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Effect Of Anti Inflammatory On Cognitive Deficits In Diabetic Rats

Eric Gueumekane Bila Lamou[1,3,4], Ghislain Loubano-Voumbi[2], Mor Diaw[1], Salimata Diagne Houndjo[1], Valentin Ouedraogo[1], Abdoul Khadir Sow[1], Abdoulaye Ba[1] Et Abdoulaye Samb[1].

1: Laboratory of physiology and functional exploration (UCAD- Senegal)
2: Laboratory of medical biology (Reference Hospital of Dolisie- Congo)
3: Douala gyneaco obstetric and paediatric hospital
4: Faculty of medicine and pharmaceutical science of Douala University

Abstract
Diabetes is a multifactorial pathology implicating a genetic predisposition and metabolic disorders acquired, which leads to the progressive deterioration of the action of insulin secretion. The international epidemiologic data's concerning the prevalence of diabetes show important disparities between the different countries studied. Whereas, it testifies uniformly from a considerable increase of its frequency in the developing countries. The previsions at the world level estimates that the number of diabetic subjects will leave from 171 million in 2000 to 366 million in 2030. This prevalence is generally underestimated because of hyperglycemia can evoluate in a silent way, during numerous years before the diagnosis is being done. The cost of management diabetes posing an important and increase problem in Public health, long term consequences linked to microangiopathy and macroangiopathy of diabetes constitute invalid pathologies and implicates a heavy management of patients. A couple of epidemiologic arguments, clinical and experimental accumulated in the course of the last 10 years, pleads in favor of a disfavourable effect of the inflammation in a low sound of adipose tissue in the up come of diabetes as well as the neuroinflammation responsible for numerous cognitive disorders notably anxiety and memory disorders. To our knowledge, there exist less data of the literature concerning the action of anti-inflammatory on cognitive disorders. In this context, the objective of our study was to evaluate the effect of acetylsalicylic acid on cognitive deficits in diabetic rat, that which could be one of the interesting therapeutic to explore. At the end of our study we discover that silence inflammation plays a major role in the pathology of diabetes. It will be partly responsible for cognitive disorders in this illness. New therapeutics aiming this inflammation could intervene in the prevention, even the treatment of diabetes and the cognitive disorders.

Keys words*: Diabetes, Inflammation, Acetylsalicylic Acid*

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I. INTRODUCTION

Diabetes is a multifactorial pathology implicating a genetic predisposition and metabolic disorders acquired, which leads to the progressive deterioration of the action of insulin secretion [1]. These abnormalities can be induced or accelerated by environmental factors such as the change of life quality, excess food (rich in glucoses and/or in lipids) and sedentary lifestyle [2]. The world prevalence of diabetes according to WHO in adults of more than 18 years passed from 4,7% in 1980 to 8,5% in 2014. In Senegal, it is estimated at 2% of the Senegalese population according to the Ministry of health and social action in 2012. This pathology increases in parallel with the oldness of populations, the urbanization, the physical inactivity and the development of obesity [2]. The international epidemiologic data's concerning the prevalence of diabetes show important disparities between the different countries studied. Whereas, it testifies uniformly from a considerable increase of its frequency in developing countries. The previsions at the world level estimates that the number of diabetic subjects will leave from 171 million in 2000 to 366 million in 2030 [3]. This prevalence is generally underestimated because hyperglycemia can evolve in a silent way, during numerous years before the diagnosis is being done [4]. The cost of diabetes management posing an important and increase problem in Public health, long term consequences linked to microangiopathy and macroangiopathy of diabetes constitute invalid pathologies and implicates a heavy management of patients. Epidemiologic, clinical and experimental arguments accumulated in recent decades, pleads in favor of a disfavourable effect of low-fat inflammation of adipose tissue in the up come of diabetes as well as the neuroinflammation responsible for numerous cognitive disorders notably anxiety and memory disorders [5]. On the other hand, anti-inflammatory had been used to correct certain complication linked

to diabetes [6]. To our knowledge, there are few data from the literature concerning the action of anti-inflammatory drugs on cognitive disorders.

In this context, the objective of our study is to evaluate the effect of acetylsalicylic acid on cognitive deficits in diabetic rat, that which could be one of the interesting therapeutic to explore.

