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Review Article

Hepatokines and Skin

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Abstract

Proteins called hepatokines are made by liver cells and are released into the bloodstream to act as hormones throughout the body. Some of them include Adropin, ANGPTL4, Fetuin-A, Fetuin-B, FGF-21, Hepassocin, LECT2, RBP4, Selenoprotein P, Sex hormone-binding globulin and insulin like growth factor 1. They are involved in the control of metabolic illnesses such diabetes and fatty liver. Hepatokines can affect metabolic processes by way of endocrine signaling, autocrinem, and paracrinem. When there is pressure on the metabolism, such as during prolonged fasting or overnutrition, the liver may release hepatokines to affect energy homeostasis and inflammation. The accompanying disease, such as fatty liver disease, arises from "impaired hepatic insulin-sensitizing substance production" if the liver is unable to complete this procedure. These proteins regulate how fat and glucose are metabolized in skeletal muscle, adipose tissue, and the liver. Additionally, hepatokines may act as mediators or biomarkers of training-induced improvements in metabolism, hence mediating the positive benefits of prolonged exercise. Through their modulation of endothelial dysfunction and inflammatory cell infiltration into artery walls, hepatokines have a direct impact on the course of atherosclerosis. Hepatokines are prospective therapeutic targets for metabolic illnesses and can function as biomarkers. Hepatokines secreted in response to physical activity cause advantageous metabolic alterations in skeletal muscle, fat, and blood vessels that can lower the risk of metabolic disorders. Additionally some of these hepatokines involved in pathogenesis of many dermatological inflammatory chronic illnesses mainly psoriasis, acne vulgaris and patterened alopecia.

Key words: Adropin, ANGPTL4, Fetuin-A, Fetuin-B, FGF-21, Hepassocin, LECT2, RBP4, lipid metabolism. SHBG, IGF-1, Psoriasis, acne, AGA.

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Origin and members:

The term "hepatokines" is derived from the Greek words heapto- (liver) and -kinos (movement), indicating proteins produced by liver cells, or hepaticytes, that are released into the bloodstream to function as hormones throughout the body. Research primarily focuses on hepatokines like Adropin, ANGPTL4, Fetuin-A, Fetuin-B, FGF-21, Hepassocin, LECT2, RBP4, Selenoprotein P, and Sex hormone-binding globulin, which play a key role in managing metabolic conditions such as diabetes and fatty liver disease. (1)

General mechanism of action:

Hepatocytes secrete hormone-like substances called hepatokines, several of which have been linked to the regulation of extra-hepatic metabolism. Hepatokines can affect metabolic processes through endocrine signaling, autocrinem, and paracrinem mechanisms.(2)

More than 560 different types of hepatokines have been reported to be secreted by hepatocytes, many of which use circulatory transport to control inflammatory and metabolic disorders in the liver or other distant organs." Hepatocytes have the ability to secrete several hepatokines into the bloodstream. In specifically, these hepatokines are structurally polypeptides and proteins that, like insulin and hypothalamic hormones, are transcribed and expressed by specific genes .(3)

General functions:

In situations where the metabolism is under stress, including extended fasting or malnutrition, the liver can secrete hepatokines that influence inflammation and energy homeostasis. If the liver is unable to finish this process, "impaired hepatic insulin-sensitizing substance production" results, which leads to the accompanying disease, such as fatty liver disease. Hepatokines help regulate the availability of nutrients and convey energy levels to a number of peripheral tissues, including the central nervous system (CNS). (4)

It has been demonstrated that hepatokines regulate the metabolism of nutrients and energy by acting directly on the liver or through distal target tissues. These proteins regulate how fat and glucose are metabolized in skeletal muscle, adipose tissue, and the liver. It is now clear that the liver synthesizes the proteins it releases in a single exercise session.. Additionally, hepatokines may act as mediators or biomarkers of training-induced improvements in metabolism, hence mediating the positive benefits of prolonged exercise. Hepatokines modify endothelial dysfunction and inflammatory cell infiltration into artery walls, which have a direct impact on the advancement of atherosclerosis.(5)

Types:

