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Hormonal Signaling Systems of the Brain in Diabetes Mellitus

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1. Introduction

Diabetes mellitus (DM) is nowadays a major global health problem affecting more than 200 million people worldwide. It is one of the most severe metabolic disorders in humans characterized by hyperglycemia due to a relative or an absolute lack of insulin or the action of insulin on its target tissue or both. Many neurodegenerative disorders, such as diabetic encephalopathy and Alzheimer's disease (AD), are associated with the type 1, insulin-dependent, and the type 2, non-insulin-dependent, diabetes mellitus (DM1 and DM2). Manifestations of these disorders in diabetic patients include alterations in neurotransmission, electrophysiological abnormalities, structural changes and cognitive deficit (Biessels et al., 2001). In the recent time attention to the neurological consequences of DM in the CNS has increased considerably.

Many approaches and tools have been used to study etiology and pathogenesis of DM and DM-associated neurodegenerative disorders, and their diagnostics and treatment. The most perspective approaches are based on a combined use of the methods of biochemistry, molecular biology and physiology, they include clinical investigations of diabetic patients and the experimental models of DM and their complications, such as the model of DM1 induced by streptozotocin (STZ) treatment of young or adult rodents, the neonatal model of DM2 induced by the STZ treatment of newborn rats, and also the models of spontaneous DM and nutritional background causing DM2, as well as the models produced by transgenic manipulations or gene knockout techniques are all successfully used to study the molecular, cellular and morphological changes in diabetic brain (Shafrir, 2010).

A severe hyperglycemia in DM1, mild hyperglycemia typical of DM2, and recurrent hypoglycemia induced by inadequate insulin therapy are the major factors responsible for the development of CNS complications in DM. The brain is mainly a glucose-dependent organ, which can be damaged by hyper- as well as by hypoglycemia (Scheen, 2010). Being a major problem in clinical practice, hypoglycemia unawareness is associated with an increased risk of coma. Note that low blood glucose level induces negative mood states, primarily self-reported “nervousness” (Boyle & Zrebiec, 2007). Moreover, patients with a history of severe hypoglycemia show a much higher level of anxiety compared to other DM patients (Wredling, 1992). The prolonged influence of mild hypoglycemia on the brain leads to deregulation of many processes in CNS, which underlines the importance of scrupulously avoiding even mild hypoglycemic episodes in patients with DM. Hypoglycemia induces

progressive reduction in cerebral glycogen and glucose, which is due to an increase in gene expression of GLUT3, the glucose transporter rather abundant in the brain (Antony et al., 2010b). Alteration of expression of GLUT3 in the cerebral cortex in hypoglycemia is the evidence for impairment of neuronal glucose transport during glucose deprivation. The impaired transport and utilization of neuronal glucose in hypoglycemia is likely to be an important factor contributing to an increase of neuronal vulnerability. The disturbances of neuronal glucose transport and metabolism in hyperglycemia are similar to those in hypoglycemia and also induce neuronal damages and CNS disorders. For example, chronic diabetic encephalopathy leading to cognitive dysfunctions and dementia may be the result of recurrent hypoglycaemia and/or chronic hyperglycaemia, both inducing cerebral vascular damages (Scheen, 2010).

A new view of the nature and pathogenesis of DM-induced cerebral complications shared by many specialists nowadays has been prompted by the results of study of functional activity of hormonal signaling systems regulated by insulin, insulin-like growth factor-1 (IGF-1), leptin, biogenic amines, purines, glutamate, and peptide hormones controlling the fundamental processes in the neuronal and glial cells. The data were obtained showing that the alterations and abnormalities of hormonal signaling systems regulated by these hormones and the changes in expression of hormones and signal proteins, the components of these systems, induce disturbances of growth, differentiation, metabolism and apoptosis in neuronal cells and contribute to triggering and development of neurodegenerative processes in the diabetic brain. The present review is devoted to the achievements in the study of the functional state of hormone-sensitive signaling systems of the brain in human and experimental DM, to the alterations and abnormalities in these systems, and to the search of new approaches in the therapy of cerebral complications of DM based on restoration of normal functioning of some signaling systems and overall integrative signaling network in the diabetic brain.

2. Insulin, insulin-like growth factor-1 and leptin in the diabetic brain

Polypeptide hormones insulin, IGF-1 and leptin, the principal players responsible for pathogenesis of DM and its central and peripheral complications, are to a large extent affected in the diabetic brain. The abnormalities in numerous signaling pathways regulated by insulin, IGF-1 and leptin lead to disturbances of the biochemical and physiological functions of the neuronal and glial cells. It was shown by many investigators that the level of these hormones in the brain is decreased in DM, and the signaling pathways regulated by insulin, IGF-1 and leptin and involving a large number of effector proteins, such as insulin receptor substrate (IRS) proteins, phosphatidylinositol 3-kinase (PI 3-kinase), protein phosphotyrosine phosphatases, AKT kinase, ERK1/ERK2 kinases and glycogen synthase kinase 3β (GSK3β), are impaired (Fig. 1). Therefore, the treatment of diabetic patients with insulin, IGF-1 and leptin, and the restoration of activity of the signaling pathways they regulate are a reliable approach in the therapy of central and neuroendocrine dysfunctions in DM.

2.1 Insulin and insulin-like growth factor-1

Insulin and IGF-1 are genetically related polypeptides with similar three-dimensional and primary structures. Insulin is synthesized predominantly in pancreatic β-cells, while IGF-1 is synthesized primarily in the liver and also in the brain. Peripheral insulin penetrates

the blood-brain barrier (BBB) and binds to brain insulin receptors (IRs), which leads to the triggering of their intrinsic tyrosine kinase activity and, as a result, to tyrosine phosphorylation and activation of IRS proteins (Boura-Halfon & Zick, 2009). Phosphorylated IRS proteins then activate p110/p85 heterodimeric PI 3-kinase, protein phosphotyrosine phosphatase and adaptor Shc/GRB2 dimer complex, which triggers the intracellular signaling cascades controlling the gene expression and, thus, regulating growth,

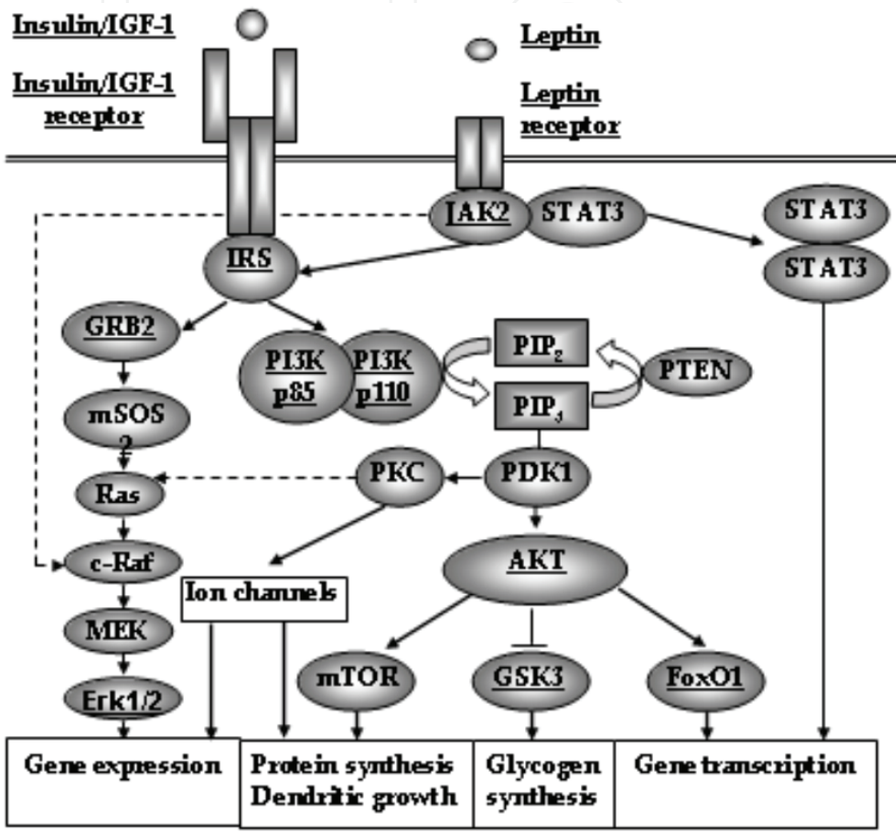

Fig. 1. Critical nodes in the insulin/IGF-1 and leptin signaling systems. The signal components of the systems whose expression and functional activity are significantly changed in DM are underlined. These changes are brain area-specific, they depend on the type of human DM, its severity and duration, DM-induced complications, and on the model of experimental DM. Abbreviations: IRS, insulin receptor substrate proteins; GRB2, growth-factor-receptor-bound protein-2; mSOS, mammalian *son of sevenless* nucleotide exchange factor; Ras, small G protein of Ras family; c-Raf, cytoplasmic serine/threonine-specific protein kinase Raf; MEK, mitogene-activated protein kinase; ERK1/2, extracellular signal-regulated kinases 1 and 2; p85/p110 PI 3K, heterodimeric p85/p110 phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homologue; PDK1, phosphoinositide-dependent kinase 1; PKC, protein kinase C; AKT, protein kinase B; mTOR, mammalian target of rapamycin; GSK3, glycogen synthase kinase 3; FoxO1, forkhead box O1 protein; JAK2, Janus kinase-2; STAT3, signal transducer and activator of transcription of the type 3; PIP_2 and PIP_3, phosphatidylinositol 3,4-diphosphate and phosphatidylinositol 3,4,5-triphosphate, respectively

differentiation and the other processes in neuronal cells. The activation of PI 3-kinase leads to phosphorylation and activation of AKT kinase that regulates the metabolism and cell survival via numerous downstream proteins in the peripheral insulin-sensitive tissues as well as in the CNS, primarily in hypothalamic neurons (Iskandar et al., 2010). AKT kinase partly facilitates signal transduction via phosphorylation and cytoplasmic sequestering of forkhead-box protein O1, a negative regulator of insulin signaling, whose nuclear translocation is associated with obesity and hyperphagia (Kitamura et al., 2006). The same signaling network is regulated by IGF-1 that specifically binds with cognate IGF-1 receptor demonstrating a close structural homology and sequence identity with IR and also possessing the tyrosine kinase activity and triggerring IRS-dependent signaling pathways.

Both IRs and IGF-1 receptors are widely expressed in the brain and are localized preferably in neuron rich structures in many brain areas, such as the granule cell layers of the olfactory bulb, hippocampal formation and cerebral cortex. The fact that these receptors are localized in the brain accounts for the role of insulin and IGF-1 in CNS functioning. Since the main function of insulin is to regulate glucose homeostasis, central insulin and brain IRs specifically recognizing the hormone modulate the energy, glucose and fat homeostasis in the brain, being involved, in addition, in the regulation of metabolism in the peripheral tissues. However, in the brain insulin performs some other functions specific of the CNS. Interacting with the other regulatory peptides and neurotransmitters, central insulin participates in controlling the feeding behavior, learning and memory, and is involved in the intercellular communication within brain structures, the hypothalamus and the limbic system in particular (Gerozissis, 2008). IGF-1 is involved in neuronal development, stimulates neurogenesis and synaptogenesis, facilitates oligodendrocyte development, promotes neuron and oligodendrocyte survival, and stimulates myelination. All this speaks about a very important role it has in preserving the integrity of neuronal cells and in protecting the brain structures from damages and injury (D'Ercole et al., 2002).

The alterations of proteins, the components of brain insulin- and IGF-1-regulated signaling cascades, typical of DM and pre-diabetic states, are the causes of the DM-associated neurodegenerative diseases. It should be emphasized that the abnormalities in brain insulin/IGF-1 signaling can be provoked by DM, being a result of the systemic changes of integral signaling network in the diabetic brain, and, on the other hand, the disturbances of the functioning of insulin/IGF-1 signaling systems of the brain induced by neurodegenerative disorders can also lead to DM. In the latter case we can talk about the central genesis of DM.

