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EFFECTS OF OBESITY IN RATS ON PROSTATE HISTOLOGY AND EXPRESSION OF LEPTIN RECEPTOR, PROLACTIN RECEPTOR, IL-6, AND NF-κB

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***Background*: Hypercaloric intake can lead to obesity, which is a major risk factor associated with chronic subclinical inflammation and many types of cancer. It can increase the serum levels of leptin, prolactin, nuclear factor kappa B (NF-κB) and interleukin (IL)-6, implicated in cell proliferation, differentiation and survival. *Aim*: To explore the effects of obesity induced by chronic hypercaloric diet in rats on the long-term expression of leptin receptor (OB-R), prolactin receptor, NF-κB, and IL-6, and the changes of histology in rat prostate. *Materials and Methods*: From postnatal day 21, experimental males were fed with normal chow or chow plus enriched hypercaloric liquid diet. On the postnatal day 90 (13 week old), the animals were euthanized for prostate histology (hematoxylin and eosin staining) and hormone receptors analysis by Western blot. *Results*: Hypercaloric diet resulted in obesity (32% higher body weight). The prostates of the obese males showed epithelium anisocytosis and compressed interstice. There was also greater volume of lipidic content, anisokaryosis, alterations of the nucleus-cytoplasm ratio, and apparent proplasia. Measures in the ventral prostate (VP) showed that alveoli area increased, but epithelium height and nucleus area were reduced. In the dorsolateral prostate, there was only reduction of nucleus area and presence of mononuclear cells in the lumen. Hypercaloric males also expressed a trend for more OB-R 130 kD in the VP, but no changes were observed with regard to prolactin receptor, NF-κB and IL-6. *Conclusion*: The obesity due to chronic consumption of hypercaloric diet affects both prostatic regions, but VP is possibly more sensitive via OB-R. We suggest that longer periods of obesity are needed to alter other receptors or the molecular markers of inflammation.**

***Key Words*: leptin, prolactin, obesity, prostate, leptin receptor, prolactin receptor, IL-6, NF-κB.**

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The prostate, an exocrine gland with reproductive functions in males, is susceptible to different types of disorders such as inflammation (prostatitis), progressive enlargement (benign hyperplasia), and cancer (CaP). All those disorders may express an insidious evolution, especially as a result of long-term exposure to risk factors that produce subtle, but steady changes in hormones and its receptors, like it occurs with obesity.

Obese individuals express higher serum levels of leptin [1, 2], and prostates with CaP exhibit more leptin receptors (OB-R) [3–5]. Thus, alterations in the expression of OB-R in the prostate may be detectable in obese individuals before they develop CaP. Similarly, obese individuals express higher serum levels of prolactin (PRL) [6, 7] and high levels of PRL elevate the prostatic expression of its receptors (PRL-R) [8]. Activation of PRL-R can facilitate cell proliferation, differentiation and survival via signaling pathways such as JAK tyrosine kinase, STAT and MAPK, which at the long run, promote the development of abnormal tissue [9]. For example, one former study showed that long-term administration of PRL resulted in the development of precancerous lesions in rats, transitioning from normal to displastic tissue in eight weeks [10]. Therefore, obese individuals may also exhibit alterations in the expression of PRL-R and subtle changes in prostatic tissue before they develop CaP.

In a recent study with adult rats, it was shown that obesity was associated with precancerous lesions after 8 weeks of chronic consumption of hypercaloric diet. For example, both the dorsolateral (DLP) and ventral (VP) prostatic regions of obese animals expressed more cases of epithelium dysplasia (30–30%), anisocytosis (70–90%), anisokaryosis (50–70%), apolarity (50–30%), low nucleus-cytoplasm ratio (50–70%), and presence of more mononuclear cells (50–70%), respectively [11]. The presence of mononuclear cells in the two prostatic regions supports the association of obesity to a state of chronic subclinical inflammation. Indeed, previous reports have shown that obesity augments the production of nuclear factor κB (NF-κB) and proinflammatory interleukins (IL-6) in cell cultures [12, 13].

Thus, based on the above-mentioned data, the present study was designed to explore the effects of obesity induced by chronic hypercaloric diet from infancy to adulthood on the long-term expression of prostatic OB-R, PRL-R, NF-κB, IL-6, and the relation to histology and changes in epithelium height, alveoli area and nucleus area. We hypothesized that obese male rats chronically fed with a hypercaloric diet from infancy to adulthood would express more OB-R, PRL-R, NF-κB, IL-6, and more histological changes in adulthood than those males fed with normal chow diet.

