[Frontiers in Bioscience 9, 277-282, January 1, 2004]

BLOOD VESSELS AND PARKINSONISM

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1. ABSTRACT

Blood vessels are the way for nutrients present outside the brain to gain access into the cerebral parenchyma. When neurons are diseased, for example by toxin exposure, reactive glial cells secrete local factors that induce microangiogenesis, probably as part of a spontaneous neuroprotective mechanism related to the increased metabolic demand. In Parkinson's disease (PD) and non human primate models of PD, nigral degeneration is associated with gliosis and microvascular proliferation. Interestingly, microangiogenesis also facilitates the entrance into the brain parenchyma of neurotoxins and harmful cytokine-releasing blood cells, both of which have been linked to neuronal cell death in PD. In the present review we discuss the potential implications of vascular-related phenomena with mechanisms of neuronal damage in PD.

2. INTRODUCTION

The cause of Parkinson's disease (PD) remains unknown. PD is characterized morphologically by loss of dopaminergic neurons in the mesencephalon and the presence of intracellular inclusions known as Lewy bodies. The highest degree of cell death occurs in the Substantia Nigra *pars compacta* (SNpc) (80-90%) (1), whereas a lesser degree is encountered in the ventral tegmental area (VTA) and in the peri- and retro-rubral catecholaminergic group (A8) (30-50%), and minimal loss is present in the periaqueductal grey matter (PAG) (3%) (1, 2). Noradrenergic neurons in the *locus coeruleus* are less affected than nigral dopaminergic neurons, although Lewy bodies are evident in this structure in idiopathic PD (3).

A similar distribution of mesencephalic lesions has been observed in monkeys showing a parkinsonian syndrome after dosing with the dopaminergic neurotoxin 1,methyl-4, phenyl-1,2,3,6, tetrahydropyridine (MPTP) (4, 5). These findings support the concept that certain subpopulations of catecholaminergic neurons are more sensitive to the factors involved in the cascade of events leading to neuronal cell death in PD. Several hypotheses exist that attempt to explain this dramatic cell loss, but the cause of the differential vulnerability between catecholaminergic cell types and specifically between dopaminergic cell groups, remains unknown.

The blood brain barrier (BBB) in primates is located in brain capillaries and is constituted by endothelial, glial and meningeal cells which are essential for control of permeability (6, 7). The BBB is vulnerable to factors that affect the vascular wall (such as trauma, ischemia, malignant tumors or hemorrhage) and it is affected by age (a known risk factor for PD). Common age-related changes of the BBB are reduced thickness of endothelial cells, vacuolar inclusions in pericytes and decreased release of aminoacids in the cerebral parenchyma. High blood pressure and inflammation also affect BBB permeability, facilitating the penetration of compounds into the cerebral extracellular space (8).

Neurotoxicity seems to be facilitated by local events involving blood vessels (BV) and reactive glial cells. Deleterious situations inducing oxidative stress and neuronal loss stimulate a localized inflammatory response that affects astrocytes and BV. As a consequence, the permeability of the BBB is altered in vulnerable areas further facilitating the entrance of neurotoxins and reactive blood cells releasing cytokines perpetuating the cycle of local neurodegeneration.

3. THE ROLE OF OXIDATIVE STRESS IN THE DEVELOPMENT OF PD

The oxidative stress hypothesis of neuronal loss is based on the imbalance between the formation of cellular pro-oxidant molecules (as superoxide and hydroxyl