The initial component of insulin/IGF-1-regulated cascades is a hormonal molecule, insulin or IGF-1, whose brain concentrations are significantly reduced in DM (Gelling et al., 2006). A significant decrease of the IGF-1 level was found in the cerebellum of insulin-deficient rats with STZ-induced DM with poorly controlled glycemia, whereas there were no changes in cerebellar IGF-1 mRNA level, which indicates the abnormalities of hormone processing and secretion in the diabetic brain (Busiguina et al., 1996). The appropriate glycemic control with insulin completely restored IGF-1 concentration in the cerebellum (D'Ercole et al., 2002). Since IGF-1, the same as insulin, crosses the BBB, a decrease of serum IGF-1 in human DM1 and STZ-induced DM also contributes to brain IGF-1 deficit leading to attenuation of IGF-1 signaling (Busiguina et al., 2000). The children with DM1 had a 50% decrease of peripheral IGF-1 level compared with control group, and in diabetic children with poor glucose control it was decreased even more compared with moderate metabolic control. In the patients with DM2 the peripheral level of IGF-1 at the early stages of the disease did not change

significantly, but began to decline markedly in prolonged DM2 and in long-term hyperglycemia (Clauson et al., 1998). It indicates the temporal dynamics of a decrease of IGF-1 and the impairments of its signaling in the diabetic brain, correlating with an increase of neurological disorders in prolonged uncontrolled DM2.

Central administration of insulin and IGF-1 restores to a great extent the function of the CNS, being in some cases the most effective co-administration of insulin and IGF-1, the latter refers mostly to the cases of much lower concentrations. It is shown that in DM1, in the case of insulin deficit, a concomitant decrease of insulin and IGF-1 levels in the brain leads to atrophy of some brain areas inducing impaired learning and memory. A combined infusion for 12 weeks of insulin and IGF-1 into the brain lateral ventricles of STZ rats prevents a decrease of the brain weight, and leads to normalization of the level of DNA and the content of proteins associated with neurons and glial cells, whose level and activity are significantly decreased in the diabetic brain. As a result, the brain DNA loss in DM1 is prevented (Serbedzija et al., 2009). The administration of IGF-1 to STZ rats prevents irrespective of the severity of hyperglycemia IGF-1 reduction in the brain and the DM-associated cognitive disturbances (Lupien et al., 2003). Anti-IGF-1 antibody infused into the lateral ventricles led, on the contrary, to deterioration of learning and memory functions of diabetic as well as non-diabetic rats. Quite often DM and its complications in human are associated with the changes in IGF-1 binding proteins, which contribute to the concentration of peripheral and central IGF-1 (Busiguina et al., 2000). The alterations of the content of these proteins are responsible for a decline in memory and for many DM-associated neurodegenerative disorders, such as AD and vascular dementia (Zhu et al., 2005).

The second component of insulin/IGF-1 signaling is IR or IGF-1 receptor. According to some reports, mice with a neuron-specific disruption of the IR gene increased food intake and diet-sensitive obesity with an increase in body fat, mild insulin resistance, elevated plasma insulin and leptin levels, and hypertriglyceridemia typical of DM2 (Bruning et al., 2000). These mutant mice also exhibited impaired spermatogenesis and ovarian follicle maturation due to deregulation of luteinizing hormone-releasing factor secretion caused by attenuation of insulin signaling in the hypothalamus. The restoration of IRs in the brain of these mice maintained energy homeostasis, improved functions of the CNS and prevented DM (Okamoto et al., 2004). The expression of IRs in the brain of mice lacking the genes encoding IR and the glucose transporter GLUT4 also improved their survival, but did not completely eliminate the symptoms of DM2 due to dysfunction of GLUT4 (H.V. Lin & Accili, 2011). The study of expression of IRs and IGF-1 receptors in the frontal cortices of 8-month-old diabetic rats with spontaneous onset of DM1 and DM2 showed that the IR expression was decreased in DM1 only, whereas IGF-1 receptor expression was decreased in both models (Z.G. Li et al., 2007). The disruption of IR expression in discrete hypothalamic nuclei led to hyperphagia and increased fat mass, which was a result of disturbances of regulation of hepatic glucose production by central insulin (Obici et al., 2002). The mice lacking the brain IR had severe hypoleptinemia as well as more severe hyperinsulinemia and hyperglycemia than the mice lacking the receptor in the peripheral tissues, which demonstrates the major role of central insulin in regulating white adipose tissue mass and glucose metabolism in the liver (Koch et al., 2008). Both neuron-specific IR knockout (NIRKO) mice and the rats with spontaneous DM exhibited a complete loss of insulin-mediated activation of PI 3-kinase and inhibition of neuronal apoptosis, and had markedly reduced phosphorylation of AKT kinase and GSK3β, leading to substantially increased phosphorylation of the microtubule-associated Tau protein at sites associated with

neurodegenerative diseases (Z.G. Li et al., 2007; Koch et al., 2008). This is one of the molecular mechanisms responsible for the altered insulin signaling and insulin resistance in the brain to be predisposed for the development of neurodegeneration, creating a clinical link between DM2 and AD and other CNS dysfunctions (Schubert et al., 2004).

The third component of insulin/IGF-1 signaling is IRS proteins. They have a key role in linking IR and IGF-1 receptor to the intracellular signaling cascades and in coordinating signals from these receptors with those generated by other neurotransmitters, peptide hormones, pro-inflammatory cytokines and nutrients. The alterations of the IRS protein functions are responsible for the failure of insulin/IGF-1 signaling not only in the peripheral tissues, but also in neuronal cells, they induce insulin resistance and, finally, cause DM and neurodegenerative diseases associated with it (Lee & White, 2004). The deletion of gene encoding IRS-2 protein leads to the weakening of hypothalamic insulin signaling and increases both food intake and hepatic glucose production (X. Lin et al., 2004). Conversely, over expression of IRS-2 in the mediobasal hypothalamus was found to significantly enhance the glycemic response to systemic insulin treatment in STZ rats (Gelling et al., 2006). It was shown that in *Irs2* gene knockout mice the embryonic brain size is 55% of that in normal animals due to the reduced neuronal proliferation in the course of development, indicating IRS-2 to be involved in the brain growth. It seems likely that IRS-2 are involved in neuroprotective effects of insulin and IGF-1, because in the hippocampus of old *Irs2* knockout mice there are formed neurofibrillary tangles containing phosphorylated Tau protein, a hallmark of neurodegenerative processes (Schubert et al., 2003). No direct evidence for IRS-2 being involved in human brain growth and differentiation is available, but breaks at the distal end of human chromosome 13 (13q) near the *Irs2* gene between micro satellites D13S285 and D13S1295 are frequently associated with microcephaly, while very distal deletions between D13S274 and D13S1311 with microcephaly and neural tube defects, suggesting a possible contribution of partial *Irs2* deficiency to microcephaly (J. Luo et al., 2000). Based on these data, the conclusion was made that the regulation of activity of IRS-1 and IRS-2 controlling the growth, metabolism and survival of neuronal cells is a new strategy aimed at prevention or cure of DM and its CNS complications. However, according to the recently obtained data, the deletion of gene encoding IRS-2 improves the functioning of the brain of mutant mice, because IRS-2 act as negative regulators of memory formation by restricting dendritic spine generation (Irvine et al., 2011). The above may be due to the fact that various groups of scientists are engaged in the study of mutant lines of animals with a large number of alterations of insulin/IGF-1 signaling, and these alterations induce different changes in the brain signaling network. With this in mind, it is clear why the functions of IRS-2 can be redistributed among the other types of IRS proteins or described as depending on the activity of upstream or downstream signal proteins interacting with IRS-2.

The downstream components of insulin/IGF-1 signaling, such as PI 3-kinase, AKT kinase and protein phosphotyrosine phosphatase 2A (PP2A) are also changed in DM and greatly contribute in etiology and pathogenesis of DM-induced neurodegenerative diseases. The main molecular mechanism in this case is a rapid and significant increase of phosphorylation of Tau protein (Clodfelder-Miller et al., 2006). The hyperphosphorylation of Tau was detected in the mouse cerebral cortex and hippocampus within 3 days after STZ treatment and can be rapidly reversed by peripheral insulin administration. The increase of Tau phosphorylation in the brain in DM partly depends on the fact that the activity of PP2A, the major protein phosphatase acting on Tau, was decreased by 44% in the cerebral cortex and by 55% in the hippocampus. This indicates that a significant decrease in PP2A activity is

likely to account for a majority of cases of a significant increase in Tau phosphorylation caused by STZ treatment. The decreased PP2A activity and Tau hyperphosphorylation on the background of insulin deficiency may increase the susceptibility of the diabetic brain to insults associated with AD, thereby contributing to the relationship between DM and heightened susceptibility to AD (Clodfelder-Miller et al., 2006).

To study the role of PI 3-kinase in the diabetic brain, it was shown by making i.c.v. infusion of LY294002, a specific inhibitor of the enzyme, into the 3rd cerebral ventricle of STZ rats that the inhibition of PI 3-kinase activity and downstream effector AKT kinase in this case leads to attenuation of the glycemic response to systemic insulin treatment (Gelling et al., 2006). The glucose-lowering effect of insulin in STZ rats after adenovirus delivery of *Irs-2* gene into the hypothalamic arcuate nucleus was increased 2-fold compared to diabetic rats receiving a control adenovirus. The same results were obtained after injection of adenovirus encoding a constitutively active AKT kinase. These findings indicate that the response to adenovirus encoding IRS-2 involves signal transduction via PI 3-kinase and AKT kinase, and the increased hypothalamic signaling either upstream or downstream of PI 3-kinase is sufficient to enhance insulin-induced glucose lowering in diabetic rats (Gelling et al., 2006). Hence, being the most insulin-responsive brain area, the hypothalamus contributes to whole-body glucose homeostasis via IRS–PI 3-kinase signaling.

The prime function of the other mechanism of neuroprotective action of insulin and IGF-1 realized via PI 3-kinase is to control the oxidative stress and susceptibility of the brain endothelium, the important contributing factors in the development of CNS disorders in DM (Okouchi et al., 2006). It was found that chronic hyperglycemia exacerbated apoptosis of human brain endothelial cells in accordance with exaggerated cytosolic and mitochondrial glutathione and protein-thiol redox imbalance. Insulin activates the PI 3-kinase/AKT kinase/mTOR kinase cascade, increases serine phosphorylation and nuclear translocation of nuclear NF-E2-related factor 2 (Nrf2), and enhances the expression of catalytic subunit of Nrf2-dependent glutamate-L-cysteine ligase, a heterodimeric enzyme participating in glutathione metabolism, and, hence, attenuates hyperglycemia-induced apoptosis via the restored cytosolic and mitochondrial redox balance. Inhibitors of IR tyrosine kinase, PI 3-kinase, AKT kinase and mTOR kinase abrogate insulin-induced Nrf2-mediated glutamate-L-cysteine ligase expression, redox balance, and the survival of human brain endothelial cells (Okouchi et al., 2006). Insulin-regulated PI 3-kinase-dependent pathways are involved in the prevention of endoplasmic reticulum stress that contributes to DM and neurodegenerative disorders (Hosoi et al., 2007). It was found that PI 3-kinase regulates the expression of CHOP protein, an endoplasmic reticulum stress-induced transcription factor involved in control of neuronal cell survival.

