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Reactive Astrocytes Are Key Players in Nigrostriatal Dopaminergic Neurorepair in the Mptp Mouse Model of Parkinson's Disease: Focus on Endogenous Neurorestoration

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Abstract: Parkinsons'disease (PD), a common neurodegenerative disorder, is characterized by progressive loss of dopaminergic (DAergic) neurons in the subtantia nigra pars compacta (SNpc) and gliosis. The cause and mechanisms underlying the demise of nigrostriatal DAergic neurons are not completely clarified, but interactions between genes and environmental factors are recognized to play a critical role in modulating the vulnerability to PD. Current evidence points to reactive glia as a pivotal factor in PD, but whether astroglia activation may protect or exacerbate DAergic neuron loss is presently the subject of much debate. Astrocytes and microglia are the key players in neuroinflammatory responses, by secreting an array of pro- and anti-inflammatory cytokines, anti-oxidant and neurotrophic factors. Here, the contribution of astrocytes and their ability to influence DAergic neurodegeneration, neuroprotection and neurorepair will be discussed. In particular, the dynamic interplay between astrocyte-derived factors and neurogenic signals in MPTP-induced plasticity of nigrostriatal DAergic neurons will be summarized together with recent findings showing that reactive astrocytes may contribute to promote DAergic neurogenesis from midbrain adult neural stem/precursor cells (NPCs). Within a host of astrocyte-derived factors, we unveiled *Wingless-type MMTV integration site (Wnt)/β-catenin* signalling was unveiled, as a strong candidate in MPTP-induced DAergic neuroplasticty/neurorepair. Understanding the intrinsic plasticity of nigrostriatal DAergic neurons and decifering the signals facilitating the crosstalk between astrocytes and midbrain neuroprogenitors may have implications for the role of stem cells technology in PD and for identifying potential therapeutic targets to promote endogenous neurorepair.

Keywords: Astrocytes, dopaminergic neurons, neurodegeneration, neurogenesis, neuroprotection, Parkinson's disease.

1. INTRODUCTION

Parkinson's disease (PD) is the second most frequent neurodegenerative disorder after Alzheimer's disease, affecting approximately 1% of the population over age 65. The main hallmark of the disease is the selective loss of dopaminergic (DAergic) neurons in the substantia nigra pars compacta (SNpc). Although most cases of PD are observed later in life, there is evidence that the disease has progressed to the point at which it is diagnosed [1]. In fact, the clinical symptoms such as rigidity, akinesia and resting tremor appear when following more than a 70-80% loss of midbrain DAergic neurons in SNpc, suggesting that compensatory mechanisms are established while the neurodegeneration progresses [2]. Current DAergic treatments improve the motor symptoms and quality of life for patients during the early stages of PD but do not prevent the progression of the disease associated with disabling side-effects [3].

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Several genes that cause certain forms of inherited PD (<10% cases) have been identified, but the majority of cases (>90%) appear to be sporadic and likely represent an interplay between both genetic and environmental influences [3-9]. More men than women develop PD, aging, menopause in women (estrogen deficiency) are recognized risk factors [10-12]. Polymorphisms in candidate genes involved in dopamine (DA) metabolism, mitochondrial function, lipoprotein metabolism, inflammation and xenobiotic detoxification have been described [9]. Rural living, pesticides and heavy metals exposures, head injury, and infectious diseases during childhood have also been suggested to increase risk, whereas, smoking and coffee exposures, dietary factors, exercising and social interactions, see [13] or the use of certain non steroidal anti-inflammatory drugs (NSAIDs) reportedly reduce the incidence/risk and or severity of PD or experimentally induced PD [14-17]. Within this context, and of particular mention, genetic factors may interact with early life events such as exposure to hormones, endotoxins or neurotoxicants, thereby influencing disease predisposition and/or severity (Fig**. 1**).

One of the most compelling pieces of evidence for the potential contribution of environmental neurotoxicants and neuroinflammation in PD was revealed in humans who de-

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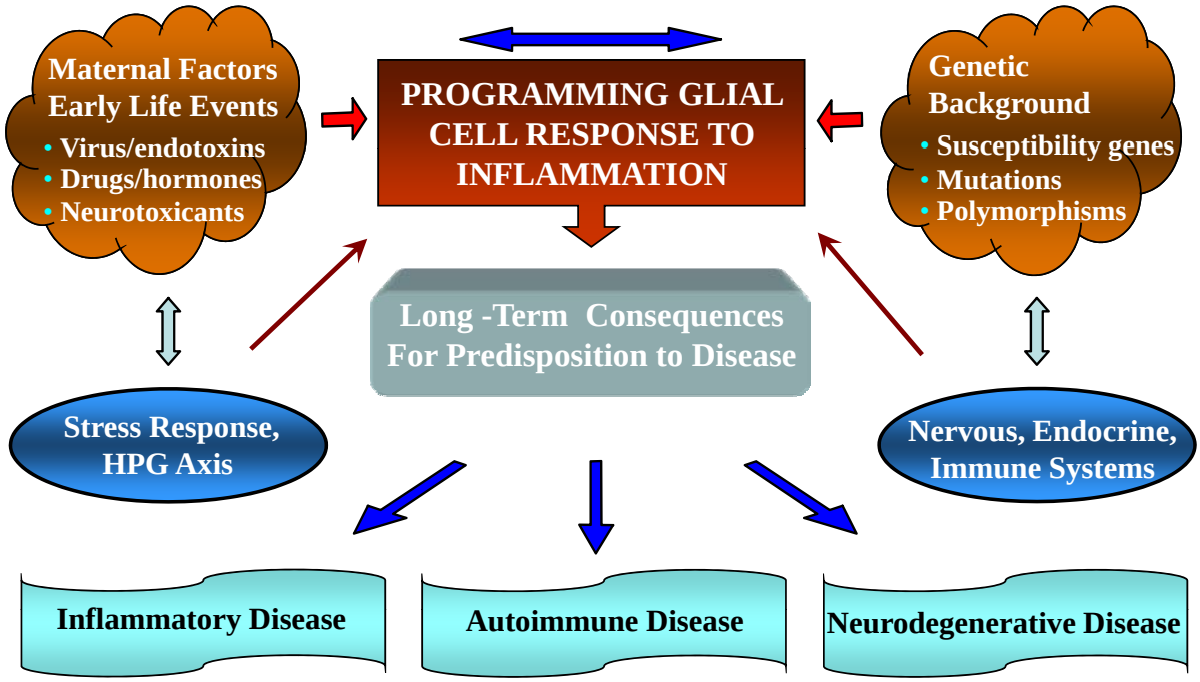

