Potential roles of functional bacterial amyloid proteins, bacterial biosurfactants and other putative gut microbiota products in the etiopathogeny of Parkinson’s Disease

EMILIA MANOLE1,2,#; LAURA DUMITRESCU2,3,#; CRISTINA NICULIȚE1,3; BOGDAN OVIDIU POPESCU1,2,3; LAURA CRISTINA CEAFALAN1,3,*

1 Victor Babeș National Institute of Pathology, Bucharest, 050088, Romania
2 Colentina Clinical Hospital, Bucharest, 020125, Romania
3 Carol Davila University of Medicine and Pharmacy, Bucharest, 020021, Romania

Key words: Alpha-synuclein, Endotoxins, Short-chain fatty acids

Abstract: An increasing number of studies provide evidence for the existence of a microbiota-gut-brain axis and its potential involvement in the development of sporadic Parkinson’s disease and other neurodegenerative conditions. The neuropathologic hallmark of Parkinson’s disease is the presence of brain intraneuronal aggregates of misfolded alpha-synuclein, known as Lewy bodies. Some gut microbiota products may trigger alpha-synuclein conformational changes in the neurons of the enteric nervous system, which can then spread to the brain in a prion-like fashion through the vagus nerve. Others may interfere with neuroinflammatory pathways and susceptibility to neurodegeneration. In this review, we assess the potential role of putative gut microbiota products in the etiopathogeny of Parkinson’s disease, with a special emphasis on functional bacterial amyloid proteins, bacterial biosurfactants, endotoxins and short-chain fatty acids. The possible roles of molecular hydrogen, a common by-product of bacterial fermentation, are also addressed.

Introduction

Parkinson’s disease (PD) is a neurodegenerative disorder of the central nervous system (CNS) resulting in progressive motor and non-motor manifestations (Berg et al., 2015; Braak et al., 2003). The etiopathogeny of sporadic cases is incompletely understood, and currently, there are no disease-modifying treatments.

Pathologically, PD is a proteinopathy characterized by misfolding, aggregation, and intraneuronal accumulation of alpha-synuclein, with subsequent neuroinflammatory changes and neurodegeneration (Braak et al., 2003; Spillantini et al., 1998; Spillantini et al., 1997; Walker et al., 2016). As in the case of other alpha-synucleinopathies, the misfolded alpha-synuclein gains amyloid properties and putative neurotoxic functions (Araki et al., 2019; Braak and Del Tredici, 2017). Self-aggregation of the misfolded alpha-synuclein results in intraneuronal aggregates known as Lewy bodies, the pathological hallmarks of PD (Araki et al., 2019; Baba et al., 1998; Braak et al., 2003; Spillantini et al., 1998; Spillantini et al., 1997; Walker et al., 2016).

Based on their previous findings concerning the topographical sequence (or stages) of Lewy pathology development in the brain of people with PD and the early

Abbreviations

BBB: blood brain barrier
CNS: central nervous system
Fap: functional amyloid in Pseudomonas
H-NS: histone-like nucleoid-structuring protein
IHF: integration host factor
IL-1β: interleukin-1 beta
iNOS: inducible nitric oxide synthase
LPS: lipopolysaccharide
NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells
PD: Parkinson’s disease
SCFAs: short-chain fatty acids
SIBO: small intestine bacterial overgrowth
TLR: toll-like receptor
TNF-α: tumour necrosis factor-alpha

*Address correspondence to: Laura Cristina Ceafalan, laura.ceafalan@umfcd.ro
#These authors contributed equally
Received: 07 August 2020; Accepted: 13 October 2020

Doi: 10.32604/biocell.2021.013452 www.techscience.com/journal/biocell

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presence of Lewy bodies in the neurons of the enteric nervous system, olfactory bulb, and dorsal motor nucleus of the vagus nerve, Braak et al. (2006) hypothesised that the alpha-synuclein misfolding process originates in the nasal mucosa and the gut (Braak et al., 2006; Braak et al., 2003; Friedland, 2015; Hawkes et al., 2007). This was further refined into the dual-hit theory, which states that a neurotropic infectious pathogen, viral or with prion-like properties, enters the brain by transynaptic retrograde transmission via the vagus and olfactory nerves, thus bypassing the circulatory system and blood-brain-barrier (BBB) (Angot and Brundin, 2009; Hawkes et al., 2007, 2009; Walker et al., 2016). The current view is that an exogenous factor triggers the initial alpha-synuclein conformational changes, which then self-propagate mainly via the olfactory and/or vagus nerve, reaching the brain (Araki et al., 2019; Braak and Del Tredici, 2017). The triggers for the pathologic amyloid transformation of alpha-synuclein remain unknown.

