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PRACA POGLĄDOWA
REVIEW

The significance and prognostic, diagnostic, and therapeutic potential of selected paracrine factors in type 2 diabetes

Znaczenie oraz potencjał prognostyczny, diagnostyczny i terapeutyczny wybranych czynników parakrynnych w cukrzycy typu 2

Mariusz Kuczera[1], Klaudia Stocerz[1], Arkadiusz Sokal[1], Magdalena Glin[1], Kinga Orlińska[2], Jan Siwiec[3], Paweł Olczyk[2]

[1]Students' Scientific Club, Department of Community Pharmacy, Faculty of Pharmaceutical Sciences in Sosnowiec, Medical University of Silesia, Katowice, Poland
[2]Department of Community Pharmacy, Faculty of Pharmaceutical Sciences in Sosnowiec, Medical University of Silesia, Katowice, Poland
[3]The John Paul II Pediatric Center, Sosnowiec, Poland

ABSTRACT

Type 2 diabetes mellitus (T2DM) is one of the most common modern "disease of affluence", characterized by hyperglycemia resulting from defective insulin secretion by pancreatic β cells and/or impaired tissue sensitivity to insulin. In Poland, the incidence of this metabolic disease is 5–8% and is still increasing. The consequences of the development of T2DM include, among others: changes in cardiovascular system, retinopathy, nephropathy and neuropathy. Due to medical progress, it is easier to control glycemia, as well as to predict the occurrence of this disease or the dynamics of its development and consequences. The molecules discussed in the article: growth differentiation factor 15 (GDF-15), mesencephalic astrocyte-derived neurotrophic factor (MANF) and fetuin-A, represent great promise both in the diagnosis and treatment of not only T2DM, but also obesity, which often accompanies T2DM. Most of the studies reported in the literature were performed on animal models, mainly mouse. This article presents arguments supporting the potential usefulness of the above-mentioned paracrine factors for prognostic, diagnostic and therapeutic purposes.

KEYWORDS

paracrine factors, type 2 diabetes, metabolic disorders

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Address for correspondence: Klaudia Stocerz, Studenckie Koło Naukowe przy Zakładzie Farmacji Aptecznej, Wydział Nauk Farmaceutycznych w Sosnowcu, Śląski Uniwersytet Medyczny w Katowicach, ul. Jedności 10, 41-205 Sosnowiec, tel. +48 32 269 98 31, e-mail: kstocerz@outlook.com

Publisher: Medical University of Silesia, Katowice, Poland

STRESZCZENIE

Cukrzyca typu 2 (*type 2 diabetes mellitus* – T2DM) to jedna z najczęściej występujących współczesnych chorób cywilizacyjnych, odznaczająca się hiperglikemią będącą skutkiem wadliwego wydzielania insuliny przez komórki β trzustki i/lub niewłaściwą wrażliwością tkanek na insulinę. W Polsce zapadalność na tę chorobę metaboliczną wynosi 5–8% i wciąż ma tendencję wzrostową. Konsekwencją rozwoju T2DM są m.in. zmiany w układzie sercowo-naczyniowym, retinopatia, nefropatia i neuropatia. Dzięki postępowi medycyny ułatwione jest kontrolowanie glikemii, jak również predykcja wystąpienia choroby bądź dynamiki jej rozwoju i następstw. Z omówionymi w artykule molekułami – różnicującym czynnikiem wzrostu 15 (*growth differentiation factor 15* – GDF-15), śródmózgowym czynnikiem neurotroficznym pochodzenia astrocytarnego (*mesencephalic astrocyte-derived neurotrophic factor* – MANF) i fetuiną-A – wiążą się duże nadzieje zarówno w diagnostyce, jak i leczeniu nie tylko T2DM, ale również otyłości, która niejednokrotnie towarzyszy T2DM. Większość badań opisywanych w literaturze wykonywana była na modelu zwierzęcym, głównie mysim. Niniejszy artykuł przedstawia argumenty przemawiające za potencjalną użytecznością wspomnianych czynników parakrynnych w celach prognostycznych, diagnostycznych, jak również leczniczych.

SŁOWA KLUCZOWE

czynniki parakrynne, cukrzyca typu 2, zaburzenia metaboliczne

INTRODUCTION

Diabetes is defined as a complex disease caused by metabolic disorders occurring in the body. It is manifested by abnormalities in the concentration of glucose circulating in human blood, which over time leads to multi-organ damage, such as: kidney disorders, vision disorders, cardiovascular disorders and many others. Diabetes mellitus (DM) is divided into: type 1 (T1DM), type 2 (T2DM), gestational diabetes and other specific types, such as maturity onset diabetes of the young (MODY), diabetes associated with genetic defects, drug-induced diabetes. Currently, it is estimated that 537 million people are affected by this disease on a global scale, and this number may increase to up to 783 million patients by 2045 [1], and according to World Health Organization (WHO), 90% of cases concern T2DM. For this reason, it is crucial to thoroughly know all mechanisms leading to T2DM development [2].

