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Relationship Between Obesity, Alzheimer's Disease, and Parkinson's Disease: an Astrocentric View

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Abstract Obesity is considered one of the greatest risk to human health and is associated with several factors including genetic components, diet, and physical inactivity. Recently, the relationship between obesity and numerous progressive and aging-related neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD) have been observed. Thus, the involvement of the most abundant and heterogeneous group of glial cells in neurodegenerative diseases, the astrocytes, is caused by a combination of the failure on their normal homeostatic functions and the increase of toxic metabolites upon pathological event. Upon brain damage, molecular signals induce astrocyte activation and migration to the site of injury, entering in a highly active state, with the aim to contribute to ameliorating or worsening the pathology. In this regard, the aim of this review is to elucidate the relationship between obesity, Alzheimer's disease, and Parkinson's disease and highlight the role of astrocytes in these pathologies.

Keywords Astrocytes · Neuroinflammation · Obesity · Alzheimer's disease · Parkinson's disease

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Introduction

Obesity is an excessive accumulation of fat stored in adipose and non-adipose tissue as triglycerides that can be broken down into fatty acids, which can negatively affect health by the increased expression of pro-inflammatory markers [1]. Globally, the prevalence of obesity is rising [2–4]. Actually, it is a public health problem, and according to the World Health Organization, it is estimated that more than 1.9 billion adults, 18 years and older, were overweight in 2014 [5]. In fact, globally, there are more than 300 million adults who are obese and 1 billion who are overweight [6]. Obesity, which is considered one of the greatest threats to human health [7], is associated with multitude of risk factors including genetic components, physical inactivity, blood lipid disorders, inflammation, and insulin resistance. All these clusters of common pathologies have been associated to metabolic syndrome, which is a risk factor for neurological diseases [8, 9].

Over the last decade, the population of obese people has also increased in epidemic proportions. For this reason, the probable association between obesity and neurodegenerative diseases has been studied with a main focus on the probability that obesity may lead to neurodegeneration, exacerbate cognitive decline, and increase susceptibility to brain damage [2, 10]. In this regard, a large number of studies have demonstrated that people who suffer from midlife obesity (measured by body mass index or central adiposity) have an augmented risk for developing Alzheimer's disease (AD) and Parkinson's disease (PD) [11].

The precise mechanisms of the relationship between fat gain and loss and cognitive functioning remain to be explained. Obesity involves a series of pathological cellular responses due to an increment in basal lipolysis and subsequent release of free fatty acids (FFA) into the bloodstream. Indeed, the increase in FFA produces the activation of non-oxidative metabolic pathways such as ceramides, lysosomal degradation,

pattern recognition receptors activation, and endoplasmic reticulum stress. Thus, the activation of these pathways are detrimental to normal cellular homeostasis and cell viability [12], thus resulting in systemic and brain inflammation, particularly in the hypothalamus, leading to cellular dysfunction, lipid droplet formation, and finally cell death [13, 14].

Neurodegenerative diseases (ND) are an important cause of disability, morbidity, and decreased quality of life, constituting the cause of 12 % of total deaths globally [1, 5]. These diseases represent a heterogeneous group of disorders, which are characterized by progressive dysfunction of neurons and astrocytes [15–18]. Recent findings suggest that astrocytes have been strongly involved in the maintenance of brain metabolism, anti-oxidant maintenance, and neuroprotection [17, 19–27]. For this reason, these cells play a critical role in the onset and progression of neurodegenerative diseases [28]. However, the cause of the progressive degeneration of neurons remains unresolved. It has been demonstrated that there is an activation of astrocytes in areas mostly affected by the disease. Both in vitro and in vivo studies suggest that astrocytes can be activated by FFAs [29]. In turn, these compounds can be elevated in subjects with obesity [30, 31]. FFAs can activate Toll-like receptors (TLR) and signaling cascades and generate nuclear translocation of the transcription factor NF-kB (nuclear factor kappa-light chain enhancer of activated B cells) [32]. This factor is implicated in several cellular processes, such as immune and inflammatory responses. After activation and nuclear translocation, NF-kB can promote the production of inflammatory cytokines like interleukin (IL)-6), tumor necrosis factor (TNF), and IL-1 [33]. According to this, in the specific case of interleukin 6, it is important to highlight that it is a cytokine not only implicated in inflammation and infection responses, but also in the adjustment of metabolic, restorative, and neural processes. It has been shown that IL-6 has been classified as a pro-inflammatory cytokine, but in some cases, it might exert restorative or anti-inflammatory activities [34].

Experimental findings identify these pro-inflammatory pathways are important regulators of different neurodegenerative pathologies [35]. Additionally, these cytokines have been recognized as an important mediator in facilitating leukocyte extravasation from the circulation through the blood-brain barrier (BBB) into the CNS parenchyma and that has been associated with neurodegeneration [36, 37]. Taking into account these evidences, the aim of this review is to elucidate the role of obesity and astrocytes in AD and PD development.

Association of Obesity with Neurodegenerative Diseases

Increasing life expectancy is concomitant with increased risk of aging-associated diseases such as neurodegenerative diseases and related health problems such as obesity. Recently, the relationship between obesity and numerous progressive and aging-related neurodegenerative diseases have been observed [38]. This relationship has been assessed in human and animal models with the aim to demonstrate that obesity might be associated to neurodegeneration by stimulating cognitive deterioration and raising the vulnerability to brain injury [39]. Although the exact mechanisms by which obesity negatively affects the brain are poorly understood, previous study has indicated that augmented inflammatory responses are key physiologic features of obesity [40]. In this respect, obesity may lead to brain inflammation and cause protein deposition, oxidative stress, morphological changes in brain cells, and alterations in important metabolic pathways [3, 4, 41].

Obesity and Astrocytes

Two of the main characteristic changes in obese population are insulin resistance and hyperglycemia; while in the first insulin levels are higher in comparison with the levels of glucose, in the second there is an abnormal increase of glucose in the blood [42–46]. The relationship between obesity and astrocytes is primarily generated by hormones. For example, astrocytes are able to synthesize different hormones such as leptin, ghrelin, and insulin [47–49], and as such, these hormones have been intensively studied because of their close relation with obesity and body weight [50, 51]. Indeed, it is shown that obese subjects show higher levels of these hormones than control subjects and this fact is correlated with the accumulation of fat tissue [51].