Arguments for the potential roles of the microbiota-gut-brain axis in the etiopathology of sporadic PD include the early involvement of the enteric nervous system, with chronic constipation that typically occurs before the motor onset of the disease (Berg et al., 2015; Martinez-Martin et al., 2007), the early presence of Lewy pathology in intestinal neurons (Braak et al., 2006; Braak et al., 2003) and presence of proinflammatory gut dysbiosis in people with PD, with increases in faecal Verrucomicrobiaceae and Akkermansia, which degrade the intestinal mucus layer, and decreases in the beneficial Prevotellaceae, Roseburia and Faecalibacterium being more consistently reported (Aho et al., 2019; Baldini et al., 2020; Boertien et al., 2019; Cattaneo et al., 2017; Cirstea et al., 2020; Gabrielli et al., 2011; Hill-Burns et al., 2017; Keshavarzian et al., 2015; Minato et al., 2017; Nishiwaki et al., 2020; Nuzum et al., 2020; Pietrucci et al., 2019; Scheperjans, 2016; Unger et al., 2016). The causal relation between the microbiota changes and PD is still unclear; however, Minato et al. (2017) found that lower baseline fecal Bifidobacterium and Atopobium correlate with PD symptom severity at 2 years. The functional impact of these differences in the composition of the gut microbiota also needs clarification, various models predicting changes in the expression of some gut microbiota metabolites, with possible consequences on its global function (Baldini et al., 2020; Bedarf et al., 2017; Cirstea et al., 2020; Nishiwaki et al., 2020; Nuzum et al., 2020). Contextual indirect evidence for the potential role of the microbiota in the etiopathology of PD also comes from epidemiological studies that show increased risk of PD in people with prior Helicobacter pylori infection (Huang et al., 2018; Nielsen et al., 2012) and with inflammatory bowel disease (Park et al., 2019; Villumsen et al., 2019; Weimers et al., 2019), the latter mitigated by early effective treatment (Peter et al., 2018). Furthermore, the risk of PD is lower in people that underwent truncal vagotomy for peptic or duodenal ulcer (Liu et al., 2017; Svensson et al., 2015), as well as in those that underwent an appendectomy and possibly tonsillectomy (Liu et al., 2020), putative explanations being disruption of the pathology dissemination pathway and removal of tissues with high alpha-synuclein load, respectively. In addition, intestinal inflammatory changes and altered intestinal barrier permeability have been reported in people with PD (Houser et al., 2018; Schwertz et al., 2018), suggesting that direct contact between alpha-synuclein found in enteric neurons and microbiota products is plausible. Another study supporting the plausibility of direct contact between human alpha-synuclein and microbiota products within the gut found that enteric neurons' overexpression of alpha-synuclein can be induced by local viral infections (Stolzenberg et al., 2017), while Uesaka et al. (2016) found that the gut lining contains a category of enteroendocrine cells having properties of neurons and being connected directly to alpha-synuclein-containing neurons (Uesaka et al., 2016). Arguments supporting the role of the gut microbiota in the etiopathology of PD also come from experimental animal models and in vitro studies, the most notable being brought by Sampson et al. (2016), who performed in vivo experiments on alpha-synuclein overexpressing mice, showing that the gut microbiota is needed for Lewy body pathology, motor impairment, and microglia activation. Such data suggested an active gut-brain signalling pathway between the microbiota and the brain (Sampson et al., 2016). Moreover, microglia activation, an important player in PD (Hirsch and Hunot, 2009), is modulated by gut bacteria in mice (Erny et al., 2015).

Amyloids are self-aggregating proteins with fibrillar morphology and beta-sheet secondary structure. In vitro studies have shown that alpha-synuclein can aggregate, forming amyloid fibres or fibrils with a cross-beta structure (Conway et al., 1998; Greenwald and Riek, 2010; Soto, 2003). These results are supported by in vivo murine experiments on the propagation of alpha-synuclein amyloid fibrils, which can spread from neuron to neuron in a prion-like fashion (Luk et al., 2012; Masuda-Suzukake et al., 2013). As mentioned, Lewy bodies are abnormal aggregations of misfolded alpha-synuclein encountered in PD and other alpha-synucleinopathies (Araki et al., 2019; Baba et al., 1998; Braak et al., 2003; Spillantini et al., 1998; Walker et al., 2016). Thus, PD is actually a type of amyloidosis in which misfolded alpha-synuclein is the pathologic amyloid, resulting in the accumulation and spread of alpha-synuclein amyloid fibrils (Araki et al., 2019), not only in the brain but also in the autonomic nerve fibres that innervate visceral organs such as the intestine and heart (Gelpi et al., 2014).

Environmental factors are thought to play important roles in triggering alpha-synuclein misfolding and Lewy body formation in sporadic PD but are largely unknown. Recent evidence shows that cross-reactivity and seeding between distinct amyloid proteins and alpha-synuclein can occur (i.e., transient protein-protein interactions between distinct amyloid proteins and native alpha-synuclein can result in the formation of amyloid alpha-synuclein) (Chen et al., 2016; Chorell et al., 2015; Evans et al., 2015; Sampson et al., 2020). Considering the dual-hit hypothesis and the large surface of the gastrointestinal tract where alpha-synuclein in enteric neurons could be exposed to the endoenvironment of the intestinal lumen, molecular xenobiotics of the gut microbiota pose a particular interest as possible triggers of the initial alpha-synuclein misfolding and self-aggregation events, which may then self-propagate along the neurons of the vagus nerves and sympathetic chains, reaching the brain.
Increasingly detailed knowledge of the mechanisms by which the gut microbiota products contribute to neurodegeneration could lead to the identification of valuable therapeutic targets and the development of therapeutic interventions that could slow down, or even stop or prevent, pathologica protein accumulation in the brain. The scope of this review is to highlight the main products of bacteria found in the gut microbiota that are potentially involved in the etiopathology of sporadic PD (see Tab. 1). Most of the existing literature reports data on short-chain fatty acids (SCFA). Relatively few data (coming mostly from animal or cellular models) are available on functional bacterial amyloid proteins, bacterial biosurfactants, endotoxins, and other categories of bacterial products. Thus, our review will provide a concise description of the possible contribution of these products to the development and spread of PD pathology. With this purpose, we will provide a critical presentation of the role of the functional bacterial amyloid proteins curli and functional amyloids in Pseudomonas (Fap), the bacterial biosurfactant rhamnomolipid, the bacterial endotoxins lipopolysaccharides (LPS), and the microbial metabolites SCFA (also see Fig. 1). We will also discuss molecular hydrogen, a common by-product of bacterial carbohydrate metabolism with putative neuroprotective effects.