The important role in regulation of insulin level in the diabetic brain belongs to the insulin-degrading enzyme (IDE). In addition to insulin, it also degrades β-amyloid peptide. Thus, in the case of hyperinsulinemia in DM2, insulin competes with β-amyloid peptide for IDE and this leads to an increase in β-amyloid peptide concentration and provokes neurodegenerative processes and the development of AD (Qiu & Folstein, 2006). The genetic studies indicate that *IDE* gene variations are associated with the clinical symptoms of AD as well as with the risk of DM2. In DM1 it was shown that the activity of IDE and the level of mRNA encoding IDE were significantly decreased in the temporal cortex of STZ rats. Since the activity of two other β-amyloid peptide-degrading enzymes, neprilysin and endothelin-converting enzyme 1, was also decreased though to a different extent in the brain of diabetic rats, the level of the β-amyloid peptide 1–40 was markedly elevated, which induced DM-

associated AD and other abnormalities of CNS (Y. Liu et al., 2011). The other authors reported a significant reduction of IDE expression in the brain of STZ mice after 9 weeks of hyperglycemia (Jolivalt et al., 2008). The treatment with insulin partially restored phosphorylation of IR and downstream components of insulin signaling system and led to restoration of IDE activity. Based on these data the conclusion was made that in both types of DM the level of β-amyloid peptides was increased, although the molecular mechanisms and the role of IDE in this case may be different.

2.2 Leptin

Leptin, the product of the *ob* gene, is mainly secreted by peripheral adipocytes, it regulates energy metabolism and body weight. Leptin deficiency in rodents and humans leads to severe obesity. Leptin penetrates into the brain through the BBB as a result of receptor-mediated endocytosis, binds to the leptin receptors located on neurons in the hypothalamus, where the density of receptors is high, and in some extrahypothalamic regions including the cortex, thalamus, cerebellum, choroid plexus and olfactory bulb (Mutze et al., 2006, Marino et al., 2011). The leptin receptor belonging to the cytokine family receptors has several isoforms, but only the full-length isoform generates an intracellular signal. Activated leptin receptors trigger the stimulation of JAK2 tyrosine kinase that phosphorylates the intracellular domain of the receptor to create a binding site for IRS proteins activating PI 3-kinase and the MEK/ERK signaling pathway (Hegyi et al, 2004). JAK2 kinase also activates the transcription factor STAT3, and the JAK/STAT pathway plays the major role in leptin signaling via the membrane receptors (Mutze et al., 2006).

Central leptin interacts with the hypothalamic nuclei and regulates energy expenditure and food intake through production of agouti-related protein (AgRP), the antagonist of melanocotin receptors (MCRs), and neuropeptide Y (NPY), and α-melanocyte-stimulating hormone (α-MSH) (M.W. Schwartz et al. 2000; Signore et al., 2008). Leptin, like insulin, is involved in the control of the excitability of hypothalamic neurons, modulates the synaptic plasticity and promotes the learning and cognition. Leptin facilitates the presynaptic transmitter release and postsynaptic sensitivity to the transmitters in the hippocampal neurons and regulates hippocampal synaptic plasticity and neuronal development. The rodents with dysfunction of leptin signaling display impaired hippocampal synaptic plasticity, and the application of leptin restores the functions of hippocampus (X.L. Li et al, 2002). In neuronal cells leptin activates JAK/STAT, MEK/ERK and PI 3-kinase signaling pathways and functions as the antiapoptotic factor regulating cell survival. The central effects of leptin are mainly mediated via PI 3-kinase and AKT kinase (Morton et al., 2005). Leptin also serves as neurotrophic factor, because it reverses the loss of dopaminergic neurons and dopamine (DA)-mediated behavior induced by the toxin destroying these neurons (Weng et al., 2007). Therefore, leptin not only protects the rescuing dopaminergic neurons from toxicity, but also preserves the DA-regulated signaling network in neurodegenerative diseases, which might prove useful in the treatment of DM-associated neurodegenerative diseases.

Some time ago in the CA1 hippocampal region of leptin receptor-deficient rodents (Zucker *fa/fa* rats and *db/db* mice) the impairments of hippocampal long-term potentiation (LTP) and long-term depression (LTD) were detected (X.L. Li et al., 2002). The animals showed deficiencies in neuronal and behavioral plasticity and, as demonstrated by the impairment of spatial memory in the Morris water-maze test, had memory deficit due, at least in part, to a deficiency in leptin receptors. The leptin administration gave no results probably because

of insensitivity of the hippocampus to the hormone. Since the deficiency in hippocampal plasticity in diabetic patients and STZ-treated animals is independent of insulin level, it can be assumed that the cause for these abnormalities is the concert functioning of leptin and insulin signaling systems and their ability to modulate other neuronal systems regulated by γ-aminobutyric acid (GABA), DA and melanocortin (Van der Heide et al., 2005). A close interrelation between the signaling pathways controlled by leptin and the dopaminergic and peptidergic signaling systems is supported by the following data obtained with experimental DM and obesity. The leptin deficiency in the obese mice lacking leptin (*Lep*$^{ob/ob}$ mice) led to a decrease in the content of somatodendritic vesicular DA and the amount of DA to be released (Roseberry et al., 2007). One possible cause is related to a decrease of the number of functionally active DA transporters controlling the synaptic level of DA. I.c.v. and parenchymal hypothalamic administration of leptin into MKR mice, a model of non-obese DM2, lacking IGF-1 receptor and having hyperglycemia, hyperinsulinemia, and hyperlipidemia, significantly increased the rate of disappearance of glucose. These effects were mediated by brain MCRs, as central administration of SHU9119, the antagonist of MCRs of the types 3 and 4 (MC_3R and MC_4R), blocked the ability of hypothalamic leptin to increase skeletal muscle glucose metabolism, glucose uptake and fat oxidation, while in the presence of the agonists of the receptors the anti-diabetic effects of leptin were retained and intensified even more (Toda et al., 2009). The involvement of hypothalamic signaling systems regulated by neurotransmitters in the regulatory effects of central leptin on the energy balance and peripheral glucose homeostasis is supported by the results of the study of non-obese diabetic MKR mice, where i.c.v. administration of leptin dramatically improved insulin sensitivity both via the hypothalamus and direct contact with the peripheral tissues (X. Li et al., 2011).

Studying the action of i.c.v. administered leptin on metabolic imbalance caused by experimental DM1 it was found that leptin normalizes the glucose homeostasis and ameliorates the functioning of CNS in STZ-treated rodents (Kojima et al., 2009; Wang et al., 2010). I.c.v. infusion of leptin reversed lethality and greatly improved hyperglycemia, hyperglucagonemia, hyperketonemia, and polyuria in STZ mice. The leptin therapy improved the expression of the metabolically relevant hypothalamic neuropeptides pro-opiomelanocortin (POMC) and NPY, and also the expression of AgRP in the brain of diabetic mice and restored their signaling cascades impaired in DM1. For the effects of leptin to be long-term, the technique of i.c.v. administration of recombinant adeno-associated virus vector (*rAAV*) encoding leptin gene (*rAAV-lep*) was developed and used in adult STZ-treated mice. The injection of *rAAV-lep* gene markedly increased the level of hypothalamic leptin, rescued the STZ mice from early mortality, gradually decreased hyperphagia to normalize food intake by the 20th week, and maintained body weight within significantly lower than the control range. The blood levels of glucose in these mice started to recede dramatically by the 2nd-3rd week to normalize by the 8th week, and euglycemia was sustained during 52 weeks of experiment. *rAAV-lep* gene injected mice did not exhibit any discernible untoward behavioral changes, nor diabetic complications (Kojima et al., 2009).

The addition of low-dose insulin to the leptin therapy provides physiological insulin level for the peripheral targets of STZ rats and leptin in this case suppresses the hyperglucagonemia, avoiding high doses of insulin required to decrease the elevated glucagon level (Wang et al., 2010). Thus, leptin administration has multiple short- and long-term advantages over insulin monotherapy of DM1, and the combined application of leptin and insulin can be recommended for the treatment of human DM1. A high efficiency of the

combined action of insulin and leptin suggests that the brain signaling systems sensitive to these hormones have the common components enabling their interaction which takes place in the hypothalamus or the other brain areas sensitive to insulin and leptin. This view finds support in the fact that leptin directly governs glucose homeostasis via activation of leptin receptors in neurons within the hypothalamic arcuate nucleus enriched by IRs (Huo et al., 2009). Summing up, the brain is a critical site for mediating leptin metabolic-improving actions in DM and the action of central leptin is in concert with the action of insulin and, probably of IGF-1.

3. Neurotransmitter signaling systems in the diabetic brain

The various neurotransmitter systems, including dopaminergic, serotonergic, cholinergic, glutamatergic, and GABAergic, undergo a significant change in DM (Jackson & Paulose, 1999; Gireesh et al., 2008; Antony et al., 2010a; Anu et al., 2010; T.P. Kumar et al., 2010) (Fig. 2). The well-coordinated activation and inhibition of different neurotransmitter systems in normal brain are disrupted in DM-associated hyper- and hypoglycemia and in the case of insulin and leptin deficit. The synergistic effect of alterations of neurotransmitter receptors leads to neurodegenerative changes in different brain areas and to the development of CNS disorders and dysfunctions.

3.1 Dopamine signaling

DA is the predominant catecholamine neurotransmitter in the brain of mammals, where it controls a variety of functions including locomotor activity, cognition, emotion, positive reinforcement, food intake, and endocrine regulation. DA also plays multiple roles in the periphery as a modulator of cardiovascular function, catecholamine release, hormone secretion, vascular tone, and gastrointestinal motility. The results obtained with diabetic animals and the clinical study of patients with DM2 showed that reduced dopaminergic activity in the brain is involved in the pathogenesis of DM2 and metabolic syndrome and is responsible for DM-induced changes in the CNS (Pijl & Edo, 2002).

The treatment of diabetic patients with selective ligands of dopamine receptors (DARs) is a promising approach to improve the functions of CNS in DM. In the recent years a selective D_2-DAR agonist bromocriptine, an ergot derivative, has been widely used in the treatment of DM, especially DM2, and obesity. Bromocriptine acts on a central target in the brain, mainly in hypothalamus, and reduces ventromedial, arcuate and paraventricular hypothalamic drive for increased hepatic glucose production, lipid synthesis and mobilization, and insulin resistance, which decreases the risk of damage of neuronal cells and the cardiovascular system in patients with DM2 (Scranton et al., 2007). It is very important that bromocriptine reduces fasting and postprandial glucose without increasing insulin level and its therapeutic effects are not associated with weight gain or hypoglycemia. The main mechanism of action of bromocriptine is based on its ability to bind with D_2-DAR coupled with the adenylyl cyclase (AC) via G_i protein, which provides the utility in resetting hypothalamic circadian organization of monoamine neuronal activities in patients with DM2. The other mechanisms include the influence of bromocriptine on signaling pathways regulated by α-adrenergic ligands and prolactin, as well as its inhibitory effect on serotonin (5-hydroxytryptamine, 5-HT) turnover in the CNS, and may also be involved in glucose-lowering effects of bromocriptine (Kerr et al., 2010).

