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Short-Term Intraperitoneal Leptin Injections on Male Wistar Rats: Histology and Histomorphometry of Pancreatic Islets and Biochemical Parameters

Inyecciones Intraperitoneales de Leptina a Corto Plazo en Ratas Wistar Macho: Histología e Histomorfometría de Islotes Pancreáticos y Parámetros Bioquímicos

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SUMMARY: Leptin, a hormone primarily produced by adipocytes, plays a crucial role in maintaining energy balance. It also affects various organs, such as the pancreas. In order to study the peripheral effect of intraperitoneal exogenous leptin treatment, 60-day-old male Wistar rats received daily injections of leptin at a dose of 8 µg/100g body weight for 5 days. Several parameters were assessed to evaluate leptin's impact on pancreas, including tissue changes and blood levels of different biochemical markers, including insulin. The results show that leptin treatment influences body weight, leading to a decrease in plasma insulin and blood glucose levels, and an increase in cholesterol and triglyceride levels in treated rats compared to controls. Histomorphometric analysis of the pancreas in treated rats, after Haematoxylin-Eosin and Fuchsin-Paraldehyde staining, reveals a significant decrease in the diameter of the pancreatic islets (islets of Langerhans) in treated rats compared with controls, which suggests the presence of a disturbance in insulin secretion.

KEY WORDS: Leptin; Pancreas; Wistar rat; Insulin; Histomorphometry.

INTRODUCTION

Leptin is considered a key factor in the regulation of food intake and energy homeostasis in mammals. It is a 16-kDa non-glycosylated protein encoded by the ob (obese) gene (Zhang *et al*., 1994), located on human chromosome 7 (Friedman & Halaas, 1998; La Cava *et al*., 2004). It is mainly produced by adipose tissue and, at lower levels, by the gastric fundic mucosa, placenta, mammary epithelium, and skeletal muscle (Friedman & Halaas, 1998; Margetic *et al*., 2002). Leptin has multiple physiological functions not only in the regulation of body weight maintenance but also in immune function, reproduction, bone growth and development, and hematopoiesis (Fantuzzi & Faggioni, 2000; Whitfield, 2001).

Leptin binds to its specific receptors, which are abundant in the hypothalamic arcuate nucleus of the central nervous system and in peripheral tissues, such as pancreatic-β cells, liver, skeletal muscle and the cardiovascular system (Rahmouni & Haynes, 2004; Münzberg *et al*., 2005). The hypothalamic actions of leptin are relatively well characterized; it acts to suppress appetite and increase energy expenditure, which reduces body fat and food intake (Havel, 2000; Pan & Myers, 2018). However, the expression of the long form of the leptin receptor (Ob-Rb) in peripheral tissues, including the endocrine pancreas, indicates that leptin can also exert peripheral actions independently of its effects in the hypothalamus (Morioka *et al*., 2007).

Previous studies have investigated the effects of leptin on glucose, cholesterol, triglycerides and insulin plasma levels. They showed that leptin decreases blood glucose and inhibited fatty acid synthesis while stimulating fatty acid oxidation, inducing anti-lipogenic effects. Leptin controls glucose and lipid metabolism both centrally, by modulating hypothalamic neurons that regulate food intake

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and energy expenditure, and peripherally, by directly influencing glucose and lipid metabolism (Poitout *et al*., 1998; Hyogo *et al*., 2002; Pereira *et al*., 2021).

The administration of exogenous leptin has been used as a potential therapeutic strategy for obesity and diabetes. However, the role of leptin in the control of insulin secretion and action has been a subject of interest and controversy for several years. Previous studies have reported conflicting results regarding the effect of leptin on pancreatic β-cell function and glucose homeostasis, depending on the experimental model, the dose and the duration of leptin administration, and the metabolic status of the subjects (Burgos-Ramos *et al*., 2016; Marques-Oliveira *et al*., 2018).

