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Thyrotropin-Releasing Hormone and Corrective Effect of Fructose-Induced Metabolic Disorders on Pancreatic β-Cell Function in Wistar Rats

Hormona Liberadora de Tirotropina y Efecto Correctivo de los Trastornos Metabólicos Inducidos por la Fructosa en la Función de las Células β Pancreáticas en Ratas Wistar

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SUMMARY: The evolution of food production causes physiological diseases in the body, an important industrial product is fructose; affecting the organ most sensitive to these products, the pancreas. At the pancreatic level, thyrotropic hormone (TRH) has membrane receptors in the β-cell; subsequently, TRH stimulates and regulates insulin release and participates in the regulation of hyperglycemia. The aim of this study is to demonstrate the effect of TRH in cases of pancreatic metabolic disorders and to provide a new vision for the prevention and/or treatment of diabetes. The investigation was carried out using Wistar rats. Animals were devised on four groups: control, TRH, Fru and Fru -TRH. At the age of 25-day, animals (Fru, Fru -TRH) received Fructose (20 %) and control groups received water; at the age of 60 days (TRH and Fru -TRH groups), the treatment with intraperitoneal injections of TRH for 7 days, control rats received the same volume of saline solution. Pancreases were collected, histologically studied and stained with eosin/haematoxylin (structural study) and fuchsin/paraldehyde (histochemical study); biochemical parameters, insulin levels, catalase activities, malondialdehyde (MDA) and inflammatory marker NO were measured. We found that TRH corrected metabolic parameters and inflammatory markers in the islets by suppressing cellular infiltration and cytoplasmic vacuolation. These results suggest that the direct action of TRH on β-cells, due to the presence of its receptor at the membrane level, can modulate tissue and functional alterations of these cells in pathological cases.

KEY WORDS: TRH; Fructose; b-cells; Oxidative stress; Rat.

INTRODUCTION

Thyrotropin-releasing hormone (TRH), produced by the hypothalamus, is a tripeptide first identified in the central nervous system (CNS) (Boler *et al*., 1969; Burgus *et al*., 1969) and later in peripheral tissues such as the pancreas (Morley *et al*., 1977). TRH stimulates the biosynthesis and secretion of thyrotropin (TSH) by the anterior pituitary, and recent studies on the role of neuropeptides in the hypothalamus have directly interpreted the action of TRH in the regulation of energy metabolism and eating behavior (Nillni *et al*., 2000). TRH also regulates the release of other hormones such as insulin and plays an active role in the regulation of hyperglycemia through a central action, the identification of TRH receptors on the surface of b-cells and their signaling pathways contribute to pancreatic islet development and autoregulation (Kulkarni *et al*., 1995).

The pancreas is an organ that is highly sensitive to disturbances in the microenvironment induced by variations in blood glucose levels and by the penetration of glucose-like substances such as fructose which is used extensively in modern diets, meaning that metabolic problems are becoming increasingly common. Fructose is used commercially on a large scale in the preparation of desserts, condiments and soft drinks which causes insulin resistance (Dekker *et al*., 2010; Nolan *et al*., 2011), obesity (Elliott *et al*., 2002) and other diseases. Thus, the prevalence of diabetes is associated with the availability of sugar (Basu *et al*., 2013). Therefore, the aim of the present study was to investigate the response of the b-cells of the Wistar rat with Fructose in vivo to intraperitoneal injection of TRH. We explored the effects on the histologic appearance of the pancreas and parameters indicative of functional status; glucose, insulin, markers of oxidative stress and inflammatory marker; suggesting than, a protective role for TRH in diabetes.

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MATERIAL AND METHOD

Animals and biology studies. Twenty-four male Wistar rats (Rattus norvegicus), 25 day of age, were housed in individual cages, fed ad libitum with a commercial diet. Two groups were formed (n=12), the first received Fru (20 %) and the second received water; at 60 day of age, half of each group of animals, received TRH (Sigma-Aldrich P 1319) at a dose of 24 µg/100 g body weight/7 days, injected intraperitoneally; then, four groups were formed: Cont, TRH, Fru and Fru-TRH. The experimental protocol is approved by the institutional Animal Care Committee of the National Administration of the Algerian Higher Education and Scientific Research (DGRSDT; https://www.dgrsdt.dz) and Use Committee of the University of Bab Ezzouar (Algiers, Algeria; Permit number for the present research project: (F00220110048) and has been achieved according to the Executive Decree no.10 n90 completing the executive Decree no. 04- 82 of the Algerian government, establishing the terms and modalities of animal welfare in animal facilities.