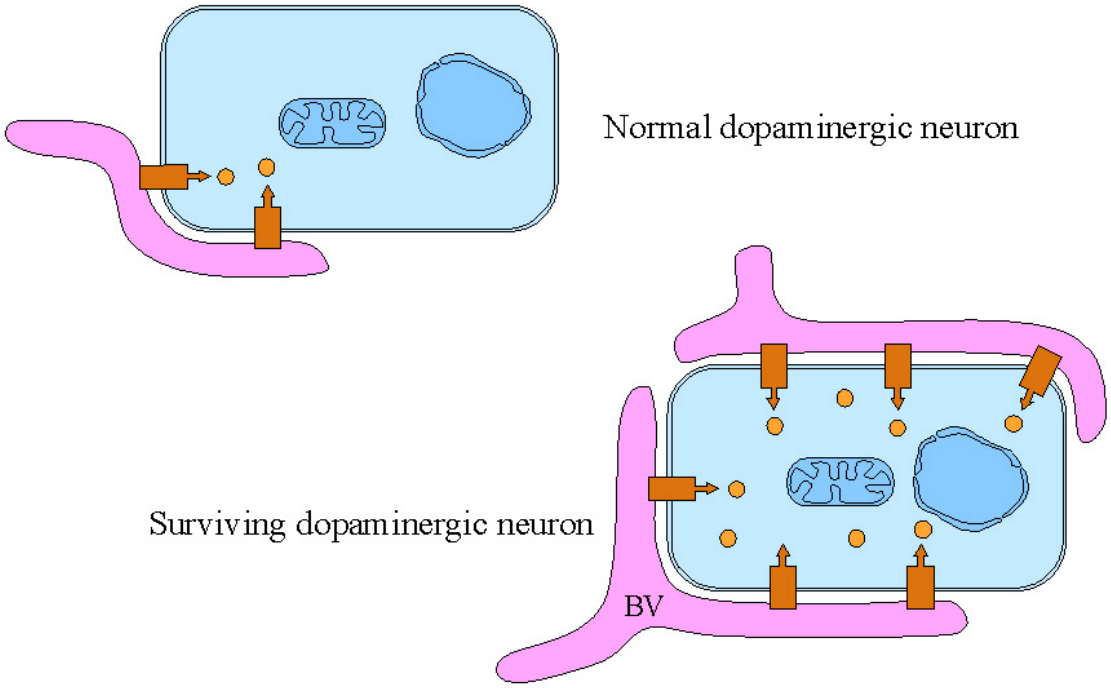

Figure 1. Hypothetic toxic effect in dopaminergic neurons due to the increase of blood vessels (BV) and ferrotransferrin receptors (red boxes with arrows). The increased uptake of iron (orange circles) can induce oxidative stress (23).

radicals) and antioxidant mechanisms. Free radicals are capable of producing cellular damage through alteration of membrane permeability (9). In PD, the neurons most vulnerable to degeneration have been shown to be particularly sensitive to oxidative stress (10). Increased lipid peroxidation has been described in the SNpc of parkinsonian patients (11), which suggests a possible exposure to free radical agents. Other findings that support this hypothesis are: i) the proportion of Fe^{2+}/Fe^{3+} in the SNpc of parkinsonian patients is higher than in control subjects (12), ii) the concentration of glutathione peroxidase and catalase are reduced in the SNpc of PD patients (13), iii) upregulation of superoxide dismutase has been described in the SNpc and nucleus basalis of PD patients (14) and iv) reduced glutathione is decreased in the SNpc of PD patients (13, 15). The density of glutathione peroxidase positive neurons is increased in preserved mesencephalic areas or regions with reduced neuronal loss (PAG, VTA and A8) but it is very low in the SNpc (16).

4. IRON AND THE BLOOD BRAIN BARRIER

Associated with the free radical theory, iron has been implicated in the pathogenesis of PD. Iron is a cofactor in the Fenton reaction and produces free radical release (17) increasing cellular oxidative stress. In this regard, iron levels have been measured in the brain of PD patients and high concentrations have been found in the globus pallidus and SN (18, 19). Iron is specifically increased in surviving melanized neurons in the SNpc, which store this metal during the course of the disease (18,19, 20, 21). Increased intracellular iron could be related to alterations in the components of the BBB that facilitate iron availability, increased transport inside the cells through specific transferrin receptors, reduced release, or by a combination of the three mechanisms (22).

It is widely known that the BBB acts as a protective barrier of the brain against harmful agents flowing in the bloodstream. Ultrastructural studies demonstrate that endothelial cells in the brain are different from those in peripheral tissue. Such differences are mainly the presence of tight junctions between brain endothelial cells that restrict flow through the BBB. Indeed, the BBB regulates the flow of substances into the brain parenchyma, allowing only the selective passage of small or lipophilic substances (23). Essential nutrients such as glucose and aminoacids (or related molecules including the dopamine precursor l-DOPA), growth factors and cytokines have limited access to the BBB (24). Iron is transported thorough the BBB by transferrin and lactoferrin (lactotransferrin) receptors (25). PD patients have an increased number of transferrin receptors in BV around SNpc melanized neurons (figure 1). Iron acquisition by neurons occurs from iron-transferrin complexes with a direct interaction with specific membrane receptors, mainly lactotransferrin receptors. Interestingly, increased intensity of immunoreactivity to lactoferrin receptors has been reported on neurons and BV in the mesencephalon of PD patients (20, 26), in particular in the SNpc where the loss of dopaminergic neurons is severe. Although increased iron availability and uptake are probably related to the hyperactivivity of surviving neurons, higher concentrations of intracellular iron determines higher risk of oxidative stress which may contribute to the pathophysiology of PD (figure 1).

