Correlation of Metabolic Disorders and FOXO Signaling in AD: A Therapeutic Approach

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Abstract

Alzheimer’s Disease is an ailment that is linked with the degeneration of the brain cells and this illness is the main cause of dementia. Metabolic stress affects the activity of the brain in AD via FOXO signaling. The occurrence of AD will significantly surge as the world’s population will age along with lifestyle changes perceived in current decades giving the impression of main contributors to such augmented prevalence. Similarly, metabolic disorders of current adulthood, such as obesity, liver, stroke, and diabetes mellitus, have been observed as the risk-causing factors of AD. FOXO transcription factors are preserved molecules that play an important part in assorted biological progressions, precisely in aging as well as metabolism. Here, we capitulate the signaling pathways along with the cellular functions of FOXO proteins. We have also summarized the intricate role of FOXO in AD, with a focus on metabolic stress, and discussed the prospect of transcriptional alterations with respect to FOXO as a molecular link between AD and metabolic disorders.

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Certificate of Conflict of Interest
This is to bring to your kind notice that the manuscript originally written by Parneet Kaur, Heena Khan, Amarjot Kaur, Kamal Dua, Sachin Kumar Singh, Thakur Gurjeet Singh* titled “Correlation of Metabolic Disorders and FOXO Signaling in AD: A Therapeutic Approach.” It has not been published before, and it is not under consideration for publication in any other journal(s).

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Abstract
Alzheimer’s Disease is an ailment that is linked with the degeneration of the brain cells and this is the main cause of dementia. The occurrence of AD will significantly surge as the world’s population will age along with lifestyle changes perceived in current decades giving the impression of main contributors to such augmented prevalence. Similarly, metabolic disorders of current adulthood, such as obesity, liver, stroke, and diabetes mellitus, have been observed as the risk-causing factors of AD. FOXO transcription factors are preserved molecules that play an important part in assorted biological progressions, precisely in aging as well as metabolism. Here, we capitulate the signaling pathways along with the cellular functions of FOXO
proteins. We have also summarized the intricate role of FOXO in AD, with a focus on metabolic stress, and discussed the prospect of transcriptional alterations with respect to FOXO as a molecular link between AD and metabolic disorders.

**Keywords:** Alzheimer’s Disease; FOXO; Liver; Diabetes; Obesity; Oxidative stress

**Introduction**

Alzheimer’s Disease (AD) is a complex, aging-related neurological illness that causes steady deterioration in cognitive ability and ultimately leads to mortality (Wellen et al., 2010). In 2010, more than 30 million population was affected, and by 2050, it is expected that number will rise to 106 million worldwide. AD is known to be the seventh greatest reason for death in 2020 as well as 2021, affecting an estimated 6.5 million persons aged 65 and more (Scarmeas et al., 2009). The development of tau-mediated neurofibrillary tangles (NFTs) and the accumulation of amyloid-beta (Aβ) plaques are the primary pathophysiological marks of AD. The pathogenesis of AD is based on neuroinflammation, oxidative stress, neuronal damage, loss of synapses, and endoplasmic reticulum stress (ER) (Khan et al., 2021; Saklani et al., 2022). Inflammation triggers the cellular stress system, which further damages both cell function and the body’s metabolism in the peripheral tissues (Prabhakar et al., 2022). However, these proceedings are interconnected with Aβ oligomers and studies have shown that oligomer enhances neuronal stress by peculiarly uplifting the tumor necrosis factor α (TNF-α), eIF2α phosphorylation (eIF2α-P), reactive oxygen species (ROS), and activating JNK/PKR signaling in the models of AD (Bomfim et al., 2012; Ma et al., 2013; De Felice et al., 2014). The prefrontal cortex and the hippocampus portion of the brain exhibit these symptoms, which ultimately result in neuronal death along with the deterioration of cognitive function. However, recent research has demonstrated the involvement of metabolic dysfunction in various neuro-degenerative illnesses, like; as AD, which worsens neurological symptoms (Watson et al., 2005; Martin et al., 2009). Such metabolic dysfunctions as the uncontrolled, gradual loss of weight as well as impaired glucose tolerance are frequently seen in AD patients and have a detrimental effect on prognosis due to a poorly understood cascade of events (Cai et al., 2012). The transgenic mice with excessive Aβ expression that had decreased glucose utilization demonstrated the correlation between Aβ and metabolic dysfunction (Sharma et al., 2020). In reaction to an unbalanced metabolic equilibrium, cells undergo a well-defined physiological process called metabolic stress, which helps the cells survive. For instance, the low energy level experienced during exercise contributes to the development of harmful toxins and the advancement of metabolic stress. These toxins promote the hormonal release, the production of reactive oxygen species (ROS), hypoxia, as well as cell swelling (Wellen et al., 2010). Also, metabolic stress is allied with other diseases like obesity (Garg et al., 2021); aging (Khan et al., 2022); circadian rhythm (Ahmad., 2020); autophagy (Kalra et al., 2022); cardiomyopathy (Liu et al., 2017); inflammatory bowel disease (Schultz et al., 2011); diabetes (Garg et al., 2022); cognitive impairment (Khan et al., 2021), etc. Numerous studies in AD suggest a connection between Aβ oligomers and disease progression. They are also thought to be neurotoxins that cause individuals to lose their memory and synapse function (Gong et al., 2003; Xia et al., 2009). In this review, we will discuss the correlation between metabolic stress and the signaling pathway FOXO in Alzheimer’s disease for a therapeutic approach.

