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Review

Role of pro-inflammatory cytokines of pancreatic islets and prospects of elaboration of new methods for the diabetes treatment

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Several relations between cytokines and pathogenesis of diabetes are reviewed. In type 1 and type 2 diabetes an increased synthesis is observed and as well as the release of pro-inflammatory cytokines, which cause the damage of pancreatic islet cells and, in type 2 diabetes, the development of the insulin resistance. That process results in the disturbed balance between pro-inflammatory and protective cytokines. Pro-inflammatory cytokines such as interleukin 1β (IL-1β), tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ), as well as recently discovered pancreatic derived factor PANDER are involved in the apoptosis of pancreatic β-cells. Inside β-cells, cytokines activate different metabolic pathways leading to the cell death. IL-1β activates the mitogen-activated protein kinases (MAPK), affects the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and activates the inducible nitric oxide synthase (iNOS). TNF-α and IFN-γ in a synergic way activate calcium channels, what leads to the mitochondrial dysfunction and activation of caspases. Neutralization of pro-inflammatory cytokines, especially interleukin 1β with the IL-1 receptor antagonist (IL-1Ra) and/or IL-1β antibodies might cause the extinction of the inflammatory process of pancreatic islets, and consequently normalize concentration of glucose in blood and decrease the insulin resistance. In type 1 diabetes interleukin-6 participates in regulation of balance between Th17 and regulatory T cells. In type 2 diabetes and obesity, the long-duration increase of IL-6 concentration in blood above 5 pg/ml leads to the chronic and permanent increase in expression of SOCS3, contributing to the increase in the insulin resistance in cells of the skeletal muscles, liver and adipose tissue.

Key words: interleukin 1β, interleukin-6, tumor necrosis factor-α, pancreatic derived factor, insulin resistance

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INTRODUCTION

Discovery of the hypoglycemizing action of insulin by Banting and Best in 1922, and the use of that hormone as a drug in treatment of diabetes is one of the greatest medical discoveries. However, as it was emphasized by the investigators, the treatment of diabetes with insulin does not lead to the disease cure. That justifies the search for the disease causes and new ways of its treatment.

Pancreas plays both exocrine and endocrine functions. Exocrine functions are performed in 70–90% by acinar cells and in 5–25% by duct cells (Burnstock, 2013). The endocrine functions are associated with cells of the Langerhans islets (only 3–5% of all cells) and pancreatic stellate cells (less than 5%) (Burnstock, 2013).

The essence of patophysiological disorders in diabetes is the abnormal metabolism and transport of glucose, associated with non-adequate insulin secretion and/or insulin resistance. These disorders lead to hyperglycaemia, and release of free fatty acids (FFA) and pro-Inflammatory cytokines. These metabolic changes result in disorders in other systems and organs such as: cardiovascular system, kidneys, urinary system or alimentary system, and disorders of processes such as skin healing, sexual disorders or muscular weakness. Usually, few years after the diabetes diagnosis or rarely even before first sympotoms are observed, some diabetic complications occur, such as micro- and macroangiopathy, retinopathy and polyneuropathy.

Type 1 diabetes (T1D), i.e. insulin-dependent diabetes, is an autoimmune disease, that is revealed in patients with genetic predispositions, and is manifested by the action of environmental factors, in particular the viral infections (Odegaard, 2012; Burnstock, 2013). Symptoms of diabetes occur after damage of 80% of cells producing insulin. During the course of the disease, the loss of the mass of the pancreatic islet cells and disorders in their function occur, and patients are dependent on exogenous insulin. In type 2 diabetes (T2D), especially in the initial stage, the insulin secretion may be close to normal, but the significant tissue resistance to insulin is observed (Odegaard, 2012; Burnstock, 2013). In the duration of disease, different factors, in particular cytokines, cause the damage and mass loss of the pancreatic islet cells. Type 2 diabetes has usually a late onset, frequently associated with obesity, a significant auto-inflammation of islets, low-grade inflammation of the adipocytes and increasing insulin resistance of hepatocytes and skeletal muscle cells (Odegaard, 201; Burnstock, 2013).

