New Adipokines

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Nouvelles adipokines

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Summary

Adipose tissue is now widely recognized as "an organ" able to synthesize and secrete hundred factors collectively called adipokines. These secreted molecules exert pleiotropic actions, notably on the regulation of glucose and lipid metabolism, inflammation, reproduction, or angiogenesis. Over the past two decades, a considerable amount of work was performed on the two "star" adipokines, leptin and adiponectin, particularly because of their involvement in energy metabolism. The present review is focused on the three most recently discovered adipokines that are clearly emerging as important actors in metabolism: apelin, fibroblast growth factor-21, and neuroregulin-4. Moreover, given a number of clinical and experimental data, these three adipokines represent promising targets in the context of metabolic disorders associated with obesity.

Keywords: adipocyte, adipokine, apelin, fibroblast growth factor-21, insulin resistance, neuroregulin-4, obesity, adipose tissue

Résumé

Le tissu adipeux est désormais largement reconnu en tant « qu'organe » capable de synthétiser et de sécréter de nombreux facteurs rassemblés sous le terme d'adipokines. Ce tissu sécrète vraisemblablement plusieurs centaines de molécules, qui exercent des actions pléiotropes, notamment sur la régulation du métabolisme glucido-lipidique, l'inflammation, la reproduction, ou l'angiogenèse. Au cours des deux dernières décennies, une somme considérable de travaux a été réalisée sur les adipokines « vedettes », la leptine et l'adiponectine, notamment en raison de leur implication dans le métabolisme énergétique. De parti pris, cette revue est focalisée sur trois adipokines de découverte plus récente, mais dont l'intérêt émerge clairement : l'apeline, le FGF21, et la neuroréguline-4. Au vu de plusieurs données cliniques et expérimentales, ces trois adipokines représentent des cibles prometteuses dans le contexte des désordres métaboliques associés à l'obésité.

Mots clés: adipocyte, adipokine, apéine, fibroblast growth factor-21, insulinorésistance, neuroréguline-4, obésité, tissu adipeux

Introduction

Over the last twenty years, considerable progresses have been made regarding the demonstration of the endocrine nature of adipose tissue (AT), dramatically illustrated in 1994 by the discovery of leptin, which exerts an anorectic effect on the central nervous system. Other adipokines have also been extensively investigated as adiponectin, interleukin (IL)-6, IL-1β, tumor necrosis factor (TNF)-α, monocyte chemoattractant protein (MCP)-1, resistin, omentin, or vaspin. However, we are far from understanding their pathophysiological implications. The complexity of this domain is documented by recent proteomic approaches, which indicate that human AT explants could secrete more than 700 distinct proteins. Therefore, the biology of AT will become more and more complicated.

Adipokines regulate important biological processes in target organs such as the brain, liver, skeletal muscle, cardiovascular and immune systems, and the endocrine pancreas (Figure 1). This could explain the close link between obesity and the metabolic and cardiovascular complications (1, 2). The production of many adipokines is deregulated in obesity (3), and could participate into disturbances of appetite and satiety, and into changes in the distribution of AT, insulin secretion, insulin sensitivity, energy expenditure, endothelial function, angiogenesis, inflammation, blood pressure, haemostasis, osteoarticular functions and reproduction. Consequently, adipokines offer promising prospects for the management of obesity-related morbidities.

Moreover, adipokines are not necessarily derived from adipocytes, but also from other cell-types present in AT that contains not only adipocytes (that represent less than half of the total number of cells present in the tissue), but also various amounts of immune cells

(macrophages, lymphocytes, granulocytes, mast cells), endothelial cells, and fibroblasts. Leptin and adiponectin are mainly derived from adipocytes, while the pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) are primarily produced by macrophages and immune cells. In addition, the secretory profiles of this heterogeneous and plastic tissue may be different according to the location of fat deposits.

Finally, we must emphasize that new data and innovative concepts, well beyond the metabolic effects of these adipokines, have emerged over the last ten years. In this review article, we decided to focus on three "new" adipokines of interest which present potential therapeutic prospects: apelin, Fibroblast Growth factor (FGF)-21, and neuregulin-4

Apelin

Discovery, structure and main functions

In 1998, Tatemoto et al. purified from bovine stomach extracts a peptide recognizing a previously discovered G protein-coupled orphan receptor, APJ, now designated the apelin receptor. APJ has a high homology with the type 1 receptor of angiotensin II (4). The apelin gene encodes a 77 amino acids protein called preproapelin (5) that undergoes a proteolytic processing giving rise to various biologically active forms of apelin: apelin 36, 17, 13, and pyroglutamate apelin-13, the latter being protected from rapid degradation by ectopeptidases. Apelin is produced by AT (mainly adipocytes), but also by many other tissues such as lung, mammary gland, testis, muscle and brain. The apelin/APJ system is involved in a wide variety of functions such as cardiovascular, fluid, and angiogenic homeostasis (6.7)

The demonstration of apelin being secreted by adipocytes, and thus being an adipokine, was conducted in 2005 by the team of Valet et al. (8). We will focus here on the current knowledge of the physiology and pathophysiology of apelin regarding the energy balance.

Apelin and carbohydrate metabolism

An initial work characterized the inhibitory role of apelin on insulin secretion (9). However, conversely, hypoglycemic properties of apelin were discovered in 2008 in mice (10), both in the fasted state and during a glucose tolerance test. This effect was observed both in obese insulin-resistant and in control mice. This was associated with increased glucose utilization by skeletal muscle and AT, and involved the phosphorylation of AMP-activated kinase (AMPK) as well as the activation of the endothelial nitric oxide (NO) synthase (10). These data were confirmed latter (11), in particular by using KO mice for the preproapelin gene (apelin -/- mice), which exhibit hyperinsulinemia and insulin resistance, decreased insulin sensitivity being exacerbated under high fat and high fructose diet (11).