In light of this, we investigated the impact of leptin after a short-term intraperitoneal treatment (5days) on the histology of the endocrine pancreas and several related parameters in Wistar rats, with the aim of obtaining a better understanding of its peripheral mechanisms of action and possible effects on pancreatic β-cells.

MATERIAL AND METHOD

Twenty male Wistar rats (n=20) aged 8 weeks, weighing 160-197g were obtained from the University's animal facility and kept since birth in a normal-sized plastic cages with stainless steel top grills, in a controlled temperature (+22-25 °C) with a 12:12 h light/dark cycle (LDC). Rats were fed standard pellet rat feed. All experimental procedures were approved by the Institutional Animal Care and use Committee of the University of Sciences and Technology, Houari Boumediene (USTHB) and were carried out according to the ethical approval number: 981-1 law of August 22, 1998, of the National Administration of Algerian Higher Education and Scientific Research.

Experimental procedure

Rats were housed individually and divided into two groups: the treated group (T) was injected intraperitoneally (i.p.) with 8 µg/100 g of body weight of recombinant rat leptin (lyophilized powder, Sigma-Aldrich®) for 5 days, while control group (C) received the same volume of 0.9 % NaCl. Body weight was daily recorded and all injections were conducted at 8:30 a.m. At the end of the experiment and after an overnight fasting, rats were euthanized by decapitation and blood was collected into 2 % EDTA tubes and centrifuged (3 000 x g for 15 min at 4 °C) to obtain plasma, which was stored at -20 °C. The pancreas was quickly removed; one part was fixed, while the other one was immediately stored at -20 °C until the beginning of assays.

Tissue homogenization

Frozen pancreas were homogenized in phosphate buffer solution (pH= 7.4). The homogenate was centrifuged (4 000 x g for 20 min at 4 °C), and the supernatants were collected for the measurement of insulin concentration.

Biochemical parameters

Glucose, triglycerides and cholesterol levels were measured using SPINREACT® Kits (Spinreact, Sant Esteve de Bas, Spain) by the enzymatic-colorimetric method and spectrophotometry (Biochrom S1200, United Kingdom).

Radioimmunoassay of insulin

Insulin plasma and glandular concentrations in samples were determined by radioimmunoassay (RIA) kit (Cisbio Bioassays®, Parc Marcel Boitaux, France) using a Perkin Elmer Wallac 1470® Gamma Counter (Finland) with a detection limit of 4.6 µUI/mL.

Histological procedure

The pancreas was fixed in 10 % formalin. After dehydration in graded ethanol and impregnation in paraffin wax, each block was cut into 4 µm-thick slices using microtome (Leica®, Germany) and stained with Haematoxylin and Eosin (Martoja & Martoja, 1967) for microscopic examination.

Paraldehyde-Fuchsine stain procedure

The staining was performed on pancreatic sections to highlight the color difference between a and β-cells (Gabe, 1968). The sections were deparaffinized with xylene (15 min) and rehydrated for 2 minutes with alcohol decreasing concentrations (100°, 95° and 70°); then put in distilled water for 4 minutes.

The paraldehyde-fuchsine staining protocol was used according to Gabe (1968) and Ewen (1962). Sections were immersed in an oxidizing mixture prepared with 2.5 % $KMnO_4$ and 5 % H_2SO_4 (V/V) until it turned red-brown, rinsed with tap water, then destained in 2.5 % sodium bisulfite.

After rinsing with tap water, sections were stained with paraldehyde-fuchsine solution for 8 minutes to color β-cells, rinsed with distilled water, then immersed in Groat's hematoxylin solution for 2 minutes and rinsed with tap water for 3 minutes to remove excess stain.

Sections were stained with Orange G-Erythrosine (V/V) for 1 minute to color a-cells, then placed in tungstic acid (4 min) and rapidly dehydrated in absolute ethanol (2 changes), clarified in xylene and a cover slip was mounted with synthetic resin.

