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Diabetes & its Complications

AMPK1/2 and Hepatic Dysfunction in Experimental Diabetes in Wistar Rats: Association with Hepatic Enzymes and Energy Metabolism

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ABSTRACT

AMPK plays a central role in hepatic energy regulation. Experimental diabetes alters this pathway, contributing to metabolic disturbances. This study evaluates hepatic AMPK1/2 expression and the inhibitory effect of dorsomorphin in diabetic rats. Twenty-four Wistar rats were divided into four groups (controls, controls + dorsomorphin, diabetics, diabetics + dorsomorphin) and followed for 14 days. Metabolic, hepatic and hormonal parameters were measured, and AMPK1/2 expression was analysed by RT-qPCR.

Diabetes induced hyperglycaemia, dyslipidaemia, decreased insulin levels and elevated transaminases. AMPK1 and AMPK2 were overexpressed in diabetic rats, whereas dorsomorphin markedly reduced their expression. Specific correlations were observed between AMPK1/2 and metabolic and hepatic parameters. Activation of AMPK1/2 appears to be an adaptive mechanism to diabetic energy imbalance. Their inhibition by dorsomorphin disrupts this response and reveals potential hepatotoxicity. AMPK remains a key target for the modulation of hepatic function in diabetes.

Keywords

AMPK1, AMPK2, Experimental diabetes, Dorsomorphin, Hepatic function.

Introduction

Glucose plays an important role in metabolism. It is not only a source of energy but also a substrate for the biosynthesis of cellular components [1]. Metabolic dysregulation of glucose homeostasis is the main consequence of the development of diabetes and the principal cause of diabetic morbidity and mortality. There are two common types of diabetes: type 1 diabetes and type 2 diabetes. Type 2 diabetes (T2D) is the most frequent form of diabetes and is characterised by undetectable insulin levels, increased hepatic fat content, impaired insulin clearance and hepatic insulin resistance [2]. T2D is associated with several hepatic abnormalities, including non-alcoholic fatty liver disease (NAFLD) and excessive hepatic glycogen accumulation [3].

The liver plays a unique role in glucose metabolism and is crucial for systemic glucose homeostasis [4]. It contributes to the management of the enteral glucose load by inhibiting its own glucose production, thereby facilitating the disposal of exogenous glucose by extrahepatic tissues such as adipose tissue and skeletal muscle [5]. The liver also plays an important role in carbohydrate synthesis, storage and redistribution [6]. The liver performs opposing functions during hyperglycaemic states (glucose uptake

and glycogen synthesis) and hypoglycaemic states (glycogenolysis and gluconeogenesis), making the physiological regulation of hepatic glucose production a complex process. Patients with type 2 diabetes (T2D) exhibit increased hepatic glucose production (HGP), the physiological regulation of which is ensured by multiple extrahepatic mechanisms [7].

AMPK is a heterotrimeric protein composed of a catalytic α subunit and two regulatory subunits, β and γ, each subunit being present in at least two isoforms. AMPK is activated in response to various metabolic stresses that generally alter the cellular AMP/ATP ratio, induced by increased ATP consumption or decreased ATP production, as observed following glucose deprivation and inhibition of mitochondrial oxidative phosphorylation, as well as during exercise and muscle contraction. Activation of AMPK initiates metabolic changes aimed at reprogramming metabolism by shifting cells from an anabolic state to a catabolic state, by blocking ATP-consuming synthetic pathways and restoring energy balance [8,9]. Several studies suggest that in the liver, AMPK activation promotes reduced lipid synthesis, stimulates fatty acid oxidation and contributes to glycaemic control [10].

However, under conditions of insulin resistance and experimental diabetes, AMPK expression and activity may be altered, thereby aggravating metabolic imbalances and promoting the progression of hepatic complications [11-13]. The study of the relationship between AMPK1/2 regulation, hepatic dysfunction and disturbances in hepatic enzymes therefore provides an essential perspective for a better understanding of the pathophysiological mechanisms of diabetes.

Materials and Methods

Experimental protocol

After dissolution of alloxan monohydrate and Compound C in an ice-cold sterile saline solution (0.9% NaCl), twenty-four (24) male Wistar rats (*Rattus norvegicus*), aged 13 to 17 weeks and weighing between 150 and 345 g, were divided into four (04) groups of n = 6 animals per group:

Group 1: Untreated controls
Group 2: Controls treated with dorsomorphin
Group 3: Diabetic rats
Group 4: Diabetic rats treated with dorsomorphin

With the exception of animals in Group 1, which received an equivalent volume of saline solution, animals in Groups 3 and 4 received a single injection of alloxan monohydrate at a dose of 150 mg/kg to induce diabetes, while animals in Groups 2 and 4 received an intraperitoneal injection of Compound C at a dose of 25 mg/kg.

