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Investigating the Link Between Alzheimer's Disease and Type 2 Diabetes Mellitus

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ABSTRACT

Within the body, enzymes play an essential role in maintaining the homeostasis. Inadequate actions of enzymes are linked to several illnesses. The primary attention on IDE as a protease enzyme involved in the degradation of insulin hormone and then has extended in last 20 years due to its numerous unique characters of the enzyme in relations to structure, function and sub cellular localization. Now evidence gradually supporting the idea that IDE might be participating in the human diseases pathogenesis like AD or T2DM. AD and T2DM are linked by the accumulation of protein aggregates called as amyloid fibrils. Despite the absence of sequence similarity between amyloidogenic proteins, all amyloid fibrils share a usual morphology, all have a β-sheet structure and are unsolvable in physiological situations and are uninfluenced by proteolytic degradation. Thus, cells evolutionary developed systems to degrade amyloidogenic species before their accumulation. Molecular chaperones are one example of such system; they help proper protein folding and stop the accumulation of misfolded proteins.

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Recent Findings:

According to Duckworth et al., 1975, the primary cleavage by the IDE enzyme seems to happen in the B-chain of insulin and further contact of a hormone to the enzyme results in several additional cleavages. As Duckworth, et al. in 1989 stated extraction and sequencing of the breakdown fragments produced from insulin by IDE action, show that the enzyme cuts the A chain of hormone at two sites and the B chain at seven sites. The determination of other characteristics and features of the enzyme like specificity and the exact linkages of an enzyme to substrate molecule required enzyme crystallization.

Summary:

In past IDE, isolated and purified from numerous mammalian tissues, such as red blood cells, skeletal muscle, liver, and brain. An enzyme in purified form contains a single polypeptide chain with a mass of 110 kDa on denaturing polyacrylamide gels. However studied by Shii et al. in 1986 under non-denaturing situations showed, IDE has a molecular weight of 300 kDa, implying that it happens as a mixture of monomer, dimer or trimer forms. Shen and colleagues in 2006 show high-resolution crystal forms of IDE in mixed with four IDE substrates which are insulin B chain, Aβ 40, amylin, and glucagon. The 3-D structures revealed that every IDE monomer is built of two halves (IDE-N, residues 43-515 and IDE-C, residues 542-1016) connected by a 28-residueextended loop (residues 516-542) and form an enclosed chamber, which keep the degradation chamber of IDE remote to substrates and repositioning of these domains allows substrate enter the catalytic chamber (Fernandez Gamba, Leal et al. 2009). By introducing mutations to the enzyme which interrupting the links between IDE-N and IDE-C, Shen and colleagues in 2006 were able to rise IDE catalytic activity 40-fold. Each half is composed of two α/β roll domains (domain 1, start from residues 43 and ended to residue 285; domain 2, start from residues 286 and ended to residue 515; domain 3, start from residues 542 and ended to residue 768; and domain 4, start from residues 769 and ended to residue 1,016) they share almost 22 % sequence similarity. the catalytic site of the enzyme located in IDE-N with the Zn2+-coordinating triplet residue of H108, H112 and E189 and the water-activating E111