Screening tests are an important element in the prevention process. It is indicated that patients who should undergo annual screening for T2DM include those with: over 45 years of age, HDL cholesterol < 35 mg/dL, triglycerides > 250 mg/dL, history of gestational diabetes, fasting blood glucose > 99 mg/dL, blood pressure > 140/90 mmHg, and are overweight or obese [3]. In T2DM, impaired functioning of pancreatic islet β cells is observed, resulting in deficiency of insulin secretion and the progressive development of insulin resistance. Patients affected by this disease most often struggle with excessive body weight with a characteristic concentration of fat tissue in the abdomen. The risk factors for the development of T2DM include genetic, metabolic and environmental factors. Available epidemiological studies prove that modification of some factors, such as obesity, low physical activity, incorrect diet; protect against the development of the disease [2].

DISCUSSION

Growth differentiation factor 15

Growth differentiation factor 15 (GDF-15) is a peptide discovered in 1990, with a molecular weight of approximately 25-30 kDa, belonging to the transforming growth factor β (TGF-β) superfamily. GDF-15 is also synonymously referred to as non-steroidal anti-inflammatory drug-activated gene 1 (NAG-1), macrophage inhibitory cytokine 1 (MIC-1), prostate-derived factor (PDF), placental bone morphogenetic protein (PLAB) and placental transforming growth factor β (PTGF-β) [4,5,6]. The human GDF-15 gene, located on chromosomes 19p12-19p13.1, consists of two exons of 309 and 891 bp, which are separated by a single intron of 1,800 bp interrupting the coding sequences at identical positions in the preprodomain of the corresponding peptides [6,7]. GDF-15 is synthesized as an inactive precursor that undergoes dimerization in the endoplasmic reticulum, which is then transported to the Golgi apparatus, where it undergoes proteolytic cleavage under the influence of furin-like proteases, and is consequently secreted as an active dimer [6]. The synthesis of this molecule takes place in particular in the placenta, prostate, kidneys and large intestine, occurring in the blood under physiological conditions at concentrations of 150–1150 pg/ml, which may be significantly increased in the course of inflammatory disorders. GDF-15 concentrations higher than physiological may be a manifestation of early tissue damage, correlating with the possibility of damage to the vascular endothelium [7]. The synthesis scheme is presented in Figure 1. The agent stimulating the biosynthesis and secretion – by specific cells (i.e. macrophages, adipocytes, cardiomyocytes) of the described regulatory factor is stress, which stimulates the release of this cytokine. Last but not least, the synthesis and release of GDF-15 is subject to strong

stimulation conditioned by p53, a transcription factor that regulates cycle progression and cell survival. The adipokine in question may have both pro- and anti-apoptotic functions [6]. GDF-15 participates in the recruitment of inflammatory cells (mast cells, macrophages) by modulating the activation and extravasation of multinucleated leukocytes [7]. GDF-15 expression correlates with age and body mass index (BMI), and is also associated with the development of insulin resistance, T2DM, metabolic syndrome, smoking, vascular diseases (atherosclerosis, pulmonary embolism), heart failure, acute and chronic inflammation, anemia and bleeding, and cancer [4]. GDF-15 is a protein that is stable in blood serum and plasma for at least 48 hours at room temperature. Due to the correlation with age and telomere length in the population, it can be considered as a marker of aging (including vascular aging) [8]. The above-mentioned factors influencing the increase in GDF-15 expression may translate into the condition of the vascular system and, consequently, its resistance to albumin exudate [9]. GDF-15 may play a significant role in the pathogenesis of atherosclerosis, namely acting as a pro- and anti-inflammatory factor depending on the stage and pathophysiological environment [10]. Several years ago, the orphan receptor – GDNF (glial cell line-derived neurotrophic factor) family receptor alpha like (GFRAL) – was identified, which is a receptor for GDF-15 that mediates the metabolic effects of GDF-15. In turn, GDF-15 fusion proteins have shown potential as a therapeutic agent in the treatment of obesity and its associated diseases [6]. GDF-15 may serve as a marker to assess the severity of diabetes progression in patients with T2DM as measured by the development of albuminuria. Both diabetes and its complications are among the areas in which differentiating growth factor 15 may find great application. Research conducted by Chung et al. [11] proves that the concentration of GDF-15 is independently and positively correlated with diabetic retinopathy in people with T2DM. The authors of the above study also suggest the possibility of using GDF-15 as a biomarker to distinguish diabetic retinopathy in patients with T2DM. In turn, Ilhan et al. [12] proved that increased GDF-15 concentration in the vitreous humor was observed in inflammatory vitreoretinal disorders. Charalambous et al. [13] report the possible involvement of GDF-15 in retinal inflammation and damage, where the level of GDF-15 may be increased in response to optic nerve damage. Coll et al. [14] demonstrated an association between treatment with the biguanide derivative metformin and increased levels of circulating GDF-15 in people without diabetes. They found that changes in GDF-15 levels in people treated with metformin were strongly associated with weight loss. Cai et al. [15] demonstrated an association of increased serum GDF-15 concentration with metabolic improvement caused by lifestyle changes in a population of overweight and obese young adults. Despite the obvious connection with body weight control, the relationship of GDF-15 with glycemic control during metformin treatment remains unclear. Literature data report the possible use of GDF-15 as a biomarker reflecting the effectiveness of metformin pharmacotherapy during treatment with this preparation [16]. In their study, Govaere et al. [17] demonstrate a positive relationship between GDF-15 expression in the liver and the severity of non--alcoholic fatty liver disease (NAFLD), which is a multisystem disease increasing the risk of T2DM. GDF-15 may serve as a marker to assess the severity of diabetes progression in patients with T2DM as measured by the development of albuminuria. GDF-15 expression was significantly higher in patients with advanced liver fibrosis. The above--mentioned study focused on the Asian population. The conclusion of the cited research results is the possible impact of GDF-15 on an increased risk of liver fibrosis, which is a consequence of the probable profibrinogenic effect of the factor in question in the liver and other tissues [16]. Differentiating growth factor 15 is a very promising and increasingly used marker to determine the progressiof many diseases. In the coming years, as further research on this peptide progresses, we will probably discover more areas in which it can be used.

