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Effect of Voglibose on Circadian Pattern of Blood Glucose and Enzymatic Antioxidants in Normal Rats

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Abstract

Aim of the study was to investigate the effect of voglibose on circadian pattern of blood glucose and enzymatic antioxidants in normal rats**.** Male albino wistar rats were selected, divided into eight groups, each group consist of six animals and subjected for investigation. Voglibose suppressed the postprandial rise of blood glucose in rats, when voglibose (0.3 mg/kg) was given 0.5hr before the administration of carbohydrates such as sucrose, maltose and starch (2 gm/kg each). Blood samples were collected from both the normal and treated animals at o hr, 1hr, 2 hr, 4 hr, 6 hr, and 8 hr respectively. This study showed that the treatment of rats with voglibose significantly suppressed the increase in plasma glucose level after loading with sucrose, maltose and starch at time intervals CT 1400 (8 pm) was significantly lower, against the time CT 2000 (2 am), CT and 0200 (8 am), CT 0800 (2 pm) and circadian pattern of antioxidants in normal rats before and after treatment with voglibose did not show any significant difference at time intervals 0200 CT (8 am), 0800 CT (2 pm), 1400 CT (8 pm), and 2000 CT (2 am).

Keywords: Voglibose • Anti-oxidants • Circadian time (CT)

Introduction

Diabetes mellitus is a group of metabolic disorder characterized by hyperglycemia. It is associated with abnormalities in carbohydrate, fat, and protein metabolism and results in chronic complications including microvascular, macrovascular, and neuropathic disorders [1].

The incidence of diabetes mellitus is rapidly increasing worldwide as well as in developing countries including India, making it a serious health problem. Currently 30 million Indians are affected by diabetes and this figure will be doubled by the year 2025. A reason for rapid increase in the number of diabetic patients worldwide is due to increasing number of ageing population, intake of caloric rich diet, sedentary life style, obesity and physical inactivity [2].

Many functions of the human body alter day by day and these types of variations cause the changes in both in disease state and in normal state [3]. Chronopharmacology involves the study of changes in the pharmacology of drugs with reference to the time of administration [4].

The most important rhythm in chronobiology is the circadian rhythm, a roughly 24-hour cycle, shown by physiological processes in plants and animals. The 24-hour clock is responsible for the release of several harmones which influence specific activities [2].

Antioxidants help to prevent the adverse effects of oxygen and can help capture and neutralize free radicals, which causes damage to the human body [5].

Voglibose inhibits a-glucosidase activity in the small intestine and delays the postprandial absorption of sucrose. Usually, the upper small intestine absorbs sucrose. Voglibose inhibits this sucrose absorption in the upper small intestine; thus, the lower small intestine absorbs sucrose after voglibose administration. Therefore, we would predict that plasma glucose levels would be increased after 6 to 8 hours with voglibose treatment before meals [6].

If the pharmacology and adverse effects of these drugs is CT (Circadian time) dependent, it can be modulated by changing the time of administration of the drugs. Any dependence of these drugs on the circadian time may provide a clue to improve the major drawback of drugs. It was studied here to examine, if any circadian factor in the pharmacological effect of drugs such as voglibose [4].

The present study denotes that oral administration of Voglibose during night-time (CT 1400 (8 pm)) could help to maintain the balance between insulin secretion and glucose utilization throughout the day in normal animals

Materials and Methods

Experiment animals

Wistar albino male rats, weighing 150-200 gm were selected for this study. The animals were obtained from the Teena Bio labs Pvt. Ltd. (Reg, no. 177/99 CPCSEA), Hyderabad, Andhrapradesh. Animals were acclimatized for 12 h L/D cycle in laboratory condition and animals were given access to feed and water ad libitum. Eight groups of 6 animals each were selected. The animals were maintained as per the principles and guidelines of the Institutional Animal Ethical Committee of Vaagdevi College of Pharmacy.

Drugs and chemicals

Voglibose was purchased from ranboxy laboratories, Hyderabad. Glucose Kit M/S Excel diagnostics pvt. Ltd. Hyderabad. Formalin was purchased from local dealers of Finer Reagents, Ahmadabad. Thiobarbituric acid was purchased from local dealers of Himedia chemicals. DPPH (1, 1-diphenyl-2-picrylhydrazyl) were purchased from local dealers of Sigma-Aldrich Company, USA. All other chemicals are of analytical grade and purchased from commercial suppliers.

