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REVIEW ARTICLE

Resistin; A Physiological Overview

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Abstract

Resistin is a novel peptide which is known to be an adipocyte-derived cytokine. It belongs to resistin like molecule family. It was revealed that resistin is an important link between obesity, insulin resistance and type 2 Diabetes Mellitus. After that, several investigations showed the important physiological activities of resistin apart from its role in insulin resistance and diabetes in many pathological conditions as cardiovascular diseases (as coronary thrombosis), malignancy, endothelial dysfunction, hypertension, thrombosis, angiogenesis, inflammation, asthma, autoimmune disease, atherosclerosis and chronic kidney disease. Moreover, several studies have underlined it's participation in reproductive functions. It is well known that resistin expression is recorded in murine white adipose tissue but in human its expression is noticed in monocytes and macrophages. The mechanism of action, receptors and signaling pathways are beginning to be distinguished. In the present review, the present data concerning the discovery, structure, tissue distribution and functional role of resistin is summarized.

Keywords: Resistin, Resistin like molecules family, inflammatory zone3, adipokines

Introduction

Adipose tissue is considered as an active metabolic tissue that secretes many metabolically essential proteins known as adipokines (e.g., adiponectin, leptin, *IL-6*, *TNF-α*and resistin among others). These adipocyte-derived proteins are presently subjected to intensive research regarding to their involvement in the regulation of adipose tissue physiology [1].

In this context, resistin is an adipocyte-derived cytokine. Also known as found in inflammatory zone 3 (*FIZZ3*) or adipocyte specific secretory factor (*ADSF*), it belongs to resistin-like molecules family that characterized by C-terminal domain rich in cysteine [2].

Resistin gene could be expressed in several cell type. In mice, adipocytes are considered the main source of resistin [2, 3], while in human, resistin primarily comes from macrophages and monocytes [4].

Resistin plays an essential role in the incidence of obesity and insulin resistance in mice [5]. Beside its roles on insulin sensitivity and glucose metabolism and through its action on many cell targets in rodents and human, it could exert pro inflammatory processes in adipose tissue [6] and vascular endothelium [7], promotes the proliferation of vascular smooth muscle cell [8] and stimulates in vitro angiogenesis[9]. Furthermore, it was revealed that resistin involved in the control of adipocyte differentiation[10].

Additionally, it was reported that resistin could affect fertility of both male and female. Indeed, expression of resistin (mRNA and protein) had been observed in many reproductive tissues such as hypothalamus [11], pituitary gland [12, 13] and testis [14].

It has been reported that resistin is involved in a variety of physiological activities such as insulin resistance [15, 16], obesity [17], type2 diabetes mellitus [17], cardiovascular diseases [18], atherosclerosis [19-21], endothelial dysfunction [21], hypertension [22, 23], thrombosis [24, 25], angiogenesis [26, 27],

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inflammation [28, 29], energy metabolism [19, 30-32]**,** feeding behavior [32], smooth muscle cell dysfunction [33], tumorigenesis [34, 35] and rheumatic diseases [36, 37]. In the present review, we spot the light on the discovery, structure, pathway and functional role of resistin in human and different animals.

Resistin discovery

Resistin, a cysteine - rich protein, belongs to resistin-like molecules family RELMs. It was discovered in 2001 in murine and named due to its ability to resist insulin. In addition, it has various synonyms as ('resistance to insulin'), adipocyte- specific secretory factor (*ADSF*) [10], or found in inflammatory zone 3 (*FIZZ3*) [38]. Human resistin is firstly expressed in peripheral blood mononuclear cells (PBMCs) and is elevated in expression during differentiation into macrophage, while murine resistin is secreted by adipose tissue [39]**.**

It was primarily isolated by three groups, each with various perspectives [3, 10, 39]. Primarily screened for secreted proteins involved in allergic pulmonary inflammation, then recognizing the protein found in inflammatory zone 1 (*FIZZ1*) and discovered the expression of a sequence related to this protein, which they named `*FIZZ3*'. Meanwhile, Lazar and colleagues discovered a new adipocyte specific copy using subtractive screening on 3T3-L1adipocytes to recognize potential targets of peroxisome proliferator activated receptor-y (*PPAR-y*) against treatment ,this transcript was stimulated during adipogenesis and inhibited by thiazolidinedione (TZD) treatment (a kind of drugs widely used for type 2diabetestreatment) [3].