The stimulatory effect of apelin on glucose transport in isolated murine adipocyte has not been currently documented, while apelin was shown to activate glucose transport in an AMPK-dependent manner in explants of human AT (12). This was also observed in the mouse 3T3-L1 adipocyte cell line, in which the process involves the phosphoinositide 3-kinase (PI3K) and protein kinase B (AKT) pathway (13). Apelin can also stimulate glucose transport and GLUT4 membrane translocation in the myocardium of C57BL / 6J mice (14), and in the H9c2 cardiomyoblasts cell line (14).

Apelin is also involved in intestinal glucose absorption. Glucose ingestion quickly triggers the secretion of apelin into the intestinal lumen of mice (15). Surprisingly, oral administration of apelin reduces the amount of the sodium glucose co-transporter SGLT1 at the enterocyte level, while GLUT4 is induced, which allows an increased intestinal absorption of glucose. These results suggest that the entrance of carbohydrate in the intestine promotes its own absorption *via* the paracrine secretion of apelin, and accordingly insulin secretion. This could also be in agreement with the inductive effects of apelin on the secretion of the incretin, glucagon-like peptide (GLP)-1 (16).

Studies evaluating the impact of apelin on glucose homeostasis have not systematically reported decreased fasting plasma glucose and insulin resistance in obese animals. By contrast, a decrease in plasma insulin in response to apelin was frequently observed in these

models. This may be the result of either improved insulin sensitivity or an inhibitory effect of apelin on insulin secretion. Thus, apelin can reduce insulin secretion stimulated by different glucose concentrations (17, 18).

Apelin and lipid metabolism

Apelin was shown to inhibit lipolysis stimulated by the β-adrenergic agonist isoproterenol *via* Gq, Gi, and AMPK signaling in isolated rodent and mature 3T3-L1 adipocytes (19, 20). However, apelin has no effect on basal or isoproterenol-stimulated lipolysis in explants of human AT or isolated human adipocytes (12). The antilipolytic effect of apelin was found after a chronic treatment in mice (21) and in transgenic mice overexpressing apelin and fed a high fat diet (22).

A chronic treatment of insulin-resistant obese mice by apelin increases fatty acid oxidation in the skeletal muscle through activation of AMPK (23). Moreover, this treatment can prevent a reduction in fatty acid and glucose oxidation in a model of heart failure related to obesity (24). In addition to the induction of fat utilization, apelin increases mitochondrial biogenesis in muscle (23) and cardiomyocytes (24) by a mechanism that requires induction of peroxisome proliferator- activated receptor- γ co-activator (PGC)-1α.

Surprisingly, the resistance to obesity of transgenic mice overexpressing apelin is correlated with an increase in their muscle vasculature. The importance of apelin in maintaining the integrity of the blood and lymph systems was recently observed in apelin -/- mice (25). In fact, their exaggerated weight gain could be related to an enhanced vascular permeability, which in turn would promote the uptake of fatty acids by AT (25). Thus, apelin would prevent obesity while preserving the integrity of the vascular network.

Energy expenditure in response to apelin was also investigated on the thermogenic aspect. Rectal temperature and oxygen consumption are greater in mice treated with apelin and receiving a normal diet, presumably through induction of uncoupling protein (UCP)1 in brown adipose tissue (21). This increase in body temperature and oxygen consumption is also

found in transgenic mice overexpressing apelin and receiving a high fat diet (22), but is not observed in a model of insulin-resistant obese mice receiving a chronic treatment with apelin (23).

Variations of plasma apelin in human disease

Many studies have reported increased plasma concentrations of apelin in obese or diabetic patients (26). Apelin 17 and pyroglutamate apelin 13 constitute the main plasma forms. According to recent data in diabetic patients, the plasma apelin level seems to be a new predictive biomarker of diabetes in ethnic Chinese Han (27). Apelin plasma levels are higher in type 1 diabetic patients compared to controls, and even higher than in type 2 diabetes (T2D) (28), which is in agreement with a previous work in type 1 diabetes (T1D) (29).

What could be the meaning of a high value of apelinemia? Is obesity implicated? Habchi *et al* (28) showed that circulating apelin concentrations were negatively correlated with glycated haemoglobin (HbA1c) in T2D, suggesting that apelinemia was associated with a better glycemic control. In T1D, the elevation of apelin might compensate for the lack of insulin but may also be explained by the insulin treatment, which is a powerful positive effector of the synthesis and secretion of apelin (8). Furthermore, T1D patients are generally non-obese, suggesting that obesity is probably not a major determinant of plasma apelin. In fact, no correlation between BMI and apelinemia has been described (26). In a recent work Krist *et al* (30) evaluated whether, in the context of weight reduction (bariatric surgery, physical exercise or caloric restriction), changes in apelinemia were mainly related to weight reduction or rather reflected a better sensitivity to insulin. Regardless of the type of strategy to reduce weight, lower apelin plasma levels were observed, as previously described (26, 31). Furthermore, plasma apelin levels are related to improved insulin sensitivity independently of BMI (31). Thus, the elevation of apelinemia observed in T2D could be, as in T1D, an adaptive mechanism to directly reduce insulin resistance and when insulin resistance is reduced, this would then allow a decrease in apelinemia.