Fig. 1 exemplifies the possible roles of functional bacterial amyloid proteins (Curli and Fap), bacterial biosurfactants, lipopolysaccharide (LPS) and short-chain fatty acids (SCFA), putatively produced by the gut microbiota, in the development and spread of sporadic Parkinson's disease (PD) pathology. PD is a proteinopathy characterized by amyloid transformation of native alpha-synuclein, with pathologic misfolding, aggregation and accumulation of aggregates (i.e., Lewy bodies, Lewy neurites) and subsequent neurodegeneration. The Braak hypothesis and dual-hit theory (see text) state that in most people with PD the alpha-synuclein misfolding process originates in the gut and olfactory mucosa, were is initiated by an unknown pathogen. The current view is that alpha-synuclein conformational changes spread transsynaptically, from the gut and olfactory mucosa neurons to the brain, via the respective nerves, by a prion-like mechanism. In this review we focus on spreading via the vagus nerve, one of the main bidirectional communication pathways of the gut-brain axis. The presence of a proinflammatory and mucolytic microbiota in people with PD, as well as lower concentrations of SCFA, results in alteration of the intestinal barrier, possibly allowing direct contact between some gut lumen xenobiotics (such as the above mentioned bacterial products) and enteric neurons that express alpha-synuclein. Moreover, intestinal inflammatory changes may increase alpha-synuclein expression in enteric neurons. In vitro and in vivo (animal models) studies suggests that the functional bacterial amyloid proteins curli and Fap, the bacterial biosurfactant rhamnomolipid and the endotoxin LPS are able to induce alpha-synuclein conformational changes and pathologic aggregation. Further details are found in Tab. 1.

Functional Bacterial Amyloid Proteins–Curli and Fap

Amyloids were initially described in association with human diseases, including the broad group of neurodegenerative proteinopathies, PD included. They consist of protein monomers, which can self-assemble, forming beta-strands perpendicular to the fibril axis, the so-called cross-beta structure (Nelson et al., 2005; Tycko, 2004).

The concept of functional amyloids was proposed for the first time by Chapman et al. (2002) who observed that curli protein produced by Escherichia coli is biochemically similar to amyloid proteins that are associated with diseases. Since then, functional amyloids have been identified in many organisms, including humans, being involved in a broad variety of physiological functions (Fowler et al., 2007; Hammer et al., 2008). It is thought that the amyloid proteins are so widespread in physiology because their fibrillar aggregate-forming structure confers them with excellent building material properties. Although functional amyloids from different organisms have the same ability to form amyloid fibrils, their monomers share little to no similarity in amino acid sequence (Schwemaker et al., 2011).

Functional bacterial amyloid proteins are extracellular proteins produced by many symbiotic and pathogenic bacteria, including Escherichia, Pseudomonas, Staphylococcus, Streptococcus, Bacillus, Mycobacteria, Citrobacter, Klebsiella, and Salmonella species, in which they support growth and survival. They are insoluble and have high mechanical and chemical stability (Otzen, 2010). One of their main roles is related to biofilm formation, an extracellular matrix with a complex structure that provides a living environment for most gut bacteria (O’toole et al., 2000). The matrix is formed by an association of amyloid proteins as scaffold and expolysaccharides (Zogaj et al., 2003). The bacterial amyloid proteins have other functions as well: forming a physical barrier with a protective role against other species of bacteria, helping to bind each other, acting as scavengers for toxins, and providing the necessary moisture (Blanco et al., 2012; Romling, 2005; Zogaj et al., 2003).

Functional bacterial amyloid proteins can induce cross-seeding amyloid formation both in vitro and in vivo (Lundmark et al., 2005; Zhou et al., 2012) and may be a template for human alpha-synuclein amyloid fibrils formation (Chen et al., 2016; Chiorelli et al., 2015; Evans et al., 2015; Sampson et al., 2020) Interestingly, functional bacterial amyloids are recognised by the innate immune system as a pathogen-associated molecular pattern, the immune response involving toll-like receptor TLR-1 and TLR-2, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and inducible nitric oxide synthase (iNOS), the same as in the case of misfolded alpha-synuclein that occurs in PD (Daniele et al., 2015; Tukel et al., 2010; Tukel et al., 2005; Venegas and Heneka, 2017).

The most studied functional bacterial amyloid proteins in connection with the microbiota-gut-brain axis are curli, the first functional amyloid discovered, and the more recently described Fap.