At the end of treatment, the fasting animals were sacrificed, blood was centrifuged (-4 °C, 3500 rpm) and stored at -20 °C for biochemical and insulin studies. Pancreases were weighed with a digital balance (Denver instrument APX-200) and some were fixed in 10 % formalin (histological and histochemical studies) and others were frozen at -20 °C for the preparation of homogenate. Oxidative stress markers and inflammation marker were measured at plasma and tissue levels.

Insulin measurement. Insulin concentrations were measured, in duplicate, in serum and homogenate using the Radio Immuno Assay-RIA kit (MP Biomedical, Solon, Ohio 44139, USA) and determined in a single assay.

Biochemical studies: Glucose (Glu), total cholesterol (TC), triglycerides (TG) and calcium (Ca^{2+}) were determined in plasma by an enzymatic colorimetric method using commercial kits (SPINEREACT, Spain).

Determination of Thiobarbituric acid reactive substances (TBARs): Malan-di-aldehyde (MDA) is the most frequently measured product of lipid peroxidation; using the thiobarbituric acid (TBA) method, the absorbance of the supernatant was readied at 532 nm (Ohkawa *et al*., 1979).

Determination of catalase activity: Catalase activity was determined by the Claiborne method (Aebi, 1984). The principle is based on the disappearance of H_2O_2 in the presence of the enzyme source at 25 °C. The absorbance was estimated at 240 nm in two steps *t*0 and after two minutes and it was calculated as millimoles of H_2O_2 consumed min-1 mg-1 protein.

Determination of Nitrogen Monoxide (NO): The conversion of nitrate to nitrite is based on a cadmium reduction reaction described in Grand (2001). The concentration measured is the sum of nitrite and nitrate.

Histological and histochemical studies. Fixed pancreatic tissues were dehydrated in ethanol baths at increasing degrees and then passed through butanol to prepare them for impregnation. Serial histological sections of 5µm thickness were cut with a Leica microtome and mounted on histological slides. The tissue appearance was given by eosin/haematoxylin staining and the histochemical appearance was revealed by fuchsin-paraldehyde staining (Ewen, 1962), which highlights insulin secretion vesicles. The images were captured using LASEZ software version 3.4. Studies of b-cell nuclei were then performed to interpret cellular activity by quantifying euchromatin. The euchromatin area was assessed using Fiji/ImageJ with the threshold method: after cropping the nucleus, the new images were converted to 8-bit format, then the percentage of heterochromatin area (AHe) was quantified in proportion to the total nuclear area (AN= 100 %), giving the percentage of euchromatin area A

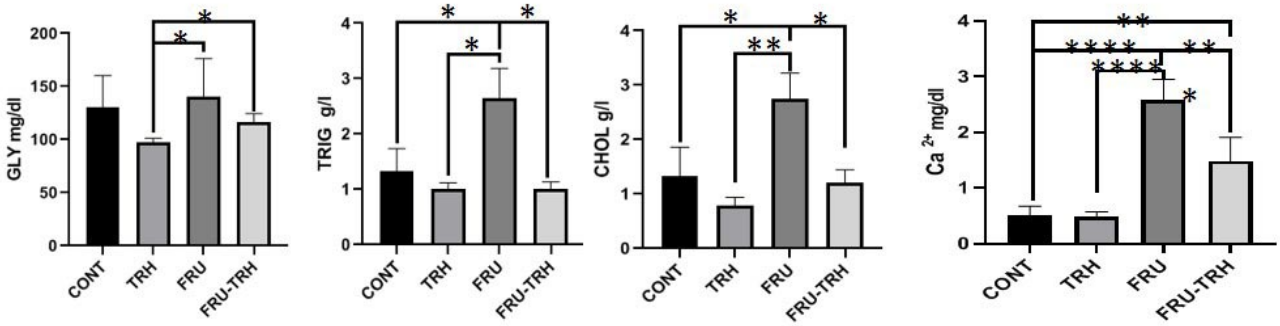

Fig. 1. Effect of TRH in biochemical parameters after the administration of Fru in Wistar rats. Control: Wistar rat control; TRH: Wistar rats control treated with TRH; Fru: Wistar rats received Fru (20 %); Fru-TRH: Wistar rats received Fru (20 %) and treated with TRH. Data are expressed as the mean ± S.E.M (*p < 0.05; **p < 0.01, ****p < 0.0001)

Eu as the difference AEu=AN-AHe, this study was carried out on two slides of three animals for each group.

