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STUDY OF SPHINGOSINE KINASE (SPHK) SIGNALLING ASSOCIATED WITH DIABETES-INDUCED COGNITIVE DECLINE IN WISTAR RATS.

BY

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Abstract

Background and objective: *Recent research suggests that sphingolipid metabolism is altered in diabetes and that an increase in ceramide levels, linked to insulin resistance, may cause cognitive impairment.The aim of this study was to determine whether sphingosine kinases (Sphks) could be used as a signalling pathway leading to cognitive impairment in diabetic rats.*

Material and methods*: The study involved 24 Wistar rats, classified as normal, untreated diabetic and treated with D-erythrodihydrosphingosine, fed glucose and food to prevent hypoglycaemia, and subjected to the behavioural test including the 8-arm radial maze. RT-PCR was then used to assess the expression of sphingosine kinases (Sphks).*

Results: *The study analysed the effects of diabetes on the weight and cognitive abilities of the rats. The results showed a significant weight loss in diabetic rats from 7 days onwards, with memory deficits and a reduction in spatial learning in a radial maze. The study also showed a significant reduction in the expression of SPK1 and SPK2 messenger RNAs in diabetic rats, suggesting inhibition of their expression due to diabetes.*

Conclusion*: Diabetes adversely affects body weight and cognitive function in rats, leading to weight loss and memory impairment. Expression of the SPK1 and SPK2 enzymes suggests a link between hyperglycaemia and enzyme expression, requiring future studies to modulate these enzymes and explore more effective therapeutic interventions for better management of diabetic patients.*

Key words*: Cognitive impairment, diabetes, rats, sphingosine kinases.*

I. INTRODUCTION

Diabetes mellitus is a growing global public health problem that is expected to affect approximately 600 million people by 2040[1]. In the Congo, the survey conducted in 2004 had reported a prevalence of 7.6% among the male population aged between 25 and 64 years [2]. With specific regard to type 2 diabetes (T2DM), this increase is linked to lifestyle changes, particularly in terms of diet, overweight and sedentary lifestyle. [3]Increased life expectancy and ageing populations worldwide are also major factors contributing to

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the T2D epidemic, a phenomenon that is particularly marked in low- and middle-income countries [1]. These trends are expected to continue in the coming years. Similar demographic trends are also observed in cognitive decline [4]. As a result, the coexistence of diabetes and cognitive impairment is increasing. It is clear that diabetes and cognitive decline do not occur randomly, but are often linked. Epidemiological studies have shown that people with diabetes are at increased risk of developing cognitive impairment. [5] Furthermore, diabetes is associated with less severe cognitive impairment. [6] These observations are of great importance in the management of patients, particularly the elderly, who are the most likely to suffer from cognitive problems, at both the dementia and pre-dementia stages, for example.

At present, diabetes treatment focuses mainly on common complications such as diabetic retinopathy, peripheral neuropathy, nephropathy and cardiovascular disease. Nevertheless, several research studies have shown that untreated chronic diabetes in patients produces interneuronal amyloid plaques in the brain, leading to neuropathological symptoms such as Alzheimer's disease (AD) [7]. Other data from diabetic patients also indicate that insulin resistance in type 2 diabetes can cause cognitive problems [7]. Evidence suggests that effective treatment of chronic diabetes does not completely cure cognitive impairment [5, 7], suggesting that the precise mechanisms associated with it are not yet fully understood. According to recent studies, most neurodegenerative diseases, whether acute or chronic, are accompanied by alterations in sphingolipid composition in various cell types of the central or peripheral nervous system (CNS or PNS). This is not surprising since sphingolipids are important cell signalling molecules in cell membranes and are sensitive to enzymatic hydrolysis. Indeed, sphingosine kinases (Sphk1 and Sphk2), which are sphingolipids (SLs), are a class of structural membrane components and bioactive mediators all containing a sphingoid base as a building block. SLs are responsible for regulating numerous cellular processes such as cell survival and apoptosis, differentiation, migration and immune responses [8; 9]. SL levels in cellular compartments and circulation are strictly controlled by a complex system of enzymes. Consequently, alterations in SL metabolism play a crucial role in the pathogenesis of many diseases [10], for example cancer [11], neurological diseases [12], metabolic diseases such as diabetes [13] and cardiovascular diseases, as well as viral [14] and bacterial infections [15]. Hence the interest of this study, which aims to verify whether sphingosine kinases (Sphks) can be used as a signalling pathway leading to cognitive dysfunction in rats with diabetes.

