AENSI Journals

Advances in Environmental Biology

ISSN-1995-0756 EISSN-1998-1066

Journal home page: http://www.aensiweb.com/AEB/

Effect of Gallic Acid on Memory and Pain of Male Diabetic Rats

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ARTICLE INFO

Article history:
Received 2 April 2014
Received in revised form
13 May 2014
Accepted 28 June 2014
Available online 23 July 2014

Keywords:
diabetes, Gallic acid, pain, memory, rats

ABSTRACT

Diabetes symptoms may cause by free radicals that cause memory problems and increases the risk of dementia. Diabetics are also at risk for nerve pain. Gallic acid has Anti-oxidant and anti- free radical properties. In this study Gallic acid administration on passive avoidance memory and pain in diabetic rats was investigated. Animal were divided into control group (healthy), diabetic with STZ (60mg/kg), 3 healthy and 3 diabetic groups who received Gallic acid(10, 50 and 100 mg / kg) for two weeks using Gavage method. Blood sugar levels were determined by taking blood from the tail. Findings show a significant memory decrease (delay in coming down the platform) in the diabetic group on all days except day of learning ($P \leq 0.01$). Gallic acid dose of 50 shows significant increase in non-diabetic rats memory in the first day ($P \leq 0.01$), third and seventh days ($P \leq 0.05$) and dose of 10 in the first day ($P \leq 0.05$). Also, there was a significant increase memory in the first day ($P \leq 0.01$), third and seventh days ($P \leq 0.05$) in diabetic groups received dose of 50 and 10 mg / kg Gallic acid. There was a significant decrease in tail pulling away reflex (delay in launching the tail) from the pain epicenter ($P \leq 0.01$) in the diabetic group and the group receiving a Gallic acid dose of 50 a significant increase ($P \leq 0.01$) in the delayed launch tail was observed. According to the findings Gallic acid having strong antioxidant effect may lead to Free radical's sweep and reduced complications of diabetes, including pain and possibly affect on certain regions of the neural pathways in the brain and improve memory in normal and diabetic rats.

To Cite This Article: Ahmad Mehraban, Alireza Ataee, Effect of Gallic Acid on Memory and Pain of Male Diabetic Rats, ***Adv. Environ. Biol., 8(12),*** *368-371, 2014*

INTRODUCTION

Diabetes is a metabolic disorder characterized by hyperglycemia, followed by defects in insulin secretion, resistance to insulin, or both. Long-term diabetes is associated with ocular, renal, cardiac and neural disorders [1]. Streptozotocin (STZ) induced diabetes results in the pancreatic β cell damage, and thus leads to a decrease in insulin and hyperglycemia [2]. Painful diabetic neuropathy is often a challenging complication of diabetes and pain resulting from peripheral neuropathy is one important clinical complaint by mellitus diabetics and it is essential to treat painful neuropathy in patient care [3].on the other hand, diabetes is associated with the central nervous system and peripheral nervous system complications [3]. Memory is one of the fundamental cognitive activities [4]. Impairment of learning and memory is a known complication of diabetes and in animal models of diabetes, such as Streptozotocin induced diabetic rates, spatial memory deficits have also been reported [3]. In previous research, many antioxidants have been found to improve cognitive function in older rates and prevent memory loss and improve learning subsequent to Alzheimer [5]. Currently, the antioxidant effect study has become one of the most important aspects of diabetes research. Poly phenols are a group of chemicals in plants, fruits and vegetables, phenolic acids includes Gallic acid (GA), Caffeic acid, Frolic acid (FA) and Propil gallat (PG) [6]. Gallic acid can be found in beverages, nuts, sumac, tea leaves, crust of oak and strawberry, pineapple, banana, lemon, grapes, apple skin and various other medicinal herbs [7-9].

Gallic acid acts as an antioxidant to protect cells from oxidative damage. Due to its biological activity, Gallic acid has been demonstrated Anti-bacterial, anti-viral, anti-inflammatory and anti-oxidant effects of the inhibition of tyrosinase activity [10]. It also prevents high fat diet-induced dyslipidemia and has shown anti-proliferative, anti-apoptotic and anti-tumor effects in prostate cancer in rats [11]. Consumption of plants containing compounds such as Catechin, Gallic acid and Caffeine could inhibit or reduce the glycation of proteins, such as albumin, to prevent the complications of diabetes [12]. Effect of Gallic acid on the reduction of

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neurological disorders, including Alzheimer's disease, which is associated with dementia and memory loss have been reported [13]. Studies have shown that oxidative stress plays an important role in the appearance of neurological and behavioral changes in diabetes patients, so investigating antioxidants effects in alleviation of diabetic neuropathic pain and cognitive activity deficits is important. Due to these characteristics, we decided to study the effect of Gallic acid on the amount of memory used and pain threshold in animal diabetic rats.