The metabolic effects of apelin described in different models emphasize its beneficial role in both energy balance and insulin sensitivity. To understand its involvement in human pathophysiology, it will be necessary to develop more reliable immunoassays to measure apelinemia. In parallel, the use of selective agonists or antagonists of APJ will clarify the involvement of this system in energy balance, and allow the development of original therapeutic strategies.

Fibroblast Growth factor-21 (FGF21)

The FGF family

FGF21 was identified as a metabolic effector with many properties. It is able to induce glucose transport in adipocytes, to improve glucose tolerance, insulin sensitivity and lipid profile, and to reduce body mass (32-34). As explained below, the mechanisms of these effects are well deciphered and involve pleiotropic actions in adipose tissue, liver, pancreas and hypothalamus. Although most of the data were obtained in rodent models, there are also data in primates and in humans, which suggest a favorable metabolic effect of this molecule.

The FGF family includes 23 members (FGF1 to FGF23) that can be classified according to their mode of action, autocrine, paracrine and endocrine. Endocrine FGF include FGF19 (and its murine orthologue FGF15), FGF21 and FGF23. While most of the paracrine and endocrine FGF possess mitogenic properties, FGF21 is unique in its metabolic properties and its lack of proliferative effect.

Signaling mechanisms of FGF21

It is now well established that the metabolic effects of FGF21 require the binding to and the activation of the receptor FGFR1c in cooperation with β-Klotho (35-37). Co-expression of FGFR1c and β-Klotho in AT, liver, muscle pancreas, hypothalamus and brainstem is required for the action of FGF21 in these tissues.

The interaction of FGF21 with FGFR1c and β-Klotho allows FGFR1c autophosphorylation and activation of various downstream phosphorylation pathways comprising the FGF receptor substrate (FRS2), ERK1/2 kinases (extracellular signal-regulated kinase 1 and 2), GSK3 (glycogen synthase kinase-3), AKT (protein kinase B), p70 ^{S6K,} Raf, SHP2 (Src-homology domain-2-containing phosphatase 2), and the STAT3 transcription factor (Signal transducer and activator of transcription-3) (33). Activation of these pathways induces the expression of many genes.

Tissues and actors relaying the metabolic effects of FGF21

The administration of FGF21 causes a rapid induction of the glucose transporter GLUT1 in white adipose tissue (WAT) (39, 40). More prolonged treatment (3 days) results in a thermogenic effect not only in brown adipose tissue (BAT) but also in WAT, with the morphological changes characteristic of an AT "browning" (41,42). An induction of lipogenesis and lipolysis is also observed in WAT.

AT is essential to target metabolic actions of FGF21, as shown in the model of AT-specific knockout of β-Klotho since insulin-sensitizing effects of FGF21 overexpression are abolished in this model (38). Similarly, deletion of FGFR1 in AT precludes the beneficial effects of FGF21 on insulin sensitivity, as well as most of its effects on weight loss and circulating lipid and hepatic changes (43, 44). This suggests that much of the effects of FGF21 on hepatic metabolism involves its action on adipocytes, and probably in part its ability to induce WAT browning.

Interestingly, adiponectin might represent one of the effectors of FGF21 in adipocytes. Indeed, the administration of FGF21 causes rapid secretion of this adipokine, and adiponectin knockout mice become resistant to the beneficial effects of FGF21 on lipid metabolism.

FGF21 is highly expressed in the pancreas, but its pharmacological actions on this organ are still poorly understood. FGF21 induces insulin gene expression and protect B cells from apoptosis in rat pancreatic islets and β-cell lines (45). Although FGF21 does not increase

insulin secretion in normal islets, it potentiates insulin secretion stimulated by glucose in diabetic mice islets, suggesting that FGF21 could avoid beta cell dysfunction (45). In addition, FGF21 reduced glucagon secretion in rodents and monkeys (39.46).

Some metabolic actions of FGF21 may involve direct effects in the brain. Intra-cerebroventricular infusion of FGF21 in rats increases energy expenditure and insulin sensitivity (47). FGF21 is detected in human cerebrospinal fluid, and can cross the blood-brain barrier. It is not detected *in vivo* in neurons, but can be strongly induced in neuronal cultures. Recent evidence suggests that FGF21 signalling in the hypothalamus and/or the brainstem is necessary for non-metabolic functions such as the control of female fertility, growth, or of the HPA axis. However, the neuronal FGF21/β-Klotho signalling does not seem necessary to modulate the insulin-sensitizing effects of FGF21 (38).

Physiological functions of endogenous FGF21

FGF21 expression is preferentially expressed in the pancreas, liver, and AT, but the relative contribution of these different tissues to systemic levels of FGF21 remains unknown. Another important question is whether FGF21 acts as a paracrine or endocrine factor.

A major physiological characteristic of FGF21 is its induction during a prolonged fasting. It has recently been documented that it is primarily the protein restriction, and not the overall caloric restriction, which is responsible for a marked induction of liver and plasma FGF21 (48). Mice overexpressing FGF21 exhibit a phenotype reminiscent of prolonged fasting, with a slowdown in growth, female infertility, a state of torpor. In this context, impaired GH signalling (47) may contribute to longer life expectancy (50). FGF21 seems to be a factor involved in the metabolic adaptation to fasting situations, especially in the case of protein restriction.

FGF21 is also an induced under many other stressful situations, such as exposure to cold, exercise and nutritional excess. The endoplasmic reticulum stress secondary to abnormalities

in lipid metabolism or mitochondrial dysfunction greatly increases the expression of FGF21, which could participate to an appropriate metabolic response.