II. MATERIALS AND METHODS

Animal

Male Wistar rats (n=20), 136 to 220 g of weight at the Laboratory of physiology and functional exploration of Cheikh Anta Diop University of Dakar. The animals were conserving for a week under a temperature of 24°c±3, water and food were available ad libitum. Ethic directives as well as the approbation of the ethic committee of Cheikh Anta Diop University of Dakar were followed and respected. All the tests were during the Day.

Distribution of groups and drug administration

Two groups were formed at the beginning of the experimentation, a control group (CG) (n=6) under saline solution at 0, 9% and a group under alloxan monohydrate 150 mg/kg (AG). After that, the animals rendered diabetic were subdivided in two groups; groups A under acetylsalicylic acid at a dose of 50 mg/kg of weight (AspG) (n=4) and another under saline solution 0, 9% (NclG) (n=4). All the animals under saline solution 0, 9% received a standard volume of 0, 3 ml. The drugs were administered under subcutaneous route

Induction of diabetes and measures of glycaemia

Diabetes had been induced by a single injection of alloxan monohydrate (sigma-Aldrich, St. Louis, United States) at 150 mg/kg of weigh by sous cutaneous route. The values of glycaemia were determined by ACCU-CHEK active lector (Roche Diagnostics GmbH Sandhofer Strasse 116 68305 Mannheim, Germany), from the capillary blood. The rats whose values of glycaemia> 300 mg/dl were considered as diabetic according to Courteix and col (1993).

Behavioral Test

Elevated Plus Maze test

Description of Test

This test enables to evaluate the level animal's anxiety. It's consisting of two opposed branches which are open (50 cm of length 10 cm of large and a thick borders of 1,5 cm) and opposed branches of the same length and width which are said closed, because lined with partitions of a height of 40 cm.

Experimental procedure

The learning phase and experimentation consists of bringing the rat in the room of experimentation 5 minutes before the start of the test to permit the rat to be used in the environment. The duration of the test is 5 mn and begins with the displacement of the rat on the central plat-form, head diriged towards a closed arm. The time spent on each branch is noted. The experimenter does not know the group which the rats belong to. This test developed by Pellow and File (1986) lies on the opposition between the natural behavior exploration of a new environment (which is the dispositive) and the fear of luminous environment which is open (open arms). Thus an anxious rat will spend more time or will enter frequently in close arms than a less anxious rat

T- Maze test

Description

This test, developed by Blodgett and McCutchen (1948), makes it possible to evaluate the alternating behavior of animals. This behavior is defined as the tendency of a rat spontaneously presenting, when confronted with a two-branch (T-shaped) labyrinth, not to return to the branch visited during a first pass, but to visit the other branch. The labyrinth used is composed of a central corridor (34 x 10 x 13cm) which opens on two side branches (20 x 10 x 13 cm). The set is placed on a table and lit evenly by the light of the room.

Experimental procedure

We conducted learning sessions for 3 days using a spontaneous alternation protocol that was conducted at 2 trials per day (one in the morning and the second in the early afternoon). Each test consists of two successive passages: on the first pass, the rat enters one of the two branches of the labyrinth where a food reward has been placed and remains confined for 1 min. The rat is then replaced from the labyrinth, where he can choose to enter one or the other branch. The total number of alternations is recorded to establish a percentage of the total number of trials. The time spent in each arm was determined for a duration of the experiment at 5 minutes

Statistical analysis

Data analysis was performed by the Graph Pad Prism Software (version 5). The numerical results of all tests are expressed as mean ± standard error (SEM). The t-Student test compared the groups of control rats and the group of rats under alloxan, and the unidirectional analysis of variance (ANOVA) on its side was used to compare the groups of diabetic rats. In all cases, P <0.05 was considered statistically significant

III. RESULTS

Time evolution of blood glucose

To verified if alloxan could induce diabetes, we injected this product at a dose of 150 mg/kg of corporal weight by sub cutaneous route in rats of group AG (Alloxan Groups) and 0,3 ml of Saline solution at 0,9% in the rat of the control group (CG)

