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VALIDATION OF DIABETES ASSOCIATED DEPRESSION BY STREPTOZOTOCIN INDUCED RAT MODEL

Sawan Mukund Ghetia and Chakrakodi Shashidhara Shastry*
Nitte (Deemed to be University), Department of Pharmacology, NGSM Institute of Pharmaceutical Sciences (NGSMIPS), Deralakatte, Mangaluru, Karnataka, India-575018.
*Corresponding Author: Dr. C S Shastry (Principal)
Nitte (Deemed to be University), Department of Pharmacology,
NGSM Institute of Pharmaceutical Sciences, Deralakatte, Mangalore, India– 575018
E-mail address: principal.ngsmips@nitte.edu.in

ABSTRACT

Diabetes mellitus is a chronic condition that is caused by decreased or no production of insulin in aloft blood sugar levels. Diabetes if left untreated, may often result in life-threatening complications including cardiovascular disease, eye disease, neuropathy, nephropathy. Diabetes-associated depression is one such disorder that has been brought into awareness in recent years. Diabetic individuals are at two-fold increased risk of developing depression compared to the general population. Desperate studies have identified some possible mechanism for correlating diabetes-related depression, yet scarcely limited research on diabetes-related depression have been published, and those described are purely observational and cross-sectional trials. The primary purpose of the study was to validate this relationship with the help of exemplary animals such as the model of streptozotocin-induced diabetes. Validation of this model will give a direct correlation between the two diseases. This study used 40 mg/kg of streptozotocin to induce diabetes. Over the study period, body weight, blood glucose level was tracked regularly. Forced Swim Test was used to study depression like behavior. From the findings it has been found that certain diabetic animals exhibited depression like behavior during the later phase of the research. A correlation between diabetes and depression can be made from the observations.

Keywords **:** Diabetes, Diabetes associated depression, Streptozotocin, Forced Swim Test, Prevalence

Introduction

Diabetes mellitus is a chronic disease which upshoot in aloft blood sugar levels due to reduced or no insulin production. International Diabetes Federation in 2017, reports that around 8.8% of the worldwide population suffered from this condition and India accounts for 10.4% of itasserting it to be the second largest country for having such condition (International Diabetes Federation, 2017). Diabetes often referred to as hyperglycemia, if left untreated for a protracted length can often event in life-threatening complications such as cardiovascular disease, eye disease, neuropathy, nephropathyetc (International Diabetes Federation, 2017). One such condition which was bring into being in the late years is diabetes associated depression (Park and Reynold, 2015).Diabetic people have been observed to have twofold increased risk of depressive disorder when compared with general population (Roy and Lloyd, 2013; Twist *et al*., 2013). Diabetes associated depressive peoplealso have 2-5 times higher risk of early mortality relative to those without depression (Twist *et al*., 2013). Desperate studies have come up with some potential mechanism correlating diabetes-related depression as in as increased activity of the HPA axis, innate inflammatory response, and increased rates of HbA1c (Moulton *et al*., 2015; Gonzalez *et al*., 2011; Metteucci and Giampietro, 2015). But barely sparse studies were reported on diabetes associated depression and those noted are merely observational and cross-sectional trial (Chirch *et al*., 2019; McCoy and Theeke, 2019; Farooqi *et al*., 2019; Picozzi *et al*., 2019). These observational studies can only associate a relative risk proportion of diabetes associated with depression or association with causal risk, but direct straight relationships can only be established through experimental models. Very few or so to say no animal models are there by clinical expertise to establish this known reality (Aswar *et al*., 2017; Shivavedi *et al*., 2017). So, to establish this relationship, further animal-based experimental modelsare required. The main intention of our study was to verify this relationship with the aid of animal exemplary such as streptozotocin induced diabetes model. Validation of this model will hand to link the two diseases to the direct relationship. This once validated model will help the researcher to evaluate novel compounds that can cure diabetes and depression simultaneously. The validated model will provide new insight to the researcher to look at the disease and to find out possible mechanistic approach that links the disease to both. It will also aid in improving patient compliance with the treatment by fostering the idea of monotherapy thus targeting the economic burden of patient.

Materials and Method

Materials

Streptozotocin was procured from HiMedia and glucose kit were obtained from Aspen laboratories.

