Parkinson’s disease and the gut: a well known clinical association in need of an effective cure and explanation

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Abstract Parkinson’s disease (PD) is a neurodegenerative disorder which leads to severe movement impairment; however, Parkinsonian patients frequently suffer from gastrointestinal (GI) problems which at present are poorly understood, scarcely investigated, and lack an effective cure. Traditionally, PD is attributed to the loss of mesencephalic dopamine-containing neurons; nonetheless, additional nuclei, such as the dorsal motor nucleus of the vagus nerve and specific central noradrenergic nuclei, are now identified as targets of PD. While the effects of PD on the somatic motor systems are well characterized, the influence on the digestive system still needs to be clarified. Recent findings demonstrate the occurrence of pathological alterations within peripheral neuronal networks in the GI tract of Parkinsonian patients. However, it remains unclear whether a real cell loss occurs, and whether this happens specifically for a subclass of autonomic neurons or if it reflects the sole loss of autonomic nerves. This review summarizes the neurochemical and morphological changes which might be responsible for impaired GI motility. Moreover, we focus on the experimental models to reproduce the altered digestive system of Parkinsonian patients since an experimental model able to mimic such features of PD is required. In the last part of the manuscript, we suggest potential therapeutic targets.

Keywords autonomic nervous system, digestive tract, dopamine, noradrenaline, Parkinson’s disease.

Abbreviations: 5-HT, 5-hydroxytryptamine; 6-OHDA, 6-hydroxydopamine; ACh, acetylcholine; CGRP, calcitonin gene-related peptide; CNS, central nervous system; DA, dopamine; DAT, dopamine transporter; ENS, enteric nervous system; GABA, gamma aminobutyric acid; GI, gastrointestinal; H&E, haematoxylin and eosine; LB, Lewy bodies; LC, locus coeruleus; L-DOPA, L-3:4-dihydroxyphenylalanine; MP, myenteric plexus; MPTP, 1-methyl-4-phenyl-1:2:3:6-tetrahydropyridine; NA, noradrenaline; PD, Parkinson’s disease; SMP, submucosal plexus; SNpc, substantia nigra pars compacta; TH, tyrosine hydroxylase; VIP, vasoactive intestinal polypeptide.

INTRODUCTION

Parkinson’s disease (PD) is a chronic, progressive neurodegenerative disorder, which is characterized by nigrostriatal dopaminergic and locus coeruleus (LC) noradrenergic neuronal degeneration with subsequent reduction of dopamine (DA) and noradrenaline (NA) levels in specific brain areas. The onset of PD is more often associated with non-motor symptoms than classic motor disturbances. 1–3 Among these, pain or [more frequently] digestive dysfunction markedly affect the quality of life of PD patients, sometimes more severely than the motor impairment itself. This gastrointestinal (GI) distress suffered in the early stages of PD is not addressed with current therapies. In fact, while the alterations of the motor systems in PD are extensively investigated, the influence of the disease at peripheral
level with an emphasis on autonomic musculature and glands in the digestive system still needs to be clarified and has not been explored in detail. Only a few suitable experimental models have been proposed to investigate GI dysfunction.\textsuperscript{4,5} Thus, there is a strong discrepancy between the high prevalence and variety of GI symptoms occurring in PD and the lack of research in this area. A few studies suggest that GI symptoms may be caused by a neurodegenerative process in the enteric nervous system (ENS), similar to what occurs in the central nervous system (CNS).\textsuperscript{6,7} In line with this, the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which causes nigrostriatal dopaminergic denervation has also been used to reproduce the ‘Parkinsonian GI dysfunction’.\textsuperscript{4}

**LEWY BODIES: PATHOLOGICAL MILESTONE OF PD**

Lewy bodies (LB) consist of neuronal inclusions detectable at subcellular level.\textsuperscript{8} Classic LB have a relative restricted distribution,\textsuperscript{9} which corresponds to dopaminergic neurons of the substantia nigra and ventral tegmental region, noradrenergic neurons of the LC, catecholamine cells of the medulla oblongata, serotonergic neurons of the raphe nuclei and specific cholinergic neurons.\textsuperscript{10} In general, classic LB involve monoamine neurons\textsuperscript{11} and appear as round structures made up of a hyaline core and a pale peripheral halo. The latter, at ultrastructural level, corresponds to filamentous material forming fibrillary elements which are characterized by the presence of the protein \(\alpha\)-synuclein. On the other hand, the central part of a LB is composed of a granular dense core. LB represent the morphological hallmark of PD and the extent of mesencephalic localization correlates with motor symptoms. In addition to classic LB, in PD, there are also atypical LB, which are called ‘cortical LB’ since they occur in telencephalic brain regions.\textsuperscript{12} Cortical LB are smaller than classic LB, possess a heterogeneous ultrastructure and are particularly abundant in the amygdala, cingulate gyrus, insular and frontotemporal isocortex.\textsuperscript{10}