MATERIAL AND METHODS

Test Animals and Classifications:

In this study, eight male Wistar rats, weighing 200-250 g were prepared in animals laboratory of Jondi Shahpoor University Ahvaz at 20 to 22 ° C , humidity of 60-55 , and 12 hours light and darkness cycles and were kept at Izeh Azad University Animals Laboratory with free access to food and water. the animals were randomly divided into 8 groups of 10 each as control (non-diabetic) healthy animals and Gallic acid or streptozotocin (STZ) were not injected to the group; diabetes induced groups with STZ (60mg/kg) [14] that did not receive the Gallic acid and 3 diabetes induced groups as well as 3 non-diabetic rats than received Gallic acid for 3 weeks (10, 50 and 100 mg / kg) by gavage method [15]. During the study period, the animals indefinitely took prepared animal feed by Pars Tehran animal food company and Izeh tap water. This research approach to experimental animals is in accord with international law and, was approved by the university ethics committee.

Blood Glucose Level:

This study uses intraperitoneally administered STZ (60mg/kg) to induce diabetes in rats [14]. After 72 h, blood samples were prepared from rat's tail, glucose test strips and blood glucose measuring device (GM110 sample of Bionimerightest, Khosro Medisa Teb *Company*), were used for determination of blood glucose. Rats with blood glucose greater than 200 mg / dL [16] were considered diabetic. All prescriptions were administrated by gavage method at 10 pm to 11 am. 24 hours after the last administration, blood glucose samples were measured again and the pain and memory tests were performed as listed below.

Gallic acid Preparation:

Gallic acid (obtained from Sigma-Aldrich, United States of America) was dissolved in normal saline and Gallic acid (10, 50 and 100 mg / kg) was administered by gavage for two weeks.

Pain Threshold Evaluation:

In this method the animal was placed in a restrainer, then the animal was placed on Tail Flick instrument, a light beam of 50 °is focused on a point at a distance of 5-7 cm from the animal's tail and the latency time when the animal flicks its tail was recorded. In order to prevent tissue damage in the tail thermal cut-off time was adjusted and controlled over 10 seconds. latency time the animal flicks its tail was recorded three times with two minutes intervals after the blood measured after the administration of Gallic acid was measured and the mean latency was recorded.

Passive Avoidance Memory Assessment Method:

This test is conducted after blood sugar tests at the second stage after two weeks of Gallic acid administration. In this test, Step Down device (on the order of Izeh Biology Lab Constructed by Mr. Mohandes pour in Ahvaz) was used. On the learning day, after measuring blood glucose in diabetic and non-diabetic groups, the rats were placed in a plastic cylinder on a wooden platform, 10 seconds later plastic cylinder was removed, latency time of rate coming down of wooden platform was recorded. Immediately after the animal down from the wooden platform, 0.5 mA electric shock for 3 seconds is applied by the bottom rod to the soles of the feet and hands of animal and then the animal was returned to the cage. The next day (The time interval of 24-hour to remind) the rat was placed on the platform with plastic cylinder, plastic cylinder is removed after 10 seconds and the latency time of rate coming down of wooden platform was recorded (The second day electric shock is not apply). The animal was given a maximum score of 300 seconds, if the rate remained on the platform for 5 minutes during the test. Then, in the third, seventh and fourteenth day, the test was repeated as the second day and latency time of rate coming down and memory recall test was performed. The results was calculated as scores per the recall for each training session, or memory, or both for each rate by the following formula.

L0; Initial latency time of down from platform in the learning day

L1; Initial latency time of down from platform on the memory test day (first, third, seventh and fourteenth days after learning) [17]

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Statistical Methods:

Data are presented as mean standard error of mean ± SEM and were analyzed using one-way analysis of variance followed by LSD test. After obtaining information from the various experimental groups, the results of the above groups were analyzed and the meaningful significance of P< 0.050 was considered. SPSS software was used for data analysis

Results:

Glucose content (blood sugar):

The result of this study showed that oral Gallic acid prescription for two weeks at doses of 10, 50 and 100mg/kg, significantly reduced blood glucose levels at induced diabetic rats (≤ P 0.001) compared to the control group, while in non diabetic rats extracts of Gallic acid did not show any significant effect on blood glucose.