Resistin structure

Resistin is a novel peptide which has 94 aa in mice, 108 amino acids in human and 109 aa in pig, sheep, goat and cattle [3, 40-44]. Resistin belongs to resistin like molecules family (RELMs), a family of C-terminal proteins rich in cysteine. This family include *RELM-α /FIZZ 1*, *RELM-ß/FIZZ 2* and *RELM-γ* which recently discovered [39,43]; all of this family are characterized by their conserved motif of cysteine.

RELM genes encode secretory proteins consists of 105 to 138 amino acids (aa) with three important domains: an amino-terminal sequence, a preserved C terminal and a variable centric section. The carboxyl (C) terminal is consists of a 10–11cysteine-rich motif sequence common among all RELM family which maintain the globular domain of the resistin monomer via five disulfide bonds formation. In addition, the N-terminal cysteine residue (Cys-26) mediates disulfide dependent dimerization. It was suggested the multimeric structure of resistin and showed that resistin was found in two different assembly states, high-molecular-weight (HMW) hexamer (the more abundant) and the substantially low molecular-weight (LMW) monomeric form(more bioactive) in mice[43]. Moreover, resistin presents in human circulation as a dimeric protein. Also, presence of disulphide and non-disulphide bonds help in formation of dimer, trimer, and hexamer forms of circulating resistin as in Figure (1) [44].

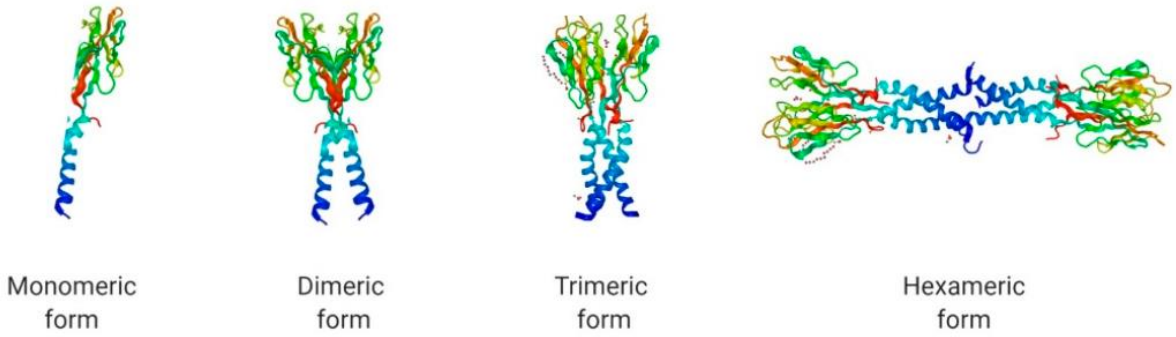

Figure (1): The Structure and specific forms of human resistin; Resistin can be found in four forms including the monomeric form, dimeric and trimeric) due to disulfide bridges. Then, hexameric protein due to disulfide and non-disulfide bridges [44].

Human resistin comes originally from adipocytes, macrophages or pre-adipocytes [43, 48, 49]. However, it has been recognized that overproduction of resistin from adipocytes is considered the main cause for elevated systemic resistin levels. Many studies showed that the main source of systemic resistin is macrophages inhuman [49]. In addition, serum resistin may elevate due to increased adipose tissue mass. Finally, there are still significant varieties in expression of resistin among the species, although there was a similarity in mouse and human resistin function [50]. While a difference in levels of resistin mRNA is apparent between macrophages and adipocytes [48].