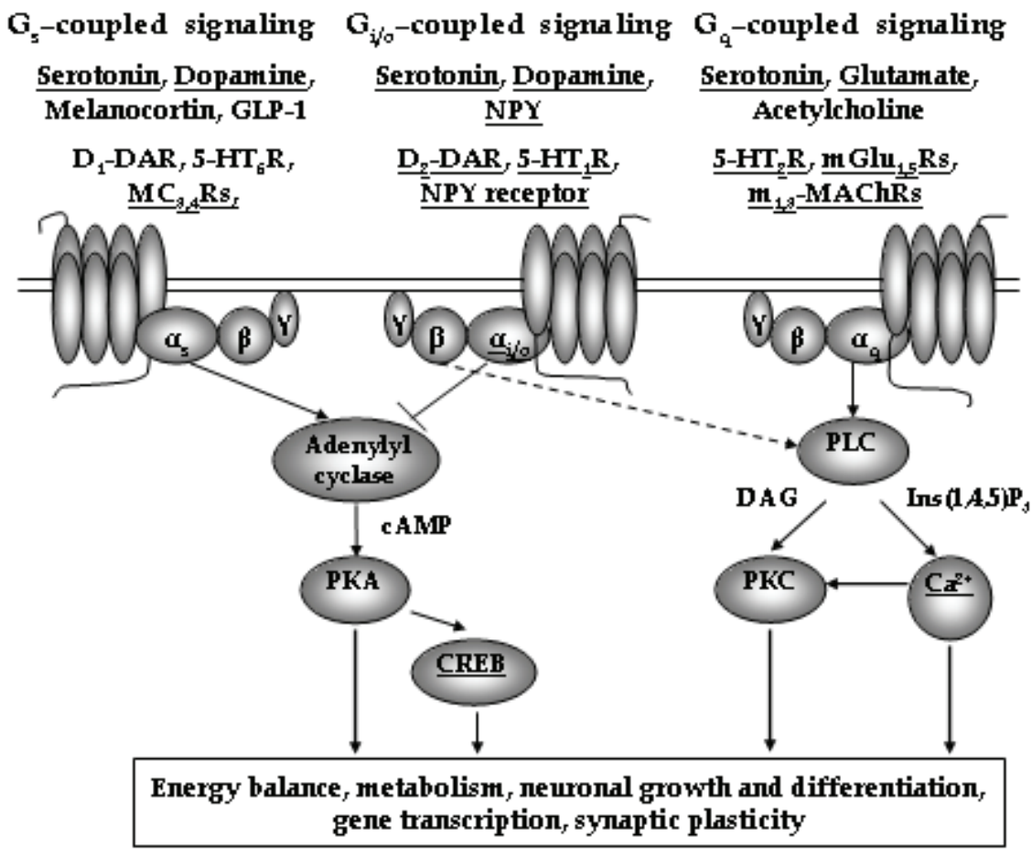

Fig. 2. G_s-, $G_{i/o}$- and G_q-coupled signaling pathways including the receptors of the serpentine type regulated by biogenic amines, glutamate, acetylcholine and peptide hormones. The signal components whose activity and expression are significantly altered in DM are underlined. Abbreviations: NPY, neuropeptide Y; GLP-1, glucagon-like peptide-1; $D_{1,2}$DARs, dopamine receptors of the types 1 and 2; 5-$HT_{1,2,6}$Rs, 5-hydroxytryptamine receptors of the types 1, 2 and 6; $MC_{3,4}$Rs, melanocortin receptors of the types 3 and 4; m$Glu_{1,5}$Rs, metabotropic glutamate receptors of the types 1 and 5; $m_{1,3}$-MAChRs, muscarinic acetylcholine receptors of the types 1 and 3; $\alpha_{s,i/o,q}\beta\gamma$, heterotrimeric G_s-, $G_{i/o}$- and G_q-proteins; PKA, protein kinase A; CREB, cAMP response element-binding; PLC, phosphoinositide-specific phospholipase C; PKC, protein kinase C; cAMP, 3′,5′-cyclic adenosine monophosphate; DAG, diacylglycerol; Ins(1,4,5)P_3, phosphatidylinositol 1,4,5-triphosphate

The treatment with bromocriptine can reverse the metabolic abnormalities in humans with DM2 and obesity and in obese experimental animals. Using 22 obese patients with DM2 it was found that bromocriptine significantly reduces both glycosylated hemoglobin level and fasting and postprandial plasma glucose concentrations, it decreases the mean plasma glucose concentration during oral glucose tolerance test, which indicates the improvement in glucose tolerance (Pijl et al., 2000). There are also reports that administration of Cycloset (bromocriptine mesylate) either as monotherapy or adjunctive therapy to sulfonylurea or insulin markedly reduces glycosylated hemoglobin, plasma triglycerides and free fatty acid levels (Scranton et al., 2007). The effects of once-daily morning Cycloset therapy on glycemic

control and plasma lipids are demonstrable throughout the diurnal portion of the day (7 a.m. to 7 p.m.) across postprandial time points. Recently it was shown that the bromocriptine therapy of 4328 patients with DM2 during 6–24 weeks leads to a significant decrease of glycosylated hemoglobin and plasma glucose levels (Kerr et al., 2010).

Bromocriptine improved the functional state of obese glucose-intolerant Syrian hamsters, inducing a decrease in their insulin resistance and markedly lowering the plasma levels of insulin and free fatty acids (S. Luo et al., 2000). These anti-diabetic effects of bromocriptine are associated with its influence on the daily rhythms of metabolic hormones and daily monoamine profiles within the hypothalamic suprachiasmatic nuclei that modulate circadian neuroendocrine activities and, thus, regulate metabolism of seasonal animals. The bromocriptine significantly reduced DA turnover during the light period and shifted daily peaks of the content of 5-HT and 5-hydroxy-indoleacetic acid (5-HIAA), the main metabolite of 5-HT, by 12 h from the light to the dark period of the day within the hypothalamic suprachiasmatic nuclei, it also increased extracellular 5-HIAA in the brain of diabetic hamsters during the dark phase toward levels observed in normal glucose-tolerant animals.

Using animal models it was found that a combined administration of agonists of D_1- and D_2-DARs is a successful approach for decreasing appetite in both STZ rats and ob/ob mice (Bina & Cincotta, 2000; Kuo, 2006). The anorectic response induced by D_1/D_2 agonists is due to their antagonistic action on hypothalamic neurons containing NPY, the most potent appetite transducer in the CNS, and on NPY-dependent signaling. In DM the NPY system is up-regulated due to increased expression of both NPY and its receptor and to enhanced release of NPY. The co-administration of D_1/D_2 agonists normalized the elevated NPY content and hyperphagic effect observed in STZ rats and *ob/ob* mice (Bina & Cincotta, 2000; Kuo, 2006). However, the response of D_1/D_2 agonist-induced appetite suppression was attenuated in diabetic rats compared to normal animals, which can be ascribed both to a decreased inhibitory action of central dopaminergic system and to enhanced activity of hypothalamic NPY neurons in DM. The insulin treatment in DM normalized the response to D_1/D_2 agonists owing to the restoration of NPY content in the hypothalamus and DA signaling.

The reduction of activity of the brain dopaminergic system in DM is mainly due to changes of the initial stages of DA-induced signal transduction which involves DARs, G_i or G_s proteins and effectors, AC and phospholipase C (PLC), generating second messengers. In many brain regions the activity of DARs and signal proteins coupled to them has DAR-specific differential alterations. The studies in this area are mostly devoted to the functional state of DARs in DM. In the early 1980s it was found that the binding of [^{3}H]-spiperone, antagonist of D_2-DAR, to striatal membranes is significantly increased in rats with DM induced by alloxan or STZ treatment, and insulin therapy leads to normalization of functioning of central dopaminergic system (Lozovsky et al., 1981). Recently it was shown that the expression of D_1- and D_2-DARs and total DAR binding (B_{max}) are increased in the cerebral cortex of STZ rats (T.P. Kumar et al., 2010). In the cerebellum D_1-DAR was down regulated and D_2-DAR up regulated, a total number of DARs being however decreased. The treatment with insulin or curcumin, an active component in rhizome of *Curcuma longa*, reduced DM-induced alteration of D_1- and D_2-DARs in the cerebral cortex and increased D_1-DAR expression in the cerebellum to near control, thereby improving the cognitive and emotional functions associated with these regions. In the hypothalamus and brainstem of STZ rats a significant decrease in the DA content and the number of D_2-DARs, and an increase in affinity of the latter were found, and the insulin therapy did not completely

reverse the DM-induced changes of D_2-DAR functions (Shankar et al., 2007). The hypothalamus and brainstem are two parts of the brain very important for monitoring the glucose status and the regulation of feeding. The hypothalamus, in addition, controls the release of pituitary hormones having a key role in regulation of the CNS and the periphery. These data indicate that the activity of the dopaminergic system in different areas of the diabetic brain either increases or decreases, which must be taken into consideration in clinic practice for successful management of DM and its cerebral complications.

The alteration of DA-regulated signaling cascades in DM is associated with their downstream components, such as the transcription factor CREB playing a pivotal role in DAR-mediated nuclear signaling and neuroplasticity (Finkbeiner, 2000) and D_1-DAR-coupled PLC involved in the neuromodulation of hippocampal LTD (J. Liu et al., 2009). It was found that STZ-induced DM produces a significant attenuation of functional activity of CREB and PLC in the cerebral cortex and cerebellum of diabetic rats and these alterations are largely eliminated by the treatment with insulin and curcumin (T.P. Kumar et al., 2010).

We showed that in the brain of rats with STZ-induced DM1, duration one month, as well as with neonatal model of DM2, duration 3 to 6 months, the sensitivity of AC to regulatory action of bromocriptine was decreased (Shpakov et al., 2006, 2007a). The inhibitory effect of bromocriptine on forskolin-stimulated AC activity and its stimulating effect on GppNHp binding of G_i proteins in synaptosomal membranes of diabetic rats were significantly decreased, predominantly in DM1. As the binding characteristics of DARs and the catalytic activity of AC did not change essentially, a suggestion was made that the impairment of bromocriptine-induced signaling in the diabetic brain was due to the reduced function of G_i proteins (Shpakov et al., 2007b). This view finds support in the fact that the regulatory effects of somatostatin and 5-HT_1R agonists acting, like bromocryptine, on AC via G_i protein-coupled receptors were decreased in the brain of diabetic rats (Shpakov et al., 2007a). The attenuation of D_2 agonist-induced suppression of appetite in STZ rats (Kuo, 2006) is also likely to be the result of reduction of G_i protein activity in the diabetic brain.

Another cause why the activity of dopaminergic system in the diabetic brain is decreased is the reduction in DA uptake and the DA transporter (DAT) expression that depend on the activity of PI 3-kinase and AKT kinase (Garcia et al., 2005). The uptake by DAT is the primary pathway for the clearance of extracellular DA and hence for regulating the magnitude and duration of dopaminergic signaling. Insulin activates PI 3-kinase and AKT kinase, increases DA uptake and blocks the amphetamine-induced DAT intracellular accumulation leading to a decrease of the number of active transporters. In DM1, which is characterized by hypoinsulinemia, the available cell surface DATs are reduced, and this leads to decrease of synaptic DA level. As a result, the DM-induced alterations in DA uptake and transport induce attenuation of synaptic DA signaling. Actually, the impairment of DA uptake and transport systems in the hippocampus of both STZ and spontaneously diabetic *WBN/Kob* rats leads to a significant decrease in the basal level of DA (Yamato et al., 2004).

3.2 Serotonin signaling

The brain serotonergic system regulates several behaviors (e.g., feeding, locomotion, reproduction, sleep, pain, aggression and stress responses) as well as some autonomic functions (e.g., thermogenesis, cardiovascular control, circadian rhythm and pancreatic function). The changes of serotonergic transmission in the diabetic brain provoke disturbances in neuronal processing and the altered plasticity of neurotransmission, and play an important role in DM-induced behavioral abnormalities. This is due first of all to the

alteration of the brain sensitivity to 5-HT, which depends on the functioning of 5-HT-regulated signaling pathways and the disturbances in the biochemical conversion, reuptake and transport of 5-HT and its metabolites. These changes cause a distorted response of neuronal cells and the CNS as a whole to 5-HT and its analogs, as well as to the drugs that increase the level of central 5-HT.

Selective 5-HT reuptake inhibitors are widely used in the pharmacological treatment of depression typical of both DM1 and DM2 and have a significant effect on the course and outcome of this medical illness (Lustman & Clouse, 2005). The 5-HT reuptake inhibitors contribute to lowering the level of hyperglycemia, decrease the rate of hemoglobin glycosylation, improve metabolic control through their positive effect on weight loss, thereby improving insulin resistance, and restore cognitive functions impaired in DM (Van Tilburg et al., 2001). It was shown that the treatment of 60 patients with depression associated with DM1 and DM2 by fluoxetine, selective 5-HT reuptake inhibitor, significantly reduces depressive symptoms and increases the sensitivity of the brain and the peripheral tissues to insulin (Lustman et al., 2000). Consequently, the approach leading to an increase of the brain 5-HT level and, thus, improving 5-HTR signaling in the CNS is a successful strategy to treat DM (Zhou et al., 2007).