1-Fetuin-A, also known as alpha-2-HS-glycoprotein (AHSG or Alpha-2-Heremans-Schmid Glycoprotein), is a hepatokine linked to heightened insulin resistance and inflammation. Encoded by the AHSG gene, Fetuin-A is part of the fetuin class of plasma-binding proteins and is more abundant in fetal blood than in adult blood.(6)

Function

Alpha2-HS glycoprotein, a serum protein produced by adipocytes and hepatocytes, consists of two polypeptide chains derived from separate proproteins, each encoded by distinct mRNA. This protein influences bone structure, endocytosis, and brain development. Its presence in both the immature cerebral cortex and bone marrow hemopoietic matrix suggests a potential role in tissue development, though its precise function remains unclear .(7)

An established site of extrahepatic expression is the choroid plexus. The two polypeptide chains that make up the mature circulating AHSG molecule are each produced by cleaving a proprotein that is transcribed from a single mRNA. There have been numerous reports of post-translational alterations. AHSG, then, is a complex proteolytically processed partly phosphorylated glycoprotein that is released and circulates in extracellular fluids and blood. Because AHSG may bind several ligands in a test tube, it has been suggested that it is involved in a number of processes, including endocytosis, brain development, and bone tissue creation. The majority of these functions need to be verified in vivo .(8)

Clinical significance

Similar to albumin, fetains are carrier proteins. Fetuin-A is a transporter of insoluble calcium phosphate by forming soluble complexes with calcium and phosphate. Fetuin-A is hence a strong inhibitor

of pathological calcification, specifically Calciphylaxis. Soft tissue calcification is shown systemically in mice lacking fetuin-A. Fetuin-A has the ability to prevent bone calcification and osteogenesis. Fetuin-A seems to prevent calcification in peripheral arterial disease but to promote it in coronary artery disease. (9)

Obesity and insulin resistance are linked to elevated levels of fetain-A. Fetuin-A increases free fatty acid binding to TLR4, which in turn increases insulin resistance. Fetuin-A promotes inflammation and insulin resistance in adipose tissue via downregulating adiponectin expression. Fetuin-A also enhances lipolysis and decreases lipogenesis in adipose tissue, which exacerbates obesity and insulin resistance .(7)

Fetuin-A is decreased by supervised exercise (that is not linked to weight loss). (10)

2- Fetuin-B causes poor insulin action and glucose intolerance, and it dramatically enhances hepatic steatosis. The protein that this gene codes for is a member of the cystatin superfamily of cysteine protease inhibitors, namely the fetuin family. Numerous different functions, such as osteogenesis and bone resorption, insulin and hepatocyte growth factor receptor modulation, and response to systemic inflammation, have been linked to fetains. Cells have the ability to release this protein. (6)

3 -ANGPTL8/betatrophin was first thought to have an impact on the proliferation of beta cells, however this has lately been questioned.The C19orf80 gene in humans codes for the protein ANGPTL8, which is also referred to as lipasin (formerly known as betatrophin). (11)

Function

The encoded 22 kDa protein belongs to the angiopoietin-like (ANGPTL) protein family and has two coiled-coil domains and an N-terminal secretion signal. But unlike other ANGPTL proteins, ANGPTL8 is an unusual member of the ANGPTL family because it does not have the C-terminal fibrinogen-like domain. (11)

It has been demonstrated that ANGPTL8 and ANGPTL3 can form complexes with an apparent stoichiometry of 3:1 for ANGPTL3 and ANGPTL8 respectively. Combining ANGPTL8 and ANGPTL3 extracellularly did not cause complex formation, suggesting that intracellular co-folding is necessary for the creation of these complexes. ANGPTL8 is produced in the hepatic tissue and released into the bloodstream; however, in order for ANGPTL8 to be secreted effectively, it needs to combine with ANGPTL3.(12)

It has been demonstrated that ANGPTL8 significantly enhances ANGPTL3's ability to inhibit lipoprotein lipase (LPL), as ANGPTL8 alone has minimal inhibitory capability. ANGPTL8 and ANGPTL3 must form a complex to inhibit LPL. Adipose tissue and the liver of mice both release ANGPTL8, and hepatic overexpression of ANGPTL8 raises blood levels of triglycerides. (11)

