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ORIGINAL ARTICLE

Dystonin/BPAG1 modulates diabetes and Alzheimer's disease cross-talk: a meta-analysis

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Abstract

Dementia is one of the diabetic complications under intensive study. Alteration of synaptic adhesion protein (SAP) associates with neurological diseases, including Alzheimer's disease. However, the regulation of SAPs in the brain of diabetes mellitus remains elusive. To pinpoint the candidate SAPs underlining the mechanism of diabetic dementia, we investigated expression profiling of SAPs in both streptozotocin (STZ)-induced diabetic mice, $App^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ mice, and amyloid precursor protein intracellular domain (AICD)-induced human neural cell line from public databases. *DST* (Dystonin/*BPAG1*) was identified upregulated in both models. Our finding suggests that DST alteration may involve in the mechanism of diabetic dementia.

Keywords Synaptic adhesion protein · Dystonin · Diabetic dementia

Abbreviations

SAP	Synaptic adhesion protein
STZ	Streptozotocin
AICD	Amyloid precursor protein intracellular domain
AD	Alzheimer's disease
BP	Bullous pemphigoid

Introduction

Diabetes mellitus is characterized by chronic hyperglycemia and various complications, such as microvascular disease, diabetic neuropathy, diabetic retinopathy, and vascular dementia [1, 2]. However, whether diabetes is associated with Alzheimer's disease remains controversial [3–7].

Jack Cheng, Hsin-Ping Liu and Su-Lun Hwang contributed equally to this work.

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Alzheimer's disease (AD) is characterized by amyloid-β aggregation in the hippocampus and resulting cognitive deficits. Interestingly, a recent study highlights the role of synaptic adhesion protein (SAP) may play on the progress of AD. Neural cell adhesion molecule 2 (NCAM2) is an enriched human hippocampal SAP, but decreased in AD patients and found degraded in mice overexpressing the human amyloid-β and resulted in disassembly of GluR1-containing glutamatergic synapses [8].

Signals of sensory organ and activity of mind, including learning, memory, perception, and decision making, are conveyed and processed through the neural signal transmission. These signals are passed from neural to neural through synapses. SAPs assemble and regulate pre- and post-synapse and links trans-synaptic junctions. Besides structure stability, SAPs mediate trans-synaptic recognition and signaling processes and involve in the regulation of synaptic plasticity [9–11].

Besides *NCAM2*, several SAPs associated with neurological disease. Mutation in neural adhesion molecule L1 (*L1CAM*) causes corpus callosum hypoplasia, retardation, adducted thumbs, spastic paraplegia, and hydrocephalus [12]. The deficiency of the close homolog of L1 (*CHL1*) causes altered axonal projections, and abnormal behavior of mice responding to the environment [13]. Junctional adhesion molecule (JAM)-C deficiency causes severe hydrocephalus in mice [14]. Beta-catenin mutations in mice cause intellectual disability [15].

Moreover, dysregulated SAPs may contribute to neurological symptoms through mediating synaptic structure, function, and stability. Diabetes is a risk factor for neurological disease, especially dementia. However, SAPs regulation in the diabetic brain is still unclear. Thus, we hypothesized that similar dysregulated expression pattern might be an indicator of the involvement of that SAP in both diabetic and dementia. Since the phenotype-based genetic association studies accelerated understanding of AD in recent years [16, 17], we performed an analysis to identify dysregulated SAPs, which may lead to dementia in diabetes mellitus.

Material and methods

Gene list of synaptic adhesion protein

List of genes encoding synaptic proteins was retrieved from SynDB [18]. These genes were uploaded to National Institute of Allergy and Infectious Diseases (NIAID) DAVID Bioinformatics Resources [19] for Gene Ontology annotation. Those annotated with biological process adhesion were collected as screening targets in this study and denoted as synaptic adhesion proteins (SAP).

NCBI GEO datasets

Expression profiles used in this study were retrieved from National Center for Biotechnology Information (NCBI) Gene Expression Omnibus database, including GEO: GSE62013 for STZ-induced diabetic mice [20], GSE92926 for $App^{NL-G-F/NL-G-F}$ mice [21], and GEO: GSE4097 for AICD-induced human neural cell line [22]. The mRNA expression of profiling of SAP was extracted and presented as bar charts, with omitting those with less than 10% of the difference in fold change relative to control.