In the late 1970s, it was shown that STZ-induced DM and hyperglycemia have a significant influence on the brain tryptophan (Trp) and 5-HT metabolism (MacKenzie & Trulson, 1978). The content of 5-HT and 5-hydroxyindoleacetic acid (5-HIAA), the main metabolite of 5-HT, as well as 5-HT turnover (5-HIAA/5-HT) is decreased in different brain areas of STZ rats with long-term hyperglycemia and in the hippocampus of spontaneously diabetic *WBN/Kob* rats (Sandirini et al., 1997; Jackson & Paulose, 1999; Yamato et al., 2004). A decrease in 5-HT level is due to the decreased uptake of Trp, the precursor of 5-HT, by the brain (Mackenzie & Trulson, 1978). An increase in the level of insulin can result in decreased plasma concentrations of large neutral amino acids (phenylalanine, valine, leucine, isoleucine, tyrosine) competing with Trp for uptake by the brain, which accounts for a low availability of plasma Trp. The other cause of a decrease of the biosynthesis of 5-HT is a long-lasting inhibition of the rate-limiting enzyme tryptophan-5-hydroxylase 2 (Herrera et al., 2005). It was shown that the Trp level and the free/total Trp ratio in the plasma and in the brain of children and adolescents with DM1 and in women with DM2 were also significantly decreased (Manjarrez-Gutierrez et al., 2009). Free fraction and free fraction/total Trp ratio were also decreased in adolescents with metabolic syndrome, although to a small extent (Herrera-Marquez et al., 2011). In the case of diabetic adolescents two groups of patients, with and without depression, were studied and it was shown that diabetic patients with depression had a lower level of Trp compared with diabetic adolescents without depression (Manjarrez-Gutierrez et al., 2009). Diabetic patients with depression had the most expressed hypoinsulinemia and more extended episodes of hyperglycemia than patients without depression. These results indicate that the degree of disturbances of brain serotonergic activity is likely to correlate with the degree of metabolic disturbances induced by DM1.

Hypoglycemia caused by fasting or by treatment of diabetic patients with peripheral insulin, like hyperglycemia associated with STZ DM, leads to disturbances in serotoninergic system of the brain (Das, 2010). Hypoglycemia increases turnover of 5-HT and decreases the level of 5-HT precursor 5-HIAA in both ventromedial and lateral hypothalamic areas, which induces a decrease of central 5-HT concentration (Shimizu & Bray, 1990). At the same time, i.c.v. administered insulin at doses 50 and 100 μUnits, which induced minimal hypoglycemia, increased 5-HT concentration in the midbrain and ponsmedulla oblongata of

hyperglycemic rats with alloxan DM and partially restored 5-HT-regulated functions of the CNS (Bhattacharya & Saraswati, 1991). It indicates the importance of the appropriate glycemic control for restoration of 5-HT metabolism in the diabetic brain.

With a decrease of concentration of 5-HT and 5-HIAA in the diabetic brain the number of different types of 5-HTRs and their affinity to available 5-HT increases inducing alteration of 5-HT neurotransmission. Thus, in the frontal cortex of STZ rats the density of 5-HT_{2A}R, coupled to PLC via G_q proteins, was significantly higher than in control group of animals (Sandrini et al., 1997). An increase in affinity of 5-HT_{2A}Rs in the cerebral cortex without any change in the number of receptors, and a significant increase in B_{max} for these receptors in the brainstem with a decrease in affinity during STZ-induced DM were also shown (Jackson & Paulose, 1999). The alterations of 5-HT_{2A}R in the cerebral cortex and brainstem are a compensatory mechanism responsible for a decrease of 5-HT level in these brain areas in DM. All these parameters returned to normal level by insulin therapy. It seems likely that up-regulation of the 5-HT_{2A}R may have a role in the regulation of insulin secretion from pancreatic islets. As is known, the increased activity of 5-HT_{2A}R in the cerebral cortex and brainstem can increase the sympathetic nerve discharge, thereby increasing the levels of circulating norepinephrine and epinephrine, which leads to inhibition of insulin release from the pancreas. In addition to insulin regulation, an increase in affinity and the number of 5-HT_{2A}Rs has a role in pathogenesis of depression and cognitive deficit in DM.

In our view, being a compensatory response of the brain to lower levels of 5-HT and its precursors, the increase of the number of 5-HTRs is also a reaction to the weakening of signal transduction through these receptors. The latter may be associated with a decreased expression or the functions of signal proteins, the components of 5-HT-regulated signaling pathways. It was shown that one week after STZ treatment the flat body posture induced by 5-HT_{1A}R agonist 8-hydroxy-2-(dipropylamino)tetralin hydrobromide (8-OH-DPAT) and head twitching induced by 5-HT_{2A}R agonist 2,5-dimethoxy-4-iodoamphetamine hydrochloride (DOI) were markedly reduced in the diabetic rats compared with control animals, which indicates that STZ-induced DM profoundly affects the sensitivity to drugs acting at 5-HT_{1A}- and 5-HT_{2A}Rs (J.X. Li & France, 2008). Insulin treatment during one week restored 8-OH-DPAT and DOI-induced behavioral effects. We found no alteration of the sensitivity of AC signaling system in the brain of STZ rats to selective agonists of 5-HT_6R coupled with G_s proteins, while the sensitivity of this system to agonists of 5-HT_{1A}R and 5-HT_{1B}R coupled with G_i proteins was significantly decreased (Shpakov et al., 2007a). We consider the weakening of 5-HT_1R-mediated signaling to be associated with decreased expression and activity of G_i proteins because, as mentioned above, a decrease in activity of the other G_i protein-coupled cascades regulated by somatostatin and DA was also detected in the brain in DM. Note that in the diabetic brain the signaling pathways involving G_s proteins were either unchanged or changed very little (Shpakov et al., 2007b). The impairment of response of the diabetic brain to 5-HT was made evident in the recent clinic study where citalopram, a selective 5-HT reuptake inhibitor, was used in the treatment of patients with DM2. It was shown that citalopram is less effective in diabetic patients compared with healthy individuals (Trento et al., 2010). The appropriate control of glucose and insulin plasma level in patients with DM2 makes it possible to increase the efficiency of citalopram treatment and the response of the hypothalamic-pituitary-adrenal axis to this drug, and to improve the clinical as well as cognitive and emotional variables.

Dysfunctions of the serotonergic system of the brain can be the result of DM, but on the other hand, they can be the cause of DM. The attenuation of 5-HT signaling in the brain

induces hyperphagia and other disturbances of feeding behavior, which, in turn, leads to the obesity and DM2 (Heisler et al., 2002). The cause of this is in that the central 5-HT activates, via 5-HT_{2C}Rs expressed on POMC neurons, signaling pathways regulated by melanocortin and its analogs via MC_4R/MC_3R located on the same neurons in the arcuate nucleus of the hypothalamus (Zhou et al., 2007; Nonogaki et al., 2008). It follows, these neurons are a potential target for 5-HT_{2C}R agonists because they receive direct input from 5-HT dorsal raphe nucleus neurons and project to the regions associated with energy regulation. 5-HT_{2C}R agonists significantly improved glucose tolerance and reduced plasma insulin in animals with obesity and DM2. 5-HT_{2C}R agonist-induced improvements in glucose homeostasis occurred at concentrations of agonist that had no effect on feeding behavior, energy expenditure, locomotor activity, body weight, and fat mass (Zhou et al., 2007). These data are supported by the results of genetic studies. It was revealed in the murine knockout studies that only deletion of the gene encoding the 5-HT_{2C} receptor produces insulin resistance and DM2 with antecedent hyperphagia and obesity, which demonstrates that 5-HT_{2C}Rs are critical for energy homeostasis (Bonasera & Tecott, 2000). It was found that three loci of single nucleotide substitution (G → A at -995, C → T at -759, G → C at -697) and $(GT)_n$ dinucleotide repeat polymorphism in the upstream region (promoter) of the 5-HT_{2C}R gene are involved in the development of obesity and DM2 in human (Yuan et al., 2000). The haplotypes containing the nucleotide substitutions are associated with higher transcription levels of the gene and thereby with resistance to obesity and DM2.

3.3 Glutamate signaling

Glutamate is the major excitatory neurotransmitter in the CNS. It exerts action via ionotropic glutamate receptors (iGluRs) – AMPA and NMDA receptors, and via metabotropic glutamate receptors (mGluRs). mGluRs are predominantly found in pre- and post-synaptic neurons in synapses of the hippocampus, cerebellum and cerebral cortex but are also present in other parts of the brain and in the peripheral tissues. mGluR subtypes are critical in gating the plasticity and memory formation. mGluRs interact with iGluRs, ion channels and membrane-associated enzymes, the generators of second messengers, that modulate the cellular response involved in the processes of differentiation and degeneration of neuronal cells. The activation of $mGlu_1R$ and $mGlu_5R$, belonging to group I of mGluRs, enhances phosphoinositide hydrolysis and mobilization of intracellular Ca^{2+} due to stimulation of PLC, induces the activation of Na^+ and K^+ channels, modulates voltage-dependent Ca^{2+} channels and inhibits glutamate release, all this being of great importance in the regulation of cascades of biochemical reactions resulting in death of neuronal cells (N.E. Schwartz & Alford, 2000). The iGluRs are ligand-gated nonselective cation channels allowing the flow of K^+, Na^+ and Ca^{2+} in response to glutamate binding. These receptors, like mGluRs, have influence on synaptic plasticity and are of prime importance in excitotoxicity. An increase or a decrease of the number of iGluRs on post-synaptic neurons leads to LTP or LTD of neuronal cell, respectively. The activation of NMDA receptors in post-synaptic neurons increases Ca^{2+} influx, leading to phospholipase A_2-mediated arachidonic acid release and neuronal injury by inhibiting the Na^+-channels.

Glutamate is essential for synaptic communication in the CNS, but inadequate increase of extracellular glutamate and excessive activation of GluRs causes toxicity in the brain leading to neurodegenerative disorders (Trudeau et al., 2004). Excessive glutamate over-activates the cognate receptors, specifically NMDA receptors, which gives the influx of high level of Ca^{2+} in the post-synaptic cell. In the diabetic brain the glutamate level and the number of

GluRs are significantly increased, which is the main cause of neurodegenerative changes in DM (N. Li et al., 1999; Tomiyama et al., 2005; Joseph et al., 2008; Anu et al., 2010) (Fig. 3).

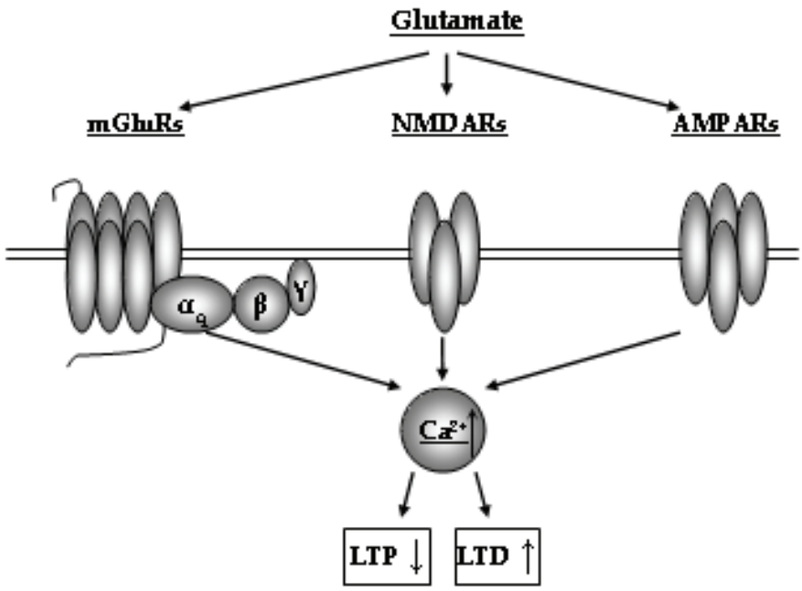

Fig. 3. Signaling pathways responsible for glutamate toxicity

Abbreviations: mGluRs, metabotropic glutamate receptors; NMDARs and AMPARs, ionotropic glutamate receptors of NMDA and AMPA types; $\alpha_q\beta\gamma$, heterotrimeric G_q-protein; LTP and LTD, long-term potentiation and long-term depression, respectively.