Different signaling pathways are closely related with the regulation of food intake. For example, one of them is the leptin signaling pathway which plays an important role in the regulation of energy homeostasis and regulation of food intake [52]. There is evidence that leptin signaling in astrocytes can modulate the metabolic response to high-fat diet [53]. According to this, different studies with animal models showed a decrease in food intake and an increase of the hormone ghrelin that is closely related with the stimulation of the hunger after deletion of leptin receptors in the brain [52].

Taking into account that main pathological alteration in obese population is the insulin resistance, it is important to stand out that insulin actions are mediated by the insulin receptor (IR), which is constituted by two alpha sub-units located in the extracellular level [54]. García-Cáceres et al. (2016) used positron emission tomography and glucose monitoring in cerebral spinal fluid in in vivo GFAP-IR KO mice and showed that lack of insulin receptors in hypothalamic astrocytes affects systemic glucose metabolism, thus raising the question of a possible effect in neuroprotection [45]. Moreover, different studies in mice have demonstrated that administration of insulin in the brain reduces body weight, and also showed that mice without insulin receptors become obese [55]. Finally, insulin is also related with dopamine

circuits [56]. In this regard, it has been demonstrated that insulin increases the activity of dopamine receptors in mice brain, while there is a decrease in the level of the enzyme tyrosine hydroxylase in obese animals [57].

Obesity and AD

AD is the most common form of dementia and a progressive neurodegenerative disease that is mainly diagnosed by its clinical features [12, 58]. Of the 5.4 million Americans with AD, an estimated 5.2 million people are 65 years of age and older and approximately 200,000 individuals are under 65 years of age. Age is an important risk factor, with one in nine people over 65 years old having AD [59]. It is important to highlight that more women than men have AD and approximately two thirds of Americans with the disease are women [60]. AD is determined clinically by progressive cognitive impairment in two or more domains, such as memory, language, calculations, orientation, and judgment, in which these alterations may be severe enough to induce social or occupational disability [61]. Neuropathologically, the two characteristic findings of the disease are deposits of aggregated amyloid β (Aβ) in neuritic plaques [62] and neurofibrillary tangles (NT), which are produced by hyperphosphorylation of Tau, a microtubule-associated protein [61, 63]. It has been suggested that Aβ could trigger changes in Tau, producing the formation of these neurofibrillary tangles, thus resulting in synaptic loss and neuronal damage [64–66].

The increased prevalence of obesity, as well as reduced age of onset of obesity in the population, may lead to much higher incidence and prevalence of diseases such as AD in younger people, which are normally considered an old-age disease [12]. Also, there is evidence that obesity accelerates memory dysfunction and neuroinflammation in AD [67]. Several studies have exposed that people with obesity have an elevated risk of developing AD and dementia [68, 69]. The overweight in the elderly of 70 to 88 years and older has also been reported as a risk factor for AD [2, 70].

The mechanisms by which overweight increased risk of AD have not been fully understood. There are multifactorial mechanisms that link obesity with AD which includes systemic inflammation, activated astroglia, plaque deposition, and diminished plaque clearance [2, 71–73]. Increased adiposity tissue is associated with insulin resistance, hyperinsulinemia, oxidative stress, and dysregulation of glucose metabolism. Consequently, these metabolic profiles might cause formation and deposition of advanced glycosylation end-products (AGEs) and precursors [72]. AGEs are neurotoxic compounds which increase aggregation by the glycation of amyloid β, as the receptors for AGEs can use amyloid β as ligands. This interaction has been previously shown to play a key role in the pathogenesis of AD [74].

Though the association of obesity and AD has been contemplated here, this should be analyzed in the context that AD may have a reciprocal action in developing hyperinsulinemia, insulin resistance, dyslipidemia, and hypertension. It is important to point that this cluster of risk factors is considered a metabolic syndrome (MS), which has been linked with AD in recent studies [75, 76]. It is important to highlight that obesity is also related with dyslipidemia and disordered fatty acid and cholesterol metabolisms, thus affecting numerous neuronal processes that have been implicated in the development of neurodegenerative disorders [77]. Table 1 shows clinical and animal studies which demonstrate the relationship between obesity and AD. These studies showed that BMI is directly associated with cognitive performance and function including memory [78–83]. Indeed, many studies assessing the brain parenchymal fraction demonstrated that obesity influences brain structure, and volume, thus triggering brain dysfunction, brain atrophy, and cognitive impairment in humans [84–86]. Besides, it has been demonstrated that high-fat diet reduces synaptic plasticity in the hippocampus and cerebral cortex in animal models [87, 88] and increases amyloid and tau aggregates in transgenic mouse models of AD [89, 90], leading to neuroinflammation, reactive gliosis, and predisposition to injury [39, 91]. Finally, studies in brain and adipose tissue in a murine model of high-fat diet-induced obesity showed elevations in amyloid precursor protein (APP), Aβ, and Tau phosphorylation in the hippocampus, demonstrating that high-fat diet-dependent obesity is associated to pro-inflammatory changes in brain and adipose tissue, which is characterized by increased levels of APP [92, 93]. Although more studies on this matter are needed, experimental findings discussed here support the idea that overweight may increase the risk of developing AD through the modulation of cerebral amyloid and tau proteins, and that relationship might be modulated by sex hormones.

Obesity and PD

PD is the second most prevalent neurodegenerative disease after AD and is a chronic and progressive disorder. PD is characterized by the death of dopaminergic neurons in the substantia nigra (SN), as well as intracellular accumulation of aggregates of α-synuclein in neurons of the brainstem, spinal cord, and cortex [101–105]. It is estimated that 10 million people worldwide and about 1 % of the population over 60 years of age are living with PD [61, 106]. It is important to highlight that men are one and a half times more likely to suffer from PD than women [106]. It is believed that at early stages, PD pathology has a focal initiation site that later propagates throughout the brain [107, 108], and initial α-synuclein accumulation occurs without neuronal death or evident symptoms [103]. Although the complete molecular mechanisms of PD progression are not well understood [109], the central