Fig. (1). Schematic representation of the impact of perinatal genetic, hormonal and environmental interactions on inflammatory glial cell response and individual resistance or susceptibility to inflammatory diseases during adult life. Genetic factors (e.g., sex, gene mutations, polymorphisms/susceptibility genes) can interact with maternal hormonal factors and external agents to which mother and fetus are exposed (drug treatments, bacteria, viruses, endotoxins, and/or environmental toxicants), to alter the development of the neuroendocrine-immune system, in particular the hypothalamic-pituitary-adrenocortical axis (HPA) and the hypothalamic-pituitary-gonadal (HPG) axis. The pivotal target of the overall interactions is glia, a key component of the neuroendocrine-immune system. Thus, an altered dialogue between the neuroendocrine and the immune system during development may irreversibly shape glial cells and «program» long-term effects in the mechanisms regulating immune responsiveness to inflammation, thereby contributing to individual vulnerability, propensity and predisposition to inflammatory, autoimmune and neuromental disorders.

veloped a parkinsonian syndrome after accidentally injecting themselves with the neurotoxicant 1-methyl-4-phenyl-1,2,3,6-tetrahydro- piridine, MPTP [18-20]. Post-mortem analysis revealed clusters of reactive microglia around nerve cells. This finding was suggested to reflect an ongoing neurodegenerative process that persisted years after the initial toxic injury and that could have been perpetuated, at least in part, by chronic neuroinflammation. Indeed, an increasing number of evidences from epidemiological, post-mortem, and animal studies suggest that innate inflammatory processes associated with glial cell activation coupled to an array of pro- and anti-flammatory mediators contribute to PD physiopathology [13, 17, 18, 21-30]. However, the role of inflammation in neurodegeneration is still controversial. In fact, the causal relationship between the two phenomena remains to be ascertained. In addition, and of major interest, inflammation can also confer neuroprotection, which makes it a double-edged sword, with important implications for the cure of neurodegenerative diseases [27]. Importantly enough, the inflammatory environment can have both detrimental and beneficial effects on adult neurogenesis, depending on the degree and timing of glial activation, the specific cellular context and intrinsic region-specific neuronal characteristics [31-36].

After a brief summary of the major neuroinflammatory features of PD, the specific aim of this review is to focus on astrocyte influencing DAergic neuron degeneration and neurorepair. Indeed, evidence has rapidly accumulated suggesting that glial cells play a much more important role in health and disease in the CNS than has been previously acknowledged. Brain development, neurotransmission, neuron survival and differentiation, inflammatory and neuroprotective pathways, blood-brain-barrier functions and neurogenesis rely on glial cells. Developing therapeutic strategies targeting both the detrimental and neuroprotective components of glial reactions may contribute to the development of novel concepts and therapeutic treatment strategies for Parkinson's disease, and hopefully other neurodegenerative disorders.

2. INFLAMMATION, NEURODEGENERATION AND PARKINSON' S DISEASE

Astrocytes and Microglia Are Key Mediators of Neuroinflammatory Responses

Astrocyte and microglia become "activated" in most CNS pathologies, including inflammatory, infectious, ischaemic and neurodegenerative diseases, such as PD (see Introduction). Activated glia may benefit the host partly by producing cytotoxic molecules that kill pathogens, virally infected cells or tumor cells, but they may also be detrimental by killing host cells, particularly neurons. Once activated, microglia display conspicuous functional plasticity and ultimately transform into macrophage-like phenotype that involves morphological changes, proliferation, increased expression of cell surface receptors and the production of neu-

rotrophic and neurotoxic factors [13]. Astrocytes respond to injury by hyperplasia and hypertrophy of cell bodies and cell processes and increased expression of the major astrocytic cytoskeletal protein, glial fibrillary acidic protein, GFAP. Importantly enough, in response to brain injury astrocytes and microglia roles are very dynamic and cell-type dependent, in that they may exert "harmful" effects, but in certain circumstances they can turn into highly protective cells, and exert anti-inflammatory, neuroprotective and pro-regenerative ("beneficial") functions, thereby facilitating neuronal recovery and repair, which poses the "To-be or not to-be (inflammed)" dilemma [27]. The precise roles exerted by astrocytes and microglia in neurodegeneration and subsequent repair processes are still highly controversial. While one view proposes an inhibitory role, where glial cells produce pro-inflammatory and cytotoxic mediators that kill neurons or form scars that barricade axonal regeneration, other findings show the ability of activated astrocytes and microglial cells to orchestrate cellular responses aimed at rapid re-establishement of tissue integrity and subsequent repair.

