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THE LIVER-BRAIN AXIS METABOLIC DYSFUNCTION AND INFLAMMATION ALONG WITH OBESITY-INDUCED NEURODEGENERATION: AN ASIAN INDIAN COMPARATIVE STUDY IN THE COHORT POPULATION

Dr. Sanatan Behera	MD (MEDICINE), DM (GASTROENTEROLOGY) AIIMS,NEW DELHI Associate Professor. Hepatology, SCB. Medical College,Hospital, Cuttack,Odisha-753007
Dr. Manasi Das	MD (MEDICINE), DM (NEUROLOGY) IPGMER and SSKM Hospital, Kolkata Assistant Professor, Neurology,IMS and SUM Hospital, Campus-2, Phulnakhara, Odisha
Prof. (Dr.) Mayadhar Barik	AIIMS,(SIR APJ Abdulkalam, Excellence Of Research & Tejaswinee Awardee) New Delhi-110029. Medical Consultant, AIIMS, Dean (R&D Cell), Health and Paramedical Allied Sciences, Advisor to Chairperson and MUREC , former Registrar, Professor, Dept.of Biochemistry & Paramedical Sciences, Mewar University, Gangrar, Rajasthan-312901

ABSTRACT **Background:** The neurodegenerative diseases in Alzheimer's disease and Parkinson's disease interaction between metabolic dysfunction and inflammation is central part into the development of Obesity-related conditions like type 2 diabetes exacerbate relationship in the non-alcoholic fatty liver disease (NAFLD). **Study Design:** Comparative study in Cohort Population. **Data Collection:** We collect the data from 2020-2025 from our laboratory and clinic and sharing our own experiences. **Methods:** Particularly in the liver we observed the Peripheral lipid accumulation (PLA) test to initiate cascade of inflammatory processe (COIP) that how extend to the brain.At the same time we noted the regulatory regions those are influencing critical metabolic rate. We find out the key lipid components and their associations. Aset of biomarkers we find out Ceramide, palmitate, lipid transporters lipocalin-2 and apolipoprotein E, those are contributing into the neuroinflammation and disrupting the blood–brain barrier integrity (BBBI)those were promoting gliosis. Peripheral insulin resistance (PIR) also further exacerbates brain insulin resistance (BIR) and their impact in neuroinflammation. **Results:** Preclinical interventions targeting peripheral lipid metabolism and insulin signaling pathways have shown promise in reducing neuroinflammation is more than (85-95%). However, translating these findings to clinical practice requires further investigation into human subjects need more sample sizes on public domain. **Conclusion:** In conclusion, metabolic dysfunction, peripheral inflammation, and insulin resistance are integral to neuroinflammation and neurodegeneration. Understanding these complex mechanisms holds potential for identifying novel therapeutic targets and improving outcomes for neurodegenerative diseases.

KEYWORDS : liver–brain axis, metabolic dysfunction, inflammation and obesity-induced neurodegeneration

INTRODUCTION:

The intricate interplay between metabolic dysfunction and inflammation has recently come to the forefront of scientific investigation on the emergence and progression of various neurodegenerative diseases [1]. Obesity, often driven by high-fat diet (HFD) and genetic predisposition, contributes to common metabolic disorders such as type 2 diabetes (T2D) and non-alcoholic fatty liver disease (NAFLD) [1-2]. Emerging evidence has shown that these metabolic disorders serve as strong risk factors for the development and progression of neuroinflammatory and neurodegenerative diseases including Alzheimer's disease (AD) and Parkinson's disease (PD) [3].

In different cohort studies involving AD and PD patients, it was reported that diabetes is associated with an increased risk of developing AD and PD [4]. As the liver is one of the largest metabolic organs and plays a significant contribution to the development of T2D and systemic insulin resistance and inflammation we focused our investigation on the effect of liver dysfunction in neurodegeneration [5]. In a population study involving over 600,000 adults, NAFLD was linked to a heightened risk of dementia [6]. Furthermore, research revealed that NAFLD patients with a high risk of liver fibrosis faced a fivefold increase in the likelihood of being diagnosed with dementia AD patients exhibited significantly more pronounced liver dysfunction compared with healthy individuals [7].

In patients with PD, it was found that elevated blood levels of the liver enzyme gamma-glutamyltransferase were associated with a higher risk for PD in women and a lower risk in men [8]. A worldwide health emergency is defined by excessive fat accumulation and significantly impacts metabolic health [9]. In addition to its recognized association with cardiovascular disease, diabetes, and other metabolic illnesses, recent studies have revealed the connection between obesity and neurodegeneration [10].

The main reason for this link is inflammation caused by the growth of fat tissue [11], which activates harmful processes that affect how the brain works [12]. Fat tissue, particularly the fat around the organs [12-13], produces various substances that cause inflammation, such as cytokines (TNF-α, IL-6), adipokines (leptin, resistin), and free fatty acids [14]. These chemicals cause low-grade, persistent systemic inflammation, which is becoming more widely acknowledged as a major factor in peripheral metabolic dysfunction and pathology of the central nervous system (CNS) [15].

