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Hesperidin, A Natural Polyphenol, Alleviates Hyperglycaemic State and Mitigates Anxiety-Like Behavior in Diabetic Male Wistar Rat

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Abstract: Strong evidence showed that diabetes mellitus induced behavioral deficits in human and animal model. In this work, diabetic males' Wistar rats displayed anxiogenic behavior in elevated plus maze, however, treatment with hesperidin modulates hyperglycemia and anxiety response. Notably, intake of hesperidin seems to be beneficial against diabetes complications related-cognitive disorders.

Key words: Diabetes · Hesperdin · Anxiety · Glycemia · Rat

NTRODUCTION

Diabetes mellitus (DM) is a chronic disorder of glucose metabolism caused by impaired secretion of insulin from pancreatic β-cells, which affects the central and peripheral nervous systems [1]. Globally its incidence is considered to be about 5% of the total population [2]. The chronic hyperglycemia of DM is coupled with eternal damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels [3]. It has been reported that long-term complication of diabetes includes initiation of degenerative processes that cause damage of brain and nerve tissues. Subsequently, it may be associated with cognitive decline and increased risk of dementia [4]. Natural products such as bioflavonoids possess very good antioxidant property [5] and inhibit lipid peroxidation in biological membranes [6]. Hesperidin is a natural bioflavonoid that possesses very good antioxidant property and it has been proved to be very effective in various neurobehavioral diseases [5, 6].

In this work, we attempted to investigate the effect of hesperidin on diabetes induced behavioral deficit in male wistar rat.

MATERIALS AND METHODS

Experimental Protocol: Male Wistar rats obtained from Pasteur Institute (Algiers, Algeria) were housed in transparent cages at a constant temperature (25±2 °C) with a 12 h/12 h light/dark cycle (Lights on at 07:30 a.m.). Rats had access to standard rodents chow and tap water *ad libitum*. Rats were divided into 04 groups each of 07 rats; Control rat (C) received daily Nacl 0.9% at 1ml/kg during 21days. Diabetic rats (DV), Hesperidin group (CHS), rats received hespiridin at dose 50mg/kg daily during 21 days diluted in 1ml/kg of Nacl 0.9%. Group (DHS), diabetic rats received 50mg/kg of hesperidin daily during 21 days. Diabetes was induced by a single intraperitoneal injection of 60 mg/kg streptozotocin, diluted in 0.1 M sodium–citrate buffer (pH 4.5). Control rats received an equivalent amount of sodium–citrate buffer. Streptozotocin-treated rats received 5% of glucose instead of water for 24 h after diabetes induction in order to reduce death due to hypoglycemic shock. After 48 hours of injection (Time to development of diabetes), diabetes was confirmed in rats by measuring urine glucose fasting with the type of test strips BILI-LABSTIX®.

Elevated Plus-Maze Test: The elevated plus-maze (EPM) test is a widely used paradigm to investigate anxiety-related behavior in rats [7]. The EPM was made of painted wood cross (Arms 50 cm long x 10 cm wide) elevated 50 cm above the floor. Two opposite arms were enclosed by walls (10 cm x 50 cm x 45 cm high) and two arms were open. The arms extended from a central platform (10 x 10 cm) [8]. The open arms in the maze that

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we use do not have a railing, but addition of a 3–5 mm high railing on the open arms of the plus maze has been used with success to increase open arm exploration. The rat was placed in the center of the apparatus facing one of the open arms, for a free exploration of 5 min. Entry into an arm was defined as the animal placing all four paws on the arm. After each test, the rat was returned to its home cage and the maze was cleaned with an alcoholic solution followed by wet and dry paper towels, prior to the next trial. Time spent in open and closed arms was measured. The test was done on 23th day of protocol.

Statistical Analysis: All data are presented as mean ± SEM. The comparison between groups was carried out by Minitab using Student test.

RESULTS

Effect on Glycemia: Diabetes increased glycemia significantly ($p<0.001$) comparatively to controls, however, this hyperglycemic state was decreased significantly by hesperidin (Fig. 1).

Effect on the Time of Spent in Closed Arms: Diabetes increased significantly time spent ($p<0.001$) in closed arms comparatively to controls (Fig. 2), however, treatment of hesperidin decreased significantly this state ($p<0.05$).

Effect on the Time of Spent in the Open Arms: Diabetes decreased significantly time spent in open arms comparatively to controls ($p<0.01$), however, hesperidin increase the time of spent in the open arms.