The synaptic level of glutamate in the brain depends on the high-affinity glutamate transporter GLAST, the major component of synaptic glutamate reuptake system, that plays an important role in the termination of glutamatergic neurotransmission and prevention of excitotoxicity, it also depends on the activity of GluRs regulating synaptic glutamate release (Danbolt, 2001). In nerve terminals specific vesicular transporters GluT1-3 allow incorporation of glutamate into synaptic vesicles. These transporters have an essential role in glutamate recycling and homeostasis in the CNS and the abnormalities of this functioning are responsible for development of neurological disorders (Benarroch, 2010). Synaptic release of endogenous glutamate is mediated with the voltage-dependent N-, L- and P/Q-type Ca^{2+} channels controlling the entry of Ca^{2+} into nerve terminals. In the diabetic brain the content of glutamate transporters and the α_{1A} subunit of P/Q type Ca^{2+} channels are changed. In the cerebellum of STZ rats the expression of the glutamate transporter GLAST gene was decreased, which indicates a decrease of glutamate reuptake (Anu et al., 2010). In the hippocampus a decrease of the level of glutamate transporters was transient, being evident mainly at the early stages of DM. This suggests that after the initial stress induced by DM the hippocampus was somehow able to respond to DM-induced stress, and after two weeks of DM the level of glutamate transporters recovered so that the values remained under control longer. After eight weeks of DM, the levels of glutamate transporters and P/Q-type Ca^{2+} channels did not change but the basal release of glutamate was significantly increased in hippocampal synaptosomes, which may underlie alterations in synaptic transmission at the later stages of DM (Baptista et al., 2011).

In the cerebral synaptosomes from STZ mice the K^+- and 4-aminopyridine-evoked Ca^{2+}-dependent glutamate release was significantly increased. The treatment of synaptosomes with a combination of ω-agatoxin IVA (a P-type Ca^{2+} channel blocker) and ω-conotoxin GVIA (an N-type Ca^{2+} channel blocker) completely inhibited K^+- or 4-aminopyridine-induced increase in glutamate release and prevented glutamate toxicity typical of the diabetic brain (Satoh & Takahashi, 2008). It means that STZ-induced DM enhanced a depolarization-evoked Ca^{2+}-dependent glutamate release in cerebral synaptosomes by stimulating Ca^{2+} entry through both P- and N-type Ca^{2+} channels. It was also shown that voltage-dependent Ca^{2+} currents through N-, P- and L-type Ca^{2+} channels were enhanced in dorsal root ganglion neurons of STZ rats and Bio Bred/Worchester diabetic rats, which directly mediated the increase of glutamate exocytosis and induced DM-associated excitotoxicity (Voitenko et al., 2000; Hall et al., 2001). These data allow the selective blockers of the Ca^{2+} channels to be considered possible drugs for the treatment of diabetic patients with neuronal disorders associated with an increased level of synaptic glutamate.

In the cerebral cortex and cerebellum of STZ rats and hypoglycemic diabetic rats the expression of NR1 and NR2B receptor subunits and $mGlu_5R$ genes and the number of the receptors were increased (Joseph et al., 2008). The activity of $mGlu_5R$ was increased, which led to stimulation of the activity of PLC coupled with $mGlu_5R$ via G_q protein and to an increase of the content of intracellular inositol 1,4,5-triphosphate receptors interacting with the second messenger phosphatidyl inositol 1,4,5-triphosphate generated by PLC. The increase of activity of NMDA receptors and the $mGlu_5R$-associated stimulation of PLC activity mediated Ca^{2+} overload in cells causing neuronal cell damage and neurodegeneration in the diabetic brain, affecting as it did the motor learning and memory ability (Anu et al., 2010). In the dorsal horn of the lumbar spinal cord of STZ rats the levels of mRNAs coding several AMPA receptor subunits (GluR1, GluR2, and GluR3), NMDA receptor subunits (NR2A and NR2B), as well as $mGlu_1R$ and $mGlu_5R$ were also up regulated (Tomiyama et al., 2005). In the deep dorsal horn of STZ rats the level of NMDA receptors with high affinity for glutamate, namely NR1/NR2A or NR1/NR2B receptors, was the highest. Also increased was the number of NMDA and AMPA receptors in the gray matter of the spinal cord of the *ob/ob* mice responsible for pain, sensory perception and muscle control (N. Li et al., 1999). Thus, the elevated level of specific GluRs/GluR subunits in the spinal cord is a precondition for the pathogenesis of sensory impairment leading to diabetic neuropathy in DM. The use of GluRs antagonists decreasing enhanced activity of these receptors in the diabetic brain significantly ameliorated hyperalgesia and allodynia in experimental DM1 (Malcangio & Tomlinson, 1998; Calcutt & Chaplan, 1997), which suggests that increased excitatory tone in the spinal cord plays an important role in the development of diabetic neuropathy. It should be pointed out that NR2B-selective antagonists are effective in suppressing hyperalgesia in STZ rats with neuropathic pain at doses devoid of negative side effects, which indicates their suitability for control of sensory symptoms induced by DM (Tomiyama et al., 2005). It is worth mentioning that some antagonists of GluRs, e.g. the NMDA receptor antagonists dextromethorphan and amantadine, are used in clinical practice in the treatment of diabetic patients and markedly ameliorate the neuropathic pain in some patients (Nelson et al., 1997; Amin & Sturrock, 2003).

3.4 GABA signaling

GABAergic inhibitory function in the cerebral cortex is of great importance in the regulation of excitability and responsiveness of cortical neurons. GABA inhibition is mediated both by

$GABA_A$ receptors, which open membrane chloride channels and stabilize the membrane potential below firing threshold, and $GABA_B$ receptors, which act via G proteins to reduce transmitter release from presynaptic terminals. The inhibitory GABA-releasing interneurons mediate the function of excitatory glutamatergic neurons in the brain regions, which contributes significantly to the control of glutamate content in brain regions and prevents glutamate toxicity induced in the brain of hypo- and hyperglycemic diabetic rats. Disruption of GABAergic inhibition induces seizures leading to neuronal damage and, therefore, the pathophysiology of many seizure disorders is the result of alteration of GABA receptor function (Antony et al., 2010a).

It was shown that the synaptic level of GABA and its release in the diabetic brain are slightly changed or remain unchanged. The extracellular basal level of GABA at dentate gyrus of STZ rats 12 weeks after the induction of DM showed no changes (Reisi et al., 2009). The content of vesicular GABA transporter was significantly decreased in hippocampal synaptosomal membranes in two week DM, although only minor changes in the release of GABA and in the loading capacity of GABA transporters were found (Baptista et al., 2011). This indicates that the alterations of GABA signaling, typical of the diabetic brain, are due to the changes in the level and functional activity of GABA receptors and down-stream signal components of GABA-regulated intracellular cascades.

Actually, the GABA binding and the gene expression of the subunits of $GABA_{A\alpha1}$ and $GABA_B$ receptors were decreased in the cerebral cortex of diabetic rats compared to control animals. In the diabetic hypoglycemic rats having two episodes of insulin-induced hypoglycemia in the course of 10 days GABA binding and expression of GABA receptor subunits were reduced to a greater extent in comparison with diabetic hyper/euglycemic animals. This is the evidence that hypoglycemia amplifies the adverse effects of hyperglycemia on GABAergic system, and the impairments of functions of GABAergic neurons in the diabetic cerebral cortex are intensified in hypoglycemia. The expression of glutamate decarboxylase, the rate-limiting enzyme of GABA synthesis, which is used as a marker of GABAergic activity, was also significantly down regulated in DM and hypoglycemia exacerbated the altered expression (Antony et al., 2010a). The same picture is found in the cerebellum, where GABA receptors are involved in control of coordination and motor learning and, like in the cerebral cortex, play a critical role in neuronal excitability and modulation of synaptic neurotransmission (Luján, 2007). In the cerebellum of STZ rats with hyperglycemia the gene expression of $GABA_{A\alpha1}$ subunit and glutamate decarboxylase was decreased and these molecular alterations were exacerbated by recurrent hypoglycemia (Sherin et al., 2010). The gene expression of CREB, a stimulus-inducible transcription activator implicated in the activation of protein synthesis required for long-term memory and seizure formation, was significantly down regulated in DM and recurrent hypoglycemia. Since CREB up-regulates endogenous $GABA_{A\alpha1}$ transcription, the decreased expression of CREB in the cerebellum of hypoglycemic and hyperglycemic rats led to the attenuation of GABAergic system and, as a result, to excitotoxic damage of neuronal cells (Sherin et al., 2010). It follows that hypo- and hyperglycemia in DM both decrease GABAergic neuroprotective function in the cerebral cortex and cerebellum, which accounts for increased vulnerability of these brain areas to subsequent neuronal damage.

3.5 Acetylcholine signaling

In the brain acetylcholine functions either as a neuromodulator, or as a neutotransmitter, activating via metabotropic muscarinic acetylcholine receptors (MAChRs) a multitude of

signaling pathways important for modulating neuronal excitability, synaptic plasticity and feedback regulation of acetylcholine release and, thus, controls the functional, behavioral and pathological states of the CNS (Dani, 2001). Acetylcholine also activates ionotropic nicotinic acetylcholine receptors that form ligand-gated ion channels in the plasma membranes of the neurons and on the postsynaptic side of the neuromuscular junction. The activation of nicotinic receptors in the CNS induces depolarization of the plasma membrane, culminating in an excitatory postsynaptic potential in neuron, the activation of voltage-gated ion channels and the increase of calcium permeability. The changes in the number and activity of the metabotropic and ionotropic acetylcholine receptors have been implicated in the pathophysiology of many diseases of the CNS, including cognitive impairment.

It was shown that in the cerebral cortex, hypothalamus and brainstem of STZ rats the number of G_q-coupled m_1-MAChRs and the expression of genes encoding m_1-MAChR were decreased with an increase in affinity of the receptor to agonists, and the binding parameters of the m_1-MAChR were reversed to near control by the treatment with insulin (Gireesh et al., 2008; Peeyush Kumar et al., 2011). In the cerebral cortex of the diabetic and control rats with insulin-induced long-term hypoglycemia the maximal binding of m_1-MAChRs and their expression were reduced to a greater extent compared with diabetic animals with hyperglycemia (Sherin et al., 2011). At the same time, in the cerebellum and corpus striatum of both diabetic rats and hypoglycemic diabetic and control rats the binding parameters and gene expression of m_1-MAChRs was, on the contrary, increased (Antony et al., 2010b). This indicates that the alterations in the initial steps of m_1-MAChR signaling in the diabetic brain are area-specific.