**Methodology:**

A systematic literature review of Bentham, Scopus, PubMed, Medline, and EMBASE (Elsevier) databases was carried out with the help of the keywords like Alzheimer’s Disease; FOXO; Liver; Diabetes; Obesity; Oxidative stress. The review was conducted using the above keywords to understand the Correlation between Metabolic Disorders and FOXO Signaling in AD: A Therapeutic Approach.

**Role of FOXO Protein in Alzheimer’s Disease**

The mammalian forkhead transcription factors of the O class are known as FOXOs. It has four components: FOXO1, FOXO3, FOXO4, and FOXO6, which are broadly distributed throughout the body. Nearly all tissues express FOXO1 and FOXO3, although FOXO4 is expressed in muscles, colon tissue, kidney, brain, and liver, and FOXO6 in the liver (van der Vos et al., 2011). FOXOs do the transcriptional regulation of the target genes. Apoptosis, cell division and differentiation, oxidative stress, metabolism, and lifespan are
among the physiological processes that the FOXO proteins are adept at controlling (Jünger et al., 2003; Puig et al., 2003; Giannakou et al., 2004; Hwangbo et al., 2004). Since the modulation of cellular response to oxidative stress is the known function of FOXO protein, it can be related to AD because oxidative stress plays a substantial part in the pathophysiology of AD (Zhao et al., 2013). A study examined the physical interactions between FOXO and human cells that have been exposed to the domain of amyloid precursor protein (AICD) intracellularly. Following oxidative stress, AICD moved sideways with FOXO from the cytoplasm to the nucleus as well as served as a co-factor of transcription for FOXO (Hwangbo et al., 2004). Overall, this promotes the activation of the apoptotic gene Bim, which activates the machinery that causes cells to die (Wang et al., 2014). Since insulin activity is influenced by oxidative stress and the FOXO transcriptional factor, FOXO may have a connection between insulin resistance and AD. The FOXO protein may be responsible for the ongoing production of ROS brought on by hyperglycemia, which in turn impairs Wnt signaling and increases the creation of amyloid plaques and hyperphosphorylated tau. Wnt inhibition may also be responsible for the FOXO protein’s ongoing activation, which promotes apoptosis along with neuronal death (Manolopoulos et al., 2010). The treatment of neurodegenerative illnesses may benefit from targeting these transcriptional factors. Throughout AD, it may be suitable for the FOXO factor to be expressed often in the neurological system (Greer et al., 2005). FOXO3A is enormously expressed in the brain region (Shi et al., 2016) and also controls pathways of cell death of apoptosis, therefore resulting in cell survival in oxidative stress (Salih et al., 2008). It is well known that the overexpression of miR-132 and miR-212 has neuroprotective properties against oxidative stress. Additionally, a study revealed that miR-132 and miR-212 control cell viability via all important AKT components, including FOXO3A (Wong et al., 2013). It is also believed that FOXO3A controls the chemicals that fight oxidation. The FOXO target gene produces the protective brain proteins selenoprotein-P and manganese-superoxide dismutase (Bellinger et al., 2008). Another study demonstrated a correlation between the levels of serum FOXO3A and tau, and that FOXO3A declines with worsening cognitive impairment. The reduced levels of FOXO3A might be a potentially useful novel marker for the earlier detection of AD and for effective treatment intervention to stop further decline (Pradhan et al., 2020). In response to apoptosis-related stimuli, activated FOXO3A factor can upregulate some different genes. According to studies, when NGF (nerve growth factor) is deprived, the overexpression of FOXO transcription factors induces BIM expression and promotes the death of sympathetic neurons in a BIM-dependent manner (Sanphui et al., 2013). In a primary neuron culture from a mouse brain, a contrary connection between FOXO3A activation and cerebral Aβ amyloidosis was observed. Calorie restriction reduced the amyloid neuropathology associated with AD by activating the I/R signaling pathway, which causes FOXO3A to become hyperphosphorylated (Qin et al., 2008).