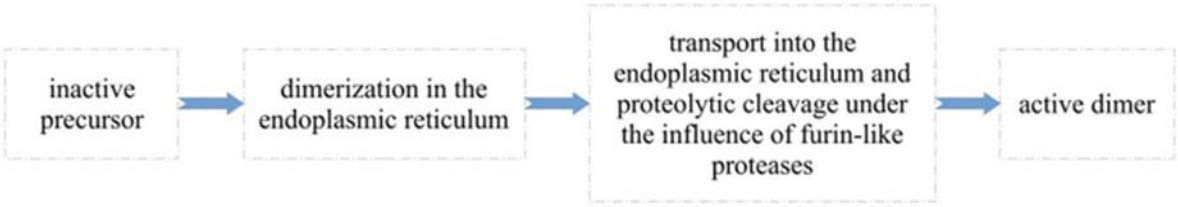

Fig. 1. Scheme of GDF-15 synthesis (according to [6], modified).

Mesencephalic astrocyte-derived neurotrophic factor

Mesencephalic astrocyte-derived neurotrophic factor (MANF) is a protein discovered in 2003 in the cells of the ventral part of the midbrain [18]. It has been classified as a neurotrophic factor (NTF) due to its protective effect on neurons and supporting their regeneration. However, subsequent studies have shown that MANF, in addition to previously known NTFs, influences the regulation of processes related to endoplasmic reticulum (ER) stress. Analysis of its structure revealed that it contains, among others: a different amino acid sequence from classic NTFs, which allowed for a better understanding of the specific functions of this factor. Its properties have made it a target for research into new therapeutic options in the treatment of diseases such as Parkinson's disease or diabetes [19,20].

MANF has a two-domain structure. The N-terminal fragment is homologous to the family of saposin-like proteins, while the C-terminal fragment is similar to SAP proteins (serum amyloid P component) – SAF-A/B (scaffold attachment factor A/B), Acinus, PIAS and Ku70 proteins which are the inhibitor of proapoptotic Bax protein [20,21].

MANF has both intracellular and extracellular effects. The mechanisms of cellular actions are based on the binding of MANF to glucose-regulated protein 78 (GRP78) within the ER. MANF bound to GRP78 inhibits its phosphorylation, which results in the stabilization of the complex of GRP78 with activating transcription factor 6 (ATF6) and prevents its (MANF) transport to the cell nucleus. MANF molecules bind to phosphatidylinositol-5-phosphate 4-kinase type-2 beta (PIP4k2b) within the ER, resulting in inhibition of protein kinase B (AKT) phosphorylation. In response to stress factors, such as proinflammatory adipokines or reactive oxygen species (ROS), MANF is released from the MANF-PIP4k2b complex into the cell cytoplasm. "Free" MANF exhibits the ability to inhibit BAX, which directly inhibits cell apoptosis processes, while in the case of ongoing inflammation it penetrates cell membranes to get into the cell nucleus, where it inhibits the NF-κB signaling path by interacting with the DNA-binding domains in the subunit p65. This results in a modification of gene expression, in a reduction in the production of pro-inflammatory cytokines within the cell, such as TNF-α, IL-1β, IL-6, and in an increase in the secretion of anti-inflammatory cytokines (IL-13, Arg1, Ym1) [18,22, 23,24].

The mechanisms of extracellular action result from the release of MANF into the intercellular space after its detachment from GRP78, where the regulatory molecule in question affects other cells through probable interaction with membrane receptors (KDELR and NPTN), which results in the inhibition of autophagy. Additionally, binding of MANF to NPTN inhibits NF-κB signaling pathways, which reduces the amount of pro-inflammatory factors produced by cells. Another mechanism of MANF extracellular action is direct penetration into cells after its binding to lipid sulfatides. This extracellular MANF is responsible for maintaining ER homeostasis and, through unknown mechanisms, inhibiting autophagy [19,22,23,24]. The development of metabolic diseases, including T2DM, is closely related to the occurrence of chronic systemic inflammation. MANF expression is dynamically regulated in response to β-cell damage due to increased insulin demand which is a direct result of tissue resistance in T2DM and inflammatory signals within the pancreas [25]. The latter, in turn, contribute to the manifestation of the anti-inflammatory properties of the discussed molecule, which was confirmed both in human and mouse pancreatic β-cells [26,27,28]. As a result of processes related to inflammatory reactions, these cells are exposed to pro-inflammatory cytokines through the activation of the NF-κB pathway, which leads to ER stress and the release of MANF, as a result of which the inflammatory process is alleviated. The mechanism of the anti-inflammatory effect of MANF begins with disruption of the binding of the NF-κB p65 subunit to target gene promoters, and then inhibiting the expression of NF-κB--dependent inflammatory genes. In addition to the previously mentioned reactions, MANF additionally inhibits the p3862 mitogen-activated protein kinase (MAPK) pathway [29].