Among the cytoxic molecules produced by activated microglia, the resident innate immune cells in CNS, nitric oxide (NO) from inducible nitric oxide synthase (iNOS), and superoxide from the plasma membrane NADPH oxidase (PHOX), represent two key harmful mediators. iNOS is not normally expressed but is induced as a part of the activation state in microglia, by cytokines [particularly interferon gamma (IFN-γ), tumor necrosis factor alpha, (TNF-α,) or interleukin-1 beta (IL-1β)], bacterial cell wall component [particularly lipolysaccharide (LPS)], and oxidative stress. Of particular mention, if iNOS and NADPH oxidase are active at the same time, then microglia might produce peroxynitrite (ONOO-), a potent toxin, which may promote nitration of various proteins, including tyrosine and produce hydroxyl radicals. Hence, the generation of the free radical NO followed by production of peroxynitrite may be implicated in neuronal cell death (Fig**. 2**). Reactive astrocytes are characterized by up-regulation of several molecules including GFAP, S100, iNOS, nuclear factorkB (NFkB), and express receptors involved in innate immunity (e.g. Toll-like receptors), participating in the regulation of astrocyte re-

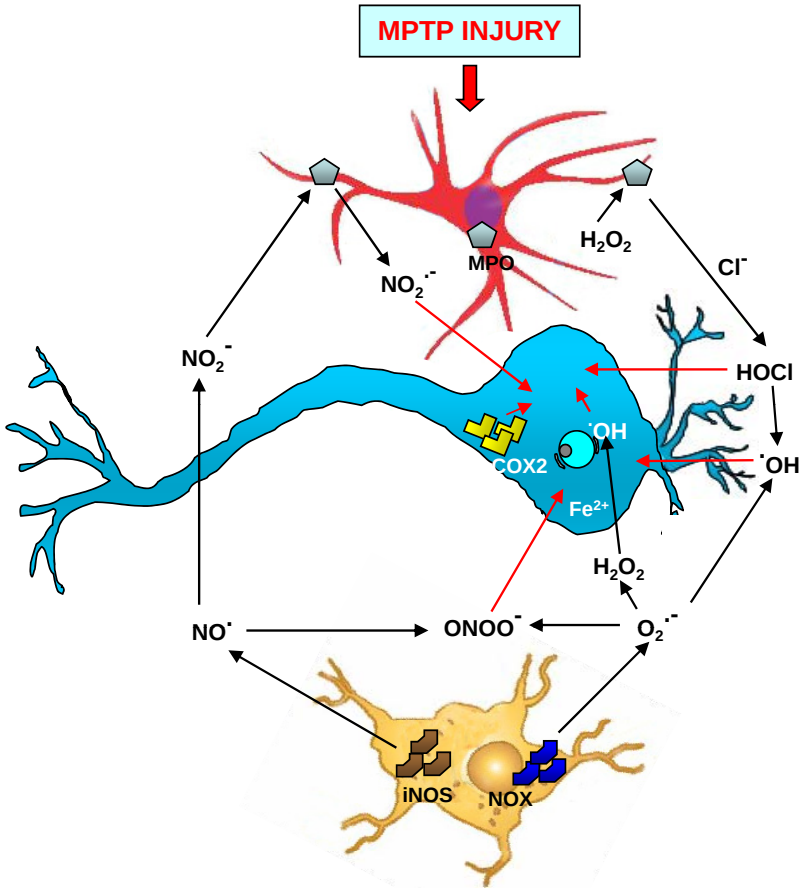

Fig. (2). Schematic representation of the effects of inflammatory and oxidative stress mediators in DAergic neuron demise. MPTP-induced oxidative stres and mitochondrial dysfunction are associated with activation of microglia resulting in increased expression of iNOS and NADPH-oxidase. When iNOS and NADPH oxidase are active at the same time, microglia might produce peroxynitrite (ONOO-), a potent toxin, which may promote nitration of tyrosine and produce hydroxyl radicals. Reactive astrocytes can express increased concentrations of myeloperoxidase (MPO) wich produce hypochlorous acid (HOCl, derived from hydrogen peroxide and chloride anion), that may damage macromolecules, thereby contributing to the pool of cytotoxic mediators [see text]. Inflammatory associated oxidative stress also originate from DAergic neurons *via* COX-2 expression. For details see text. iNOS: indicble nitric oxide; COX-2: ccyclooxyggensae 2, MPO: myeloperoxidase.

sponse to injury. In addition, reactive astrocytes express receptors for growth factors, chemokines, hormones, and produce a wide array of chemokines and cytokines that act as immune mediators in cooperation with those produce by microglia.

Among the various degenerative diseases, inflammation has recently emerged as a common denominator, being variously implicated as a critical mechanism responsible for the progressive nature of the diseases. The first evidence for an involvement of inflammation in PD dates back to 1988 [29], when McGeer and coworkers described the up-regulation of major histocompatibility complex (MHC) molecules in PD brains. Later, Mogi and coworkers reported increased levels of beta2-microglobulin, the light chain of MHC, in the striatum of PD patients [27-29]. Accumulation of ROS, NO, prostaglandins (PGs) and pro-inflammatory cytokines (including TNF-α, IL-1β and IFN-γ) in the SN of PD patients further supported that a state of chronic inflammation characterizes PD brain. Activation of the complement system and increased mRNA levels of complement components have been found in affected brain regions.

Consistent with the inflammation hypothesis, epidemiological analysis has indicated that nonsteroidal anti-inflammatory drugs (NSAIDs) may prevent or delay the progression of PD, see [14, 15]. Nevertheless, the long-term therapy with this class of drugs is characterized by significant adverse effects on gastrointestinal tract and kidneys and cardiovascular events has been reported, which may limit their clinical use in chronic conditions [13]. In this regard, it seems important to mention, that the nitric oxide (NO)-NSAID HCT1026 [2-fluoro-α-methyl(1,1'-biphenyl)-4-acetic-4-(nitrooxy)butyl ester], NO-flurbiprofen, belongs to a novel class of anti-inflammatory agents obtained by derivatization of conventional NSAIDs with a NO-releasing moiety which strongly reduce their untoward side effects without altering the anti-inflammatory effectiveness, that was recently shown to mitigate DAergic degeneration in rodent models of PD [16, 17].