Table 1 Studies showing a relationship between obesity and AD pathology

Subject to study	Focus of the study	Results and conclusion	References
Human	Post-mortem non-demented obese individuals	Presence of increased levels of hippocampal Aβ, APP, and Tau protein, compared with non-obese individuals	[94]
	BMI	Inverse relationship between BMI and cognitive function	[79, 82]
	Indices of central obesity	Demonstrated a directly association between obesity and poorer cognitive test performance	[95]
	BMI, early adulthood, early and late midlife	Found that be obese at two of three stages was associated with lower memory and executive function scores	[83]
	BMI and middle-aged	An elevated level of BMI is related with lower cognitive performance	[78, 81]
	Brain and obesity	Obesity may influence brain structure and volume	[84, 86, 96]
	Obesity and sex	Increased BMI was related with poorer cognitive performance in middle-aged men but not middle-aged women	[80, 81]
Animal	Diet-induced obesity	Induced elevations in APP, amyloid β, and Tau phosphorylation in rats and wild-type mice shown	[92, 93]
		Incremented amyloid and tau pathology in transgenic mouse models of AD	[89, 90]
		A range of memory and learning skills were found affected	[87, 88]
		Reduced synaptic plasticity in the hippocampus and cerebral cortex	[87, 88]
		Increased neural apoptosis in the hippocampus and hypothalamus	[97, 98]
		Disrupted BBR permeability	[87, 99, 100]
		Leads to brain inflammation, reactive gliosis and predisposition to injury	[39, 91]

focus has always been on the damage of the dopaminergic neurons and reduction of dopamine, but a role for glial cells in mediating pathological or neuroprotective responses in PD is becoming increasingly recognized [61].

Several studies indicated that some factors might be associated with risk of developing PD. These factors include age, genetic factors, environmental toxins, oxidative stress, mitochondrial dysfunction, body shape, low physical activities, and poor diet. Other investigations used a semiquantitative food-frequency questionnaire in 110 PD case patients and 287 control subjects and showed that a high-fat diet, especially that one with increased intake of animal fat, is a risk factor for PD pathogenesis [110]. People with obesity and who are overweight are more physically inactive than normal weight people [111, 112], and lower levels of physical activity may increase the risk of developing PD [113]. On the other hand, other studies have suggested that obesity/overweight might be associated with PD due to disturbances of eating behavior which are associated with abnormal hypothalamic neurotransmission [114, 115].

The relationship between obesity and PD was revealed when overweight subjects demonstrated a depletion in their striatal dopamine receptor availability (D2) [116], and that dopamine played an important role in both obesity and PD, having in common the loss of dopaminergic neurons, and lower dopamine levels in the hypothalamus and striatum [117–119]. The relationship between obesity and dopamine levels can explain in part these findings. The mechanisms associated to obesity and PD are multifactorial. In this context, fat acting as a substrate for lipid nigrostriatal dopaminergic neurotoxins and overweight acting as a systemic metabolic modulator may increase body's vulnerability to impairment from neurotoxins. Experimental evidences from positron emission tomography (PET) support that obese transgenic animal model exhibits increased striatal dopaminergic neurons susceptibility to methamphetamine and kainic acid [2]. Additionally, dopamine has a key role in the regulation of food intake [114, 115, 120].

Recent epidemiological studies have demonstrated a potential association between obesity/overweight and the risk of PD. In a prospective study with 451 Japanese-American subjects in Hawaii, the authors reported that greater midlife triceps skinfold thickness was correlated with higher risk of PD, which is independent of BMI [121, 122]. Nevertheless, studies correlate BMI with disease severity and cognitive decline and dyskinesia in PD [123], and it was reported that high-fat diet may confer a greater susceptibility to environmental toxins and accelerate the pathogenesis of PD [124]. Finally, Briceño and colleagues carried out a cross-sectional study including 177 healthy controls and 177 PD patients and demonstrated that overweight/obesity was more common among patients with PD, in comparison with non-demented patients [97]. Also, preclinical studies using animal models link obesity and PD. For example, high-fat diet exacerbated the progression of parkinsonism by increasing dopamine depletion in the substantia nigra in mice and also by the reduced capacity of nigral dopaminergic terminals to cope with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurotoxicity [124–126]. Although some studies were not able to provide substantial evidences about the association between

BMI, weight change, and waist circumference with the risk of PD [127, 128], others showed a clear relationship between obesity and PD and a correlation among BMI increase, inflammation, and PD disease severity [97, 121–126].

Neuroinflammation

Neuroinflammation is a term used to describe a mixture of neurotoxic and neuroprotective responses originated in the CNS by glial cells, as a defense mechanism that is associated with neutralization of an insult, destruction of injured cells, and repair of function and structure of the brain [129, 130]. Neuroinflammation is characterized by an integrated response of the different cells of CNS [131, 132], including neurons, glial cells, and the infiltrating leukocytes [133]. Neuroinflammatory responses may be helpful or harmful, as these mechanisms are associated with normal brain development and function, as well as with neuropathological processes during brain injury and neurodegeneration [134, 135]. There are two types of neuroinflammation. Firstly, acute inflammation, as a defensive response that helps to repair the impaired site, and secondly, chronic neuroinflammation that results from deleterious and more persistent stimuli [136]. Acute neuroinflammation develops quickly with the presence of pain, whereas chronic inflammation develops slowly [130].

Nowadays, it is broadly recognized that not all forms of neuroinflammation are necessarily detrimental for CNS function [133]. An efficient inflammatory response does not only removes pathogens and abnormally aggregated proteins but also results in beneficial, self-limiting, and healing processes [130, 133, 137]. In contrast to acute neuroinflammation, chronic neuroinflammation is a long-lived, persistent response that starts with an initial inflammatory stimulus but becomes self-propagating. Inflammatory factors produced by astrocytes, together with released damage-associated molecular patterns (DAMPs), can further increase inflammation and glial activation, leading to a vicious inflammatory cycle and the damage of local tissues. This long-term inflammation can have disastrous consequences in the CNS, ranging from loss of synapses to impaired cognition and lastly neurodegeneration [138–141]. The concept that the neuroinflammation is prejudicial implies that astroglial activation precedes and causes neuronal degeneration [142].

Obesity and Neuroinflammation

The adipose tissue not only stores fatty acids but also produces and releases a large number of other active compounds such as FFAs, resistin, TNF-α, IL-6, IL-1β, and others. Studies have reported that plasma FFA levels are usually elevated in obesity because the increased adipose tissue mass releases more FFA and its clearance may be reduced, which will further increase the rate of FFA release into the circulation [33].

There is evidence that FFAs can activate inflammatory and innate immune responses and trigger a phenomenon known as lipotoxicity in the brain. Recent studies demonstrated that acute elevation of plasma FFA activated the pro-inflammatory NF-kB signaling resulting in increased astrocytic expression of several inflammatory cytokines such as TNF-α, IL-1β, and IL-6. The brain is very sensitive to inflammatory mediators, and there is substantial data indicating that these inflammatory mediators play a critical role in the inhibition of different signaling pathway and in the induction of endoplasmic reticulum (ER) stress in hypothalamic neurons [143].

