dose had been injected into them, i.e. acute increase in blood glucose level not only alleviates seizure but also protects animals against most intense phases of the seizure which can lead to death. One possible cause for the disparity between our finding and previous studies could be the result of different hyperglycemia-induction models, i.e. acute hyperglycemia induction by glucose injection versus chronic hyperglycemia that induced by STZ. Another potential reason could be the result of different in seizure-induction models. Some studies have shown, for example, non-diabetic hyperglycemia has aggravated seizures in the rats were subjected to flurothyl seizure test, but has decreased seizure severity in kainic acid-induced seizure model.[8,15] Although, these reasons are not compelling enough and probably there are other reasons.

According to data have obtained from present study, seizure phases progression bouts in diabetic and diabetic+Glibenclamide mice had no differences compared to control group, but as said, it was dramatically decreased in non-diabetic hyperglycemic mice. This decrease was begun in period 5 of injections or day 10 of experiment, and the most dominant decrease was seen on periods 6 and 7, i.e. days 12 and 14 of experiment. Probably, this gradual seizure reduction was due to the gradual rise in blood glucose levels during days 1 to 24 of experiment. Moreover, because this effect was not seen at low and normal levels of blood sugar, it was probably caused by supra physiological levels of blood glucose, i.e. BS>250 mg/dl. Again, non-diabetic hyperglycemic mice have spent much more time in second phase of seizure compared to control group. The increase in duration of phase 2, may initially have been seemed undesirable, however, it is probably due to the increased resistance of animals and their efforts to deal with getting into the more severe phases of the seizures.

It has previously been demonstrated that reducing the amount of energy availability can cause neuronal damage during seizure.[14,15,24] As well, excessive amount of glutamate and cytosolic calcium can lead to neural damage in which exacerbate by reduced energy availability.[15,25] So, increased blood glucose levels can lead to seizure severity reduction. Moreover, KATP channels may also be contributed. KATP channels have been found at high density in a variety of other cell types, including cardiac, smooth, and skeletal muscle, and some brain neurons.[26] In neurons, KATP channels opening in response to metabolic stress including ischemia, hypoxia, hyperglycemia and hypoglycemia can lead to inhibition of electrical activities, thereby, result in seizure severity reduction.[26,27] Again, KATP have been found in substantia nigra pars reticulata - SNPR – in which acts as a central gating system in the propagation of seizure.[28,29] It is possible that hypoglycemia, as an ATP depletion condition, could leads to seizure progression and thus, explain the lower seizure threshold on phase 5 in hypoglycemic mice.[27] On the other hand, neurons of the substantia nigra pars reticulate have GABAergic inhibitory projections to the thalamic and cortical neurons. Hyperglycemia can induce depolarization in these neurons via KATP channels closing, which inturn, inhibitory outputs are increased and seizure severity is decreased. However, the aforesaid mentioned mechanisms have not been proven and details remained unclear, yet.

Another probable mechanism is the existence of neurons that are inhibited by glucose rather than be stimulated, i.e. glucose-inhibited neurons instead of glucose-excited neurons. In general, in glucose-excited neurons, glucose metabolism leads to KATP channel closure, triggering membrane depolarization, whereas in glucose-inhibited neurons, the inhibitory effect of elevated glucose is mediated by an ATP-independent K^+ channel.[30] Some studies have demonstrated that glucose-inhibited neurons have been found in some CNS regions, including NTS, DMV and hypothalamus.[30-32] The mechanism of glucose-induced neuronal inhibition is not well understood. Several mechanisms have been proposed, including activation of an electronic Na^+ pump, activation of ATP sensitive Cl^- channels, or inhibition of Na^+/K^+-ATPase.[30,33,34] Oomnra et al. have reported in 1974 that glucose stimulates the Na^+/K^+-ATPase pump resulting in hyperpolarization and inhibition of the hypothalamic neurons, although, it is not well recognized, yet. Song et al. in 2001, Routh et al. in 2002 and Fioramonti et al. in 2007, have proposed glucose-induced activation of post-synaptic Cl^- channels to explain the inhibitory action of glucose on the hypothalamic neurons, however, the Cl^- theory has been rejected by recent studies.[30,35-37] Burdakov et al. have demonstrated that at least in the hypothalamic neurons, the final effector mediating

glucose induced inhibition are K^+ currents, in addition, they found that glucose-induced inhibition may engage multiple types of K^+ channels.[38] In general, increased blood glucose level, possibly via aforesaid inhibitory mechanisms may have contributed to seizure severity reduction, although as said, details are less understood.

Again, some studies have reported the existence of neurons that contain the peptide transmitters orexins/hypocretins.[32,39,40] Orexinergic projections were found widely throughout the brain, specially, in regions that contribute to arousal, metabolism and appetite regulation.[41] It have been demonstrated that orexin neurons are more activated during wakefulness and are relatively silent during slow-wave sleep.[42,43] Indeed, exogenously administration of orexin activates sympathetic tone, increases locomotor activity and wakefulness, and alters feeding behaviors.[32,44,45] Moreover, orexin neurons play a role in phenomenon of postprandial somnolence.[46] Muroya et al. have found that glucose inhibits intracellular calcium signals in some orexin neurons in rat and some other studies have revealed that glucose hyperpolarizes and inhibits 80 to 100 percentage of orexin neurons.[47] Interestingly, this inhibition have been seen in supra-physiological levels of blood glucose, i.e. BS >5 mM, remember we have seen hyperglycemic anticonvalsant effect on supra-physiological levels of blood glucose, too.[48] As described above, orexin neurons have stimulating effects on brain areas and high glucose concentration inhibits orexin neurons, so hyperglycemia may decrease neuronal activity in this way and results in reduced seizure severity.

Conversely, MCH neurons that project widely throughout the brain, have opposite physiological roles compared to orexin neurons.[49,50] Generally, MCH neurons activation promote sleep, suppress locomotor activity and energy expenditure.[32,50] Burdakov et al. have shown that about 80% of MCH neurons have been excited by glucose.[32] So, based on aforesaid mentioned, it is possible that high glucose concentration, even via excitatory mechanisms, be able to inhibit brain areas contributed to seizure and causes reduced seizure severity.

CONCLUSION

In summary, we found that acute non-diabetic hyperglycemia not only have had no aggravating effect on seizure susceptibility but also have shown anticonvulsive effect and reduced seizure severity tremendously. Moreover, hypoglycemia has decreased threshold of the most severe phase of the seizures and showed proconvulsive effect. We have found no differences in diabetic and diabetic+Glibenclamide mice compared to control group. While many literatures have reported that hyperglycemia aggravates seizure susceptibility, our data support the hypothesis that acute non-diabetic hyperglycemia may reduce seizure severity and so act, vice versa.

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