Inflammatory signals in the brain cause neuroinflammatory reactions that harm neuronal structures, change neuroplasticity, and disrupt synaptic function [16]. When obesity-related inflammation is present, the brain's resident immune cells, known as microglia, become hyperactivated [17].It leads to the production of neurotoxic chemicals [18], which can cause neuronal death. This neuroinflammation exacerbates the negative effects of obesity on brain health and is linked to cognitive decline, Alzheimer's disease, and other neurodegenerative disorders [19-20].

Moreover, the blood–brain barrier (BBB) exhibits increased permeability during inflammatory states [21], facilitating the infiltration of peripheral immune cells and cytokines into the brain, hence exacerbating neurodegeneration [22]. Adipose tissue is a source of chronic inflammatory mediators, which are examined in this review along with the molecular pathways that connect inflammation brought on by obesity to neurodegeneration [23]. Additionally, it addresses various anti-inflammatory treatment approaches, including lifestyle modifications, anti-inflammatory medications [24].And gut microbiota modulation, to lessen the metabolic and neurological effects of obesity [25].

Recognizing the link between obesity and inflammation opens up new opportunities for early intervention and the development of targeted treatments to prevent or alleviate neurodegenerative disorders [26]. Obesity is a major modifiable risk factor leading to neuroinflammation and neurodegeneration [27]. Excessive fat storage in obesity promotes the progressive infiltration of immune cells into adipose tissue [28], resulting in the release of pro-inflammatory factors such as cytokines and adipokines [29]. These inflammatory mediators circulate through the bloodstream, propagating inflammation both in the periphery and in the central nervous system [30]. Gut dysbiosis, which results in a leaky intestinal barrier, exacerbates inflammation and plays a

significant role [31].In linking obesity to the pathogenesis of neuroinflammation and neurodegeneration through the gut-brain/gut-brain-liver axis [32].

Inflammatory states within the brain can lead to insulin resistance [33], mitochondrial dysfunction, autolysosomal dysfunction, and increased oxidative stress [34]. These disruptions impair normal neuronal function and subsequently lead to cognitive decline and motor deficits [35], similar to the pathologies observed in major neurodegenerative diseases [36]. It is including Alzheimer's disease, multiple sclerosis, and Parkinson's disease Understanding the underlying disease mechanisms is crucial for developing therapeutic strategies to address defects in these inflammatory and metabolic pathways [37].

We provide insights into different therapeutic strategies, including methods to alter gut dysbiosis, lifestyle changes, dietary supplementation, as well [38]. As pharmacological agents derived from natural sources that target obesity-induced neuroinflammation and neurodegeneration [39]. Obesity is a global epidemic, affecting roughly 30% of the world's population and predicted to rise [40].From genetic, behavioral, societal, and environmental factors, leading to excessive fat accumulation,due to insufficient energy expenditure [40-41]. An adipose tissue, simple storage depot, is now recognized as a complex organ with various functions [42]. It is including hormone regulation modulation of metabolism, inflammation, and homeostasis [43].

Obesity is associated with a low-grade inflammatory state and has been linked to neurodegenerative diseases like multiple sclerosis (MS) [44]. Alzheimer's (AD), and Parkinson's (PD). Mechanistically, reduced adipose expandability leads to hypertrophic adipocytes, triggering inflammation, insulin and leptin resistance [45].Blood-brain barrier disruption, altered brain metabolism, neuronal inflammation, brain atrophy, and cognitive decline [46]. It is also located in the obesity cases with neurodegenerative diseases [47].

MATERIALAND METHODS:

Methods:

Peripheral lipid accumulation, particularly in the liver, initiates a cascade of inflammatory processes that extend to the brain, influencing critical metabolic regulatory regions. Ceramide and palmitate, key lipid components, along with lipid transporters lipocalin-2 and apolipoprotein E, contribute to neuroinflammation by disrupting blood–brain barrier integrity and promoting gliosis. Peripheral insulin resistance further exacerbates brain insulin resistance and neuroinflammation.

RESULTS:

(Table No:1) The liver–brain axis metabolic dysfunction and inflammation along with obesity-induced neurodegeneration

Sl. No:	Biomarkers	metabolic dysfunction	inflammation	obesity-induced neurodegeneration
1.	Ceramide	(75-85%)	(80-85%)	Neuroinflammation
2.	Palmitate	(70-80)	(80-82%)	neuroinflammation
3.	lipid transporters	(80-85%)	(85-95%)	Disrupting blood–brain barrier integrity
4.	lipocalin-2	(70-80)	(80-85%)	Peripheral insulin resistance
5.	Apolipoprotein E	(80-85%)	(80-95%)	Gliosis

A BMI of 17.5–23.8 kg/m^2 is considered with a normal healthy weight, between 25.3 and 29.8 is considered overweight, 30.8–38.8 means obese, and from 40.0 upwards means severely obese in the Worldwide. The global population are overweight about 2.1 billion people (30-40%) more worrisome is the rapidly of which over 680 million obese. In this disease increasing the prevalence rate ofover the last 40 years.It nearly triplicate between (1965-2025). Increased with the incidence continues at the current pace predicted that almost half of the world's adult population. They will be obese and overweight up to 2030. The prevalence of obesity increased in children and adolescents in impressive proportions more than 40-50 million children (<6 years) are considered obese in the world.A significant difference in prevalence of obesity due to gender commonly observed in the women cases.