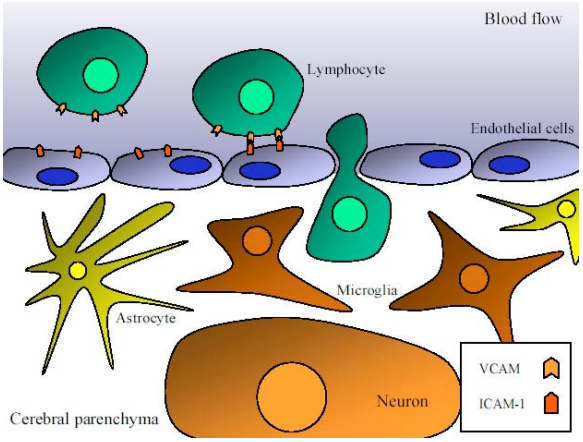

Figure 2. Adhesion phenomena produced in the brain. VCAM and ICAM-1 expression facilitate the entrance of blood cells into the cerebral parenchyma through the BBB.

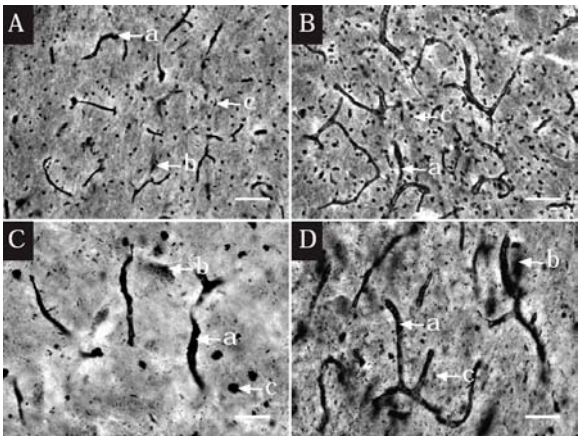

Figure 3. Reticuline silver impregnation in the SNpc of normal (A, C) and MPTP-treated (B, D) *Macaca fascicularis* monkey. Note the increased vascularization in SNpc of MPTP-treated (B, D) compared to control monkey (A, C). At a higher magnification (C, D) a close relation between blood vessels (a), pigmented neurons (b) and glial cells (c), can be observed. Scale bar: A, B: 100 µm; C, D: 50 µm.

5. BLOOD VESSELS CHANGES DURING NEURODEGENERATION

Ultrastructural studies and analysis with magnetic resonance imaging techniques have shown that the BBB seems to be preserved in experimental parkinsonism (27, 28). However, an increase of intercellular adhesion molecules (ICAM-1) and blood cells into the brain extracellular space has been reported in SNpc of parkinsonian animals (29). This suggests that an active recruitment of cells occurs after a nigral lesion, and the later onset of proinflammatory reactions could perpetuate the toxic phenomena (figure 2).

Neovascularization in the brain occurs after different insults that induce neuronal loss (30). For example, hypoxia, hypoglycemia, or inflammation are triggers for an angiogenic response (31, 32, 33, 34). Although we do not know the exact mechanisms of neuronal loss in PD, neuropathological analysis revealed that parkinsonian patients showed increase number of endothelial cells nuclei (multiplied by a factor of 2.5) (35). This increase could be related to augmented number and density of BV or changes in the thickness of the vascular wall. In that regard, morphometric studies have demonstrated an increase of 25% in the area occupied by BV in the SNpc of MPTP-treated monkeys (figure 3) and mice (36, 37). The increased vascularization in parkinsonism seems to be induced, or at least perpetuated, by dopaminergic cell loss. Neuronal loss signals neighboring cells like astrocytes, macrophages, platelets or T-cells, which in turn release factors involved in microangiogenesis. Angiogenesis in the affected parenchyma could also be related to high demands of metabolites from surviving neurons. Neurons and BV have a close physical relationship (figure 3) (38), suggesting that increase vascularization could play a dual role: i) protect against degeneration due to the delivery and uptake of nutrients and neuroprotective factors, and ii) increase the availability of neurotoxins, which directly or indirectly promote monocyte or lymphocyte migration that perpetuates the inflammatory reaction by releasing endogenous cytotoxic compounds such as cytokines. Pro-inflammatory cytokines such as TNF-alpha as well as IL-1beta are elevated in the SNc of patients with PD (39, 40, 41, 42, 43). As predicted by their function, the increases in these pro-inflammatory cytokines are coupled with increases in apoptosis-related proteins and oxidative stress in PD patients (44, 45).