Statistical analysis. Data were analyzed using Graph pad version 8.0.1. Normality was verified with Shapiro Wilk test; Brown-Forsythe ANOVA test, Ordinary one-way ANOVA and Welch's ANOVA test were used, the t test was used to compare groups of animals in pairs, the results are expressed as the mean ± ESM. Differences were considered statistically significant at $P \leq 0.05$.

RESULTS

Biochemical parameters. In Fru group, fructose administration significantly increased blood glucose, triglyceridemia, cholesterolemia and Ca2+ compared with the corresponding control and TRH groups; concentrations of these parameters were decreased in Fru-TRH group (Fig. 1).

Insulin RIA. In the Fru group, insulin levels were significantly decreased compared with the TRH and Fru-TRH groups ($p < 0.05$, Fig. 2).

Oxidative stress. Plasma catalase activities were decreased in Fru group and were increased in TRH and Fru-TRH groups compared with control group, in tissular fraction; it was significantly decreased in Fru group ($p < 0.05$, Fig. 3). Inversely, plasma MDA concentration increased in Fru group compared with others groups (Fig. 3), tissular MDA was increased in Fru group (vs CONT, **P < 0.01: vs TRH. ****P < 0.0001; vs Fru-TRH, ****P < 0.0001).

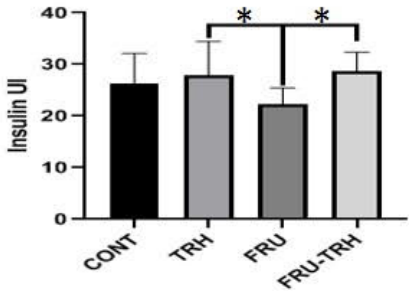

Fig. 2. Effect of TRH in insulin levels after the administration of Fru in Wistar rats. Control: Wistar rat control; TRH: Wistar rats control treated with TRH; Fru: Wistar rats received Fru (20 %); Fru-TRH: Wistar rats received Fru (20 %) and treated with TRH. Data are expressed as the mean ± S.E.M (*p < 0.05)

Nitrogen Monoxide (NO). NO significantly increased in Fru group compared to controls ($p < 0.05$, Fig. 4), treatment with TRH significantly lowered levels of these markers (Fig. 4).

Histo-histochemical and Morphometric analysis. As shown in Figure 4, pancreatic sections taken from the control and TRH groups revealed regular and distinct islets of Langerhans encapsulated by fibrous membranes and well differentiated from the exocrine parenchyma. In addition, islets were composed of aggregates of polygonal b-cells with pale cytoplasm and rounded nuclei (Fig. 6. A, B, D). In the Fru group, histological alterations were observed in the structure of the islets, β-cells with cytoplasmic vacuolization and cell infiltration were observed. The capsule between the endocrine and exocrine areas was indistinct with the presence of pycnotic nuclei (Fig. 6. C).

