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Effect of Deoxynojirimycin on Glycogenesis in Liver of Mice, *Mus norvegicus albinus*

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A B S T R A C T

DNJ was studied for its efficacy in glycogenesis metabolism. Streptozotocin (STZ) is known to induce diabetes. Mice were exposed to different doses (40mg/kg.bw and 60mg/kg.bw) and periods of 30 days of STZ and DNJ. Exposure to STZ resulted in the increase in the blood glucose levels with the corresponding decrease in liver glycogen and increase in glycogen phosphorylase and glucose-6-phosphatase activities indicating an acceleration of glycogenolysis in liver and decreased peripheral utilization of glucose. Mice treated with the combination of STZ and DNJ showed again hyperglycemia which was less in degree when compared to hyperglycemia observed in animals treated only with STZ. However, the hyperglycemia in lower dose of STZ with DNJ was insignificant especially at 30 days of exposure. It is concluded that.DNJ at a dose of 60 mg/Kg/b.w. exhibited anti-hyperglycemic activity at longer period of exposure in mice. The anti-hyperglycemic activity could be attributed to the expression of insulin gene with associated changes in glycogen metabolizing enzymes.

Introduction

Leaves and roots of mulberry plants are having hypoglycemic properties and are used in the treatment of diabetes (Andallu *et al.*, 2002). Mulberry leaf extract acts as a natural inhibitor of α-glucosidase due to Deoxynojirimycin (DNJ) and its derivatives (Katsube *et al.*, 2006). Extractive from leaves of *morus alba* suppressed the post prandial blood glucose and insulin (Nakamura *et al.*, 2009). Mulberry contains a natural product, deoxynojirimycin (DNJ) which is known to inhibit α-glucosidase. Keeping in view of this the efficacy was the efficacy of DNJ was studied in treating Diabetes type II.

Materials and Methods

Male healthy Swiss albino mice, *Mus norvegicus albinus* of five weeks old with an average weight of 25g were obtained from

Tamil Nadu Veterinary and Animal Sciences University, Chennai, India. The mice were allowed to acclimatize for a period of fifteen days. They are maintained at temperature 25º±1º C and relative humidity 50±3%. The animals were kept on 12h D/N conditions and had free access to standard pellet diet and tap water *ad libitum*. The animals were divided in to six groups of five mice each. They were housed in metabolic cages, one in each. A few groups of animals were dosed Streptozotocin (STZ) via intraperitoneal to induce diabetes and few groups were administered orally every day with DNJ using gastric intubation tube at 9 AM for a period of 30 days to the respective groups. The following is the division of groups used for the present investigation. 30 days Treatment: Group A1: Control; Group B1: Normal + DNJ (40 mg/kg b.w.); Group B2: Normal + DNJ (60 mg/kg b.w.); Group C1: Diabetic Control; Group D1: Diabetic + DNJ (40 mg/kg b.w.); Group D2: Diabetic + DNJ (60 mg/kg b.w.). Control mice were received equivalent amounts of distilled water and were treated in the similar ways. After scheduled treatment the mice were sacrificed by decapitation. Blood samples were collected from the aorta and liver and kidney were isolated at 15±1° centigrade. Liver glycogen was estimated by the method of Morales *et al*, (1973), Glycogen phosphorylase was assayed by the method of Leloir *et al*, (1962) and Glucose 6-phosphatase was assayed by the method of Hikaru *et al*, (1959) The data obtained for each parameter were analyzed for their significance according to the methods of Duncan multiple range tests by Duncan (1955). The significance was calculated at 5% level (P<0.05).

Results and Discussion

From the data presented in figure 1 the liver glycogen levels decreased significantly on exposure to STZ. In contrast there was significant increase in glycogen level in mice treated with DNJ at both doses (40 mg/kg b.w. and 60 mg/kg b.w.). From the figure 2 and figure 3 it is observed that corresponding to the decrease in glycogen content the activities of glycogen phosphorylase and glucose-6-phosphotase significantly increased in the mice treated with STZ. The glycogen phosphorylase and glucose-6-phosphotase activities exhibited an increase in the animals exposed to DNJ and in diabetic control with DNJ. But the increase was less in degree compared with the animals treated only with STZ. The increased activities of hepatic phosphorylase and glucose-6-phosphotase showed the enhanced glucogenolysis in the liver of STZ treated mice. Glycogen is normally stored in the liver and muscle and provides the body with readily available source of energy if blood glucose levels decreased. Glycogen is therefore useful for providing a readily available source of glucose for the body.