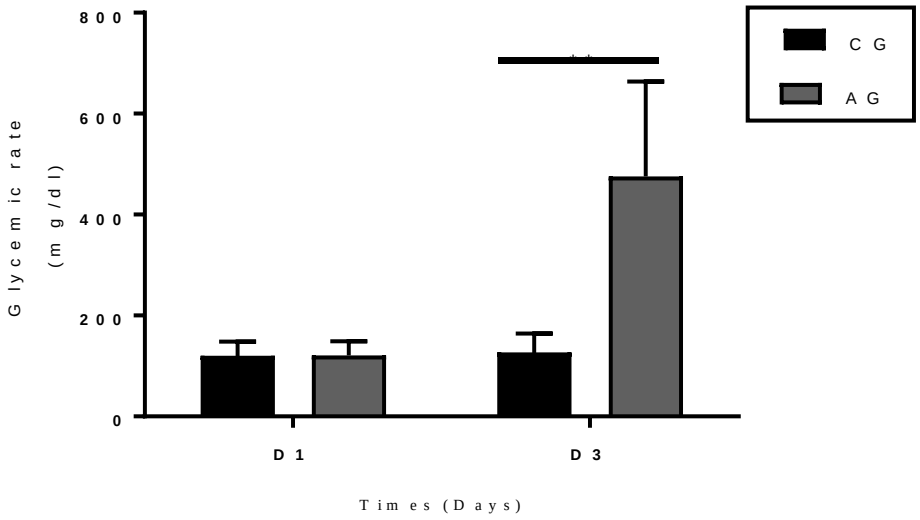

Figure 1: Value of glycaemia

Our results showed after statistical analyses a significant difference between the CG and the AG at D3 with a P=0, 03 (n=6 for the CG and n=14 for the AG)

Effect of acetylsalicylic acid on glycaemia

To determine the effect of acetylsalicylic acid on glycaemia, diabetic rats received a single dose of 50 mg/kg

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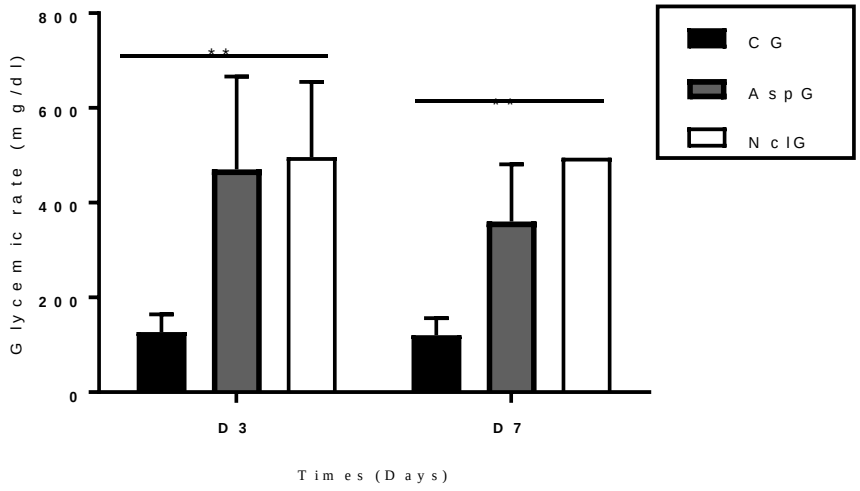

Figure 2: Compares of values of glycaemia of D3 and D7 between the different groups

We have observed a difference statistically significant at D3 between the CG and the AspG with a p=0, 03 and n=6 for the CG and n=4 for the AspG. At D7 equally a difference statistically significant was observed between the same groups with P=0,001, n=6 for the CG and n=4 for the AspG

Temporal Evolution of body weight

In order to follow the state of rats' health we measure their weight at D1, D3, D5, and D7.