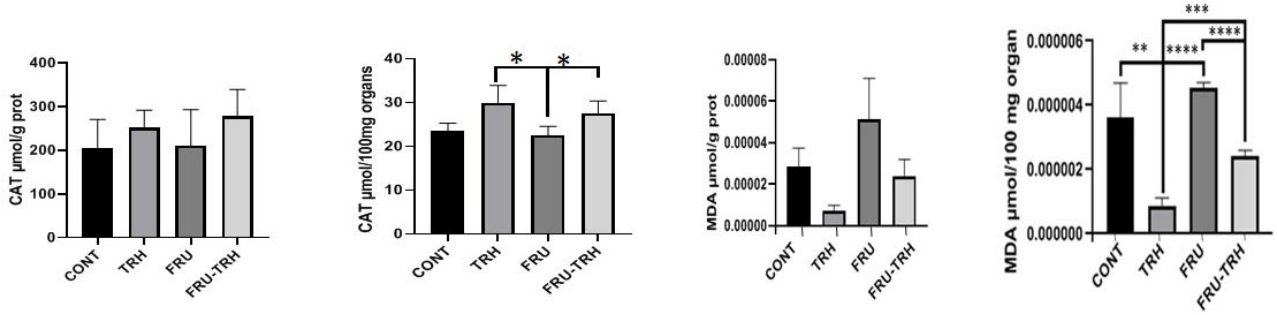

Fig. 3. Effect of TRH in oxidative stress markers after the administration of Fru in Wistar rats. Control: Wistar rat control; TRH: Wistar rats control treated with TRH; Fru: Wistar rats received Fru (20 %); Fru-TRH: Wistar rats received Fru (20 %) and treated with TRH. Data are expressed as the mean ± S.E.M (*p < 0.05; **p < 0.01, ***p < 0.001; ****p < 0.0001)

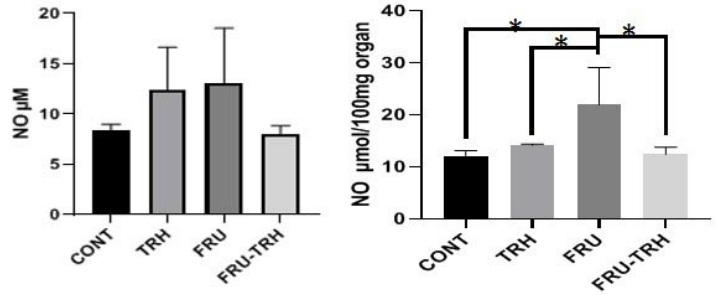

Fig. 4. Effect of TRH in the inflammation markers NO after the administration of Fru in Wistar rats. Control: Wistar rat control; TRH: Wistar rats control treated with TRH; Fru: Wistar rats received Fru (20 %); Fru-TRH: Wistar rats received Fru (20 %) and treated with TRH. Data are expressed as the mean ± S.E.M (*p < 0.05)

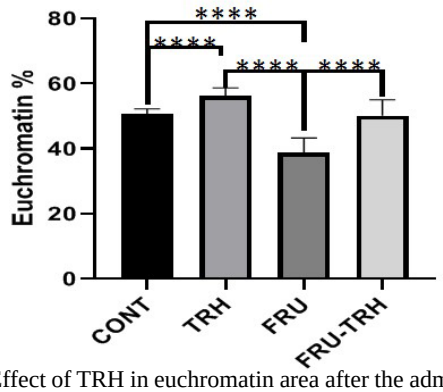

Fig. 5. Effect of TRH in euchromatin area after the administration of Fru in Wistar rats. Control: Wistar rat control; TRH: Wistar rats control treated with TRH; Fru: Wistar rats received Fru (20 %); Fru-TRH: Wistar rats received Fru (20 %) and treated with TRH. Data are expressed as the mean ± S.E.M (****p < 0.0001)

Histochemical staining shows a normal appearance of the structure and distribution of β-cells associated with the purple colored surface in Cont, TRH and Fru-TRH groups, in opposition to the Fru group, which shows a clearly visible alterations in cell organization and distribution (Fig. 7).

The quantification of euchromatin area showed a significant decrease in its percentage in Fru group (vs CONT, vs TRH and vs Fru-TRH****p < 0.0001).

