Medical Hypotheses 104 (2017) 48–53

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Parkinson's disease; the hibernating spore hypothesis

Ketil Berstad [a,*], Johanna E.R. Berstad [b]

[a] Norwegian Drug and Therapeutic Formulary, Oslo, Norway
[b] Unit of Oral and Maxillofacial Surgery, Department of Head and Neck Surgery, Division for Head, Neck and Reconstructive Surgery, Oslo University Hospital, National Hospital, Oslo, Norway

ARTICLE INFO

Article history:
Received 25 January 2017
Accepted 25 May 2017

Keywords:
Parkinson's disease
Actinobacteria
Actinomyces
Fungi
Ray fungus
Alpha-synuclein
Hyphae
Spores
Macroautophagy
Mold
Gut microbiota
Olfactory

ABSTRACT

The authors support the hypothesis that a causative agent in Parkinson's disease (PD) might be either fungus or bacteria with fungus-like properties – *Actinobacteria*, and that their spores may serve as 'infectious agents'. Updated research and the epidemiology of PD suggest that the disease might be induced by *environmental factor(s)*, possibly with genetic susceptibility, and that α-synuclein probably should be regarded as *part of the body's own defense mechanism*. To explain the dual-hit theory with stage 1 involvement of the olfactory structures and the 'gut-brain'-axis, the environmental factor is probably *airborne* and quite '*robust*' entering the body via the nose/mouth, then to be swallowed reaching the enteric nervous system with retained pathogenicity. Similar to the essence of smoking food, which is to eradicate microorganisms, a viable agent may be defused by tobacco smoke. Hence, the agent is likely to be a '*living*' and not an inert agent. Furthermore, and accordant with the age-dependent incidence of LPD, this implies that a *dormant viable agent* have been escorted by α-synuclein via retrograde axonal transport from the nose and/or GI tract to hibernate in the associated cerebral nuclei. In the brain, PD spreads like a *low-grade infection*, and that patients develop symptoms in later life, indicate a *relatively long incubation time*. Importantly, *Actinomyces* species may form *endospores*, the hardiest known form of life on Earth. The authors hypothesize that certain spores may not be subject to degradation by macroautophagy, and that these spores become reactivated due to the age-dependent or genetic reduced macroautophagic function. Hence, the hibernating spore hypothesis explains both early-onset and late-onset PD. Evaluation of updated available information are all consistent with the hypothesis that PD may be induced by spores from fungi or *Actinobacteria* and thus supports Broxmeyer's hypothesis put forward 15 years ago.

Introduction

In 2002, Broxmeyer concluded in his paper 'Parkinson's: another look' [1]: '…the preponderance of convincing evidence, … points to a chronic infectious cause, not viral and most likely of the family Actinomycetales ……'. The aim of the present report is to support and revitalize Broxmeyer's hypothesis.

Among US Medicare beneficiaries aged 65 and older, age-standardized Parkinson disease (PD) prevalence in White men was approximately twice that in Blacks and in Asians [2]. PD prevalence and annual incidence appear to continue to increase into old age, and is higher in men than in women [2,3]. Breckenridge et al. [4] recently confirmed that cigarette smoking is inversely associated with PD risk, whereas rural living, farming, well-water consumption and some pesticides seem to be environmental risk factors.

Tanner et al. [5] found little concordance in twins when the disease develops after age 50 years, but complete concordance in monozygotic twins for disease onset before this age (early-onset). Furthermore, 5%–10% of PD can be ascribed monogenetic mutations (e.g. SNCA, LRRK2), where some may lead to early-onset, whereas other to late-onset PD (LPD) [6]. Monogenetic mutations are recognized to play a significant role among the 5–10% having early-onset PD (EPD), and, except for a minor subset, is unlikely as the disease-causing factor among the much more common LPD [5]. Despite substantial research, the exact role of genetics in PD pathogenesis has remained unclarified [6,7].

The epidemiology of PD may to some extent resemble that of peptic ulcer disease, which is caused by the bacterium *Helicobacter pylori*. One striking common feature is cases of accumulation of the disease among members of the same household. In case of peptic ulcer disease, this was initially attributed genetic factors, but was later ascribed infection, either between members of the household

* Corresponding author at: Norwegian Drug and Therapeutic Formulary, PB 5070 Majorstuen, N-0301 Oslo, Norway.
E-mail address: k-bers@online.no (K. Berstad).

http://dx.doi.org/10.1016/j.mehy.2017.05.022
0306-9877/

or from an unidentified common source. Spread of PD between individuals seems less likely. But given that about 15% of patients have a first-degree relative with the disease, typically without a clear mode of inheritance [8], and, though not validated by further papers after 1987, members of the same household can develop PD in a relatively short space of time [9], a common 'external' source can be assumed.

Many now believe that an abnormality along the 'gut-brain'-axis is a plausible explanatory model for PD [10,11], and favor the idea of PD being induced by an environmental factor [12,13]. Consequently, this environmental factor or agent must be something ingested through eating or drinking, and/or attained via breathing and then swallowed along with saliva or mucus. Alternatively, it must be something found between the nose/mouth and colon that is 'brought to life' by some other factor. Numerous candidates as causative agents have been proposed; toxins, metals, pesticides, bacteria, viruses [14], various medications and in particular antibiotics, nutrients and components secondary to altered gut microbiota.