Histomorphometric analysis

The procedures utilized a hardware consisting of a HIROCAM® MA88-500-megapixel high-resolution color digital camera mounted on an OPTIKA® Trinocular photonic microscope. The diameter of pancreatic islets was measured using TSView® image analysis software (version 6.2.4.5, Tucsen Imaging Technology). Four sections were examined for each animal in both groups.

Statistical analysis

All data were expressed as mean ± SEM (Standard Error of the Mean). Groups were compared using Student's t-test. The differences were considered significant at $P < 0.05$.

RESULTS

Changes in body weight gain and food intake

The Delta body weight of leptin-treated group increased gradually during the 5 days of treatment but remained lower than the control group (P> 0.05) (Fig. 1). While the average daily food intake was significantly reduced in leptin-treated group (P=0.0046) compared to control (Fig. 2).

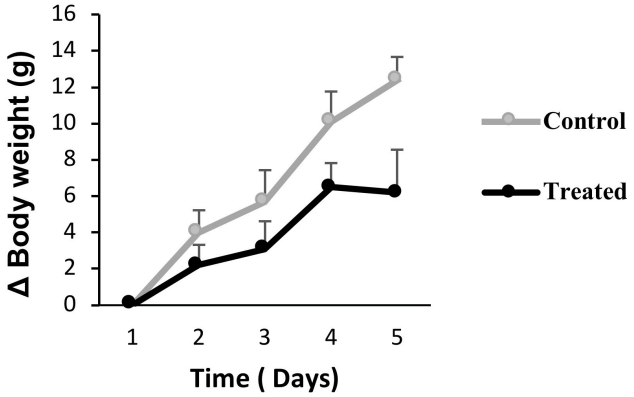

Fig. 1. Effect of intraperitoneal leptin injections on body weight in treated and control groups. Bars represent Mean ± SEM.

Biochemical parameters and hormonal assays

Daily leptin injections decreased blood glucose levels (P=0.51, - 4.21 %) (Fig. 3A) and increased triglycerides (P=0.80, +6.69 %) (Fig 3B) and cholesterol (P=0.30, +32.88 %) (Fig. 3C) in the treated group compared to the control, but the differences was not statistically significant (P>0.05). Furthermore, in contrast to the control group, plasma insulin levels in the leptin-treated group decreased non-significantly (-12.75 %, P>0.05), while glandular insulin levels increased non-significantly (+13.23 %, P>0.05) (Table I).

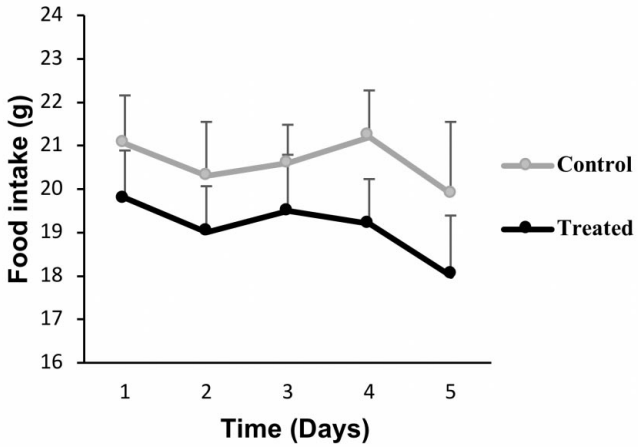

Fig. 2. Effect of intraperitoneal leptin injections on food intake in treated and control groups. Bars represent Mean ± SEM.