Experimental design

Albino Wister male rats 7-8 weeks old, weighing 150-200 gm are selected for the study. Grouped into 8 containing 6 animals in each group. Animals are acclimatized for 12 h L/D cycle in laboratory condition and animals were given access to feed and water ad libitum. Eight groups of 6 animals each were

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selected. Group 1, 3, 5, 7 served as a normal control received carbohydrate solution. Group 2, 4, 6, 8 served as a treatment group in which carbohydrate solution and voglibose (0.3 mg/kg) was administered orally [7].

Circadian time selection

It was studied by recording the responses before and after drug treatment at different circadian time such as CT 0200, CT 0800, CT 1400 and CT 2000 Latin square design has been followed to determine the psychopharmacological response [4].

Carbohydrate loading with voglibose and determination of blood glucose in rats

Screening of blood glucose levels after carbohydrate loading (2 g/kg) was performed one week before the experiments and rats showing a blood glucose level of 160 mg/dL or above at 0.5h after sucrose loading was used in the experiments. After overnight fasting, carbohydrates are administered to control groups. Then voglibose (0.3 mg/kg) aqueous solution was given orally to test groups (5-6 rats per group). At 0.5h after voglibose administration, a carbohydrate solution was given orally. The carbohydrates used were sucrose, maltose, and soluble starch (2 g/kg each) [7]. Rats were treated with voglibose (0.3 mg/kg orally), at CT 0200, CT 0800, CT 1400 and CT 2000 respectively [4] (Table 1).

Blood samples were collected by puncture of retro-orbital plexus on at 0, 1, 2, 4, 6 and 8 h and the blood glucose levels were determined by using GOD-POD method [8].

After blood and plasma collection, the pancreas was excised, washed with cold saline, blotted and kept at 30C. Some of the tissue was fixed in 10% formalin, dehydrated in ethanol series (50–100%), cleared in xylene, and embedded in paraffin wax. The pancreas was minced and homogenized for the analysis [9].

Biochemical tests

Thiobarbituric acid reactive substances (TBARS) assay: The reaction of thiobarbituric acid (TBA) with malondialdehyde (MDA), a secondary product of lipid peroxidation has been widely adopted as a sensitive assay method for measurement of lipid peroxidation in biological fluids. Aliquotes of 0.5 ml distilled water and 1 ml 10% TCA were added to a volume of 0.5 ml tissue homogenate, mixed well and centrifuged at 3000 rpm for 10 min. To 0.2 ml supernatant, 0.1 ml thiobarbituric acid (0.375%) was added. The total solution was placed in a water bath at 80°C for 40 min and then cooled at room temperature. The absorbance of clear supernatant was measured at 532 nm using spectrophotometer. Standard graph was plotted using TEP (1, 1, 3, 3-tetra ethoxy propane) [10].

Catalase Activity: Catalase activity was assessed by method of Luck, wherein the breakdown of Hydrogen peroxide is measured. In this 3 ml of H_2O_2 phosphate buffer (0.05 M. pH 7) was added to 0.05 ml of the supernatant of tissue homogenate. The absorbance was measured after 1 minute at 240 nm using UV spectophotometer. The results were expressed in 5 H_2O_2 activity calculated against blank [11].

DPPH (2,2-diphenyl-1-picrylhydrazyl) assay: The free radical scavenging activity of the test drug was measured *in vitro* by 1, 1-diphenyl-2-picrylhydrazyl (DPPH) assay. In this measurement is made from bleaching of purple colouredmethanolic solution of DPPH. To 1 ml of sample, 4ml of 0.004% methanolic solution of DPPH was added and incubated for 30 minutes in dark. Then absorbance recorded at 517 nm. Inhibition of free radical by DPPH in % was calculated in following way:

% Inhibition = (A blank – A sample)/A sample × 100 [12]

Statistical analysis

Results are expressed as Mean ± SD. The statistical analysis of data was done by the one way analysis of variance (ANOVA) followed by the Paired t test. The probability level less than 0.05 were considered as significant.