Although less studied, the astrocytic reaction represents another important feature of neuroinflammation accompanying PD. Post-mortem studies in PD brains indicated an almost 30% increase in GFAP cell density, as detected by quantitative analysis, see [24]. A prolonged activation of astrocytes stimulated by cytokines released from microglia and damaged neurons is implicated in chronic neurodegenerative diseases such as PD, but the crosstalk between damaged neurons and reactive astrocytes still remains poorly understood. Given the cardinal role of astrocytes in the maintenance of brain omoestasis, energy metabolism, and in particular the defense against oxidative stress, an impairment of astrocyte-neuron crosstalk may contribute to disease progression and impair the recovery process. Dysfunction and/or degeneration of astrocytes may critically reduce their neuroprotective functions and impair neurogenesis causing a further delay in the recovery from neurodegeneration. Interestingly, post-mortem studies in PD brains showed reduced astrocyte cell density in the affected SNpc, when compared to GFAP-positive cells in the ventral tegmental area, and the catecholaminergic cell group A8, regions that are less affected in PD brain [24]. Thus, a disturbed and/or insufficient astrocytic function in the face of highly activated microglial phenotype might represent a critical vulnerability factor compromising DAergic neuron self-repair ability.

It seems important to recall that GFAP-expressing cells can contribute to cell genesis both as stem cells and as important cellular elements of the neurogenic microenvironment, with clear implications for self-recovery/neurorepair, which further highlight the critical role of astrocytes in the injured brain [31-34].

3. GLIAL PATHWAYS INVOLVED IN DAERGIC NEUROPROTECTION: FOCUS ON ASTROCYTES

The cardinal protective role of astrogliosis in response to acute CNS injury was highlithed in the study of Faulkner and co [35] showing that the selective ablation of reactive astrocytes resulted in greater neuronal and oligodendrocyte death, greater inflammatory infiltration, less recovery of the blood brain barrier (BBB), and more profound functional deficits [35]. As it will be apparent from the findings gathered in this section, the integrity of astrocytes appears a prerequisite for the mitigation of the harmful consequences of either acute or chronic CNS injury, and for the promotion of a successful restoration of neuronal function and/or the replacement of the damaged cells.

3.1. Astrocytes and Synaptic Homeostasis

For long time, astrocytes have been considered as passive partners of neurons in the CNS. In the last two decades, however, this view has been challenged by the demonstration that astrocytes express a wide variety of receptors, including neurotransmitter receptors, neuropeptide, growth factors, cytokines and toxins [36, 37]. Astrocytes maintain homeostasis at the synapse by removing excess of Glu, the major CNS excitatory transmitter, by the Glu transporter, found exclusively in astrocytes. Gamma-aminobutyric acid (GABA) is removed from the synaptic cleft by astrocytes, and is in part, recycled by the GABA shunt. Astrocytes are extensively linked by gap junctions, not only to other astrocytes, but also to oligodendrocytes and ependimocytes. Hence, astrocytes are very active players in neuronal and glial signaling, modulating synaptic transmission by the release of chemical transmitters, such as Glu, GABA and ATP [36, 37]. Given the central role of astrocytes in establishing and maintaining CNS homeostasis, it is not surprising that important adaptive consequences are observed during either acute or chronic brain injury.

3.2. Astrocytes and Nigrostriatal DAergic Neuroprotection

Under normal conditions, astrocytes exert a fundamental protective function against oxidative stress, and this function appears of particular importance for DAergic neurons of the SNpc, due to enzymatic and non enzymatic auto-oxidation of DA generating H_2O_2, to the high toxicity of DA metabolites, and the interactions between iron (which is highly concentrated in SN) and H_2O_2 in the Fenton reaction, leading to highly toxic radicals. Astrocytes protect neurons from energy depletion by releasing lactate from glycogen stores, forming the astrocyte-neuron lactate shuttle [36, 37, 41, 42]. Astro-

cytes have a higher concentration of anti-oxidant molecules such as vitamin E, ascorbate, superoxide dismutase (SOD) and GSH than neurons, and can protect neurons from oxidative damage. GSH is one key molecule in the detoxification of H_2O_2, since its release from astrocyte protects the surrounding neurons from ROS and RNS (**BOX1**). This function appears of particular importance for SN DAergic neurons since H_2O_2, a product of DA conversion *via* monoamine oxidase (MAO), that is formed during dopamine autoxidation and extraneruronal metabolism of dopamine by MAO-B isozyme, is performed by astrocytes [1]. Then, changes in glial MAO-B activity as a result of astrocyte dysfunction can significantly impact in DAergic functioning. In this connection, it is important to recall that aging, which is a principal risk factor for PD, is characterized by increased MAO-B activity. Consistently, the experimental genetic approach leading to up-regulation of MAO-B activity in astrocytes mimicked age-related increase in enzyme activity, as well as the selective and progressive loss of DAergic neurons in the SN accompanied by motor deficit typical of experimental parkinsonism [43]. Interestingly, these effects were associated to local microglial activation in the SN [43].

Another key anti-oxidant mechanism regards efflux of GSH from astrocytes, which is mediated by the ATP-dependent transporter, multidrug-resistance associated protein (Mrp1), shown to dynamically respond to the changing redox mileu [44]. The expression and activation of anti-oxidant response element (ARE) represents an interesting feature astrocyte neuroprotective effects: both basal and activated expressions are higher in astrocytes, as compared to neurons. Oxidative stress can up-regulate the rate-limiting enzyme in GSH production (i.e. Glu cysteine ligase), increase the expression and membrane targeting of Mrp1 export pump, enhance expression and binding of astrocytic NF-E2-related factor 2 (Nrf2), which translocates to the nucleus and binds to ARE. Importantly, binding to ARE up-regulates a cluster of anti-oxidant genes, including those for GSH, those involved in astrocyte-neuron lactate shuttle and cholesterol synthesis [37, 44, 45].

