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Chapter 20

Astrocytes Role in Parkinson: A Double-Edged Sword

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1. Introduction

Parkinson Disease (PD) is the second most chronic neurodegenerative disorder in the world, after Alzheimer´s Disease (AD), and is estimated to affect about 1% of the population over 60 years of age. PD is caused by the disruption of dopaminergic neurotransmission in the basal ganglia, which causes a reduction in the numbers of dopaminergic neurons in the substantia nigra and formation of cytoplasmic inclusions called Lewy bodies [1].

Both in normal and pathological circumstances, astrocytes are critical supporters of neuronal function in processes such as antioxidant protection, glutamate clearance, the development and/or maintenance of blood brain barrier characteristics, the release of gliotransmitters and cytokines [2-4]. In recent years, much research on PD has focused on the astrocytic-neuronal crosstalk, suggesting that this interaction is important for future therapies against neurodegenerative processes. During brain damage events, astrocytes become transiently or permanently impaired, and the subsequent impact on neuronal cells may lead to pathological conditions such as PD [5-7].

In the present chapter, we provide a brief overview of the astrocytic functions and the pathophysiological events elicited during PD. Additionally, we explore the beneficial and damaging consequences of reactive astrogliosis in dopaminergic neurons during PD, particularly on oxidative damage, which is a main component of numerous neuropathological conditions, and that may have a damaging effect in astrocytic functions. We also highlight some of the cellular and animal models currently used in Parkinson research, such rotenone, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and paraquat as inducers, which have many similar features with this disease. Finally, a brief overview of the future perspectives in astrocytic protection during Parkinson development is discussed.

2. Parkinson´s disease

PD is a progressive neurodegenerative disorder caused by the neuronal death in the substantia nigra (SN), degeneration of dopaminergic neurotransmission, and the presence of α-synuclein and protein inclusions in neuronal cell bodies (Lewy bodies) [4-5,7]. Main symptoms of Parkinson are asymmetrical bradikinesia, rigidity, resting tremor and postural instability. Other non-motor symptoms that generate serious disability problems have also been noted, including fatigue, pain, Lewy Body dementia, psychosis, depression, and apathy [1]. Although there is not a cure for the disease, the most used and cheaper treatment for PD continues to be Levodopa [1,8]. However, about 40% of patients developed motor fluctuations and dyskinesias after 4 to 6 years of treatment [1], demonstrating that further pharmacological research is needed in order to counterbalance side effects. In this aspect, treatments using long-acting dopaminergic agents or a continuous dopaminergic effect in the striatum have been associated with less severe motor complications, given alone or in combination with L-dopa [9]. Some pharmacological agents that have shown promising applications, include dopamine agonist like apomorphine and ropinirole, and catechol-O-methyltransferase (COMT; EC 2.1.1.6) inhibitors [9].

Numerous reviews and articles agree that the exact cause of PD remains unknown [1,9-10]. Mutations in various proteins such as leucine-rich repeat kinase 2 (LRRK2; EC 2.7.11.1), Parkinson protein 2 (PARK2), probable cation-transporting ATPase type 13A2 (ATP13A2; EC 3.6.3-), phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1; EC 2.7.11.1), and Parkinson disease (autosomal recessive, early onset) 7 protein (DJ-1) have been observed in familiar cases of Parkinson, which only accounts for 10-15% of diagnosed cases [6,11-12]. Interestingly, LRRK2, PINK1, and DJ-1, which are present in mitochondrial membranes, have been suggested to play a role in reactive oxygen species (ROS) production by a defective maintenance of the mitochondrial membrane potential [12-13].

A number of environmental factors have been found to induce PD-like symptoms, and are currently used in animal and cellular models of the disease. Environmental factors include vascular insults to the brain, oxidative stress, neuroleptic drugs and repeated head trauma. [6,14]. Additionally, the exposure to pesticides like rotenone or 1-methyl-4-phenylpyridinium (MPP^+) and heavy metals (manganese) increases the risk of PD development [6, 10, 14-15]. In this aspect, numerous epidemiologic and toxicologic studies have examined pesticides as a risk factor for PD and parkinsonism and the possible mechanisms by which pesticides may act [14-17].

Initiation and progression of PD is dependent upon cellular events, including failures in the protein degradation machinery, oxidative stress, mitochondrial dysfunction, defects in mitochondrial autophagy (mitophagy) and the continuous accumulation of α-synuclein, driven through cell to cell interactions between glial cells and neurons that ultimately lead to apoptosis [7,10,18]. Previous studies pointed that astrocytic α-synuclein deposition initiates the recruitment of phagocyte microglia that attacks and kills neurons in restricted brain regions [7,19], correlating this α-synuclein accumulation with nigral neuronal cell death [20], and suggest the importance of astrocytes in the initiation of the disease. Conversely, astrocytes

also have beneficial roles during PD progression [21-22]. For example, astrocytes express different antioxidant molecules such as glutathione peroxidase (EC 1.11.1.9), which have been inversely correlated with the severity of dopaminergic cell loss in the respective cell groups in patients with PD [4].

3. Astrocytes in PD

3.1. Astrocytic functions

Astrocytes are the most common cell type in the mammalian brain, conforming the glia with oligodendrocytes and microglia [23]. They are characterized by the expression of the intermediate filaments glial fibrillary acidic protein (GFAP) and vimentin (Vim). Astrocytes are essential for the metabolism of the brain, transporting multiple nutrients and metabolic precursors to the neurons by the malate-asparte shuttle and other transporters [24]. There are two main types of astrocytes in the SNC: Protoplasmic astrocytes, which envelope neuronal bodies and synapses and fibrous astrocytes which interact with the nodes of Ranvier and oligodendroglia [7]. Current research has shown that only protoplasmic astrocytes have an increase in the accumulation of α-synuclein, whereas fibrous astrocytes do not [7,19].

Current knowledge indicates that astrocytes are critical for some cellular processes, such as the development and/or maintenance of blood–brain barrier characteristics, the promotion of neurovascular coupling, the attraction of cells through the release of chemokines, K^+ buffering, release of gliotransmitters, release of glutamate by calcium signaling, maintenance of general metabolism, control of the brain pH, metabolization of dopamine and other substrates by monoamine oxidases (MAOs; EC 1.4.3.4), uptake of glutamate and γ-aminobutyric acid (GABA) by specific transporters and production of antioxidants [2-3,25-27] (Figure 1). Recent evidence has shown that astrocytes are arranged in non-overlapping domains forming a syncytial network that may contact approximately 160.000 synapses, thus integrating neural activity with the vascular network [4,28]. In this aspect, astrocytic terminal processes, known as endfeet, contact the brain vasculature and enwrap the neuronal synapses, enabling the modulation of both neuronal activity and cerebral blood flow, following an elevation in intracellular Ca^{2+} levels in the endfeets [24,29].

During brain damage (including diseases, brain injury and oxidative stress), these astrocytic functions become transiently or permanently impaired, and the subsequent impact on neuronal cells may lead to pathological conditions and neurodegenerative diseases [3,26]. Neurons are more susceptible to injury than astrocytes, as they have limited antioxidant capacity, and rely heavily on their metabolic coupling with astrocytes to combat oxidative stress [3]. However, severe brain damage also results in astrocyte dysfunction, leading to increased neuronal death [30].

As previously stated, astrocytes exert both neuroprotective and neurodegenerative roles, depending on the molecules released by them, and the pathological or normal circumstances of their microenvironment [6]. For example, astrocytes release antioxidant molecules like

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