MATERIALS AND METHODS

Animals. Twelve Wistar male rats (*Rattus norvegicus albinus*) were purchased and shipped at 4 weeks

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Abbreviation used: CaP – cancer of prostate; DLP – dorsolateral prostate; IL – interleukin; NF-κB – nuclear factor κB; OB-R – leptin receptor; PRL-R – prolactin receptor; VP – ventral prostate.

of age from a certified laboratory animal supplier in Mexico (Circulo ADN). They were housed in groups of six rats in large Plexiglas cages (50 × 30 × 20 cm) and kept in a colony room in a 12–12 h reverse Light-Dark cycle (lights off at 8:00 h). Water and commercial rat chow (Lab Diet 5001) were provided *ad libitum*. All the experimental procedures were carried out according to the Official Mexican Norm for use and care of laboratory animals (NOM-062-ZOO-1999) and the International Guiding Principles for Biomedical Research, and approved by the Animal Care Committee of the Instituto de Investigaciones Cerebrales, Universidad Veracruzana.

Groups and treatments. On the day of weaning (3 weeks of age), rats were randomly assigned to: 1) normal diet or 2) hypercaloric diet. Males in the normal diet group received regular rodent chow (Lab Diet, 5001), whereas those in the hypercaloric group received regular chow plus additional liquid diet during ten weeks; consisting of 97 kcal/100 ml, 15% protein, 30% fat, 54% carbohydrates. Sufficient liquid hypercaloric diet was provided *ad libitum* (at least 100 ml *per* rat/day) and body weight was recorded every week (Fig. 1).

Prostate samples and histology. At 13 weeks of age, rats were euthanized with an overdose of sodium pentobarbital (120 mg/kg i.p.). An abdominal incision was performed and the prostate was carefully removed and placed into a container with 0.9% saline solution. The prostate was identified under a dissecting microscope (MEJI, EMZ-TR) as VP and DLP [10, 11, 14]. The left halves of VP and DLP were processed for histology. The tissue samples were soaked in 10% formalin for 24 h, then dehydrated in ascending grades of ethyl alcohol, treated with xylene, embedded in paraffin wax, sliced (5 µm thick) with a microtome (RM 2125RT Leica, Germany), mounted on slides at 52 °C (containing pork skin-based gelatin 2.5 mg/100 ml) and then processed for standard hematoxylin and eosin (H&E) staining technique. Upon dehydration in ethanol ethanol/xylene, and xylene, the slides were cover slipped with Permount (SP15-500 Fisher chemicals), air dried, and observed under light microscope Optisum Mic 990 (Desego, Mexico). Photomicrographs were taken at ×4, ×20 and ×40 (×100 for nucleus diameter) and analyzed by the same experimenters. The histological analysis included epithelium height (mm), nucleus area (mm^2) and alveoli area (mm^2). Similar to previous reports, we also assessed normality of the prostate by taking into consideration 12 histological features following 3-dimensional microscopic observations (Table 1) [10, 11, 14].

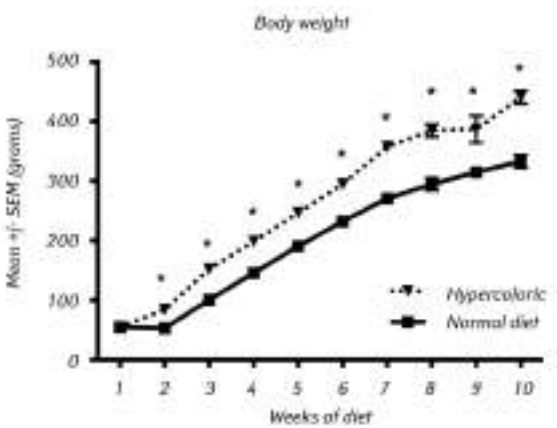

Fig. 1. Males fed with a hypercaloric diet were overweighed starting at the second week, and continued obese by 10th week (>30% body weight). Two-way ANOVA (time x group), followed by a Bonferroni's multiple comparisons test