side chains. IDE-N and IDE-C have large connections and form a space that is sufficient to accommodate a target with the size of a folded insulin molecule. Structure elucidation by X-ray crystallography of human IDE crystal, suggests that the IDE selects its substrate on the basis of size and charge distribution. The catalytic chamber of an enzyme is big enough to fit only relatively short peptides (most likely to be of IDE, IDEo can bind substrates and IDEc cannot, however, IDEc is able to degraded substrate after substrates are captured within the catalytic cavity. The crystal structure of a substrate free IDE by Im et al., in 2007, shows the "closed" state is a more stable structure. The substrate inside catalytic chamber undergoes structural changes to form β- pleats with two distinct areas of IDE for its degradation. IDE cuts insulin B chain, Aß, amylin, and glucagon at several locations. Shen, et al., IDE–substrate structures reveal that the C termini of insulin B chain, Aß and amylin make large connections with the inner cavity of IDE, which is extremely positively charged. Additionally, Glucagon, ANPs, and IGF-II, which at their C termini lacks positive charges, are excellent IDE targets, therefore substrates which in their C terminus sequence lakes substantial positive charges and avoid the charge repulsion from IDE-C are better IDE targets. IDE, is a highly conserved thiol-metalloendo peptidase, with a thiol group required for activity, it is categorized as member of M16A family of metallopeptidases described by an inversion sequence at the catalytic site (HxxEH) which identified by site-directed mutagenesis study and as compared to the usual sequence His-Glu-Xaa-Xaa-His (HExxH) seen in neprilysin (NEP) (M13 family) and other members of the family. Due to this inverted arrangement of catalytic site residue, IDE has been attributed to a new super family of metalloprotease,. The MEROPS database of peptide places this enzyme in the M16 class, the family is identified by a letter "M" representing the catalytic type of the proteolytic enzymes i.e., metalloprotease along with a unique number 16. The M16 family is further subdivided into three sub families namely M16A, M16B, and M16C. IDE is included in the M16A subfamily along with pitrilysin, M16B includes mitochondrial processing peptidase beta subunit (Saccharomyces cerevisiae) and M16C includes eupitrilysin (Homo sapiens). Optimum pH for IDE action is at neutral pH (7.0-8.0)[1].

IDE Sub cellular Localizations

50-95 % of IDE activity was found to be cytoplasmic. Authier et al., 1995 and Rabkin et al., 1992 found small amounts of IDE on the plasma membrane, endosomes, and peroxisomes. Peroxisomes contain the highest relative IDE levels (i.e., enzyme per mg protein), which is not shocking because IDE has a peroxisomal targeting sequence. Even with this targeting sequence, peroxisomes organelles have a tiny part (1-2%) of the total cellular IDE.

IDE Expression, Biochemistry

In Human, IDE enzyme is produced as a single polypeptide with 1019 amino acids residues coded by a gene mapped to chromosome 10q. It discovered in nearly every tissue and cell type tested and almost ubiquitously distributed in all sub cellular location. Several line of evidence with in vitro studies, cell transfection, inhibition with monoclonal antibodies and IDE-deficient mice, suggested IDE as a major protease in insulin catabolism[2]. Despite its function in insulin degradation, information about how IDE expression is controlled is limited. Multiple IDE mRNA ranges have been found, that can be categorized into those with a long 3'UTR (~2 to 6 kb) and those with a very short 3'UTR (~300 b). Biochemical characters of IDE have been widely analyzed using purified enzyme from various sources and have proven that IDE accumulates as a stable homo dimer.

IDE Function

IDE is a highly conserved multifunctional protein. It appears some of its roles are associated with its catalytic action, whereas other roles seem to be independent of proteolysis.

IDE regulates the levels of insulin, Ab in vivo

Two IDE substrates, insulin and Ab, are central keys in the T2DM and AD pathogenesis, respectively. Additionally, to its role in insulin degradation, IDE also destroy Ab in neuronal and microglial cell cultures. Kurochkin in 1994 shown IDE hydrolyses A b. Farris, et al., 2003 reported that IDE deficiency caused by a >50% reduction in Aβ degradation and a similar deficit in insulin degradation in the liver. The IDE −/− mice indicated increased cerebral accumulation of endogenous Ab, a hallmark of AD, and had hyperinsulinemia and glucose intolerance, hallmarks of T2DM. Altogether Farris, et al., reports suggest that IDE hypo function may participate to AD and T2DM. Morelli, results showed that recombinant rat IDE (rIDE) was capable of destroying all of the synthetic Ab variations related to human disease. In 2004, Farris showed that missense mutations which naturally happening within IDE gene in a GK rat model of T2DM reduced 15 to 30% catalytic efficiency of IDE enzyme in the degradation of both insulin and Ab.