Mice deficient in ANGPTL8 exhibit significantly reduced absorption of very low-density lipoprotein (VLDL)-derived fatty acids into white adipose tissue (WAT), despite an increase in post-heparin plasma lipoprotein lipase (LPL) activity. According to the ANGPTL3-4-8 model, this reduced fatty acid uptake by WAT is likely due to the enhanced fatty acid uptake by the heart and skeletal muscle, which have higher LPL activity in ANGPTL8-null animals.(12)

It was suggested that ANGPTL8 would speed up beta-cell cell division. Mice injected with ANGPTL8cDNA had hypoglycemia (low blood sugar), most likely as a result of pancreatic activity. ANGPTL8 therapy of human islets, however, does not promote beta-cell division. Additionally, research using ANGPTL8 knock-out mice indicates that ANGPTL8 clearly has a role in regulating plasma triglyceride levels, but does not support a role in controlling beta cell proliferation. (13)

The retraction of the original study officially put an end to the theory that ANGPTL8 stimulates beta cell proliferation, and these investigations provide a pretty solid basis for that conclusion. Mice's glucose and insulin tolerance does not appear to be affected by ANGPTL8 deletion .(14)

Clinical significance

It was thought that ANGPTL8 or its human homolog might work well as a therapy for type 2 diabetes, and possibly even type I. Unfortunately, ANGPTL8's promise as a type 2 diabetes treatment

is restricted because recent results seriously cast doubt on its capacity to enhance beta-cell reproduction. One potential treatment approach for hypertriglyceridemia is ANGPTL8 inhibition. [15]

Because of its advantageous metabolic effects, FGF-21, an insulin-sensitizing hormone, is a desirable pharmacological target. [16]

The FGF21 gene in mammals encodes fibroblast growth factor 21 (FGF-21), a member of the endocrine subfamily of the fibroblast growth factor (FGF) family, which also includes FGF23 and FGF15/19. FGF21 functions as the primary endogenous activator of its receptor, which is composed of the co-receptors β-Klotho and FGF receptor. [17]

Members of the FGF family are involved in various biological processes such as embryonic develop-ent, cell growth, morphogenesis, tissue repair, and tumor progression. They also possess strong mitogenic and cell survival abilities. [16]

FGFs interact with one of four FGF receptors through a complex binding process that involves both the receptor and heparin via a heparin-binding domain. Endocrine FGFs, which lack this domain, are able to circulate freely in the bloodstream.[17]

Function

Role in glucose metabolism in adibocytes:

FGF21 increases adipocytes' absorption of glucose, but not that of other cell types. The action of this is additive to insulin activity. Phosphorylation of FRS2, a protein connecting FGF receptors to the Ras/MAP kinase pathway, is linked to FGF21 therapy of adipocytes. Adipose tissue in ob/ob mice that get FGF21 injection had higher levels of Glut1. When overexpressed in transgenic mice, FGF21 also guards against diet-induced obesity in animals and, when given to diabetic rodents, decreases blood glucose and lipid levels. Animals treated with FGF21 exhibit enhanced lipid excretion, fat utilization, and energy expenditure. [18]

portion of the hepatic gluconeogenesis and ketogenesis process:

Mice deficient in FGF21 have defective gluconeogenesis and ketogenesis, and are unable to adequately stimulate PGC-1α expression in response to a prolonged fast. [19]

FGF21 stimulates the phosphorylation of fibroblast growth factor receptor substrate 2 and ERK1/2 in the liver. Acute FGF21 injection results in increased levels of key regulators involved in gluconeogenesis, lipid metabolism, and ketogenesis, such as glucose-6-phosphatase, phosphoenolpyruvate carboxykinase, 3-hydroxybutyrate dehydrogenase type 1, and carnitine palmitoyltransferase 1α. Additionally, FGF21 injection is associated with lower levels of free fatty acids and circulating insulin. While FGF21 administration boosts PGC-1α mRNA and protein expression, PGC-1α is not necessary for FGF21's effects on glucose metabolism in mice. [20]

Clinical significance

Serum FGF-21 levels are notably elevated in patients with type 2 diabetes mellitus (T2DM), indicating a potential link to the condition's pathophysiology. Additionally, higher levels of FGF-21 are associated with liver fat accumulation in non-alcoholic fatty liver disease and with increased BMI in humans, suggesting that obesity may result in resistance to FGF21. [21]

4- Adropin (24).

