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Exenatide Alters Gene Expression of Neural Cell Adhesion Molecule (NCAM), Intercellular Cell Adhesion Molecule (ICAM), and Vascular Cell Adhesion Molecule (VCAM) in the Hippocampus of Type 2 Diabetic Model Mice

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCE 1 Esen Gumuslu
CEF 1 Naci Cine
BC 1 Merve Ertan Gökbayrak
AB 2 Oguz Mutlu
DF 2 Ipek Komsuoglu Celikyurt
E 2 Guner Ulak

1 Department of Genetics, Kocaeli University, Medical Faculty, Kocaeli, Turkey
2 Department of Pharmacology, Kocaeli University, Medical Faculty, Kocaeli, Turkey

Corresponding Author: Oguz Mutlu, e-mail: oguzmutlu80@hotmail.com
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Background: Glucagon-like peptide-1 (GLP-1), a potent and selective agonist for the GLP-1 receptor, ameliorates the symptoms of diabetes through stimulation of insulin secretion. Exenatide is a potent and selective agonist for the GLP-1 receptor. Cell adhesion molecules are members of the immunoglobulin superfamily and are involved in synaptic rearrangements in the mature brain.

Material/Methods: The present study demonstrated the effects of exenatide treatment (0.1 µg/kg, subcutaneously, twice daily for 2 weeks) on the gene expression levels of cell adhesion molecules, neural cell adhesion molecule (NCAM), intercellular cell adhesion molecule (ICAM), and vascular cell adhesion molecule (VCAM) in the brain tissue of diabetic BALB/c male mice by real-time quantitative polymerase chain reaction (PCR). Diabetes was induced by streptozotocin/nicotinamide (STZ-NA) injection to male mice.

Results: The results of this study revealed that hippocampal gene expression of NCAM, ICAM, and VCAM were found to be up-regulated in STZ-NA-induced diabetic mice compared to those of controls. A significant decrease in the gene expression levels of NCAM, ICAM, and VCAM were determined after 2 weeks of exenatide administration.

Conclusions: Cell adhesion molecules may be involved in the molecular mechanism of diabetes. Exenatide has a strong beneficial action in managing diabetes induced by STZ/NA by altering gene expression of NCAM, ICAM, and VCAM.

MeSH Keywords: Diabetes Mellitus • Genetic Association Studies • Mice, Inbred BALB C

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Background

Diabetes is a worldwide health problem currently affecting over 200 million people worldwide. It causes hyperglycemia and disturbs the effects of insulin in the human body. Approximately 90% of all diabetic patients have type 2 diabetes mellitus [1]. Although the causes of type 2 diabetes are not understood clearly, abnormal β-cell function resulting in relative insulin deficiency resistance is a hallmark [2]. In addition to various conventional agents used for the treatment of type 2 diabetes, incretin mimetics are capable of long-term improvement in β-cell function [3]. GLP-1 is a potent glucoincretin hormone and is a potentially important drug in the treatment of diabetes in view of its ability to improve insulin secretion in patients with impaired glucose tolerance and type 2 diabetes [4,5]. GLP-1 is also an insulinotropic agent through its ability to stimulate insulin gene expression and proinsulin biosynthesis [6] and acts as a potent β-cell growth factor [7]. GLP-1 increases the expression level of the β-cell specific transcription factor pancreatic and duodenal homeobox gene-1 (PDX-1) [7,8]. Although predominantly localized to pancreatic islets, GLP-1 receptor expression was documented both in the rodent [9,10] and human brain [11,12]. Studies with rat primary hippocampal cells established that the cells express GLP-1 receptors and that GLP-1 activation stimulated adenyl cyclase, leading to an increase in intracellular cAMP in a manner similar to that of pancreatic β-cells. Exenatide, the first incretin-mimetic, is a potent and selective agonist for the GLP-1 receptor [9,13] and has been widely used for the treatment of type 2 diabetes mellitus [14].

In the present article we focus our attention on the superfamily of adhesion molecules, neural cell adhesion molecule (NCAM), intercellular cell adhesion molecule (ICAM), and vascular cell adhesion molecule (VCAM), which are proteins located on the cell surface that are involved in binding with other cells or with the extracellular matrix in a process called cell adhesion. Essentially, cell adhesion molecules help cells stick to each other and their surroundings. Specifically, we consider NCAM, ICAM, and VCAM as causes of diabetes and as potential targets for diabetes. NCAM is a member of the immunoglobulin (Ig) superfamily of adhesion molecules, which are encoded by a single gene. A high degree of NCAM polysialylation on neuronal processes promotes a variety of developmental events, such as axonal growth and fasciculation, cell migration, initiation of synaptic reorganization, and synaptogenesis. The expression of PSA-NCAM is particularly high in the developing brain [15].