Throughout the experimental period, animals were maintained in standard cages under controlled conditions (12 h/12 h light/dark cycle, temperature 22 ± 2 °C), with ad libitum access to water and a standard balanced diet. A 12-hour fasting period was applied before experimental procedures. To prevent acute post-injection hypoglycaemia, a 5% glucose solution was administered ad libitum during the first 24 hours following injection to rats in Groups 3 and 4.

This experimental protocol was approved by the Ethics Committee of Marien Ngouabi University and was conducted in accordance with international guidelines for the use of laboratory animals [14].

The choice of male Wistar rats aged 13 to 17 weeks for this study is justified by their physiological maturity, genetic stability, low hormonal variability and predictable response to experimental treatments, particularly with respect to diabetes and AMPK activation or inhibition. This model is therefore suitable for testing hypotheses related to energy regulation and hepatic dysfunction in experimental diabetes [15].

Measurement of Blood Glucose, Body Weight and Confirmation of Diabetes

Blood glucose was measured using a portable glucometer (OnCall Plus II, ACON®), and body weight was measured using a precision electronic balance. Blood samples were collected by incision at the tip of the tail on capillary blood after a 12-hour fast. Blood glucose and body weight measurements were performed on days 1, 3, 5, 7 and 14.

Rats presenting fasting blood glucose levels > 280 mg/dL (≈ 15.5 mmol/L) on the third day post-injection were considered diabetic and included in the study [16].

Blood and tissue sampling and sample preparation

After a 12-hour fast on day 14 (D14), rats were anaesthetised by inhalation of diethyl ether. Blood was collected by orbital sinus puncture. Samples were centrifuged at 3000 rpm for 10 minutes, and the resulting serum was stored at −80 °C until biochemical analyses. Hepatic tissues (liver) were collected after decapitation and dissection of the male rats. The organ was then weighed using a precision balance and stored at −80 °C.

Biochemical and immunological parameter assays

Biochemical parameters were measured using a CyanStart spectrophotometer with Cypress Diagnostics reagents. Insulin and adiponectin concentrations were determined by the ELISA method using reagents obtained from SunLong Biotech Co., LTD, with lot numbers SL0373Ra for insulin and SL0032Ra for adiponectin. Intra- and inter-assay coefficients of variation (CVs) for insulin and adiponectin were as follows: intra-assay CV < 10% and inter-assay CV < 12%.

Molecular expression of AMPK

Molecular expression analysis was performed by RT-PCR. RNA was extracted from hepatic tissues using the Total RNA Purification Kit PI17200-37 (Norgen Biotek Corp, Canada), in accordance with the manufacturer's recommendations.

Two pairs of primers encoding AMPK1 and AMPK2, supplied

by Inqaba Biotec, were used (Table 1). The Luna Universal One-Step RT-qPCR Kit E3005S (New England BioLabs) was used for amplification. Amplification parameters were as follows: reverse transcription at 55 °C for 10 seconds, followed by activation at 95 °C for 60 seconds, denaturation at 95 °C for 10 seconds and annealing at 60 °C for 30 seconds. Melting curve analysis was subsequently performed with cycles at 95 °C for 15 seconds, 60 seconds at 60 °C and 95 °C for 15 seconds. Expression levels were evaluated using the Livak method with the formula Rq = 2^−(ΔΔCt) [17]. A positive relative quantification (Rq) value corresponds to overexpression, whereas a negative value corresponds to underexpression.

Table 1 : Primer pairs used.

Gene	Primer sequences
hAMPKa1	Forward: GAC AGC CGA GAA GCA GAA AC Reverse: AGG ATG CCT GAA AAG CTT GA
hAMPKa2	Forward: GAC GGG TTG AAG AGA TGG AA Reverse: CCT GCA TAC AAT CTG CCT GA
GAPDH	Forward: GTC CAC TGG CGT GTT CAC CA Reverse: GTG GCA GTG ATG GCA TGG AC

Statistical analyses

Data are expressed as mean ± standard deviation. Statistical analyses were performed using GraphPad Prism software version 5.0. Comparisons between groups were carried out using one-way or two-way analysis of variance (ANOVA), followed by Bonferroni or Tukey post-hoc tests. When data were not normally distributed, the non-parametric Kruskal–Wallis test followed by Dunn's test was used. Correlations between biochemical and molecular variables were assessed using Spearman's correlation test. Statistical significance was set at $p < 0.05$.

Results

General characteristics of the studied animal population

The metabolic effects of diabetic induction and dorsomorphin administration were evaluated by monitoring body weight and fasting blood glucose over a 14-day period. As shown in Figures 1A and 1B, these parameters exhibited significant alterations reflecting both the diabetic state and the effect of treatment.