The STZ-induced DM and insulin-induced hypoglycemia both lead to a significant increase of the binding of another G_q-coupled m_3-MAChR in the cerebral cortex and cerebellum but the extent of changes induced by hypoglycemia was significantly higher compared to DM, which indicates the detrimental effect of recurrent hypoglycemia on cholinergic system in the brain (Antony et al., 2010b; Peeyush Kumar et al., 2011; Sherin et al., 2011). This allows a conclusion that the imbalance in glucose homeostasis affects acetylcholine metabolism and cholinergic muscarinic neurotransmission in the brain, and changes the expression and function of cholinergic receptors. The study of 7-week- and 90-week-old STZ rats showed that in the brainstem of both groups of animals the number of m_1-MAChRs was significantly decreased whereas the number of m_3-MAChRs greatly increased compared to their respective controls, and the insulin treatment reversed the binding parameters of m_1- and m_3-MAChRs to near control level (Balakrishnan et al., 2009). In the cerebral cortex of 7-week-old STZ rats the number of m_1-MAChRs decreased by 28 %, while the number of m_3-MAChRs increased by 30 %. In the cerebral cortex of 90-week-old diabetic rats the number of m_1- and m_3-MAChRs increased by 43 and 23 %, respectively, and the level of acetylcholine was significantly increased compared to control (Savitha et al., 2010). These alterations of m_1- and m_3-MAChR expression correlate with cholinergic hypofunction in short-term and prolonged STZ-induced DM. It should be noted that m_1- and m_3-MAChRs are abundantly expressed in the brain regions involved in cognition, including the cerebral cortex, hippocampus and striatum (Porter et al., 2002).

As a rule, most animal models of obesity and hyperinsulinemia are associated with increased vagal cholinergic activity that is strongly associated with the m_3-MAChR expressed in the brain and the peripheral tissues (Gautam et al., 2008). The absence of m_3-MAChR protects the animals against experimentally or genetically induced obesity and obesity-associated metabolic deficit and greatly ameliorates the impairments in glucose homeostasis and insulin sensitivity. The m_3-MAChR-deficient mice are largely protected

against obesity-associated glucose intolerance, insulin resistance, hyperinsulinemia, and hyperglycemia triggered by a high-fat diet, chemical disruption of hypothalamic neurons by gold-thioglucose, and genetic disruption of the leptin gene. These data favor the fact that the m_3-MAChR and other subtypes of MAChRs can represent a potential pharmacologic target for the treatment of DM, obesity and associated neurological disorders.

Along with insulin, some substances, vitamin D_3 and curcumin in particular, which differ in the chemical nature and the mechanism of action are also capable of restoring the functions of cholinergic system in the diabetic brain. Vitamin D_3, as well as insulin, markedly recovers the altered gene expression of m_1- and m_3-MAChRs in the cerebral cortex and cerebellum of STZ rats and binding parameters of these receptors to near control (P.T. Kumar et al., 2011). Vitamin D_3-induced improvement of the cholinergic system and glucose homeostasis in the diabetic brain is due to the influence of vitamin D_3 on activity of pancreatic m_3-MAChR followed by enhanced synthesis and secretion of insulin and reduction of the neuronal disorders in DM (P.T. Kumar et al., 2011). It was found, in addition, that vitamin D_3 restores the disrupted expression of IR in the cerebral cortex of diabetic rats. Curcumin possesses powerful anti-diabetic properties and has the ability to modulate MAChRs thereby ameliorating the impaired cognitive functions in DM (Peeyush Kumar et al., 2011).

Ionotropic nicotine acetylcholine receptors are also involved in the pathogenesis of neurodegenerative processes in DM. Note that the stimulation of nicotinic acetylcholine receptors and MAChRs provokes opposing physiological and behavioral responses, which is due to the existence of multiple nicotinic and muscarinic receptor subtypes and their different anatomical distributions in the CNS. For example, nicotine administration inhibits food intake, increases metabolic rate, and leads to reduced adiposity (M.D. Li et al., 2003), while the activation of m_3-MAChRs induces hyperphagia and obesity (Gautam et al., 2008).

α7-Nicotinic receptors highly expressed in the course of brain development are implicated in memory, attention and information processing (Picciotto et al., 2000). In the cortex of STZ rats the expression of α7-nicotinic receptors was markedly increased. The receptors significantly influenced the activity within the cortex circuitry, and DM-associated deregulation of this activity could contribute to disorders involving the cerebral cortex (Peeyush Kumar et al., 2011). Alongside with the increase in α7-nicotinic receptors expression, in the cerebral cortex of diabetic rats were revealed the increased acetylcholine esterase and the decreased choline acetyl transferase mRNA levels, which indicates fast acetylcholine degradation and a subsequent down stimulation of acetylcholine receptors causing undesirable effects on cognitive functions. These changes in the expression of acetylcholine esterase and choline acetyl transferase in DM led to a reduction of cholinergic neurotransmission efficiency due to a decrease in acetylcholine levels in the synaptic cleft, thus contributing to progressive cognitive impairment and other neurological dysfunctions in DM. Insulin therapy and curcumin substantially regularize the increased expression of acetylcholine esterase and choline acetyl transferase, and significantly revert up-regulation of α7-nicotinic receptor in the cortex of STZ rats improving the cognitive functions, such as learning and memory.

4. Peptide hormones in the diabetic brain

4.1 Melanocortin signaling

The DM2 and obesity of humans and animals are strongly associated with variations in a gene encoding MC_4R coupled with AC via G_s proteins (Farooqi et al., 2003) (Fig. 2). MC_4R

expression is restricted primarily to the brain, where it is widely expressed. MC_4R agonists α-MSH, a product of POMC, and melanotan II promote a negative energy balance by decreasing the food intake and increasing the CNS activity and energy expenditure, whereas hypothalamic AgRP, MC_4R antagonist, on the contrary, increases food intake (Balthasar et al., 2005). MC_4R pathways also regulate glucose metabolism and insulin sensitivity (Fan et al., 2000; Obici et al., 2001; Nogueiras et al., 2007). Central injection of the MC_4R agonist reduces insulin secretion, while administration of the MC_4R antagonist increases serum insulin levels. Furthermore, elevated plasma insulin level was detected in the young lean MC_4R knockout mice, and impaired insulin tolerance before the onset of detectable hyperphagia or obesity (Fan et al., 2000; Haskell-Luevano et al., 2009). The mice with functionally inactive MC_4R had obesity strikingly reminiscent of the agouti syndrome, which indicates that the disturbances in MC_4R signaling pathways were the primary cause of the agouti obesity. The available data indicate that hypothalamic melanocortin system controls adiposity levels rapidly and perhaps more efficiently than the other CNS signaling pathways (Nogueiras et al., 2007). It should be emphasized that the hypothalamic melanocortin system is regulated by leptin. It must be really so because the conditions associated with low leptin levels, such as fasting or genetic leptin deficiency, provide for decreased hypothalamic POMC mRNA level as well as increased expression of AgRP (Havel et al., 2000). Leptin infusion is followed by an increase in POMC mRNA level as well as in MC_4R mRNA level and inhibits the production of AgRP (Gout et al., 2008).

Despite the lack of data on the relationship between neurodegenerative diseases and the alterations of the hypothalamic melanocotrin system in obesity and DM, a suggestion was made that a decreased activity of this system and increased expression of AgRP are the prime causes of neurodegenerative processes in the diabetic brain. As is known, MC_4R-mediated improvement of cognitive functions involves neuroprotective action, regenerative trophic effects, promotion of adaptive plasticity, and suppression of damage pathways triggered by apoptotic and inflammatory factors (Tatro, 2006). The treatment with Nle^4,D-Phe^7-MSH, a selective MC_4R agonist, reduced postischemic tissue injury and improved the recovery of behavioral functions even when the treatment began as late as 9 hours after ischemia. The neuroprotective effect of Nle^4,D-Phe^7-MSH was prevented by MC_4R antagonists (Giuliani et al., 2006). The treatment blocked the ischemia-induced impairment of spatial learning and memory for at least 12 days due to the MC_4R-mediated reduction of death of hippocampal cells. Because a very high dose of MC_4R agonists actually enhanced learning, it was assumed that their effect is likely to have involved neurotrophic action of melanocortin, including promotion of neurite sprouting and functional recovery from nerve injury. The regulatory effects of α-MSH and selective MC_4R agonists on neuronal plasticity and survival could be mediated by their influence on neuronal signaling pathways regulated by other neurotransmitters. It was shown that MC_4R activation by agonists exerts the inhibitory effect on hypothalamic neurons through inhibition of neuronal firing rate and facilitation of GABA transmission (Nargund et al., 2006). This suggests the central melanocortin system to be responsible for a large number of neurodegenerative processes in the CNS previously associated with the other signaling systems of the brain.

Studying the activity of antibodies against extracellular loops of MC_3R and MC_4R strong evidence was obtained for the involvement of central melanocortin system in DM and obesity. Hofbauer and coworkers immunized the rats with peptides corresponding to the N-terminal extracellular domain MC_4R and to the first and third extracellular loops of MC_3R (Hofbauer et al., 2008; Peter et al., 2010). The antibodies to the N-terminal domain of MC_4R

acted as partial agonists and decreased the level of cAMP in cell cultures. In rats injected with peptide corresponding to the N-terminal domain of MC_4R, like in the case of blockade of hypothalamic MCRs, the food intake, body weight, plasma insulin and triglycerides levels increased significantly (Hofbauer et al., 2008). Antibodies against peptide derived from the first loop of MC_3R amplified AC stimulating effect of α-MSH; contrary to this, antibodies against the peptide derivatives of the third loop of the same receptor reduced the effect of hormone, acting as non-competitive antagonist. In rats injected with peptide derived from the third loop of MC_3R, the body weight and blood pressure were increased and motor activity was decreased. In plasma the levels of triglycerides, insulin and leptin were significantly increased compared with control. At the same time, the rats injected with peptide derived from the first loop had no changes of physiological and biochemical parameters (Peter et al., 2010). These data indicate that peptides derived from the MCRs and the antibodies to them directly influence melanocortin signaling pathways and cause changes in brain signaling, their action being receptor- and site-specific, i.e. depends on the antigenic determinants they correspond to, and can either inhibit or enhance signal transduction via the cognate receptor. This is in good agreement with the results obtained with other peptides, the derivatives of extracellular and intracellular regions of G protein-coupled receptors (Shpakov, 2011). Thus, peptides derived from the extracellular loops of MCRs and the other receptors involved in the functioning of the brain are a promising tool in the study of pathogenesis of DM and its CNS complications and give a perspective approach to develop new models of DM and obesity based on antibody-induced deregulation of the central signaling network controlled by hormones of different nature.

4.2 Neuropeptide Y signaling

NPY, a 36-amino acid peptide, stimulates feeding and decreases energy expenditure. NPY, one of the most abundant brain peptides in the paraventricular and arcuate nuclei and in the other regions of the hypothalamus is implicated in regulation of the feeding behavior, energy balance, and pituitary secretion. Disruptions in NPY signaling due to high or low abundance of NPY and cognate receptors deregulate the homeostatic milieu to promote hyperinsulinemia, hyperglycemia, fat accrual, and overt DM. In STZ rats the activity of hypothalamic NPY neurons was significantly increased, and induced marked hyperphagia (Sindelar et al., 2002; Kuo et al., 2006). STZ rats between 3 and 14 weeks after induction of DM1 had a significant increase (35–200 %) of NPY concentration in the paraventricular and the ventromedial nuclei and lateral hypothalamic area of hypothalamus, the major appetite-regulating areas sensitive to hyperphagic and polydipsic action of NPY. The concentration of NPY was also increased in the arcuate nucleus and medial preoptic area, the regions involved in modulating hormone secretion. A significant increase of NPY level was found in the hypothalamic sites of diabetic rats 6 months after STZ treatment, and insulin therapy for 3 months completely prevented the STZ-induced increments in NPY levels in all hypothalamic sites (Sahu et al., 1990).