Results

The antihyperglycemic effects of voglibose after loading with sucrose, maltose, or starch were examined and the results are shown in Table 1. The blood glucose level before loading did not significantly differ among the groups (84.88-109.7 mg/dL). When the voglibose solution was orally administered 0.5 h before carbohydrate loading, the increase in blood glucose was significantly decreased at 2hr, 4hr, 6hr in all four test groups. But here it shows more significant effect during night time 1400 CT (8 pm) when compared with remaining three experimental groups (CT 2000 (2 am) CT and 0200 (8 am) CT 0800 (2 pm).

In antioxidant activity i.e., DPPH, Catalase, TBARS assay were measured in all four experimental groups. That did not show any any detectable rhythm in control and experimental animals (Tables 2 and 3).

Discussion

The present study has investigated the circadian pattern of blood glucose, lipid peroxidation and antioxidants in normal rats before and after treatment

Table 1. Drug administration at different times.

Groups	Morning (8 am)	Afternoon (2 pm)	Night (8 pm)	Mid night (2am)
Control	1.sucrose, maltose, and soluble starch (2 gm/kg each)	3.sucrose, maltose, and soluble starch (2 gm/kg each)	5.sucrose, maltose, and soluble starch (2 gm/kg each)	7.sucrose, maltose, and soluble starch (2 gm/kg each)
Test	2.sucrose, maltose, and soluble starch (2 gm/kg each) + Voglibose(0.3 mg/kg)	4.sucrose, maltose, and soluble starch (2 gm/kg each) + Voglibose(0.3 mg/kg)	6.sucrose, maltose, and soluble starch (2 gm/kg each) + Voglibose(0.3 mg/kg)	8.sucrose, maltose, and soluble starch (2 gm/kg each) + Voglibose(0.3 mg/kg)

Table 2. Values of anti-hyper gycemic effect in different groups of experimental rats expressed as Mean ± SD.

TIME (hr)	Anti Hyperglycemic Activity (Blood Glucose Concentration(mg/dl))					
	0 hr	1 hr	2 hr	4 hr	6 hr	8 hr
Morning(control)	84.88 ± 5.03	111.55 ± 6.71	139.55 ± 3.25	168 ± 3.48	142.22 ± 4.33	129.33 ± 8.80
Morning (test)	94.66 ± 5.82	119.55 ± 3.54	97.33 ± 8.23*	96.44 ± 3.34***	111.11 ± 1.98**	119.55 ± 14.43
Afternoon(control)	97.33 ± 5.59	128.88 ± 1.85	151.11 ± 3.06	184 ± 4.34	150.22 ± 2.49	121.77 ± 9.60
Afternoon (test)	106.22 ± 7.21	127.11 ± 7.06	111.55 ± 10.68*	121.77 ± 4.06**	116.44 ± 3.55**	115.55 ± 1.98
Night (control)	108 ± 7.96	132.88 ± 8.98	161.33 ± 8.98	191.55 ± 9.25	152.44 ± 7.45	125.33 ± 4.64
Night (test)	109.77 ± 3.82	136 ± 3.09	100 ± 5.06**	106.22 ± 5.13***	117.33 ± 5.81**	132 ± 5.14
Midnight (control)	92 ± 6.83	115.11 ± 7.21	145.33 ± 4.98	168 ± 8.15	154.66 ± 5.64	124.44 ± 6.28
Midnight (test)	92.44 ± 5.37	126.66 ± 5.21	123.11 ± 7.74	123.55 ± 6.34*	119.11 ± 3.26**	110.66 ± 6.56

with voglibose. The results obtained were compared with the circadian pattern of control animals. The altered circadian pattern observed in blood glucose of treated animals is probably due to destabilization of the vital equilibrium between insulin secretion and glucose utilization.

Taira M, et al. [6] have shown that Voglibose Administration before the Evening Meal Improves Nocturnal Hypoglycemia in Insulin-Dependent Diabetic Patients with Intensive Insulin Therapy (Figures 1-7).

Table 3. Values of % H_2O_2 scavenging activity, DPPH, MDA Levels of different groups of rats expressed as Mean ± SD.