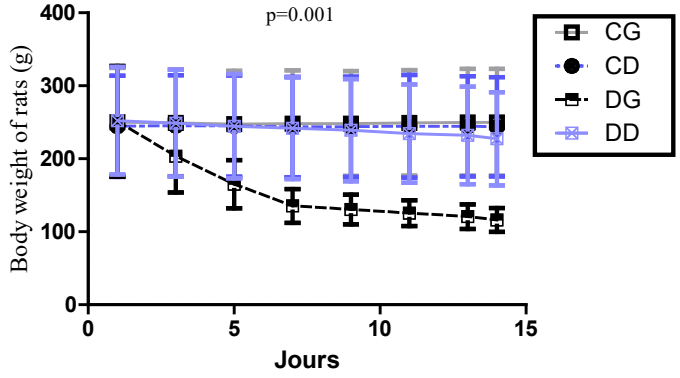

Figure 1A: Changes in body weight.

During the study, diabetic rats (DG and DD) showed a significant reduction in body weight compared with control groups (CG and CD). In non-diabetic rats, dorsomorphin treatment (CD) did not induce marked weight changes, whereas it appeared to moderate weight loss in treated diabetic animals (DD). Results are expressed as mean ± SEM. Statistical analysis was based on two-way ANOVA followed by Bonferroni post-hoc test.

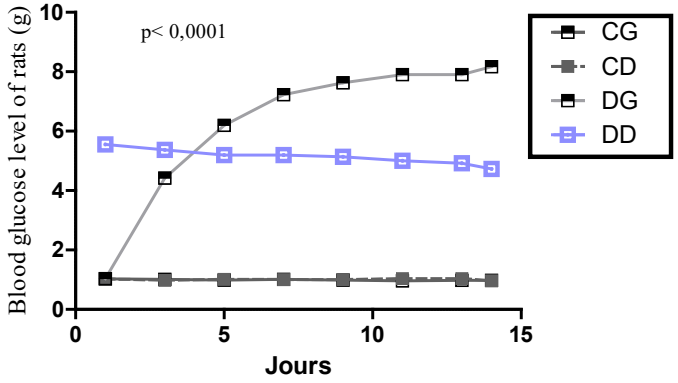

Figure 1B: Changes in fasting blood glucose.

In rats from DG and DD groups, alloxan induced a significant and sustained hyperglycaemia from the third day onwards, confirming the success of diabetic induction. Dorsomorphin treatment did not restore normoglycaemia in diabetic rats (DD), but appeared to partially reduce glucose levels. No significant glycaemic effect was observed in treated control rats (CD). Results are expressed as mean ± SEM. Statistical analysis was performed using two-way ANOVA followed by Bonferroni post-hoc test.

Biochemical and hormonal parameters

Table 2 illustrates variations in biochemical parameters observed in Wistar rats from the four experimental groups: healthy controls, controls treated with dorsomorphin, diabetic rats and treated diabetic rats. Compared with control groups, diabetic rats showed a significant increase in total cholesterol ($p = 0.0001$), triglycerides ($p < 0.001$), HDL-cholesterol ($p < 0.007$) and LDL-cholesterol ($p < 0.002$).

Table 2: Biochemical parameters.

Parameters	healthy Controls n=6	Controls + Dorso n=6	Diabetics n=6	Diabetics + Dorso n=6	P Value
Total Cholesterol (g/L)	0.51 ± 0.20	0.35 ± 0.24	0.89 ± 0.17	0.96 ± 0.22	0.0001***
Triglycerides (g/L)	0.92 ± 0.13	1.08 ± 0.14	1.60 ± 0.27	1.94 ± 0.05	< 0.001***
HDL Cholesterol (g/L)	0.17 ± 0.03	0.22 ± 0.05	0.06 ± 0.04	0.04 ± 0.05	< 0.007***
LDL Cholesterol (g/L)	0.24 ± 0.09	0.21 ± 0.11	0.56 ± 0.23	0.90 ± 0.08	< 0.002***

Abbreviations: HDL-cholesterol: High-Density Lipoprotein Cholesterol; LDL-cholesterol: Low-Density Lipoprotein Cholesterol; Significance: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