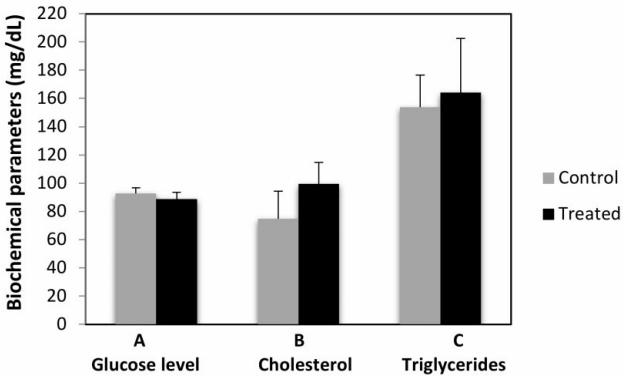

Fig. 3. Effect of leptin's injections on biochemical parameters in control and treated groups: A- Glucose level, B- Cholesterol and C- Triglycerides. Bars represent Means ± SEM.

Table I. Insulin, glandular insulin and morphometric study in control and treated groups.

	Control	Treated
Insulin (µUI/mL)	24.81 ± 87.24	21.65 ± 12.75[a]
Glandular insulin (µUI/mL)	1513.42 ±	1713.69 ± 95.04[a]
Mean diameter pancreatic islets (µm)	93.84 ± 3.59	76.33 ± 4.73[b]

Data are expressed as means ± SEM. a Treated vs Control P>0.05 b Treated vs Control P<0.01

Histological study

Histological study of endocrine pancreas using Hematoxylin and Eosin and morphometric analysis

Pancreatic sections of controls revealed a regular and well-defined pancreatic islets (Fig. 4a), grouped in clusters of weakly stained polygonal cells, separated by a network of blood capillaries (Fig. 4b). Similarly, the sections of the leptin-treated group showed the same appearance of the islets, without significant difference in structure and staining compared to the previous group (Fig. 4c), except for the cytoplasmic volume of the cells (Fig. 4d). The morphometric assessment of pancreatic islets showed a significant decrease in diameter (P=0.002, -18.66 %) (Table I).