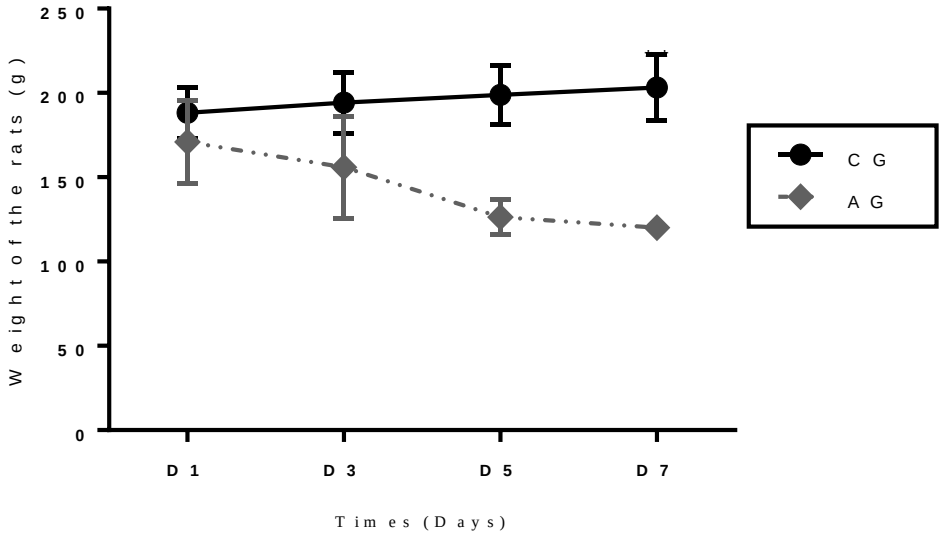

Figure 3: Temporal evolution of body weight

Our results showed a difference statistically significant at D7 between the two groups, P< 0,005, n=6 for the control group and n=14 for the group under alloxan.

Effect of acetylsalicylic acid on body weight

To verify if acetylsalicylic acid could influence the variation of weight in diabetic rats, we injected by sub-cutaneous route this drug at a dose of 50 mg/kg from D3 to D7 in rats of the AspG.

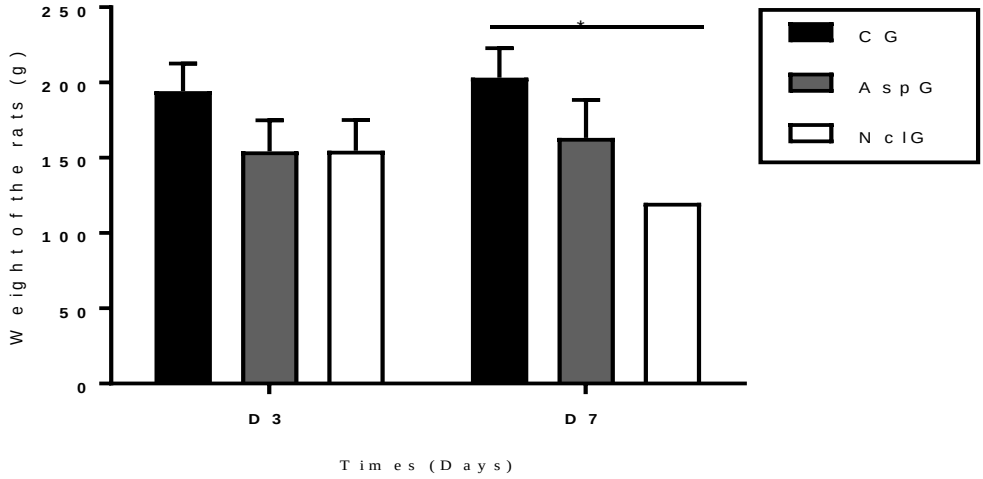

Figure 4: Effect of acetylsalicylic acid on the body weight

Our results showed at D3 no significant statistically difference of the weight between the three groups with a p=0, 6; n=6 for the CG, n=4 for the AspG and n=4 for the NclG group. However a difference statistically significant was noted at D7 between the CG and NclG with a p=0, 01 n=6 for the CG and n=3 for the NclG.

Finally no difference statistically significant between the CG and AspG, p< 0, 1; n=6 for the CG and n=4 for the AspG.

Behavioral study

Elevated plus Maze test

To verify if the acetylsalicylic acid had an effect on anxiety in diabetic rats, we used this behavioral test between the different groups.

