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Maladies Mitochondriales

Mitochondrial dysfunctions in Parkinson's disease

Dysfonctions mitochondriales dans la maladie de Parkinson

C.A. Gautier [a,b,c], O. Corti [a,b,c], A. Brice [a,*,b,c,d]

[a] Inserm, U 975, CRICM, hôpital de la Pitié-Salpêtrière, 75013 Paris, France
[b] UPMC Université Paris 06, UMR_S975, 75013 Paris, France
[c] CNRS, UMR 7225, 75013 Paris, France
[d] Department of Genetics and Cytogenetics, hôpital de la Salpêtrière, AP–HP, 75013 Paris, France

INFO ARTICLE

Article history:
Received 12 February 2013
Received in revised form
3 June 2013
Accepted 4 June 2013
Available online 9 October 2013

Keywords:
Parkinson's Disease
Mitochondria
Oxidative stress
Disease models

Mots clés :
Maladie de Parkinson
Mitochondrie
Stress oxydant
Modèles animaux

ABSTRACT

Neurodegenerative disorders (ND) include a wide spectrum of diseases characterized by progressive neuronal dysfunctions or degeneration. With an estimated cost of 135 billion € in 2010 in the European Union (Olesen et al., 2012), they put an enormous economic as well as social burden on modern societies. Hence, they have been the subject of a huge amount of research for the last fifty years. For many of these diseases, our understanding of their profound causes is incomplete and this hinders the discovery of efficient therapies. ND form a highly heterogeneous group of diseases affecting various neuronal subpopulations reflecting different origins and different pathological mechanisms. However, some common themes in the physiopathology of these disorders are emerging. There is growing evidence that mitochondrial dysfunctions play a pivotal role at some point in the course of neurodegeneration. In some cases (e.g. Alzheimer's disease, amyotrophic lateral sclerosis), impairment of mitochondrial functions probably occurs late in the course of the disease. In a subset of ND, current evidence suggests that mitochondrial dysfunctions play a more seminal role in neuronal demise. Parkinson's disease (PD) presents one of the strongest cases based in part on post-mortem studies that have shown mitochondrial impairment (e.g. reduced complex I activity) and oxidative damage in idiopathic PD brains. The occurrence of PD is largely sporadic, but clinical syndromes resembling sporadic PD have been linked to specific environmental insults or to mutations in at least 5 distinct genes (α-synuclein, parkin, DJ-1, PINK1 and LRRK2). It is postulated that the elucidation of the pathogenic mechanisms underlying the selective dopaminergic degeneration in familial and environmental Parkinsonism should provide important clues to the pathogenic mechanisms responsible for idiopathic PD. Hence, numerous cellular and animal models of the disease have been generated that mimic these environmental or genetic insults. The study of these models has yielded valuable information regarding the pathogenic mechanisms underlying dopaminergic degeneration in PD, many of which point towards an involvement of mitochondrial dysfunction. In this short review we will analyze critically the experimental evidence for the mitochondrial origin of PD and evaluate its relevance for our general understanding of the disease.

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* *Corresponding author.*
E-mail address : alexis.brice@upmc.fr (A. Brice).

0035-3787/$ – see front matter © 2013 Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.neurol.2013.06.003

RÉSUMÉ

La maladie de Parkinson, d'étiologie inconnue, est associée à une dégénérescence des neurones dopaminergiques de la voie nigro-striée. L'élucidation des mécanismes physiopathologiques de la maladie constituerait une étape clé dans la mise au point de thérapies permettant de ralentir la progression de la maladie. Ces mécanismes sont, à ce jour, inconnus. Toutefois, un faisceau convergent d'observations permet de soupçonner que des défauts mitochondriaux constituent un événement précoce de la dégénérescence dopaminergique. Ces soupçons se basent sur l'étude des cas sporadiques ainsi que sur celle des modèles d'intoxication et des modèles génétiques de la maladie. Dans cette revue, nous proposerons une analyse critique des éléments incriminant des dysfonctions mitochondriales dans ces différents modèles. Nous discuterons de leur pertinence vis-à-vis des formes sporadiques de la maladie ainsi que des perspectives thérapeutiques ouvertes.