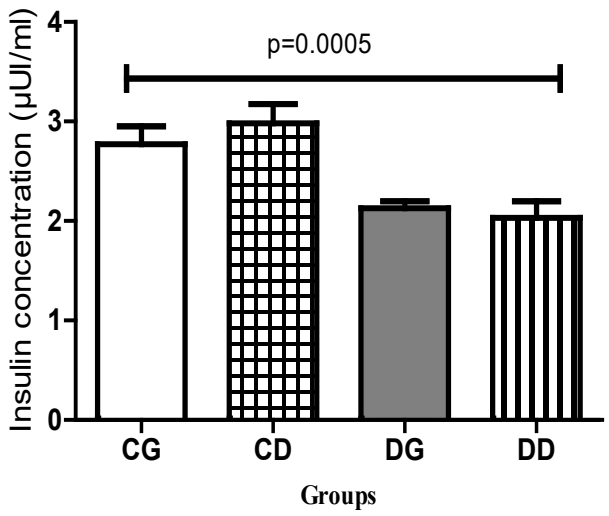

Figure 2: Serum insulin concentration.

In diabetic rats (DG), a marked decrease in insulin levels was observed, associated with alloxan-induced cytotoxicity on pancreatic β-cells. Dorsomorphin treatment did not result in significant recovery of insulin levels in treated diabetic rats (DDG). Data are presented as mean ± SEM (p = 0.005).

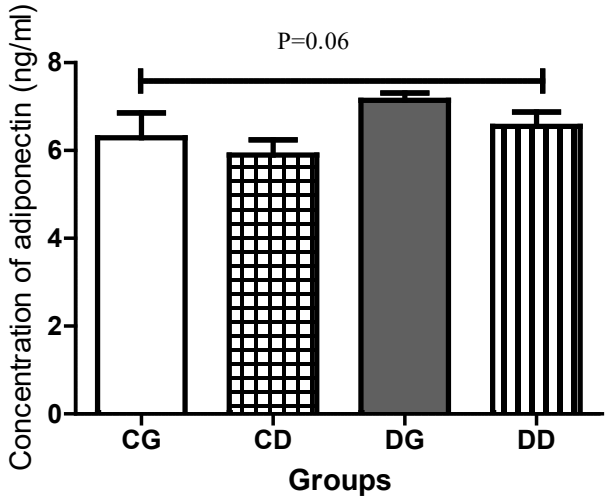

Figure 3: Serum adiponectin concentration.

Untreated diabetic rats (DG) showed a significant increase in adiponectin levels, consistent with metabolic disturbances observed in diabetes and insulin resistance. In treated diabetic rats (DD), a moderate but non-significant increase in this hormone was observed, suggesting a potential regulatory effect of dorsomorphin via the AMPK pathway. Data are expressed as mean ± SEM (p = 0.06).

Hepatic parameter profile (AST and ALT)

Analysis of serum transaminase activities showed marked variations between experimental groups. Compared with healthy controls, dorsomorphin administration in non-diabetic animals induced a significant increase in transaminases (p = 0.005), suggesting a hepatotoxic effect of the treatment. In untreated diabetic rats, transaminase activities remained elevated compared with healthy controls, reflecting hepatic injury classically associated with diabetes. Dorsomorphin administration in diabetic rats did not further aggravate hepatic lesions, as transaminase levels remained lower than those observed in healthy rats treated with dorsomorphin and similar to untreated diabetic rats. This observation suggests that, in an already metabolically disturbed context, the potential hepatotoxic effect of dorsomorphin may be attenuated or masked by pre-existing diabetes-related alterations.

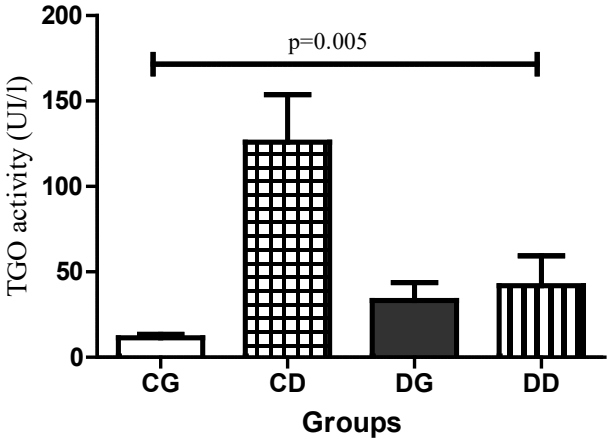

Figure 4A: Serum AST concentration.

CG (control rats), CD (control rats + dorsomorphin), DG (diabetic rats), DD (diabetic rats + dorsomorphin). Data are expressed as mean ± SEM.