3.3. Hormones and Astroglial-induced DAergic Neuroprotection

Interestingly enough, hormones of the stress and reproductive axes powerfully interact with the astroglial cell compartment. Importantly, astrocytes and macrophages/ microglial cells are critical targets for steroid hormones. In fact, they express hormone receptors, such as GRs, and are both a source and target of cytokine, growth and neurotrophic factor activities in the brain. Thus, besides other endogenous regulators, GCs are candidate endogenous regulators of astroglial cell function. In glial cells, GCs are known to modulate the expression of a variety of glial proteins, including GFAP [39, 40]. Of major interest, GCs are potent inhibitors of iNOS-derived NO in activated glial cells. Then, the major endogenous anti-inflammatory molecules, GCs may play active roles under *in vivo* conditons in which increased CNS levels of cytokines would have several adverse consequences. Consistently, a deficiency in major endogenous anti-inflammatory signaling pathways in GR-deficient mice, dramatically exacerbates the vulnerability of nigral dopaminergic neurons to neurotoxicant-induced cell death [13, 39, 40]. Based on these and other results, we proposed that GC-bound GRs represent crucial vulnerability factors in experimentally-induced Parkinsonism [27, 39, 40].

Gender and the sex steroid background also appear to strongly modulate vulnerability to PD, for comprehensive reiew, [10-12]. A number of epidemiological studies have reported that the incidence and prevalence of PD is higher in men than in women. The clinical results are supported by a body of experimental evidence indicating that the nigrostriatal DAergic system is subject to modulation by E_2 in rodents and non human primates and that E_2 exert important neuroprotective effects indifferent models of PD. Besides the recognized genomic and non-genomic mechanisms of action, evidence has been also gathered on a glial involvement in E_2 neuroprotective effects [10, 11, 46-48]. Earlier studies clearly established that neurons and glia express enzymes for steroid synthesis and metabolism [46-48]. For example, P450-aromatase which converts androgens to estrogens in the brain is present in glial cells. In addition, glial receptors for major steroid hormones undergo profound alterations under neurodegenerative conditions [46-48]. Indeed, early embryonic life exposure to P450-aromatase deficiency in transgenic mice, wich results in E_2 deficiency in the ventral midbrain, increased vulnerability of the nigrostrial DAergic system to neurotoxicant-induced experimental parkinsonism, supporting a critical role of this hormone for midbrain DAergic neurons [11]. Of particular mention, within the brain, E_2 *via* either ER-alpha and/or ER-beta, has been shown to exert anti-inflammatory activity on activated macrophages and activated microglial cells *in vitro*, as revealed by the prevention of LPS-induces production of pro-inflammatory cytokines including TNF-alpha, iNOS-induced NO, COX-2, PGE2, and metalloproteinase-9 (MMP-9) and *via* E_2 moduation of NF-kB [10]. Importantly enough, gender differences are present in the response of both astrocytes and microglia in experimental models of PD [10]. Several lines of evidences indicated that endogenous levels of E_2 were critical for the degree of microglia activation and the loss of DAergic neuron functionality both at striatal and SNpc levels. On the other hand, E_2 was shown to promote significant "beneficial effects" within the astrocyte cell compartment. Indeed, E_2 has been reported to exert important neuroprotective effects against neurotoxin-induced astrocyte damage/death, thereby implicating E_2-induced increased astrocyte survival/expression of dopaminergic neurotrophic factors, as part of the mechanisms of the hormone [10].

Collectively, the mentioned informations suggests that hormones of the stress and gonadal axes, virus or endotoxin exposures can significantly influence DAergic neuron vulnerability, also through their immunomodulatory effects at the level of astrocytes and/or microglia (Fig. **3**).

4. GLIAL PATHWAYS INVOLVED IN DAERGIC ENDOGENOUS NEURORESTORATION: FOCUS ON ASTROCYTE-NEUROPROGENITOR CROSSTALK

4.1. Astrocytes and DAergic Survival, Neurotrophic and Pro-regenerative Factors

Importantly, the intrinsic capacity of nigrostriatal DAergic neurons to spontaneously recover following MPTP injury