FGF21 in human diseases

Currently there is no clear association between the genetic components of the FGF21 signalling pathway and hereditary diseases. However, a polymorphism in a FGF21 exon was found to be associated with carbohydrate food intake (49) and a polymorphism in the 3 'non-coding region was associated with the metabolic syndrome, obesity, and diabetes (50).

Moreover, changes in circulating levels of FGF21 have been reported in situations of altered metabolism leading to consider this hormone as a new biomarker. However, the interest of FGF21 is limited by the high inter-individual variability of the plasma concentrations (0.05 to 5.5 ng / ml) in healthy individuals.

Importantly, it was observed that circulating levels of FGF21 are 20-50% higher in obese patients or T2D compared to healthy subjects (51-54) suggesting that FGF21 could be an independent predictor of T2D and metabolic syndrome (51, 52), while T1D patients have lower plasma levels of FGF21 (53).

Increased plasma FGF21 levels were also reported in the Cushing's syndrome (55), in women in pre-eclampsia (56), while anorexia nervosa was associated with a FGF21 decrease (57).

Is FGF21 a promising therapeutic target?

In view of the beneficial metabolic effects of FGF21, several pharmaceutical companies developed FGF21 analogues, particularly with a longer half-life than the native molecule.

In addition antibodies with agonist properties on FGFR1 or β-Klotho were developed. In particular, a monoclonal antibody capable of binding with high affinity to β-Klotho activates the FGFR1/β-Klotho signalling pathway and exerts favorable metabolic effects in the cynomolgus monkey (44).

Another possibility to enhance the action of FGF21 is to increase its endogenous levels by increasing its synthesis and/or inhibiting its degradation. However, this approach is complicated by the lack of knowledge of the tissues that contribute to circulating levels of FGF21, the respective roles of circulating and local forms of this factor, and the proteases involved in its degradation. Recently, it was nevertheless proposed that oxyntomodulin can reduce body weight by activating the transcription and secretion of liver FGF21 (58).

The first proof of concept clinical study was published in 2013 by using a daily subcutaneous injection of the FGF21 analogue LY2405319. During a phase IB clinical study (59), 46 obese patients with T2D were randomized between placebo and three doses of LY2405319 (3, 10, and 20 mg/day) for 28 days. Eight patients discontinued treatment, one due to a hypersensitivity attributed to the drug. Significant effects on LDL-cholesterol (-29%), triglycerides (-46%) and HDL cholesterol (+20%) were observed. In addition, a small but significant reduction in weight was observed. Although there was no significant change in blood glucose, lower insulin levels strongly suggest improved insulin sensitivity. There results on the beneficial metabolic effects of the FGF21 analogue in obese and diabetic patients are encouraging.

The neuroregulin-4 (Nrg4), a new adipokine that targets the liver

This last example of a very recently discovered adipokine (60) illustrates the interest and power of 'omics' approaches to identify new adipokines of unknown function.

The authors specifically identified proteins synthesized and secreted by BAT, whose major function is to ensure thermogenesis assuming that BAT would be capable of secreting factors acting at a distance to modulate energy homeostasis. The results highlighted that neuroregulin-4 (Nrg4), which preserves energy balance by limiting hepatic lipogenesis, was preferentially secreted by BAT.

At first, they performed a transcriptomic analysis of the mRNAs that are strongly induced during differentiation of brown murine preadipocytes *in vitro*. The analysis was oriented

towards the identification of mRNA which structure predicted secreted factors. After a stringent selection, Nrg4 was identified being expression with a prominent expression in BAT, compared to WAT and other tissues.

Furthermore, the expression of Nrg4 was induced after cold exposure or after treatment of brown adipocytes in culture by norepinephrine.

Nrg4 belongs to a protein family containing epidermal growth factor (EGF)-like motifs, which are synthesized as transmembrane precursors and undergo proteolytic processing. The fragment released extracellularly then acts on the target cells as an autocrine/paracrine or endocrine factor. Nrg4 secretion was recovered in the culture medium of transfected cells overexpressing this factor.

The neuregulins transmit their signal through activation of ErbB receptors, and particularly of the ErbB4 form. Using the conditioned medium of Nrg4-overexpressing cells it was found that Nrg4 activated phosphorylation of ErbB3 and ErbB4 selectively in cells that express these receptors.

To assess whether Nrg4 was involved in the thermogenic function of BAT, wild mice or knockout Nrg4 (Nrg4 -/-) were exposed to cold. No difference in rectal temperature was detected between wild type or invalidated animals during exposure to cold, or in the expression of the uncoupling protein UCP1 in BAT. These data suggest that Nrg4 is not directly involved in thermogenesis in BAT, but may act on other tissues after being secreted by adipocytes.

Accordingly, in order to identify Nrg4-target organs, the authors generated a fusion protein between Nrg4 and alkaline phosphatase, and then measured the ability of Nrg4 to bind to tissues by histochemical studies. This elegant approach showed that Nrg4 binds significantly and specifically to the liver. This binding was greatly reduced when it was measured in the presence of an excess of the extracellular binding domains of ErbB3 or ErbB4. These data

indicate that the liver is a target tissue of Nrg4, probably due to its binding to receptors of the ErbB family.