Curli
Curli is an extracellular protein produced by Enterobacteriaceae, especially by E. coli and Salmonella (Evans and Chapman, 2014; Olsen et al., 1989; Tursi and Tukel, 2018; Zogaj et al., 2003). It contributes to biofilm formation, gut colonization, immune
TABLE 1

Bacterial products that may play a role in the etiopathogenesis of sporadic Parkinson’s disease

| Bacterial product | Possible mechanisms | Supporting evidence |
|-------------------|---------------------|---------------------|
| **Functional bacterial amyloid proteins** | | |
| *Curli*—functional bacterial amyloid protein, produced by Enterobacteriaceae (e.g., *E. coli*, *Salmonella*); main role is in bacterial biofilm formation; the expression of the Csg subunits is highly regulated by local environmental factors and is coordinated at the level of the biofilm community. | CsgA and CsgE promote human alpha-synuclein conformational changes and fibrillation (i.e., cross-species seeding)—possibly deleterious in PD. CsgC inhibits human alpha-synuclein conformational changes—possibly beneficial/protective. May induce intestinal mucosa immune responses—possibly deleterious. | Experimental—*in vitro* studies (Chorell et al., 2015; Evans et al., 2015) and *in vivo* PD models (Chen et al., 2016; Sampson et al., 2020) |
| *Fap*—functional bacterial amyloid protein, produced by many *Pseudomonas* strains and other bacteria; main role is in bacterial biofilm formation. | Fap can induce alpha-synuclein conformational changes and fibrillation. Removing the three imperfect repeats of the FapC subunit slows down the fibrillation of alpha-synuclein, but does not prevent it. | Experimental—*in vitro* studies (Christensen et al., 2019) |
| **Bacterial biosurfactants** | | |
| *Rhamnolipid*—glycolipid biosurfactant produced by *Pseudomonas* and other bacteria; main roles are in modulating bacterial biofilm formation, bacterial motility and protection against monocyte-derived macrophages and polymorphonuclear leukocytes. | Rhamnolipid enhances aggregation of human alpha-synuclein, inducing formation of alpha-synuclein fibril-like structures—possibly deleterious. | Experimental—*in vitro* studies (Andersen et al., 2018) |
| **Endotoxins** | | |
| *Lipopolysaccharide (LPS)*—endotoxin produced by Gram-negative bacteria; bacterial virulence factor. | LPS increases human alpha-synuclein expression and triggers/enhances its aggregation, inducing PD-like pathology, alters the intestinal and blood-brain barriers, induces innate immunity responses and activates the microglia. | Experimental—*in vitro* studies (Bhattacharyya et al., 2019) and *in vivo* PD models (Kim et al., 2016; Liu and Bing, 2011) |
| **Bacterial metabolites** | | |
| *Short chain fatty acids (SCFA)*—butyrate, acetate and propionate are the main metabolites of bacterial carbohydrate metabolism. | SCFA promote intestinal motility and maintain the integrity of the intestinal barrier (which prevents direct contact between enteric alpha-synuclein and amyloidogenic xenobiotics and the passage into circulation of substances that may have proinflammatory or neurotoxic effects); may also modulate microglia activation—possibly protective. | Experimental—*in vivo* studies (Sampson et al., 2016) Human studies—reduced concentration of SCFA in PD fecal samples (Unger et al., 2016); decreased butyrate production capacity of gut microbiota in PD (Cirstea et al., 2020); increase of SCFA in PD plasma samples, possibly reflecting altered intestinal barrier (Shin et al., 2020). |
| *Molecular hydrogen*—common bacterial byproduct resulting from carbohydrate fermentation; it is used for the detection of hydrogen-producing small intestine bacterial overgrowth | Molecular hydrogen easily passes membranes; it has antioxidant properties (neutralizes hydroxyl radicals); may play a role in neuroprotection; may decrease inflammation—possibly beneficial role in PD. | Experimental in vivo studies—in mouse and rat models molecular hydrogen may slow-down the progression of PD pathology (Fu et al., 2009; Fujita et al., 2009). Human studies—fecal microbiota in PD is less abundant in hydrogen-producing bacteria (Scheperjans et al., 2015; Suzuki et al., 2018); PD microbiota produces lower amounts of molecular hydrogen (Ostojic, 2018; Suzuki et al., 2018; Yoritaka et al., 2013); positive results of small pilot trial of hydrogenated water in PD (Yoritaka et al., 2013). |
activation and cell invasion (Barnhart and Chapman, 2006). It may induce intestinal mucosa immune response (Nishimori et al., 2012; Oppong et al., 2015) and regulate gut epithelial barrier, allowing bacterial translocation (Oppong et al., 2013). It possesses all the properties of amyloids (Chapman et al., 2002; Nilsson, 2004), but it differs from disease-associated amyloids because its beta-sheet assembly is the product of a dedicated and strictly regulated biogenesis pathway and not of pathologic misfolding (Blanco et al., 2012).

The major subunit of curli is CsgA, which is capable of self-polymerizing in vitro. As a result, beta-sheet-rich amyloid fibres are formed (Chapman et al., 2002; Dueholm...
et al., 2011; Wang et al., 2007). CsgA amyloids form a very stable cross-beta structure that establishes close interactions with side chains on adjacent beta-sheets (Collinson et al., 1999; Chapman et al., 2002; Gerstel and Romling, 2001; Nelson et al., 2005; Shewmaker et al., 2009). The curli fibres are very stable, resistant to protease degradation and to denaturation by detergents (Chapman et al., 2002).

The potential pathologic role played by curli in PD was highlighted by an in vivo experiment where gut exposure to the functional bacterial amyloids curli produced by E. coli enhanced the aggregation of human alpha-synuclein in Fisher 344 rat brains and transgenic Caenorhabditis elegans muscle (Chen et al., 2016). Recently, Sampson et al. (2020) also found that the mono-colonisation of mice that overexpress human alpha-synuclein with curli-producing E. coli accelerates the development of alpha-synuclein aggregation in the gut and the brain and exacerbates gastrointestinal dysfunction and motor impairment, by a curli-dependent cross-seeding mechanism; oral administration of a gut-restricted amyloid inhibitor reduced these findings (Sampson et al., 2020).