The regulation of tissue sensitivity to insulin by MANF is the subject of observations carried out in mouse models. Overexpression of MANF in the hypothalamus has been shown to trigger insulin resistance by increasing the activity of PIP4k2b, a negative regulator of insulin signaling [30]. MANF supplementation in aged mice was also found to significantly improve tissue insulin sensitivity, regardless of body weight [22,31]. Taking into account the results of the described studies, it can be assumed that insulin resistance may be tissue- or cell-specific, which results in differences in their response to increasing MANF concentrations [22].

MANF may prevent the occurrence of ER stress by regulating the UPR (unfolded protein response) pathway or directly acting as a protection factor against ER stress, preventing apoptotic cell death that could lead to the development of diabetes [25,32]. Experiments conducted in mice have shown that systemic MANF deficiency is associated with the occurrence of diabetes. Last but not least, MANF protects pancreatic β-cells against glucotoxicity and is essential for their proliferation and survival [22,33].

The latest studies conducted in groups of people at high risk of the disease development and in populations of patients diagnosed with T2DM show that the concentration of MANF is in them significantly reduced. These experimental results are different from previous reports showing an increase in plasma MANF concentration in people with newly diagnosed T1DM and T2DM compared to the control group [22].

In the light of new research, it can be assumed that this effect is related to a temporary compensatory reaction of the body, intended to prevent the occurrence of ER stress and thus slow down the development of the disease. This mechanism could be considered analogous to the phenomenon of increased insulin secretion in the initial stage of T2DM. In the further course of T2DM, which is accompanied by glucotoxicity and/or lipotoxicity, the concentration of MANF decreases and, consequently, the disease becomes more severe [34,35].

It was found that blocking the action of MANF results in acceleration of lipogenesis and intensification of steatosis in HepG2 hepatocytes (human liver cancer cell line) while overexpression of MANF results in inhibition of this process [22]. The role that MANF plays in the development of obesity is the subject of research conducted on mouse models. Some of them showed that MANF derived from hepatocytes may have a strong effect in inducing the browning of adipose tissue, thus increasing energy expenditure, which resulted in alleviation of diet-induced obesity. Another study demonstrated that in obese mice treated with a recombinant, long-acting form of MANF protein (MANF-Fc), produced from the fusion of the MANF protein with a mouse Fc fragment of IgG, there is a significant reduction in body weight gain and fat mass, which is also the result of an increase in energy expenditure of the body, as well as significant improvement in glucose tolerance and insulin sensitivity [29]. In studies conducted on obese mice and humans with metabolic disorders such as insulin resistance, prediabetes or diabetes, increased plasma concentrations of MANF were observed. It can be assumed that this concentration cannot be increased to a level that would allow to prevent-obesity, therefore only increasing the concentration to an appropriate value, as a result of pharmacological treatment, would enable achieving a therapeutic concentration [32].

MANF, as well as its recombinant derivatives such as MANF-Fc, can be considered in many therapeutic aspects. This is the result of the mechanism of action of this factor, which could prevent the development of T2DM already at the stage of insulin resistance by increasing tissue sensitivity to insulin and improving glucose tolerance. Another synergistic mechanism may be the alleviation of inflammatory processes within pancreatic β cells, thus protecting them against apoptosis. In addition, the use of MANF could alleviate the course of T2DM and additionally prevent the development of comorbidities. Of course, despite many advances increasing knowledge about MANF, many issues remain unresolved. Further research is needed to address these issues, which may provide new perspectives for the treatment of metabolic diseases [20,34].