Function

***Metabolic**

Adropin's function in metabolic regulation is one of the main topics of interest. Studies suggest that adropin could be essential for the metabolism of fats and carbohydrates. It may play a part in controlling blood sugar levels because it has been linked to insulin sensitivity .[22]

Adropin levels have been related to changes in body weight and energy expenditure in animal studies. According to certain research, mice with higher amounts of adropin, for instance, are often more resilient to diet-induced obesity. [23]

***Cardiovascular**

Adropin seems to have effects on the heart as well. It has been connected to the control of endothelial function, which is necessary to preserve the integrity of blood vessels. Endothelial cell dysfunction may be a factor in diseases like hypertension and atherosclerosis. According to certain research, adropin may preserve cardiovascular health by encouraging blood vessel dilatation and lowering oxidative stress. [24]

***Central nervous system**

In the brain, namely in the hypothalamus, adropin is produced. The regulation of numerous physiological systems, including as metabolism and energy balance, is largely dependent on the hypothalamus. Adropin's brain presence raises the possibility that it plays other roles in the central nervous system, though these are currently being investigated .[25]

***Gonads and sexual development**

By enhancing the expression of GPR19 and steroidogenic proteins through redox potential modulation, adropin therapy dramatically enhanced the number of sperm and testicular testosterone in mice. [26]

Adropin and GPR19 are highly expressed in the corpus luteum and granulosa cells of large antral follicles in the mouse ovary. [27]

According to a separate study, adropin may have a part in quickening pubertal development .[28]

Clinical significance

Adropin has garnered attention as a possible biomarker and therapeutic target for diseases like obesity, diabetes, and cardiovascular disease because of its role in metabolic and cardiovascular processes. To fully comprehend the exact mechanisms of adropin activity and its possible clinical applications, however, a great deal more research is required. [23]

1-In adipocytes:

ANGPTL4 can increase cAMP-stimulated lipolysis and inhibit lipoprotein- lipase. [29]

Clinical significance

ANGPTL4 is key in many malignancies and plays a role in the metastatic process by controlling invasiveness, cancer cell motility, and vascular permeability. Furthermore, ANGPTL4 protects cells from anoikis, a sort of programmed cell death that happens when contact-dependent cells split from the surrounding tissue matrix. [30, 31] This is in addition to encouraging the creation of tumors.

secreted by tumors With its capacity to bind to integrins, ANGPTL4 can start downstream signaling and generate superoxide, both of which can accelerate the growth of tumors. ANGPTL4 promotes metastasis by severing endothelial cell connections through successive interactions with integrin, VE-cadherin, and claudin-5. ANGPTL4, and particularly its C-terminal fragment (cANGPTL4), are essential mediators of an increase in cellular energy flux necessary for the epithelial-mesenchymal transition (EMT) via an ANGPTL4:YWHAG (14-3-3γ) signaling axis. By interacting with specific phosphorylation signals on target proteins, the ANGPTL4:YWHAG signaling axis enhances EMT competency and confers metabolic flexibility. One immediate effect is that ANGPTL4 powers multiple ABC transporters with sufficient cellular energy, hence enabling EMT-mediated chemoresistance. [31]

ANGPTL4 is an additional potent angiogenic factor that exhibits increased expression in both hypoxia retinal Müller cells in vitro and ischemic retina in vivo. Higher amounts of ANGPTL4 expression, which was restricted to areas of retinal neovascularization, were seen in the vitreous and aqueous humor of patients with proliferative diabetic retinopathy .[32]

It has been shown that ANGPTL4 is a potent inhibitor of the lipoprotein lipase (LPL) enzyme, which raises serum TG levels and inhibits the clearance of triglycerides (TG). Biochemical studies indicates that ANGPTL4 separates the catalytically active LPL dimer into inactive LPL monomers, hence partially deactivating LPL.However, results also suggest that ANGPTL4 functions as a conventional, non-competitive inhibitor by binding to LPL and reversibly inhibiting substrate hydrolysis. [33]

***Relation between hepatokines and skin diseases:**

Sex hormone binding globulin (SHBG) is one of the hepatokines that binds to sex hormones (estradiol, testosterone)