In humans, the main source of serum resistin are PBMCs, bone marrow, macrophages [51]**.** To a less extent, serum resistin also present in hypothalamus, GIT epithelium(mainly epithelium of colon), pituitary gland , skeletal muscle, adrenal glands, spleen, pancreas, placenta trophoblastic cells, goblet cells, synovia [18, 50-52], testis [14] and may astrocyte [12]. Circulating resistin is elevated in inflammatory conditions[53]. In addition, the production of resistin within adipose tissue of human appears to mostly indicate secretion by inflammatory cells [53-55]. Munir *et al*. [56] reported that resistin concentrations within the follicular fluid in pig and humans are 0.32 and from 5 to 50 ng/mL respectively [56], dependent on the estrous cycle stage [57]. It was found that the circulating resistin level is significantly increased in patients which suffer from diabetes and obesity [45]. Moreover, expression of resistin in murine adipocytes is stimulated by high glucose levels but inhibited by *TNF-α*, while human resistin is strongly stimulated by different inflammatory stimuli containing *IL-6, IL-1β, TNF-α*, lipopolysaccharides (LPS), in macrophages and PBMCs [58].

Table (1): Distribution of resistin, RELM-α, β and γ in rodent and human tissues.

Tissue	**Resistin**		**RELMα**		**RELMß**		**RELMγ**					
	Rodent	Human	Rodent		Rodent	Human	Rodent					
	[1]P	[2]R	P	R	P	R	P	R	P	R	P	R
[3]WAT	√	√	√	√	√						√	
Pre-adipocytes	√		√	√								
Adipocytes	√	√	√	√								
[4]PBMCs				√							√	
Hypothalamus	√		√									
Pituitary gland	√											
Adrenal gland	√		√									
Spleen	√		√								√	
Skeletal muscle	√		√	√								
Pancreas	√		√	√								
Placenta			√		√							
[5]GI-tract	√		√		√		√		√	√	√	
Lung			√		√	√				√	√	

[1]P, protein expression, [2]R, mRNA expression, [3]WAT, white adipose tissue, [4]PBMCs, peripheral blood mononuclear cells, [5]GI, Gastrointestinal**.**

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Difference between human and mouse resistin

Concerning to human resistin, is a polypeptide of 12.5 kDa and consists of 108 amino acids. Also, human resistin gene located on chromosome 19 and only has 59% sequence similar to mouse resistin [59, 60]. In addition, human resistin showed reversible conformational changes dependent on concentration [43], and is considered the cause of its pathological and physiological activities [18, 51]. It was revealed that concentration of circulating resistin in human ranges from 7 to 22 ng/mL and its concentrations in healthy offspring are significantly low in males vs. females during pubertal development [45, 61]. Human resistin is present in two dissimilar forms: an oligomer form (660 kDa) and a trimmer form (45 kDa). The differences between the two forms and their biological activities were not clarified [51]. It was reported that murine resistin oligomers and trimers were less biologically active than in human [45, 59]**.**

Concerning to mouse resistin, is a polypeptide of11 kDa and consists of 94 amino acids (aa). Also, the plasma levels of resistin range from 36–43 ng/ml and its concentrations are significantly lower in males vs. females. At the level of genome, the resistin gene (RETN) was found on murine chromosome 8 and human chromosome 19 at an identical distance from insulin receptor gene [58]. The carboxyl-terminal has been suggested as the binding site of resistin receptor [62]**.** Disulfide and non-disulfide bonds are essential in the higher-degree assembly case formation(dimers, trimers, and hexamers) for plasma resistin [44,58]**.** These bonds are capable of stabilizing the structure of resistin, which help to make it highly resistant in denaturing environments [59].