When visualized by light microscopy, both typical and cortical LB possess a pale eosinophilic structure which stains for thioflavin-S. Nowadays, characterization of LB is more commonly performed using immunohistochemistry, as LB can be stained by antibodies to several proteins including ubiquitin, \(\alpha\)-synuclein, parkin, synphilin-1, torsin A, and other proteins in the multienzymatic pathway ubiquitin proteasome system.\textsuperscript{13} In addition, LB contain various heat shock proteins and other molecules that play an important role in the physiology of the cell growth such as cyclins.\textsuperscript{14} Finally, LB can be labelled for typical fibrils, other cytoskeletal proteins, and components of the autophagy pathway.\textsuperscript{10}

Initially considered to directly cause neuronal degeneration, at present, LB are considered a marker of an ongoing degenerative process in which they play a defensive role as dynamic structures possessing powerful enzymatic activity.\textsuperscript{15} Strikingly, apart from the occurrence of LB in the CNS, their presence is now well established also in the whole digestive system at the level of the myenteric (MP) and submucosal (SMP) plexuses from the upper oesophagus to the rectum.\textsuperscript{6,15,16}

Despite their ubiquity, it remains to be established whether LB are uniformly distributed or if they follow a distribution gradient within the GI tract and to what extent they occur specifically in neurons that produce DA, NA, or non-catecholamine neurons. Nonetheless, the parallel between brain and enteric neurons with regard to the occurrence of such typical inclusions characterizing PD is highly suggestive of a common intracellular dysfunction which operates in the affected neurons of the CNS and the digestive tract. This is in line with the recent concept of PD as a systemic disorder {rather than a motor disturbance} which may affect other organs. In fact, digestive symptoms, and GI pathology may precede the motor symptoms, indicative of commonalities in the systemic disease process. In line with this hypothesis, data in a recent paper by Phillips et al.\textsuperscript{17} suggested that PD may start in the gut, with the biochemical alterations subsequently being transported to the brainstem via the vagus nerve.

**PARKINSONS DISEASE: BEYOND CENTRAL DOPAMINERGIC NEURONS**

It is well-known that PD is an extrapyramidal motor disorder which is caused by the massive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc). We are now aware that PD should be considered a multiple degenerative disorder where more than one nucleus in the brain is lost. In fact, several studies have shown that other brainstem nuclei are involved.\textsuperscript{18} Although the impairment of such nuclei may occur simultaneously to produce autonomic disorders in PD, the specific alterations in the peripheral nervous system of PD patients seem to prevail in causing autonomic dysfunction.

In the CNS, catecholamine nuclei other than SNpc are regularly affected. In particular, there is now compelling evidence that the NA-containing nucleus...
of LC is damaged as much as the SNpc, leading to a profound loss of NA in a variety of brain areas. Moreover, dysfunction of the noradrenergic system precedes the DA damage during the natural course of the disease, as recently demonstrated by biochemical\textsuperscript{19} and imaging\textsuperscript{20} studies in humans and hypothesized by preclinical studies in various animal species (for a comprehensive report see the reviews of Mavridis et al.\textsuperscript{21} and Gesi et al.\textsuperscript{22}). Furthermore, in a recent review, Fornai et al.\textsuperscript{8} showed the impact of NA deficit on the survival of nigral DA neurons and provided novel therapeutic approaches; the importance of the LC in PD was first suggested by Rye and DeLong\textsuperscript{23}, when they stated it was ‘time to focus on the locus’ to understand the disease process. In fact, the loss of NA seems to play a role in disease progression and facilitate motor complications during DA replacement therapy.\textsuperscript{24}