To explore the role of Nrg4 in energy balance, normal mice or Nrg4 -/- mice were subjected to a normal or a high fat diet. With the standard chow, there was no difference in weight between the two genotypes. By contrast, during a high fat diet, the Nrg4 -/- mice exhibited a greater weight gain, increased body fat, and a reduction in lean body mass. The plasma triglyceride levels were also higher as were blood glucose and fasting insulin. Accordingly, the glucose tolerance tests or insulin sensitivity indicated that Nrg4 deficiency exacerbated glucose intolerance and insulin resistance in mice fed high fat diet. Regarding the liver, the Nrg4 -/- mice had elevated triglyceride content and increased plasma concentration of alanine aminotransferase. This effect was not related to liver Nrg4 invalidation because it was not possible to reproduce it after injection of a small interfering RNA of Nrg4 specifically targeting the liver. Interestingly, a large study of gene expression in the liver of these animals indicated that the absence of Nrg4 was associated with induction of mRNA of many actors of the lipogenic pathway (fatty acid synthase, acetyl-CoA carboxylase, malic enzyme, stearoyl-CoA desaturase-1 ...). This was secondary to a major increase in the transcriptional factor controlling lipogenesis, SREBP1. By contrast, in Nrg4 knockout, the mRNA expression of genes involved in fatty acid oxidation, gluconeogenesis, or mitochondrial oxidative phosphorylation remained unmodified. The absence of Nrg4 therefore results in abnormal induction of hepatic lipogenesis and predisposes the animals to high fat diet-induced fatty liver.

In order to explore a direct action of Nrg4 on hepatic lipogenesis, primary cultures of mouse hepatocytes expressing ErbB4 receptor were used. Under these conditions, lipogenesis induced by an agonist of the LXR nuclear receptor was markedly inhibited in the presence of Nrg4, which behaves as a potent anti-lipogenic effector, causing trans-repression of gene encoding LXR.

It was important to analyse possible variations of Nrg4 expression under pathological metabolic conditions, foremost during obesity. In mice with high fat diet or genetically obese *ob/ob* and *db/db*, Nrg4 expression was strongly reduced in the epididymal WAT, but also in BAT. In a large cohort of subjects with a wide range of BMI, the expression of the Nrg4 mRNA in the subcutaneous AT was negatively correlated with the body mass index and hepatic lipid content. In addition, after matching on BMI, the expression of Nrg4 mRNA levels was lower in patients with impaired glucose tolerance or T2D than in individuals with normal glucose tolerance. These observational data in humans, associated with the liver phenotype of Nrg4 deficient mice, suggest that inadequate Nrg4 expression in AT could be involved in the pathogenesis of non-alcoholic fatty liver disease.

Accordingly, it was possible to anticipate that Nrg4 overexpression could prevent metabolic disorders associated with obesity. Mice overexpressing Nrg4 in their AT were thus generated. During normal diet or as a result of exposure to cold, no abnormalities were detected between the two genotypes. By contrast, the transgenic mice have a significantly lower weight gain, and most have a frank reduction of fatty liver and plasma triglycerides under a high fat diet. Mirror of what was observed in Nrg4 -/- mice, mice overexpressing Nrg4 in their AT have a significant decrease in the expression of genes involved in hepatic lipogenesis, such as SREBP1. In obesity induced by high fat diet, Nrg4 overexpression in AT is sufficient to limit lipogenesis and hepatic steatosis, and to improve glucose tolerance and insulin sensitivity.

Therefore, the discovery of this new adipokine with potent liver antilipogenic activity and favorable effects on glucose and lipid metabolism offers new therapeutic opportunities in the context of non-alcoholic steatohepatitis.

Conclusion

The obesity treatments have limited effectiveness on the long time (diet, physical activity, pharmacological treatment), or are associated with significant morbidity and mortality (bariatric surgery). It therefore remains crucial to develop new anti-obesity therapeutic

strategies. Adipokines have demonstrated their potential roles in the regulation of appetite, satiety, energy expenditure, or inflammation and thus constitute prime targets for the treatment of obesity and its comorbidities. After the discovery of leptin more than twenty years ago, the field of investigation in the world of adipokines continues to expand, and gives hope for future progress in pathophysiological understanding and therapeutic.

References

1. Blüher M, Mantzoros CS. From leptin to other adipokines in health and disease: facts and expectations at the beginning of the 21st century. Metabolism 2015; 64: 131-45.
2. Sahin-Efe A, Katsikeris F, Mantzoros CS. Advances in adipokines. Metabolism 2012; 61: 1659-65.
3. Blüher M. Adipose tissue dysfunction in obesity. Exp Clin Endocrinol Diabetes 2009; 117: 241-50.
4. Tatemoto K, Hosoya M, Habata Y, Fujii R, Kakegawa T, Zou MX, et al. Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor. Biochem Biophys Res Commun 1998, 251 : 471-6
5. Castan-Laurell I, Dray C, Knauf C, Kunduzova O, Valet P. Apelin, a promising target for type 2 diabetes treatment? Trends Endocrinol Metab 2012, 23 : 234-41
6. Chapman NA, Dupré DJ, Rainey JK. The apelin receptor: physiology, pathology, cell signalling, and ligand modulation of a peptide-activated class A GPCR. Biochem Cell Biol 2014; 92: 431-40.
7. Knauf C, Drougard A, Fournel A, Duparc T, Valet P. Hypothalamic actions of apelin on energy metabolism : new insight on glucose homeostasis and metabolic disorders. Horm Metab Res 2013, 45 : 928-34

8. Boucher J, Masri B, Daviaud D, Gesta S, Guigné C, Mazzucotelli A, et al. Apelin, a newly identified adipokine up-regulated by insulin and obesity. Endocrinology 2005, 146 : 1764-71

9. Sörhede Winzell M, Magnusson C, Ahrén B. The APJ receptor is expressed in pancreatic islets and its ligand, apelin, inhibits insulin secretion in mice. Regul Pept 2005; 131: 12-7.