Curli gene expression
Curli expression is controlled both on the cellular level and within the bacterial biofilm community by environmental signals and chemical gradients, like temperature, oxygen or osmolarity (Gerstel and Romling, 2001; Olsen et al., 1993a; Prigent-Combaret et al., 1999). The seven genes for curli (csg) are located in two divergently transcribed operons, csgDEFG and csgBAC (Hammar et al., 1995; Rudd, 2000). One of the most complex regulated promoters of the E. coli genome is the csgDEFG (Ishihama, 2010). There is also an internal regulation of curli expression by csgD, the master regulator of curli biogenesis and the first gene product of csgDEFG operon (Evans and Chapman, 2014), which is necessary for transcription of the csgBAC operon. CsgD is a member of the FixJ/LuxR family of transcriptional regulators coordinating the expression of some biofilm components such as cellulose and curli (Brombacher et al., 2003; Hammar et al., 1995; Ogasawara et al., 2011). The csgDEFG promoter expression is modulated by transcriptional regulators, such as the catabolite represor/activator protein Cra, the CAMP receptor protein CRP, the protein RcdA (Brown et al., 2001; Ogasawara et al., 2010b; Reshamwala and Noronha, 2011; Shimada et al., 2012; Zheng et al., 2004).

In E. coli there are two DNA global regulatory protein complexes which modulate curli gene expression in an antagonistic way—i.e., integration host factor (IHF), which promotes curli gene expression while the histone-like protein (H-NS) represses it (Gerstel et al., 2003; Ogasawara et al., 2010a; Olsen et al., 1993b). The regulatory proteins, both negative and positive, bind simultaneously in a competitive way. CsgDEFG transcript is also regulated by small regulatory ribonucleic acids (RNAs), both negatively (e.g., by OmrA, OmrB, McaS, GcvB, RprA) and positively (e.g., by ArcZ, SdsR) (Holmqvist et al., 2010; Jørgensen et al., 2013; Mika et al., 2012; Monteiro et al., 2012; Olsen et al., 1993b).

Curli structure and CsgA amyloid assembly
Curli has two subunits, CsgA, the major one, and CsgB, the minor one. They are encoded by csgBAC operon (Collinson et al., 1996, 1997; Olsen et al., 1993a). CsgA is a soluble peptide, secreted across the outer membrane, in an unstructured form (Collinson et al., 1991; Chapman et al., 2002; Cherry et al., 2005; Gibson et al., 2007; Olsen et al., 1993a), and together with CsgB fibrils, which act as a nucleator, it is transformed into an amyloid structure (Hammar et al., 1996; Hammer et al., 2007), by nucleation-precipitation (Desvaux et al., 2009). In vitro CsgA polymerization involves three phases: A lag phase, a fibre elongation phase and a stationary phase (Chapman et al., 2002; Wang et al., 2007). The CsgA can adopt toxic oligomeric forms, thus the cells that assemble functional amyloids like curli developed mechanisms to limit this cytotoxicity associated with preamyloid oligomers: Employment of chaperones to prevent inappropriate aggregation; localization of amyloidogenic proteins to specific regions in or outside the cell; temporal control to minimize toxic oligomeric intermediates (Blanco et al., 2012). The interactions between CsgA and other Csg components (CsgC-G) support all these mechanisms.

A third protein, CsgC, is periplasmic and is proposed to have a role in subunits secretion (Gibson et al., 2007; Taylor et al., 2011) and maybe in CsgA folding and assembly of the mature curli protein (Gibson et al., 2007). This is a beta-sheet rich protein that has an immunoglobulin-like fold and a conserved CXC motif. Other roles presumed to be played by CsgC involve the regulation of CsgG outer membrane assembly and pore activity (Taylor et al., 2011). CsgD is a protein that controls and helps biofilm formation by managing curli production (Brombacher et al., 2003; Hammar et al., 1995; Ogasawara et al., 2011; Romling et al., 2000). Proteins CsgE, CsgF, and CsgG are involved in the outer membrane secretion apparatus. CsgG participates in the formation of a pore-like structure in the outer membrane, required for secretion of CsgA and CsgB into the extracellular space (Epstein et al., 2009; Narita et al., 2004; Robinson et al., 2006). Here, the two subunits participate to form amyloid fibres (Hammer et al., 2007). CsgE and CsgF play chaperone-like functions supporting the secretion and the attachment of curli fibres to the cell surface (Nenninger et al., 2011; Robinson et al., 2006). CsgF membrane-associated and surface-exposed protein is essential for CsgB surface exposure and for effective CsgA polymerization (Chapman et al., 2002; Epstein et al., 2009; Hammer et al., 2007; Nenninger et al., 2009). CsgE, a periplasmic protein, is considered to directly direct CsgA to the CsgG pore-like structure and mediate its secretion, as it inhibits CsgA polymerization in vitro (Nenninger et al., 2011).

Interaction with alpha-synuclein
The above-mentioned study of Sampson et al. found CsgA to be involved in human alpha-synuclein fibril formation (Sampson et al., 2020). Chorell et al. (2015) showed that CsgE accelerates human alpha-synuclein amyloid formation.
Interestingly, CsgC was found to inhibit amyloid formation of human alpha-synuclein in vitro (Chorell et al., 2015; Evans et al., 2015).