Fetuin-A

Cystatins are cysteine peptidase inhibitors that play key roles in pathological and physiological processes occurring in the body. These include type 1, type 2, type 3 and unclassified. Fetuins belong to type 3 cystatins – plasma proteins. However, their target peptidases have not been identified so far. The fetuin family consists of two paralog proteins, i.e. fetuin-A and fetuin-B. They are encoded by duplicate genes located in the 3q27 region of chromosome [36]. Fetuin-A, also called α2-Heremans-Schmid glycol-protein (AHSG), was discovered less than 80 years ago [37]. It has been isolated from the blood plasma of many living creatures, including humans, but also pigs, rats, gerbils, birds, marsupials and cows. It forms a group of orthologous plasma glycoproteins with a molecular weight of 60 kDa, consisting of two amino acid chains. Chain A contains 282 amino acids, chain B contains 27 amino acids, linked together by one disulfide bond. It occurs in blood, embryonic cells, hepatocytes and monocytes. It is also present in the cerebrospinal fluid, but its origin there is currently unknown. The discussed process of fetuin-A biosynthesis is most pronounced in the liver and, to a lesser extent, in monocytes, macrophages and adipocytes [38]. The results of the research by Harbuwono et al. [39] and Roshanzamir et al. [40] require particular emphasis, because according to them obese people may experience increased biosynthesis and secretion of fetuin-A. The latter is also increased in the course of hyperglycemia and hyperinsulinemia. The intensity of the mentioned processes is significantly reduced during periods of fasting and increased physical exercise [39]. In fetal life, the plasma concentration of fetuin-A may be 50 times higher than that observed in healthy adults, whose plasma AHSG concentration does not change beyond a precisely defined value range of 300––1000 μg/ml [39,41]. Cohort studies have shown that the highest AHSG concentration was recorded in premature infants born between 24 and 30 weeks of pregnancy, up to 2–3 times higher than in full-term children. During the same studies, it was shown that the level of fetuin-A in the blood plasma of children born after the 37th week of pregnancy is equal to the concentration in adults [42]. The described signal mediator fetuin-A, characterized by variability in

plasma concentrations in pathological conditions, has numerous biological functions, including: participating in the regulation of osteogenesis, endocytosis, transduction of the "insulin signal", the growth of brain tissue, and functioning as an acute phase protein in the modulation of inflammation. One of the most common clinical conditions to which fetuin-A contributes is T2DM. Increased concentration of AHSG in blood plasma increases the risk of T2DM by 23% [36,37]. The described adipokine plays one of the key roles in the etiopathogenesis of T2DM, constituting an endogenous, non-competitive inhibitor of the tyrosine kinase associated with the insulin receptor subunit β [37]. Fetuin-A binds to tandem domains of fibronectin type 3 present in the extracellular portion of the transmembrane β subunit of the insulin receptor. This causes the inhibition of the tyrosine kinase pathway stimulated by insulin, contributing to the development of insulin resistance [36,38].

In 2013, WHO described obesity as an epidemic of the 21st century affecting people all over the world. Obesity is caused by abnormal metabolic processes occurring in the body. Recent reports indicate that increased plasma levels of fetuin-A are associated with obesity. Valuable information was provided by studies conducted on rats, which showed that individuals with higher concentrations of AHSG circulating in the blood account for an increased percentage of individuals suffering from obesity. However, rats in which the level of fetuin-A was artificially reduced showed resistance to obesity associated with a high-calorie diet [36,43]. Individual studies indicate that aerobic exercise, weight loss, treatment with metformin and pioglitazone reduce the concentration of AHSG circulating in the blood [36]. Therefore, it can be said that this gives hope to people with a high BMI who also struggle with T2DM, or pre-diabetes to improve their health. Research conducted on people struggling with T2DM and at the same time fasting for religious reasons has shown that losing a few kilograms helps in controlling glycemia. In the mentioned studies, participants fasted for 14 days, and in some people the level of fetuin-A circulating in the blood decreased for up to 4 weeks, which correlated with improved health. It should be noted that fasting is not a method recommended by WHO for the treatment of T2DM [39,44].

Many differences can be observed in the functioning of the body of women and men, resulting from, among others, different hormonal balance. However, the mechanism of pathogenesis of various diseases is very similar or even identical in both sexes, including the development of T2DM. Cohort studies indicate a positive correlation between development of T2DM and fetuin-A concentration in both women and men. However, a correlation was slightly higher in women. There may be many reasons for this small difference. It is assumed that it is related to the different distribution of adipose tissue and differences in its composition. A full answer to this issue requires further research [45].

More and more pro-inflammatory markers are being discovered in the human body, which are involved in the development of insulin resistance and, later, T2DM. Fetuin-A actively participates in the movement of macrophages to adipose tissue and also increases the expression of pro-inflammatory cytokines, such as IL-6 and TNF-α, reducing adiponectin expression [46].

Mechanism of hypoglycemic action of fetuin-A is presented in Figure 2.

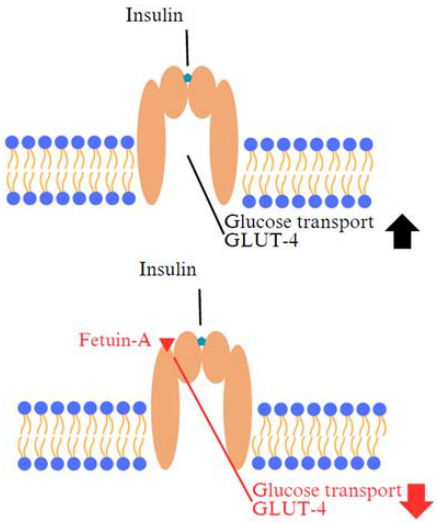

Fig. 2. Mechanism of blocking insulin transport by fetuin-A (according to [47], modified). 1) Insulin binds to two alpha subunits and activates the insulin receptor, which results in stimulation of glucose transport by stimulating GLUT-4 transporters. 2) Fetuin-A binds to the insulin receptor and blocks the beta subunit, which ultimately leads to inhibition of the receptor and inhibition of insulin transport by GLUT-4 transporters.