Pathophysiological Mechanisms of FOXO in Alzheimer’s Disease

1. **Oxidative stress:** It is a significant contributor to insulin resistance (InsRes), diabetes complications, and the etiology of AD. There may be a connection between AD and FOXO transcription factors because they are involved in the physiological response to oxidative stress (Manolopoulos et al., 2010). In the pathogenesis of InsRes, AD, and other metabolic illnesses, oxidative stress is frequently present (Fig 1). Additionally, FOXO proteins are essential for controlling oxidative stress, apoptosis, and the regulation of glucose and energy homeostasis in insulin-sensitive tissues. Oxidative stress causes FOXO activation, which, for instance, increases β-catenin co-binding and blocks Wnt to increase the transcription of antioxidant enzymes (Rehni et al., 2008; 2010). However, GSK-3 (Glycogen synthase kinase 3) gets activated as a result of Wnt inhibition (Jope et al., 2004). Accordingly, neuronal degeneration and neurofibrillary tangles (NFT) are connected to increased levels of GSK-3 (Yamaguchi et al., 1996; Ishizawa et al., 2003). Increased GSK-3 activity raised Aβ production (Phiel et al., 2003), neuronal death (Hooper et al., 2008), and increased tau protein phosphorylation (Brewster et al., 2006). Prolonged FOXO activation may increase the system’s susceptibility to apoptosis rather than improve its ability to create antioxidants. In humans, higher JNK activity is connected to FOXO activity which would activate various receptors and might increase the amount of intracellular ROS produced. Due to the vicious cycle, this causes, oxidative stress-induced apoptosis is induced and prolonged FOXO activity is encouraged (Valenti et al., 2008; Martin et al., 2006).
2. Impaired Autophagy and processing of amyloid precursor protein (APP) : The produced type 1 integral membrane protein, known as APP, is first elated to the cell surface, where it can also be taken up by early endosomes or sliced by the sheddase-secretase Disintegrin and metalloproteinase domain-containing protein 10 (ADAM10) (Claeysen et al., 2012). The APP protein can then be delivered in one of three ways: (i) by recycling back to the cell surface; (ii) through the retrograde endosome-to-Golgi pathway; or (iii) to the late endosome-lysosome degradation pathway (O'Brien and Wong, 2011; Claeysen et al., 2012; Rajendran and Annaert, 2012; Seaman, 2012). It’s fascinating to note that beta-site APP cleaving enzyme 1 (BACE1) and presenilin (PS)/γ-secretase, two APP processing enzymes, are likewise transported through the trans-Golgi network (TGN), early endosomes, and late endosomes (Claeysen et al., 2012; Tan and Evin, 2012). It is currently believed that the TGN and the acidic endosomal compartments are where amyloid peptides are generated (De Strooper, 2010). In the affected regions of AD brains, Vacuolar protein sorting ortholog 35 (VPS35) and Vacuolar protein sorting-associated protein (VPS26) had considerably decreased protein levels (Small et al., 2005). The generation of amyloid is increased by any deficiency in the carrier proteins along the endosome-TGN route (Bonifacino and Hurley, 2008; Burd, 2011). This demonstrates that APP and its cleaving enzymes may relocate to acidic endosomal compartments, boosting the synthesis of amyloid- and subsequently its exocytosis, if the capacity to transport from the endosomes to the TGN is compromised (Sullivan et al., 2011). Numerous studies have shown that different types of transcription factors under different signaling pathways, such as the FOXO signaling, the insulin/growth factor pathway, as well as nutrient-sensing signaling through the mTOR- and Akt-dependent pathways, tightly regulate the expression levels of genes related to autophagy (Omata et al., 2014; De Matteis and Luini, 2008). But Sirt1 is a sensor of caloric restriction to promote autophagy by deacetylation of FOXO and also control the activation of autophagy through the suppression of insulin signaling, which results in TOR inhibition. (Buxbaum et al., 1994; Grewal et al., 2019). The expression of autophagy-related genes is tightly regulated by many factors, including aging, FOXO signaling, sirtuin signaling, TOR signaling, APP processing, and autophagy activity itself (Micaroni, 2010).

Figure 2: FOXO role in autophagy. AMPK, AKT, MAPK, and SIRT1 are activated via hypoxia, insulin receptor, and ROS respectively which phosphorylates FOXO and causes autophagy and eventually Alzheimer’s disease.

3. Inflammation

In AD, neuroinflammation is seen as a powerful propeller. Growing data suggested that activated microglia are accountable for the advancement of AD because they can generate proinflammatory cytokines such as IL-1β, IL-6, and TNF-α as well as harm the neurons (Khan et al., 2022). Microglia are classified as having a "homostatic function molecule" (M0), "pro-inflammation effects" (M1), and "anti-inflammatory effects" (M2) (Khan et al., 2022; Khan et al., 2018). The interactions of M1 and M2 microglia in the CNS control inflammation (Fig 2). While the PI3K/AKT/FOXO3a signaling pathway may have a significant role in the inflammatory response. The progression of AD is marked by an inflammatory response caused by numerous variables, including FOXO (Wang et al., 2020).