Resistin secondary structure consists of an α-helix and six β- sheets for each chain [43]. Resistin secondary structure is important for the biological activity and the selectivity of tissue [51]**.** Also, the resistin activity may be

adjusted by the cooperation with proteins as heparinase and other RELM members[63]**.** In murine adipose cells, glucocorticoids, growth hormones, prolactin, testosterone regulate expression of resistin and it is suppressed by insulin, adrenaline, and somatotropin. The sequence of resistin amino acids in cow, pig, human and mice show 73, 58, 80, and 57 % homology respectively [64].

Functional role of resistin

Since, the discovery of resistin in 2001 as a factor linking between diabetes and obesity by impairing glucose tolerance and insulin sensitivity, researchers had focused on its biological functions in the body besides its role in obesity& diabetes as glucose homeostasis, Insulin resistance, obesity and DM2, Inflammation and Reproductive system.

Resistin and glucose homeostasis

Regarding the role of resistin in glucose metabolism, it was reported that administration of murine resistin to *3T3-L1* cells (adipocyte cell type) cultured in *vitro*, skeletal and cardiac myocytes reduced glucose uptake induced by insulin into the cells [3, 50, 65]. The levels of resistin were higher in obese mice and when normal mice were treated with recombinant resistin with impaired insulin action and glucose tolerance was observed [3]. In addition, administration of anti resistin Ab improved insulin sensitivity in mice suffers from obesity. In mice, insulin resistance in liver occur due to Central and peripheral administration of recombinant resistin as in Figure (2) [19, 66]. The administration of resistin in vitro lower insulin release from INS-1E cells (rat pancreas cell) and islets of pancreas at normal and excessive concentrations of glucose [67], and also lower glucagon release from G9 cells (Hamster insulinoma cell) and islets of pancreas at 1 mM, but it stimulates release of glucagon at 6 mM glucose[68].