CONCLUSIONS

With the development of science and the discovery of new molecules, new possibilities appear for the prediction and development of many diseases, including T2DM. A review of selected paracrine factors shows that they can be a valuable predictive tool for this disease measured by various parameters. With new information emerging and the discovery of previously unknown molecules, new possibilities appear for the prediction and monitoring of the development of many diseases, including T2DM. Each of the molecules discussed, i.e. GDF-15, MANF and fetuin-A, seem to be promising factors allowing to fight against the metabolic diseases among others T2DM.

Author's contribution

Study design – M. Kuczera, K. Stocerz, A. Sokal, M. Glin, K. Orlińska, J. Siwiec, P. Olczyk
Data collection – M. Kuczera, K. Stocerz, A. Sokal, M. Glin
Manuscript preparation – K. Stocerz, A. Sokal, M. Kuczera, M. Glin, K. Orlińska, J. Siwiec, P. Olczyk
Literature research – K. Stocerz, A. Sokal, M. Kuczera, M. Glin
Final approval of the version to be published – K. Orlińska, J. Siwiec, P. Olczyk

REFERENCES

1. Harreiter J., Roden M. Diabetes mellitus: definition, classification, diagnosis, screening and prevention (Update 2023). [Article in German]. Wien. Klin. Wochenschr. 2023; 135(Suppl 1): 7–17, doi: 10.1007/s00508-022-02122-y.
2. Galicia-Garcia U., Benito-Vicente A., Jebari S., Larrea-Sebal A., Siddiqi H., Uribe K.B. et al. Pathophysiology of type 2 diabetes mellitus. Int. J. Mol. Sci. 2020; 21(17): 6275, doi: 10.3390/ijms21176275.
3. Pippitt K., Li M., Gurgle H.E. Diabetes mellitus: screening and diagnosis. Am. Fam. Physician 2016; 93(2): 103–109. Erratum in: Am. Fam. Physician 2016; 94(7): 533.
4. Piechota W., Krzesiński P. Czynnik różnicowania wzrostu 15 (GDF-15) w ocenie ryzyka sercowo-naczyniowego. Pediatr. Med. Rodz. 2018; 14(1): 9––19, doi: 10.15557/PiMR.2018.0001.
5. Kempf T., Eden M., Strelau J., Naguib M., Willenbockel C., Tongers J. et al. The transforming growth factor-beta superfamily member growth--differentiation factor-15 protects the heart from ischemia/reperfusion injury. Circ. Res. 2006; 98(3): 351–360, doi: 10.1161/01.RES.0000202805.73038.48.
6. Verhamme F.M., Freeman C.M., Brusselle G.G., Bracke K.R., Curtis J.L. GDF-15 in pulmonary and critical care medicine. Am. J. Respir. Cell Mol. Biol. 2019; 60(6): 621–628, doi: 10.1165/rcmb.2018-0379TR.
7. Niu Y., Zhang W., Shi J., Liu Y., Zhang H., Lin N. et al. The relationship between circulating growth differentiation factor 15 levels and diabetic retinopathy in patients with type 2 diabetes. Front. Endocrinol. (Lausanne) 2021; 12: 627395, doi: 10.3389/fendo.2021.627395.
8. Hellemons M.E., Mazagova M., Gansevoort R.T., Henning R.H., de Zeeuw D., Bakker S.J.L. et al. Growth-differentiation factor 15 predicts worsening of albuminuria in patients with type 2 diabetes. Diabetes Care 2012; 35(11): 2340–2346, doi: 10.2337/dc12-0180.
9. Lajer M., Jorsal A., Tarnow L., Parving H.H., Rossing P. Plasma growth differentiation factor-15 independently predicts all-cause and cardiovascular mortality as well as deterioration of kidney function in type 1 diabetic patients with nephropathy. Diabetes Care 2010; 33(7): 1567–1572, doi: 10.2337/dc09-2174.
10. He X., Su J., Ma X., Lu W., Zhu W., Wang Y. et al. The association between serum growth differentiation factor 15 levels and lower extremity atherosclerotic disease is independent of body mass index in type 2 diabetes. Cardiovasc. Diabetol. 2020; 19(1): 40, doi: 10.1186/s12933-020-01020-9.
11. Chung J.O., Park S.Y., Cho D.H., Chung D.J., Chung M.Y. Relationship between plasma growth differentiation factor-15 levels diabetic retinopathy in individuals with type 2 diabetes. Sci. Rep. 2020; 10(1): 20568, doi: 10.1038/s41598-020-77584-z.
12. Ilhan H.D., Bilgin A.B., Toylu A., Dogan M.E., Apaydin K.C. The expression of GDF-15 in the human vitreous in the presence of retinal pathologies with an inflammatory component. Ocul. Immunol. Inflamm. 2016; 24(2): 178–183, doi: 10.3109/09273948.2014.981549.
13. Charalambous P., Wang X., Thanos S., Schober A., Unsicker K. Regulation and effects of GDF-15 in the retina following optic nerve crush. Cell Tissue Res. 2013; 353(1): 1–8, doi: 10.1007/s00441-013-1634-6.
14. Coll A.P., Chen M., Taskar P., Rimmington D., Patel S., Tadross J.A. et al. GDF15 mediates the effects of metformin on body weight and energy balance. Nature 2020; 578(7795): 444–448, doi: 10.1038/s41586-019-1911-y.
15. Cai L., Li C., Wang Y., Mo Y., Yin J., Ma X. Increased serum GDF15 related to improvement in metabolism by lifestyle intervention among young overweight and obese adults. Diabetes Metab. Syndr. Obes. 2021; 14: 1195––1202, doi: 10.2147/DMSO.S302033.
16. Gao F., Li C., Wang Y., Lu J., Lu W., Zhou J. et al. Growth differentiation factor 15 is not associated with glycemic control in patients with type 2 diabetes mellitus treated with metformin: a post-hoc analysis of AIM study. BMC Endocr. Disord. 2022; 22(1): 256, doi: 10.1186/s12902-022-01176-3.