This study was planned to determine altered gene expression levels of molecules NCAM, ICAM, and VCAM by chronic exenatide treatment in the hippocampus of diabetic BALB/c male mice by real-time quantitative polymerase chain reaction (PCR) to determine if antidiabetic therapy can treat the imbalances in their expression. We administered streptozotocin/nicotinamide (STZ/NA) intraperitoneally for the formation of a diabetes model in mice.

Material and Methods

Experimental procedure

Male BALB/cByJ mice (Uludag University, Turkey) weighing 35–45 g were housed 4 to 5 per cage (L30×W20×H12.5 cm) in an animal colony facility for 2 weeks. The animals were maintained at a constant room temperature (22±2°C) during 12-h light/dark cycle (light onset at 07:00 h). Tap water and food pellets were provided ad libitum. All procedures complied with the European Community Council Directive of 24 November 1986, and the Ethics Committee of Kocaeli University granted ethics approval (HAYDEK 13/8-2011).

Type 2 diabetes mellitus was induced in overnight-fasted BALB/c mice by a single intraperitoneal injection of 100 mg/kg of streptozotocin, 15 min after the intraperitoneal administration of 240 mg/kg nicotinamide (STZ/NA). After the STZ/NA treatment, non-fasting glucose level was monitored. Hyperglycemia was determined on day 7 after the injection by elevated blood glucose levels. Only mice confirmed to have permanent type-2 diabetes were used in the study. Exenatide was administered subcutaneously (0.1 µg/kg) twice daily, initiated on day 13 and continued for 2 weeks after the diabetic model procedure. BALB/c mice were assigned to 3 experimental groups (n=5–7/each group): a control group, a type-2 diabetic group, and an exenatide-treated diabetic group. Streptozotocin (STZ) (Sigma, St. Louis, MO, USA) was dissolved in 50 mM of cold citric acid buffer (pH 4.5) and nicotinamide (NA) (Sigma, St. Louis, MO, USA) dissolved in saline. Exenatide (Byetta®) was the product of Lilly (Lilly Ltd. Sti. Istanbul, Turkey). The control group received both vehicles. All drugs were freshly prepared at the time of use and given at 0.1 ml per 10 g. Control, type-2 diabetic, and exenatide-treated diabetic BALB/c mice were sacrificed and brain tissues were processed for experimental analysis to examine gene expression of NCAM, ICAM, and VCAM in diabetes and effects of chronic exenatide treatment on these adhesion molecules.

Tissue sampling, isolation of RNA, and quantitative RT-PCR

Mice were sacrificed by cervical dislocation. Both parts of the hippocampus were dissected and put in liquid nitrogen. Total RNA was obtained by the RNeasy Mini Kit extraction procedure (Qiagen, Valencia, CA, USA). Tissues were homogenized in RLT lysis buffer containing β-mercaptoethanol using a Thermo Savant FastPrep FP120 Homogenizer. Sample homogenates were put into RNeasy Mini Spin columns (Qiagen) and exposed

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Table 1. Primer sequences of genetic studies.

Gene	Primary sequence
Beta2 microglobulin	(F) 5' TGA CTT TGT CAC AGC CCA AGA TA 3' (R) 5' AAT CCA AAT GCG GCA TCT TC 3'
BACT	(F) 5' AGC CAT GTA CGT AGC CAT CCA 3' (R) 5' TCT CCG GAG TCC ATC ACA ATG3'
NCAM	(F) 5'-AGC CCA AAC CAG CAG CGG ATC TC-3' (R) 5'-GTC CTC AGC CGT GAC CAC AC-3'
ICAM	(F) 5'-GCT ACC ATC CCA AAG CTC GAC AC-3' (R) 5'-GCT CCA GGT ATA TCC GAG CTT CAG-3'
VCAM	(F) 5'-CCG GAT CTC AGG TGG CTG CAC AA-3' (R) 5'-CAC CCC ATT GAG GGG ACT GTC TG-3'

Table 2. Gene expression levels in streptozotocin/nicotinamide (STZ/NA)-induced diabetus mellitus and effects of exenitide on gene expression levels of NCAM, ICAM, and VCAM in type-2 BALB/cByJ mice (fold changes). Type 2 diabetes mellitus was induced in overnight-fasted mice by a single intraperitoneal injection of 100 mg/kg of streptozotocin, 15 min after the intraperitoneal administration of 240 mg/kg nicotinamide. Exenatide was administered subcutaneously (0.1 µg/kg) twice daily (n=5–7/each group), initiated on day 13 and continued for 2 weeks after the diabetic model procedure. Hippocampal samples of these animals were used to determine gene expression levels of NCAM, ICAM, and VCAM by using quantitative real-time PCR. Statistical evaluation of gene expression levels was performed using REST (Relative Expression Software Tool) program.