S.No	Groups	%H_2O_2 scavenging	DPPH Assay	MDA levels (n. moles/mg of tissue)
1.	Control morning (8 am)	25.83 ± 2.79	52.22 ± 23.57	5.55 ± 0.49
2.	Test morning (8 am)	20.26 ± 2.54	50 ± 14.14	4.75 ± 0.21
3.	Control afternoon (2pm)	17.68 ± 0.59	51.11 ± 6.28	6.05 ± 0.63
4.	Test afternoon (2 pm)	16.30 ± 0.50	45.55 ± 4.71	4.95 ± 0.91
5.	Control night (8 pm)	23.50 ± 2.88	52.22 ± 1.57	5.35 ± 1.06
6.	Test night (8 pm)	20.20 ± 2.62	48.88 ± 12.57	6.2 ± 0.42
7.	Control mid night (2 am)	27.51 ± 0.93	36.66 ± 14.14	5.85 ± 0.91
8.	Test mid night (2 am)	26.91 ± 3.47	45.55 ± 10.99	5.75 ± 0.21

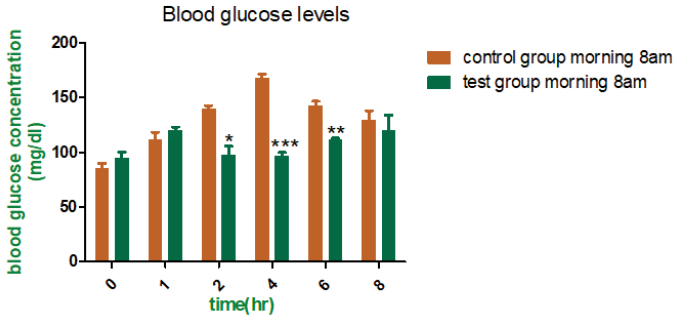

Figure 1. Graph showing anti hyperglycemic effect of voglibose in morning time (8 am).

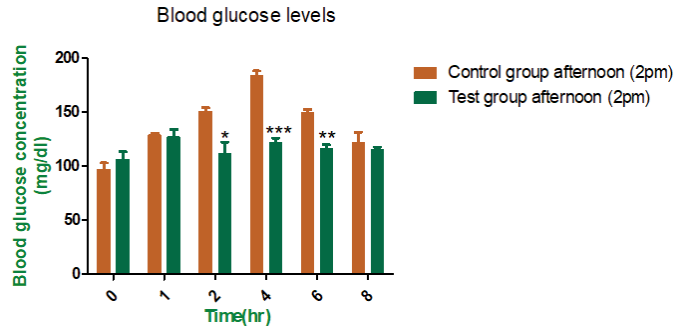

Figure 2. Graph showing anti hyperglycemic effect of voglibose in afternoon (2 pm).

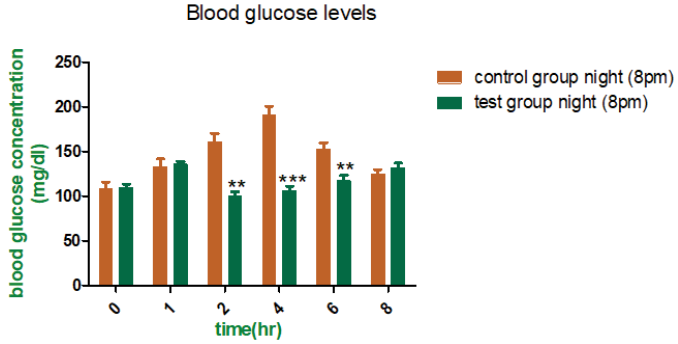

Figure 3. Graph showing anti hyperglycemic effect of voglibose in night time (8 pm).

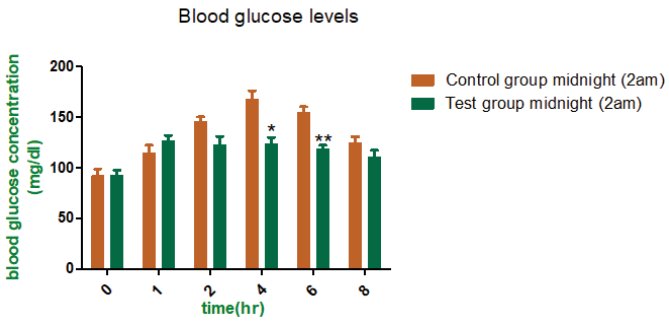

Figure 4. Graph showing anti hyperglycemic effect of voglibose in mid night (2 am).