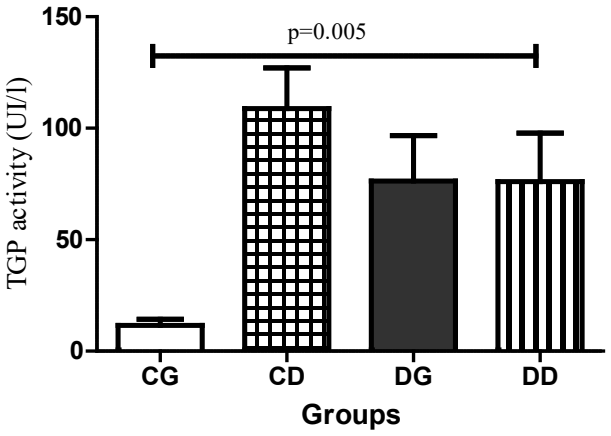

Figure 4B: Serum ALT concentration.

Molecular expression of AMPK1/2

Molecular expression of AMPK1

RT-qPCR analysis revealed a significant increase in AMPK1 gene expression in untreated diabetic rats (DR), corresponding to a 2.1-fold increase compared with controls ($p = 0.0019$). Dorsomorphin administration induced a 37% decrease in expression in control rats (CRD vs CR) and a 42% decrease in diabetic rats (DRD vs DR). These observations confirm the specific inhibitory action of dorsomorphin on AMPK1 transcription.

CR (control rats), CRD (control rats + dorsomorphin), DR (diabetic rats), DRD (diabetic rats + dorsomorphin). Data are expressed as mean ± SEM. Statistical analysis: ANOVA followed by Kruskal–Wallis post-test, $p = 0.0019$.

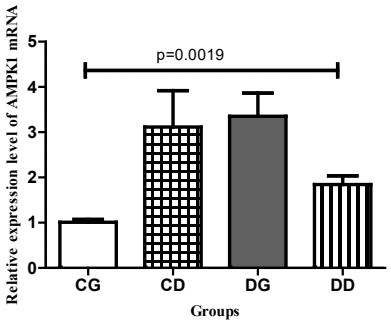

Figure 5 : AMPK1 expression measured by RT-qPCR in the different experimental groups.

Molecular expression of AMPK2

In untreated diabetic rats (DR), AMPK2 expression was significantly increased (+3.9-fold vs CR; $p = 0.0004$). Dorsomorphin administration reduced this expression by 60% in control rats and by 68% in diabetic animals, indicating an adaptive response to metabolic stress and high sensitivity to pharmacological inhibition.

CG (control rats), CD (control rats + dorsomorphin), DG (diabetic rats), DD (diabetic rats + dorsomorphin). Data are expressed as mean ± SEM. Statistical analysis: ANOVA followed by multiple comparison test, $p = 0.0004$.

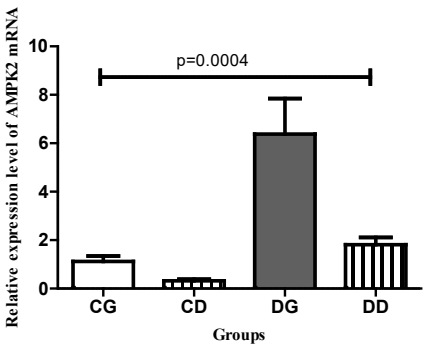

Figure 6: AMPK2 expression measured by RT-qPCR in the different experimental groups.

Biochemical and molecular correlation analysis

Correlation analysis revealed specific associations between AMPK expression or activity and various metabolic and biochemical serum parameters.

AMPK1 expression showed a significant negative correlation with insulin (Figure 7), suggesting that reduced insulin-mediated anabolic activity may be associated with compensatory activation of AMPK-dependent catabolic pathways. A similar negative correlation was observed with triglycerides (Figure 8), indicating that AMPK1 may contribute to reduced synthesis or accumulation of circulating lipids, in accordance with the recognised lipolytic and antilipogenic role of this kinase.

Conversely, AMPK1 activity showed significant correlations with hepatic transaminases. A positive association was observed with AST (Figure 9) as well as with ALT (Figure 10), which may reflect AMPK activation in response to hepatocellular stress or increased membrane permeability related to hepatic injury. This relationship suggests that AMPK1 may be mobilised as an adaptive mechanism aimed at limiting metabolic damage induced by inflammation or glucose overload in the liver.

Regarding AMPK2, the activity or expression of this isoform was associated mainly with adipocytic and lipid parameters. A significant positive correlation with adiponectin (Figure 11) confirms the known interdependence between AMPK2 and this insulin-sensitising adipokine, adiponectin being a potent activator of the AMPK pathway in various metabolic tissues. AMPK2 expression was also positively correlated with total cholesterol (Figure 12) and triglycerides (Figure 13), suggesting that this isoform may respond to circulating lipid excess in an attempt to restore metabolic homeostasis.