Groups	Target gene 1 NCAM	Target gene 2 ICAM	Target gene3 VCAM
Diabetic + vehicle	3,202 ↑	2,493 ↑	3,123 ↑
Diabetic + exanitide	3,745 ↓	2,095 ↓	2,142 ↑↓

↑ – Increase (fold change) in expression; ↓ – decrease (fold change) in expression; NCAM – cell adhesion molecule; ICAM – intercellular cell adhesion molecule; VCAM – vascular cell adhesion molecule.

to further processes according to the manufacturer's instructions. An on-column DNase digestion was performed to cancel residual genomic DNA contamination. RNA samples were eluted in RNase-free water, and concentration was recorded spectrophotometrically using a NanoDrop ND-1000 Spectrophotometer (NanoDrop ND-1000; NanoDrop Technologies, Wilmington, DE). Then, cDNA was formed using the RevertAid First Strand cDNA synthesis kit (Fermentas Inc., Maryland, USA). Quantitative RT-PCR was used according to recent studies [16,17]. Standard curves were get via serial dilutions of beta-globulin gene. Primers specific to genes under investigation (Table 1) were bought from Integrated DNA Technologies (Iowa, USA) and IONTEK Inc. (Merter, Istanbul, Turkey). Expression of genes were normalized using the BACT housekeeping gene.

Statistical analyses

Hippocampal gene expression profile comparisons were performed between the following mouse data sets: type-2 diabetic mice *vs.* vehicle treated mice and type-2 diabetic mice *vs.* exenatide-treated diabetic mice. Statistical evaluation of gene expression levels of NCAM, ICAM, and VCAM were analyzed using REST (Relative Expression Software Tool) software.

Results

To evaluate effects of type-2 diabetes and long-term exenatide treatment on expression levels of cell adhesion molecules, we measured NCAM, ICAM, and VCAM gene expression of diabetic and exenatide-treated mice by quantitative RT-PCR. STZ-NA treatment significantly upregulated NCAM, ICAM, and VCAM gene levels of type-2 diabetic BALB/cByJ mice (3.202-, 2.493-, and 3.123-fold increase, respectively) compared to controls. Our findings are in parallel with Baydas et al. [18] who found that NCAM 180 and NCAM 120 expression were increased in diabetic rats. Moreover, Xu et al. [19] demonstrated that expression of VCAM-1 significantly increased in the partial cerebral cortex, hypothalamus, and hippocampus of diabetic rats. They also reported that ICAM-1 expression was significantly increased in the partial frontal and temporal cortex of diabetic rats.

Importantly, 2-week treatment with exenatide induced a downregulated expression in hippocampus gene transcripts of the genes under investigation compared to untreated diabetic subjects. Exenatide treatment decreased the gene expression of NCAM, ICAM, and VCAM in type-2 diabetic mice by 3.745-;

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2.095-, and 2.142-fold, respectively, compared to untreated diabetic mice. Table 2 illustrates the Q-RT PCR gene expression data (fold change) for the expression of the genes under investigation.

Discussion

Type 2 diabetes mellitus is an ever-increasing, health, social, and economic burden for developed countries and currently affects over 200 million people worldwide. Several efficacious drugs are currently available to ameliorate type 2 diabetes mellitus, and incretin therapy has also been approved. GLP-1 is an incretin hormone and is secreted from L cells in the intestine in response to food intake. It binds to the GLP-1 receptor that is coupled to a cAMP second messenger pathway [20]. GLP-1 has an important physiological function in augmenting postprandial insulin secretion. GLP-1-based antidiabetic drugs have drawn particular attention as an effective new strategy to regulate blood glucose and to reduce apoptotic cell death of pancreatic beta cells in type 2 diabetes mellitus [21]. An important disadvantage of GLP-1 is that it has a very short effective life of around 2–5 minutes in the blood [22]. To prolong the active half-life of GLP-1, modifications have been made to prevent it from being degraded by enzymes. Currently, exenatide, a potent and selective agonist for the GLP-1 receptor [9,13], is widely used for the treatment of type 2 diabetes mellitus [14].