Type 2 Diabetes Mellitus (T2DM)

Multiple lines of evidence from biochemical and genetic study point to the possibility that IDE is participated in the T2DM pathogenesis. In T2DM

Goto-Kakizaki rat model, missense mutations causing switches in two amino acids (H18R and A890V) were these changes are related to hyperglycemia. Additionally, cell transfection studies revealed that these two mutations were essential to decrease IDE function by 30%. In another animal model experiments, IDE-null mice indicated a ~3-fold rise in insulin concentrations and significant hyperglycemia as compared to wild-type animals. Concerning IDE concentrations in human's with T2DM, an mRNA expression, and proteomic study revealed that IDE, amongst other factors of the insulin pathway, was considerably decreased in T-cells and muscle tissue of T2DM patients as compared to controls. It appears that the biological function of IDE in insulin homeostasis is disturbed in the insulin resistance situations. If, in neurons, as it has been shown, IDE expression is under insulin signaling in peripheral tissues, insulin resistance results in lower IDE levels and slower insulin degradation. It is known that persistent insulin stimulation eventually results in insulin resistance that may sustain the reduction in IDE expression. Additionally, an indirect way by which IDE may influence T2DM is the breakdown of amylin, another amyloidogenic peptide that accumulates in the islets and participates to pancreatic cell damage.

Alzheimer's disease (AD)

There is convincing data for the contribution of IDE in the course of Aß deposition in the brain. The expression and action of IDE have been reported to be decreased in the hippocampus and cortex in the brain of AD patients. As showed by Morelli et al. in 2004 with the use of sandwich ELISA in cortical micro vessels from AD brains affected with broad cerebrovascular Aß accumulation, IDE levels were raised, and still, its action was highly decreased, indicating inhibition or inactivation of the protease. As Caccamo et al., 2005 and Shinall et al., 2005, suggested that part of the loss of IDE action in AD brain is due to posttranslational alterations such as oxidative damage in susceptible areas of the CNS, to which IDE is very sensitive. However, it is remarkable to note that in three different transgenic mice models of familial AD, IDE raises its expression and activity in reaction to Aß deposition and in the link to astroglial activation around the plaques. These data indicate that the anomalies in IDE expression, processing or action found in AD are not the results of Aβ accumulation and could rather happen as part of upstream mechanisms in the AD pathogenesis

IDE: A link between Alzheimer's and type 2 diabetes mellitus

In both diseases, a locally expressed protein is accumulated in amyloid deposits with a gradual decline in the number of cells of the respective proteins. One of the links between T2DM and AD are reported by Janson et al., in 2004, which is Amyloid deposition in islet and brain cells, they stated there is more islet amyloid in AD patients than controls. In T2DM patients with brain amyloid, the level of amyloid raised with longer duration of T2DM. Accumulation of amyloid in the brain and pancreatic islet cells signifies a pathogenic relationship among AD and T2DM. A study of transgenic mice establishes that extra deposition of pancreatic amyloid cause to β-cell dysfunction, trouble in glucose homeostasis and T2DM. A study in humans by Miklossy et al., in 2010 reported on autopsy, islet amyloid polypeptide and hyper phosphorylated tau were discovered in pancreatic islet cells of subjects with T2DM. Additionally, study by Peila et al., in 2002 revealed that a raised amount of amyloid plaques and neurofibrillary tangles in the hippocampus have been discovered on autopsy in diabetes patients. A community-based study shows islet amyloid was more frequent in AD subjects than in non-AD controls, but there was no raised frequency of brain amyloid in T2DM subjects compared with no diabetic controls. Although, Janson et al., in 2004 reported when cerebral amyloid was present, the degree of deposition linked with the duration of T2DM. T2DM and AD are illustrated by similar pathological descriptions in the islet and brain (Aß polypeptide in the brain of AD patients and islet amyloid originated from islet amyloid polypeptide (IAPP) in the pancreas in T2DM. Aß and IAPP can naturally form into amyloid aggregates. Small amyloid aggregates of either of these two polypeptides are cytotoxic. In the case of IAPP, evidence reports by O'Brien et al., 1995 which propose that abnormal accumulation happens originally intracellularly, and after cell death, these fibrils accumulate intracellularly. Likewise, a parallel procedure is happening in AD. Schwartz et al., in 1965 suggested that there might be an association between amyloid deposits in the brain and islets of pancreatic. The frequency of Islet amyloid was more in AD patients than in control subjects. Although, brain amyloid was not increased in patients with T2DM compared with control subjects, however the concentration of diffuse and neuritic plaques, when present, was related to the duration of T2DM. Ott 1999 and Arvanitakis 2004 suggested T2DM as a risk factor for AD, based on their frequent co-occurrence. A study by Watson in 2003 revealed that rising insulin concentration in human rises Aß concentration in CSF, signifying that chronically high insulin concentration may enhance the deposition of Aß in the brain as amyloid plaques. It has been suggested