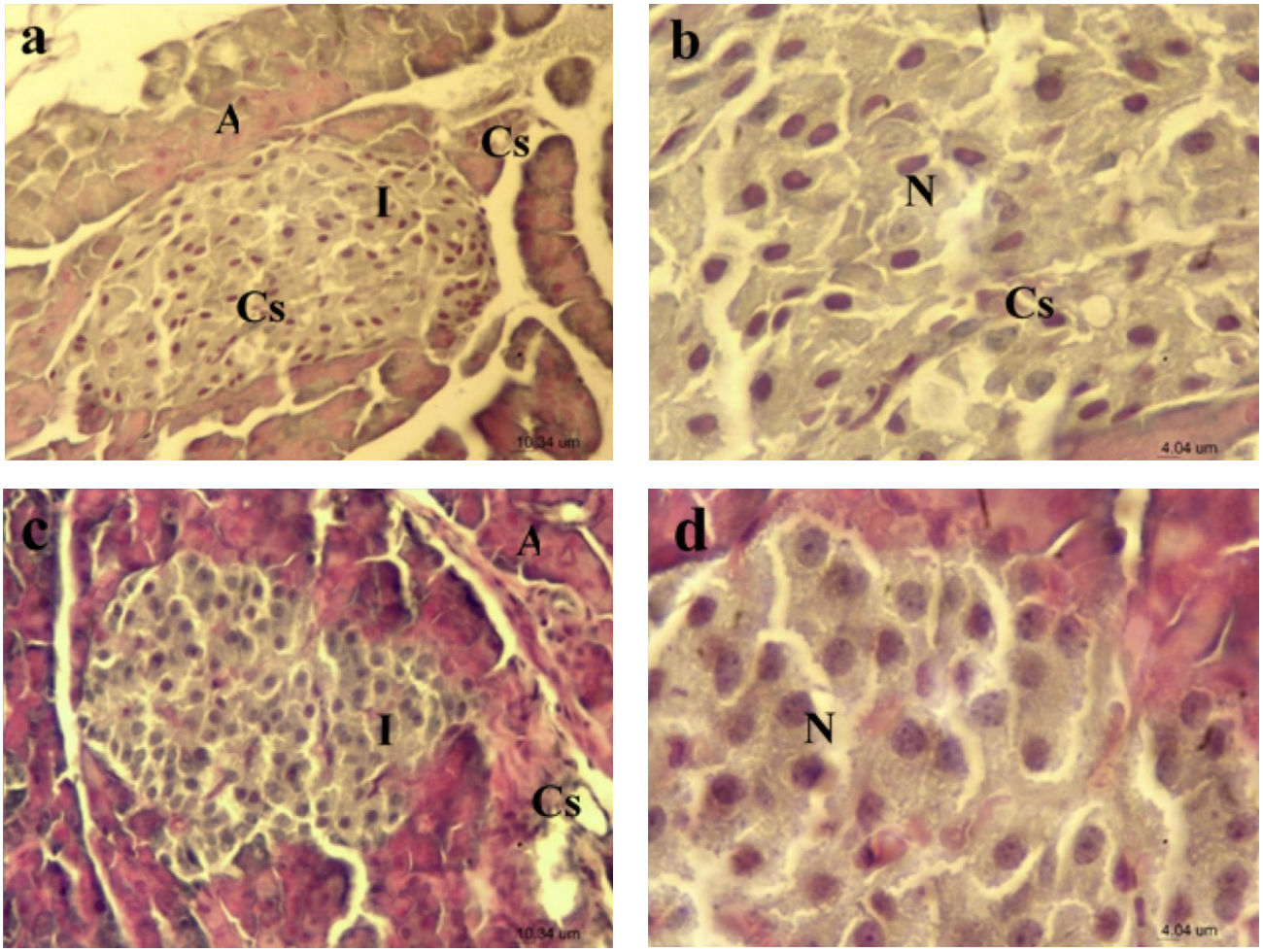

Fig. 4. Histophysiological observations of pancreatic islets in control and leptin-treated groups of male Wistar rats. Sections of pancreatic islets stained with Hematoxylin and Eosin from (a) control group at 400-fold magnification (scale bars = 10,34 μm), (b) control group at 1000-fold magnification (scale bars = 4,04 μm), (c) leptin-treated group at 400-fold magnification (scale bars: 10,34 μm) and (d) leptin-treated group at 1000-fold magnification (scale bars: 4,04 μm).

Histological study of endocrine pancreas using Paraldehyde-Fuchsine staining

Pancreatic islets from the control group showed that most cells were b-cells due to the presence of purple granules in their cytoplasm. These cells filled the center of the islet, while the a-cells that were scattered between the b-cells or at the periphery, appeared clear with orange staining (Fig. 5. a, b). In the leptin-treated group, there was a decrease in the density of purple-stained cells within the β-cell granules, but orange-stained a-cells were still present, with no apparent differences comparted to the control group (Fig. 5 c, d).