Finally, AMPK2 expression showed a positive correlation with serum transaminases AST (Figure 14) and ALT (Figure 15), reinforcing the hypothesis of AMPK pathway activation in situations of hepatic injury. This response may constitute a protective mechanism aimed at reducing lipotoxicity and oxidative stress induced by dysglycaemia and hyperlipidaemia observed in the diabetic model.

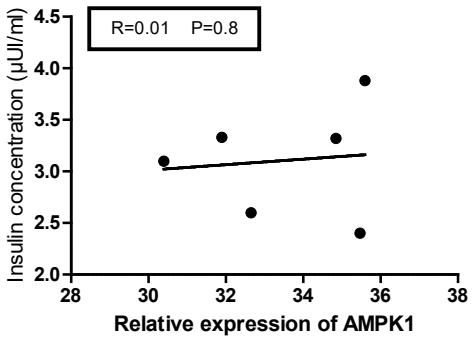

Figure 7 : Correlation between AMPK1 expression and insulin.

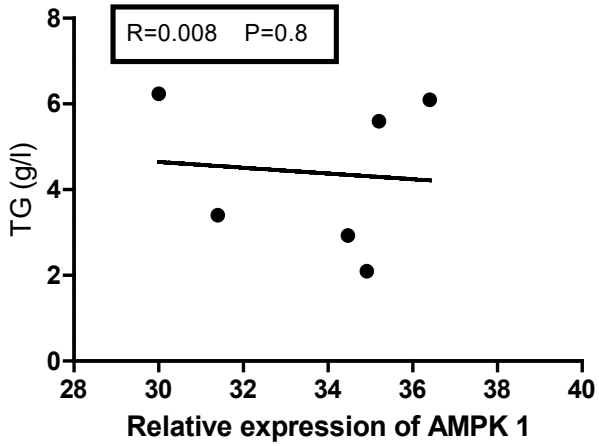

Figure 8 : Correlation between AMPK1 expression and triglycerides.

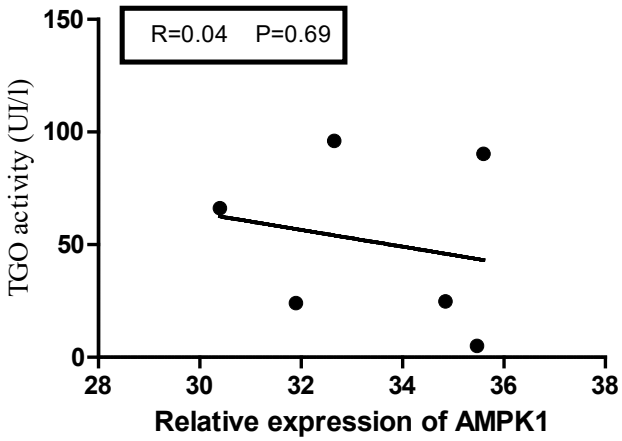

Figure 9 : Correlation between AMPK1 activity and GOT.

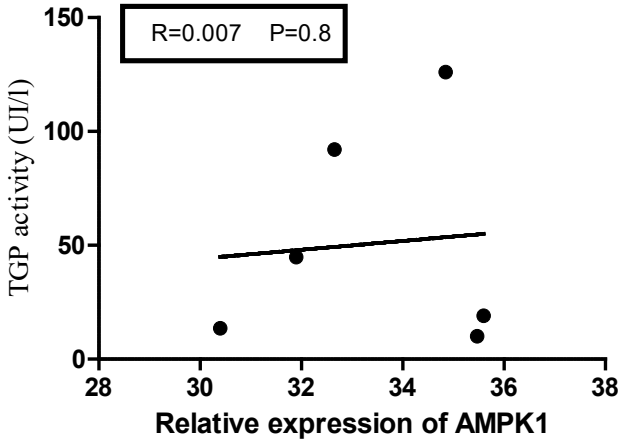

Figure 10 : Correlation between AMPK1 activity and GPT.

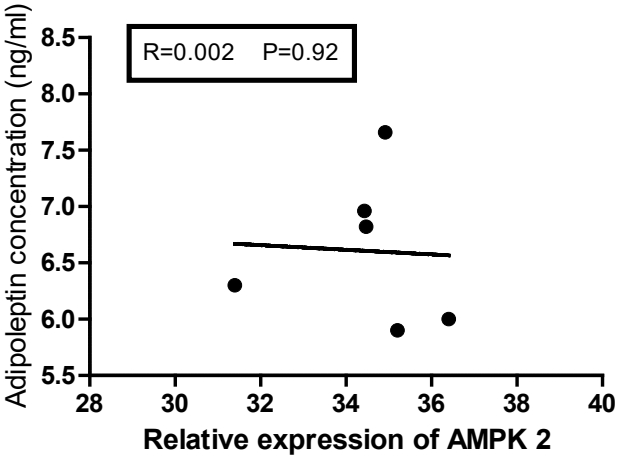

Figure 11 : Correlation between AMPK2 activity and Adiponectin.