Western blot. The right halves of VP and DLP were processed for protein expression via Western blots. NP-40 lysis buffer and mini protease inhibitor cocktail Tablets (1 tablet/10 ml lysis buffer; Roche-Diagnostics, USA) was used for protein extraction. Protein concentration was determined spectrophotometrically using a Pierce BCA protein assay kit (Thermo Fisher Scientific, USA). Protein electrophoresis was done in SDS-PAGE gels (10% for PRL-R, OB-R and 12% for p-NF-κB p50 and IL-6). Samples were treated under reducing conditions with Laemmli buffer. Later, proteins were transferred to nitrocellulose (Bio Rad, USA) (for PRL-R, OB-R and p-NF-κB p50) and PVDF (Immobilon-P, Millipore, USA) membranes (for IL-6), respectively; followed by washing with TBS-Tween 1% and blocking with TBS-Tween- nonfat milk 5% for 1 h at room temperature. After washing, membranes were incubated during 18 h at 4° C with primary antibodies: mouse monoclonal anti-PRL-R (dil 1:500, ab2772; Abcam, USA), the following mouse monoclonals from Santa Cruz Biotechnology Inc., USA: anti p-NF-κB p50 (dil 1:1000, sc-271908), anti-OB-R Antibody (B-3) (dil 1:200, sc-271908), and anti-IL-6 IgG2b (dil 1:200, sc-57315) and rabbit polyclonal anti GAPDH (dil 1:500, sc-25778; Santa Cruz Biotechnology, USA). Then, washed membranes were treated with the corresponding secondary antibodies for 1 h at room temperature, AP Goat-anti mouse (IgG1, dil 1:500, ab97020; Abcam, USA) and AP Goat-

Table 1. Characterization of histology in the prostate of adult rats. Normal features were inferred from the number of cases observed in normal diet males of the present study

Histological feature	Region	Normal diet (expected)	Hypercaloric diet
Epithelium form	DLP	Cubic	Cubic
	VP	Columnar	Columnar
Epithelum size	DLP	Even	Anisocytosis +
	VP		Anisocytosis ++
Epithelium papillae	DLP	Scarce	Scarce
	VP		Scarce
Interstice space	DLP	Even	Compressed ++
	VP		Compressed +
Interstice content	DLP	Collagen	Mononuclear +
	VP		collagen
Nucleus size	DLP	Even	Anisokaryosis ++
	VP		Anisokaryosis +
Nucleus location	DLP	Basal cell polarity	Polar
	VP		Non-polar
Nucleus-Cytoplasm ratio	DLP	1:3	1:2
	VP		1:3
Myoepithelium	DLP	Euplasia	Proplasia
	VP		Euplasia
Pattern (at ×4)	DLP	Tubular	Tubular
	VP		Tubular
Lumen content	DLP	Amorphous	Mononuclear ++
	VP		Amorphous
Chromatin	DLP	Heterochromatin	Hetero/euchromatin
	VP		Hetero/euchromatin

anti rabbit IgG1 (dil 1:1000, sc: 2004, Santa Cruz Biotechnology, USA). Finally, proteins were detected with 1-StepTM NBC/BCIP (Thermo Fisher Scientific, USA). Membranes were scanned in ChemiDoc XRS+ (Bio Rad, USA) and protein density was analyzed in Image J 1.52n software (Wayne Rasband, National Institutes of Health, USA). GAPDH expression was used as loading control for PRL-R, OB-R and p-NF-κB p50, and total protein stained with Coomassie for IL-6 [15]. Protein expression was reported as normalized density to loading control.

Statistical analysis. Body weight (grams) was analyzed with a two-way repeated measures (time X group) analysis of variance (ANOVA), followed by a Bonferroni's multiple comparisons test to detect individual differences between the normal diet and hypercaloric diet. Twelve histological features were described (see Table 1) to figure out normal or abnormal conditions of prostatic tissue. In addition, epithelium height (mm), alveoli area (mm^2) and nucleus area (mm^2) were analyzed with an unpaired *t*-test (one-tailed). The density of OB-R, PRL-R, IL-6, and p-NF-κB bands in Western blot was analyzed with an unpaired *t*-test (one-tailed). All statistical analyses were performed using GraphPad Prism version 8.00 for Mac, GraphPad Software, USA, www.graphpad.com and alpha level was set at $p < 0.05$.

RESULTS AND DISCUSSION

The ANOVA detected a main effect of time $F(3.268, 32.68) = 471.1$, $p < 0.0001$; a main effect of group $F(1, 10) = 141.7$, $p = 0.001$; and an interaction between time and group $F(9, 90) = 7.780$, $p < 0.001$. Our results indicated that hypercaloric males were heavier starting from the second week of diet, and remained obese until the 10th week (Fig. 1).