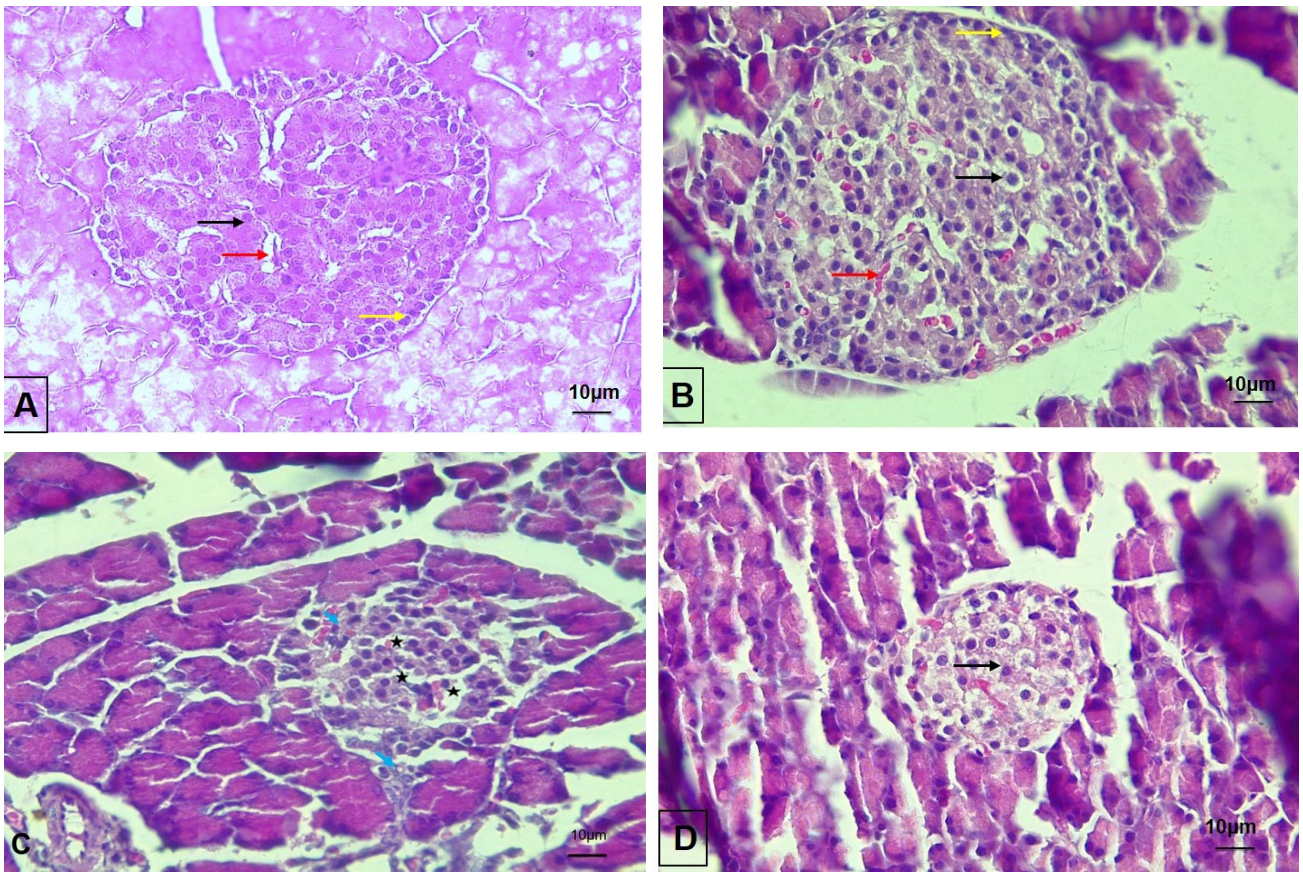

Fig. 6. Pancreatic histology after eosin/haematoxylin staining after the administration of Fru in Wistar rats: A: Wistar rat control; B: Wistar rats control treated with TRH; C: Wistar rats received Fru (20 %); D: Wistar rats received Fru (20 %) and treated with TRH (G: GX 400 Scale 10µM). β-cells, α -cells, Blood capillary, Ruptured dilated blood vessel, Inflammatory site.
→ β cells, → α cells, → Blood capillary, → Ruptured dilated blood vessel, Star = Inflammatory site.

DISCUSSION

In the pancreas, the membrane transporter GLUT11 is expressed for fructose and glucose (Reckzeh & Waldmann, 2020), at the plasma membrane of pancreatic b cells, GLUT2 is expressed with a lower affinity for fructose compared to glucose (Mueckler & Thorens, 2013). Fructose is not classified as a stimulator of insulin secretion (Grant *et al.*,