17. Govaere O., Cockell S., Tiniakos D., Queen R., Younes R., Vacca M. et al. Transcriptomic profiling across the nonalcoholic fatty liver disease spectrum reveals gene signatures for steatohepatitis and fibrosis. Sci. Transl. Med. 2020; 12(572): eaba4448, doi: 10.1126/scitranslmed.aba4448.
18. Petrova P., Raibekas A., Pevsner J., Vigo N., Anafi M., Moore M.K. et al. MANF: a new mesencephalic, astrocyte-derived neurotrophic factor with selectivity for dopaminergic neurons. J. Mol. Neurosci. 2003; 20(2): 173–188, doi: 10.1385/JMN:20:2:173.
19. Yang S., Li S., Li X.J. MANF: a new player in the control of energy homeostasis, and beyond. Front. Physiol. 2018; 9: 1725, doi: 10.3389/fphys.2018.01725.
20. Yu Y., Liu D.Y., Chen X.S., Zhu L., Wan L.H. MANF: a novel endoplasmic reticulum stress response protein–the role in neurological and metabolic disorders. Oxid. Med. Cell. Longev. 2021; 2021: 6467679, doi: 10.1155/2021/6467679.
21. Hellman M., Arumäe U., Yu L.Y., Lindholm P., Peränen J., Saarma M. et al. Mesencephalic astrocyte-derived neurotrophic factor (MANF) has a unique mechanism to rescue apoptotic neurons. J. Biol. Chem. 2011; 286(4): 2675–2680, doi: 10.1074/jbc.M110.146738.
22. Tang Q., Li Y., He J. MANF: an emerging therapeutic target for metabolic diseases. Trends Endocrinol. Metab. 2022; 33(4): 236–246, doi: 10.1016/j.tem.2022.01.001.
23. Henderson M.J., Richie C.T., Airavaara M., Wang Y., Harvey B.K. Mesencephalic astrocyte-derived neurotrophic factor (MANF) secretion and cell surface binding are modulated by KDEL receptors. J. Biol. Chem. 2013; 288(6): 4209–4225, doi: 10.1074/jbc.M112.400648.
24. Yagi T., Asada R., Kanekura K., Eesmaa A., Lindahl M., Saarma M. et al. Neuroplastin modulates anti-inflammatory effects of MANF. iScience 2020; 23(12): 101810, doi: 10.1016/j.isci.2020.101810.
25. Ikegami H., Babaya N., Noso S. β-Cell failure in diabetes: Common susceptibility and mechanisms shared between type 1 and type 2 diabetes. J. Diabetes Investig. 2021; 12(9): 1526–1539, doi: 10.1111/jdi.13576.
26. Cunha D.A., Cito M., Grieco F.A., Cosentino C., Danilova T., Ladrière L. et al. Pancreatic β-cell protection from inflammatory stress by the endoplasmic reticulum proteins thrombospondin 1 and mesencephalic astrocyte-derived neutrotrophic factor (MANF). J. Biol. Chem. 2017; 292(36): 14977–14988, doi: 10.1074/jbc.M116.769877.
27. Hakonen E., Chandra V., Fogarty C.L., Yu N.Y., Ustinov J., Katayama S. et al. MANF protects human pancreatic beta cells against stress-induced cell death. Diabetologia 2018; 61(10): 2202–2214, doi: 10.1007/s00125-018-4687-y.
28. Danilova T., Galli E., Pakarinen E., Palm E., Lindholm P., Saarma M. et al. Mesencephalic astrocyte-derived neurotrophic factor (MANF) is highly expressed in mouse tissues with metabolic function. Front. Endocrinol. (Lausanne) 2019; 10: 765, doi: 10.3389/fendo.2019.00765.
29. Wu T., Liu Q., Li Y., Li H., Chen L., Yang X. et al. Feeding-induced hepatokine, Manf, ameliorates diet-induced obesity by promoting adipose browning via p38 MAPK pathway. J. Exp. Med. 2021; 218(6): e20201203, doi: 10.1084/jem.20201203.
30. Yang S., Yang H., Chang R., Yin P., Yang Y., Yang W. et al. MANF regulates hypothalamic control of food intake and body weight. Nat. Commun. 2017; 8(1): 579, doi: 10.1038/s41467-017-00750-x.
31. Sousa-Victor P., Neves J., Cedron-Craft W., Ventura P.B., Liao C.Y., Riley R.R. et al. MANF regulates metabolic and immune homeostasis in ageing and protects against liver damage. Nat. Metab. 2019; 1(2): 276–290, doi: 10.1038/s42255-018-0023-6.
32. Pakarinen E., Lindholm P., Saarma M., Lindahl M. CDNF and MANF regulate ER stress in a tissue-specific manner. Cell. Mol. Life Sci. 2022; 79(2): 124, doi: 10.1007/s00018-022-04157-w.
33. Lindahl M., Danilova T., Palm E., Lindholm P., Võikar V., Hakonen E. et al. MANF is indispensable for the proliferation and survival of pancreatic β cells. Cell. Rep. 2014; 7(2): 366–375, doi: 10.1016/j.celrep.2014.03.023.
34. Wang C., Peng J.J., Miao H., Liu D.F., Zhang L.L. Decreased plasma MANF levels are associated with type 2 diabetes. Biomed. Environ. Sci. 2021; 34(3): 236–40, doi: 10.3967/bes2021.030.
35. Wu T., Zhang F., Yang Q., Zhang Y., Liu Q., Jiang W. et al. Circulating mesencephalic astrocyte-derived neurotrophic factor is increased in newly diagnosed prediabetic and diabetic patients, and is associated with insulin resistance. Endocr. J. 2017; 64(4): 403–410, doi: 10.1507/endocrj.EJ16-0472.
36. Ochieng J., Nangami G., Sakwe A., Moye C., Alvarez J., Whalen D. et al. Impact of fetuin-A (AHSG) on tumor progression and type 2 diabetes. Int. J. Mol. Sci. 2018; 19(8): 2211, doi: 10.3390/ijms19082211.
37. Wang Y., Koh W.P., Jensen M.K., Yuan J.M., Pan A. Plasma fetuin-A levels and risk of type 2 diabetes mellitus in a Chinese population: a nested case-control study. Diabetes Metab. J. 2019; 43(4): 474–486, doi: 10.4093/dmj.2018.0171.