Different mechanisms leading to the apoptosis of β-cells of pancreatic islet are suggested for T1D and T2D

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Abbreviations: TNF-α, tumor necrosis factor-α; IL-1β, interleukin 1β; IFN-γ, interferon-γ; PANDER, PANcreatic DERived factor; MAPK, mitogen-activated protein kinases; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; iNOS, inducible nitric oxide synthase; IL-1Ra, IL-1 receptor antagonist; IL-17, interleukin 17; IL-6, interleukin 6; SOCS, Suppressor of Cytokine Signaling

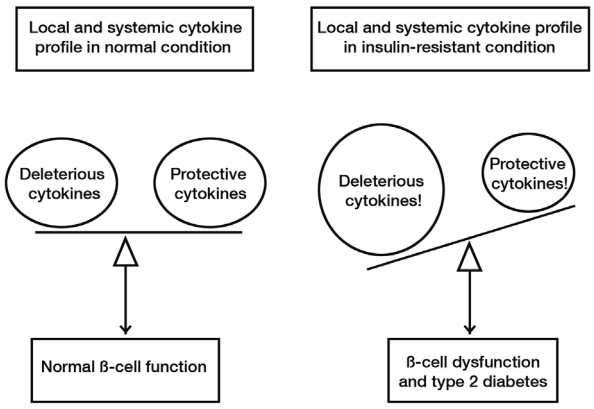

Figure 1. Different mechanisms of pancreatic β-cells apoptosis in type 1 and type 2 diabetes (modified from Cnop, 2005).

(Cnop, 2005). In T1D, insulitis results in the exposure of β-cells to secreted pro-inflammatory cytokines and NO. That results in the alteration of their functions. It was shown that the long-term exposure to IL-1β, TNF-α and INF-γ leads to the β-cell death (Eizirik, 2001). In particular IL-1β and INF-γ induce the sequence of processes regulated by transcription factors NF-ϰB and STAT-1, respectively, leading to the cell apoptosis (Cnop, 2005). On the other hand, in T2D the long-term exposure to elevated levels of glucose and free fatty acids (FFAs) results in the dysfunction of β-cell and may induce their apoptosis. High levels of FFA are reported to be toxic to β-cell and this effect is amplified by the high concentration of glucose. The β-cell apoptosis might be related to FFA causing the ER stress. The detailed mechanism has to be determined but it is NF-ϰB and NO independent (Cnop, 2005). Different mechanisms triggering the β-cell death are associated with cytokines and nutrients. For cytokines, the NF-ϰB-dependent mechanism related to activation of caspase-3 is proposed. In turn, nutrients act via the mechanism which is independent from NF-ϰB (Cnop, 2005).

The disruption of insulin signalling in parenchymal cells of insulin-responsive tissues causes their insulin resistance. Several molecular mechanisms are proposed, including the ER stress, glucotoxicity, lipotoxicity, adipokines or hormones (Lee, 2013). However, the mechanisms at the cellular level are not well understood. The effect of purinergic signaling on the increase in the glucose concentration in blood and the release of pro-inflammatory cytokines was discussed and both promote the insulin resistance (Cieślak, 2014).

Obesity itself causes the elevation of the pro-inflammatory cytokines concentration in blood and in peripheral tissues (Memon, 2013; Wieser, 2013; Lee, 2013). Currently, it is known that in the development of obesity induced inflamation the adipose tissue macrophages participate in the formation of the insulin resistance and typ 2 diabetes (Lee, 2013). Similarly, hyperglycaemia causes the increased secretion of cytokines, what was shown in the culture of human endothelial cells (Asakawa, 1997). Several mechanisms are responsible for the insulin resistance: oxidation stress, stress of endoplasmic reticulum, amyloid deposits in the pancreatic islet cells, accumulation of ectopic lipids in muscles, liver and pancreas, as well as lipotoxicity and glucotoxicity (Harding, 2002; Esposito, 2002; Weir, 2004; Memon, 2013).

Glucotoxicity refers to the harmful effect of elevated glucose concentration (Kaiser, 2003; Cnop, 2012). Hyperglycemia may lover the β-cells mass by inducing apoptosis that is not compensated by an increase in the cell proliferation and neogenesis (Kaiser, 2003). Lipotoxicity is related to the accumulation of lipid intermediates in the non-adipose tissue, leading to cellular dysfunction and death. The cellular mechanisms of lipotoxicity include metabolic interference and cellular stress responses such as oxidative stress, endoplasmic reticulum (ER) stress, and possibly autophagy (Cnop, 2012; Sharma RB, 2014).