2. MATERIALS AND METHODS

2.1. Animals and treatments

Our study was carried out in the laboratory of the Marien Ngouabi Faculty of Health Sciences, in the experimental neuropathology unit. Male Wistar rats aged between seven (07) and ten (10) weeks from the Faculty of Health Sciences animal house were purchased and used. They were housed in polystyrene cages and maintained under optimal temperature and humidity conditions (21 ± 1◦C and 55 ± 2% humidity) under a 12 h light/dark cycle and free access to food and water. Animals were acclimatized to laboratory conditions for 2 weeks prior to the start of the experiment. The study was conducted in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health.

The animals were divided into three (03) groups of 08 rats each, and treated as follows:

- Group 1 received distilled water and served as a control group (**GT**);

- Group 2: diabetic rats given distilled water (**DTN**);

- Group 3: diabetic rats treated with D-erythro-dihydrosphingosine: SPK1 and SPK2 inhibitor (DEDHS). (**DTT**)

The products (distilled water and DEDHS) were administered orally for 28 days.

2.2. Diabetes induction and blood glucose measurement

Diabetes was induced by a single intraperitoneal administration of alloxane monohydrate at a dose of 150 mg/kg body weight. Animals were placed in individual cages, with free access to food and 5% glucose solution, to avoid hypoglycemic shock. Three days after alloxane monohydrate administration, diabetes was confirmed by measuring blood glucose levels using a glucometer (*On Call Plus II*). A drop of blood obtained through a small incision at the tip of the tail was used to measure blood glucose levels on days 1, 7, 14, 21 and 28. Only rats with blood glucose levels above 180 mg/dl were selected for the experiment.

- **Weight evolution:**

Selected rats were weighed on an electronic scale from day one before the onset of diabetes (start of manipulation) and then throughout the days (7, 14, 21 and 28).

2.3. Evaluation of cognitive deficit

Two behavioral tests were set up to assess the decline in cognitive ability:

- **Object recognition test**

This test is based on the rodents' attachment to exploring objects, particularly an unfamiliar one. It assesses short-term memory capacity. It is based on rodents' natural exploration behavior. The test is performed in three different stages: introduction to the context (familiarization), acquisition and regular recall. After familiarization with the arena, rats are treated and placed in the arena in the presence of two similar objects (training phase). Each object is recorded in terms of the time spent exploring it. During the test phase, the animals face one known object (discovered during the training phase) and one unknown object.

- Familiarization stage

The animal was first introduced to the device without an object and allowed to explore the environment for 10 minutes. This step reduced the anxiety-provoking aspect of the

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environment. The rat was then locked in its cage for 15 minutes.

- Acquisition stage

In the second phase, two identical objects were presented to the animal. Rats were positioned on opposite sides of the object in the apparatus and left to explore two identical objects for a period of 10 minutes.

- Recall stage

After 24 hours, one of the two objects was replaced by a second. The animal was introduced into the device and allowed to observe both objects, the familiar one and the new one, for 10 minutes. The type of object and its position (right or left) were randomly alternated for each animal. The time invested in exploring the new object was evaluated as a percentage of the total time spent exploring the two objects. Time spent touching, sniffing or being very close to the object was considered as exploration. We then distinguished between the time allocated to the familiar object (TF) and the time allocated to the new object (TN).