Statistics

Student's *t* test was used to evaluate the significance of the difference between groups. The difference was considered to be significant for p value < 0.05 and was denoted with an "*" sign in the graph.

Results

Out of 1814 synaptic proteins in *Mus musculus* retrieved from SynDB [18] (supplementary table 1), 217 were annotated with Gene Ontology biological process cell adhesion (GO:0007155), 217 with biological adhesion (GO:0022610), 101 with regulation of cell adhesion (GO:0030155), 141 with cell-cell adhesion (GO:0098609), and 35 with regulation of cell-substrate adhesion (GO:0010810). Removing duplicated ones, a list of non-redundant 221 synaptic adhesion proteins (SAP) (supplementary table 2) served as screen targets in the following analysis. The screening strategy was illustrated in Fig. 1.

To identify the dysregulated synaptic adhesion protein in the brain of the diabetic mice, we observed expression pattern of SAP genes in the hypothalamus of streptozotocin (STZ)-induced diabetic mice [20]. Out of the 221 SAPs, only 195 were available in the dataset and profiled (supplementary table 3), with 14 showing significant change compared to the control, as shown in Fig. 2. Five genes, including *Cntn4* (Contactin-4), *Col5a1* (Collagen alpha-1(V)), *Dst* (Dystonin/*BPAG1*), *Lamb2* (laminin beta2), and *Tgfb1* (Transforming growth factor beta-1), were upregulated, while other nine genes were downregulated compared to control.

To further screen whether these 14 genes participate in neurological disease, we observed their expression pattern in the brain of $App^{NL-G-F/NL-G-F}$ mice [21], which pathogenic Aβ are raised because of carrying three mutations related to familial Alzheimer's disease. The fold change of these 14 SAPs was profiled. Among these 14 SAPs, only *Bcl2*, *Dst*, *Lamb2*, and *Tgfb1* showed significant change compared to the non-transgenic control (Fig. 3). Therefore, the other 10 SAPs with non-significant