Experimental Groups

The study was approved by NGSM institute of pharmaceutical sciences IAEC (IAEC number-NGSMIPS/IAEC/JULY-2018/106). Fifty Wistar rats of either sex were procured for the study. The animals were housed in the NGSM Institute of Pharmaceutical Sciences (NGSMIPS) animal facility in standard propylene cage and maintained under controlled temperature of 23±1 ºC with controlled humidity and 12 hr. day night cycle. The animals were fed with regular chow diet and water *ad libitum*.

Animals were divided into two groups

I. Disease control group administered with Streptozotocin (STZ) (40mg/kg *i.p.)*

II. Normal control group received normal saline (5ml/kg *p.o.).*

Glucose levels were estimated after 48 hours of STZ injection in disease control group. Animals with blood glucose concentrations above 200 mg/dL were selected for further study.

Body weight and blood glucose levels were tracked every week for both the groups until study period end i.e., 4 weeks. Also, both the test groups were assessed for depressive behavior every week during the course of the study. Forced swim test (FST) was performed to assess the depressive behavior.

Assessment of parameters

Fasting Blood Glucose

Rat were fasted overnight. Blood was collected from tail vein and plasma was separated by centrifugation at 6000 rpm for 10 minutes. Fasting blood glucose was measured using GOD-POD method.

Body weight

Body weight was monitored throughout the experiment on 7th, 14th, 21st and 28th day of the study i.e., every week.

Forced Swim test

Forced swim test was conducted in two sessionsprior to STZ administration with a 24hr period in a 20 cm diameter and 40cm tall plexiglass container with clean water filled to 30 cm level. Animal was allowed to swim for a total of 15min in the first session without recording the immobility time and in the second session which is 24hr after acclimatization period, animals were allowed to swim for 5min during which the immobility time was recorded. Similarly, FST was performed at the end of each week during the entire study period. The animals were dried and kept under a bulb and returned to their respective cage (Castagne *et al*., 2011; Porsolt *et al*., 1977).

Statistical analysis

The data were exhibited as Mean ± SD and the difference between the groups were calculated by unpaired t test using GraphPad Prism 6.0. $P<0.05$ was considered as statistically significant.

Results

Body weight

Body weight of the animals were monitored throughout the study period, at the end of each week for a period of four weeks. There was no significant difference found between the test groups (Fig.1).

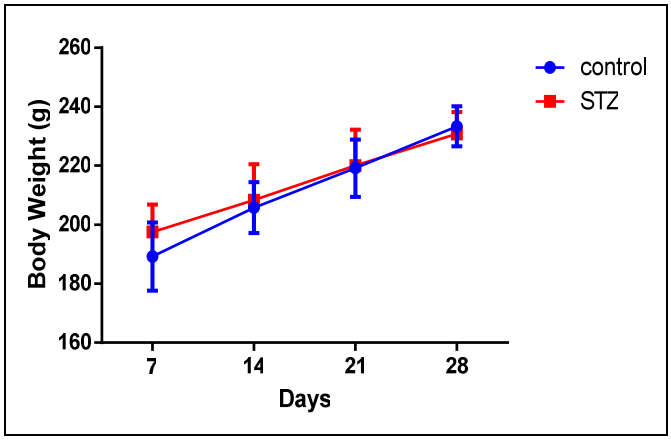

Fig. 1 : Body weight comparison between normal control group and streptozotocin administered group. Body weight was recorded every 7th day for one months.

Glucose levels

Blood glucose levels of normal group and streptozotocin administered group were monitored throughout the study period on 7th day to three consecutive weeks (Fig. 2). Glucose level of disease control was found to be significantly high when compared to normal control.