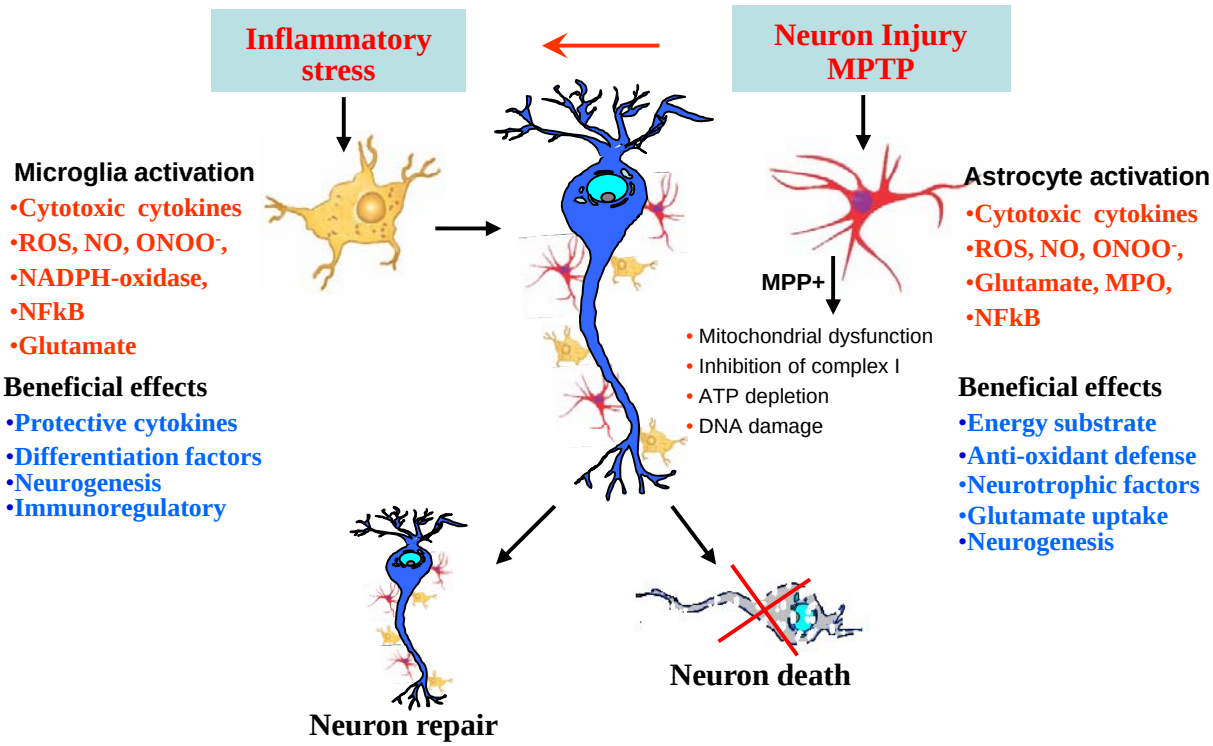

Fig. (3). A schematic representation of glial-mediated detrimental and beneficial inflammatory pathways in PD. Injury of nigrostriatal DAergic neurons, as a result of specific chemical insults (e.g., MPTP), and/or a combination of genetic/environmental factors leads to astrocyte and microglia activation. MPTP is metabolized by astrocytes to 1 methyl-4-phenylpyridinium (MPP+) which is concentrated in DAergic neurons. Microglial-derived cytotoxic mediators further exacerbate inflammation and oxidative stress. Astrocytes and microglia can protect neurons by scavenging radicals and glutamate, by harboring receptors for endogenous anti-inflammatory molecules (such as GCs or estrogens), by providing energy support, trophic factors, «protective» cytokines and by stimulating repair/neurogenesis. Under conditions of chronic inflammatory stress, activated astrocytes and microglia may become dysfunctional and over-express a variety of cytoyoxic mediators eventually resulting in DA neuron demise.

and the age-dependent loss of self-repair ability, may suggest that among the multiple mechanisms at play, the one intimately associated to glial responses likely represent important factors involved in remodeling the impaired nigrostriatal milieu and/or/ promoting/enhancing endogenous protective/repair mechanisms. Of note, astrocytes are well known to express and release a panel of growth factors, *in vitro*, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CTNF), glial derived growth factor (GDNF), neurotrophin-3 (NT-3), basic fibroblast growth factor (FGF2), activity-dependent neurotrophic factor (ADN), hepatocyte growth factor (HGF), and mesencephalic astrocyte-derived neurotrophic factor (MANF) [13, 36-38, 49-52]. Astrocytes can also synthesize and release proteolytic enzymes, in particular the matrix metalloproteinases (MPPs) which play an important role in ECM degradation and remodelling. Of special interest, astrocytes function as support for migrating neuronal precursors in the developing brain and may also function as neuronal precursors in adult CNS [13, 31-33]. Importantly, key astrocyte's factors are necessary for ventral midbrain (VM) DAergic neuron development and survival [49-53]. In particular, *Wingless-type MMTV integration site (Wnt)* family members (i.e. Wnt1 and Wnt5a) are expressed in VM astrocytes together with DA-specific transcription factors, such as Pax-2, En-1 and Otx-2. In addition, VM astrocytes induce the proliferation and differentiation of mesencephalic Daergic progenitors into DAergic neurons [53].

4.2. Reactive Astrocytes and Wnt/β-catenin Signaling in DAergic Neurorescue

Recently, the Wnt (*wingless-type MMTV integration site1*) pathway has emerged as an essential signaling cascade that regulates multiple processes in developing and adult tissues, including differentiation, neuron survival, axonal extension, synapse formation and plasticity, neurotrophin transcription and neurogenesis [54]. The *Wnt/β-catenin* signaling pathway appears to play a central role in the generation of DA neurons in the ventral midbrain (VM) [53], but little is known on the role of *Wnts* in the adult intact or PD midbrain. Using the MPTP-lesioned mouse model which recapitulates many of the pathogenetic processes operative in PD, molecular profiling of 92 mRNA species in ventral midbrain (VM) uncovered a robust and persistent up-regulation of the canonical Wnt agonist, *Wnt1*, further supported by in Situ hybridization histochemistry and Western blot analysis [55]. Interestingly enough, *a*ctivated VM astrocytes were identified as candidate components of *Wnt1* signaling, and activation of Wnt1 pathway proposed as key actor in DA recovery upon MPTP-induced nigrostriatal DA plasticity [55]. Hence, activation of *Wnt1*/β-catenin pathway appears

determinant for the maintenance of a normal complement of TH^+ neurons in the adult midbrain.

4.3. Crosstalk Signaling Pathways in Astrocyte-DA Neuron Dialogue Are Triggered Upon Cytotoxic Insults: A Paracrine Protective Role for Astroglial Born Wnt1

Given that midbrain DA ergic neurons are exquisitely sensitive to oxidative stress and growth factor withdrawal and since astroglial-derived growth and neurotrophic factors are recognized to protect neurons from a variety of pro-apoptotic stimuli, including serum deprivation (SD), 6-OHDA or MPP^+ we next investigated astrocyte-neuron crosstalk *in vitro*, under these cytotoxic conditions [56]. In particular, in the light of the indication that Wnt components are expressed in adult astrocytes, and that *Wnt1* transcription is induced in VM astrocytes upon MPTP injury [55, 56], we thus reasoned that astroglial *Wnt1* expression might represent a more general compensatory self-protective signal, and addressed whether the cytotoxic cascade induced by the different neurotoxic insults might trigger the activation of a common self-defensive pathway in astrocyte-neuron co-cultures, *in vitro*, that might converge to the stabilization of *β-catenin* in DA neurons . Indeed, *β-catenin* functions as a pivotal molecule in defense against oxidative stress, and can also act as a coactivator for several nuclear receptors involved TH neurons development, maintenance and neuroprotection [56]. Thus, activation of *Wnt1/β-catenin* appeared one attractive pathway that might work in concert with astrocyte-derived factors to maintain the integrity and protect TH^+ neurons. Fascinatingly, we found that *Wnt1*-induced neuroprotection was closely integrated with the astroglial response to oxidative stress and inflammation upon injury, and was shown to require *β-catenin* stabilization to convey pro-survival signals to the nucleus, whose expression likely underlie the observed neuroprotection. We then proposed that modulation of astroglial *Wnt1/β-catenin* pathway may tip the balance between apoptosis and the programing of cell survival/neurorescue in these models [56]. An in-depth understanding in the molecular pathways and their crosstalk underlying midbrain neuroprotection will be crucial to identify new avenues for pharmacological and cell replacement therapies against Parkinson's disease.