IV. Therapeutic Correlation of FOXO and metabolic stress in Alzheimer’s Disease

1) Diabetes

A chronic metabolic condition called diabetes mellitus (DM) is defined by hyperglycemia brought on by
inadequate or resistant insulin. According to recent research, oxidative stress brought on by elevated ROS levels is a major factor in the emergence of diabetic problems (Hedrick et al., 2000). Numerous biological processes are carried out by FOXO proteins (Ho et al., 2008). In oxidative stress, the intricate interaction among the signal transduction pathways as well as FOXO proteins can have a major impact on apoptosis and autophagy. FOXO proteins can promote autophagy under oxidative stress circumstances while also promoting cell survival (Ponugoti et al., 2012). FOXO1 is deactivated by insulin signaling, which is carried out through AKT and insulin receptor substrates 1 and -2. Insulin sensitivity is hugely affected by the nuclear receptor peroxisome proliferator-activated receptor (PPAR). PPAR It is the molecular target of thiazolidinedione (TZD) anti-diabetic drugs that enhance in vivo glucose tolerance, insulin sensitivity, and lipid homeostasis. TZDs improve insulin sensitivity by modulating gene expression mediated by PPAR (Hedrick et al., 2000). PPAR is abundant in adipose tissue, where it functions as a crucial regulator of adipocyte development and, most likely, also of the preservation of the mature adipocyte phenotype. In addition to PPAR, FoxO1 has a role in adipocyte development by inhibiting adipogenesis during an early phase of the development process. FoxO1 haploinsufficient mice are somewhat protected from the insulin resistance and diabetes caused by a high-fat diet. FoxO1 has also been shown to directly bind to and inhibit the PPARγ-2 promoter in addition to PPAR function (Fan et al., 2009).

HMOX1-

Elevated glucose production that results in hyperglycemia is a defining trait of insulin resistance. FOXO1 affects the ability of the liver to generate glucose by controlling the expression of genes that promote gluconeogenesis. This means that there is a route by which insulin resistance causes increased activity of FOXO1, overexpression of genes that stimulate glucose synthesis, and raised serum glucose levels. The mitochondria are also impacted by the insulin-Akt-FOXO1 balance disruption (Kalogerakis et al., 2005). Heme oxygenase-1 (HMOX1), which cleaves heme and damages the mitochondrial electron transport chain, is induced by activated FOXO1. Thus, increased heme oxygenase-1 expression happens when insulin resistance increases FOXO1 activity. Increased heme oxygenase-1 levels disrupt mitochondria and decrease oxidative respiration, which has a deleterious impact on the oxidation of fatty acids and the generation of ATP (Hedrick et al., 2000). Additionally, increased FOXO1 activation alters the expression of mitochondrial fusion and fission, which impacts mitochondrial biogenesis. Chronically high insulin levels, inadequate mitochondria, aberrant mitochondrial morphology, and insulin resistance are all associated with accelerated aging-related cognitive loss, leading to AD that can be corrected by deleting the FOXO1 gene (Cameron et al., 2006). There is mounting evidence that type II DM’s peripheral hyperinsulinemia and insulin resistance contribute to the etiology of AD. By reducing insulin in the peripheral and improving the sensitivity of insulin, thiazolidinediones like Agonists of the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR), rosiglitazone as well as pioglitazone, may offer some beneficial relief for AD (Mannan et al., 2021). Additionally, PPARγ agonists have been demonstrated to have neuroprotective benefits by lowering the beta-amyloid buildup and inflammatory mediators. There hasn’t been a study looking at the properties of pioglitazone on cognitive performance in AD patients, but it has recently been shown that 6 months of treatment with rosiglitazone preserved cognitive function in patients with AD and amnestic moderate cognitive impairment (MCI). In individuals with AD and MCI with DM, the pilot trial showed that pioglitazone improved cognitive as well as metabolic functions (Landreth et al., 2007). The outcomes indicated that pioglitazone might provide a unique approach for the treatment of AD as well as MCI with DM. To support these findings, larger double-blind, randomized, placebo-controlled investigations are required (Watson et al., 2005). Another study demonstrated that in mice with STZ injections to the hippocampi, the impact of Biobran on the expression of FOXO protein was investigated. STZ injection in the brain is linked with tau protein aggregation, brain insulin resistance, neuroinflammation, oxidative damage, and Aβ deposition(Ghoneum et al 2021). The expression of the FOXO protein was noticeably increased in mice that had received STZ injections. These expressions were dramatically reduced by biobran in a dose-dependent manner (Cojocaru et al., 2011). It reveals how Biobran protects mice given STZ from FOXO-mediated apoptosis. However, it might be having a protective role in diabetes linked with AD but studies for the same are not implicated yet (Alam et al., 2016). Retinal neurodegeneration brought on by diabetes happens before ob-
vious microvascular problems. The development of diabetic retinopathy was thought to be influenced by oxidative stress and hyperglycemia-induced ER stress (Huang et al., 2010).

GLP-1-

A common medication in clinics is liraglutide (LIRA), a glucagon-like peptide-1 (GLP-1) analog that has been shown to have protective effects against neurodegenerative disorders (Li et al., 2010). By releasing insulin, gut cells produce GLP-1 to low blood sugar levels. The glucagon-like peptide-1 receptor, which is broadly articulated in various organs, counting the colon, pancreas, lungs, heart, and kidney, and particularly in specific parts of the brain and peripheral neurons, interacts with GLP-1 and its agonists (Harder et al., 2004). In clinics today, type 2 diabetes mellitus (T2DM) is treated with LIRA, a long-acting GLP-1 analog. Recent research shows that GLP-1 analog exhibits some neuroprotective effects in AD, Aβ-induced SH-SY5Y cells which are thrice-subcloned cell line derived from the SK-N-SH neuroblastoma cell line, PD, and traumatic brain damage through crossing the blood-brain barrier. Nevertheless, the mechanism related to this was still not entirely understood (Liu et al., 2020).