Passive Avoidance Memory:

There was a significant decrease in this part of the memory study in different days show in diabetic group compared to control in coming down the platform in all days except learning day (≤P 0.01), also a comparison between control group and controls receiving Gallic acid for two weeks at doses of 10, 50 100mg/kg showed that the latency in coming down the platform has increased in all days except the day of learning. The increase is significant on the first day (≤ P0.01), third and Seventh (≤ P0.05) on group receiving Gallic acid at doses of 50 and the first of group receiving Gallic acid at doses of 10; Also memory increased in diabetic groups receiving Gallic acid for two weeks at doses of 10, 50 100mg/kg compared to diabetic group without Gallic acid intake and the increase is significant in the first day (≤ P0.01), third and Seventh (≤ P0.05), in diabetic group receiving 50 and 10 mg Gallic acid, however, the increase was not significant in the diabetic group receiving 100 mg Gallic acid.

Pain Threshold Analysis:

Evaluation of pain threshold latency time when the animal flicks its tail off the heat center (≤ P0.01) between control and diabetic groups show a significant decrease in diabetic group pain threshold and only Gallic acid dose of 50 show significant increase (≤ P0.01) in pain threshold in rats. Moreover, in non diabetic rates, none of the doses of Gallic acid was significant in pain threshold.

Discussion and Conclusions:

Pharmaceutical preparations for the treatment of diabetes has many side effects for the patient so in recent decades the use of herbal medicines have increased in the treatment of a variety of diseases, especially diabetes (18). Results of this study showed Gallic acid use leads to a sharp decrease in blood glucose content, increased memory and pain decreased with increased pain threshold in diabetic rats and also caused an increase in the memory of non-diabetic rats. Diabetic patients are at risk of nerve injury that often causes pain in the patient. In some cases, the pain is so severe that do not treat with the usual painkillers improve [3].

Though, the main cause of neuropathy is unknown, researchers believe diabetes impairs NO production and because NO causes dilation of blood vessels and the free passage of oxygen and oxygen deficiency decreases tissue and causes pain. Flavonoids are poly phenols with biological activities such as inhibition of platelet aggregation, accumulation of free radicals, improving NO performance and minimizing lipoproteins with low density in plasma [19]. The role of glycemic control in diabetic neuropathy is unknown, although some studies have shown that neuropathy symptoms may improve by diabetic treatments. other studies affirms the usefulness of some drugs or drug classes including Tricyclic agents, Gabapentin, Capsaicin, Mexiletine, opiates and are antioxidants [3,20].

Whereas diabetes and chronic hyperglycemia, production of reactive oxygen (ROS) which causes oxidative damage increases. Gallic acid has great ability in cleaning ROS, for example, anion superoxide, hydrogen peroxide, hydroxyl radicals, and hypochlorite, and also anti-mutagenic and anti-tumor activity [21,22]. Previous studies have shown that grape seed extract that is abundant in Gallic acid is effective in the treatment of hypo perfusion and various amounts of Gallic acid increase in latency time of coming down from platform in Parkinson's disease in passive avoidance memory [15,17]. Balo et al (2005) showed that memory impairment in an old mouse improved by using grape seed extract (GSE) that is attributed to the antioxidant properties of poly phenols such as Gallic acid [23].

These antioxidant substances in the brain tissue are effective in prevention and treatment of disorders of oxidative damage and possibly Gallic acid as a potent antioxidant is able to improve learning and memory [23]. Valizadeh (2012) revealed that 10-day oral administration of Gallic acid can improve spatial learning and memory deficits induced by injection of Aβ in Alzheimer's disease animals [24]. In addition, it marked that T-antioxidant of this group is due to increase the level of enzymes related to antioxidant system such as glutathione peroxidase and on the other hand these substances viable to produce lipid peroxide oxidation

products such as malondialdehyde [15]. Oxidative damage in cells of the peripheral nervous often causes increased Glial cell and nerve fibers activity leading to the release of pro inflammatory factors, such as cytokines and glutamate that can cause the amplifier sensitivity to painful stimuli and peripheral neuropathic pain [25]. Greg et al show that combined antioxidant treatment reduces pain and improves chronic pancreatitis [26]. in this study, Gallic acid improved memory in diabetic rats as well as non-diabetics that is consistent with the previous studies though, methodology, time span and the sample induced ailment in this research differs from that of previous researches. Gallic acid is excellent free radicals sweeper. Given its anti oxidant effect, plant extracts containing Gallic acid show anti-diabetic effects and reduce the incidence of myocardial infarction and oxidative damage in liver and kidney [27]. In sum, diabetes induction results in impaired passive avoidance memory and reduced pain threshold in rats and treatment with Gallic acid, possibly through reduction of oxidative stress improve memory and pain in diabetic rats and may affect on certain nerve pathways in specific areas influencing memory and learning to improve memory in normal and diabetic rats, as well. This study is of a great value in the field of public health, although animal experiments need to be confirmed in human studies that requires future investigation.

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