The oxidation stress and stress of endoplasmic reticulum cause the intensified production of pro-inflammatory cytokines in cells, and therefore an induction of the inflammatory processes (Hotamisligil, 2005). With progression of the disease, the immune cells such as macrophages infiltrate in/or around Langerhans islets in the pancreas and also become a source of the pro-inflammatory cytokines. Studies by Lee suggest, that obesity induced inflamation is mediated mainly by adipose tissue macrophages (ATMs) (Lee, 2013).

In less than 10% of patients, diabetes results from the disorder in the exocrine activity of pancreas and that is referred to as type 3c diabetes (Burnstock, 2013). In type 3c the disorder in thexocrine/endocrine axis occurs, especially between duct and Langerhans islet cells, and that process is associated with the release of pro-inflammatory cytokines (Movahedi, 2004; Bertelli, 2005; Burnstock, 2013).

ROLE OF CYTOKINES IN DISORDER OF B-CELLS ACTIVITY

Mechanism of disorder of the pancreatic islet cells is different in type 1 and type 2 diabetes. In T1D the decrease in the insulin synthesis occurs as a result of the progressing damage of β-cells caused by apoptosis resulting from the autoimmune disorder. The pro-inflammatory cytokines are also involved in that process (Pickup, 2000; Wang, 2010; Wieser, 2013). In T2D, the progressing disorders in the β-cell activity and progressing decrease in their number are associated with the increasing blood concentration of cytokines, chemokines and free fatty acids (FFAs), as well as chronic hyperglycaemia (Böni-Schnetzler, 2009; Wang, 2010). In humans, FFAs induce the release of IL-1β, IL-6 and IL-8 (Böni-Schnetzler, 2009). Prolonged exposition of β-cells to these factors results in the excessive production and release of free radicals and activation of caspases. These processes inhibit the insulin secretion and enhance the apoptosis of the pancreas β-cells (Wang, 2010).

Participation of pro-inflammatory cytokines such as interleukin 1β (IL-1β), tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) in type 1 diabetes is well understood (Kawasaki, 2004; Wang, 2010). The increased concentration of these cytokines was detected both in blood and in Langerhans islets. Currently, it is known that in diabetes the pancreatic islets are infiltrated by some immune cells, including lymphocytes and macrophages, which are also the source of pro-inflammatory cytokines (Kawasaki, 2004; Ehses, 2009; Wang, 2010). The adipose tissue is another significant source of cytokines. Cytokines released from the adipose tissue are referred to as adipocytokines (Achima, 2008; Wang, 2010). These compounds are classified as adipocytes specific cytokines — leptin, resistin, adiponectin, visfatin and omentin, and cytokines not specific to adipocytes — IL-6, IL-1β, TNF-α (Ahima, 2006; Bassols, 2009; Wang, 2010). Recently, the presence of protein similar to cytokines and called *PAN-*

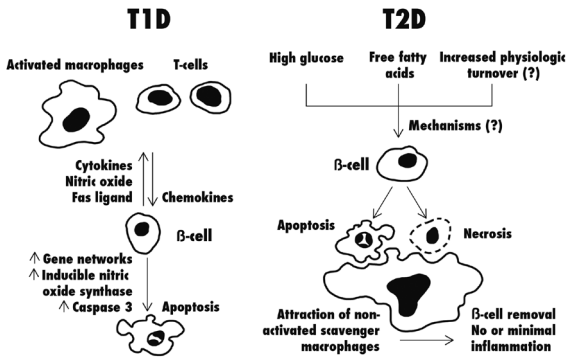

Figure 2. Roles of cytokines in regulation of pancreatic β-cell function.
Role of cytokines in regulation of pancreatic β-cell function. The disturbed balance of deleterious and protective cytokines in islets and plasma in the development and progression of β-cell dysfunction and type 2 diabetes (modified form Wang C, 2010).

creatic DERived factor (PANDER) was discovered. It is localized in cytosolic compartment and secreted from α and β cells. It was hypothesized that in humans PANDER participates in the β-cells apoptosis (Yang, 2005; Wang, 2012). Among secreted cytokines there are compounds of pro-apoptotic and pro-inflammatory activity such as IL-1β, TNF-α, IFN-γ and resistin, which also inhibit the insulin secretion, as well as cytokines protecting β-cells — adiponectin and visfatin (Wang, 2012). With progression of diabetes, the balance between amount of pro-inflammatory and protective cytokines is disturbed by increased synthesis and secretion of pro-inflammatory cytokines.