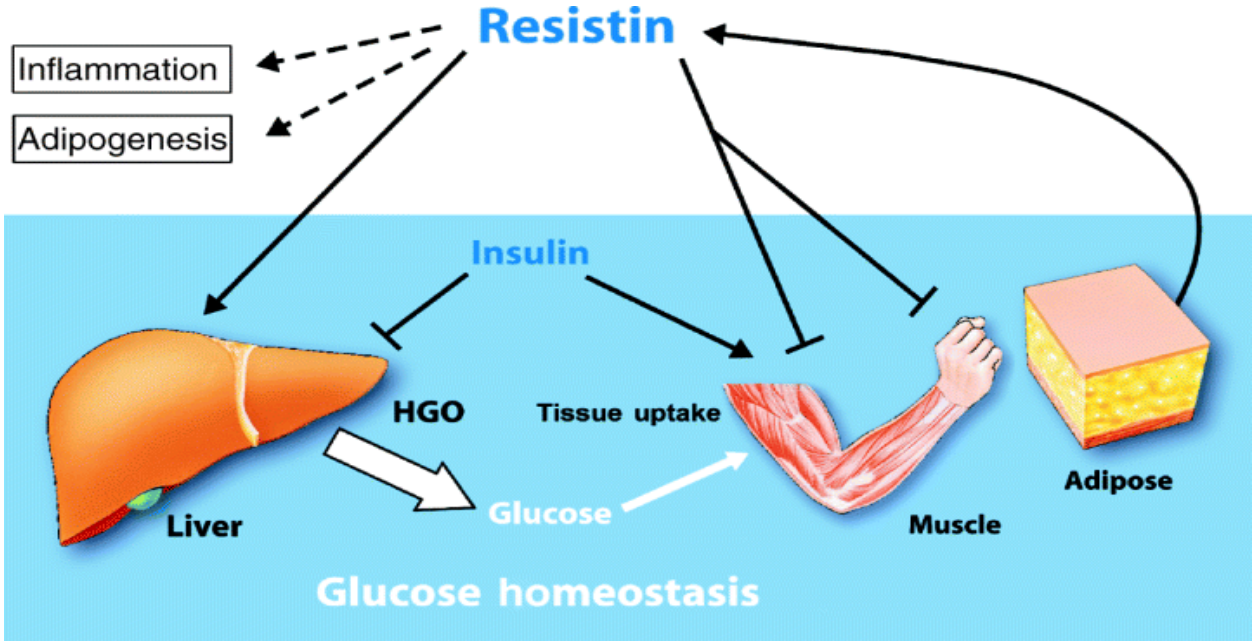

Figure (2): Biological role of murine resistin in glucose homeostasis [93]**.**

Furthermore, resistin promotes insulin resistance each in primary cultures of hepatocytes of mice and inside the liver of a mouse model with high liver-specific resistin expression [69]. On the other hand, insulin sensitivity improved by the neutralization of resistin with an anti-resistin Ig G in diet-induced over weight mice [3]. In addition, deletion of resistin improve insulin sensitivity of liver in high-fat-fed mice besides white

adipocytes and muscle insulin sensitivity in obese mouse (ob/ob) " a mutant mouse that eats excessively due to mutations in the gene responsible for the production of leptin as an animal model of type II diabetes", causing a lowering of the production of glucose and an elevation in peripheral glucose uptake [70]. In knockout mice resistin decrease glucose levels related to a decrease within gluconeogenic enzymes expression in liver, this is occur after fasting [70]. Additionally, in mice, resistin lowered the phosphorylation of AMP-activated kinase (AMPK) in hepatocytes, myocytes, and adipocytes [66, 71, 72] and the inhibition of resistin induce the AMPK phosphorylation, which is occur in glucose metabolism.

Role of resistin in obesity and insulin resistance

Unlike rodents, in humans the function of resistin controversial in obesity and of insulin resistance induction. Obese individuals have elevated macrophagic infiltration from adipose tissue, compared to lean individuals, show elevated resistin expression in adipose tissue [5, 39]. Contrary to white adipose tissue in mice, the expression of resistin mRNA lowered in isolated white adipose tissue in human [40, 73]. In human adipocyte, the poor expression of resistin owing to the loss of genomic binding site of PPARγ (peroxisome proliferator-activated receptor γ), that controls the Retn gene expression in adipocyte of mice [74]. Despite of these inter species differences, it has been found that human resistin derived from macrophages induces insulin resistance in human [75]**.** Several studies showed gene expression of human resistin in lean and obese individuals, where, gene expression of resistin was elevated in abdominal adipose tissue of obese persons [40, 76]. On the other hand, [73] found that there was no apparent relationship between obesity and expression of resistin**.**

Role of resistin in inflammation

In human, PBMCs considered the essential source of plasma resistin while in rodents adipocytes considered the main source of plasma resistin. High level of resistin protein was found in the region of inflammation in the patients suffer from rheumatoid arthritis.Although there are important receptors for resistin in mice as tyrosine kinase-like orphan receptor 1 (*ROR1*), and Toll-like receptor 4 (*TLR4*), but the inflammatory effects of human resistin are mediated byadenylyl cyclase-associated protein1 (*CAP1*). Stimulation of this receptor with resistin in human leads to elevation in level of intracellular cAMP followed by stimulation of both Phosphokinase A (*PKA*) and Nuclear factor kappa B (*NF-kB)* pathways that lastlly leads to increase expression of inflammatory cytokines as *IL6*, *IL-1b* and *TNF-α* in monocytes that has been proved in both in-vivo and in-vitro studies [77]. On the other side, inflammatory cytokines like lipopolysaccharides (*LPS*), *TNF-α*, *IL6* and *IL1* are capable of significantly increasing expression of resistin mRNA in mononuclear cells of peripheral blood in human [49]. C-reactive protein (*CRP*) lead to higher expression of resistin mRNA and protein level indicating resistin role in inflammation [78]. Not only in PBMCs, but also in white adipose tissue, resistin stimulates inflammatory cytokinesproduction as *IL-6*, *IL-8*, and *TNF-α* that leads to an inflammatory condition in this tissue[6]**.**