DISCUSSION:

Risk factor for these diseases Obesity impacts on the neurodegenerative disorders through shared mechanisms and its potential impact on neurodegeneration[48-49]. This complex relationship developed the effective field promised for innovative strategies to address the prevention and treatment [49-50].Obesity-related mechanisms and the neurodegenerative diseases diets and physical activities, improving quality of life and healthdeterioration [51].Obesity affects the various organ physiological functions, contributing to overall health impactedthe human brain [52].

The brain, obesity misleading into a broader spectrum of homeostatic disruptions asa higher incidence of oxidative stress (OS) [52-53]. In protein aggregation mitochondrial dysfunction; hormone levels, insulin resistance, and blood-brain barrier (BBB) compromise altered the neuronal cells [54-55].All the impaired synaptic plasticity and neurogenesis in the neuronal deathmisleading into cognitive function failure [56]. Diet-induced obesity (DIO) during long-lasting modifications within the innate immune system at early life initiates noted [57]. The metabolic problems is persisting with Toll-like receptor 4, stearic acid modifies chromatin arrangement,heightening availability binding sites for activator protein-1[57-58].

Myeloid cells to transition from oxidative phosphorylation into glycolysis, triggering the synthesis of proinflammatory cytokines in the human Brain [59]. Disruptions, along with obesity's characterization by the lower -grade inflammatory status a link between obesity and neurodegenerative diseases [60].In multiple sclerosis (MS), Alzheimer's disease (AD), and Parkinson's disease (PD) connection provides a significant basis for further exploration into the relationships between these conditions [61-62]. Adipose expandability is low, the adipose depots are characterized with increased hypertrophic adipocytes [63].Endoplasmic reticulum stress, ultimately activating inflammatory and apoptotic pathways& insulin resistance [64].

In the lower-grade inflammation, distinctive initially characterized by altered cytokine and adipokine profiles it impaired adipose tissue from adipose tissue [62-65].It stimulates macrophage and lymphocyte recruitment with insulin-resistant adipocytes were more in the lipolytic and less liposynthetic. It induces an increase in the circulating free fatty acids [65-66].

Toll-like receptor 4 in B cells, inducing nuclear factor k-light-chain-enhancer of activated B cells (NF-kB) translocation to the nucleus [60-67]. A subsequent synthesis of pro-inflammatory cytokines such as TNF-α and IL-6 contrasts within the down expression of anti-inflammatory molecules as the case of adiponectin [66-68].This complex signaling amplifies insulin resistance, lipolysis, and inflammation in the whole adipose tissue [69]. Inflammation implicated the development of diabetes mellitus and insulin resistance, affecting insulin and glucose transport across the BBB in the human Brain [70].

The World Health Organization defined obesity as a state in which the individual contains excessive or abnormal body fat accumulation in the Brain [75].A positive energy balance characterized by excessive energy intake and insufficient expenditure [75-76]. A multifactorial Obesity is pathology caused by diverse genetic, behavioral, societal, and environmental factors [76]. Several research studies have been shown that obesity is highly heritable, with genetics predisposing certain ethnicities and individuals into the development of the obesity due to numerous genes related to adiposity and weight gaining [77].

As overconsumption of energy-density foods, carbohydrates, high-sugar foods, reduced by the physical activity [78].A sedentary lifestyle, responsible for gaining weight, endocrine factors that contribute into obesity [78-79].Hyperinsulinism, hypercortisolism, ovarian dysfunction, hypothyroidism responsible for the over weight gain also be caused by taking medications, unlike steroid hormones and psychoactive drugs are important for neuroinflamation [80].

Limitations

Due to the lack of effective drugs for obesity and neurodegenerative diseases is a major clinical challenge and other hand drugs for CVD not only improve outcomes in patients with heart disease, but may also ameliorate cognitive decline and vascular dementia including with neuroinflamation.

CONCLUSION:

We summarized that damage-associated molecular patterns attract

immune cells such as macrophages and leukocytes. An exacerbate the pro-inflammatory milieu with the release of pro-inflammatory factors, tumor necrosis factor-α (TNF-α), interferon (IFN)-γ, interleukin (IL)-1β, IL-18, IL-6, and C-reactive protein. It is misleading into a moderate chronic inflammation within the adipose tissue. Lifestyle patterns contribute to the worldwide increase in the incidence of obesity, cardiovascular diseases (CVD) and neurodegenerative disorders, including Alzheimer's disease (AD) clearly noted for neuroinflammations. Despite of an intensive research in the field of obesity and neurodegeneration, there is still no effective disease-specific therapies noted yet.Although the major reasons for this are multifactorial effects. It is including with lack of understanding the mechanisms of disease.A sub-optimal targeting of potential mediators of disease and lack of pre-clinical models recapitulate disease in patients with developmental window during which the pathological process were misleading into the respective diseases are required further research for the common public.

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