6. ASTROGLIOSIS IN PD

In PD neuronal dopaminergic cell loss is associated with astrogliosis (46), yet the role of astrocytes in this disease remains unclear. As we have previously mentioned, astrocytes are constituents of the BBB and recent studies suggest that astrocytes could modulate blood flow according to the energetic needs of working neurons via calcium changes in astrocytic end feet (47, 48). The interaction between astrocytes and endothelial cells is crucial in the formation of the BBB (figure 4) (49). During development, astrocytes are generated prior to endothelial cells and both cell types are closely connected in the adult brain (50). However during angiogenesis, adhesion molecules and cellular junction components alter the relationship between astrocytes and vascular endothelium, with consequences still unclear (51). The phenotype of endothelial cells is probably induced by astrocytes, and in fact, cultured rat astrocytes kept in the absence of other cell types, develop into endothelial cells (52). Hence, the role of astrocytes in the development of endothelial cells and the integrity of the BBB is important in pathological conditions such as PD, in which the increase of BV and astrocytes could be closely related (figure 4). Moreover, the proliferation of BV could be induced by astrocytes as they can release angiogenic factors (53), induce the expression of adhesion molecules like ICAM-1 in endothelial cells (29) and facilitate the active recruitment of blood cells into the parenchyma (figure 2) (54).

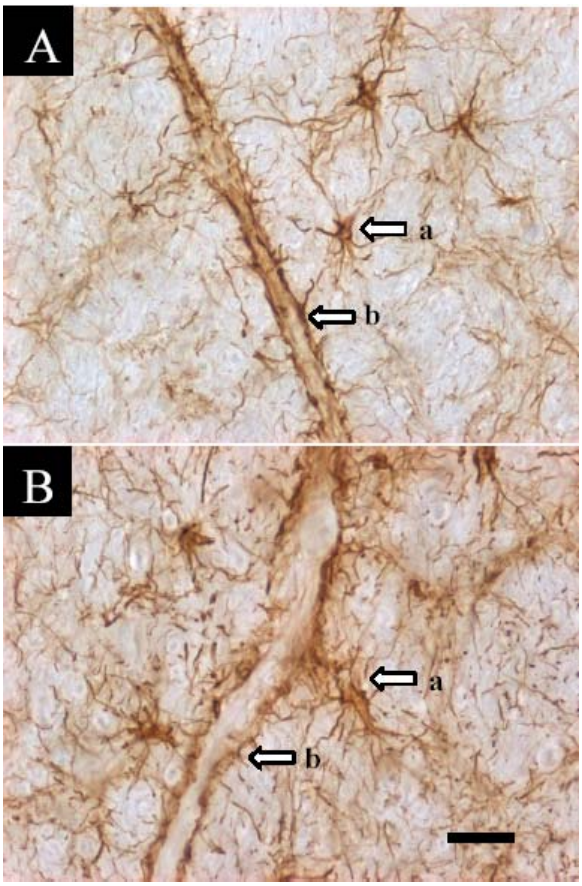

Figure 4. Immunohistochemistry for Glial Fibrilary Acidic Protein (GFAP) in SNpc of *Macaca fascicularis* monkey. Note the close relation between astrocytes (a) and blood vessels (b) in both control (A) and MPTP-treated monkeys (B). Scale bar: 50 μm.

6. CONCLUSIONS AND PERSPECTIVES

Nigral cell loss in PD and animal models of PD is associated with gliosis and changes in the microvasculature that may contribute to the pathophysiology of this disease. Astrocytosis-induced microangiogenesis facilitates the transport of nutrients, metabolites, inflammatory compounds and the recruitment of blood cells inside the brain parenchyma. Angiogenesis can increase the oxidative stress in vulnerable regions by enhanced delivery of toxins to neurons. The intracellular accumulation of iron observed in dopaminergic surviving neurons is facilitated by the upregulation of transferrin receptors in endothelial cells surrounding these cells. In summary, although the changes in vascularization in parkinsonism may represent intrinsic mechanisms to meet the higher requirements of hypermetabolic surviving dopaminergic neurons, there is evidence supporting the concept that astrocytosis-induced microangiogenesis perpetuates dopaminergic cell loss by indirectly increasing oxidative stress and release of cytotoxic cytokines. A manipulation of vascularization in experimental models of PD may help understand the mechanisms of cell loss and identify new targets for the treatment of PD.

7. ACKNOWLEDGMENTS

The authors would like to thank Dr. Pablo Caviedes for comments on this manuscript. Supported by FIS 99/123 and FEDER FD1/97-1931 (M.T.H.), and NIH NINDS RO1-NS40578-01 (M.E.).

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Key words: Parkinson's disease, MPTP, Inflammation, Blood Vessels, Glia, Iron, Review

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