that there might be competition among insulin and Aß for degradation by the IDE enzyme. According to Qiu 1998; Vekrellis 2000, IDE degrades both extracellular Aß -protein and the intracellular domain of APP. Animal models studies by Farris and Miller in 2003, have also revealed that absence of IDE rises Aß accumulation in mouse brain. Kurochkin and Goto (1994) reported the initial evidence that IDE involved in Aß 42 degradation, they established that rat IDE in purified form, efficiently degrades synthetic Ab 42 in vitro. Consequently, McDermott, Gibson 1997, and Perez et al., 2000 showed that an IDE-like action from soluble and synaptic membrane fractions of post-mortem human brain both degrade Aß 42 peptides; furthermore, Qiu et al., 1998 stated that IDE doesn't differentiate between endogenous and synthetic Aß 42 as substrate in vitro. Insulin as a substrate with low Km (Km =∼0.1 μM) competes with another substrate of IDE, Aß (Km >2 μM), thus, if the insulin concentration rises in the brain, it would prevent IDE to cuts Aß efficiently, and subsequently cause Aß neurotoxicity, and then AD. In agreement with this, it has been suggested by Cook 2003, Craft 2000 and Ling 2002, that Aß deposition in AD can be raised by excessive concentration of insulin. According to Gasparini in 2001, Insulin is believed to help decrease Ab toxicity by raising its cellular release and stimulating tissue clearance. In cell cultures, it was revealed that insulin reduces intracellular levels of Ab 42. A study by Shiiki et al., 2004, revealed that Ab 40 removal from the brain was reduced by 30% in old rats, while inhibitors of neprilysin and IDE reduced Ab efflux by 25% to 30%. In the same report, the co-administration of insulin with Ab 40 decreased the removal rate of Ab 40 and raised the level of unbroken Ab 40 in the brain. The outcomes of this report match those found in humans by Watson et al., 2003, in which systemic insulin infusions led to a rise in CSF Ab 42. One option is that insulin competes with Ab 40 for transcytosis transport using the insulin receptor at the BBB. Though, insulin receptor kinase inhibitor failed to affect Ab clearance rate. Decreased in insulin signaling correlated with reduced IDE levels and increased Aß levels. In the STZ model, reduced insulin signaling due to lack of insulin may lead to down regulation of IDE concentration, likewise causing to increased deposition of Aß and raised AD risk. Insulin signaling participates in several brain functions involving cognition and memory that are reduced in AD. Actually, insulin resistance raised inflammation and reduced metabolism is key pathological features of both AD and diabetes. Furthermore, pharmacological blocked of IDE decreases insulin degradation, amylin, and Aß, The link between Aß metabolism and insulin is getting increasing attention. As the report by Solano 2000 and Gasparini 2001 showed insulin treatment raised sAPPα secretion and also decreased the Aß deposition in neuronal cells. It has been showed by Mattson, in 1997, that insulin can defend neurons from Aß -induced neurotoxicity. Thus, sAPPα may role in modulation of synaptic plasticity, neurite outgrowth, synaptogenesis, and cell survival. Insulin also control the extracellular degradation of Aß through IDE. Insulin concentration can regulate IDE expression. According to Zhao 2004 report, Insulin by phosphatidylinositol3-kinase (PI3K) pathway rises IDE protein levels. In this regards, IDE knockout mice showed raised cerebral Aß levels. In contrast, over expression of IDE in the APP double transgenic mice reduced their brain Aß concentration, and stopped Aß plaque formation. Additional support for this connection was offered by the results that lacking insulin signaling (decreased PI3K subunit P85) was linked with decreased IDE in AD brains and in transgenic mice as mentioned by Zhao in 2004. Aß degrading action of IDE was revealed to be lower in AD brains compared to controls. On the other hand, Aß oligomers cause rapid and major interruption of signaling by brain cell IRs. It has been established by Zhao 2008; de Felice 2009, treatment with Aß oligomer to hippocampus produced a rapid and extensive loss of neuronal surface IRs explicitly on dendrites bound. Aß oligomer-treated neurons revealed raised levels of IRs in their cell bodies, signifying redistribution of IRs. This leads to reduced reaction to insulin. Consistent with this hypothesis De Felice, indicated that Aß oligomer caused major down regulation of membrane surface IRs. Aß oligomer-induced loss of membrane IRs might represent an important early mechanism underlying memory impairment and other pathological features of AD. Additional study in this field by de Felice has shown that Aß oligomers-induced neuronal oxidative stress. Additionally, it has been established by Bomfim 2012 that Aß oligomerinduces increase in pro inflammatory tumor necrosis factor-alpha (TNF-α) levels and it causes unusual activation of a c-Jun N-terminal kinase (JNK) in neurons, which eventually leads to serine phosphorylation of IRS-1. IRS-1 serine phosphorylation blocks the downstream insulin signaling, which activates, in turn, peripheral insulin resistance as showed by de Felice, (2013).