**PARKINSONS DISEASE: BEYOND THE CNS AND TOWARDS THE GI TRACT**

Besides the classic somatic motor impairment, virtually all patients with PD at some stage of the disease develop a few autonomic dysfunctions, which sometimes precede motor symptoms. In addition to the CNS, many other systems appear affected in PD including cardiovascular, GI, urogenital, thermoregulatory and pupillomotor functions.\textsuperscript{25}

The autonomic impairment occurring in the heart of PD patients is mainly due to a damage involving solely the axon terminals of postganglionic neurons, where the noradrenergic innervation is severely impaired.\textsuperscript{26}

Gastrointestinal dysfunction is an important feature of PD as first described by James Parkinson.\textsuperscript{27} This represents the most common autonomic disorder of the disease, involving the entire digestive tract with different manifestations depending on the affected segment (Table 1). A questionnaire revealed a high frequency of GI disorders in PD patients (mean score of 23.6 in PD patients vs 5.6 in age-matched controls as assessed in the SCOPA-OUT survey), increasing with severity of the disease.\textsuperscript{8} In contrast, differences in non-motor disturbance frequency were much less (mean score of 9.5 in PD patients vs 5.5 in control subjects in the NMSQuest questionnaire).\textsuperscript{25} In PD patients, hypersalivation is an early symptom, with a frequency around 75–88%.\textsuperscript{1–3} Paradoxically, in PD, saliva production is typically diminished.\textsuperscript{2} In fact, higher frequency of drooling in PD patients with dysphagia (86%) compared with those without swallowing difficulties (44%) suggests that inefficient and infrequent swallowing rather than an increased production of saliva is responsible for hypersalivation.\textsuperscript{2}

Altered swallowing (dysphagia) is a frequent complaint of PD patients, being reported in 50–90% of PD patients.\textsuperscript{1–3} Patients can develop dysphagia either at the onset or later in the course of the disease; however, it does not seem to be related to disease severity or duration.

Delayed gastric emptying has been reported in PD patients.\textsuperscript{2,28} Patients with PD often experience dyspep-

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DA, dopamine; GI, gastrointestinal; LB, Lewy bodies; LC, locus ceruleus; L-DOPA, L-3,4-dihydroxyphenylalanine; NA, noradrenaline; TH, tyrosine hydroxylase.
sia and heartburn, caused either by a reduced peristalsis or gastro-oesophageal reflux. An increase in the delay in gastric emptying time has been reported in different stages of PD and is relieved by L-3,4-dihydroxyphenylalanine (L-DOPA) administration.

There is limited information on small intestine motility in PD. Dilatation of the small intestine in PD patients has been shown by manometric and radiological studies; however, it is unknown how this alteration is related to the clinical picture. No difference in the motility of Oddi’s sphincter, which controls entry of secretions from the liver, pancreas, and gallbladder into the duodenum was found.

Constipation, most frequently caused by an altered colonic motility, appears to be the most common GI symptom in PD patients. Other factors which may contribute to constipation in PD are reduced fibre and water intake secondary to diminished thirst sensation, lack of physical exercise, and reduced tone of the diaphragm and abdominal muscles. Constipation occurs at all stages of PD, including before the onset of motor symptoms, in a preclinical stage.

Barium studies and endoscopy failed to reveal an obstruction or any other mucosal abnormality in PD patients. Anorectal dysfunction was observed at different stages of PD and it is influenced by the on- and off-stage conditions, with improvement in the on stage, and worsening in the off-stage. Anorectal manometry, electromyography and defecography revealed an altered coordination of the contraction and relaxation processes of the abdomino-pelvic and puborectal muscles and impaired anal sphincter function.

Neuronal network and neurotransmitters in the digestive tract in Parkinson’s disease

Gastrointestinal motility is controlled by extrinsic and intrinsic innervation. The extrinsic innervation arises from two sources, vagal and spinal nerves. The spinal afferents can be subdivided into splanchnic and pelvic. Vagal afferents arise from neurons of the nodose and jugular ganglia, splanchnic and pelvic spinal afferents arise from the dorsal root ganglia. Autonomic motor innervation follows sympathetic and parasympathetic pathways. Preganglionic sympathetic neurons are located in the intermediate zone of the thoracolumbar spinal cord, and inhibit GI motility. Preganglionic parasympathetic input arises from the dorsal motor nucleus of the vagus in the medulla oblongata, inducing an increased gut motility. The extrinsic innervation is also responsible for GI secretion and absorption.