No cases of dysplasia or metaplasia were observed. However, males fed with hypercaloric diet expressed different prostatic histology compared to males fed with normal diet. Table 1 shows some of the differences between non-obese *vs*. obese rats in the DLP and VP portions, respectively. In general, obese rats showed epithelium anisocytosis (different cell size), compressed interstice and the lumen contained round cells (i.e. mononuclear cells), suggesting an ongoing (mild) inflammatory process. In VP, there was nucleus apolarity, prominent nucleoli and vacuolated cytoplasm. The DLP showed greater refringent droplets (suggesting more lipidic content), anisokaryosis (different nucleus size), alterations of the nucleus-cytoplasm ratio, and general apparent proplasia (Fig. 2, 3).

There was a reduction of the epithelium height and nucleus area, but increased alveoli area in the VP (Table 2), presummably as consequence of greater volume of prostatic liquid. In the DLP, however, there was only a reduction of nucleus area (Table 2). With regard to OB-R, PRL-R, NF-κB, and IL-6, the statistical analysis failed to detect significant differences (Fig. 4, Table 2). However, we detected a trend for significance

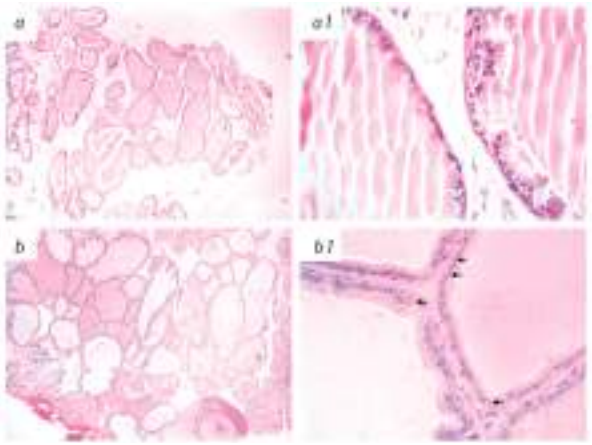

Fig. 2. Photomicrography (×4, ×40) of DLP of rats fed with normal diet (*a, a1*) or hypercaloric diet (*b, b1*). Alveoli area is observed more distended in *b*. Presence of mononuclear cells is observed in *b1*. Arrows show different cell size (anisocytosis)

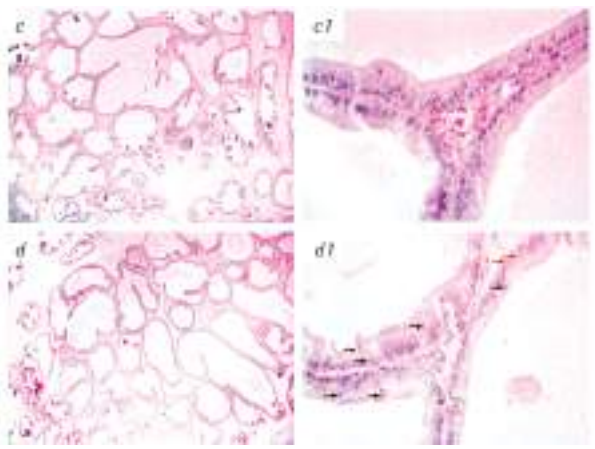

Fig. 3. Photomicrography (×4, ×40) of VP of rats fed with normal diet (*c, c1*) and males fed with hypercaloric diet (*d, d1*). Black arrows show nucleus apolarity. Red arrows show prominent nucleoli

($p = 0.08$) in higher expression of OB-R 130 kD in the VP of hypercaloric males.

The present study was designed to assess the effects of obesity on histological modifications and on the expression of OB-R, PRL-R, NF-κB, IL-6 in the two regions of the prostates of young rats. As expected, hypercaloric males became obese by the 2nd week of diet, and continued so (> 30% of body weight than controls) until the 10th week of diet (Fig. 1). The features of the abnormal prostate histology were evident in the obese rats. Judging by histological features, VP seems to be more sensitive to the effects of hypercaloric diet/obesity than DLP.