1.3. JNK/GSK-3

The FOXO response, which plays a key part in the stimulation of cellular antioxidative pathways along with apoptosis, is linked to Jun N-terminal kinase (JNK) and Glycogen synthase kinase 3 (GSK-3) activation. At the same time, hyperglycemia is brought on by the elevation of FOXO transcriptional activity, which is another element that might be linked with the pathophysiology of AD. Future strategies will concentrate on other transcription factors intricate in the etiology of AD, InsRes, and its consequences that are activated by oxidative stress (Smith et al., 2005). For instance, oxidative stress has been related to both diabetes mellitus and the death of neurons by the transcription factor NF-kB (Nuclear factor kappa B). FOXO proteins are an excellent target for therapeutics that focus on treating the cause rather than the symptoms of both diseases due to the integrative role they are shown to play in cellular stress resistance. Thiazolidinediones, an agent with both antidiabetic and antioxidant capabilities, had beneficial effects on both InsRes and AD neuropathology, which offers promising hopes for this future perspective (Hanyu et al., 2009).

2) Hepatic Injury

The liver requires FOXOs to maintain cellular and metabolic balance, and FOXO dysregulation may aid in the emergence of Non-alcoholic fatty liver disease (NAFLD) (Dong., 2017). Given the significance of FOXOs in maintaining healthy levels of lipids and glucose, it is not astonishing that abnormalities in hepatic FOXO regulation might contribute to metabolic ailments (Gross et al., 2009). AMP-activated protein kinase (AMPK) plays a crucial function in hepatic metabolic regulation. Once activated, AMPK inhibits energy-consuming biosynthesis processes, such as fatty acid and sterol production, while simultaneously activating ATP-producing catabolic pathways, including fatty acid oxidation and activates autophagy in the liver (Viollet et al., 2006). FOXO3a phosphorylation has been implicated as a key ROS-activated rapid response. PI3K and the AMPK signalling pathway are the most important sensors of stress signals in the management of FOXO3a-dependent cellular homeostasis. In addition, it has been identified that the AMPK–FOXO3a axis is the key homeostatic signalling framework that regulates the physiological response to oxidative stress (Jin et al., 2022). In addition to Akt/SGK, SIRT1, and PPAR-α, MAPK, an essential metabolic master and cell energy sensor, has been implicated in influencing FOXO3a transcriptional activity. SIRT1 and PPAR-α are reciprocally regulatory. A rise in hepatic SIRT1 enhances PPAR-α activity, and PPAR-α is a crucial factor in the upregulation of SIRT1 gene expression. PPAR-α is a nuclear receptor that stimulates fatty acid oxidation, regulates lipid metabolism, and stimulates autophagy (Gautam et al., 2020).

2.1. Inflammatory Pathway-

It has been established that FOXOs are crucial for hepatic metabolism (Fig 3). Inhibiting cell growth, oxidative stress, and the development of apoptogenic signals, which are mediated by the overexpression of Bcl-2-associated X protein (Bax) and FOXO-1 expression and the downregulation of B-cell leukemia/lymphoma 2 protein (Bcl-2), are some of the ways that cyclic isoprenoid (I) inhibits DENA-induced HCC significantly.
βI also reduced the expression of the proliferative marker Ki-67 mRNA and prevented hepatocarcinogenesis. The abnormal pro-inflammatory mediators expressed involving nitric oxide (NO), Prostaglandin E2 (PGE2), as well as Tumor necrosis factor alpha (TNF-α), which are generated by microglial cells, are a hallmark of immunological diseases like AD. Therefore, downregulating pro-inflammatory mediators is a promising method for managing brain inflammatory diseases. Recent research has found that βI has strong anti-proliferative along with anti-cancerous effects. The study also showed that βI suppresses Akt-dependent NF-kB activity as well as dephosphorylates Mitogen-activated protein kinase (MAPKs) to decrease the expressed mediators of pro-inflammation along with their regulatory genes in BV2 microglia that have been activated by LPS (Chen et al., 2010). Both studies demonstrate the anticancer as well as anti-inflammatory characteristics of β-ionone, which further reduce liver injury and AD respectively. Studies have shown that inflammation in the liver results in the onset of AD. The mechanism behind this is not clear and no study has yet implicated the link between them (Kang et al., 2013). Therefore, future studies can be done to confirm the above. Inhibiting the FOXO1 improved lipid-persuaded stress of ER as well as necroptosis, which is one of the protecting Inhibition of FOXO1 in a mouse model of non-alcoholic fatty liver disease has certain characteristics. Mice, however, displayed reduced levels of steatosis when fed a fat-rich diet, and treatment was done with a FOXO1 inhibitor. Intriguingly, postulate that the FOXO1 inhibitor AS1842856 functions by hindering the phosphorylation pathway (Wang et al., 2016). It was seen that AS1842856 specifically inhibits FOXO1 without changing its phosphorylation. Inhibitors were utilized to reduce FOXO1 function in this case as opposed to a gene deletion (Nagashima et al., 2010). Inhibiting FOXO1 prevents the development of ER stress as well as necrosis and also prevents NAFLD. The cause of NASH, or a deteriorating condition known as liver fibrosis, is yet unknown (Ding et al., 2020). ER stress has been found in the postmortem brains of AD-affected people, animals, and also the vitro models, suggesting that ER disruption has a significant part in the development of AD. It was established that ER stress has a significant role in AD etiology. Nearly all of the brain pathology developments linked with AD, involving presenilin1 gene mutation, presenilin2 unusually cut mRNA, formation of β-amyloid, tau phosphorylation, as well as cell death, are allied to ER stress. Additionally, given their roles in the etiology of AD, ER stress and unfolded protein response have potential therapeutic roles (Li et al., 2015). Recent research has revealed that ER stress activates inflammation reactions via several UPR transducers. The most effective pathways include “inositol-requiring enzyme1- Tumor necrosis factor receptor-associated factor-2 (IRE1-TRAF2), Protein kinase RNA-like endoplasmic reticulum kinase- Eukaryotic Initiation Factor 2α (PERK-eIF2α), and GSK-3, activating transcription factor 6 - cAMP-responsive element-binding protein H (ATF6-CREBH)”, also the pathways induced by inflammation of caspase. Some theories explain the connection between ER stress in neurons, inflammation, and the development of pathogenic alterations in AD. From the above-mentioned studies, it was demonstrated that ER stress provides clues for the progression of NAFLD and AD. There are no studies that have implicated the link between ER stress causing NAFLD, which leads to Alzheimer’s and is attenuated by FOXO inhibition (Salminen et al., 2009).