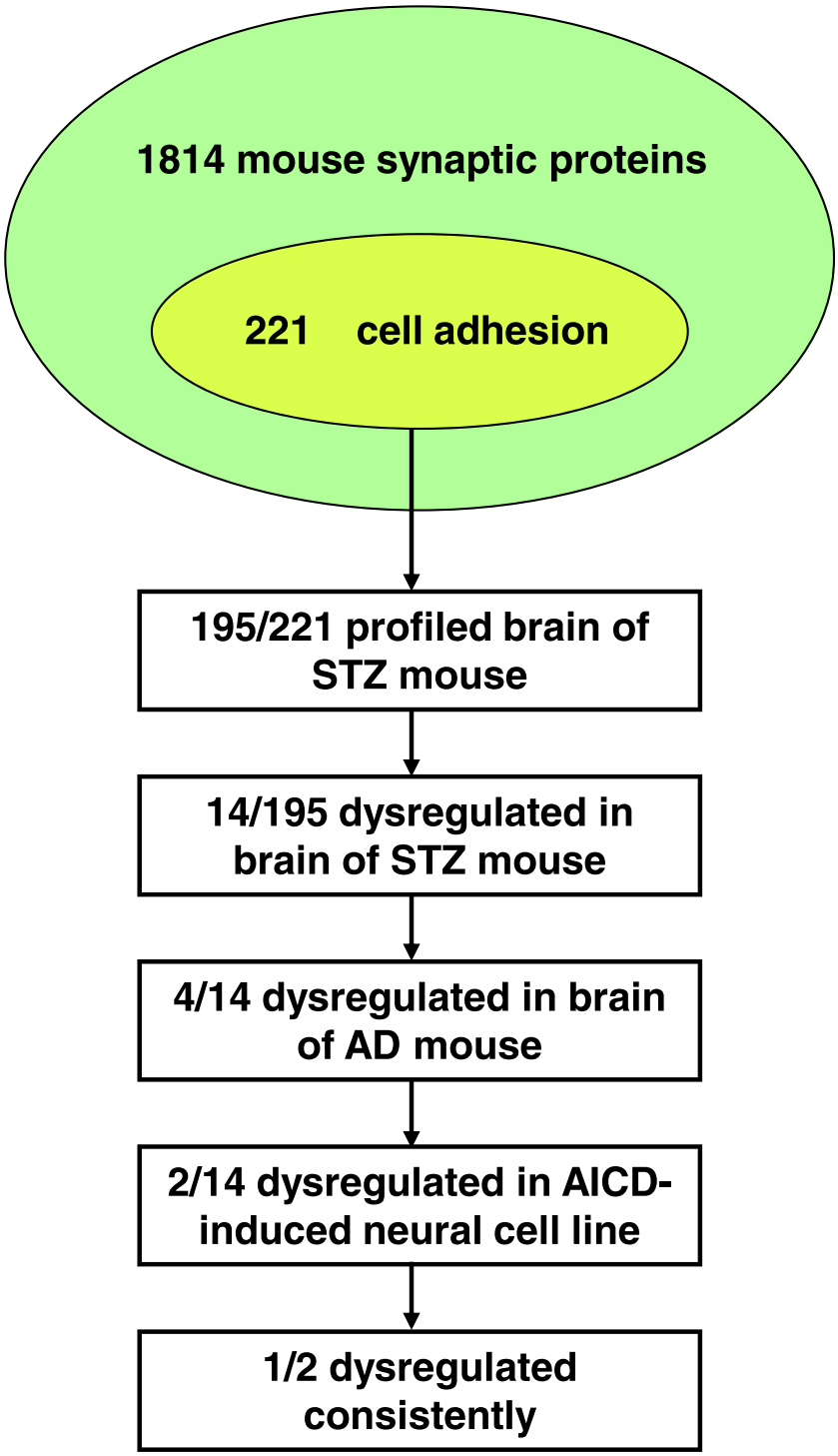

Fig. 1 Strategy for screening candidate synaptic adhesion protein, which is dysregulated in diabetes mellitus and may lead to dementia

expression were ruled out in this stage. However, the raw expression data of these 14 SAPs were extracted in supplementary table 4 for reference.

To further screen whether these four genes participate in neurological disease, we observed their expression pattern in amyloid precursor protein intracellular domain (AICD)-induced human neural cell line, which characterized by destabilization of the actin cytoskeleton and clustering of actin near cellular membrane [22]. These four SAPs was profiled (Fig. 4, supplementary table 5 and 6). Among these 4 SAPs, only *DST* showed significant change compared to control. While the expression patterns of *Lamb2* in STZ-induced mice and *LAMB2* in AICD-induced cell were opposite to each other, the expression patterns of *DST* showed consistent upregulation in both diabetic and neurodegeneration models.