Mechanisms Associated to Neuroinflammation in Obesity

Previous studies have shown that hypothalamic dysfunction induced by inflammation causes neural dysregulation and neurodegeneration in obesity [144]. Studies have demonstrated an augmented expression of pro-inflammatory cytokines and activation of IkB kinase-β (IKKβ)/nuclear factor-kβ in the hypothalamus induced by high-fat diet. NF-kB is a critical modulator of immunity and inflammation in the CNS. NF-kB activation is stimulated mainly by IKKβ, in which this phosphorylates and degrades Ikβ proteins, thus liberating NF-kB to enter the nucleus and inducing the transcription of different inflammatory genes. During the immune response and inflammation, IKKβ/NF-κB activation is stimulated by different cell-membrane receptors including Toll-like receptors (TLRs).

It has been demonstrated that long-chain saturated fatty acids, possibly acting through TLR-3 and TLR-4, stimulate the generation of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6 [145–147]. Also, it has been reported that TLR-4 is expressed by activated astroglia in diet-induced obese (DIO) mice [148], which also activates NF-κβ signaling [149] thus leading to disrupted leptin and insulin signaling in the hypothalamus [148, 150]. Cytokine receptors such as TNF-α receptors have been shown to be mediating neuroinflammation in overweight. Experimental approaches of loss of function have showed that TNF-α receptor knockout [151, 152] reduced dietary-induced obesity in mice. Also, overnutrition leads to perturbations in the endoplasmic reticulum system. This perturbation activates IKKβ/NF-κβ signaling in the hypothalamus and results in an energy imbalance [153, 154]. ER stress could be a downstream event that ultimately triggers pro-inflammatory processes in the hypothalamus [146]. Recent studies indicated that ER stress and defective autophagy may activate IKKβ/NF-κB signaling pathway to generate hypothalamic inflammation [155, 156]. Furthermore, investigations on inflammatory cytokine expression identified the kinase c-jun *N*-terminal kinase (JNK) as

major intracellular contributors to the induction of inflammation. Compared with lean controls, obese tissues showed increased JNK activity in the liver, muscle, adipose tissue [155, 157], and the hypothalamus [158, 159]. JNK responds to diverse stress signals, including ER stress, pro-inflammatory cytokines, FFAs, and reactive oxygen species (ROS) [157, 160, 161]. Finally, independently of the mechanism involved, the common fact is that the hypothalamus is the main site of inflammation caused by the intake of high-fat diet, thus this process represents an early agent to the development of obesity and insulin resistance [146, 162–164].

Neuroinflammation in AD

Current evidences have shown that many compounds involved in the development of inflammatory processes are present in the CNS of patients with such neurodegenerative diseases [136]. Activated microglia and reactive astrocytes are observed in patients with these diseases, and it seems like that glial activation might have dual effects by degrading Aβ [165–167] and inducing neuroinflammation and neuronal dysfunction. The increase in Aβ concentration in aged transgenic AD mice are associated with increased concentrations of pro-inflammatory cytokines, including TNF-α, IL- 6, IL- 1α, and GM-CSF [168]. These results suggest that pathological accumulation of Aβ is a key factor that drives neuroinflammatory responses in AD.

There is evidence suggesting that the pro-inflammatory environment in the brains AD patients and in mouse models of cerebral amyloidosis induces brain damage. For example, the risk of developing dementia from mild cognitive disability is increased in AD patients with elevated concentrations of TNF-α and reduced concentrations of TGF-β in the CSF [169]. In a clinical trial with elders suffering from metabolic problems, it was shown that elevated levels of inflammation in plasma and serum had a negative effect on cognitive performance [170]. In animal models of AD, neuroinflammation is known as a response to sustained Aβ overproduction and deposition, in which includes involvement of the complement system and production of cytokines [171–173]. Janelsins and cols using quantitative real-time RT-PCR detected early activation of inflammatory processes in the entorhinal cortex and the hippocampus of the triple transgenic model (3xTg) of AD at 3 months of age [174]. The neuroinflammatory process was concurrent with the production and accumulation of intracellular Aβ, but occurred prior to any significant extracellular Aβ plaque deposition, which manifests at about 12 months of age in the 3xTg mice [174]. This neuroinflammation was characterized by a selective trend of increasing expression of TNF-α and monocyte chemoattractant protein-1 (MCP-1), which was not detected for 21 other cytokines tested [174]. Hoozemans and colleagues performed a study by analyzing important characteristics of the neuroinflammatory response in AD patients and control cases in a range between 52 and 97 years old. The authors used immunohistochemistry and antibodies directed against CD68 (KP1), HLA class II (CR3/43), and glial fibrillary acidic protein (GFAP). In this study, the authors found that the association between neuroinflammation and AD is stronger in relatively young AD cases compared with old AD cases, with an age-dependent presence of microglia and astrocytes, which is indicative of a neuroinflammatory response [175]. Finally, inflammation has a significant and important role in metabolic illness being a main risk factor for developing AD. Nevertheless, old individuals with metabolic syndrome did not have an enhanced risk of cognitive disability [176].

Neuroinflammation in PD

The neuroinflammatory processes in PD is characterized by the presence of activated glial cells in the substantia nigra from patients with PD or intoxicated by MPTP [177]. The implication of glucocorticoids (GCs) on this matter has been assessed. For example, an elevation in the systemic level of glucocorticoids (GCs) after the stimulation of the hypothalamic–pituitary–adrenal axis [178] was observed, which is in accordance with another study showing the role of glucocorticoid receptors (GRs) in the death of dopaminergic neurons and in neuroinflammation in models of PD. The results showed a loss of dopaminergic neurons induced by MPTP toxicity [179]. This increased loss of dopaminergic neurons was associated and directly related with an increased microglial and astroglial reaction, an enhanced production and release of pro-inflammatory mediators, and a decreased expression of anti-inflammatory factors [178], suggesting that glucocorticoids may adjust the brain inflammation to balance between a pro- and anti-inflammatory stimuli during neurodegeneration.