4.4. Inflammation, Reactive Astrocytes, Wnt Signaling and Adult Neurogenesis

The question of how adult neurogenesis is maintained in the adult brain is the subject of intense investigations [57-60]. It is believed that neuronal precursors can proliferate only in a restricted microenvironment provided by specific cell types and their particular arrangement. Neurogenesis, is the process leading to the generation of new functional neurons, from "progenitor" cells, and include the proliferation and neuronal fate specification, along with maturation of the immature neurons and ultimately integration of the new neuronal progeny into functional neuronal circuits [57, 58]. Neural stem cells (NSC) can be defined as cells that continuously self-renew and have the potential to generate cells of both glia and neuronal lineages (multipotential). Adult neurogenesis constitutes an adaptive response to challenges imposed by the internal state. Factors that govern the generation, differentiation, integration and survival of new neurons include a host of molecules such as growth and neurotrophic factors, hormones, neuropeptides, and an array of inflammatory mediators including a number of cytokines and chemokines, as well certain neurotransmitter molecules. On the other hand, despite the increasing numbers of studies, there is as yet, no conclusive evidence for generation of midbrain DA neurons *in vivo* in experimental models of basal ganglia injury which might provide a significant endogenous restoration of functional SNpc DAergic cell bodies [61-63].

The discordant results obtained to date suggest that the relationship between adult neurogenesis and PD may be more complex than previously anticipated. In this respect, it seems highly possible that the neuroinflammatory component of the disease might play a key role. Indeed, within this frame, accumulating evidence clearly indicate that neuroinflammation can have dual, benefical/harmful effects on adult neurogenesis [64-68]. The dynamic, plastic and interactive properties of glial cells raised the possibility that astrocytes and microglia under certain circumstances might provide a neurogenic microenvironment for neuronal precursors, but under other conditions, might have detrimental influences on neurogenic processes in the adult brain. Recent findings indicate that interleukins 1β and 6, may be involved in astroglial modulation of adult neurogenesis [69]. In addition, certain specifically activated microglial cells can induce neural cell renewal in the adult CNS [64]. Hence, microglia pretreated with IL-4 or IFN-γ induced neurogenesis and oligodendrogenesis in NPCs derived from the SVZ, whereas LPS-pretreated microglial cells blocked both processes in aNPCs [64], in line with reports that inflammation associated with LPS block adult neurogenesis [66, 68] supporting a critical role for a specific inflammatory milieu in dictating promotion or inhibition of adult neurogenesis.

On the other hand, the key role of astrocytes in the context of adult neurogenesis is well recognized [70, 71]. With regard to astrocytes and DAergic neurodevelopment the impact of glia-neuron crosstalk for DA neuron survival, proliferation and differention are well recognized. On the other hand, earlier studies showed the ability of adult SVZ precursors cultured on type 1 astrocyte monolayers to undergo extensive neurogenesis [70, 71]. The presence of multipotent clonogenic neural stem cells in the adult mouse midbrain/hindbrain with functional neurogenic and DAergic potential was recently reported [63, 72]. Our studies, support the functional neurogenic ability of midbrain neuroprogenitors isolated from adult mice [55]. In addition, we have shown that among different experimental settings, only the direct co-culture paradigm between midbrain astrocytes and midbrain-derived NPCs can induce the DAergic phenotype, suggesting that astrocyte-derived factors contributed the induction of the DAergic neuronal phenotype. The fact that MPTP injury and certain pro-inflammatory chemokines can induce the expression of Wnt1 in astrocytes of the VM, indicate not only region specificity but also a defined inflammatory milieu in the modulation of Wnt1 induction in astrocytes [55]. Indeed, Wnt/β-catenin-regulatory mechanisms are known to be required for activation of adult neurogenesis both *in vitro* and *in vivo* [55]. The involvement of Wnt/β-catenin signaling was further supported by the finding that