Functional amyloids in Pseudomonas (Fap)

Other bacterial functional amyloids, analogous to curli amyloid produced by *Escherichia coli*, are functional amyloids in *Pseudomonas* (Fap), produced by many *Pseudomonas* strains (Dueholm et al., 2010).

Fap expression is controlled by a single six-gene operon, *fap* (Dueholm et al., 2010). Dueholm et al. (2013) showed that the *fap* operon is a molecular machine for functional amyloid formation. The major Fap subunit is FapC. It consists of 316 amino acid residues plus a 24-amino acid signal sequence (Bleem et al., 2018; Dueholm et al., 2010). Its structure includes three imperfect sequence repeats, R1-3, of 37 amino acid residues (Dueholm et al., 2010), separated by two “linker” regions, L1-2 (Dueholm et al., 2013). Similar to curli, Fap can induce alpha-synuclein conformational changes and fibrillation (Christensen et al., 2019). Recently, Christensen et al. (2019) demonstrated that removing the three imperfect repeats of FapC slows down the fibrillation of alpha-synuclein, but does not prevent it.

Another Fap structure is FapB, a nucleator protein, analogous with CsgB of curli that has a 38% sequence identity to FapC and is supposed to serve as a template for rapid polymerization of the fibrils outside the cell (Bleem et al., 2018; Dueholm et al., 2010). The rest of the proteins encoded by the *fap* operon constitute four other subunits: FapF subunit which forms the outer membrane pores participating in amyloid precursors translocation (Rouse et al., 2017), FapA subunit represented by chaperones guiding monomers through the periplasm and FapE and FapD, auxiliary regulators and proteases (Dueholm et al., 2013). FapF is thought to represent a precursor of the signalling peptides called bacteriocins (Dirix et al., 2004).

Barnhart and Chapman revealed that *fapA-F* function is analogous to the *E. coli csg* operons (csgBCD and csgDEFG) (Barnhart and Chapman, 2006). *Fap* operon does not include a transcription factor equivalent to CsgD, organization of *fap* genes into a single operon needing no internal transcription factor, as Dueholm et al. showed (Dueholm et al., 2013). These authors proposed that Fap are extracellular biofilm components of equal importance to polysaccharides, other proteins, and extracellular DNA (Dueholm et al., 2013).

Using a combination of bioinformatics and protein engineering, Bleem et al. (2018) examined the FapC sequence in greater detail. They identified specific motifs implicated in amyloid formation and established the particular significance of the third repeat motif in promoting fibril formation, contributing to understanding the mechanism of amyloid polymerization in *P. aeruginosa* (Bleem et al., 2018). The authors observed that mutations in the third repeat of FapC, R3, reduced amyloid propensity, increasing its susceptibility to exogenous inhibitors. They also showed the existence of a disulphide bond between two monomers in a second conserved sequence region, a CX2XC motif near the C-terminus of FapC, which could serve as an additional molecular reinforcement in mature fibrils. Christensen et al. (2019) demonstrated that the disulphide bond formation delays fibrillation in *Pseudomonas*, but also delays fibrillation of human alpha-synuclein (Christensen et al., 2019).

All the above data could be used to find effective inhibitors of fibril formation and biofilm establishment in vivo, as new therapeutic targets within the microbiota-gut-brain axis, with the aim of preventing or slowing down the progression of PD and other neurodegenerative conditions.

**Biosurfactants–Rhamnolipid**

There are few data regarding the rhamnolipids produced by gut bacteria and their ability to induce alpha-synuclein misfolding.

Rhamnolipids are biosurfactant glycolipids produced by bacteria like *Pseudomonas* sp., which modulate bacterial biofilms (Pamp and Tolker-Nielsen, 2007). They are composed of a glycosyl head group, mono- or di-rhamnose, and a branched carboxylated alkyl chain, beta-hydroxydecanoic acid (Lang and Wullbrandt, 1999).

Rhamnolipids have many functions, such as modulation of bacterial motility (Wang et al., 2014) and bacterial biofilm development (Pamp and Tolker-Nielsen, 2007); they can modify the cell surface of bacteria (Sotirova et al., 2009), participate in protein transport across the human stratum corneum (Meyer-Hoffert et al., 2011) and protect against monocyte-derived macrophages and polymorphonuclear leukocytes (Van Gennip et al., 2009). Although rhamnolipids are known to affect many proteins, like bovine serum albumin (Sanchez et al., 2008), alpha-lactalbumin, myoglobin (Andersen and Otzen, 2014), less is known about gastrointestinal tract protein damage (Markou and Apidianakis, 2014).

Andersen et al. (2018) reported the impact of rhamnolipid on the aggregative behaviour of the alpha-synuclein (Andersen et al., 2018). Their group showed that alpha-synuclein, which is natively unfolded, can suffer amyloid conformational changes when exposed to biosurfactants, such as the rhamnolipid produced by *P. aeruginosa* (Andersen et al., 2018). The monomeric rhamnolipid enhances the ability of alpha-synuclein to permeabilize membranes, and the micellar rhamnolipid can induce the formation of a protein beta-sheet structure with a worm-like fibrillary appearance (Andersen et al., 2018). Moreover, in the absence of rhamnolipid, alpha-synuclein can reduce biofilm formation by *Pseudomonas*; conversely, at physiological temperatures, rhamnolipid induces the rapid formation of alpha-synuclein fibril-like structures (Andersen et al., 2018).