Effect on the Time of Spent in Center: Diabetes decrease significantly ($p<0.001$) time of spent (s) in center comparatively to controls. Treatment with hesperidin increases significantly this state (Fig. 4).

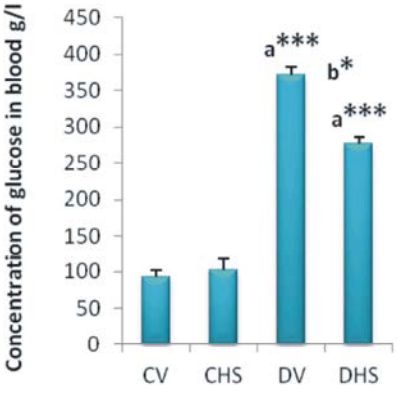

Fig. 1: Concentration of glucose in blood, (n=07* $p<0.05$;** $p<0.01$;*** $p<0.001$)

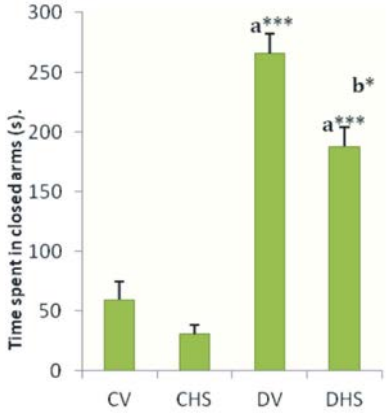

Fig. 2: Time spent in closed arms (s)., (n=07* $p<0.05$; ** $p<0.01$;*** $p<0.001$)

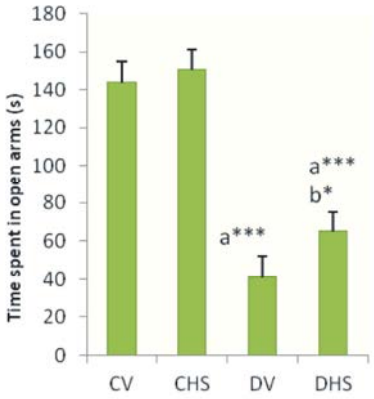

Fig. 3: Time spent in open arms (s)., (n=07* $p<0.05$; ** $p<0.01$;*** $p<0.001$)

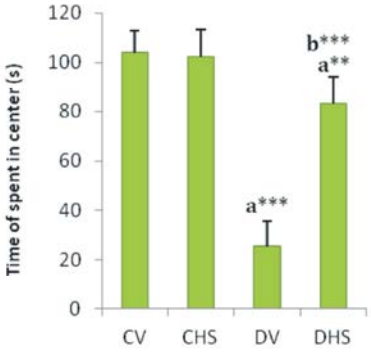

Fig. 4: Time spent in center., (n=07* $p<0.05$; **$p<0.01$;*** $p<0.001$)

DISCUSSION

In diabetic animals, the present data indicated a marked increase in glucose levels as compared to control rats. These results run parallel with the studies of Schalaan *et al*. [9] and Ahmed *et al*. [10]. Administration of STZ caused rapid destruction of pancreatic â-cells in

rats, which led to impaired glucose stimulated insulin release and insulin resistance. Elevation of blood glucose may be attributed to the reduced entry of glucose to peripheral tissues, muscle and adipose tissue [11], increased glycogen breakdown [12] and increased gluconeogenesis and hepatic glucose production [13]. Treatment with hesperdin decease glycemia level in diabetic rats. The decrease in elevated serum glucose levels is in agreement with the results of Jung *et al*. [14]. Several bioflavonoids, ubiquitously present in plants and common components of human diets have been reported to improve hyperglycemia in diabetes mellitus by affecting glucose transport [15, 16], insulin-like properties [17] and insulin-receptor function [18]. Hesperidin, citrus bioflavonoids, exhibit biological and pharmacological properties, such as anti-inflammatory, anticarcinogenic, lipid-lowering and antioxidant activities [19, 20]. In our study, diabetic rats displayed anxiogenic behavior revealed by the decrease of time of spent in open arms. Many studies used this principal change as an indice of anxiety [21, 22]. Impairments in cognitive function have been observed in diabetic patients and also in animal models of diabetes [23, 24]. Treatment with hesperidin was indicated to reduce anxiety-behavior in diabetic rats. Anxiolytic- effect of hesperidin was refferd to it anti-oxydant capacity [25], modulation of brain transmission and HPA activation remain possible.

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