Role of resistin in reproductive system

Resistin action at hypothalamus–pituitary levels

Resistin expression has been observed in the murine hypothalamus [12]. Resistin was detected in the CSF of human with lower levels than that in the serum [79]**.** However, its role on GnRH remains un-determined. In the pituitary gland, it was revealed that resistin mRNA expression was significantly elevated in prepubertal rodents [12], whereas it elevated until 28 days of age, this suggesting that the expression of pituitary resistin is determined by age. The AdipoRs expression are decreased, whereas there was an elevation in GH level after in vitro culturing of rat pituitary cells [14], but to our knowledge, there is no data that describe resistin effect on secretion of gonadotropin. However, in bats, it was reported that serum resistin levels had

negative correlation with serum LH level [80]. Moreover, resistin not only affect GnRH neurons in the hypothalamus and gonadotrophs on pituitary gland, but also it affect gonads of both sex Figure (3) [81-83].

Resistin expression in the ovary

several studies showed that resistin had a role in female reproduction, because expression of resistin had been recorded in ovaries of human [84], cattle, rodents [85] and pigs [56, 57]. It was revealed that resistin presented in cumulus cells and granulosa cells of human, in addition to theca cells of large follicles and the primary follicles oocytes [84]. In bovine, resistin is expressed in follicles with different size (small 6mm) whereas, it is localized in granulosa cells, cumulus, theca cells and oocytes as in Figure (4). Moreover, it is present in corpus luteum [85]**.** Interestingly, resistin mRNA do not expressed in murine granulosa cell cultures [85]. Resistin decreases bovine granulosa cell steroidogenesis [85, 86]; however, it had a stimulatory effect on the secretion of progesterone (P4) in rodents [86]. In granulosa cells of human, it was documented that resistin had an inhibitory effect on the secretion of estradiol (E2) and progesterone in response to IGF1[84]. However, in human theca cells [56], pig ovaries [57, 87] and bats [88] resistin increases the production of estrogen at physiological doses. On the other hand, in pig follicles, resistin had inhibitory effect on gonadotropin and *IGF1*-induced steroid hormone secretion [89]. These reverse findings may be due to the presence of different isoforms f or resistin that may show the diversity in function in various species. So, the resistin receptors remain unknown and resistin role in steroid genesis in ovaries does not clear. Despite the previous data, which reported that resistin not played role in the maturation and development of oocytes [90, 91].

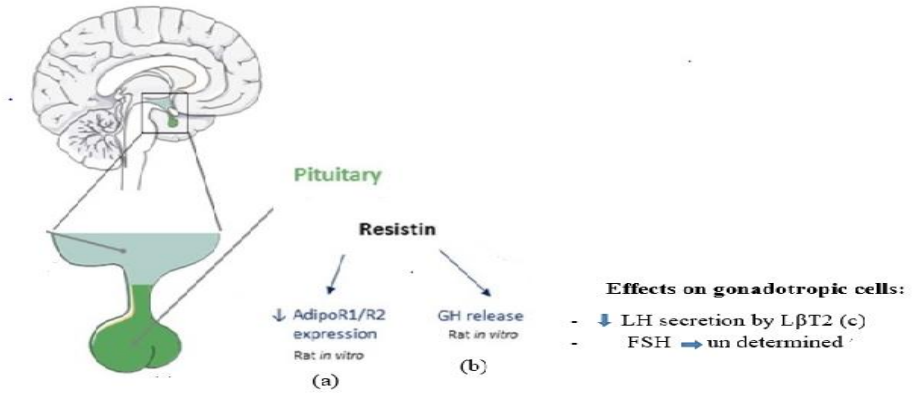

Figure (3): Resistin effects of on GnRH and LH/FSH expression or secretion[81].(FSH)- Follicle-stimulating hormone; (LH) - luteinizing hormone, (AdipoR1/R2)- adiponectin receptors; (GH)- growth hormone. → activation; — (a) [14], (b) [82], and (c) [83].