Studies performed in transgenic models reported increased TNF-α levels in the substancia nigra of mice overexpressing human α-synuclein, and this increase in TNF-α levels in vivo contrasted with the changes in TNF-α protein levels induced in vitro [180]. Other studies have shown that one of PD genes (DJ-1) is expressed in astrocytes and microglia, and it is known that these expression levels are upregulated in PD patients [181]. Astrocytes from DJ-1 knockout mice produce major levels of cyclooxygenase-2 (COX2) and IL-6 after lipopolysaccharide (LPS) treatment [182]. Mutations in *parkin* are the most common cause of recessively inherited PD [183]. It is demonstrated that this mutation may lead to the degeneration of dopaminergic neurons induced by LPS in the substancia nigra pars compacta (SNpc) of *parkin* knockout mice [184]. Aged *parkin* knockout mice showed enhanced astrogliosis in the striatum and abnormal microglial activation in the midbrain [185]. Altogether, these experimental

evidences suggest that *parkin* plays an outstanding role in the regulation of inflammation in PD [186].

Role of Astrocytes in Neuroinflammation

Astrocytes are the most abundant group of glial cells, representing approximately around 20 to 40 % of the total brain cell population. These glial cells are recognized to modulate extracellular glutamate level, form a "glial scar" after injury and have powerful pro-inflammatory responses as pivotal regulators of CNS inflammatory responses. After a brain injury, molecular signals induce astrocyte activation and migration to the site of the damage [18, 20, 21, 26, 187]. Astrocytes enter a highly active state, which are suggestive to contribute to ameliorating or worsening the pathology [21, 188, 189]. Astrocytes are part of the BBB [24, 190], therefore, these cells influence the entrance of cells into the CNS and also the activity of invading cells [191]. Activated astrocytes produce a number of cytokines and participate in mediating immune responses within the CNS [192]. Table 2 shows different functions of astrocytes.

The involvement of astrocytes in neurodegenerative diseases is associated with the loss of their normal homeostatic functions and the increase of toxic functions induced by damage. Intracellular aggregates in surviving astrocytes in various neurodegenerative diseases have been observed. The presence of these aggregates disturbs astrocytic functions in different ways that could be damaging to neuronal viability [58]. In this respect, astrocyte activation is one of the most important processes of the cellular responses to brain lesion and chronic neurodegeneration. Due to their different shapes, which can reflect their functional phenotypes, astrocytes can adopt from a quiescent state, as seen in the normal uninjured CNS, to reactive-like state, as observed after damage or illness [158, 204–206].

Table 2 Biological functions of astrocytes

Astrocyte functions	
Function	Reference
Blood-brain barrier (BBB) induction and maintenance	[193]
Metabolic support	[194]
Providing energy to neurons	[195]
Regulation of extracellular pH	[196]
Synthesis of precursor for glutamate and GABA production	[197]
Release of cytokines and chemokines	[198]
Forming "glial scar" after injury	[199]
Brain homeostasis	[188]
Brain energy metabolism	[200]
Modulate extracellular glutamate level	[201]
Spatial buffering	[202]
Neuroinflammation	[203]

It is important to highlight that inflammation, as stated above, has the ability to influence neuronal homeostasis by modulating intracellular mechanisms such as oxidative stress and ER stress. Oxidative stress is characterized by high levels of superoxide and hydrogen peroxide and has been involved in neuronal damage and cell death related with neurodegenerative diseases [207]. Large amounts of ROS and pro-inflammatory cytokines are produced by activated immune cells. In turn, ROS can activate NF-kB and favor the production of pro-inflammatory cytokines [208]. Inflammation and oxidative stress are highly related and therefore co-exist. There is evidence that high-fat diet is closely related with oxidative stress in diverse brain areas including the hippocampus [209, 210]. Besides, brain oxidative stress is associated with astrocyte activation, production of pro-inflammatory cytokine in the brain, and also with cognitive disability after high-fat diet consumption [91, 100]. Many cytokines, such as interleukins 1 and 6, are involved in the initiation and modulation of reactive astrogliosis, thus contributing to pathological inflammatory responses. Moreover, under different pathological situations, these factors are implicated as mediators of important processes such as neuroprotection and remyelination [211]. In different studies of injury models, interleukins 1β and 6 KO mice showed retarded astrocyte activation and enhanced BBB permeability, suggesting that cytokine-induced astrogliosis is very prominent to restore BBB integrity after trauma [212–216]. Other in vitro studies have demonstrated that cytokines, specifically IL-1, IL-6, and TNF, can favor the production of neuroprotective mediators [217]. There is evidence showing that TLR on cultured astrocytes induces the production of neurotrophic factors [218]. A similar action is displayed by chemokines such as CCL2 and CXCL12 which has an important role in the migration of neural progenitors in brains during development [219]. CCL2 is upregulated in diverse pathological stages in astrocytes and microglia [220, 221]. Other important chemokine in the CNS named CX3CL1 is expressed by astrocytes and neurons and has a role as an inhibitor of microglial-induced toxicity, as evidenced in three different in vivo models of neurotoxicity [222]. Finally, these studies may suggest that due to the production of cytokines and chemokines, reactive astrocytes may induce regeneration in the lesioned CNS (Fig. 1). Moreover, pro-inflammatory cytokines produced by astrocytes such as TNF-α facilitate leukocyte leakage from the bloodstream over the blood-brain barrier into the CNS parenchyma [223–226]. For instance, van Kralingen and colleagues found high levels of inflammatory cytokines in the CNS after injury. Also, in different neurological conditions affecting the integrity of the BBB, elevated levels of specific cytokines like IL-1β and TNF-α have been found [227].