10. Dray C, Knauf C, Daviaud D, Waget A, Boucher J, Buléon M, et al. Apelin stimulates glucose utilization in normal and obese insulin-resistant mice. Cell Metab 2008, 8 : 437-445

11. Yue P, Jin H, Aillaud M, Deng AC, Azuma J, Asagami T, et al. Apelin is necessary for the maintenance of insulin sensitivity. Am J Phsyiol Endocrinol Metab 2010, 298 : E59-67

12. Attané C, Daviaud D, Dray C, Dusaulcy R, Masseboeuf M, Prévot D, et al. Apelin stimulates glucose uptake but not lipolysis in human adipose tissue ex vivo. J Mol Endocrinol 2011, 46 : 21-8

13. Zhu S., F. Sun, W. Li, Cao Y, Wang C, Wang Y, et al. Apelin stimulates glucose uptake through the PI3K/Akt pathway and improves insulin resistance in 3T3-L1 adipocytes. Mol Cell Biochem 2011, 353 : 305-13

14. Xu S, Han P, Huang M, Wu JC, Chang C, Tsao PS, et al. In vivo, ex vivo, and in vitro studies on apelin's effect on myocardial glucose uptake. Peptides 2012, 37 : 320-6

15. Dray C, Sakar Y, Vinel C, Daviaud D, Masri B, Garrigues L, et al. The intestinal glucose-apelin cycle controls carbohydate absorption in mice. Gastroenterology 2013, 144 : 771-80

16. Wattez JS, Ravallec R, Cudennec B, Knauf C, Dhulster P, Valet P, et al. Apelin stimulates both cholecystokinin and glucagon-like peptide 1 secretions in vitro and in vivo in rodents. Peptides 2013, 48 : 134-6

17. Guo L, Li Q, Wang W, Yu P, Pan H, Li P, et al. Apelin inhibits insulin secretion in pancreatic beta-cells by activation of PI3-kinase-phosphodiesterase 3B. Endocr Res 2009, 34 : 142-54

18. Ringström C, Nitert MD, Bennet H, Fex M, Valet P, Rehfeld JF, et al. Apelin is a novel islet peptide. Regul Pept 2010, 162 : 44-51

19. Yue P, Jin H, Xu S, Aillaud M, Deng AC, Azuma J, et al. Apelin decreases lipolysis via G(q), G(i), and AMPK-dependent mechanisms. Endocrinology 2011, 152 : 59-68

20. Than A, Cheng Y, Foh LC, Leow MK, Lim SC, Chuah YJ, et al. Apelin inhibits adipogenesis and lipolysis through distinct molecular pathways. Mol Cell Endocrinol 2012, 362 : 227-41

21. Higuchi K, Masaki T, Gotoh K, Chiba S, Katsuragi I, Tanaka K, et al. Apelin, an APJ receptor ligand, regulates body adiposity and favors the messenger ribonucleic acid expression of uncoupling proteins in mice. Endocrinology 2007, 148 : 2690-7

22. Yamamoto T, Habata Y, Matsumoto Y, Yasuhara Y, Hashimoto T, Hamajyo H, et al. Apelin-transgenic mice exhibit a resistance against diet-induced obesity by increasing vascular mass and mitochondrial biogenesis in skeletal muscle. Biochim Biophys Acta 2011, 1810 : 853-62

23. Attané C, Foussal C, Le Gonidec S, Benani A, Daviaud D, Wanecq E, et al. Apelin treatement increases complete fatty acid oxidation, mitochondrial oxidative capacity, and biogenesis in muscle of insulin-resistant mice. Diabetes 2012, 61 : 310-20

24. Alfarano C, Foussal C, Lairez O, Calise D, Attané C, Anesia R, et al. Transition from metabolic adapatation to maladaptation of the heart in obesity : role of apelin. Int J Obes 2015, 39 : 312-20

25. Sawane M, Kajiya K, Kidoya H, Takagi M, Muramatsu F, Takakura N. Apelin inhibits diet-induced obesity by enhancing lymphatic and blood vessel integrity. Diabetes 2013, 62 : 1970-80

26. Castan-Laurell I, Dray C, Attané C, Duparc T, Knauf C, Valet P. Apelin, diabetes, and obesity. Endocrine 2011, 40 : 1-9

27. Ma WY, Yu TY, Wei JN, Hung CS, Lin MS, Liao YJ, et al. Plasma apelin : a novel biomarker for predicting diabetes. Clin Chim Acta 2014, 435 : 18-23

28. Habchi M, Duvillard L, Cottet V, Brindisi MC, Bouillet B, Beacco M, et al. Circulating apelin is increased in patients with type 1 or type 2 diabetes and is associated with better glycemic control. Clin Endocrinol 2014, 81 : 696-701

29. Alexiadou K, Kokkinos A, Liatis S, Perrea D, Katsilambros N, Tentolouris N. Differences in plasma apelin and visfatin levels between patients with type 1 diabetes mellitus and healthy subjects and response after acute hyperglycemia and insulin administration. Hormones (Athens) 2012, 11 : 444-50

30. Krist J, Wieder K, Klöting N, Oberbach A, Kralisch S, Wiesner T, et al. Effects of weight loss and exercise on apelin serum concentrations and adipose tissue expression in human obesity. Obes Facts 2013, 6 : 57-69

31. Heinonen MV, Laaksonen DE, Karhu T, Karhunen L, Laitinen T, Kainulainen S, et al. Effects of diet-induced weight loss on plasma apelin and cytokine levels in individuals with metabolic syndrome. Nutr Metab Cardiovasc Dis 2009, 19 : 626-33