Radial arm maze

According to Olton and Samuelson (1976), the concept of the eight (8)-arm maze is widely used to assess memory and spatial information management abilities in different species of animals. The maze consists ~~of~~ a center from which eight branches emerge, arranged like the spokes of a wheel. A food pellet (45 mg) was placed at the end of each branch and was not replaced during the test, allowing for a maximum of 8 rewards. Firstly, with the diet, the body weight of these animals was reduced to 85% of its initial values, and this weight was maintained throughout the study. In the center of the platform, the animals were arranged facing the same branch for each trial and for each rat (the maze branches were numbered from 1 to 8). The animal continued to get lost in the maze until it encountered eight branches (four legs had to reach the entrance edge). Errors made during branch visits were recorded in chronological order. The different groups of animals were tested after each week, with an interval period of seven (07) days.

2.4. Collection of behavioral test parameters

Each stage of the behavioral tests was recorded using a camera in order to make better use of the various parameters used as variables in each test.

2.4.1. Rat sacrifice and seahorse sampling

Once treatment had been completed after 28 days, rats in three (03) groups were euthanized by cervical dislocation, then decapitated. Once the brains had been removed from the skull, the brain structure, in particular the hippocampus, was rapidly harvested and cleaned with phosphate-buffered saline. These samples were then stored in sterile vials and immediately frozen at -80°C for use in molecular analysis.

2.5. Molecular analysis of the sphingosine 1 phosphate (S1P) signaling gene

2.5.1. DNA extraction from rat hippocampal tissue

DNA was extracted using the “ReliaPrepTM gDNA Tissue (Promega)” kit, in accordance with the manufacturer's instructions. The amount of DNA in each sample was assessed using Qubit 3.0 fluorescence technology (Qubit® 3.0 Fluorometer, Life Technology). This assay enabled us to evaluate the amount of DNA in ng/µL.

2.5.2. Amplification by RT-PCR.

Extracted DNA underwent PCR using the Fast-track diagnostics kit.

Mode opératoire :

Step 1: Preparing the Mix

Ingrédients	Volume for one sample
Buffer (Tampon)	12,5 µl
Ppmix (SONDE)	1,5 µl
Enzyme	1 µl
Amorce sens	0,5 µl
Amorce antisens	0,5 µl
ADN	9 µl

The sequences of **sphingosine 1 phosphate (S1P)** and β2-microglobulin (eurofins®, France) primers used are listed in Table I.

Table I: Sequence of primers used

Target	Forward Sequence 5’—3’	Reverse Sequence 5’—3’	T° de fusion
SPHK1	GGTTCCTCCAGTTGGTGAGG	TTTTGCTCAACTTCGCCACG	59.96 °C
SPHK2	GAGTATTACAAGACAGGCCAGC	CACGTGCATGGTTTTGTCGT	58.80 °C
B2-µGLOBINE	TCGCAACCTCAGGAACAGAC	CAGGAAAGGGGGCTTAGTGG	60 °C

Second step: **Mic (thermocycler) programming**

Step	Times	Temperature
Initial denaturation		3 min
Denaturation 94 ° C		30 secondes
Hybridization 94 ° C		8 secondes
Final Extension 60°C		34 secondes
cycles number		40

Step 3**: Expression of sphingosine 1 phosphate (S1P) signaling gene**

We evaluated this expression using Livak's method with the formula

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Rq = 2^-(ΔΔCt). A positive value of relative quantification (Rq) corresponds to overexpression and a negative value to underexpression. S1P expression in each sample was performed in duplicate and the level normalized to β2-microglobulin.

2.6. Statistical analysis

The mean of the data was expressed ± SD. Comparison between two groups was performed using Student's t-tests. Results were examined using ANOVA for multiple comparisons. Figures and graphs were created using GraphPad Prism 5 software. A value of P <0.05 was considered statistically significant.

III. RESULTS

III. 1. Body weight of Wistar rats

Rats in different groups were weighed from D 1 to D 28. Group 1 (GT) included normal rats and group 2 included diabetic rats without sphingosine kinase 1 and 2 inhibitors. Group 3 (DTT) included diabetic rats with sphingosine kinase 1 and 2 inhibitors. Statistical analysis using the Kruskal-Wallis test showed a significant weight reduction from day 7 onwards. (P =0.027, for each group, n =8). These results support the hypothesis that hyperglycemia reduces body weight.