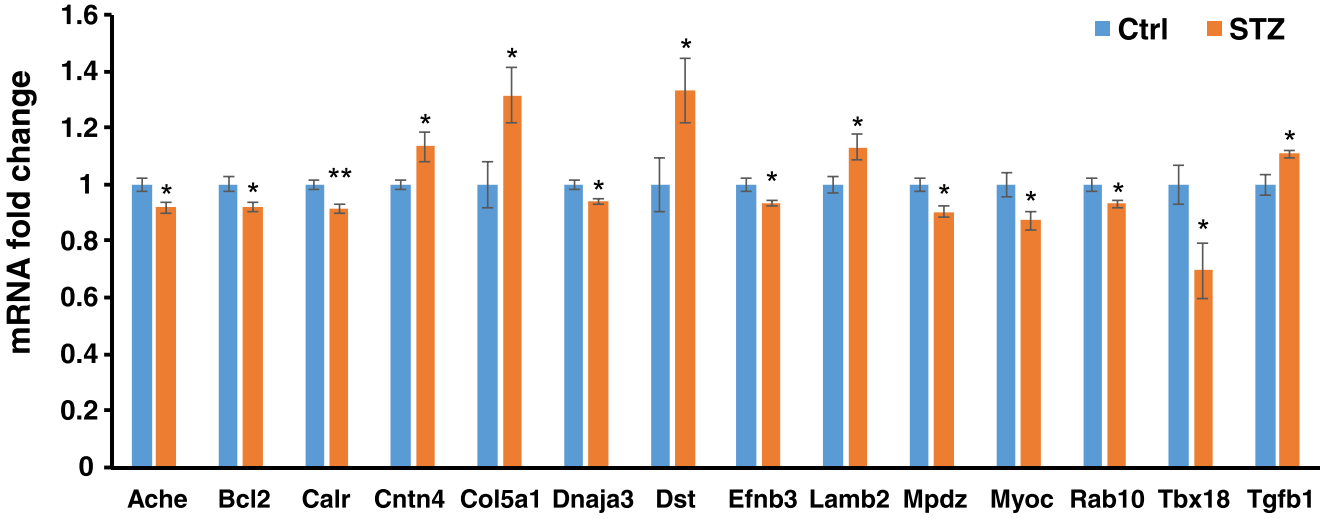

Fig. 2 Transcription level of synaptic adhesion protein in the brain of streptozotocin (STZ)-induced diabetic mouse. Gene expression fold change relative to control. Data are represented as mean ± SEM. Single asterisk and double asterisk is denoted for p value < 0.05 and 0.01 for Student's t test respectively. *Ache*, acetylcholinesterase; *Bcl2*, B cell leukemia/lymphoma 2; *Calr*, calreticulin; *Cntn4*, contactin 4; *Col5a1*, collagen type V alpha 1; *Dnaja3*, DnaJ heat shock protein family (Hsp40) member A3; *Dst*, dystonin; *Efnb3*, ephrin B3; *Lamb2*, laminin alpha 2; *Mpdz*, multiple PDZ domain protein; *Myoc*, myocilin; *Rab10*, RAB10 member RAS oncogene family; *Tbx18*, T-box18; *Tgfb1*, transforming growth factor beta 1

Discussion

In this study, we screened the expression for the SAPs in the diabetic brain and identified dysregulation of 14 genes including *DST*. We further screened the expression of these genes in AICD-induced human neural cell line and observed the consistent pattern of DST upregulation.

The pancreatic β cells, which secrets insulin, appear to have evolved from a neuronal precursor [23] and share many features with neurons in the central nervous system, such as the infrastructure and the function to express the neurotransmitter GABA [24]. Moreover, the SAPs neuroligin and neurexin have been identified to regulate glucose-stimulated insulin secretion [25]. Therefore, our finding that SAPs dysregulation under diabetic circumstances may imply the perspective that the involvement of insulin metabolism in the regulation of SAPs also in the neurons, but not only in the pancreatic β cells.

DST gene encodes dystonin protein, with multiple isoforms of large size expressed in neurons, is a group of the cytoskeletal linker, interacting with actin, microtubule, networks, cellular membrane, or membrane-bound organelles [26, 27].