NCAM, ICAM, and VCAM are cell adhesion molecules, which affect nervous system structure during development, and cause synaptic changes in the mature brain. These molecules also play roles in migration of cells, growth of axons, peripheral axon regeneration, and synaptic plasticity [23–25]. Expression of VCAM-1 and ICAM-1 has been shown to be significantly increased in multiple brain regions, including the partial frontal and temporal cerebral cortex, basal ganglia, hippocampus, and thalamus, in diabetic rats at 4 weeks after induction of diabetes [19]. Moreover, Baydas et al. [18] postulated that expression of NCAM alters in the hippocampus in diabetes mellitus. Herein, we studied the effects of exenatide treatment on gene levels of NCAM, ICAM, and VCAM in the hippocampus of STZ-NA-induced diabetic mice. Our results reveal that levels of these adhesion molecules were impaired in the diabetic animals and that exenatide treatment induces significant expression alterations in these adhesion molecules.

NCAM is expressed by Müller cells and astrocytes during normal developmental angiogenesis [26]. NCAM affects brain structure during development and plasticity of synapses in the adult brain. It was observed that NCAM was upregulated during the regeneration of retinal ganglion cells [27,28] and in chemically-induced brain damage [29]. Baydas et al. [18] postulated that STZ significantly increased NCAM 180 and NCAM 120 levels, while NCAM 140 was decreased in hippocampus of rats, and pointed out that NCAM expression was disturbed in diabetic mice.

ICAM-1, also known as CD54 (Cluster of Differentiation 54), is a protein that is encoded by the ICAM-1 gene in humans [30]. The ICAM-1 protein is continuously present in low concentrations in the membranes of leukocytes and endothelial cells, but its expression dramatically increases in response to proinflammatory stimuli [31]. Soluble ICAM-1 may modulate leukocyte adhesion and migration. Hyperglycemia upregulates cell adhesion molecules expressed on the vascular endothelium. Recent evidence suggests that ICAM-1 not only promotes atherogenesis [32] but also exacerbates organ damage [33]. It has been previously observed that ICAM is increased in diabetic animals after cerebral ischemia and reperfusion [34–36]. Jing et al. [34] postulated that ICAM-1 mRNA and protein levels dramatically increased in brain cortical tissues after forebrain cerebral ischemia. Diabetic hyperglycemia further enhanced the up-regulation of ICAM-1 induced by ischemia. It is known that hyperglycemia upregulates ICAM-1 in vascular endothelial cells [37,38]. Diabetic hyperglycemia further increased the mRNA and protein levels of ICAM-1 in the frontal cortex compared with the normoglycemic ischemic animals. Previous studies have suggested that hyperglycemia may cause ICAM-1 increases through the activation of IL-1β and the p38 MAPK pathway [35,38].

VCAM-1 is one of the major endothelial receptors that mediate leukocyte adhesion to the vascular endothelium. It may play an important role in the pathogenesis of atherosclerosis because VCAM-1 function in leukocyte adhesion and transmigration is crucial and its expression is induced early in nascent atheroma plaques [39]. VCAM-1 expression increases under vascular stress conditions such as insulin resistance and chronic hyperglycemia [40].

Because the occurrence of diabetes is often associated with a variety of different genes and genetic factors (e.g., racial, heredity, and environment), more studies with larger sample sizes are needed in future studies to better understand the relationship between genetic analysis and disease [41]. In recent studies, the Fabp4 and Pten gene expression and correlation in the liver, muscle, and adipose tissues of type 2 diabetes mellitus (T2DM) rats was shown to be increased, suggesting that the increased expression of PTEN and FABP4 may play an important role in the insulin resistance of T2DM [42]. In another study, the correlation between the Apolipoprotein E (APO E) gene polymorphisms and diabetic nephropathy was investigated, and it was suggested that development of diabetic neuropathy was associated with APO E polymorphisms in Asian populations [43].

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Conclusions

Current diabetes therapy is a complex approach aimed at reducing plasma glucose concentration and preventing the development of or slowing the progression of already existing diabetic complications. The mechanisms by which diabetes changes the gene expression levels of cell adhesion molecules, and by which exenatide alters these changes, remain to be defined. The results of our study indicate that cell adhesion molecules may be involved in the molecular mechanism of diabetes and exenatide because altering gene expression of NCAM, ICAM, and VCAM is a promising approach to managing type 2 diabetes.

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