EDITORIAL

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Neuroprotection in Parkinson's Disease: a Realistic Goal?

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The current issue of CNS Neuroscience & Therapeutics contains an interesting review by Kinecses and Vecsei [1] on the progress in our knowledge related to the pathophysiological mechanisms of Parkinson's disease (PD) and on the development of putative neuroprotective molecules. Since the seminal discovery by Oleh Hornykiewicz that degeneration of DA neurons within the substantia nigra pars compacta (SNc) and the consequential dopamine depletion in the striatum was the cause of neurological symptoms in PD [2], thousands of reviews have been written on the subject, some of them possibly superfluous. Nevertheless, we found this last work enjoyable in terms of readability and in the way the authors decided to tackle such a difficult enterprise. This brief literature review is obviously far from comprehensive or exhaustive, as it would be impossible to summarize 50 years of fruitful research in the PD field in a few pages. The main contribution of this review is the general overview of the pathomechanism field and a survey of the literature that it provides on the hot topic of neuroprotection. Indeed, molecules able to slow and halt dopaminergic neuronal loss represent the highest ambition of PD research, drug companies and not least, patients. In recent years, research has advanced to the point that halting the progression of PD, restoring lost function, and even preventing the disease might be considered realistic goals [3]. Nevertheless the ultimate goal of preventing PD may take years to achieve, and no strong experimental confirmation hitherto is available for any of the compounds described by Kinecses and Vecsei [1] and others that the authors have not cited.

Essentially, this limit is likely to be due to the fact that we do not extensively know the pathogenesis of the disease. Certainly, the last two decades have seen a great progress in the knowledge of the pathological mechanisms involved, generally in neurodegeneration [4,5]. Mitochondrial dysfunction, excitotoxicity, neuroinflammation, oxidative stress as well as protein aggregation are considered to be the mean pathways leading to apoptosis [1,6]. The research aims to understand this intricate cascade of events as of primary importance for the developing strategies to slow the progression of PD.

Important clues concerning the pathogenesis of PD have been achieved from epidemiological studies suggesting several environmental factors linked to the disease. Pesticide or herbicide exposure seem to cause an energy failure of dopaminergic neurons subsequent to a mitochondrial dysfunction similar to that observed in case of MPTP intoxication [7] and indeed, rural living (where the use of pesticide is widespread) represents a risk factor for sporadic PD [8]. On the other hand, genetic alterations leading to abnormal protein aggregation, or excessive oxidative stress, or alteration of apoptotic mechanisms account for the less common familial cases [9–11].

In addition to the fact that we do not know what exactly causes most cases of PD, another complication in the development of molecules capable of modifying the disease course is that their efficacy is regularly tested on animals rendered Parkinsonian by dopaminergic toxins. Although these models are useful tools for studying the physiopathology of PD, in the field of neuroprotection research, the obstacle is represented by the quite dissimilar temporal course and anatomopathological features of these bench models from the human disease. For instance, the MPTP, or the 6-OHDA intoxicated animal models (the most extensive used), show a monophasic acute-subacute effect even when applying the intoxication protocol slowly, which does not replicate the nigrostriatal neuodegeneration of idiopathic PD. Of interest, post-mortem human studies have suggested that substantia nigra dopaminergic neuron death begins at least 5–10 years before the onset of motor symptoms [12–15] (Figure 1). Moreover, these animal models are obtained by using specific dopaminergic neuron toxin, whereas the human disease is characterized by the involvement of an ample variety of neurotransmitters [16]. Although PD is primarily clinically defined as an extrapyramidal disorder, it is also characterized by wide range nervous system damage not only motor, but even cognitive, behavioral, and autonomic. It is enough to know that on the basis of a series of anatomic studies, it was proposed that the PD pathology begins in the dorsal motor nucleus of the vagus, in the medulla oblongata and that there is also an early involvement of the olfactory bulb [17] (Figure 1).

We do not know if PD will be prevented, indeed research into neuroprotective molecules of proven efficacy still represents a challenge for neuroscientists.