PRO-INFLAMMATORY CYTOKINES — INTERLEUKIN 1β (IL-1β), TUMOR NECROSIS FACTOR-α (TNF-α) AND INTERFERON-γ (IFN-γ)

IL-1β

IL-1β is one of the most important pro-apoptotic and pro-inflammatory cytokines, responsible for disorders in β-cells activity and closely related especially to pathogenesis of type 2 diabetes. Effect of the IL-1β action on β-cells is due to the decrease of secretion and decreased number of pancreatic islet β-cells (Dinarello, 2010). It is supposed that there is a strict relation between the inflammation and induction of the tissue insulin resistance, what affects the subsequent development of type 2 diabetes (Weir, 2004; Shoelson, 2006; Donath, 2009; Donath, 2011; Memon, 2013). The autoinflammatory processes in pancreatic islets are caused not only by IL-1 β, but also by glucose, FFAs and leptin (Dinarello, 2010).

In pancreatic β-cells, IL-1β affects two metabolic pathways. It activates the mitogen-activated protein kinases (MAPK), including extracellular signal-regulated kinase (ERK). On the other hand it affects the NF-ϰB (Larsen, 2005). NF-ϰB are transcription factors involved in responses to cellular stressors such as cytokines, free radicals and bacterial or viral antigens. Both pathways are necessary for expression of the gene encoding the inducible nitric oxide synthase (iNOS), which besides IL-1β participates in the process of β-cells death (Larsen, 2005). The nitric oxide synthases (NOSs) are a family of enzymes catalyzing the synthesis of nitrogen(II) oxide from L-arginine in a presence of NADPH and molecular oxygen. NOSs include the constitutive and inducible isoforms. Expresion of inducible isoform (iNOS) can be activated in many cell types by cytokines through the activation of the trancription factors NF-ϰB and STAT-1alpha. The long-lasting activation of NF-ϰB results in the permanent decrease of expression of proteins specific to β-cells — insulin, glucose transporter 2 (GLUT-2), pancreatic and duodenal homeobox 1 (PDX-1), what co-exists with the increase in activity of iNOS (Wang, 2010). Anderson et al have shown that expression of PDX-1mRNA was suppressed independently from NO formation (Andersson, 2005). Their results also sugest that cytokines induce the functional inhibition of murine β-cells in both NO-dependent and NO-independent way (Andersson, 2005). It was shown that sulforaphane, radix clematidis extract, guggulsterone and Rother compounds protect β-cells against apoptosis induced by cytokines (IL-1β, IFN-γ) *via* repressing both the NF-ϰB activation and expression of iNOS (Kim, 2008; Lv, 2008; Song, 2009).

In humans, administration of IL-1 receptor antagonist (IL-1Ra) inhibits the expression of pro-inflammatory factors, the release of which is assisted by FFAs (Böni-Schnetzler, 2009). It is hypothesized that administration of IL-1 receptor antagonist or antibodies neutralizing IL-1β may weaken the inflammation of pancreatic islets, and in consequence decrease the disorders in synthesis and secretion of insulin (Böni-Schnetzler, 2009; Dinarello, 2010; Donath, 2011).

Other possible mechanism of induction of pancreas β-cells apoptosis by IL-1β and IFN-γ is the damage of the endoplasmic reticulum (ER stress) by affecting the Ca^{2+} pump (Eizirik, 2013). Research of Maedler *et al.* (2002) has show that 20 h incubation of human pancreatic islet cells in medium of high glucose concentration results in the significant increase of IL-1β synthesis by β-cells. These results suggest the participation of IL-1β in the process of glycotoxicity of β-cells.

The hope for formulation of new way of the T2D diabetes treatment is given by results of Osborn *et al.* (2008) who administered antibodies against IL-1β in diabetic animals. After 13 weeks of antibodies administration, the reduction of glycated hemoglobin, decrease of the proinsulin concentration in blood serum, decrease of insulin concentration, and decrease of the pancreatic islets size were found. Neutralization of IL-1β also resulted in the significant decrease of serum amount of amyloid A (SAA), which is considered as an indicator of the pancreas inflammation processes.