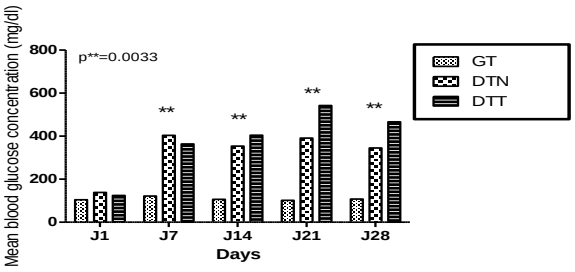


Figure 1: Average blood glucose levels in the three different groups of Wistar rats.

III. 2. Glycaemic profile

In rats, alloxan monohydrate at 150 mg/kg was administered to group 2 (DTN) and group 3 (DTT) rats which were complemented with an inhibitor of SPK 1 and 2. Rats in the first group (GT) were normal, while rats in the second group (DTN) were diabetic without a sphingosine kinase 1 and 2 inhibitor. The group of diabetic rats with a sphingosine kinase 1 and 2 inhibitor is called DTT. Statistical comparison revealed a significant difference between groups 1 and groups 2 and 3 at D7 (P=0.0033, n=8 per group). The results indicate that rats in groups 2 and 3 have diabetes.

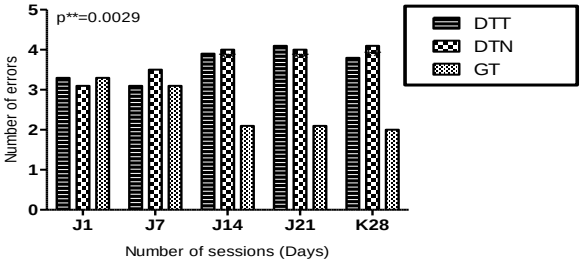


Figure 2: Radial arm maze task: Spatial learning Average number of errors for each session.

III. 3. Behavioural analysis

- **Radial arm maze**

In order to determine whether diabetes had an impact on cognitive abilities, spatial learning was measured in an 8-arm radial maze. The animals were subjected to a working memory test in which, at each session, they had to explore all eight arms of the radial maze. Returning to a previously visited arm was considered an error. In addition to the errors made, the number of correct visits to the arms in the first eight choices was also recorded. There was a significant difference between the group of normal rats and the group of diabetic rats, depending on whether or not they had received a supplemental Sphingosine phosphate kinase 1 and 2 inhibitor (p=0.0029; n=8 per group). These data clearly show that diabetes affects working memory and that the Sphingosine kinase 1 and 2 inhibitor does not improve working memory in diabetic rats.

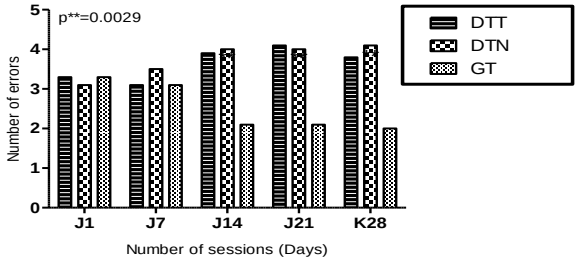
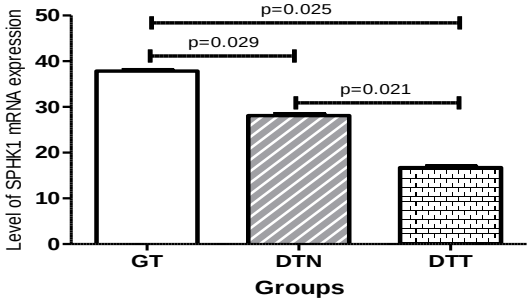


Figure 3: Radial arm maze task: Spatial learning Average number of errors for each session.

Group 1 of normal rats (GT) is compared with group 2 (DTN) of diabetic rats without sphingosine kinase inhibitor 1 and 2, and group 3 (DTT) of diabetic rats with sphingosine kinase inhibitor 1 and 2 in a radial arm maze task. The mean number of errors was considered for each session.