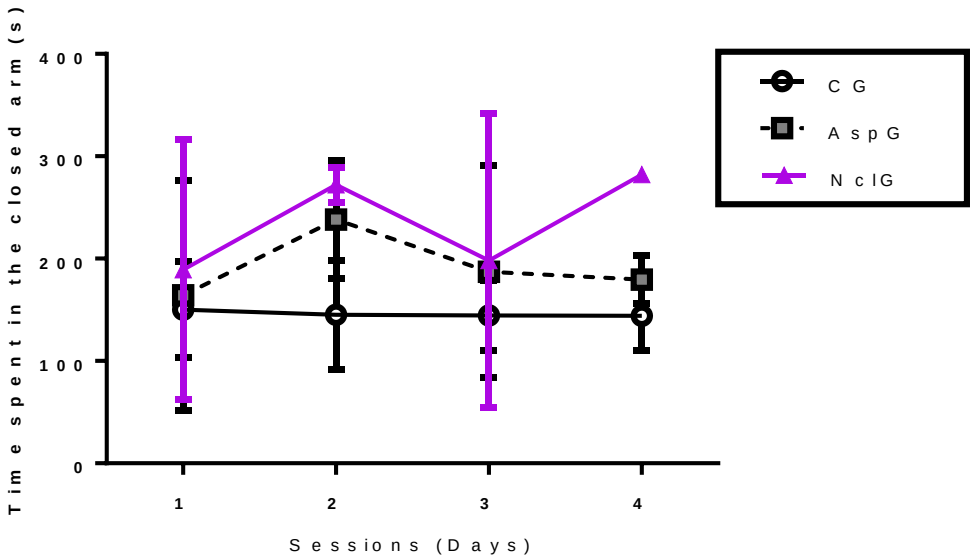

Figure 5: Evaluation of the anxiety by the Elevated Plus Maze test

The time spent in the closed arm is more important in rats of the GNCL group as well as the difference as concerns other group are not significant.

T-Maze test

In order to evaluate a short term memory in rats, we used this test

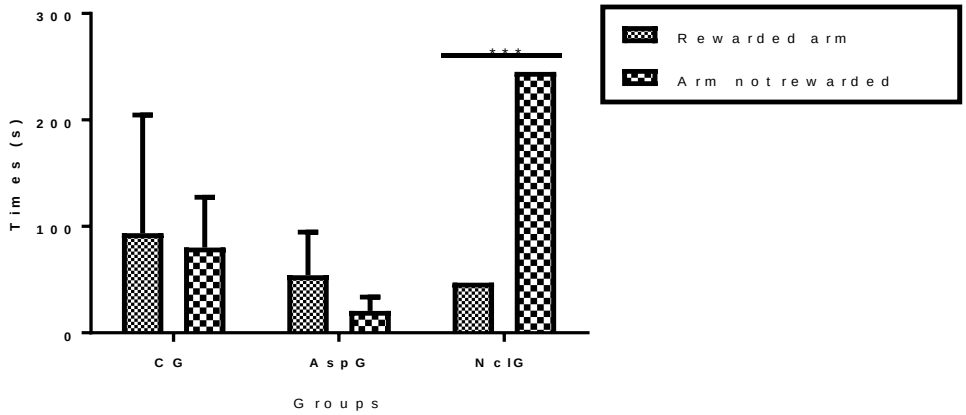

Figure 6: Evaluation of the short-term memory by the T-Maze

Our results show that NclG rats spend more time in the unrecompensed arm with a difference statistically significant p=0,009; n=4.

IV. DISCUSSION

The aim of this work was to investigate the effect of Acetylsalicylic Acid on cognitive deficits in diabetic rats. Thus, we observed hyperglycemia on day 3 after injection of alloxan monohydrate (150 mg / kg). We also noted that Acetylsalicylic Acid has no hypoglycemic effect. In addition, our results showed that Acetylsalicylic Acid has a protective effect on body weight. Finally, we showed that acetylsalicylic acid improves cognitive disorders.

Mechanisms of diabetes induction

Diabetes mellitus develops in response to an alteration of β-cells in pancreatic islets secreting insulin [7]. This deterioration can come from a diabetes mellitus for which the β-cells of the islets are destroyed by the auto-immune system or as a diabetic response secondary to other essential diseases such as pancreatic disease, to excess hormones. Anti-insulin, drug-induced conditions, or genetic abnormalities other than those associated with perceived diabetes [8]. In our study, we induced diabetes by injecting a single dose of 150 mg / kg of subcutaneous alloxan monohydrate. In fact, alloxan monohydrate could induce lesions in the pancreas and thus destroy beta cells of Langerhans Islands [9]. Although in this study, we did not verify this hypothesis, however we note that our results are in agreement with those of the literature [10]. It should also be noted that the subcutaneous route to inject the alloxan monohydrate used in our work, would be better compared to other routes including the intraperitoneal route. Indeed, compared to the work of Cortright et al. 2008 [11] and Coronado et al. 2011 [12], we observed a good state of health of animals materialized by a weight loss only from the 7th day. These results suggest that Alloxan monohydrate would be less toxic by the subcutaneous route.