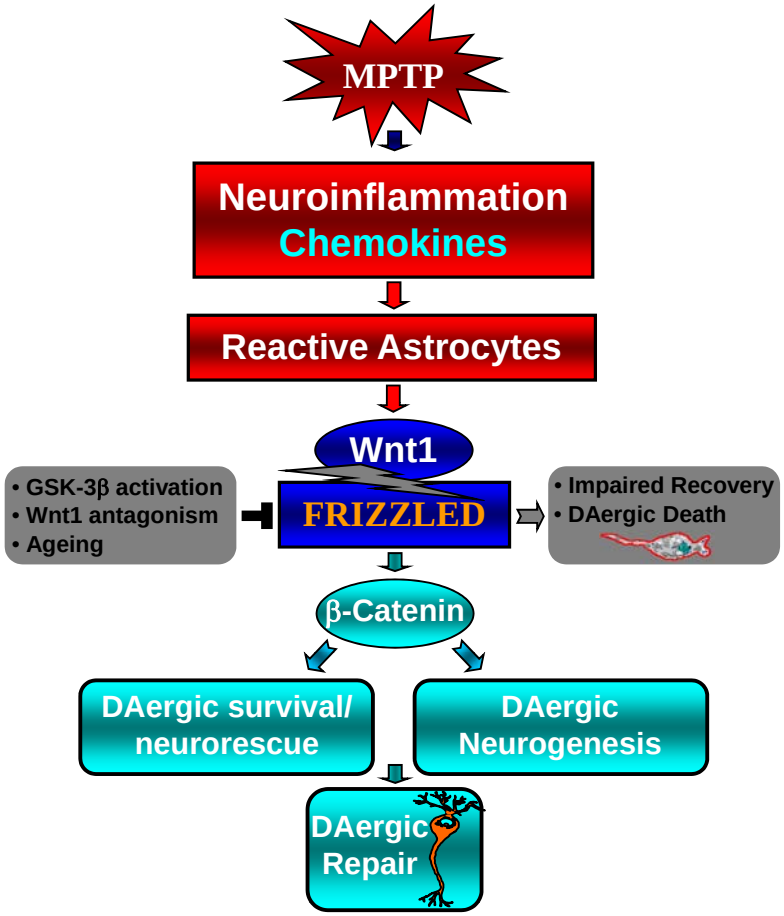

Fig. (4). Schematic illustration of Wnt1/β-catenin signaling as a key player in neuroprotection *via* dopaminergic neuron-astrocyte crosstalk and promoting neurogenesis *via* neuroprogenitor-astrocyte crosstalk. A simplified scheme linking reactive astrocytes and Wnt/beta-catenin signaling to nigrostriatal injury and repair in the MPTP mouse model of PD. Astrocyte-derived Wnts, particularly *Wnt1*, the integrity of DA neurons *via* blockade of GSK-3β-induced phosphorylation and proteosomal degradation of the neuronal pool of β-catenin. Activation of Wnt/β-catenin signaling can also promote neurogenesis from adult midbrain progenitors. Neurotoxic injury or increased oxidative load as a result of aging may antagonize Wnt/β-catenin signaling in DA neurons by up-regulating active GSK-3β, leading to β-catenin degradation and increased DA neuron vulnerability. Neuronal injury also triggers reactive astrocyte expression of a panel of growth and neurotrophic factors, anti-oxidant and neuroprotective mechanisms, among which astrocyte Wnt1 may function as a vital component of DA neurons self-protective machinery shifting the balance towards the programming of cell survival/neurorescue on the on hand, and promoting neurogenesis on the other.

recombinant Wnt1 protein induced neurogenesis in aNPC derived from the midbrain.

All together, our results in conjunction with the data of the literature, suggest a model in which adult midbrain astrocytes, under specific neuroinflammatory conditions, can re-express region-specific factors, including Wnt1, contributing to the regulation of diverse aspects of DAergic neuron homeostasis in the injured VM, including amelioration of the impaired nigral milieu, mitigating DAergic neuron death, and/or enhancing survival, expansion, differentiation of DA progenitors.In addition we suggested reactive astrocytes of the ventral midbrain and Wnt/β-catenin signaling as strong candidate players in MPTP-induce DAergic neuroplasticity [55, 56] (Fig. **4**).

5. CONCLUSION

In summary, astrocytes are provided by a number of adaptive and region-specific mechanisms that can be activated during brain injury. Thus, while two ways of communication between DAergic neurons and glia contribute to maintain neuron homeostasis within the vulnerable midbrain, under conditions of excessive oxidative and nitrosative stress and aberrant production of cytotoxic mediators (e.g. during chronic neurodegenerative conditions), astrocytes and microglial cells may became dysfunctional and are no longer able to efficiently protect nigral DAergic neurons, nor to promote neurorecovery . In this scenario, and given the crucial role of astrocyte-neuron interactions in neuronal growth, survival, differentiation, neurogenesis and synapse formation, alterations in astrocyte-neuron crosstalk as a result of gene mutations, aging, early life events, hormones, endotoxins and neurotoxicants, may then significantly increase the vulnerability of the nigrostriatal DAergic system to either acute or chronic injury.

The question, therefore, arises as to whether astrocytes in the adult brain might be reactivated to regain stem cell features and help repair the damaged/dysfunctional DAergic neurons. Thus, blocking the harmful factors released by in-

jured astrocytes, replacing astrocytes either modified or unmodified in culture, together with cocktails of neurotrophins and anti-oxidant, may provide data needed for effective and safe therapeutic approaches targeting astrocytes and endogenous astrocyte precursors to promote DAergic neuron neurorescue/neuroprotection. We strongly believe that understanding the complex interactions required for successful DAergic recovery and how these mechanisms may be dysregulated in PD may lead to novel therapeutic approaches in the field of endogenous regeneration and PD. In particular, improving the efficiency of neurogenesis and/or functional integration of newly produced neurons, as well as targeting astrocytes to promote in situ nigrostriatal recovery may represent novel avenues to be explored in PD experimental models.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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PATIENT'S CONSENT

Declared none.

LIST OF NOMENCLATURE USED

NSAIDs	=	Anti-inflammatory drugs
COXs	=	cyclooxygenases
DDC	=	diethyldithiocarbamate
ER-α	=	estrogen receptor-α
ER-β	=	estrogen receptor-β
GFAP	=	glial fibrillary acid protein
GRs	=	glucocorticoid receptors
GSH	=	glutathoine
H_2O_2	=	hydrogen peroxide
HPA axis	=	hypothalamic-pituitary-adrenocortical
iNOS	=	inducible nitric oxide
IFN-γ	=	interferon-γ
IL-1α	=	interleukin-1α
IL-1β	=	interleukin-1β
LPS	=	Lipopolysaccharide
MPTP	=	1-methyl-4-phenyl-1,2,3,6-tetrahydropiridine
MAO-B	=	monoaminooxidase B
NO	=	nitric oxide
PD	=	Parkinson's disease
ROS	=	Reactive oxygen species
6-OHDA	=	-hydroxydopamine
SNpc	=	Subtantia nigra pars compacta
TH	=	Tyrosine hdroxylase
TNF-α	=	Tumor necrosis factor α

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