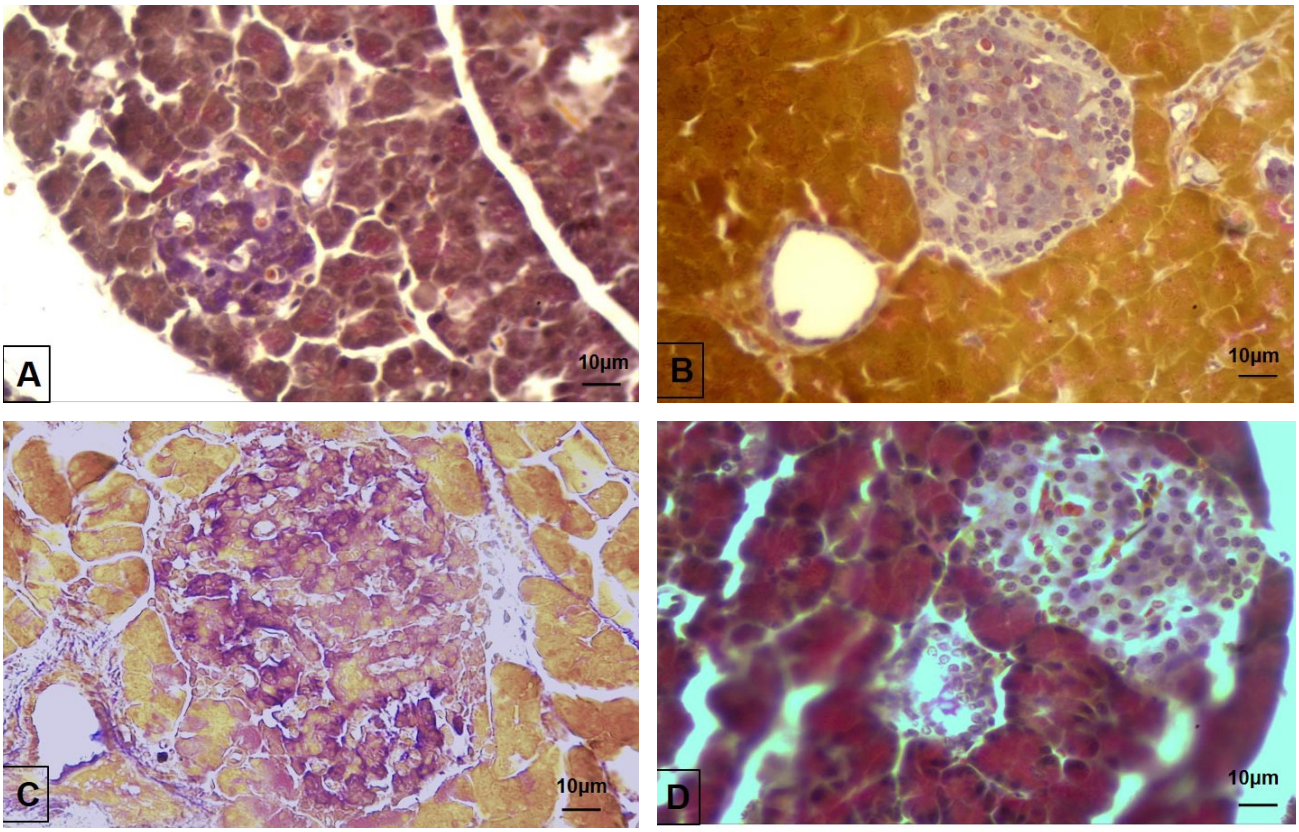

Fig.7. Histochemical study of Pancreatic after fuchsin-paraldehyde staining after the administration of Fru in Wistar rats: A: Wistar rat control; B: Wistar rats control treated with TRH; C: Wistar rats received Fru (20 %); D: Wistar rats received Fru (20 %) and treated with TRH (G: GX 400 Scale 10µM).

1980), but it affects insulin secretion directly and indirectly by regulating appetite (penetration of Fru into the enterocytes via GLUT5) (Fiorentino *et al*., 2023). In our study, administration of fructose decreased insulinemia and increased glycaemia; these results were corrected after the intraperitoneal injection of TRH.

TRH has a direct effect on the pancreas due to the presence of its receptors on b-cells (Yamada *et al*., 2000) and its storage in the same insulin-secreting granules during neonatal life (Basmaciogullari *et al*., 2000). Therefore, TRH may affect the pancreatic microenvironment leading to altered expression of various pancreatic β-cell genes (Luo & Yano, 2005), and it may play a role in inducing the differentiation of adult stem cells into functional b-cells in damaged pancreatic tissue, which could be important for diabetes therapy (Luo *et al*., 2013). According to the study by Strbák (2018), the presence of TRH in b-cells ensures appropriate constitutive low insulin secretion and promotes the proliferation of insulin-producing cells by reversing cellular aging. Glucose-induced TRH release has an autocrine effect that leads to direct insulin secretion through an autocrine and paracrine mechanism (Luo *et al*., 2013; Strbák, 2018).