**Endotoxins–Lipopolysaccharide**

Research has shown a correlation between PD and alterations in gut microbiota, as well as gastrointestinal inflammation (Heintz-Buschart et al., 2018; Hill-Burns et al., 2017; Houser et al., 2018; Houser and Tansey, 2017; Nuzum et al., 2020; Schwierz et al., 2018). Various studies report an increased level of pathogenic Gram-negative bacteria (Proteobacteria, *Enterobacteriaceae*, *Escherichia* sp.)
in individuals with PD (Keshavarzian et al., 2015; Li et al., 2017; Scheperjans et al., 2015).

LPS is an endotoxin derived from Gram-negative bacteria cell walls, which is associated with increased oxidative stress and intestinal inflammation (Fang, 2016; Guo et al., 2015; Loffredo et al., 2020; Nighthot et al., 2017). LPS is composed of 3 distinct units, a hydrophobic hexa-acetylated lipid A moiety, a polysaccharide domain O-antigen, and a core oligosaccharide that covalently bonds the two other entities (Bhattacharyya et al., 2019). It is known that LPS can modulate alpha-synuclein aggregation in vitro and cause many pathological PD-like effects in experimental in vivo models (Kim et al., 2016; Liu and Bing, 2011).

In PD, the intestinal barrier is disrupted and LPS can enter the systemic circulation (Parashar and Udayabanu, 2017). A recent study found that increased serum levels of zonulin (a protein responsible for the disassembly of intercellular tight junctions) (Ajamian et al., 2019) are correlated with serum LPS in patients with neurodegenerative diseases (Loffredo et al., 2020). The permeability of intestinal tight junctions may also be increased by LPS (Choi et al., 2018; Fang, 2016). Alteration of the intestinal barrier could be involved in the etiopathology of PD by facilitating direct contact between enteric alpha-synuclein and amyloidogenic xenobiotics (including bacterial products of the gut microbiota, LPS itself being potentially amyloidogenic) and by allowing passage of LPS and other xenobiotics into the bloodstream – with potential neurotoxic and neuroinflammatory consequences, increasing susceptibility to neurodegeneration in the presence of misfolded alpha-synuclein (Van and Derkinderen, 2019). Moreover, LPS may also induce intestinal inflammatory changes (possibly enhanced in the presence of proinflammatory gut microbiota) and local overexpression of alpha-synuclein, as seen in animal models (Van and Derkinderen, 2019), thus increasing exposure to amyloidogenic factors.

In vitro studies are in agreement with the above, the exposure to LPS of IEC-6 cells resulting in a reduction and altered distribution of the tight junction markers ZO-1 (zonula occludens protein-1) and E-cadherin around the cell membrane (Gorecki et al., 2019). The same study showed that in vivo, the administration of LPS to transgenic Thy-1-aSyn mice, a murine PD model, led to early motor manifestations as compared to untreated Thy-1- aSyn mice.

Other rodent models receiving LPS treatment exhibited hallmarks of PD pathology and other characteristic features: microglial inflammation in the substantia nigra, reduced dopamine production and motor impairments (Sharma and Nehru, 2015), increased alpha-synuclein expression (Kelly et al., 2014), selective dopaminergic neuronal loss and nigrostriatal alpha-synuclein aggregation (He et al., 2013). LPS induces peripheral inflammation and neuroinflammation through the TLR-4/NF-kB pathway, as well as the increased production of inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) (Mafra and Fouque, 2015; Pérez-Pardo et al., 2019). The presence of proinflammatory cytokines impairs the BBB integrity and is responsible for the enhanced susceptibility to toxins from the gut (Bodea et al., 2014). Over-activation of microglia causes damage to neurons (Kannarkat et al., 2013; Zhang et al., 2005).

Alpha-synuclein misfolding and aggregation are favored by the inflammatory environment (Gao et al., 2011). Nuclear magnetic resonance spectroscopy, Bhattacharyya et al. (2019) showed that the direct interaction of LPS with alpha-synuclein modulates the protein’s conformation into alternative nucleating forms and stabilizes the α-helical intermediates in the alpha-synuclein aggregation pathway (Bhattacharyya et al., 2019). After misfolding and aggregation, alpha-synuclein is released into the extracellular space and can enter another cell, where it can serve as a template for further misfolding of monomeric alpha-synuclein (Angot and Brundin, 2009; Brundin et al., 2008; Dunning et al., 2012).

Bacterial Metabolites–Short-Chain Fatty Acids and Molecular Hydrogen

Recent data show that some metabolic pathways are enriched in the faecal microbiota of people with PD, suggesting increased production capacity of potentially deleterious metabolites such as p-cresol, phenylacetylglutamine and methionine, while pathways with beneficial metabolites, such as the SCFAs butyrate pathway, are reduced (Baldini et al., 2020; Cirstea et al., 2020). Consistent findings concern the SCFAs, which we will further discuss, along with molecular hydrogen, another by-product of bacterial carbohydrate metabolism, with putative neuroprotective effects.

Short-chain fatty acids

SCFAs are fermentation products generated by bacteria, including those in the gut microbiota, through various metabolic pathways (Sampson et al., 2016). The most abundant SCFA in the human body are butyrate, acetate and propionate (Dalile et al., 2019). They are used locally by colonocytes, as well as absorbed in the colon and are transported to the liver via the portal circulation (Morrison and Preston, 2016), where they are used as energy substrates for hepatocytes (Schonfeld and Wojtczak, 2016), while a minor fraction enters the systemic circulation (Boets et al., 2015). SCFAs maintain the integrity of the intestinal barrier, regulate intestinal motility, mucus production and several immunological processes in the body (Canani et al., 2011; Lewis et al., 2010; Unger et al., 2016). Most SCFA can reach the CNS and cross the BBB (Perry et al., 2016; Sampson et al., 2016). A study on mice showed that they can decrease the permeability of the BBB and increase the expression of occludin in the BBB tight junctions (Braniste et al., 2014).