Why Parkinson's disease could be caused by fungi or *actinobacteria*

α-Synuclein – part of the body's defense mechanism

The characteristic Lewy pathology (bodies and neurites) in the diseased neurons contain aggregates composed of amyloid fibrils of misfolded variant of the protein α-synuclein (α-syn). Apart from Lewy body dementia and a subset of patients within Alzheimer's disease, Lewy pathology (LP) have until recently been regarded as distinctive of PD not found in other neurodegenerative diseases [15].

Prior to aggregation, α-syn exists as a mixture of the natively unfolded and partially folded conformations. Under normal, non-pathological conditions, this equilibrium is toward unfolded conformation. However, the equilibrium is unstable and shifted toward misfolded amyloidogenic conformation(s) by subtle changes in its environment [16].

Aggregates of misfolded α-syn is regarded pathological and related to PD pathogenesis. Many environmental factors promote misfolding and aggregation of α-syn, and different conformations may adopt depending on the environmental modulators [16]. α-Syn may induce toxicity by several mechanisms [17], has been ascribed prion-like properties [18], and to inhibit mitochondrial energy production [19].

Given that healthy neurons contain abundant unfolded α-syn, and that α-syn misfolding and aggregation are linked to the PD pathology, it is plausible that the misfolding and aggregation of α-syn is somehow involved in or part of the body's response to a potentially harmful agent. It is thus likely that a harmful agent is attempted encapsulated and/or defused by α-syn in an effort to prevent the agent from causing harm [20,21]. Therefore, it may be that α-syn should be regarded as the nervous system's 'police on patrol', striving to trap and disarm potentially harmful agents. After being captured at the nerve endings, the authors hypothesis is that, a dormant viable agent is escorted by α-syn within the axons as retrograde axonal transport, and subsequently 'imprisoned' inside inclusion bodies as Lewy bodies and neurites where it may hibernate. The latter being similar to the way in which tubercle bacilli are encapsulated in the lungs and spirochetes seem to be encapsulated by β-amyloid in the brains of patients with Alzheimer's disease [22–25].

Studies of families with a history of PD have resulted in the identification of a series of familial mutations, leading to EPD (e.g. A30P, E46K, A53T, G51D) or LPD (e.g. H50Q). Mutations in the gene for α-syn that dwindle its aggregation and fibril amplification (e.g. G51D, H50Q) [26], are accordant with α-syn being neither a triggering factor nor a causative agent in PD. This assumption, and knowing that mutation that increases both the aggregation and fibril amplification of α-syn (e.g. A53T) [26] is related to EPD, indicates that α-syn in some way is part of the body's defense mechanism as 'police on patrol' or 'wranglers' [17,20,21].

Hence, despite misfolded α-syn by itself may induce neurotoxicity and aggravate the disease in a prion-like manner, it is most likely an initiating unknown agent, and not misfolded α-syn, that is the triggering factor and thus the true cause of PD.

Transport nerves

One common feature of neurons that contain LP with misfolded α-syn is that they all have long, thin axons with a thin or absent myelin sheath. Neurons with long, robust axons or thick myelin sheaths appear to be protected from this pathology, and do not contain misfolded α-syn [27].

In PD, the brain with LP-containing neurons undergoes sequential changes as the disease progresses. Braak and Del Tredici et al [27–29] divided PD into six stages, with stage 1 being the areas affected first. One is the dorsal motor nucleus of the vagus nerve (DMNX) in the brainstem and probably also the posterior motor nucleus of the glossopharyngeal nerve (PMNIX) within its immediate proximity. The other area affected in stage 1 is the anterior olfactory structures (AOS) – the olfactory bulb and the anterior olfactory nucleus. Noteworthy is that stage 1 involvement can be confined to the olfactory bulb alone [28].

From the DMNX, the vagus nerve innervates the gut via the enteric nervous system (ENS). The vagus and its branches have thin myelin sheaths and long, thin axons – up to 1 meter. Both Lewy bodies and Lewy neurites are observed in the ENS. In the initial stages of PD, it is striking how structures immediately adjacent to the affected nuclei as DMNX remain unaffected. Hence, PD appears to be 'selective' in terms of which nerve nuclei are primarily exposed to a potential harmful agent [27,28].

In a study at Wallenberg Neuroscience Centre in Lund, Sweden, α-syn was extracted from the *substantia nigra* of a deceased PD patient. Brain lysates and synthetic recombinant α-syn fibrils were injected into the gut wall of rats, and both were subsequently traced along the vagus nerve to the DMNX [30]. In human, truncal, but not selective, vagotomy may protect against PD development [31]. Harding et al [32] found that nasal exposure of spores of the common *stachybotrys* (black toxic) mold induced brain inflammation and spatial memory deficit in mice. Furthermore, also in mice but using fibrils of either human or mouse α-syn, Rey et al. [33] provided the first evidence of a transneuronal, progressive propagation of PD-like α-syn pathology from the olfactory bulb to central brain regions. These studies, and knowing that several pathogens as viruses, bacteria and toxins may enter via the nose to reach the brain via retrograde axonal transport [33–37], may support the hypothesis that a potential causative agent in PD may enter in the periphery, most likely in the nose, mouth, throat, stomach or gut, and then is escorted by α-syn via retrograde axonal transport to the brain.

Accordingly, at least five steps seem essential for a potential causal agent: First, the agent must encounter both the olfactory nerve, probably the glossopharyngeal nerve, and the ENS. Secondly, the agent must be able to induce the formation of misfolded α-syn in these nerve endings and/or their nuclei. Thirdly, the agent must be able to 'travel' via these three nerves, and via the vagus nerve or the spinal canal to the brain and brainstem [37]. Then the agent must induce the formation of LP seen in stage 1 (AOS and DMNX), and finally PD.