Diabetes & its Complications

Sugary Insights: A Biochemical Perspective

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ABSTRACT

Diabetes mellitus (DM) is a disease of the peripheral organs while Diabetes inspidus (DI) is a disease of the brain. Both forms of diabetes are characterized by excess levels of blood sugar or glucose. Whereas the former is due to insulin resistance or insufficiency the latter is due to insufficiency of hypophyseal anti-diuretic hormone (ADH). But the causes underlying the accumulation of glucose in circulation are different for DM and DI. Diabetes mellitus is of two types. While type1 diabetes (T1D) is due to autoimmune destruction of insulin-producing pancreatic islets of Langerhans (IL), type 2 diabetes (T2D) is a lifestyle disease due to exhaustion of IL to produce insulin in response to hyperglycemia. Whereas glucose fuel unavailability in the mitochondria leads to deficit of energy production in the form of ATP, its accumulation in blood leads to complications due to inflammatory damage to blood vessels. Recently, Alzheimer's disease (AD) has been hypothesized to be type3 Diabetes (T3D), presumably caused by insulin resistance in the brain, an organ absolutely dependent upon glucose as fuel for ATP biosynthesis. Whereas AD and DM are characterized by dementia and cognitive decline respectively, their known cellular biomarkers are different namely neuronal amyloid peptide (APβ), Tau, glial TDP-43 for AD and islet amyloid polypeptide (IAPP) for DM. DM also has a genetic component namely HLA-DQB1, CTLA-4, INS genes. Biomarkers of insulin receptor (IR) desensitization/functionality like neuron-specific GLUT-8 need to be demonstrated in mouse models of AD, DM and humans before irreversible senile dementia characteristic of AD can be equated with reversible cognitive decline of type 2 DM, for it may have additional yet unknown causes.

Keywords

Introduction

Diabetes mellitus (DM) and Alzheimer's disease (AD) are two seemingly different diseases which share certain features the most relevant of which being age related cognitive decline. The age factor has led to these features being termed as senile. While DM type1 has a genetic component, HLA-DQB1, CTLA-4, INS variant genes which manifest at a younger age and therefore classified as juvenile, type 2 the metabolic form manifests in older adults and therefore referred to as senile like AD [1]. The common basis for equating these two diseases is the belief that these are mediated via the insulin receptor. Nevertheless, whereas DM is essentially reversible AD is not. Notably, cognitive decline associated with altered insulin receptor function can be reversed with anti-diabetic measures but the memory loss of AD is irreversible. According to a current estimate, 20 million people are suffering from AD whereas DM cases are in far excess, around two hundred and fifty million, a clear indication that all DM patients do not necessarily progress to AD. Unlike DM, hyperglycemia is not a feature of AD and nor does insulin treatment increase brain glucose uptake, which leads to the perception that even though the two diseases have overlapping features, DM may not be the primary biochemical lesion in AD [2].

Perspective

Insulin receptor (IR), the central moiety implicated both in DM and AD, is expressed from a single gene located on human chromosome 19p 13.2–19p 13.3. It has 22 exons, 11 each of which encode a protein subunit α or β. Two isoforms of IR are generated by the alternative splicing of exon 11 in a tissue specific manner. IR-A with a shorter and less glycosylated α subunit is widely

distributed in brain while the longer more glycosylated isoform IR-B is expressed in peripheral classical insulin-sensitive tissues [3-4]. Insulin binds to α subunit of IR, activates its β subunit tyrosine-kinase activity by autophosphorylation and transduces signals through phosphorylation of insulin receptor substrates IR-1 and IR-2 [5-7].

Glucose uptake occurs via GLUT-1 to 8 transporters which have different cellular distribution as well as sensitivities to insulin and glucose, GLUT-4 and 8 being insulin and glucose sensitive isoforms. The expression of GLUT-I and GLUT-3, the major transporters in brain is reduced in AD. This would affect the availability of glucose. Impairment of glucose metabolism was evident from the affected levels of several glucose metabolizing enzymes of Krebs cycle and pentose phosphate shunt pathway, pyruvate dehydrogenase complex, α-ketoglutarate dehydrogenase complex, transketolase and thiamine diphosphate in the brain of AD patients [8,9].