Whitton and Hems (1975) observed a decrease in liver glycogen in rat perfused with STZ and impairments in glycogen synthesis. Gardner, et.al, (1993) suggested that regulation of glucose-6-phosphatse by insulin plays a role in the suppression of hepatic glucose production during feeding. Clore et.al, (2000) exhibited that glucose-6-phosphatase activity is increased and glcokinase (Gk) activity is decreased, resulting an increase in net glucose release in patients with type II diabetes. Glycogen phosphorylase is a promising treatment strategy for attenuating hyperglycemia in type II diabetes (Baker *et al*, 2005). In our study the increased liver glycogen in DNJ treated mice suggested the condition of hypoglycemia. The lower levels of glucose-6-phosphotase could lead to the decrease in the hydrolysis of glucose-6-phosphate to glucose.

Fig.1 Percentage of increase/decrease over control in glycogen (g/100g wet tissue) in liver of the mice on exposure to different doses of DNJ and STZ at 30 days

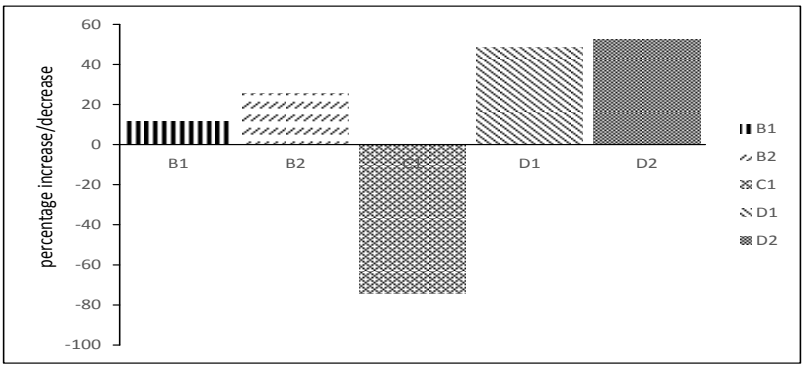


Fig.2 Percentage of increase over control in glycogen phosphorylase (µmoles of Pi n Liberated/h/mg protein) in liver of the mice on exposure to different doses of DNJ and STZ at 30 days

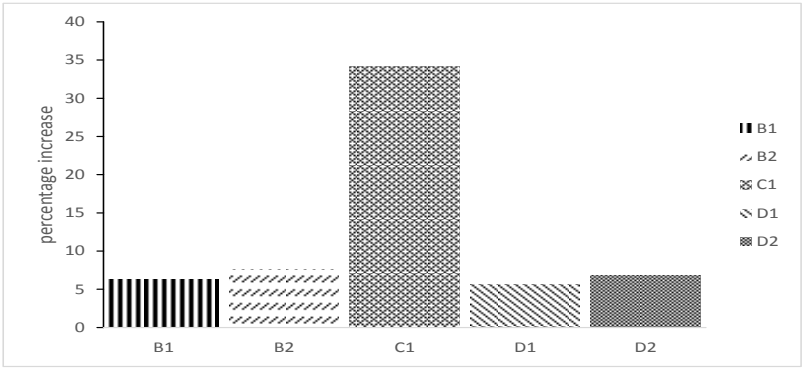
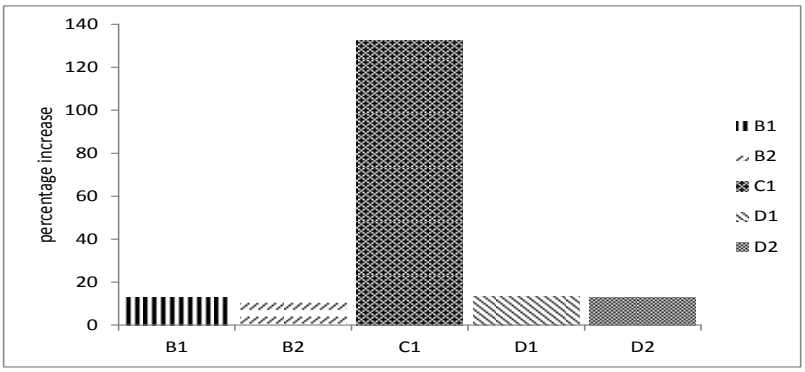


Fig.3 Percentage of increase over control in Gulcose-6-phosphatase (µmoles of Pi formed/mg protein/h) in liver of the mice on exposure to different doses of DNJ and STZ at 30 days



In turn phosphorylase is subjected to allosteric inhibition by glucose-6-phosphate. So that breaking of glycogen is slowed down the concentration which is build up in the liver. In addition glucose-6-phosphate allosterically activates glycogen synthesis. Further glycogen phosphorylase level also decreased which may be another cause for

decreased breakdown of glycogen to glucose. The total system is thus regulated both allosterically by substrates and products and by post translational modification of enzymes in response to DNJ.

Conclusion

It can be concluded that the hyperglycemic effect of STZ on carbohydrate metabolism of mice might be counter acted by DNJ and normalized it. This indicates DNJ alleviation of STZ induced type II diabetic in mice.

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