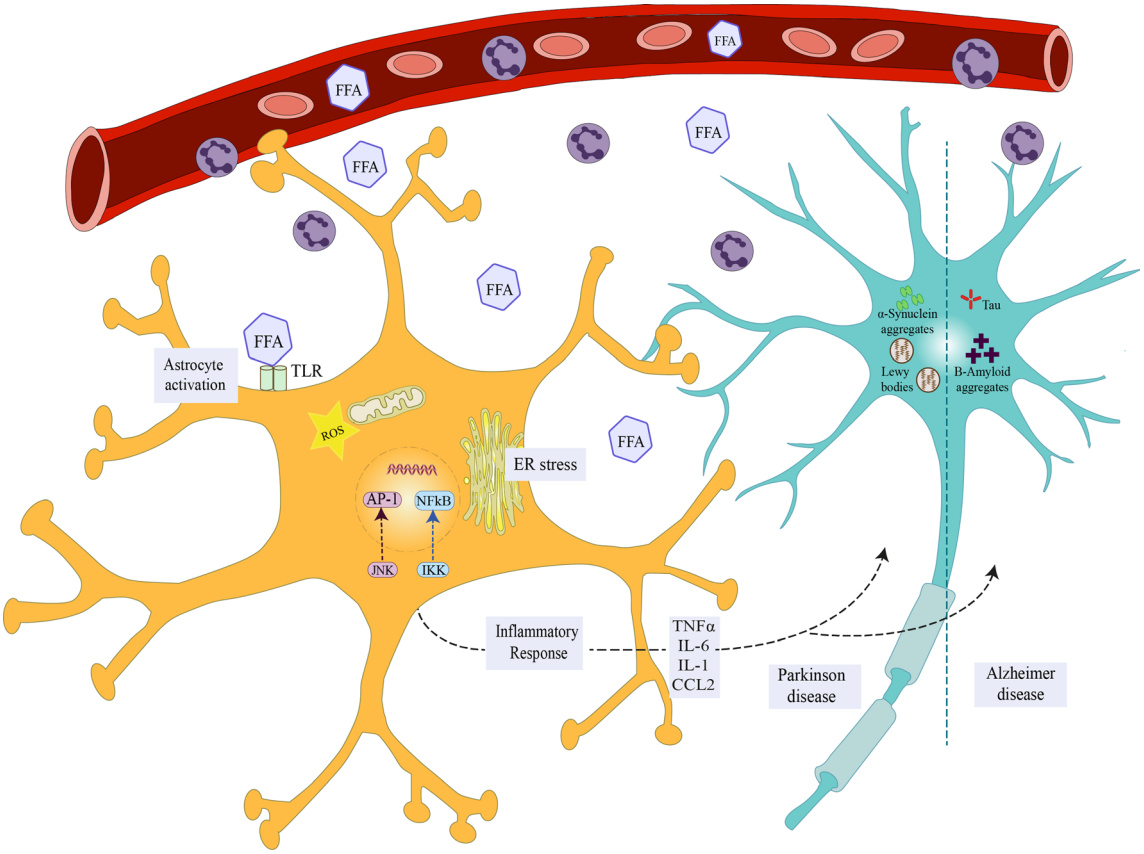

Fig. 1 Obesity involves a series of pathological cellular responses due to increment in basal lipolysis and subsequent release of free fatty acids into the bloodstream and the inflammation in the brain, particularly in the hypothalamus. Indeed, the increase in FFA produces endoplasmic reticulum stress, astrocytes activation, and activation of Toll-like receptors, leading to the activation of a signaling cascade and the activation of the transcription factor NF-kB and AP-1 in the nucleus. NF-kB can induce the production of inflammatory cytokines, such as TNF-α, IL-6, IL-1, and CCL2. Obesity also provokes neurodegeneration and a progressive dysfunction of neurons and astrocytes, as common pathological mechanisms in Alzheimer's disease, which is characterized by deposits of aggregated amyloid β (Aβ) and the presence of Tau protein. On the contrary, in Parkinson's disease, it is common the intraneuronal aggregates of α-synuclein (called Lewy bodies). These mechanisms lead to neuronal dysfunction and neuronal loss in both diseases

Astrocytes Are Important Regulators of Neuroinflammation

Astrocyte Pro- and Anti-inflammatory Mechanisms

Evidence indicates that there are two types of astrocytes activation such as pro-inflammatory and anti-inflammatory (Fig. 2). Pro-inflammatory (M1), a classical activation mechanism, is characterized by the production of pro-inflammatory proteins like cytokines (Table 3), including interleukins 1β, 6, and 12 and tumor necrosis factor alpha, and other cytotoxic compounds such as nitric oxide (NO), which may promote the increase of pro-inflammatory responses during damage [186]. Also, as widely accepted, upon CNS injury, activated astrocytes can produce and secrete pro-inflammatory molecules that will trigger neuroinflammation, including CCL2 and prostaglandins expressions [228–233].

As described above, there are two types of alternative activation phenotypes. In this regard, the second is the alternative M2 (anti-inflammatory) phenotype, which suppresses an immune response by neutralizing the typical M1 phenotype and promotes the resolution of the damage. The second phenotype (M2) produces different proteins like anti-inflammatory cytokines (Table 4), in which some of them are interleukins and transforming growth factor beta [186]. In addition, fundamental anti-inflammatory roles of astrocytes have now been demonstrated by several experiments in diverse models of CNS injury and disease [206].

Astrocytes and AD

Astrocyte activation is an important component of the cellular responses against brain injuries and chronic neurodegeneration [188]. Also, it is a pathologic response in AD and is related with the accumulation of Aβ and/or the raising number of degenerating synapses and neurons [251]. It has been reported in studies with tissue from patients with AD that activated astrocytes were closely