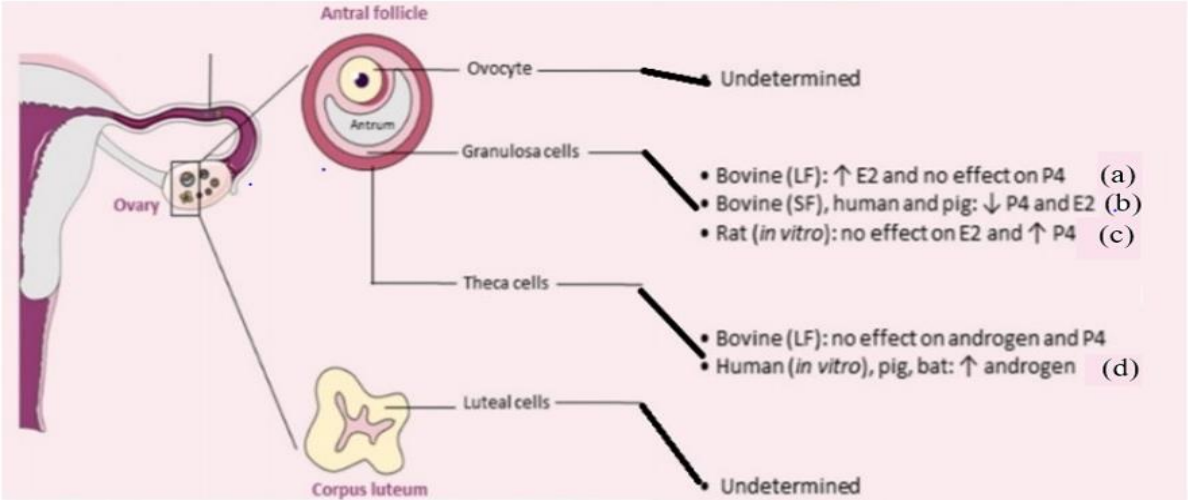

Figure (4): Effects of resistin on granulosa and function of theca cells and oocyte (steroidogenesis, proliferation and oocyte maturation) in different species [81]. (P4)- Progesterone; (T)- testosterone; (E2)- estradiol; (SF)- small follicles; (LF), large follicles. ↑- increase, ↓- decrease. (a) [86], (b) [84, 86, 89],(c) [85], (d) [56, 57, 87, 88].

Resistin expression in testes

Nogueiras *et al*. [14], revealed that in rat testes, Leydig interstitial cells have higher resistin mRNA than that presents in the Sertoli cells inside testis as in Figure (5). In addition, gonadotropins, leptin and nutritional status of animal regulated this expression. Moretti *et al.* **[92]** demonstrated that, resistin level was lower in serum than that in human semen [92].To our knowledge, there are restricted studies on resistin roles on the function of testes. The Sertoli cells may help in the proliferation of Leydig interstitial cells via secretion of resistin [14]**.**