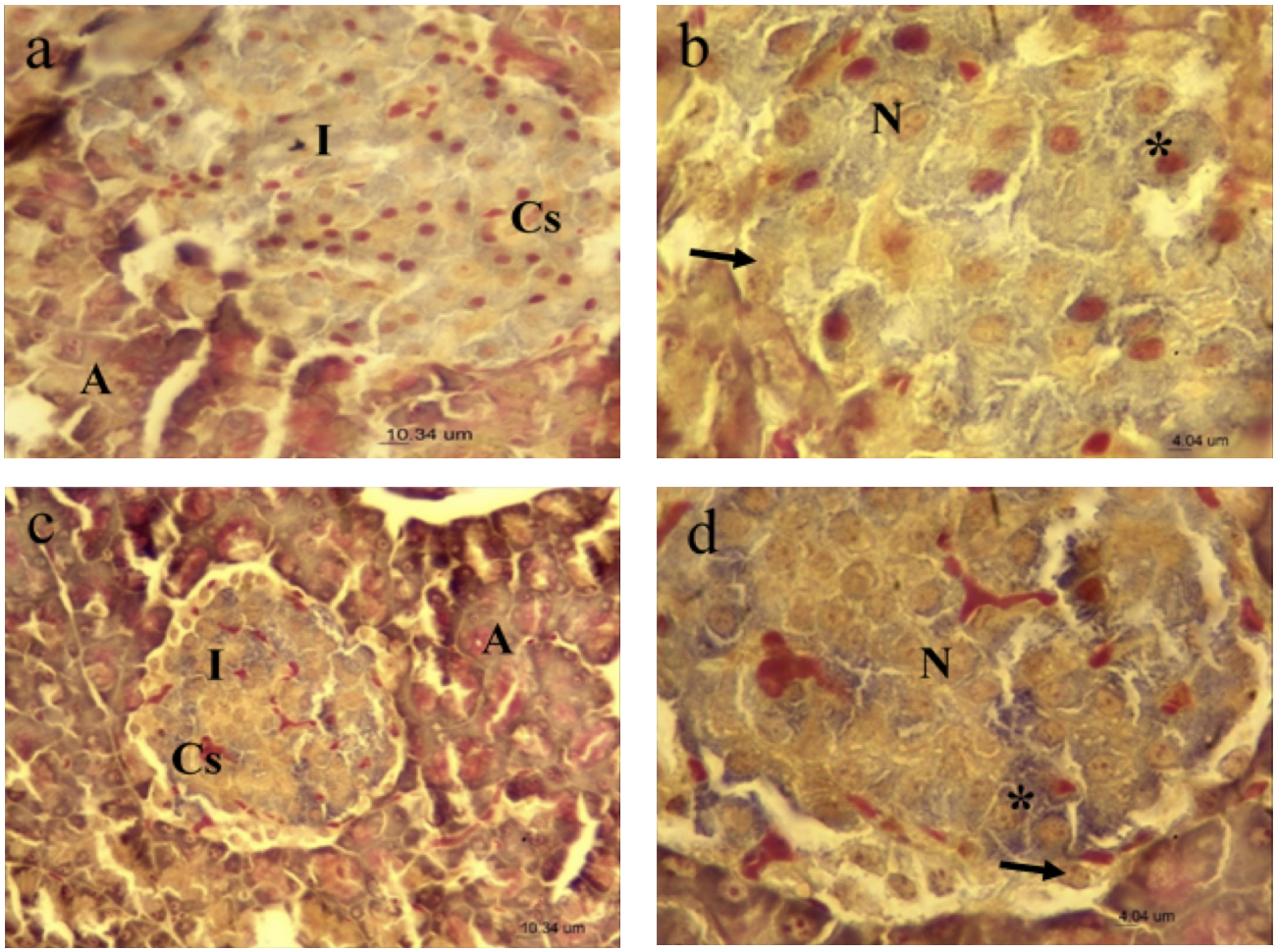

Fig. 5. Sections of pancreatic islets stained with Paraldehyde-Fuchsine from (a) control group at 400-fold magnification (scale bars = 10,34 µm). (b) control group at 1000-fold magnification (scale bars = 4,04 µm), (c) leptin-treated group at 400-fold magnification (scale bars = 10,34 µm) and (d) leptin-treated group at 1000-fold magnification (scale bars = 4,04 µm). A: acinus; I: islet; Cs: blood capillaries; N: nucleus; (*) β-cell with purple granules in the cytoplasm; (Æ) a-cell stained in orange.

DISCUSSION

Previous studies have reported that central leptin plays a major role on feeding and body weight via its hypothalamic receptors (Friedman & Halaas, 1998; Havel, 2000), and leptin's ability to significantly reduce food intake and body weight in a dose-dependent manner after central administration is well established (Satoh *et al*., 1997; Bruijnzeel *et al*., 2011). By contrast, relatively less attention has been paid to an intraperitoneal administration of this protein on body weight and peripheral organs. In this context, this study aims to show the peripheral effect of intraperitoneal injection of exogenous leptin (08 µg/100 g BW) on eating behavior and the endocrine pancreas.