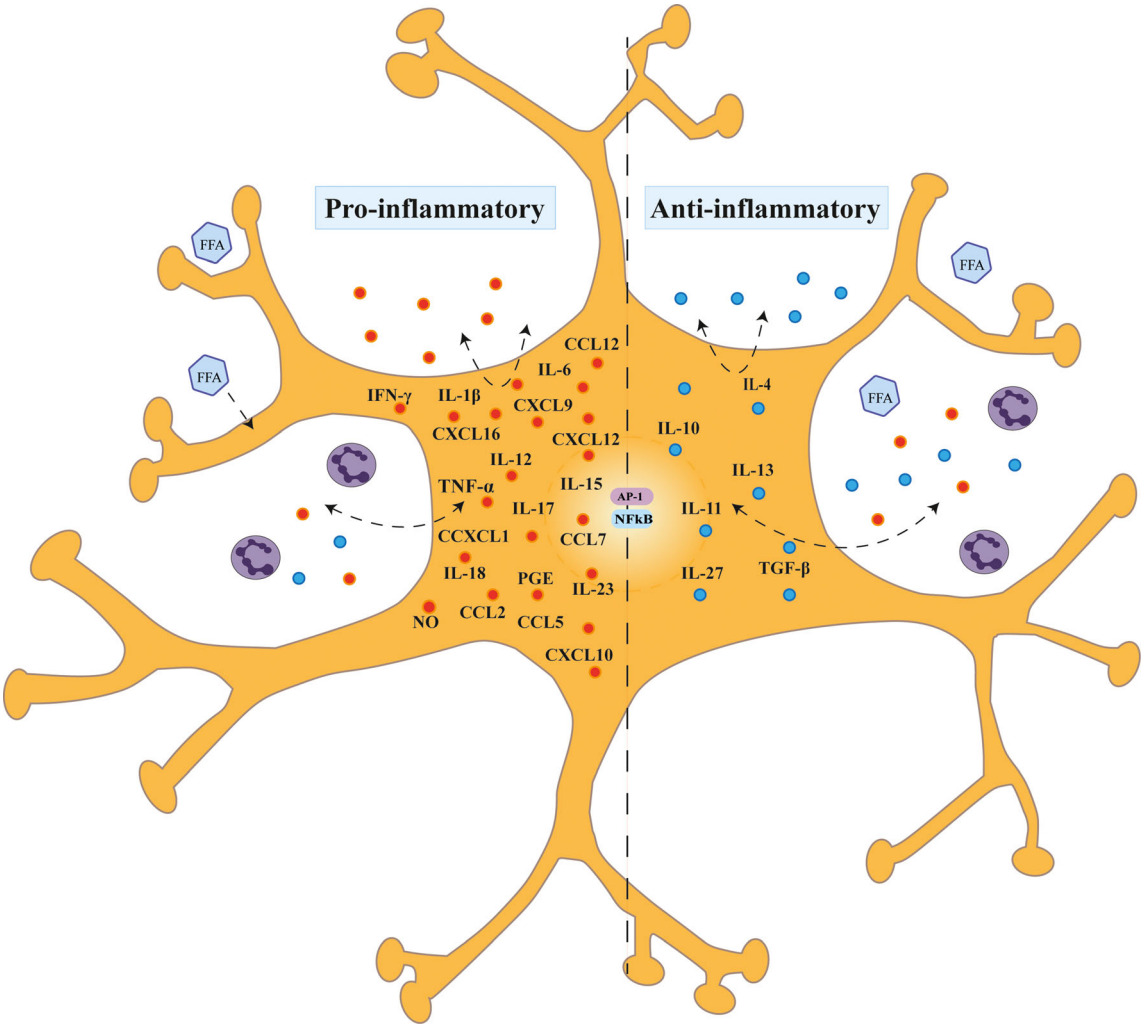

Fig. 2 Inflammatory mediators and cytokine receptors are expressed in the CNS by astrocytes and other glial cells at low levels. Specific factors implicated in reactive astrogliosis comprise large polypeptide growth factors and cytokines such as IL-1, IL-4, IL-6, IL-10, TNF-α, and TGF-β. Glial cells activation is followed by enhanced secretion of these factors, inducing damaging effects in the CNS. As discussed earlier, astrocytes activation produces a different range of downstream mediators, including cytokines, NO, and ROS and loss of fundamental functions, which are important for neuronal homeostasis and synapses maintenance

associated and related with amyloid plaques in the molecular layer of the cerebral cortex [252]. Thus, astrocytes might be activated by human Aβ [253], indicating a correlation between this protein and subsequent alterations in astrocyte function. This astrocyte activation process, called astrogliosis, is characterized by increased expression of the astrocyte marker glial fibrillary acidic protein (GFAP), and this process takes place around Aβ deposits in the brain parenchyma and the cerebral microvasculature [251, 254]. Astrocytes can accumulate amyloidogenic material resulting from local neurodegeneration, and then astrocytes might undergo apoptosis and produce the formation of GFAP+ amyloid plaques [253].

There are several studies regarding the capacity of astrocytes to internalize and degrade Aβ deposits under in vitro and ex vivo conditions [165, 173, 255]. For example, some studies have shown the presence of Aβ deposits in post-mortem human AD brain and in animal models of AD [255–257]. Investigations with fluorescently labeled astrocytes transplanted into AD mouse brains [258] showed that glial cells are capable to migrate and internalize deposits of Aβ and that wild-type astrocytes can clear Aβ plaques [259]. Functional experiments also demonstrated the ability of astrocytes to phagocyte and degrade Aβ deposits in vitro [173]. These findings are very significant to note the role of astrocytes in AD. Further, in vitro analyses indicated that treatment of astrocytes with Aβ leads to an increase in calcium-wave signaling between these glial cells [260]. To support these studies, Johnston et al. [261] showed that in cells expressing the familial AD presenilin 1 (PSEN1) mutation, calcium fluctuations in astrocytes occurred at lower ATP and glutamate levels than in wild-type astrocytes. These studies support a model in which calcium signaling between

Table 3 Astrocytic molecules released during CNS injury

Category type	Molecule	Generalities	Pro-inflammatory	Anti-inflammatory	Reference
Cytokine	IL-1β	Involved in normal neurofunction	X		[234, 235]
	IL-4	Activation, stimulation, and differentiation of B cells		X	[236]
	IL-6	Promote neuropathic pain behavior following an injury	X		[34, 237]
	IL-10	Antagonizes Th1 cell development		X	[238]
	IL-11	Hematopoietic cytokine		X	[218]
	IL-12	Promotes differentiation of T cells into Th1 cells	X		[218]
	IL-13	Downregulated production of pro-inflammatory mediators		X	[239, 240]
	IL-15	Activates diverse pro-inflammatory signaling mechanisms	X		[206]
	IL-17	Mobilizes phagocytes and granulocytes	X		[241]
	IL-18	Drives the local production of IL-1β and IFN-γ	X		[186]
	IL-23	Promotes acquired immune response and Th17 cell expansion	X		[218]
	IL-27	Promotes Th1 and suppresses Th17 differentiation		X	[242]
	Interferon-γ	Macrophage activation	X		[243]
	TNF-α	Enhances the expression of various adhesion molecules	X		[192, 244]
	TGF-β	involved on inflammation and repair upon damage		X	[245]

these glial cells is modified by the illness process, which could promote neuronal dysfunction or death under certain conditions [61]. Finally, it is very important to highlight that research about the role of neuroglia in the progression of AD is increasing. Analysis of astrogliosis in old patient's brains has illustrated a relation between the degree of astrogliosis and cognitive decline [189].

Astrocytes and PD

The role of astrocytes in the progression of PD has not been well characterized, although astrogliosis was detected at the late stages of the disease [262, 263]. It is thought that astrocytes are involved at early stages before neuronal loss is evident and at advanced stages when neurodegeneration occurs [264]. The substantia nigra has low density of astrocytes compared with other brain regions, and it has been speculated that a premature astroglial atrophy may have a role on the development of PD [265].