32. Kim KH, Lee MS. FGF21 as a stress hromone : the roles of FGF21 in stress adpatation and the treatment of metabolic diseases. Diabetes Metab J 2014, 38 : 245-51

33. Gimano RE, Moller DE. FGF21-based pharmacotherapy- potentially utility for metabolic disorders. Trends Endocrinol Metab 2014, 25 : 303-11

34. Itoh N. FGF21 as a hepatokine, adipokine, and myokine in metabolism and diseases. Front Endocrinol 2014, 5 : 107

35. Ogawa Y, Kurosu H, Yamamoto M, Nandi A, Rosenblatt KP, Goetz R, et al. Beta-Klotho is required for metabolic activity of fibrobalst growth factor 21. Proc Natl Acad Sci (USA) 2007, 104 : 7432-7

36. Kharitonenkov A, Dunbar JD, Bina HA, Bright S, Moyers JS, Zhang C, et al. FGF-21/FGF-21 receptor interaction and activation is determined by beta-Klotho. J Cell Physiol 2008, 215 :1-7

37. Adams AC, Cheng CC, Coskun T, Kharitonenkov A. FGF21 requires beta-Klotho to act in vivo. Plos One 2012, 7 : e49977

38. Ding X, Boney-Montoya J, Owen BM, Bookout AL, Coate KC, Mangelsdorf DJ, et al. Beta-Klotho is required for fibroblast growth factor 21 effects on growth and metabolism. Cell Metab 2012, 16 : 387-93

39. Kharitonenkov A, Shiyanova TL, Koester A, Ford AM, Micanovic R, Galbreath EJ, et al. FGF-21 as a novel metabolic regulator. J Clin Invest 2005, 115 : 1627-35

40. Ge X, Chen C, Hui X, Wang Y, Lam KS, Xu A. Fibroblast growth factor 21 induces glucose transporter-1 expression through activation of the serum response factor/Ets-like protein-1 in adipocytes. J Biol Chem 2011, 286 : 34533-41

41. Chau MD, Gao J, Yang Q, Wu Z, Gromada J. Fibroblast growth factor 21 regulates energy metabolism by activating the AMPK-SIRT1-PGC-1alpha pathway. Proc Natl Acad Sci (USA) 2010, 107 : 12553-8

42. Fisher FM, Kleiner S, Douris N, Fox EC, Mepani RJ, Verdeguer F, et al. FGF21 regulates PGC-1α and browning of white adipose tissues in adaptive thermogenesis. Genes Dev 2012, 26 : 271-81

43. Adams AC, Yang C, Coskun T, Cheng CC, Gimeno RE, Luo Y, et al. The breadth of FGF21's metabolic actions are governed by FGFR1 in adipose tissue. Mol Metab 2012, 2 : 31-7

44. Foltz IN, Hu S, King C, Wu X, Yang C, Wang W, et al. Treating diabetes and obesity with a FGF21-mimetic antibody activating the βKlotho/FGFR1c receptor complex. Sci Transl Med 2012, 4 : 162ra153

45. Wente W, Efanov AM, Brenner M, Kharitonenkov A, Köster A, Sandusky GE, et al. Fibrobalst growth factor-21 improves pancreatic beta-cell function and survival by activation of extracellular signal-regulated kinase ½ and Akt signaling pathways. Diabetes 2006, 55 : 2470-8

46. Kharitonenkov A, Wroblewski VJ, Koester A, Chen YF, Clutinger CK, Tigno XT, et al. The metabolic state of diabetic monkeys is regulated by fibrobalst growth factor-21. Endocrinology 2007, 148 : 774-81

47. Sarruf DA, Thaler JP, Morton GJ, German J, Fischer JD, Ogimoto K, et al. Fibroblast growth factor 21 action in the brain increases energy expenditure and insulin sensitivity in obese rats. Diabetes 2010, 59 : 1817-24

48. Laeger T, Henagan TM, Albarado DC, Redman LM, Bray GA, Noland RC, et al. FGF21 is an endocrine signal of protein restriction. J Clin Invest 2014, 124 : 3913-22

49. Chu AY, Workalemahu T, Paynter NP, Rose LM, Giulianini F, Tanaka T, et al. Novel locus including FGF21 is associated with macronutrient intake. Hum Mol Genet 2013, 22 : 1895-902

50. Zhang M, Zeng L, Wang YJ, An ZM, Ying BW. Associations of fibroblast growth factor 21 gene 3' untranslated region single-nucleotide polymorphisms with metabolic syndrome, obesity, and diabetes in a Han Chinese population. DNA Cell Biol 2012, 31 : 547-52

51. Bobbert T, Schwarz F, Fischer-Rosinsky A, Pfeiffer AF, Möhlig M, Mai K, et al. Fibroblast growth factor 21 predicts the metabolic syndrome and type 2 diabetes in caucasians. Diabetes Care 2013, 36 : 145-9

52. Chen C, Cheung BM, Tso AW, Wang Y, Law LS, Ong KL, et al. High plasma level of fibroblast growth factor 21 is an independent predictor of type 2 diabetes : a 5.4-year population-based prospective study in Chinese subjects. Diabetes Care 2011, 34 : 2113-5

53. Xiao Y, Xu A, Law LS, Chen C, Li H, Li X, et al. Distinct changes in serum fibroblast growth factor 21 levels in different subtypes of diabetes. J Clin Endocrinol Metab 2012, 97 : E54-8

54. Dushay J, Chui PC, Gopalakrishnan GS, Varela-Rey M, Crawley M, Fisher FM, et al. Increased fibroblast growth factor 21 in obesity and nonalcoholic fatty liver disease. Gastroenterology 2010, 139 : 456-63