Function

Testosterone and estradiol control various aspects of sexual differentiation and gonadal development. They are transported in blood to their target tissues by several steroid-binding proteins one of them, known as sex hormone-binding globulin (SHBG), which binds to biologically active androgens and estrogens, with an affinity four to five times greater than that of albumin.[34]

Clinical significance in dermatology

Androgenetic alopecia (AGA), a specific pattern of baldness affecting both males and females, has been associated with an increase in cardiovascular risk, including diabetes, metabolic syndrome, and dyslipidemia. It was found to be associated with decreased serum levels of SHBG. (35-38)

SHBG could play a role in the etiology of diabetes type 2, by changing the biological effects of sex hormones on body tissues such as muscle, liver, and fat. Additionlly, SHBG has been shown to have direct effects against estrogen, and this could be the reason for hyperglycemia in patients with AGA. (39)

Some authors have suggested that patients with AGA are more likely to get diabetes as a result of hyperandrogenism, insulin resistance, and metabolic syndrome, which is more frequent in patients with AGA than controls. (40)

***Insulin-like growth factor 1**(IGF-1), a hepatokine formerly known as somatomedin C, is a 7.5-kD polypeptide found in high levels in plasma and is detectable in most tissues with multifunctional actions mediating signals for cell proliferation, differentiation and IGF-1R inactivation in skin results in a disrupted epidermis. (41)

***Clinical significance in dermatology:**

The IGF-I receptor is located in the basal epidermal layer of normal human skin, where it could regulate keratinocyte proliferation. It is also thought that it is overexpressed in hyperproliferative skin disorders such as Psoriasis .(42)

Psoriasis which is a polygenic, chronic inflammatory autoimmune disease thought to depend on the activation of lesional and/or circulating immune cells and their secreted molecules such as cytokines, chemokines, and growth factors, ultimately leading to keratinocyte hyperproliferation, epidermal thickening and angiogenesis with marked dilatation of blood vessels. One of the essential growth factors involved in the pathogenesis of psoriasis is (IGF-1). (43)

IGF-I abnormal levels in psoriatic patients have been associated with unfavorable lipid profiles and consequently increased cardiovascular mortality. (44)

Thus, IGF-I contributes to inflammatory pathways of both metabolic syndrome and psoriasis .(45)

Acne vulgaris Acne is a very common distressing disease caused by many factors such as excessive sebum secretion, inflammation, follicular keratinization, and Cutibacterium acnes. (46)

Increased sebum production, abnormal sebum composition, sebum peroxidation, and inflammatory lipid production contribute to the formation of primary acne lesions. (47)

Recent studies have focused on glycemic load, and hyperinsulinemia caused by high glycemia has been connected to an increase in the concentration of insulin-like growth factor (IGF)-1, which has been found to influence androgen metabolism and lipogenesis. .(48)

Moreover, IGF-1 has been shown to upregulate inflammatory cytokines in many cells including immortalized sebocytes .(49)

A correlation between the severity of acne and the level of serum IGF-1 has also been reported .(50)

Seborrheic dermatitis is a common chronic inflammatory skin condition affecting sebaceous areas of the scalp, hairline, eyebrows, nasolabial folds, chest and back and characterized by erythematous papules and plaques with a greasy scale crust. (51)

Multiple factors are involved in its pathogenesis including lipids secreted from sebaceous glands on the skin surface, Malassezia colonies producing free fatty acids, and lipid peroxides activating inflamematory cytokines leading to keratinocyte proliferation and differentiation .(44)

IGF-1 stimulates sebocyte proliferation and differentiation which results in stimulating lipogenesis. It also promotes the proliferation of keratinocytes and stimulates 5α-reductase and androgen synthesis and androgen receptor signal transduction, leading to increased sebum secretion. (52)

Conclusion:

The liver releases hepatokines to affect inflamemation and energy homeostasis. They work directly on the liver or on distal target organs to regulate energy and nutrition metabolism. If the liver is unable to complete this procedure, the corresponding disease, such as fatty liver disease, arises from "impaired hepatic insulin-sensitizing substan-

ce production and other several diseases." Moreover, these hepatocytes promote many inflammatory skin dermatoses, mainly psoriasis, acne, and androgenetic alopecia.

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