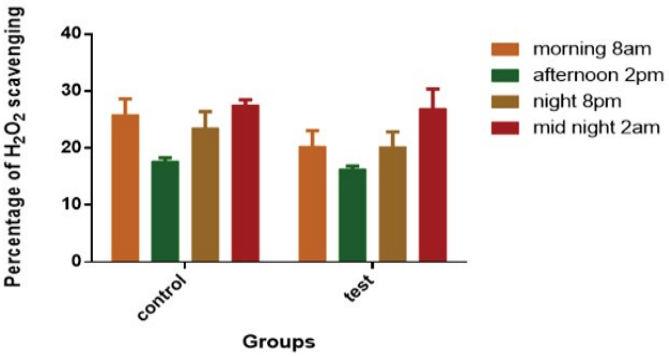

Figure 5. Graph showing percentage of H_2O_2 scavenging activity of different groups of rats.

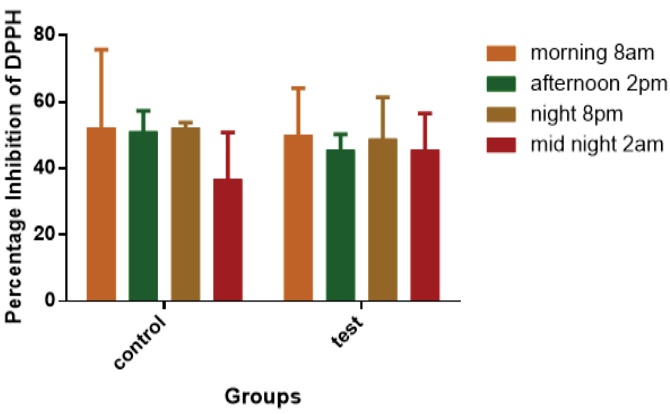

Figure 6. Graph showing the percentage inhibition of DPPH of different groups.

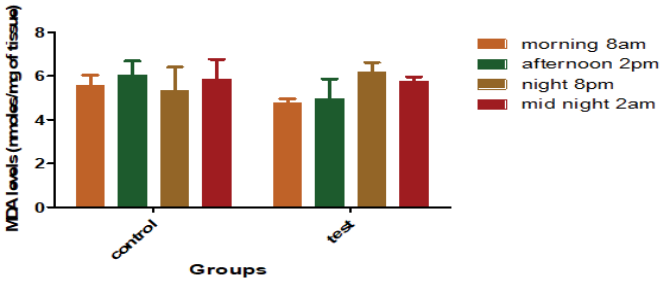

Figure 7. Graph showing the malondialdehyde levels of different groups of rats.

When the voglibose solution was orally administered 0.5 hr before sucrose loading, the increase in blood glucose was significantly decreased at 2 hr and 4 hr with 0.3 mg/kg of voglibose and compared with the control group. This study showed that the treatment of rats with voglibose significantly suppressed the increase in plasma glucose level after loading with sucrose, maltose and starch at time intervals CT 1400 (8 pm) was significantly lower, against the time CT 2000 (2 am) CT and 0200 (8 am) CT 0800 (2 pm).

Anti-oxidant activity

Overproduction of reactive oxygen species and inefficient antioxidant potential has been implicated in the pathogenesis of several diseases including diabetes mellitus. Oxidative stress plays a major role in the progression of diabetes and its complications.

But here the present study has investigated the circadian pattern of lipid peroxidation and antioxidants in normal rats before and after treatment with voglibose did not show any significant difference at time intervals 0200 CT (8 am), 0800 CT (2 pm), 1400 CT (8 pm) and 2000 CT (2 am).

Conclusion

The present study thus concludes that oral administration of Voglibose during night-time could help to maintain the balance between insulin secretion and glucose utilization throughout the day in normal animals. Further studies are however warranted to extend our observations to diabetic subjects could lead to new insights for the diagnosis and management of diabetes mellitus.

Voglibose might be beneficial for the prevention of human diabetes by suppressing intestinal α-glucosidase activities during night time CT 1400 (8 pm).

Conflict of Interest

The author shows no conflict of interest towards this manuscript.

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