55. Durovcová V, Marek J, Hána V, Matoulek M, Zikán V, Haluzíková D, et al. Plasma concentrations of fibroblast growth factors 21 and 19 in patients with Cushing's syndrome. Physiol Res 2010, 59 : 415-22

56. Stepan H, Kley K, Hindricks J, Kralisch S, Jank A, Schaarschmidt W, et al. Serum levels of the adipokine fibroblast growth factor-21 are increased in preeclampsia. Cytokine 2013, 62 : 322-6

57. Dostálová I, Kaválková P, Haluzíková D, Lacinová Z, Mráz M, Papezová H, et al. Plasma concentrations of fibroblast growth factors 19 and 21 in patients with anorexia nervosa. J Clin Endocrinol Metab 2008, 93 : 3627-32

58. Habegger KM, Stemmer K, Cheng C, Müller TD, Heppner KM, Ottaway N, et al. Fibrobalst growth factor 21 mediates specific glucagon actions. Diabetes 2013, 62 : 1453-63

59. Gaich G, Chien JY, Fu H, Glass LC, Deeg MA, Holland WL, et al. The effects of LY2405319, an FGF21 analog, in obese human subjects with type 2 diabetes. Cell Metab 2013, 18 : 333-40

60. Wang GX, Zhao XY, Meng ZX, Kern M, Dietrich A, Chen Z, et al. The brown fat-enriched secreted factor Nrg4 preserves metabolic homeostasis through attenuation of hepatic lipogenesis. Nat Med 2014, 20 : 1436-43

Figure 1: Regulatory of many biological functions by adipokines

Figure

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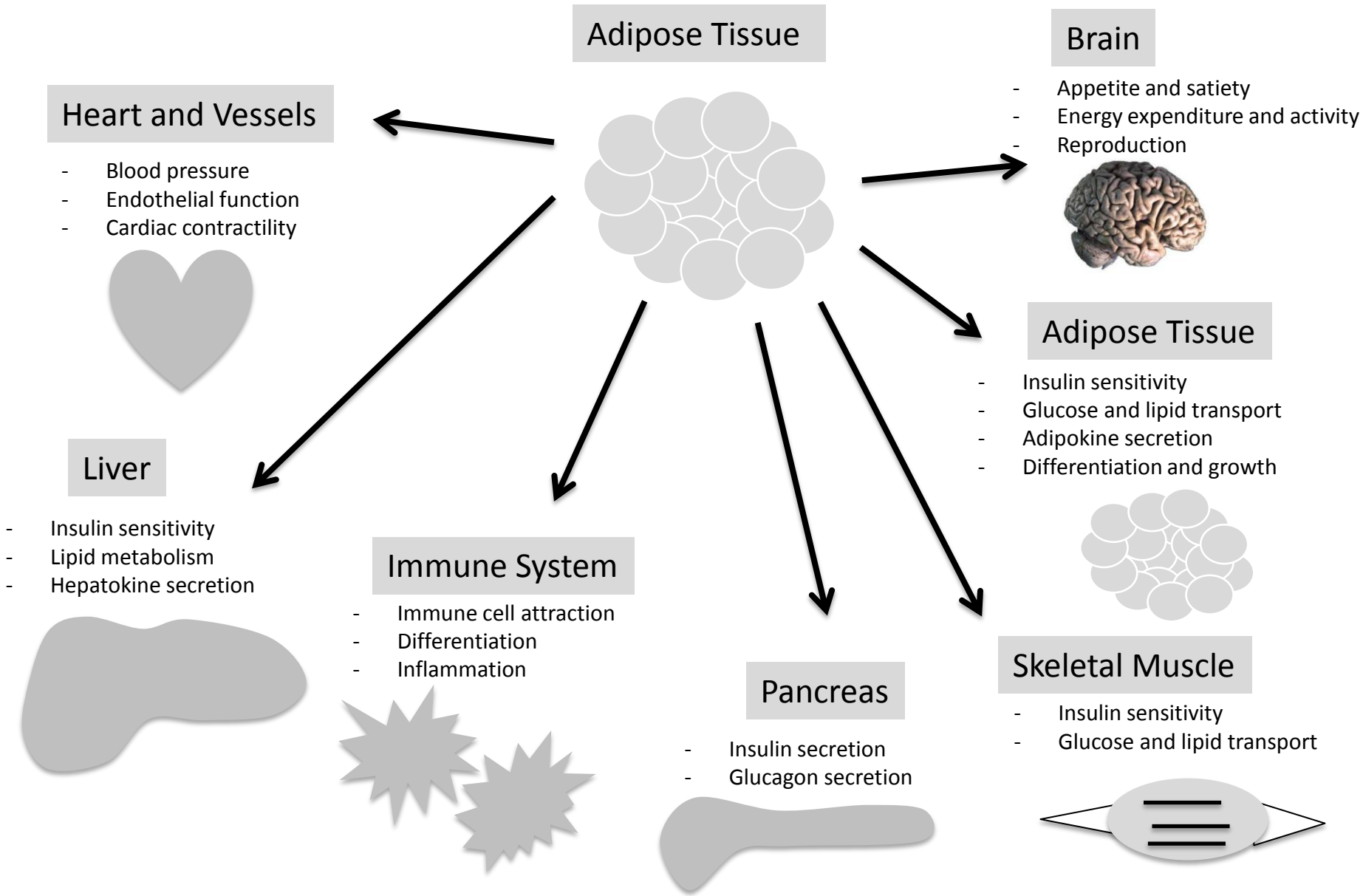

New Adipokines

Nouvelles adipokines

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