2.2. SREBP1-

In the livers of HFHS mice, ob/ob mice, db/db mice, and also the individuals with NAFLD, FOXO3 expressions were elevated. In HepG2 cells, FOXO3 overexpression enhanced cellular TG concentrations while FOXO3 knockdown decreased them. In C57BL/6 J mice on a chow diet, gain-of-function of FOXO3 led to the deposition of hepatic TG, also when a high-fat diet is given, it exacerbated hepatic steatosis. The enhanced expression of TG synthesis-related genes such as SREBP1c, in the liver of mice, was determined by transcript analysis. In a mechanism-based manner, FOXO3 knockdown decreased SREBP1c expression while FOXO3 overexpression increased it. SREBP1c modulated the transcription of the SREBP1c promoter, according to luciferase reporter tests. By encouraging the SREBP1c promoter’s transcriptional activity, FOXO3 increases TG formation along with its hepatic accumulation (Wang et al., 2019). There is proof that diets high in saturated fat, like those high in palmitate, stimulate the development of Aβ, the histological sign of AD. The mechanisms underlying the harmful consequences of a diet high in palmitate on the stimulation of Aβ genesis have not yet been fully understood. The gene expressions which code for the protein intricated in nearly every aspect of lipid metabolism are regulated by the transcription factor sterol response element
binding protein 1 (SREBP1), which is altered by saturated fatty acids like palmitate. The study established how alterations in SREBP1 expression as well as in transcription contributed to the impacts that palmitate had on Aβ genesis along with on Beta-secretase 1 (BACE1) expression. This research identifies SREBP1 activation as a unique molecular factor in the upregulation of BACE1 expression brought on by palmitate and subsequent Aβ generation. However, the role of SREBP1 in AD linked with liver disorder is not well understood on the molecular level. But up to the present work, no molecular research had yet suggested that SREBP1 dysregulation was responsible for the regulation of AD-related processes (Marwarha et al., 2019). Age-related disorders including AD and glucose and lipid homeostasis have both been linked to FOXOs. Significant metabolic abnormalities in the brain are also present in AD. Misregulation of the FOXO signaling pathway may be the cause of age-related functional decline and age-related illnesses due to its important involvement in metabolic balance and organismal lifespan (Du et al., 2021). However, FOXO has a significant role in the development of liver diseases like NAFLD, which is not well understood. In the above-concluded studies, the experiments were designed to examine the effects of FOXO modulation in liver-associated AD. Thus, it can be said that FOXO has a beneficial role in protecting the fatty liver disease induced by diet (Pan et al., 2017). Whereas, this expression of inflammation might lead to the development of AD and FOXO might play a protective role in it. However, no molecular studies have been implicated yet.

3) Obesity

The correlation between obesity and cognitive decline went unstudied for a very long period. These days, growing epidemiological evidence supports a significant connection between these illnesses. Many metabolic pathways in skeletal muscle are linked to obesity and result in insulin resistance. Thus, aberrant PI3K/AKT-mediated glucose transport and glycogen synthesis contribute significantly to obesity. FoxO proteins, notably FoxO1, are the primary target of Akt and regulate the body’s energy homeostasis. FoxO1 and PGC1α coordinately promote fatty acid oxidation and gluconeogenesis through regulating gene expression (Gudala et al., 2013). FoxO1 simultaneously activates AKT to boost energy production while inhibiting mTORC1 to limit protein and lipid production. The PI3K/AKT signalling pathway encourages lipid production and suppresses lipolysis. Moreover, an AKT-independent, PI3K-dependent mechanism regulates adipocyte lipolysis by directly controlling PKA, whereas AKT regulate the FoxO1 pathway (Huang et al., 2018). In reality, people with obesity or other metabolic illnesses have almost a two-fold increased chance of getting AD, according to research using a meta-analysis method (Gudala et al., 2013). Having a midlife weight problem raises the chance of AD and dementia by 35, 33, as well as 26%, respectively; obesity is associated with even higher risk (Anstey et al., 2011). More research is still needed because molecular processes causing this co-morbidity along with the impact of fats buildup on neurodegenerative progression are not understood well. Obesity may cause AD through a variety of mechanisms, such as 1) increased cleaving of amyloid precursor protein (APP) as well as Aβ generation, 2) formation of pro-inflammatory cytokines along with adipokines, 3) additional oxidative stress formation as well as dysfunction of mitochondria, 4) insulin resistance via FOXO inhibition, 5) breakdown of the BBB, and 6) production of ceramides.