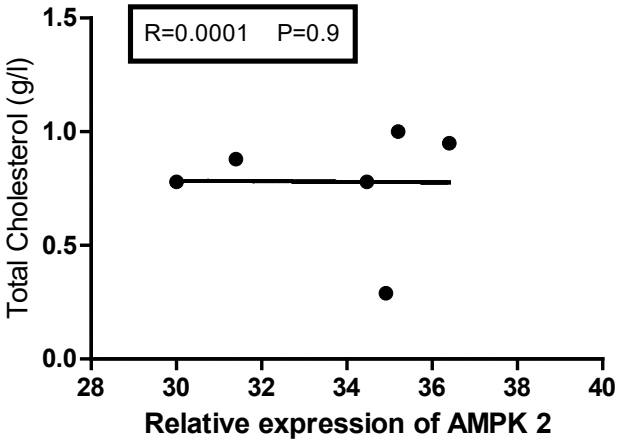

Figure 12 : Correlation between AMPK2 expression and total cholesterol concentration.

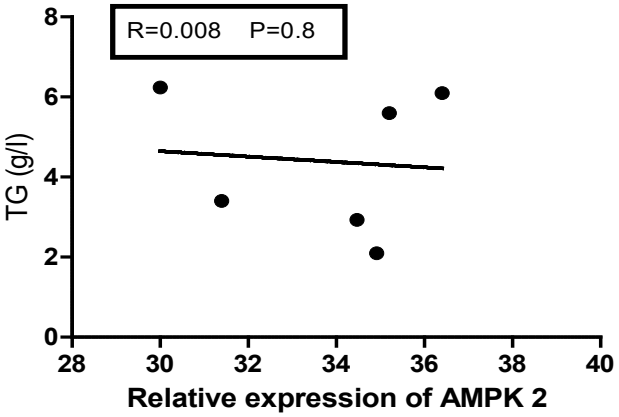

Figure 13 : Correlation between AMPK2 expression and triglyceride concentration.

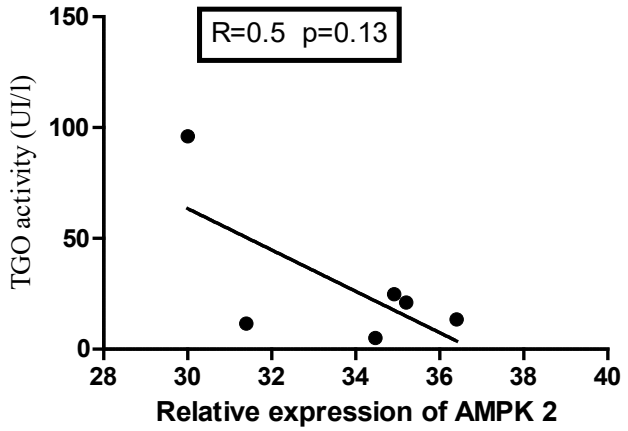

Figure 14 : Correlation between AMPK2 expression and GOT concentration.

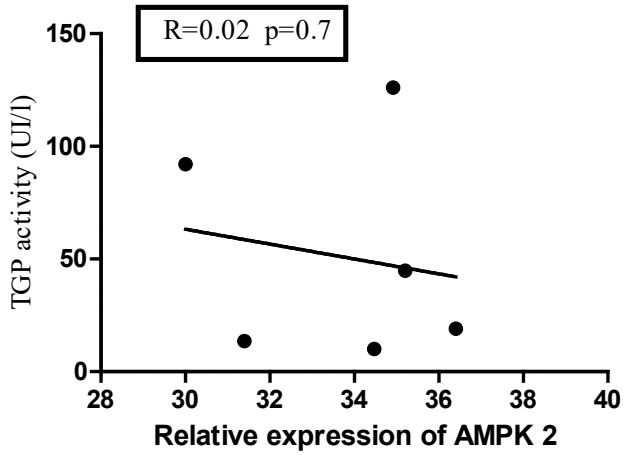

Figure 15 : Correlation between AMPK2 expression and GPT concentration.

Discussion

The main objective of this study was to investigate the relationship between AMPK1/2 regulation, hepatic dysfunction and disturbances in hepatic enzymes in alloxan-induced diabetes in Wistar rats. Our results show that the diabetic state is accompanied by profound metabolic disorders, including persistent hyperglycaemia, dyslipidaemia (increased triglycerides and total cholesterol), a marked decrease in insulin levels and alterations in hepatic enzymes, corroborating the classical observations of insulin-deficient diabetes. The increase in triglycerides, total cholesterol and HDL/LDL fractions in diabetic rats is consistent with dysregulation of lipoprotein synthesis and reduced peripheral glucose utilisation, which are typical of alloxan-induced diabetes [18-20].