Other potential way for treatment of patients with diabetes is an administration of IL-1 receptor antagonist (IL-1Ra) (Larsen, 2007; Ehses, 2009; Lacraz, 2009; Klueh, 2013). Research on animals revealed that administration of IL-1Ra lowers *in vitro* the release of pro-inflammatory cytokines and chemokines (Ehses, 2009). Research *in vivo* revealed that administration of such antagonist reduced the hyperglycaemia, decreased the proinsulin/insulin ratio and improved the tissues insulin sensitivity (Ehses, 2009). Furthermore, the decrease in secretion of pro-inflammatory cytokines and chemokines (eg. IL-1β, IL-6, TNF-α) was observed (Ehses, 2009). Also in humans with T2D, administration (IL-1Ra) competitive antagonist anakinra resulted in a significant lowering of glycated hemoglobin, glucose concentration in fasting state, lowered proinsulin/insulin ratio and concentration of IL-6 in blood (Larsen, 2007; Donath, 2008). However, the insulin resistance of tissues was not affected (Larsen, 2007).

TNF-α and IFN-γ

Mechanism of action of TNF-α and IFN-γ in apoptosis of the Langerhans islet cells is not fully recognized. This process is dependent on the interferon regulatory factor 1 (IRF-1). The mechanism of the β-cells damage by TNF-α and IFN-γ is realized by a synergic action of both cytokines by activation of Ca^{2+} channels, what leads to dysfunction of mitochondria and activation of caspases (Chang, 2004). The apoptosis inhibitor XIAP (X chromosome-linked inhibitor of apoptosis) protects β-cells against harmful influence of TNF-α and IFN-γ (Wang, 2010). XIAP belongs to apoptotic suppressor protein family, sharing a conserved motif termed baculovirus IAP repeat, wchich disable the transmission of the apoptotic signal by formation of a complexes with various pro-apoptotic proteins, mainly caspases 3, 7 and 9 and TNF receptor-associated factors TRAF1 and TRAF2. In humans, this protein (XIAP) is produced by a gene named *XIAP* and located on the X chromosome.

The elevated concentration of TNF-α was detected in blood of patients with type 2 diabetes (Pickup, 2000; Chen, 2007). It was shown that in animals production of TNF-α by adipocytes leads to the induction of the inflammatory processes, what constitutes the basis for pathogenesis of the insulin resistance in T2D (Hotamisligil, 1993; Steinberg, 2006). Steinberg *et al.* (2006) have shown that by activating the TNF receptor (TNFR) in the skeletal muscle cells, TNF-α lowers the activity of 5'AMP-activated protein kinase (AMPK), *via* increased activity of protein phosphatase 2C (PP2C), what might be one of the causes for the insulin resistance. That in turn decreases both *in vitro* and *in vivo* phosphorylation of Acetyl-CoA carboxylase (ACC), and subsequently represses oxidation of fatty acids, increases accumulation of diacylglycerol (DAG) in skeletal muscles, and causes growth of the insulin resistance (Steinberg, 2006). Increase of the TNF-α concentration coexists especially with obesity. Metformin, a drug used in the diabetes therapy, causes in an indirect way an increase of the AMPK activity (Dziewulska, 2010). Activation of AMPK results in the increased glucose uptake by the skeletal muscle cells and increased oxidation of fatty acids in mitochondria. IFN-γ causes the increased expression of pancreatic derived factor (PANDER), what proves that this cytokine in that way also participates in the diabetes pathogenesis and contributes to the β-cells death (Xu, 2005).