The intrinsic innervation consists of the ENS which is further subdivided into the myenteric (Auerbach’s) and submucosal (Meissner’s) plexus (MP and SMP respectively). The ENS resembles the CNS functionally and chemically, as both systems share some neurotransmitters, such as acetylcholine (ACh), NA, DA, 5-hydroxytryptamine (5-HT), gamma aminobutyric acid (GABA) and many peptides (see later). The neurons belonging to the ENS are intrinsic afferent neurons, interneurons, and motor neurons. Although the ENS can function independently from the CNS (hereby the definition of metasympathetic nervous system), it maintains communication with the latter through the sympathetic and parasympathetic neurons.

While the extrinsic innervation of the gut seems preserved in PD from a morphological point of view, several reports suggest that GI symptoms associated with PD may be caused by a neurodegenerative process in the ENS that mirrors what occurs in the CNS; however, the biochemical correlates remain poorly explored. Furthermore, it is not clear to what extent there is an impairment of both noradrenergic and cholinergic innervation.

The CNS and the ENS share a common origin and have functional and chemical similarities. The ENS in fact derives from neural crest cells that migrate to the cranial portion of the gut and subsequently move caudally to reach the entire GI tract. The ENS contains a number of neurons similar to those found in the spinal cord, and many neurotransmitters classically described in the CNS have also been identified in the ENS. These include ACh, NA, DA, 5-HT, GABA and glutamate, but a great number of other neurotransmitters and hormones also participate in the regulation of functions in the GI tract: vasoactive intestinal polypeptide (VIP), nitric oxide, neuropeptide Y, calcitonin gene-related peptide (CGRP), galanin, motilin, adenosine triphosphate, tachykinins, neuropeptide, endogenous cannabinoid and opioid, substance P, gastrin-releasing peptide, somatostatin, cholecystokinin, adenylyl cyclase-activating polypeptide, carbon monoxide and others.

Dopamine seems to be a major candidate for the impairment of GI function in PD since its levels were found to be decreased in the ascending colon from PD patients (Table 1). Although the gut contains DA, only recently this catecholamine has been confirmed as an intrinsic neurotransmitter of the ENS. In fact, DA, tyrosine hydroxylase (TH), and the DA transporter (DAT) co-localize within a subset of ENS neurons. In rats, DA modulates GI exocrine secretion, fluid absorption, motility, blood flow and cytoprotection, and it
appears to act via the activation of D1A receptor subtypes that are largely distributed along the digestive tract.46

Dopamine receptors have been identified throughout the digestive tract and appear decreased in the MP of PD patients.3,15,16 In PD patients suffering from chronic constipation, Singaram6 found fewer DA myenteric neurons containing LB, especially those neurons containing VIP or TH. More recently, the presence of alpha synuclein aggregates has been reported.37

As reported above, the impairment of GI autonomic neurons can occur before those in the basal ganglia. In fact, increased bowel movements in aged people are associated with an increased risk of PD, since Parkinsonian motor symptoms appear about 10 years after the onset of GI dysfunction.38 This suggests that intestinal biopsies that count the loss of DA neurons and occurrence of LB may predict the subsequent development of PD [Table 1].

It remains unclear why the loss of DA neurons in the gut determines inhibition of contractility and constipation. A recent study on enteric DA in transgenic mice lacking DA receptors suggests that, in addition to the effects mediated by D1A receptors reported above, endogenous DA may act via axonal D2 receptors. This effect inhibits the release of ACh from enteric neurons thereby decreasing the strength of neurotransmission in prokinetic pathways.39,40 In fact, anti-dopaminergic drugs [i.e. domperidone and sulpiride] that act by blocking the D2 receptors are prokinetic and promote the motility of the gut. This contrasts with the physiological role of NA [the other catecholamine of the ENS], which mainly derives from the extrinsic innervation. Indeed, the sympathetic noradrenergic pathways to the GI inhibit motility and constrict the sphincters. It could be speculated that, in the gut, the loss of DA neurons in the MP in PD is compensated by the activity of noradrenergic postganglionic sympathetic nerves. This may contribute to inhibit the contraction of the gut leading to altered motility. Another hypothesis is that occurrence of DA deficiency could allow the binding of NA to up-regulated DA receptors, thus leading NA to produce effects on the gut motility similar to DA [prokinetic effects, which are opposed to its physiological role] [Table 1].

Thus, the role of DA in determining bowel motility is far from clear.