To date, several studies support the neuroprotective role of astrocytes in PD [24, 27, 61, 266]. As in other neurodegenerative diseases, these studies have revealed an increase in the number of astrocytes expressing GFAP in PD [61] and showing the presence of anti-oxidant pathways that might contribute to their neuroprotective role. The research evidence indicated that in control brains, the levels of glutathione-peroxidase-positive cells were higher in the dopaminergic cell areas, more resistant to PD pathology [61]. The increase in the levels of glutathione-peroxidase-containing cells reflects a protective mechanism against oxidative stress [267]. Also, an accumulation of α-synuclein in the cytoplasm of protoplasmic astrocytes at

Table 4 Astrocytic pro-inflammatory molecules released during CNS injury

Category type	Molecule	Generalities	Pro-inflammatory	Anti-inflammatory	Reference
Chemokine	CCL2	Attracts memory T cells, B cells, and monocytes	X		[246]
	CCL5	Interacts with CCR1, CCR3, and CCR5+ cells	X		[246]
	CCL7	Recruits diverse leukocyte and dendritic cells	X		[206]
	CCL12	Recruits monocytes	X		[206]
	CCXCL1	Attracts neutrophils and macrophages	X		[246]
	CXCL9	Attracts predominantly T cells, B cells, and NK cells	X		[246]
	CXCL10	Related with CXCL9	X		[247]
	CXCL12	Attracts T cells, activated B cell monocytes, and mast cells	X		[248]
	CXCL16	Membrane-bound chemokine	X		[249]
Small intercellular effector molecules	PGE	Diverse pro-inflammatory effects	X		[206]
	NO	Promotes the deleterious effects on resident cells in the CNS	X		[250]

initiation stage of the disease has been found [268]. This accumulation was more distributed than Lewy bodies and also present areas without Lewy bodies [269], suggesting that astrocytes can capture the altered α-synuclein that has escaped from axon terminals [270]. Also, Lee and colleagues demonstrated in both cell culture and animal models of PD that α-synuclein is transmittable from neuron to neuron [271] and from neuron to astrocytes [270]. In addition, in vivo studies using transgenic mice overexpressing α-synuclein, driven by the neuronal promoter PDGF-β, showed that α-synuclein immunoreactivity was detected in both neurons and astrocytes [270]. In humans, PET studies have shown a pronounced activation of microglia in various regions of the brain in subjects with PD [272, 273]. Importantly, the presence of synuclein-positive astrocytes in PD samples correlated with neuronal cell death in the substantia nigra [274].

Therapeutic Strategies

Astrogliosis as Therapeutic Target

Based on the pathogenic role of astrocytic dysfunction, the strategy to restore or enhance astrocytic functions might be an attractive way to promote neuroprotection in a variety of brain disorders [15]. Various studies using different types of transgenic models have shown that reactive astrogliosis is beneficial and neuroprotective during early stages of neurodegenerative diseases. However, astrocytic function in neuroprotection is greatly compromised during chronic neuroinflammation [275]. New perspectives for therapeutic strategies include the replacement of dysfunctional astrocytes or pharmacological treatments. An explicit example is the replacement of neurotransmitters, such as levodopa for PD or memantine for the treatment of AD [61]. Several experimental studies have revealed that reactive astrocytes can protect CNS cells in different ways such as preventing or reducing oxidative stress by increasing glutathione production [276–280], improving mitochondrial membrane potential and mitochondrial volume [20, 281, 282], inducing neuroprotection via adenosine release [283] and neuroglobin expression [284, 285], and facilitating BBB repair [286]. However, it is important to highlight that reactive astrocytes can play harmful roles during injury or disease, due to the increase of the abnormal effects such as production of reactive oxygen species or some inflammatory cytokines [287–289]. Thereby, reactive astrocytes have a tremendous potential to influence injuries and/or disease effects in a positive or negative way, as determined by specific signaling events and molecular mechanisms [288–290].

Neuroinflammation as Therapeutic Target

Taking into account the important role of neuroinflammation in the initiation and progression of neurodegenerative diseases, it is desirable to develop therapies by targeting the inflammatory pathways mediated by activated glial cells. For example, minocycline, a semi-synthetic tetracycline analog, which acts as a lipophilic molecule, can easily cross the BBB and has anti-inflammatory and neuroprotective properties in multiple inflammation-related neurological diseases [291, 292]. Also, substances such as the glucocorticoids, which are well known for their anti-inflammatory effects, have been widely used in clinical studies for brain inflammation [293].

Other substances used as therapeutic tools are the non-steroidal anti-inflammatory drugs (NSAIDS), such as aspirin, salicylic acid (SA), ibuprofen, and celecoxib [294, 295]. Aspirin has shown to reduce neuroinflammation and neurodegeneration [296], thus promoting the resolution of inflammation [297]. SA is a metabolite product of aspirin, which is widely used for the treatment of myocardial infarction and cardiovascular diseases [295]. Previous clinical studies using NSAIDS did not show encouraging results, but some methodological problems have been proposed to lead to their failure and encourage new investigation targeting neuroinflammation [298]. Lastly, it has been demonstrated that gonadal hormones, such as estradiol and testosterone, selective estrogen receptor modulators (SERMs; raloxifene and tamoxifen), or tibolone, a selective tissue estrogenic activity regulator (STEAR) might regulate the reactive glia upon brain damage [20, 281, 284, 299–302]. Future studies should focus on identifying more specific drug targets with the aim to understand the fundamental processes of inflammation at different stages of the disease progression.

Concluding Remarks

Obesity is considered one of the greatest risk to human health and has a significant role in cognitive dysfunction and aging-associated cognitive disorders including dementia. Thus, the high prevalence of obesity, as well as reduced age of onset in the population, may lead to higher incidence and prevalence of AD and PD. Nowadays, there is evidence that peripheral inflammation induced by obesity and high-fat diet may trigger local inflammation in the hypothalamus altering synaptic plasticity and contributing to the neurodegenerative processes deteriorating cognitive functions. After a brain injury, molecular signals induce astrocyte activation and migration to the site of injury. Astrocytes enter a highly active state that may ameliorate or worsening the pathology at early and late stages, respectively. Recent findings suggest that astrocytes are actively involved in the maintenance of brain metabolism, anti-

oxidative maintenance, and neuroprotection during pathology. For this reason, these cells play a critical role in the onset and progression of several neurodegenerative diseases. Thus, the involvement in neurodegenerative diseases of the most abundant and heterogeneous group of glial cell in the brain, the astrocytes, is caused by a combination of the loss of their normal homeostatic functions and the gain of toxic functions in disease that trigger the release and production of pro-inflammatory and anti-inflammatory molecules during pathological diseases of the central nervous system. New studies about the role of astrocytes during early and late stages of neurodegeneration are guaranteed.

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