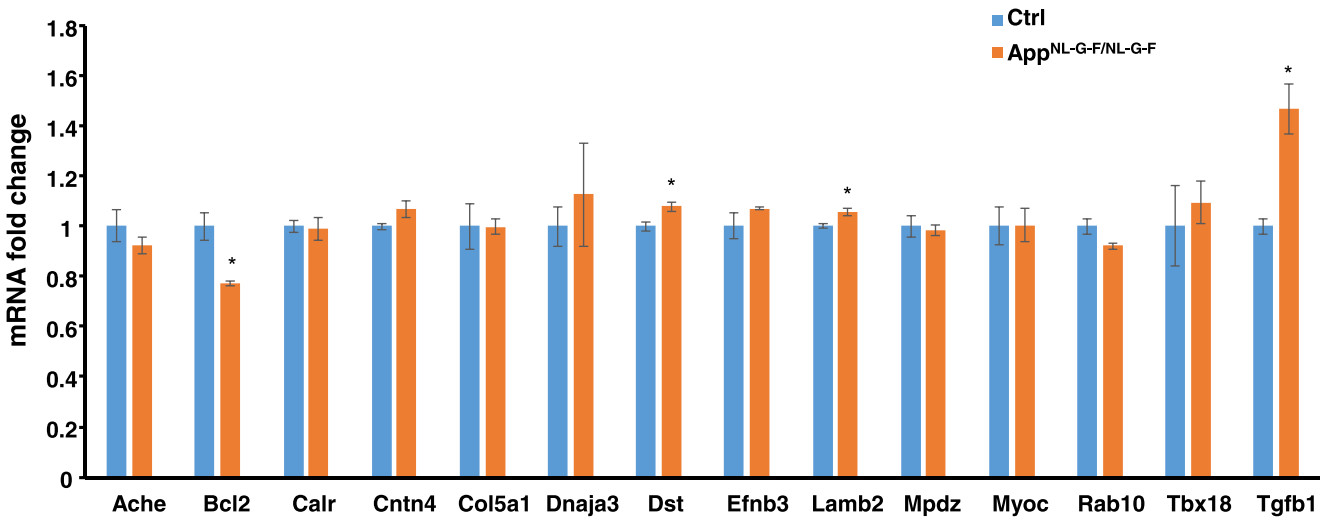

Fig. 3 Transcription level of synaptic adhesion protein in brain of mouse model of App$^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$. Gene expression fold change relative to control. Data are represented as mean ± SEM. *ACHE*, acetylcholinesterase; *BCL2*, B cell leukemia/lymphoma 2; *CALR*, calreticulin; *COL5A1*, collagen type V alpha 1; *DNAJA3*, DnaJ heat shock protein family (Hsp40) member A3; *DST*, dystonin; *EFNB3*, ephrin B3; *LAMB2*, laminin alpha 2; *MPDZ*, multiple PDZ domain protein; *MYOC*, myocilin; *TGFB1*, transforming growth factor beta 1

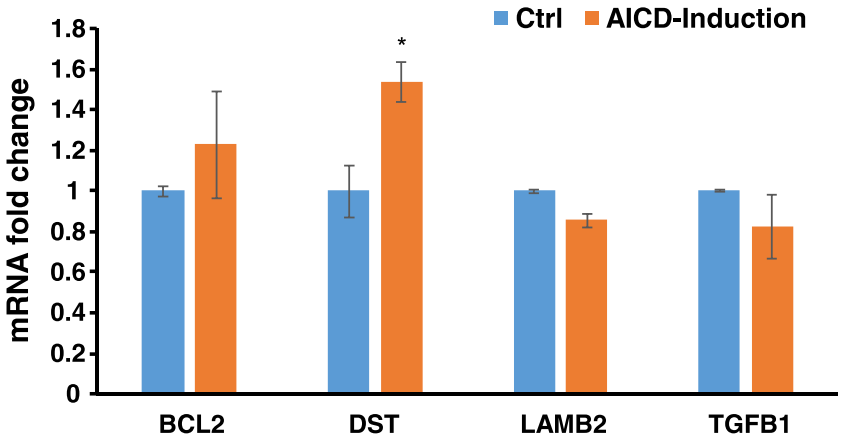

Fig. 4 Transcription level of synaptic adhesion protein in human neural cell line with APP intracellular domain (AICD) induction. Gene expression fold change relative to control. Data are represented as mean ± SEM. *BCL2*, B cell leukemia/lymphoma 2; *DST*, dystonin; *LAMB2*, laminin alpha 2; *TGFB1*, transforming growth factor beta 1

Dystonin participates in construction and stability of cytoskeleton, intracellular transportation, and maintenance of organelle integrity. DST knock-out mice harbor a lethal symptom called dystonia musculorum, which may be resulted from neuron degeneration [27].

DST, also known as *BPAG1*, which stands for Bullous pemphigoid (BP) antigen 1, is the marker of this disease. BP is a subepidermal blistering disease involving autoimmune response [28] and is significantly associated with the neurological disorder, including dementia, epilepsy, multiple sclerosis, cerebral stroke, and Parkinson's disease [29]. Independent studies confirmed the BP association with neurological and psychiatric diseases, especially dementia [30, 31]. Although autoimmune response in BP was speculated to involve in neurological diseases [29], and the mechanism requires further study, as a hallmark of BP, DST overexpression associates with dementia. Moreover, *DST* overexpression can be observed in the AICD-induced human neural cell line. These shreds of evidence suggested that *DST* overexpression may be a common phenomenon, or even a driving force, for the progression of neurological diseases, especially dementia.

Interestingly, the occurrence rate of diabetes in BP patients is significantly higher than that of the non-BP control (20~23% and 2.5~3.6% respectively) [32]. Moreover, BP can be induced in diabetic patients by administration of dipeptidyl peptidase-4 inhibitors [33, 34]. However, the causative relation linking BP and diabetes is not well established until now [35]. Therefore, our finding that DST dysregulation under diabetic circumstances may imply the genetic event as a clue to pinpoint the underlying mechanism.

In conclusion, we identified *DST* to be the only SAP gene consistently dysregulated in both brains of STZ-induced mice and AICD-induced neural cell model. SAP dysregulation may lead to instability of synapse and hence neurological disorders. This study is the first to highlight *DST* dysregulation in diabetes mellitus may contribute to dementia.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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