In the rats with DM2 the level of NPY and the activity of arcuate nucleus NPY neurons were also increased, which led to hyperphagia and obesity, and may have contributed to hyperinsulinemia and altered pituitary secretion, and the insulin treatment returned the activity of NPY system (Maekawa et al., 2006). The level of mRNA encoding NPY was increased in cells of the arcuate nucleus of young 11-week-old Goto-Kakizaki rats having hyperphagia associated with leptin resistance. Following i.c.v. injection of the NPY-Y1

receptor antagonist 1229U91, the amount of food intake in Goto-Kakizaki rats was indistinguishable from that in Wistar rats, thus eliminating hyperphagia. Note that in NPY-deficient diabetic mice the mean daily food intake did not change, while in wild diabetic mice it increased two-fold. Alongside, in NPY-deficient mice the level of mRNA encoding POMC was decreased by as little as 11%, but in wild diabetic mice by 65%. Proceeding from these results, the conclusion was made that NPY is required both for an increase of food intake and for a decrease of POMC gene expression in DM (Sindelar et al., 2002).

The NPY signaling system is tightly associated with dopaminergic, melanocortin and leptin systems of the brain. The increased content of hypothalamic NPY plays a major role in attenuating the anorectic response of D_1/D_2-DARs agonists in STZ rats (Bina, Cincotta, 2000; Kuo, 2006). Leptin directly restrains the release of NPY and cohorts from the hypothalamic NPY neuronal network, and the complete absence of leptin or hypothalamic leptin receptors induces up-regulation of NPY signaling, which promotes unabated hyperphagia and fat storage (Kalra, 2008). The NPY and melanocortin signaling systems in the arcuate nucleus, where NPY and α-MSH are expressed, act in concert but have opposite functions. Hypothalamic NPY pathways favor anabolic processes and increase the food intake, whereas POMC neurons do the reverse. As a result, in hypothalamus signaling systems both form a complex network integrating hormonal (e.g., insulin and leptin) and metabolic (e.g., glucose) signals of energy homeostasis and initiating the adaptive responses of the diabetic brain (Fioramonti et al., 2007).

4.3 Glucagon-like peptide-1 signaling

Glucagon-like peptide-1 (GLP-1), a 30-amino-acid peptide hormone, is responsible for modulating blood glucose concentrations by stimulating glucose-dependent insulin secretion and by activating β-cell proliferation. GLP-1 is effective in restoring first-phase insulin response and lowering hyperglycemia in DM2 (Doyle & Egan, 2007). GLP1 also functions in the brain as a neurotransmitter, has the growth factor-like properties and protects neurons from neurotoxic influence, controlling learning behavior, memory and synaptic plasticity (Hamilton & Holscher, 2009; Hamilton et al., 2011). The action of GLP-1 is realized via GLP-1 receptors that in the brain affect neuronal activity through regulation of intracellular cAMP-dependent pathways, modulation of Ca^{2+} channels, activation of ERK1/ERK2 kinases and other second messenger systems involved in transmitter vesicle release (Gilman et al., 2003) (Fig. 2).

GLP-1 receptor agonists, exendin-4 and Liraglutide, like the inhibitors of GLP-1 degradation (dipeptidylpeptidase IV inhibitors), have been approved for treatment of DM2 (Lovshin & Drucker, 2009; Holst et al., 2011). Note that Liraglutide, analog of human GLP-1 with prolonged half life having a fatty acid palmitoyl group conjugated to the side-chain of Lys^{26} and an $Arg^{34}Ser$ substitution, is now widely used in DM2 therapy (Lovshin, Drucker, 2009). Exendin-4 and Liraglutide injected subcutaneously for 4, 6, or 10 weeks once daily in *ob/ob*, *db/db* and high-fat-diet-fed mice enhanced proliferation rate of progenitor cells by 100–150 % and stimulated differentiation into neurons in the dentate gyrus (Hamilton et al., 2011). The GLP-1 receptor antagonist exendin(9–36) significantly reduced progenitor cell proliferation in these mice. Exendin-4 and Liraglutide enhanced LTP in the brain and once-daily injection of the GLP-1 analog with $Ala^{8}Val$ substitution enhanced LTP in the brain and reduced the number of amyloid dense-core plaques in mice with insulin resistance and in patients with DM-associated obesity and AD (McClean et al., 2010). These results demonstrate that the

GLP-1 analogs show promise in the treatment of neurodegenerative diseases induced by DM, because they cross the BBB and increase neuroneogenesis. The GLP-1 analogs, such as GLP-1 with the substitution of $Ala^8$2-aminobutyric acid, with the increased stability to dipeptidyl peptidase IV elicit the insulinotropic activity and improve the central and peripheral symptoms of DM2 (Green & Flatt, 2007). The dipeptidyl peptidase-stable analogs of GLP-1 stimulate AC activity in neuronal cells and the AC stimulating effect correlates with their neuroprotective properties.

5. Conclusion

The data presented in this review suggest that alterations and disturbances occurring in a majority of hormonal signaling systems in the diabetic brain are responsible for the functioning of the CNS, the central regulation of peripheral functions as well as for memory, cognitive processes, emotion, and social behavior. These alterations leading to the DM-associated CNS disorders and centrally induced diseases of the peripheral systems are likely to develop via several mechanisms.

The first mechanism is associated with the appearance of damages in one of the signaling systems that may be caused by alterations in the expression or functional activity of sensory, adaptor or effector protein, a component of this system, and also by a deficit or, on the contrary, an excess of hormonal or hormone-like molecules that specifically regulate the system. The damages may be a result of hyperactivation, weakening or modification of the functions of signal protein due to mutations in the translated region of the gene encoding this protein or in the untranslated regions responsible for gene transcription, or else be induced by gene polymorphism in human DM. The other causes are the gene knockout and the mutations leading to gain, loss or modification of the function of signal proteins in experimental models of DM. The changes in concentration and availability of signal molecules can be ascribed to abnormalities in the systems responsible for their synthesis, transport and degradation. In the case of insulin and IGF-1 that penetrate the BBB, a decrease or increase of their level in plasma induces the corresponding alterations of insulin and IGF-1 levels in the brain, which directly affects the functioning of the signaling pathways regulated by these hormones. DM1 gives rise to peripheral hypoinsulinemia which leads to insulin deficiency in the brain, and DM2 to moderate hyperinsulinemia which leads to an increase of central insulin concentration. The abnormalities in one single signaling system influence the activity of the other signaling cascades coupled with and depending on it and induce changes in their functional activity which is a compensatory response of the brain to the primary local dysfunction of hormonal signaling. If the abnormalities are not eliminated, then the changes of brain signaling will amplify and cause deregulation of a comprehensive neuronal signaling network, which resembles “a domino effect”. As a result, the disturbances are systemic and irreversible; they have influence on the signal transduction pathways regulated by insulin, IGF-1, leptin, biogenic amines, glutamate, and neuropeptides.

The second mechanism is based on the systemic response of the hormonal signaling systems in the brain to significant and prolonged changes of cerebral glucose homeostasis, the state of recurrent hypoglycemia and severe long-term hyperglycemia. This causes alterations in the energy balance in the neuronal and glial cells, inducing different compensatory changes in the signal network to allow maintaining the activity of the brain in the case of inadequate glucose concentrations. The short-term fluctuations in cerebral glucose level cause

temporary changes in brain signaling, they are reversible and do not significantly affect the physiological functions of the brain, but the long-term alterations of the level and its large amplitude provoke dramatic and irreversible changes and cause the neurodegenerative disorders. For example, a prolonged and untreated DM1 with markedly expressed hyperglycemia as well as DM1 with intensive therapy using high doses of insulin and inadequate control of glucose plasma level, leading to recurrent hypoglycemia, are the major factors causing abnormalities in several signaling systems in parallel including the glutamatergic system responsible for development of glutamate excitotoxicity and CNS disorders.

Until recently, it was generally accepted that abnormalities and alterations in the neurotransmitter systems of the brain and the associated neurodegenerative disorders are the complications of DM and their role in the etiology of this disease is not very important. In the last few years, however, the conception of central genesis of DM has been significantly extended (Cole et al., 2007; de la Monte, 2009). According to this conception, there are cases when the abnormalities in the hormonal signaling systems of the brain will trigger the mechanism leading to insulin resistance or insulin deficiency and, as a result, to the development of DM and its central and peripheral complications. The following factors contribute to DM, a dysfunction in the leptin and the melanocortin systems (leptin and melanocortin model of DM2), and alterations in the 5-HT_{2C}R-coupled serotonergic and the D_2R-coupled dopaminergic systems (Bonasera & Tecott, 2000; Heisler et al., 2002; Zhou et al., 2007; Hofbauer et al., 2008; Toda et al., 2009; Peter et al., 2010). In the years to come, this list will, no doubt, be extended with the results of study of the forms of DM with central genesis. Some neurodegenerative diseases are considered to be pre-diabetes or specific forms of earlier DM, e.g. AD is referred to as the third type of DM (de la Monte, 2009).

The etiology of DM should be studied in order to find the most optimal strategy for adequate therapy and clinical management of DM and its CNS complications. The neuronal abnormalities precede DM as its causal factors; therefore it seems appropriate to eliminate the changes in the central signaling systems responsible for these abnormalities, and then to use the effective treatment of DM without high doses of insulin causing dangerous hypoglycemic episodes. A high efficiency has been shown in the case of combined use of insulin and IGF-1 and the drugs that improve the function of dopaminergic, serotonergic, melanocortin, GABAergic and glutamatergic systems. The approaches based on restoration of the functioning of a comprehensive signaling network of the brain are a new avenue of the treatment of DM of both central and peripheral genesis. This will allow avoiding many side effects of insulin monotherapy negatively affecting the CNS in diabetic patients.

6. Acknowledgment

This work was supported by Grant No. 09-04-00746 from the Russian Foundation of Basic Research and Program of the Russian Academy of Sciences "Fundamental Sciences – Medicine" (2009–2011). We express our thanks to *Inga Menina* for linguistic assistance.

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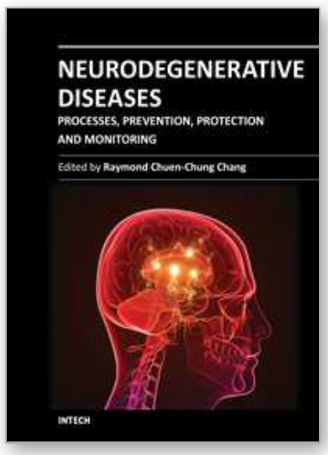

Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring

Edited by Dr Raymond Chuen-Chung Chang

ISBN 978-953-307-485-6
Hard cover, 558 pages
Publisher InTech
Published online 09, December, 2011
Published in print edition December, 2011

Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring focuses on biological mechanisms, prevention, neuroprotection and even monitoring of disease progression. This book emphasizes the general biological processes of neurodegeneration in different neurodegenerative diseases. Although the primary etiology for different neurodegenerative diseases is different, there is a high level of similarity in the disease processes. The first three sections introduce how toxic proteins, intracellular calcium and oxidative stress affect different biological signaling pathways or molecular machineries to inform neurons to undergo degeneration. A section discusses how neighboring glial cells modulate or promote neurodegeneration. In the next section an evaluation is given of how hormonal and metabolic control modulate disease progression, which is followed by a section exploring some preventive methods using natural products and new pharmacological targets. We also explore how medical devices facilitate patient monitoring. This book is suitable for different readers: college students can use it as a textbook; researchers in academic institutions and pharmaceutical companies can take it as updated research information; health care professionals can take it as a reference book, even patients' families, relatives and friends can take it as a good basis to understand neurodegenerative diseases.

How to reference

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Alexander Shpakov, Oksana Chistyakova, Kira Derkach and Vera Bondareva (2011). Hormonal Signaling Systems of the Brain in Diabetes Mellitus, Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring, Dr Raymond Chuen-Chung Chang (Ed.), ISBN: 978-953-307-485-6, InTech, Available from: http://www.intechopen.com/books/neurodegenerative-diseases-processes-prevention-protection-and-monitoring/hormonal-signaling-systems-of-the-brain-in-diabetes-mellitus

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