# NLRP3, Insulin, and Alzheimer's Disease

Subjects: Neurosciences

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Alzheimer's disease (AD) is the most common form of neurodegenerative dementia. Metabolic disorders including obesity and type 2 diabetes mellitus (T2DM) may stimulate amyloid β (Aβ) aggregate formation. Activation of the inflammasome complex, particularly NLRP3, has a crucial role in obesity-induced inflammation, insulin resistance, and T2DM. The abnormal activation of the NLRP3 signaling pathway influences neuroinflammatory processes.

Keywords: obesity ; inflammasome ; Alzheimer's disease

## 1. Overview

Alzheimer's disease (AD) is the most common form of neurodegenerative dementia. Metabolic disorders including obesity and type 2 diabetes mellitus (T2DM) may stimulate amyloid β (Aβ) aggregate formation. AD, obesity, and T2DM share similar features such as chronic inflammation, increased oxidative stress, insulin resistance, and impaired energy metabolism. Adiposity is associated with the pro-inflammatory phenotype. Adiposity-related inflammatory factors lead to the formation of inflammasome complexes, which are responsible for the activation, maturation, and release of the pro-inflammatory cytokines including interleukin-1β (IL-1β) and interleukin-18 (IL-18). Activation of the inflammasome complex, particularly NLRP3 (nucleotide-binding oligomerization domain (NOD)-like receptor protein 3), has a crucial role in obesity-induced inflammation, insulin resistance, and T2DM. The abnormal activation of the NLRP3 signaling pathway influences neuroinflammatory processes. NLRP3/IL-1β signaling could underlie the association between adiposity and cognitive impairment in humans. Herein, we present the role of obesity-related diseases (obesity, low-grade chronic inflammation, T2DM, insulin resistance, and enhanced NLRP3 activity) in AD. Moreover, we also discuss the mechanisms by which the NLRP3 activation potentially links inflammation, peripheral and central insulin resistance, and metabolic changes with AD.

## 2. Background

AD, believed to contribute to 60–70% of neurodegenerative dementia cases, is a complex disorder that develops gradually and progressively with symptom progression over time, from mild forgetfulness to severe mental impairment. According to the World Alzheimer Report, it is estimated that 50 million people worldwide have dementia, and the number of people with dementia is projected to increase to 82 million by 2030 and to 152 million by 2050 [1].

Although aging is the leading risk factor for the development of Alzheimer's disease, growing evidence, also from animal models, indicates that metabolic dysfunctions may have a crucial role in the etiology of AD [2][3]. Obesity and T2DM are reported to be related to AD [3][4]. It has been hypothesized that central nervous system (CNS) inflammation takes part in the progression of chronic neurodegenerative diseases, but the mechanisms are still unclear. It is also possible that T2DM, or even prediabetes, can modulate the expression of brain pro-inflammatory cytokines in AD [5]. Additionally, both prediabetes and T2DM promote microglia activation in the mice AD model, thus confirming that the inflammatory process may serve as a link between AD and T2DM [6].

Obesity, characterized by hypertrophy and hyperplasia of adipocytes, is accompanied by chronic local inflammation [7]. Excessive accumulation of fat leads to enhanced expression and release of pro-inflammatory cytokines including tumor necrosis factor α (TNFα), interleukin-6 (IL-6), adipokines, and monocyte chemoattractant protein-1 (MCP-1), which further recruit immune cells to intensify inflammation in adipose tissue [8][9]. Additionally, adipose tissue also contains numerous immune cells, and its total number increases dramatically with the grade of obesity. The downregulation of M2 macrophages with anti-inflammatory phenotype and the activation of M1 macrophages with pro-inflammatory phenotype can exaggerate inflammation and insulin resistance in adipocytes [10]. Innate immune cells such as macrophages can induce inflammatory reactions through detection of pathogen- or danger-associated molecular patterns (PAMPs or DAMPs) using a wide range of pattern-recognition receptors (PRRs) [11][12]. Adiposity-related inflammatory factors lead to the formation of inflammasome complexes. Inflammasomes are cytosolic multiprotein complexes that recognize both

PAMPs and DAMPs. These high-molecular-weight factors are responsible for the activation, maturation, and release processes of the pro-inflammatory cytokines IL-1β and IL-18. Moreover, obesity-related factors are important activators of inflammasome-derived cytokines [13][14].