Influence of acetylsalicylic acid on the weight

Most animal models of diabetes have shown a decrease in animal body weight [13]. This decrease in body weight is due to an alteration of the health status of the animals. Indeed, after the release of ROS in the pancreas, glucose causes intoxication of cells causing dysuria [14]. Our results are in agreement with those of the literature [13]. However, we noted that the anti-inflammatory treatment improves the weight of the animals, which would be in our opinion, a first on the action of anti-inflammatory on certain anthropometric parameters

Acetylsalicylic acid and regulation of glycaemia

Salicylates are among the most commonly used nonsteroidal anti-inflammatory drugs. The benefit of salicylates in the treatment of diabetes has long been recognized and numerous pharmacological studies in vitro and in vivo have demonstrated a beneficial effect of salicylates on glycemic control [15]. In this study, we noted that the administration of acetylsalicylic acid at a dose of 0.5 g per day in the rat resulted in an improvement in blood glucose. Indeed, it is accepted that diabetes is accompanied by an inflammatory state and particularly that of the pancreas [16]. These results confirm previous studies on the effect of nonsteroidal anti-inflammatory drugs on diabetic disease [17]

Impact of acetylsalicylic acid on psychiatric disorders in diabetic illness

Emotional symptoms, including depression, anxiety and stress, are very common in people with diabetes [18]. Studies report the prevalence of anxiety disorders are also higher in diabetic patients than in the general population, especially among women and low-income individuals [19]. Although the current hypothesis of the occurrence of diabetes is of psychogenic origin, other factors could intervene. In our study, we noted the presence of anxiety disorders in rats made diabetic with alloxan monohydrate. Our results confirm those of the literature. However, this study does not provide any physiopathological explanation for the appearance of disorders in animals. We can agree with the literature that emotional origin may be partly the cause. In addition, although much less known about the correlates of anxiety symptoms, people with diabetes and anxiety often have poor glycemic control, making it a major assumption [20]. In this study, our rats were subjected to a state of hyperglycemia without treatment; this could partly explain the appearance of these psychiatric disorders.

In contrast, treatment with acetylsalicylic acid leads to an improvement in anxiety disorders. Our data further suggest that Acetylsalicylic Acid is an adjuvant therapeutic solution in the prevention of psychiatric disorders.

Impact of acetylsalicylic acid on a short term memory in the course of diabetes

Poorly controlled diabetes is known to affect the brain resulting in memory and learning problems and even an increased incidence of dementia [21]. Numerous studies have shown that hyperglycemia causes hypertrophy of the hippocampus, which is responsible for the disorders observed [22]. In our study, we noted memory problems in diabetic rats that were in saline. However, the animals under Acetylsalicylic Acid did not have memory problems. Our data suggest that the anti-inflammatory drug could prevent memory problems in diabetic subjects. It should be remembered that in this study, we did not attempt to understand the mechanism by

which Acetylsalicylic Acid exerts its neuroprotective effect on memory disorders, nevertheless we can suggest that by its mechanism of action, the Acetylsalicylic acid could inhibit the pathway of inflammation of cyclooxygenase 2 and prevent hypertrophy of the hippocampus [23]

V. Conclusion

Silent inflammation plays a major role in the pathogenesis of diabetes. She would be partly responsible for the cognitive disorders in this disease. New therapies targeting this inflammation could intervene in the prevention, or even the treatment, of diabetes and these cognitive disorders. Hence the interest of this study which showed us that Acetylsalicylic Acid could improve certain complications and cognitive disorders related to diabetes including anxiety and short-term memory. This study could open new avenues of research on the mechanisms of action of acetylsalicylic acid in the prevention of anxiety disorders and memory.

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