We report the presence of proplasia and considered it as the state of tissue in which activity is (apprently) increased above that of euplasia, characterized by signs of extension of tissue, amount of secretions, vacuoles, vascularization, cell size, and nucleous size. However, our measures indicated that hypercaloric diet did not increase cell size or nuclei. Thus, we suggest that hypercaloric diet facilitated general proplasia, which induced compression of the cells and nuclei. In addition, we reported the presence of nucleus apolarity in epithelial cells. Apolarity may be a morphological manifestation

Table 2. Mean values of prostate histological and molecular measures in DLP and VP. Rats were fed with normal (regular) chow or enriched with hypercaloric liquid diet

Variable	Diet		Statistics
	Normal	*Hypercaloric*	*Unpaired t-test*
Epithelium Height (μm)	*mean*	*mean*	
DLP	14.93	15.05	t=0.05627, df=10, p=0.47
VP	21.09	14.25	t=3.858, df=10, p=0.001 *
Alveoli Area (μm^2)			
DLP	100,752	122,088	t=1.056, df=10, p=0.15
VP	91,016	151,862	t=3.001, df=10, p=0.006 *
Nucleus Area (μm^2)			
DLP	28.78	24.02	t=3.637, df=10, p=0.002 *
VP	28.97	23.59	t=2.495, df=10, p=0.01 *
OBR49 kD (nd)			
DLP	30092	50730	t=1.089, df=10, p=0.15
VP	31961	35981	t=0.4803, df=10, p=0.32
OBR53 kD (nd)			
DLP	40138	49382	t=0.6899, df=10, p=0.25
VP	36185	37095	t=0.1072, df=10, p=0.45
OBR130 kD (nd)			
DLP	30045	42379	t=0.6780, df=10, p=0.25
VP	23234	37663	t=1.502, df=10, p=0.08
PRLR50 kD (nd)			
DLP	25377	22620	t=0.2982, df=10, p=0.38
VP	22878	23342	t=0.08497, df=10, p=0.46
PRLR60 kD (nd)			
DLP	28878	27772	t=0.1449, df=10, p=0.44
VP	22627	25903	t=0.8923, df=10, p=0.19
IL-6 (nd)			
DLP	35312	27811	t=0.9709, df=10, p=0.17
VP	-	-	-
NF-κB (nd)			
DLP	13134	12078	t=0.1796, df=10, p=0.43
VP	10959	17039	t=1.234, df=10, p=0.12

Notes: nd – normalized density. IL-6 was not detected in VP.

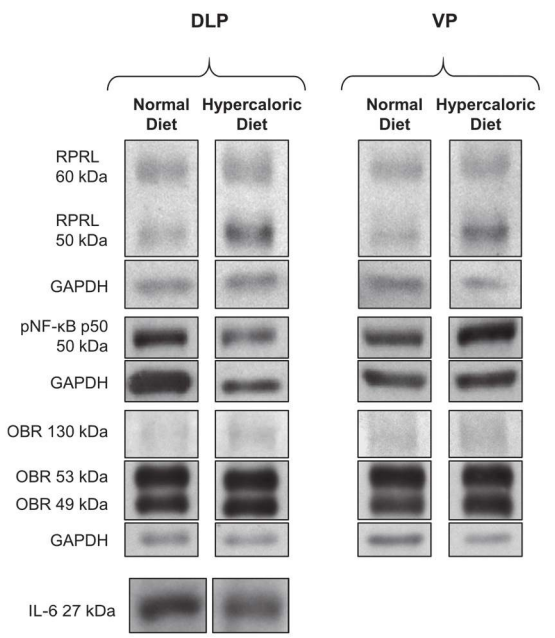

Fig. 4. Western blots of OB-R, PRL-R, IL-6, and p-NF-κB of rats fed with normal diet or hypercaloric diet

of the extrusion of cells of the epithelial layer into the lumen of the acini. Extrusion is a stereotypical epithelium response that can increase under the influence of various factors, including a hypercaloric diet.

Obesity is a known risk factor for the development of cancerous and precancerous prostatic lesions [16]. This is relevant considering that obesity rate in some countries (i.e. USA) affects up to 42.8% of the population [17]. In the present study we showed that obesity alone in young males induced by hypercaloric diet from infancy to adulthood provoked histological modifications, and well as changes in epithelium height, nucleus size and alveoli area. Interestingly, in a previous report it was shown that hypercaloric diet in adulthood (8–16 weeks of age) resulted in histopathological modifications of the prostate. Accordingly, hypercaloric diet and obesity alone affect the prostate of both young and adult males, although the prostate of adults appears to be more sensitive to the effects of hypercaloric diet. One former study showed that consumption of high animal-fat products (45% kcal fat) during ten weeks (from 6 to 16 weeks of age) caused faster progression of CaP and a reduction of natural antioxidants such as glutathione peroxidase-3 than controls that consumed only 10% kcal fat. Accordingly, high-fat diet provoked oxidative stress and higher susceptibility to develop mutations and intraepithelial neoplasias [18]. In addition, other studies have shown that chemically-induced tumors are more likely to develop into cancer in animals that consume animal fat, compared to animals fed with control diet [19]. In our study, rats consumed 30% kcal fat, which might suggest that long-term consumption of diets with > 30% kcal fat may be long-term responsible for alterations of the prostatic tissue.