Our results show that leptin has a non-significant decreasing effect on body weight and food intake in treated rats, but this remains moderate due to the brevity of the treatment; the decrease is visible on the last day of the injection when the major effect begins to be seen. The same results were found by Patel & Ebenezer (2008), who showed that leptin administered intraperitoneally at low microgram doses in the range of 1 to 25 mg/kg BW for 30 min over a period of 24 h suppresses food intake in fasted rats, this effect has a fairly rapid onset and a relatively short duration of action. Even via an implanted mini-pump; administration of leptin to STZ-induced diabetic mice does not result in a significant change in body weight compared to control mice on STZ. However, mice treated with 5 or 10 mg/day of leptin for 4 weeks initially tended to lose weight and then gain it after day 12 (Denroche *et al*., 2013).

Leptin provides a signal to the hypothalamus and hindbrain (Chen & Heiman, 2000) to decrease the expression

of neuropeptides such as agouti-related protein (AgRP) and neuropeptide Y (NPY) which are orexigenic (Coppari *et al*., 2005; Van De Wall *et al*., 2008) and increase the expression of other neuropeptides that are anorectic such as POMC (Proopiomélanocortine) and CRH (Corticotropin-Releasing Hormone) (Cowley *et al*., 1999; Su *et al*., 2012).

However, intraperitoneal administration of leptin may induce indirectly a stimulation of vagal afferents by releasing other peripheral satiety factors, such as cholecystokinin (Matson *et al*., 1997; Friedman & Halaas, 1998) and bombesin (Ohki-Hamazaki *et al*., 1997).

On the other hand, our treatment increases non significantly plasma triglycerides and cholesterol levels in the treated group compared to control, the same results were found previously after intravenous injection in rats with recombinant murine leptin (1 mg/kg body weight) which induced an increase in plasma triacylglycerols that was not associated with changes in total plasma cholesterol, and which could be due to a decrease in the clearance of circulating triacylglycerols in the form of chylomicra or Very Low Density Lipoproteins (VLDL) (López-Soriano *et al*., 1998).

Leptin plays an integral role in cholesterol homeostasis; it downregulates cholesterol biosynthesis, upregulates cholesterol catabolism, decreases VLDL cholesterol concentrations, and promotes biliary clearance of plasma cholesterol (VanPatten *et al*., 2001; Igel *et al*., 2002).

While our results show that intraperitoneal leptin treatment slightly decreases blood glucose levels in treated adult rats, a previous study showed that subcutaneous treatment at a dose of 10μg/kg BW for 8 days in C57BL/6 mice significantly increased them (Birk & Rubinstein, 2007). In addition, other studies have shown that high-dose leptin administration reverses hyperglycemia in type 1 diabetes rodent models (Fujikawa *et al*., 2010; Wang *et al*., 2010), and normalizes blood glucose in a dose-dependent manner in streptozotocin-diabetic mice (Denroche *et al*., 2013).

Burgos-Ramos *et al*. (2015) results show that leptin is involved in the regulation of blood glucose levels by reducing its rise. This inflation is induced by the increase in insulin levels in the brain, by modifying hepatic glucose metabolism (Burgos-Ramos *et al*., 2015).

In this study, leptin injection induced a decrease in plasma insulin levels, in contrast to its increase inside the gland. These results are not significant between the treated and the controls over this short period. Chen & Heiman (2000) reported that plasma insulin levels were reduced by 55 % after 35 days of subcutaneous leptin injections. Similar outcomes were observed following leptin infusion, which significantly reduced plasma insulin levels and suppressed glucose-stimulated insulin secretion in a dose-dependent manner (Cases *et al*., 2001) or maintaining the latter's decrease in STZ diabetic mice (Denroche *et al*., 2013).