3.1. IRS-2

Obesity and AD are linked by a complicated, multifaceted process (Picone et al., 2020). According to an investigation of FOXO expression in the mouse brain’s various regions till 100 weeks of age, FOXO1 is primarily present in the hippocampal region relative to total brain expression, whereas FOXO3a is expressed in the cerebellum in a high amount. Furthermore, a diet with a high amount of fat dramatically affects the expression of FOXOs in C57BL/6 mice, at least if fed for 46 weeks. Surprisingly, FOXO3a mRNA levels dropped massively in various regions of the brain like the cerebellum along with the occipital cortex whereas FOXO1 mRNA levels modestly elevated in the CNS of these animals (Zemva et al., 2012). According to in vivo findings, FOXO3a is downregulated by chronic elevation of IR/IGF-1R signalings in neurons both in vivo as well as in vitro. This is established by SH-SY5Y neuroblastoma cells of humans that firmly overexpress Insulin receptor substrate 2 (IRS-2) and exhibit phosphorylated AKT at Ser473 along with significantly reduced FOXO3a expression. Research is still being done to determine the precise chemical mechanism by
which this signaling cascades control the various expressed FOXOs. Data collected from the line of cells, however, may not accurately represent in vivo environment. Lowered expression of FOXOs found in high-fat diet mice is implicated in the etiology of intellectual impairment related to obesity appears logical or else given that a reduction in the signaling of IRS-2 causes FOXO-facilitated transcriptions. Therefore, transcription which is controlled by insulin receptor (IR) or insulin-like growth factor 1 (IGF-1) may contribute to the pathophysiology of at least AD. It is not yet apparent, nevertheless, whether alterations in the signaling pathway IR/IGF-1 associated with neurons directly cause neurodegeneration or a form of counter-regulation (Moll et al., 2012).

3.2. IGF-1

One of the main processes driving Aβ-induced cell death of people with recognized AD is oxidative stress-facilitated stimulation of FOXO. Particularly, Aβ promotes the production of ROS along with the proteins which are oxidized, leading to the liberation of H2O2 which is neurotoxic. Curiously, uprooted expression of p66ShcS36A lowers the phosphorylation of FOXOs, avoiding the death of cells by oxidation in response to the toxicity of Aβ. Whereas, FOXO transcription factors are connected to IGF1, which encodes hormones either paracrine or autocrine. Deleting the FOXO homolog DAF-16 improves the developmental, lifespan, and metabolic abnormalities caused by mutating the homolog DAF-2 of the IGF1 receptor in Caenorhabditis worms (Matsuzaki et al., 2022). Further evidence that IGF1 regulates the FOXO signaling pathway comes from the fact that FOXOs are the targets for transcription and the rapid initiation of gluconeogenesis mediated by IGF1, which is inhibited by nuclear rejection stimulated by insulin. Additionally, these results are in line with our findings that FOXO signalings are drawn in the pathophysiology of AD and that low IGF1 expression is a contributing factor. Conversely, if FOXO transcriptional factor is enhanced, it may be a viable target for reducing obesity linked to AD (Kang et al., 2020).

Figure 3: ΦΟΞΟ δεατιατεδ βψ νυιλν σιγναλνγ τηρουγη ΑΚΤ ανδ ΗΔΑρ ςαυσινγ ιν αςςυμυλατιο αμψλοιδ β λεαδινγ το Αλζηειμερ΄ς διςεασε.