Our results did not show any accompanying effect of the different molecular markers caused by hypercaloric diet. However, a trend in higher expression of OB-R 130 kD in the VP may suggest that this receptor undergoes early negative effects caused by obesity indicating that hypercaloric diet seemed to affect intracellular signaling related to JAK tyrosine kinase, STAT and MAPK [9].

It has been argued that regulated activation of those molecular cascades can inhibit the development of cancer through facilitation of immune responses, but chronic unregulated activation can promote histological alterations by activating transcription of genes related to cell differentiation and proliferation.

Our results also showed that chronic hypercaloric intake and obesity induced the presence of mononuclear cells, mainly within the lumen of DLP, but did not affect the long-term expression of NF-κB or IL-6 in adulthood. Higher expression of NF-κB was expected in hypercaloric males because it induces the expression of various pro-inflammatory genes, including those encoding IL-6. NF-κB also regulates the survival, activation and differentiation of immune cells and inflammatory T cells. It is possible that NF-κB or IL-6 require longer periods of obesity to induce detectable changes in the prostate.

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ГІСТОЛОГІЧНА СТРУКТУРА ПЕРЕДМІХУРОВОЇ ЗАЛОЗИ ТА ЕКСПРЕСІЯ РЕЦЕПТОРА ЛЕПТИНУ, РЕЦЕПТОРА ПРОЛАКТИНУ, ІЛ-6 ТА NF-κB У ЩУРІВ З ОЖИРІННЯМ

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Стан питання: Надмірне споживання калорій може призвести до ожиріння, яке є основним фактором ризику, пов'язаним із хронічним субклінічним запаленням та багатьма типами раку. Воно може підвищувати сироваткові рівні лептину, пролактину, NF-κB та інтерлейкіну (ІЛ)-6, що беруть участь у проліферації, диференціації та виживанні клітин. ***Мета:*** Вивчити вплив ожиріння, спричиненого хронічною гіперкалорійною дієтою у щурів, на довгострокову експресію рецептора лептину (OB-R), рецептора пролактину (PRL-R), NF-κB та ІЛ-6, а також зміни гістології у передміхуровій залозі щурів. ***Матеріали та методи:*** Починаючи з 21-го дня після народження, експериментальні самці отримували нормальну їжу або корм з додаванням збагаченої гіперкалорійної рідкої їжі. На 90-й день після народження (у віці 13 тиж) тварин евтаназували, після чого проводили гістологічне дослідження передміхурової залози (забарвлення гематоксиліном та еозином). Рівень рецепторів гормонів та маркерів запалення оцінювали за допомогою вестерн-блот аналізу. ***Результати:*** Гіперкалорійна дієта спричинила ожиріння (збільшення маси тіла на 32%). У передміхуровій залозі тварин з ожирінням спостерігалися анізоцитоз епітелію та стиснення інтерстиції. Також відмічали вищий вміст ліпідів, анізокаріоз, зміни ядерно-цитоплазматичного співвідношення та очевидна проплазія. Вимірювання вентральної частини передміхурової залози показали, що площа альвеол збільшилася, але висота епітелію та площа ядра зменшилися. У дорсолатеральній частині передміхурової залози спостерігалося лише зменшення площі ядра та наявність мононуклеарних клітин у просвіті. У тварин на гіперкалорійній дієті також виявлено тенденцію до підвищення експресії OB-R 130 кДа у вентральній частині передміхурової залози, але у них не спостерігалося жодних змін щодо PRL-R, NF-κB та ІЛ-6. ***Висновок:*** Ожиріння, спричинене хронічним споживанням гіперкалорійної їжі, впливає на обидві ділянки передміхурової залози, але вентральна частина, можливо, є більш чутливою завдяки OB-R. Ми припускаємо, що потрібні більш тривалі періоди ожиріння, щоб змінити інші рецептори або молекулярні маркери запалення.

Ключові слова: лептин, пролактин, ожиріння, передміхурова залоза, рецептор лептину, рецептор пролактину, IL-6, NF-κB.

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