IDE polymorphism

The IDE gene is mapped on chromosome 10q and coding area and non-coding area, of this gene during evolution are highly conserved. Genetic studies in humans are still controversial about the possible relationship of polymorphisms or haplotypes in the

IDE gene and the risk for T2DM and AD. Yet, population background may play a part in these divergent results. For instance, associations of IDE polymorphisms with T2DM in Finnish and Korean populations have been reported[4]. Identification of characterization of genetics risk factors is one of the great interest in studies of diseases. Several different lines of evidence suggest a role for the gene coding the IDE in AD and T2DM, concluding IDE gene as a promising candidate for analysis:

1. Studies have recognized a possible role that IDE plays in the degradation and clearance of Ab from microglial cells and neurons;
2. The gene coding IDE is found on chromosome 10q23–q25, in an area which is a susceptibility locus for AD, has been mapped via several independent linkage studies by Bertram, et al., Myers, et al. and Pericak-Vance, et al., in 2000 and Li 2002. These Linkage reports have highlighted there is a susceptibility gene for AD in a wide genomic area of almost 460 Mb of chromosome 10, within which many genes are located.
3. Additionally, other linkage studies also have found a susceptibility gene for T2DM in the almost same area as AD susceptibility gene mapped to chromosome 10. IDE is a candidate gene in this area, which is in the Goto-Kakizaki rat model, has been linked with non-obese T2DM. IDE activity is reduced by 30% in the diabetic GK rat model.
4. A report by Cook 2003 revealed that the levels of IDE mRNA in the hippocampus of AD patients in present of ApoE ε4 allele were considerably lesser than AD and control subjects without the ApoE ε4 allele. The output of these results indicates that decrease IDE expression is related with the high-risk factor for AD and suggests that IDE may cooperate with ApoE to affect Aβ metabolism.
5. According to a study of Ertekin-Taner, in 2000, a risk for AD and plasma Aß levels, show linkage to chromosome 10q.
6. According to a study of Farris et al., 2003, IDE-null mice model of T2DM show high levels of insulin and glucose intolerance.

Therefore, IDE gene is a functional and positional candidate for both diseases. Consequently, scientist tries by studies of different IDE polymorphism, find some connection between these two diseases and IDE gene, I will review some of this publication in below: In 2001, Abraham, et al., analyzed all of the axons, untranslated areas plus 1000 bp of the 5′flanking sequence of IDE gene, they detected eight SNPs, five in the coding sequence and three in the 5′ flanking sequence. None of them altered the amino acid sequence and no major connection was found with any SNP independently in any of the subjects or with any haplotypes. In 2000, Bertram et al. in an Original report by studies familiar AD subjects, indicate genetic marker, the microsatellite D10S583 have a maximum LOD score for AD, which is actually mapped at 36 kb 5′ to axon 1 of the IDE gene (in KNSL1) (Figure 2.7), as a linkage between IDE and AD, but study of the same marker by Cardiff in a case-control study and also by Abraham, Myers et al. 2001 was clearly negative (Abraham, Myers et al. 2001). Boussahaa, et al., 2002 studied ten SNPs in IDE gene, but they report does not reveal any important connection between SNPs of the IDE gene and AD. Karamohamed, Demissie et al. in 2003 report that rs1887922 SNPs in 3' termination of IDE shown association with HbA1c levels, fasting plasma glucose (FPG), and mean fasting plasma glucose (mFPG).

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