Neurotoxicity of AD is attributed to extracellular amyloid plaques composed of the Aβ peptide released by the proteolytic cleavage of the transmembrane amyloid precursor protein (APP) and intracellular, neurofibrillary tangles (NFTs) composed of the hyperphosphorylated microtubule associated protein (MAP) tau protein while hyperglycemia-associated toxicity of islets of Langerhans in DM is due to impaired processing of pro Islet amyloid polypeptide (pro-IAPP) to IAPP leading to beta cell loss [10-15]. While aggregates of misfolded IAPP affect insulin secretion from pancreatic islets of Langerhans hyperglycemia leads to inflammatory cerebral damage namely neuropathy, retinopathy via vascular route [16,17].

Glycogen synthase kinase-3β (GSK-3β) is tau kinase involved in hyperphosphorylation. Inhibition of GSK-3β stimulates levels of anti-inflammatory cytokine, interleukin-10 (IL-10) and decreases the levels of pro-inflammatory cytokines via toll-like receptor, interleukin-1β (IL-1β), interleukin-6 (IL-6), interferon-Y (IFN-Y), implicated in regulating neuroinflammation [18]. Insulin mediated activation of IR exerts an inhibitory effect on GSK-3β activity via phosphorylation and thereby suppression of neuroinflammatory cytokine responses [19]. In vitro studies with isolated neurons challenged with synthetic Aβ oligomers have demonstrated activation of N-methyl-D-aspartate receptor (NMDAR) neuronal receptors via secretion of neuroinflammatory metalloproteinase MMP-9. Stimulation of excitotoxic NMDAR led to calcium influx and activation of neurotoxic enzymes like calpain and calcineurin. It was also observed that synthetic Aβ induction of neurofibrillary tangles was primarily due to dysregulation of neuronal deacetylase HDAC6, which normally would export misfolded proteins to proteasomes for degradation. HDAC6 was observed to be trapped in NFTs and produced instead abnormal acetylation of microtubule associated (MAP) tau [20]. Both GSK-3β activity and MMP-9 levels are increased in AD [21].

Ubiquitous TAR-DNA binding protein (TDP-43) is a transcriptional repressor, mRNA binding protein, and splicing factor. Absence of TDP-43 in normal brains and presence in NFTs in the microglia of human post-mortem AD brains suggested that it also contributes to neurotoxicity and pathogenesis of the disease. The suggested role in AD pathology involves lysosome biogenesis linked to Aβ but not so far with IR, glucose or DM [22-24]. Aβ, which has been linked to TDP-43, is averred to be a cerebral antimicrobial peptide (AMP) [25]. Therefore it is tempting to speculate that Aβ could have been generated in response to infections [26-28].

Although IR is involved in cognitive decline of DM and AD, the receptor subtypes in brain and peripheral tissues differ in structure and functions. Hyperglycemia is a characteristic feature of DM type 2 but not of AD. Moreover, insulin does not induce a significant glucose uptake in the brain as compared to peripheral tissues. Hence neurotoxicity underlying senile dementia of AD can be attributed to NFTs and TDP-43 whereas diabetic neuropathy is due to vascular hyperglycemia. Hyperglycemia and hyperinsulinemia of DM type 2 lead to downregulation of peripheral IR and insulin resistance but not brain IR. Biomarkers of IR desensitization in type 2 DM need to be ascertained as a consequence of overstimulation. Since DM type 2 is reversible, the mechanism of reversal of refractoriness of IR needs to be studied in depth [22,29,30].

Conclusion

In view of the structural and functional dissimilarities of brain and peripheral IR, AD should not be referred to as type3 Diabetes for it may not be the primary biochemical lesion underlying senile dementia of AD while it is the primary cause of cognitive decline in type 2 DM [31]. Age related withdrawl of estradiol, ovarian reproductive hormone in women has been linked to reduction in glucose utilization and ATP biosynthesis in cerebral mitochondria, levels of GLUTs, disturbance in calcium homeostasis, increased oxidative damage, Aβ levels and initiation of reliance on myelin fats over glucose for ATP biosynthesis, cognitive changes and memory loss, in short, mimicking clinical picture of AD [32]. Type3 Diabetes terminology for AD could be misleading and give rise to the belief that it can be reversed like DM type 2 with excercise, dietary management and even preventable by a diabetes vaccine against autoimmune damage to IL in the offing. In fact, in view of reports of microbial infections in AD brains, considering AD to be type3 diabetes would hamper research to detect alternative etiologies and devise effective treatment strategies for AD [33].

Acknowledgement

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