IL-6

Role of IL-6 in the induction of inflammatory processes is not unequivocal. The literature reports indicate its both pro-inflammatory and protective action. It was shown, that blood concentration of IL-6 is elevated in patients with T1D and T2D (Kado, 1999; Pickup, 2000; Mirza, 2012). In healthy individuals, the blood concentration of IL-6 is lower than 5 pg/ml (Kado, 1999). Although IL-6 is produced and released by different types of cells, the adipose tissue cells are responsible for 10-35% of IL-6 release to the peripheral blood (Mohamed-Ali, 1997). Immunological cells, in particular macrophages, present in the adipose tissue are responsible for the release of most IL-6, but also TNFα and IL-1β (Fain, 2004). IL-6, but not TNF-α or IL-1β, can, in combination with TGF-β, induce Th17 cell generation from native T cells (Kimura, 2007). IL-6 plays an important role in regulation of balance between Th17 cells and regulatory T cells (Treg) (Kimura, 2007; 2010). Interleukin-17, cloned and described by Rouvier *et al.* (1993) is a pro-inflammatory cytokine. The subpopulations of Th cells were first described by Mossman and Coffman (Mosmann, 1986). In patients with T1D, IL-17A causes the increased expression of pro-inflammatory chemokines in pancreatic islet cells (Gieco, 2013). The Th17 cells are typical pro-inflammatory cells promoting the inflammatory reactions in tissues and development of autoimmunological diseases, and play the protective role in the bacterial inflammatory diseases (Bettelli, 2007). Regulatory T lymphocytes (Treg) are a sub-population of lymphocytes responsible for suppression of overintensified or autoreactive immunological response specific for a Niven antigen. Regulatory T cells suppress the proliferation of effector lymphocytes and also their release of pro-inflammatory cytokines. Research of Ryba-Stanisławowska *et al.* (2013) confirmed the participation of IL-6 in regulation of the balance between Th17 and regulatory T cells in the peripheral blood of patients with T1D, what was associated with the elevated concentration of IL-6 in the blood serum.

Resistance to insulin is an important factor responsible for the progression of type 2 diabetes. That is associated with the increased level of cytokines in blood, what leads to the development of the low-grade inflammation. Research indicated that IL-6 may contribute to both initiation of the insulin resistance and an increase of the tissue insulin sensitivity (Sarvas, 2013). The mechanism of how the elevated concentration of IL-6 influence both processes is currently not fully understood. That paradoxical effect of the increased IL-6 concentration on the insulin signaling includes activation of 5'AMP-activated protein kinase (AMPK) and involvement of molecules like leptin, SOCS3 and SOCS1 (Suppressor of Cytokine Signaling) (Ueki, 2004; 2008; Sarvas, 2013). It is hypothesized that similar to IL-6, leptin also plays an important role in development of the tissue insulin resistance. Some authors consider IL-6 as the marker of the insulin resistance (Sarvas, 2013). The chronic elevated concentration of IL-6 results in the increased expression of SOCS3 and SOCS1 proteins, that contribute to the increase of the insulin resistance in skeletal muscles, liver and adipose tissue. The SOCS proteins are one of the most important endogenous regulators of the pro-inflammatory response, which block the signal initiated by endosomal Toll-like receptors (TLR). The SOCS3 protein inhibits the production of pro-inflammatory cytokines in the pathway dependent on the NF-ϰB activation, and inhibits the production of interferon by blocking STAT3 (signal transducer and activator of transcription) activated by the IL-6R receptor. Sarvas and coworkers (2013) presented the probable mechanism of IL-6 action in the development of the tissues resistance and sensitivity to insulin. Under physiological conditions, eg. after exercise, concentration of IL-6 in blood significantly increases and then returns fast to the normal value. Such rapid and short-lasting increase of IL-6 concentration does not cause the increased expression of SOCS3, but results in the increased insulin sensitivity of tissues (Sarvas, 2013). Therefore, the short-lasting increase of the IL-6 concentration is positive for maintaining the normal insulin sensitivity of peripheral tissues (Sarvas, 2013). Contrary, the long-lasting increase of the IL-6 concentration, which occurs in T2D and obesity, leads to the chronic and permanent increase of SOCS3 expression (Sarvas, 2013).

Type 2 diabetes is a risk factor for premature occurrence of arteriosclerosis, and consequently the cardiovascular diseases. In patients with T2D, the increase of the blood IL-6 concentration co-exists with the increase of the glucose concentration. Especially the sudden hyperglycaemia causes the elevation of concentration of this

cytokine in blood (Esposito, 2002). Since the oscillatory hyperglycaemia is more toxic for the artery endothelial cells than continuous hyperglycaemia, it is supposed, that high concentration of IL-6 might also be a risk factor for developing the arteriosclerosis (Esposito, 2002). The effect of long-lasting hyperglycaemia is multiplied by phases of oscillatory increase of glycaemia and amplified by the impaired glucose tolerance status. An antioxidant glutathione protects against the increase of the cytokine concentration induced by hyperglycaemia (Esposito, 2002). This might prove that hyperglycaemia is the main cause for the oxidation stress in diabetes.