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1. PD and mitochondrial dysfunctions: establishing the connection

Parkinson's disease (PD) is a frequent and debilitating disease resulting in part from the progressive degeneration of the dopaminergic neurons of the substantia nigra pars compacta. It was first described in 1817 by James Parkinson in his ''Essay on the Shaking Palsy''. It was not until the 1950's and the work of Arvid Carlsonn that PD was linked to a depletion of dopamine in the striatum due to the degeneration of nigral DA neurons (Iversen and Iversen, 2007). Then, our understanding of the causes of the disease somewhat stalled for three decades. The jump start came in the early 1980's when Bill Langston observed that some intravenous heroin users in San Francisco were developing an acute Parkinsonian syndrome symptomatically indistinguishable from sporadic PD. He later uncovered that the disease was caused by poisoning with 1-methyl 4-phenyl 1,2,3,6 tetrahydropyridine (MPTP), an impurity in the purification process of the synthetic heroin used by this group of addicts (Langston et al., 1983). MPTP and its metabolite 1-methyl 4-phenylpyridinium (MPP +), were later shown to be inhibitors of complex I of the mitochondrial respiratory chain (Nicklas et al., 1985). They also have the ability to cause a Parkinsonian syndrome in rodents and primates, offering the first reliable PD animal models. The link between mitochondrial dysfunctions and Parkinson's disease was suggested for the first time. It later appeared that MPP+ is an excellent substrate for the dopamine autotransporter (DAT), so that it tends to accumulate in dopaminergic neurons, which explains their specific vulnerability to cell death (Tolwani et al., 1999).

The mitochondrial hypothesis is further sustained by the observation that post-mortem extracts of substantia nigra from PD patients displayed a reduced activity of complex I of the mitochondrial electron transport chain (Schapira, 1989). This defect correlates with increased oxidative damages in the mitochondrial DNA, which encodes for 13 subunits of the mitochondrial electron transport system complexes (Alam et al., 1997). Platelets and the frontal cortex of PD patients also display reduced complex I activity suggesting that dopaminergic neurons might be especially sensitive to systemic complex I defects (Benecke et al., 1993; Mann et al., 1992). This notion is further substantiated by the observation that the chronic and systemic injection of rotenone, a potent complex I inhibitor, can result in an atypical Parkinsonian syndrome accompanied by DA neurodegeneration although other types of neuronal structures appear to be affected in this model (Betarbet et al., 2000; Höglinger et al., 2003). Of note, mutations in the gene encoding mitochondrial DNA polymerase gamma (*POLG*), the enzyme that synthesises mitochondrial DNA (mtDNA), have been linked to cases of Parkinsonism (Siciliano et al., 2001; Luoma et al., 2004). In addition, it has been suggested that specific mitochondrial DNA haplogroups or point mutations may increase the risk for PD, although the evidence is generally poor (reviewed by Schapira, 2008). Nevertheless, clonally expanded somatic mitochondrial DNA deletions, associated with respiratory defects, have been shown to accumulate specifically in human dopaminergic neurons from the substantia nigra, providing a possible molecular basis to the preferential vulnerability of these neurons in PD (Bender et al., 2006; Kraytsberg et al., 2006).

It is not clear yet why DA neurons would be sensitive to complex I defects that are too low to induce energetic failure. Betarbet et al. suggested the possible intermission of oxidative stress. In addition to its direct effects on bioenergetics, complex I deficiency also has the ability to increase mitochondrial oxidative stress. Under normal conditions, mitochondria are the main source of reactive oxygen species (ROS) in the cell. ROS are produced at the level of complex I and complex III (Cadenas et al., 1977). A partial inhibition of complex I disturbs the electron flow through the electron transport system, favoring the one electron reduction of oxygen at the level of cytochrome oxidase, leading to the formation of the superoxide anion $O_2^{\bullet -}$. Complex I bears four iron-sulfide clusters in its quaternary structure. These clusters are easily reduced by $O_2^{\bullet -}$, further damaging complex I capacity and fueling a vicious cycle progressively leading to bioenergetic failure. Quickly following Betarbet's study, another group showed that the partial inhibition of complex I activity by rotenone spurs the production of ROS in isolated mitochondria (Votyakova and Reynolds, 2001). In animal models, the chronic exposure to MPTP or rotenone results in an elevation of markers of oxidative stress in the substantia nigra (Sriram et al., 1997). Interestingly, Paraquat (PQ), a widely used herbicide and a free radical producing agent, causes Parkinsonian syndromes without direct effects on complex I

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