III. 4. SPK1 and SPK2 mRNA expression

We also assessed SPK1 and SPK2 mRNA expression levels in rats from three groups. After statistical analysis, our data showed significant differences between rats in groups 1, 2 and 3 (p*=0.025 in Figure 4A). Furthermore, we observed a decrease in SPK2 expression in diabetic rats, with a significant difference between group 2 and group 3 rats (p*=0.031, Figure 4 B). These results suggest that diabetes inhibits SPK1 and SPK2 expression.



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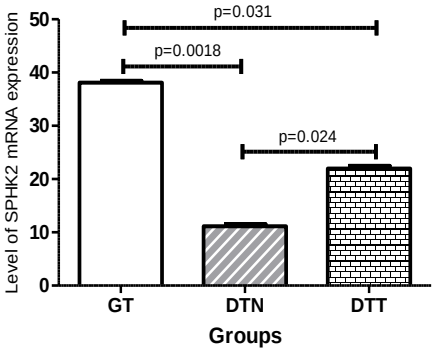

Figure 4: SPk1 and SPK2 mRNA expression levels in the hippocampus of wistar rats.

GT: control rats; GTN: untreated diabetic rats; DTT: diabetic rats treated with D-Erythro-dihydrosphingosine (DEDHS).

VI. DISCUSSION

Bioactive lipid molecules, such as sphingolipids, are lipid chain molecules that form part of the cellular lipid membrane and are naturally present in the human body and perform crucial functions in cell membranes as well as in signalling inside and outside cells. [16] These molecules include sphingosine and sphingosine-1-phosphate (S1P), which play an important role in various processes including proliferation, differentiation and apoptosis [13]. Sphingosine can be converted to S1P by two enzymes, sphingosine kinase 1 (SPHK1) and sphingosine kinase 2 (SPHK2). Previous studies have shown that the balance of sphingolipid signalling is essential for maintaining body homeostasis. [18, 19] With this in mind, changes in SL metabolism may influence the cause of numerous diseases, such as cancer, neurological diseases, metabolic diseases such as diabetes, cardiovascular diseases, as well as viral and bacterial infections [15]. The aim of this study is to verify whether sphingosine kinases (Sphks) can be used as a signalling pathway during cognitive decline caused by alloxanic diabetes in rats.

V. 1. Link between diabetes and cognitive dysfunction

When alloxan monohydrate was administered at 150 mg/kg to rats, we observed a decrease in body weight (Figure 1). This was followed by an increase in blood glucose levels (Figure 2). In addition, we used the eight-branch radial maze behavioural test to assess memory and learning capacity (Figure 3). These results showed, on the one hand, the induction of diabetes and are in agreement with those of other researchers regarding the period of development of hyperglycaemia [20, 21] and on the other hand, memory dysfunction. [22, 23] These authors have shown that the reduced performance of rats in memory and spatial learning tasks is due to an alteration in synaptic connections [24] as a result of a reduction in neuronal plasticity [22, 24].

Previous studies have shown a link between poorly controlled hyperglycaemia and memory. [25, 26] According to Medjdoub (2013) [27], chronic hyperglycaemia is associated with insulin resistance (IR), which also affects certain parts of the brain. This causes a decrease in autophosphorylation of the receptor for this hormone and activates the expression of protein kinase C, a protein that dephosphorylates the insulin receptor. According to **Craft** (2009) [28], insulin receptors (IR) have been identified in the hippocampus and medial temporal cortex, which partly explains the memory problems. Problems with LTP (long-term potentiation) and spatial memory have been observed in mice with reduced IR expression in the hippocampus [29] (Grillo et al., 2015).

In our research, we observed reduced working memory in diabetic rats and problems with exploratory behaviour during spatial learning (p=0.0029; n=8 per group, Figure 3) due to the number of errors made during open-arm entry visits observed in the eight (08) branch radial maze test. It has been shown that type 1 diabetes is often linked to a reduction in reasoning speed and mental flexibility [30] (Brands et al., 2005), and that type 2 diabetes also has an impact on learning and memory [31] (Awad et al., 2004).