Several studies have investigated the link between SCFA and PD (Girstea et al., 2020; Shin et al., 2020; Unger et al., 2016). Unger et al. (2016) found a significantly reduced concentration of acetate, propionate and butyrate in faecal samples from patients with PD compared to healthy controls. Moreover, SCFA-producing bacteria, such as Roseburia and Faecalibacterium, are more abundant in healthy individuals (Bedarf et al., 2017; Hopfner et al., 2017; Keshavarzian et al., 2015; Li et al., 2017; Nishiwaki et al., 2020; Nuzum et al., 2020).

Administration of sodium butyrate (a histone deacetylase inhibitor) has proven beneficial in animal models of PD,
improving motor impairment and dopamine deficiency (Paiva et al., 2017; Sharma et al., 2015; St Laurent et al., 2013). However, in germ-free mice overexpressing alpha-synuclein, administration of SCFA led to microglia activation, alpha-synuclein aggregate formation and neuroinflammation (Sampson et al., 2016). A recent study analysed the possible remote effects of SCFA on the CNS, by measuring their plasma concentration (Shin et al., 2020). In contrast to faecal samples, plasma SCFA were increased in PD, the authors suggesting that this paradoxical finding could be the result of intestinal wall leakage caused by gut dysbiosis and local low-grade inflammation (Shin et al., 2020).

Gut microbial composition and SCFA production can be regulated indirectly by the ingestion of probiotics or prebiotics, the latter acting as a substrate for bacteria in the colon (Gibson et al., 2017; Leblanc et al., 2017; Sanders, 2008). Diet can also positively influence the microbiome and it has been suggested that a vegetarian diet increases the availability of fermentable substrates and may have a beneficial effect on the clinical course of PD (Derrien and Veiga, 2017; Hegelmaier et al., 2020; Klimenko et al., 2013; Wong et al., 2018).

Molecular hydrogen
Molecular hydrogen is a common bacterial by-product resulting from carbohydrate fermentation. It is produced by the human gut microbiota and easily crosses membranes, reaching the bloodstream and being exhaled – thus its use in the hydrogen breath test for the detection of small intestine bacterial overgrowth (SIBO) (Ostojic, 2018). It has antioxidant properties, neutralizing hydroxyl radicals, and may decrease inflammation, with putative neuroprotective effects (Ohta, 2014).

Experimental evidence coming from mouse and rat models suggest that molecular hydrogen may slow down the progression of PD pathology (Fu et al., 2009; Fujita et al., 2009). Moreover, a small pilot double-blind placebo-controlled randomized trial found that 1 litre of hydrogenated water per day improves motor outcomes in people with PD, at 48 weeks (Yoritaka et al., 2013). Other data from human studies suggest that the faecal microbiota of people with PD is less abundant in hydrogen-producing bacteria (e.g., Prevotella) compared to that of healthy controls (Scheperjans et al., 2015; Suzuki et al., 2018). Small studies also suggest that the small intestine microbiota of people with PD may produce lower amounts of molecular hydrogen, as measured in the exhaled air (Ostojic, 2018; Suzuki et al., 2018; Yoritaka et al., 2013).

Conclusions
An increasing number of studies suggest that sporadic PD may start in the gut and olfactory mucosa, Lewy pathology spreading to the brain, via the vagus and olfactory nerves, through a prion-like mechanism.

Gut dysbiosis is present in people with PD compared to healthy controls, but the causality relation between the composition and function of the gut microbiota and sporadic PD has not been proven yet. In this review we brought together the latest data, coming mostly from in vitro studies and animal models, regarding the bacterial products that can trigger alpha-synuclein misfolding in experimental settings and thus may be involved in the etiopathology of sporadic PD. Available evidence suggests that products of bacteria found in the gut may result in alteration of the intestinal barrier, may lead to overexpression of enteric alpha-synuclein and may play key roles in triggering alpha-synuclein self-propagating misfolding events that result in alpha-synuclein self-aggregation and formation of Lewy bodies. Microbiota products that enter the bloodstream may also have neuroinflammatory and neurotoxic effects and may interfere with neuroprotection pathways, modulating neuronal susceptibility to neurodegeneration.

Currently, there are no disease-modifying treatments for neurodegenerative conditions, including PD. Amyloidogenic bacterial products, especially functional bacterial amyloid proteins, biosurfactants and endotoxins are possible triggers of the initial pathologic alpha-synuclein misfolding in sporadic PD, making them potentially attractive therapeutic targets for preventing or slowing down the progression of the disease. This theory however has a series of limitations, mainly related to the lack of direct evidence on the interaction between the amyloidogenic bacterial products and alpha-synuclein within the human gut. Further research is needed.

Funding Statement: This work was supported by the Ministry of Research and Innovation in Romania, under Grants No. PN 1N/2019_19.29.02.01 and No. 7PFE/2018.

Conflicts of Interest: The corresponding author is a member of the Editorial Board of the journal. The authors declare that they have no other conflicts of interest to report regarding the present research paper.

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