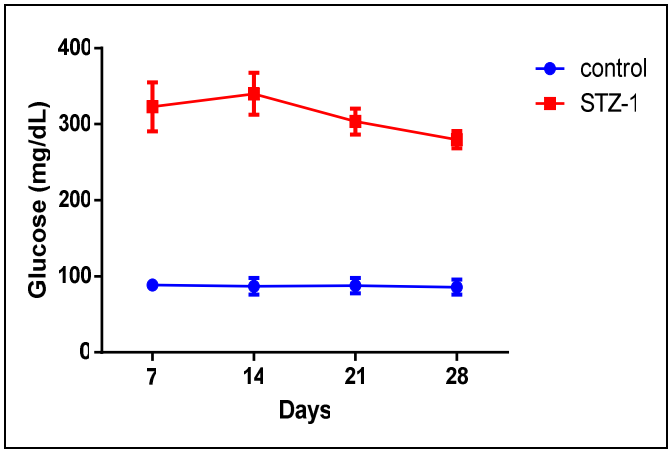

Fig. 2 : Glucose level of normal control and STZ administered animals

Effect of diabetic condition on behavior in diabetic rats

Animals were screened for depression like behavior by Forced Swim Test (FST) on the 7th day of every week for 4 consecutive weeks. Increase in immobility time indicated depressed like behavior in rats (Fig. 3). ten animals in the STZ control group showed increase in immobility time on the 21st day and 28th day. Rest of the animals in STZ group showed similar behavior as that of control group. About 22% of the diabetic animal showed depressive symptoms.

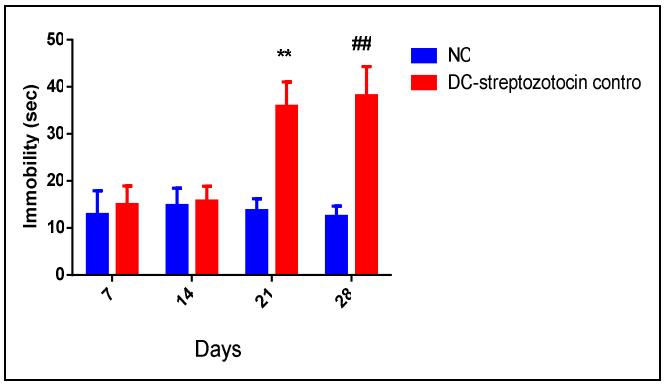

Fig. 3 : Effect of diabetes on behavior. Statistical analysis was performed using unpaired t-test. **p<0.01 compared with normal control.

Discussion

Depression is twice as prevalent in patients with diabetes than in general population (Badescue *et al*., 2016). The preponderance for diabetes associated depression increases as diabetic complications gets elevated (Badescue *et al*., 2016). It may occur due to change in quality of life related to diabetes, increased HPA axis activity, oxidative stress, also may be due to biochemical changes happening due to diabetes (Kyroce and Tsigos, 2016).

Sparse studies were reported on diabetes associated depression and those noted are merely observational and cross-sectional trial trial (Chirch *et al*., 2019; McCoy and Theeke, 2019; Farooqi *et al*., 2019; Picozzi *et al*., 2019). These observational studies can only associate a relative risk proportion of diabetes associated with depression or association with causal risk, but direct straight relationships can only be established through experimental models. So, the main purpose of our study was to establish this factual relationship into reality. Chronic hyperglycemic condition for 30 days in rats clearly displayed depression like effect. .STZ induced diabetes is a common animal model for diabetes, with marked increase in blood glucose levels (Mostafavinia *et al*., 2016). Concordance results were observed in our study where, STZ injection was successfully inducing diabetes. According to the study conducted by40mg/kg STZ has successfully induced hyperglycemic condition in rats and was confirmed by monitoring blood glucose levels every week for four consecutive weeks. Results of this study was evident to prove that chronic hyperglycemic condition showed depression like symptoms (Aswar *et al*., 2017). Analogous kind of results were displayed by our study.

Our results showed that the weight of the animals had not increased significantly during the course of study. This was in concordance with the observation found in another study (Zafar and Naqui, 2010). Depressive behavior in our study was assessed by increased immobility time in FST. Our results showed that animals which have increased immobility time were depressed. Mostly the depressive like symptoms in the disease control group were found in the third and fourth week of the study period. These results were complementary to the results obtained from (Aswar *et al*., 2017). As mentioned, the primary purpose of this study was to validate diabetes associated depression in animal model of rats using STZ model. To the best of our knowledge, this is the one of the rare animal study to establish the direct relationship between diabetes associated depression. However, our study does not focus on the mechanistic correlation between diabetes and depression. Besides there are many hypotheses postulated for the development of depression in diabetic patients which was not taken into consideration in our study. These could be the limitation of our study.

Conclusion

Based on the observation obtained from our study it can be conclude that chromic hyperglycemic condition in rats showed depression like behavior. Alongside, this study paved new pathway and approaches for the researcher to look into new dimensions of diabetes associated depression phenomenon in the near future.

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