Our results on markers of oxidative status in the blood and pancreas of rats treated with TRH injections showed an increase in the antioxidant capacity of catalase and a decrease in the oxidation of polyunsaturated lipids (MDA), inverse with FRU group.

In the structural appearance, the islets of Fru group presents many vacuolations, dilated and infiltration of inflammatory cellular, NO values confirmed this alteration, these results were concurred with in the studies of Hong *et al*. (2020) and Wang *et al*. (2023), ROS were implicated as a major inducer of cell necroptosis (Hong *et al*., 2020). Overexpression of antioxidant enzymes, such as catalase, can protect beta cells from reactive oxygen species (ROS)-induced toxicity (Duprez *et al*., 2012). According to Sarre *et al*. (2012), glucose acutely reduces mitochondrial oxidative stress. However, Duprez *et al*. (2012), suggest that high concentrations of glucose (supra-physiological glucose) may induce oxidative stress in b-cells over a prolonged period. Elevated levels of circulating free fatty acids induced lipotoxicity in pancreatic islets, causing tissue damage (Torre-Villalvazo *et al*., 2018), and increased pancreatic fat concentration may be a precursor to b-cell dysfunction and

later development of metabolic syndrome (Chansela *et al*., 2022). This dysfunction is revealed by the low percentage of euchromatin, confirming the decrease in cellular activity in the presence of fructose. This is confirmed by our results for cholesterolemia and triglyceridemia, which were significantly higher in the Fru group; these values were significantly reduced in both TRH groups.

Our results on intraperitoneal injection of TRH reveal an improvement in the structural appearance of islets, in addition, suppression of the toxic effect of biochemical parameters, oxidative stress and markers of inflammation resulting from fructose administration, thus suggesting the protective effect of TRH on b cells in the presence of metabolic disorders and in the more accentuated stage such as diabetes.

MORZOUGLAL, N.; BOUCHEFA, H.; GHOZLANI, A. & HADJ-BEKKOUCHE, F. Hormona liberadora de tirotropina y efecto correctivo de los trastornos metabólicos inducidos por la fructosa en la función de las células β pancreáticas en ratas Wistar. *Int. J. Morphol., 43(3)*:986-992, 2025.

RESUMEN: La evolución de la producción de alimentos provoca enfermedades fisiológicas en el organismo. Un producto industrial importante es la fructosa, que afecta al órgano más sensible a estos productos: el páncreas. A nivel pancreático, la hormona tirotrópica (TRH) posee receptores de membrana en la célula β; posteriormente, la TRH estimula y regula la liberación de insulina y participa en la regulación de la hiperglucemia. El objetivo de este estudio fue demostrar el efecto de la TRH en casos de trastornos metabólicos pancreáticos y ofrecer una nueva perspectiva para la prevención y/o el tratamiento de la diabetes. La investigación se llevó a cabo con ratas Wistar. Los animales fueron divididos en cuatro grupos: control, TRH, Fru y Fru -TRH. A los 25 días de edad, los animales (Fru, Fru -TRH) recibieron fructosa (20 %) y los grupos control recibieron agua; a los 60 días de edad (grupos TRH y Fru -TRH), el tratamiento con inyecciones intraperitoneales de TRH durante 7 días, las ratas control recibieron el mismo volumen de solución salina. Se recolectaron los páncreas, se estudiaron histológicamente y se tiñeron con eosina/hematoxilina (estudio estructural) y fucsina/paraldehído (estudio histoquímico); se midieron los parámetros bioquímicos, los niveles de insulina, las actividades de la catalasa, el malondialdehído (MDA) y el marcador inflamatorio NO. Encontramos que la TRH corrigió los parámetros metabólicos y los marcadores inflamatorios en los islotes al suprimir la infiltración celular y la vacuolización citoplasmática. Estos resultados sugieren que la acción directa de la TRH sobre las células β, debido a la presencia de su receptor a nivel de membrana, puede modular las alteraciones tisulares y funcionales de estas células en casos patológicos.

PALABRAS CLAVE: TRH; Fructosa; Células β; Estrés oxidativo; Rata.

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