Despite the scarce knowledge on the role of D2 and D1 receptors, it is also unclear which receptor activity prevails in the presence of different DA concentration [which varies from the healthy state to the disease] and it is uncertain what happens to the pattern of expression of DA receptor subtypes following DA denervation. In particular, are both D1-like and D2-like DA receptors equally up-regulated or is there a selective prevalence of one subtype? Is the ability of NA in the gut to bind to D1 and D2 receptors comparable? In the absence of DA is it possible that NA becomes the main endogenous agonist for DA receptors? Since the DA replacement therapy in PD is largely based on the use of D2-like preferring agonists, what is the impact of the ongoing DA substitution therapy on the prevalence of constipation?

EXPERIMENTAL MODELS TO UNDERSTAND GASTROINTESTINAL IMPAIRMENT IN PD

The heterogeneity of pathological findings leading to a variety of alterations of GI motility and the difficulty in reconciling the physiology of the bowel with the processes occurring during PD, underscore the need for appropriate animal models to investigate in depth the GI impairment in PD. This is also justified by the lack of an in depth knowledge of the physiological role of DA in the gut. At present, an ideal animal model is lacking. In fact, despite the plethora of research efforts aimed at elucidating the etiology of central nigrostriatal damage, only a few studies mimic the GI symptoms in PD. This lack of data is quite surprising considering how critical proper GI function is to the patient’s quality of life.

There are several in vivo models of PD including the 6-hydroxydopamine [6-OHDA] rat model and the MPTP mouse model. The last model is useful to study the neurochemical and histopathological alterations. Since MPTP can be simply injected i.p., this neurotoxin may be administered chronically to mimic the progressive dopaminergic degeneration which replicates closely the pattern observed in PD. In fact, MPTP is converted into the toxic metabolite MPP+ which is then selectively taken up by the DAT within DA neurons [Fig. 1].

The neurotoxin MPTP leads to motor Parkinsonism in primates and rodents, although only mice [but not rats] develop central Parkinsonism following MPTP exposure. However, peripheral damage can also be produced in rats exposed to MPTP. In fact, Szabo et al.41 proposed a rat model in which MPTP produces inhibition of duodenal spike activity, and a decrease in gastric acid and pancreatic secretion. In the same model, Eaker et al.5 found chronic migrating myoelectric complex disruption and prolongation of irregular spike activity. These authors found decreased DA levels in the jejunal MP, although this occurred only for higher doses compared with those required to
disrupt migrating myoelectric complex activity. As expected, despite peripheral toxicity, DA levels in the CNS were not affected by MPTP in the rat. In fact, very high doses (lethal) of MPTP need to be administered to obtain nigrostriatal damage in this species, while the peripheral toxicity occurs at low doses. This administration of low amounts of MPTP creates a Parkinson-Like Disease in which GI alterations necessarily depend uniquely on peripheral damage, since the CNS is intact. Only the administration of a peripheral ganglionic blocker would allow MPTP to be administered at high doses in the rat to obtain nigrostriatal damage in the absence of lethality, but this would conversely limit the ability of the neurotoxin to act peripherally (for details on this issue refer to Giovanni et al.42,43).

In an in vitro study, in the mouse colon Hanani44 observed that MPTP induces acute muscle relaxation, being presumably due to rapid NA release from nerve endings. MPTP produces a swift non-specific catecholamine release that is followed 1 week later by a permanent damage, the initial release being non-related to the subsequent damage. More recently, the effects of MPTP on the mouse colon have been evaluated in vivo by Anderson et al.4 These authors found that, at 10 days after the administration of a total dose of 60 mg kg$^{-1}$ of MPTP there was a 40% reduction of TH positive neurons which was associated with early behavioral and electrophysiological changes consisting of increased stool frequency and colon motility. Despite the excellent use of the neurotoxin in the proper animal species and the right time window used for the analysis of the neuropathological effects induced by MPTP in the colon, it remains unclear whether TH positive neurons are selective for DA, NA or even, though unlikely, adrenaline.