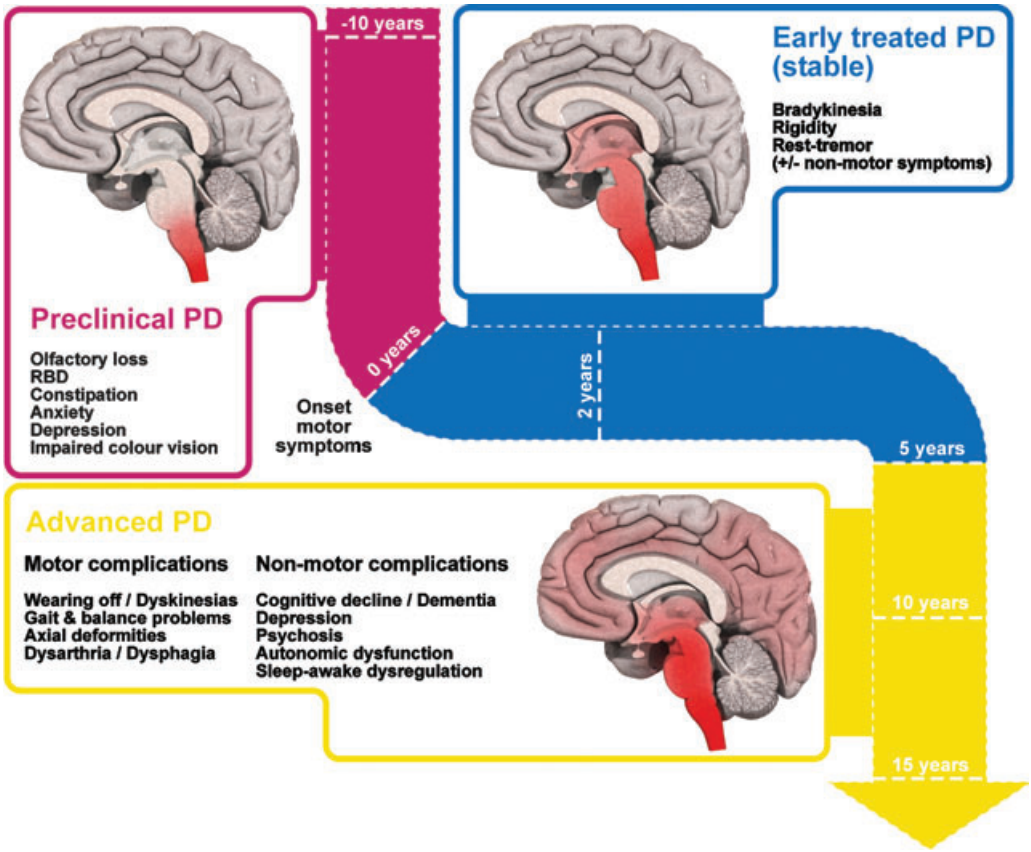

Figure 1 This figure shows how Parkinson's disease progresses from the earliest symptoms (often nonmotor symptoms) to diagnosis and start of treatment through to the early and advanced stages of the condition. Copyright© 2010, Boehringer Ingelheim. All rights reserved.

If the current Parkinsonian animal models represent a poor tool for predicting neuroprotective drugs, on the other hand, studies conducted on PD patients manifest other concerns. The primary pitfall is that many of the drugs proposed to interfere with the disease course are clinically effective on the PD symptoms, confounding the clinical assessments, that is, MAO-B inhibitors or dopamine agonists. Moreover, nondopaminergic drugs such as creatine might alter the measure outcome by giving a nonspecific effect of a sense of well being. Thus, to overcome the problem of the symptomatic effects in PD progression of the suspected neuroprotective molecules, the delayed-start clinical trial design, also called the randomized-start design, has been performed [18]. This protocol is based on the assumption that if there is a disease-modifying effect, the group treated with a placebo for the first half of the study should be worse in comparison to the group treated with the drug for the entire study. However, this kind of protocol has a fundamental drawback. For obvious medical/ethical reason, the placebo-treated patients should not be composed of advanced PD patients requiring a considerable therapy, but by early or mild PD subjects. However, these groups of patients, in comparison to advanced, manifest a slower progression rate of the disease and poor quantifiable changes in clinical scales. Even with a long-lasting study, changes in clinical outcome could be difficult to detect [19,20] and even if a neuroprotective effect is detected, it could be linked to a preservation of compensatory mechanisms rather than to a true neuroprotection.