Exogenous leptin is known to act centrally and exert positive effects on peripheral insulin signaling which involve leptin-insulin crosstalk (Burgos-Ramos *et al*., 2016), including changes in peripheral hormones that affect insulin sensitivity and glucose metabolism (Burgos-Ramos *et al*., 2015).

In vivo and *in vitro* studies have shown that leptin suppresses insulin secretion via its lipopenic effect on islet cells (Cases *et al*., 2001) and can have an inhibitory effect on insulin gene expression and secretion in isolated murine and human islets and b-cell lines (Morioka *et al*., 2007). Moreover, leptin can directly affect insulin secretion by reducing its mRNA expression and secretion in pancreatic b-cells (Emilsson *et al*., 1997; Berthou *et al*., 2011).

In rats, leptin decreases β-cell size (Park *et al*., 2008; D'Souza *et al*., 2014), which is consistent with our islet morphometric study. The significant decrease in the diameter of islets, injected with leptin, in treated group proves that despite the short duration of treatment, leptin may have affected β-cell size, since the absence of leptin signaling in pancreatic ObR-KO mice increases p70S6K and PKB/Akt phosphorylation, which are important in determining β-cell size and survival, respectively, and likely contribute to the increase in β-cell size and islet mass (Morioka *et al*., 2007). In addition to its inhibitory effect on insulin secretion, which can be reduced by increasing glucose and GLP-1 concentrations (Ronveaux *et al*., 2015), leptin suppresses Ca2+ influx (Morioka *et al*., 2007) and maintains β-cells in a hyperpolarized state (Kieffer *et al*., 1997) by increasing β-cell membrane K+ conductance (Chen *et al*., 2013) via their respective Kv2.1 channels (Wu *et al*., 2015) and KATP channel trafficking (Lim *et al*., 2009; Park *et al*., 2013) in a strikingly similar manner, without effect on other membrane proteins and ion channels (Wu *et al*., 2015).

In summary, our results indicate that short-term intraperitoneal administration of leptin at a dose of 8 μg/ 100 g body weight had less impact than reported in other studies with central infusion. Its effect on body weight and food intake and its influence on the histophysiology of pancreatic islets and insulin secretion by β-cells remain moderate.

BOUCHEFA, H.; GHOURI, I.; MORZOUGLAL, N.; GHOZLANI, A.; AIT SAI, T. & HADJ-BEKKOUCHE, F. Inyecciones intraperitoneales de leptina a corto plazo en ratas Wistar macho: Histología e histomorfometría de islotes pancreáticos y parámetros bioquímicos. *Int. J. Morphol, 44(1)*:231-238, 2026.

RESUMEN: La leptina, una hormona producida principalmente por los adipocitos, desempeña un papel crucial en el mantenimiento del equilibrio energético. También afecta a diversos órganos, como el páncreas. Para estudiar el efecto periférico del tratamiento con leptina exógena intraperitoneal, ratas Wistar macho de 60 días de edad recibieron inyecciones diarias de leptina a una dosis de 8 µg/100 g de peso corporal durante 5 días. Se evaluaron diversos parámetros para evaluar el impacto de la leptina en el páncreas, incluyendo cambios tisulares y niveles sanguíneos de diferentes marcadores bioquímicos, incluyendo la insulina. Los resultados muestran que el tratamiento con leptina influye en el peso corporal, provocando una disminución de los niveles plasmáticos de insulina y glucosa en sangre, y un aumento de los niveles de colesterol y triglicéridos en ratas tratadas en comparación con los controles. El análisis histomorfométrico del páncreas en ratas tratadas, tras la tinción con hematoxilina-eosina y fucsina-paraldehído, revela una disminución significativa del diámetro de los islotes pancreáticos en ratas tratadas en comparación con los controles, lo que sugiere la presencia de una alteración en la secreción de insulina.

PALABRAS CLAVE: Leptina; Páncreas; Rata Wistar; Insulina; Histomorfometría.

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