With regard to hepatic assessment, the elevation of transaminases in diabetic rats suggests hepatocellular cytolysis, a mechanism most often reported in states of chronic hyperglycaemia and oxidative stress that characterise experimental diabetes [21]. Dorsomorphin administration in non-diabetic rats also resulted in a significant increase in transaminases, indicating a hepatotoxic effect of the AMPK inhibitor. This finding supports the hypothesis that inhibition of the AMPK pathway disrupts cellular energy homeostasis mechanisms and renders the liver more vulnerable to stress, as suggested by some studies [18,22]. However, the apparent hepatotoxic effect of dorsomorphin in non-diabetic animals deserves particular attention. Compound C (dorsomorphin) is widely used as an AMPK inhibitor but has well-documented off-target effects and complex cellular actions (including modulation of additional pathways), which may explain deleterious consequences on hepatic integrity when AMPK signalling is blocked in a non-stressed liver. Recent studies have highlighted that Compound C can influence other kinases and transporters and induce AMPK-independent cellular responses, reinforcing the need for cautious interpretation of effects attributed solely to AMPK inhibition [23].

Molecular analyses showed marked overexpression of AMPK1 and AMPK2 in untreated diabetic animals, reflecting adaptive activation of the AMPK pathway in response to energy difficulties related to reduced insulin levels and hyperglycaemia. This increased activation may represent a compensatory mechanism aimed at promoting fatty acid oxidation, inhibiting lipogenesis and restoring hepatic energy balance, as described in numerous studies [24,25]. The marked inhibitory effect of dorsomorphin, reducing AMPK1 and AMPK2 expression by 37% to 68% depending on the groups, confirms the effectiveness of this compound as a pharmacological inhibitor of the AMPK pathway, in accordance with previous observations [26,27].

Correlation analyses highlighted differentiated functional relationships between the two isoforms. AMPK1 showed a negative correlation with insulin levels and triglycerides, and positive correlations with transaminases. These results suggest that AMPK1 is mobilised in a context of insulin deficiency to limit lipid anabolism and promote catabolic pathways, and may also be associated with markers of hepatic stress, possibly because its activation occurs in response to hepatocellular metabolic stress [18]. AMPK2 showed positive correlations with adiponectin and lipid parameters (total cholesterol and triglycerides), as well as with transaminases. The association with adiponectin is notable, as this adipokine is a recognised activator of the AMPK pathway in the liver and improves insulin sensitivity via AMPK/SIRT1 activation and reduction of gluconeogenesis; these interactions have been documented in recent studies on AMPK/adiponectin signalling and their hepatoprotective role. Positive correlations with lipids may reflect compensatory activation of AMPK2 in response to circulating lipid overload [28].

Although our results yielded positive findings, several limitations should be acknowledged, including the use of animal models and a pharmacological inhibitor that is not perfectly selective, which may limit or complicate the interpretation of our results. A more

advanced potential strategy would involve the use of gene therapies to directly modulate AMPK expression in specific tissues, in order to optimise activation or inhibition of this pathway according to therapeutic needs [29,30]. We did not evaluate the phosphorylation status (p-AMPK) by Western blot, which would provide a direct functional readout of kinase activity; similarly, detailed histological analyses (quantification of steatosis, inflammation and fibrosis) and assessment of downstream pathway protein expression (ACC, SREBP1c, PGC-1α, SIRT1) would further clarify the proposed mechanisms. Finally, Compound C may exert off-target effects that would require confirmation through complementary approaches (AMPK α1/α2 knock-down or knock-out, or the use of selective activators) [31].

Conclusion

Our results demonstrate that AMPK1/2 is strongly involved in hepatic adaptation to experimental diabetes and that pharmacological inhibition by dorsomorphin significantly modifies these responses, with measurable metabolic and hepatocellular consequences. These findings support the interest of a targeted and cautious modulation of the AMPK pathway as a therapeutic option to limit metabolic hepatic dysfunction, while highlighting the need for more precise pharmacological tools and in-depth mechanistic analyses. Thus, this study opens the way to new therapeutic approaches for treating not only type 2 diabetes but also its associated complications, such as hepatic and cardiovascular diseases. AMPK-targeted therapies, combined with approaches such as gene therapy and personalised medicine, could revolutionise diabetes management by offering more effective, specific and durable treatments. AMPK activation, in particular, represents a promising strategic axis for restoring balanced metabolism and reducing the complications of this chronic disease.

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