Another way to measure the hypothetical neuroprotective effect is to quantify a specific biomarker of dopaminergic neuron loss, to recognize the true effect on disease progression from the symptomatic effects. Actually, brain radio assay imaging seems to be appropriate for this goal: however, in two large clinical trials [21,22], the dopamine agonists employed interfere with the radioligand binding, hampering the results [23,24].

A point to be mentioned about the neuroprotection strategies applied in human disease is the time lag between the clinical and anatomopathological onset of the disease. However, dopaminergic neuron loss precedes by years the clinical disease onset and as soon as the first clinically clear motor symptom appears, the ventrolateral area of the SNc is already severely destroyed (about 70% of neuron loss) [12,13]. In this context, it appears clear that a hypothetical neuroprotection strategy in PD would start too late to be significantly beneficial (Figure 1). How can we perform neuroprotection before the clinical evidence of the disease? It is clear that a key challenge would be to find an early marker of the disease, which could identify individuals likely to develop the disease [25].

Recent research has thrown some light on this: numerous potential biomarkers have now been identified, ranging from neuroimaging to wet biological markers such as blood and cerebrospinal fluid (CSF) [26]. Compelling evidence has shown that positron emission tomography (PET) or single photon emission computed tomography (SPECT) imaging uses a radiolabelled compound as a probe of dopamine transporters (DAT), sensitive enough to detect a subclinical degeneration of the dopaminergic system [27,28]. Hence, they can be very useful in studying the progression of presynaptic dopaminergic degeneration, thus detecting patients in the premotor phase of PD [29]. The American Academy of Neurology (AAN) guidelines [30] also consider magnetic resonance imaging (MRI) as potentially useful for a differential diagnosis of PD from other forms of Parkinsonism. In addition, of potential interest for early diagnosis of PD is the evidence that the sense of smell is affected in the initial stages of the neurodegenerative process. Unfortunately, hyposmia has insufficient specificity for smell testing to be used as a single screening test for premotor PD. Recently, a two step approach of combining olfactory testing and DAT SPECT imaging seems to be able to overcome this drawback, having both high sensitivity and specificity in diagnosing premotor PD [31].

In conclusion, we would like to point out that the research into neuroprotective molecules of proven efficacy still represents a challenge for neuroscientists. The first difficulty is to prove the real efficacy of the potential therapy, either in animal models or in large cohorts of patients free from the pharmaceutical interests of the big companies. Finally, although neuroprotective therapy remains a higher priority in the field of PD, as well as of all neurodegenerative diseases, at the same time, we believe that a neuroprotective strategy is really successful when performed in the early stages of the disease that unfortunately do not correspond to the onset of motor deficits. Thus, parallel to exploration of molecules modifying the disease course, we must improve our ability in premotor diagnosis for an authentic advancement in the treatment of PD. In reality, the promising results seem to please the researchers and vested financial interests more than the patients. We do not know if PD will be prevented, without doubt we can reduce the risk so far known. Recently, a large body of experimental and epidemiological evidence has highlighted the paramount role of dietary factors in counteracting DA degeneration [32]. Therefore, although rapidly advancing basic research is developing reliable diagnostic tools to improve promptness of diagnosis and more effective disease modifying therapies, promotion of healthy lifestyle choices might help to promote neuroprotection and reduce the risk of PD in the general population.

Conflicts of Interest

The authors declare no conflict of interests.

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