There are two types of signaling pathways that activate one of the inflammasomes, the NLRP3 inflammasome: the canonical and noncanonical signaling pathways [15]. The canonical pathway depends on caspase-1 and involves inflammasome complexes detecting pattern PRR proteins and inducing recruitment of procaspase-1. The noncanonical signal pathway is mainly dependent on mouse caspase-11 or human caspase-4 and caspase-5. The noncanonical inflammasome is activated by lipopolysaccharide (LPS) [16].

Recent advances have highlighted that various pathways could be regulators of the pathological features in Alzheimer's disease. We present current knowledge of the metabolic dysregulations, including the NLRP3 inflammasome activation, and their contribution to AD pathology.

## 3. Alzheimer's Disease

From the clinical point of view, AD is accompanied by a progressive decline in memory and executive functions, as well as impairment of daily living activities [17]. The first, early symptoms of AD have been associated with the loss of episodic memory and difficulties in learning new information. When AD progresses, there is greater memory loss, cognitive impairment, and behavioral change, along with dysfunction of language and speech [18][19].

Neuropathological lesions in AD are associated with multiple changes at the cellular level. The typical histopathological features include Aβ formation and accumulation, mitochondrial damage, loss of synapses, activation of microglia (gliosis) and astrocytes (astrocytosis), phosphorylation of tau, and neurofibrillary tangles formation (NFT) [20]. All of these pathological processes lead to neuronal death, which is observed in the brains of AD patients.

The metabolic dysfunction may stimulate the Aβ aggregate formation [4][21]. Furthermore, AD, obesity, and T2DM share similar risk factors and some clinical and biochemical features. These particular features are associated with chronic inflammation, increased oxidative stress, and impairment in insulin signaling and energy metabolism [22][23]. Additionally, due to the potential multifactorial role of obesity in pathological processes seen in AD, obesity could serve as a risk factor for this disease [24].

## 4. Inflammasome NLRP3 and AD

Although the inflammasome signaling in the CNS is mainly attributed to microglia, the key innate immune cells of the brain, expression of inflammasome components have also been found in other cell types of the CNS including neurons, astrocytes, perivascular CNS macrophages, oligodendrocytes, and endothelial cells [25][26][27][28]. Inappropriate NLRP3 signaling pathway has implications in neuroinflammatory processes [29][30].

Data from both animal models and clinical studies indicate that activation of NLRP3 is linked to pathogenic mechanisms in AD. High levels of IL-1β in the brain induce tau protein hyperphosphorylation and neuronal damage [31]. In turn, accumulation and deposition of Aβ, as well as NFT formation, cause the release of mature IL-1β via activation of NLRP3 in microglia [32][33][34]. Therefore, overexpression of IL-1β may aggravate the central chronic inflammatory response. In AD microglial excessive NLRP3 activation and elevated IL-1β concentration can exacerbate tau hyperphosphorylation, neurofibrillary tangles formation, and synaptic dysfunction induced by a detrimental chronic inflammation [35]. NLRP3 activated by Aβ can induce enhanced production of IL-1β, promote microglial synthesis, and release proinflammatory cytokines and neurotoxic factors [36].

*Nlrp3*-null mutation protects against cognitive deficits in aged mice and mouse models of AD [36][37]. Administration of NLRP3 or caspase-1 inhibitors resultes in a significant increase of microglia ability to clear Aβ deposits, as well as in reduced Aβ deposition, and improvement in cognitive impairment and hyperactive behavior [36][38].

To sum up, it could be stated that the interrelation between NLRP3 and AD pathology is a vicious cycle.

## 5. Conclusions

The above evidence clearly shows that obesity-related inflammation initially located in adipose tissue may finally have systemic effects on other organs and systems, including the CNS. As it has been shown, inflammasomes can act as a link between obesity, insulin resistance, and the development of neuroinflammation in neurodegenerative diseases, including AD. Although the adiposity-related mechanism of inflammasome activation is still unclear, inflammasomes may be a

therapeutic target in the treatment of obesity. Further studies on inflammasomes could result in the development of innovative precision medicine approaches for the management of obesity and its complications, including those of neurodegenerative origin. The problem that should be considered when discussing inflammasome-targeted treatment is the multitude of stimulant compounds and, in addition, many physiological as well as pathological results of NLRP3 activity. The inhibition of NLRP3 should be balanced to avoid any other side effects. Unfortunately, to date, there is no NLRP3 inflammasome-targeted drug admitted to treatment. However, it should be highlighted that prevention and proper treatment of obesity and obesity-related diseases might lower the risk of AD. Finally, exercise and a low caloric/low-fat diet are a must for all overweight/obese patients.

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