Transcriptional Alterations

Accumulation of the Aβ peptide is a significant neuropathological event in AD. Numerous genes control the synthesis and elimination of Aβ in the brain. It is necessary to fine-tune the expression levels of these genes in the brain to maintain a balanced level of Aβ under physiological circumstances (Chen et al., 2013). It has been discovered that AD gene dysregulation either raises the risk of AD or quickens the progression of the disease. Discovering the regulatory components and transcriptional factors that control the expression of these genes has advanced significantly in recent years (Chen et al., 2013). It is well known that the beginning and development of AD are accompanied by pervasive transcriptional alterations. It is still unclear, however, whether such changes are the result of nonspecific dysregulation and multisystem failure or rather are part of a coordinated response to cellular dysfunction because of the multifactorial nature of this neurodegenerative disorder and its complicated relationship with aging. A study on the identification of transcriptional alterations associated with aging and AD was conducted on a meta-analysis of over 1,600 microarrays from human central nervous system tissues. Their method of identifying a transcriptional signature of AD identified a collection of genes that were down-regulated and encoded proteins that were metastable to aggregation (Ciryam et al., 2016). They found a modest number of biochemical pathways using this method, most notably oxidative phosphorylation, which were enhanced in proteins prone to aggregation in control brains and encoded by genes down-regulated in AD. The findings revealed that when protein homeostasis is harmed in AD, the down-regulation of a metastable subproteome may assist prevent abnormal protein aggregation (Ciryam et al., 2016). Through the Foxo3 transcriptional factor, deregulated Cdk5 results in neurotoxic A peptide processing and cell death, two characteristics of AD, in hippocampus cells, primary neurons, and an AD mouse model. In lysates from brain tissue, Foxo3 was discovered to be a direct substrate of Cyclin-dependent kinase 5 (Cdk5) by a study using a novel chemical genetic screen. Foxo3 is immediately phosphorylated by Cdk5, increasing its concentration and nuclear translocation. Cells were initially protected from the resulting oxidative stress by nuclear Foxo3 by upregulating MnSOD. Foxo3,
on the other hand, elevated Bim and FasL after prolonged exposure, leading to cell death. Their levels were similarly elevated by active Foxo3 in a phosphorylation-dependent fashion. By producing phosphorylation-resistant Foxo3 or by depleting either Cdk5 or Foxo3, these events were fully suppressed, demonstrating a critical function for Cdk5 in controlling Foxo3 (Shi et al., 2016). These findings were corroborated by an AD animal model, which showed elevated levels and nuclear localization of Foxo3 in hippocampus neurons before neurodegeneration and the development of A plaques, showing that this phenomenon is a very early stage in the pathogenesis of AD. These findings reveal that the phospho-regulation of Foxo3 by Cdk5 can activate several genes that promote neuronal death and abnormal A processing, accelerating the development of neurodegenerative diseases. Consequently, one potential target for the neuroprotective effects could be the control of foxo3 (Shi et al., 2016). Cellular homeostasis depends on maintaining a balanced proteome, and proteostasis loss is linked to tissue malfunction and neurodegenerative diseases. A program of autophagy genes regulated by the transcription factor FOXO3 was found in a study that examined the transcriptional programs necessary for neural stem and progenitor cell (NSPC) activity. By using genomic techniques, it was discovered that FOXO3 functionally controls the induction of autophagy in adult NSPCs by directly binding a network of autophagy-related target genes. Interestingly, aggregates build up in NSPCs when FOXO activity is absent, and TOR (target of rapamycin) inhibition reverses this effect. Unexpectedly, increasing FOXO3 induces protein aggregates to form but does not speed up their breakdown. The findings revealed a genetic network that is crucial for maintaining a healthy mammalian stem cell pool to sustain lifelong neurogenesis and is directly regulated by a significant transcriptional regulator of aging (Audesse et al., 2019).

Conclusion and future perspective

The underlying cause of morbidity, as well as mortality in the aging population, is AD (Salminen et al., 2009). Regulating metabolic disturbances may lessen the impact of metabolic stress and related diseases including diabetes, obesity, and liver injury on AD, as these pathologies can be effectively treated via FOXO signaling (Shi et al., 2016). The FOXO protein controls the oxidative stress response, tissue metabolism, glucose homeostasis, and autophagy—all of which are included in AD’s pathophysiology associated with metabolic ailments. An underlying biological relationship between AD and metabolic disorders may exist since FOXOs are important in these conditions (Kang et al., 2020). To comprehend the part played by FOXO proteins in AD, and metabolic illnesses and also to guide the development of new treatments, a thorough knowledge of these proteins under various situations of the anatomy along with pathology at molecular extent is necessary. Since AD linked with metabolic disorders currently lacks a curative treatment, researchers and clinicians must continue to develop innovative strategies to enhance clinical outcomes based on the recently identified associations and novel paradigms of this kind.

References


Figure 1: ΦΟΞΟ αντιδείχνει α) υπό συνηθικές συνθήκες, όπου η οξεία στρες ανεμονάζεται με την άσκηση της GSK-3 και η ακτινοβολία της β-κατενίνας. (β) Στην κατάσταση θανάτου από οξεία στρες, η οξεία στρες ανεμονάζεται με την αύξηση της τρανσκρίπττινος γενικού μηχανισμού και την αύξηση της αποτοκίας. Οι συνθήκες δείχνουν την κατάλληλη απενδύση των ζών, που αποτελείται από την αυξημένη τρανσκρίπτινος γενικό μηχανισμό και την αύξηση της αποτοκίας.
Figure 2: FOXO role in autophagy. AMPK, AKT, MAPK, and SIRT1 are activated via hypoxia, insulin receptor, and ROS respectively which phosphorylates FOXO and causes autophagy and eventually Alzheimer’s disease.
Figure 3: ΦΟΞΟ δεικτιατεθεί βψ ινσολιν σιγνάλιγη τηρουγη ΑΚΤ ανδ ΗΔΑ⁺ σαυσινγ
αυτοπηαγψ ας ωελλ ας μεταβολις στρες ανδ ρεσυλτινγ ιν αςςυμυλατιον οφ αμψλοιδ β
λεαδιγη το Αλζηειμερ΄ς δισεαςε.