38. Ricken F., Can A.D., Gräber S., Häusler M., Jahnen-Dechent W. Post--translational modifications glycosylation and phosphorylation of the major hepatic plasma protein fetuin-A are associated with CNS inflammation in children. PLoS One 2022; 17(10): e0268592, doi: 10.1371/journal.pone.0268592.
39. Harbuwono D.S., Sazli B.I., Kurniawan F., Darmowidjojo B., Koesnoe S., Tahapary D.L. The impact of Ramadan fasting on fetuin-A level in type 2 diabetes mellitus. Heliyon 2021; 7(5): e06773, doi: 10.1016/j.heliyon.2021.e06773.
40. Roshanzamir F., Miraghajani M., Rouhani M.H., Mansourian M., Ghiasvand R., Safavi S.M. The association between circulating fetuin-A levels and type 2 diabetes mellitus risk: systematic review and meta-analysis of observational studies. J. Endocrinol. Invest. 2018; 41(1): 33–47, doi: 10.1007/s40618-017-0697-8.
41. Guo V.Y., Cao B., Cai C., Cheng K.K., Cheung B.M.Y. Fetuin-A levels and risk of type 2 diabetes mellitus: a systematic review and meta-analysis. Acta Diabetol. 2018; 55(1): 87–98, doi: 10.1007/s00592-017-1068-9.
42. Robinson K.N., Teran-Garcia M. From infancy to aging: Biological and behavioral modifiers of fetuin-A. Biochimie 2016; 124: 141–149, doi: 10.1016/j.biochi.2015.12.016.
43. Chekol Abebe E., Tilahun Muche Z., Behaile T/Mariam A., Mengie Ayele T., Mekonnen Agidew M., Teshome Azezew M. et al. The structure, biosynthesis, and biological roles of fetuin-A: a review. Front. Cell Dev. Biol. 2022; 10: 945287, doi: 10.3389/fcell.2022.945287.
44. Selvaraju V., Babu J.R., Geetha T. Multiplexed measurements of salivary fetuin-A, insulin, and adiponectin as potential non-invasive biomarkers in childhood obesity. Cytokine 2022; 153: 155843, doi: 10.1016/j.cyto.2022.155843.
45. Sujana C., Huth C., Zierer A., Meesters S., Sudduth-Klinger J., Koenig W. et al. Association of fetuin-A with incident type 2 diabetes: results from the MONICA/KORA Augsburg study and a systematic meta-analysis. Eur. J. Endocrinol. 2018; 178(4): 389–398, doi: 10.1530/EJE-17-1053.
46. Kim J.E., Kim J.S., Jo M.J., Cho E., Ahn S.Y., Kwon Y.J. et al. The roles and associated mechanisms of adipokines in development of metabolic syndrome. Molecules 2022; 27(2): 334, doi: 10.3390/molecules27020334.
47. Bourebaba L., Marycz K. Pathophysiological implication of fetuin-A glycoprotein in the development of metabolic disorders: a concise review. J. Clin. Med. 2019; 8(12): 2033, doi: 10.3390/jcm8122033.