According to Allen et al (2004), [32] cognitive decline over a 7-year follow-up period is more pronounced in patients with diabetes, particularly the elderly. A relationship between diabetes and dementia is common [33] (Duron et al., 2008). The hippocampal synaptic plasticity of elderly insulin-powered diabetic rats is lower than that of young people. Similarly, it appears that the duration of diabetes influences the impact; in insulin-privileged rats, prolonged hyperglycemia affects hippocampal neurons. The harmful consequences of hypoglycemia were also observed. One week later, diabetic rats were euthanised after receiving high doses of insulin or saline. According to Biessels and Gispen (2005) [23], rats suffering from hypoglycemia had a greater reduction in neuronal capacity in the hippocampus. Based on this information, it is possible that increased glycaemia has an impact on cerebral metabolism in general, as well as on the molecular mechanisms of memory and learning, which may lead to neurocognitive problems.

V. 2. Expression of SPK1 and SPK2 mRNAs

In order to evaluate the mRNA expression of SPK1 and SPK2 signalling markers in the prefrontal cortex, we examined the expression of SPHK1 and SPHK2 in the hippocampus of the three (03) groups of rats in our study. We observed that SPHK1 and SPHK2 were expressed in the hippocampus of normal rats in group 1 with a significant difference (p*=0.025, Figure 4 A) compared with those in groups 2 and 3, diabetic rats, without and with SPHK1 and SPHK2 inhibitors, respectively. However, we observed a decrease in SPHK2 expression in the hippocampus of untreated diabetic rats, with a significant difference (p*=0.031; figure 4 B) between diabetic rats in group 2 and group 3 without and with sphingosine kinase 1 and 2 inhibitors, respectively. These data suggest that hyperglycaemia inhibits the expression of SPHK1 and SPHK2 by altering working memory and that the inhibitor of SPHK1 and SPHK2 facilitates the expression of SPHK2 and does not improve this memory in diabetic rats.

In contrast to these results, two independent studies recently revealed an alteration in S1P metabolism with a reduction in the expression and enzymatic activity of SphK1 or SphK2 and

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an increase in S1P lyase, the S1P-degrading enzyme. [34, 35] Enzymatic deregulation resulting in decreased S1P was again associated with Aβ deposition and lesion progression in AD [34, 35]. In addition to the active potential of the SphK1 isoform, it has been shown that deregulation of SphK2 could have a more significant impact on Alzheimer's Disease (AD) lesions and progression. Indeed, SphK2 was the major isoenzyme in the rodent brain [36,37,38], and SphK2 activity and mRNA levels were much higher than those of SpK1. [36, 35] Recently, SphK2 has been shown to largely regulate S1P production in the brain by inactivating the SphK2 germline. [37] As mentioned previously, the role of SphK2 has been studied in AD patients, but the results are still in memory. Where a decrease in S1P level was linked to a reduction in SphK2 activity in the hippocampus and temporal cortex. [35] An increase in SphK2 activity was observed in the frontal cortex. [39] The ambiguous results may simply reflect the complexity of SphK2 regulation and function. According to Neubauer et al. (2013), [40] SphK2 has the ability to generate an S1P that promotes cell proliferation or death and survival relative to the subcellular compartment.

V. CONCLUSION

This study clearly shows that diabetes negatively affects body weight and cognitive function in rats, highlighting correlations between hyperglycemia, weight loss and memory loss. The results showed that, particularly in diabetic rats, cognitive performance was significantly reduced over time, while the administration of sphingosine kinase inhibitors did not completely restore these functions. At the same time, variations in SPK1 and SPK2 mRNA expression suggested a crucial link between hyperglycemia and enzyme expression. The decrease in the enzymatic expression of SPK1 and SPK2 messenger RNA in diabetic rats reinforces the idea that regulation is altered by diabetes. These results pave the way for future studies aimed at modulating these enzymes as a therapeutic strategy, exploring more effective therapeutic interventions and improving our understanding of the mechanisms underlying memory and cognitive disorders associated with diabetes. The challenge for researchers and clinicians is to find new ways of reducing these effects in diabetic patients.

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