THE PANCREATIC DERIVED FACTOR (PANDER)

The pancreatic derived factor (PANDER) is a recently discovered cytokine present in the pancreas α- and β-cells (Xiang, 2012). In humans PANDER is involved in apoptosis of α- and β-cells (Yang, 2005; Wang, 2012). It is supposed, that expression of PANDER is activated by the insulin resistance and hyperglycaemia (Wang, 2012). The chronic exposition of β-cells to saturated fatty acids such as palmitic acid (PA) leads to their apoptosis by activation of metabolic pathways dependent on JNK kinases (c-Jun N-terminal kinases) (Xiang, 2012). Long-lasting exposition of pancreatic islet cells to palmitic acid results in the increased expression of PANDER, significant increase of phosphorylation of JNK kinase and activation of caspase3 (Xiang, 2012). Results of Xiang et al. revealed, that administration of the specific JNK inhibitor (SP600125) resulted in the decrease of PANDER expression, induced by palmitic acid (Xiang, 2012). Recently, in humans the expression of PANDER was shown in liver cells (Wang, 2012). Binding of PANDER to the cell membrane of liver cells induces the insulin resistance and an increase of glucogenesis (Wang, 2012). In mice, inactivation of the liver PANDER significantly decreased the liver steatosis, insulin resistance and hyperglycaemia (Wang, 2012).

SUMMARY

Numerous reports confirm that pro-inflammatory cytokines contribute to functional disorders of the pancreatic islet cells and participate in the diabetes pathogenesis. In progression of diabetes, the production of pro-inflammatory cytokines increases, what results in the increase of their concentration both in pancreatic islets and in blood. That in turn results in distortion of balance between amount of pro-inflammatory and protective cytokines. The pro-inflammatory cytokines such as interleukin 1β (IL-1β), tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ), as well as recently discovered pancreatic derived factor (PANDER) are involved in the pancreas β-cells apoptosis. The source of pro-inflammatory cytokines are macrophages migrating to pancreatic islets and adipocytes of the adipose tissue. Interleukin 1β is a cytokine having the most potent pro-apoptotic and pro-inflammatory effect. Inside the β-cells it activates mitogen-activated protein kinases (MAPK), including the extracellular signal-regulated kinase (ERK), and affects the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-ϰB). Both these metabolic pathways are necessary for induction of production of inducible nitric oxide synthase (iNOS), which together with IL-1β participates in the β-cells apoptosis. It is supposed that repressing the activation of NF-ϰB and expression of iNOS might be the efficient way for protection of pancreas cells against apoptosis induced by IL-1β and other cytokines. Some identified compounds as sulforaphane, radix clematidis extract, guggulsterone and other protect β-cells against the apoptosis induced by cytokines (IL-1β, IFN-γ) via repressing the activation of NF-ϰB and expression of iNOS. The hope for the new treatment of type 2 diabetes is bound to administration of antibodies against IL-1β and antagonist of the IL-1 receptor, what might weaken the inflammatory process in pancreatic islets. Probably, inactivation of the pancreatic derived factor (PANDER) in patients with diabetes may decrease the liver steatosis, insulin resistance and hyperglycaemia.

TNF-α and IFN-γ in the synergic action induce the β-cells apoptosis. That occurs *via* activation of Ca^{2+} channels, what leads to dysfunction of mitochondria and activation of caspases. The apoptosis inhibitor XIAP linked to the X protects β-cells against harmful influence of TNF-α and IFN-γ. The important patomechanism of TNF-α action is caused by repression of activity of 5'AMP-activated protein kinase (AMPK) by the increased activity of protein phosphatase 2C (PP2C). The significant cause of growing insulin resistance is the decreasing phosphorylation of acetyl-CoA carboxylase (ACC), what results in inhibition of fatty acid oxidation and increased accumulation of diacylglycerol in skeletal muscles. One might suppose, that lowering the TNF-α concentration would increase the AMPK activity, and consequently increase the glucose uptake by the skeletal muscle cells, and increased oxidation of fatty acids in mitochondria.

Interleukin-6 plays an important role in the regulation of balance between Th17 cells, and regulatory T cells (Treg). It is hypothesized that the long-lasting increase of the IL-6 concentration in blood above 5 pg/ml, observed in type 2 diabetes and obesity, leads to the chronic and permanent increase in the SOCS3 expression, and therefore contributes to the increased insulin resistance in the skeletal muscles, liver and adipose tissue. Therefore, the blood concentration of IL-6 should be kept below that level, to maintain the correct sensitivity of peripheral tissues to insulin.

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