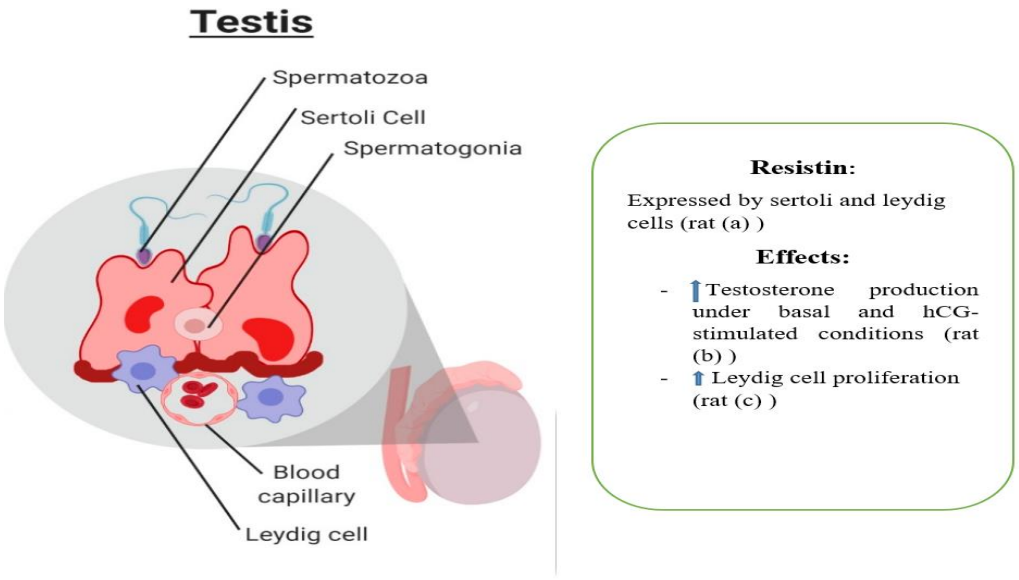

Figure (5): Effects of resistin on testicular cell functions (steroidogenesis, proliferation in rodents. T, testosterone; hCG, human chorionic gonadotropin[44].(a) and (c) [94], (b) [14].

Conclusion

Since resistin discovery as a 'linkage' between diabetes mellitus and obesity, many studies dedicated the role of resistin and its biological functions. In addition, resistin had been incriminated in several disease processes. Beside to cardiovascular diseases, resistin has been exhibited to have role in the incidence of angiogenesis, thrombosis, hypertension and asthma. Although resistin is known to be an adipokine, resistin is expressed from many other organs and cells as macrophages, monocytes, lung, liver and bone marrow and plays an essential role in the inflammation throughout the body. Moreover, its expression can be organized by various determinants as (nutritional, age, hormonal status and gender). Additionally, it was documented that resistin is expressed in the hypothalamo–pituitary–gonadal axis of both sexes in different species. Finally, from the previous data, more studies are required to understand the receptors, the mechanism of action, signaling pathways and functional role of resistin specially in the reproduction.

Conflict of interest

The authors declare no conflict of interest.

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الملخص العربي

الوجه الفسيولوجى للريزيستين

مني بكري علي ، نوره السيد عبدالحميد ، رضا محمد عبدالعزيز ، محمد محمد حماده
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يعتبر الريزستين عديد الببتيد حيث انه مشتق من الخلايا الدهنية. وكذلك ينتمي إلى عائلة resistin like molecules. وقد اظهرت الابحاث أن الريزستين يعتبر عامل مشترك بين السمنة ومقاومة الأنسولين ومرض السكري من النوع الثانى. كما أظهرت العديد من الدراسات الأنشطة الفسيولوجية الهامة للريزيستين بصرف النظر عن دوره في مقاومة الأنسولين ومرض السكري في العديد من العمليات البيولوجية مثل أمراض القلب والأوعية الدموية (مثل تخثر الشريان التاجي)، والأورام الخبيثة، والخلل في بطانة الاوعية الدموية، وارتفاع ضغط الدم، والتخثر، والالتهابات، والربو، وأمراض المناعة الذاتية وتصلب الشرايين وأمراض الكلى المزمنة. علاوة على ذلك، أكدت العديد من الدراسات مشاركته في الوظائف الإنجابية. ومن المعروف أن افراز الريزستين يكون من الأنسجة الدهنية البيضاء للفئران ولكن في الإنسان يفرزمن المكروفاج. وقد أوضحت العديد من الدراسات التمييز بين آلية العمل ومستقبلات ومسارات الريزيستين. وفي هذا العمل تم تلخيص المعلومات الحالية عن الريزستين حول اكتشافةوتركيبة وتوزيعه ودوره الوظيفي فى الأنسجة. وأيضا تمت مناقشة الفروق لمستوى الهرمون فى البلازما والانسجة المختلفة في الانسان والحيوانات المختلفة.