There are several issues that remain to be addressed using the MPTP model. For instance, the specific location of the neurons which undergo degeneration following MPTP is still unknown. Are these cells submucosal or are they localized in the MP? Are they scattered in the enteric wall? Is any loss of mucosal cells ever documented, since part of the amine precursor uptake decarboxylation cells in the GI are TH positive? Which TH immunopositive neurons are affected: dopaminergic, noradrenergic or both? Is the extrinsic noradrenergic (therefore TH positive) innervation preserved? Is any TH protein content (as assessed by SDS-PAGE and immunoblotting) ever measured following MPTP treatment? Was any concomitant hematoxylin and eosine (H&E) staining performed? This latter point is critical to conclude that a real cell loss occurs, since a loss of the TH protein could account by itself for the loss of TH positive cells in the absence of any real cell loss. We believe that a concomitant staining for TH and the DAT, joined with H&E staining, would provide important information for the site specificity of catecholamine cell loss. Similarly, it is critical to perform a quantitative measurement of neurotransmitter levels [DA, NA, adrenaline] to understand what occurs in the mouse colon after MPTP treatment. Thus, further studies aimed at identifying the nature of neuronal loss and neurotransmitter levels are necessary. Moreover, measurement of nigral cell loss in the same mice is critical to interpret the physiological alterations of colon motility within the appropriate scenario of

**Figure 1** Mechanism of action of MPTP. The cartoon shows a dopamine [DA] neuron under the influence of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP] systemic administration. As well known for central DA neurons, MPTP is believed to damage peripheral DA neurons in the gut by a preliminary step consisting of the conversion of MPTP into its toxic metabolite 1-methyl-4-phenyl-pyridinium [MPP+] by the ubiquitous enzyme monoamine oxidase B [MAO B]. MAO B is abundantly expressed in the gastrointestinal tract. Once generated, MPP+ is then selectively taken up by the catecholamine neurons via the selective DA transporter [DAT], which concentrates the neurotoxin within the cytosol of the enteric neuron. MPP+ is thought to damage the cell by inhibiting complex I of the mitochondrial respiratory chain. This mechanism may also be responsible for the changes of enteric noradrenergic neurons, since MPP+ is also selectively taken up by the norepinephrine transporter [NET].
mixed peripheral and central DA/NA alterations, which are supposedly characteristic of PD.

The GI tract has been evaluated also in another model of PD, based upon the systemic exposure to the neurotoxin 6-OHDA, which allowed Eaker et al.\textsuperscript{5} to find in the mouse gut, a decrease in catecholamine levels. This convergent effect suggests a similar vulnerability of catecholamine neurons of the CNS and ENS during experimental Parkinsonism, which transcends the specific experimental model.

PRESENT AND POTENTIAL THERAPEUTIC STRATEGIES TO IMPROVE GI SYMPTOMS IN PD

As a consequence of the scarce experimental investigation and the novelty of the present topic, both as a clinical ‘hot spot’ and as a research field, the therapeutic approaches for treating GI dysfunction in PD are scarce and endowed with severe side effects [Table 1]. An effective treatment strategy is sorely needed; this will require the further analysis of DA dysfunction in the gut [see the section ‘Neuronal network and neurotransmitters in the digestive tract in Parkinson’s disease’], and further research aimed at elucidating the mechanisms underlying gut impairment in PD.

Traditionally, anticholinergic drugs (trihexyphenidyl, benztropine) were used to reduce the excess of saliva and drooling in PD. However, the side effects, such as blurred vision, dry mucous membranes, urinary retention, constipation, memory impairment, confusion, hallucinations, limited their usefulness. Injection of the botulinum neurotoxin in the parotid gland or in the cricopharyngeal muscle has been tested in a small number of PD patients, with some improvement in hypersalivation or dysphagia.\textsuperscript{2} Possible complications of this approach are excessive dry mouth and dysphagia, due to the weakness of pharyngeal muscles.

Among the prokinetic drugs, DA antagonists are used in PD patients to enhance gastric emptying ameliorating gastro-oesophageal reflux and constipation.\textsuperscript{13} Among these drugs cisapride has been removed from the US Market because of its cardiotoxicity, while domperidone is commonly used, with metoclopramide being less common. Both domperidone and metoclopramide block D\textsubscript{2} receptors, however, the former is less likely to cross the blood–brain barrier and it is less safer for use in PD patients.

When treating constipation in PD, the first step is to increase fibre or fibre supplements [methylectulose, psyllium] and fluid intake. The next step consists of the use of a stool softener and subsequently an osmotic laxative [sorbitol, lactulose, polyethylene glycol].\textsuperscript{2}

Administration of apomorphine has been reported to significantly improve manometric parameters in a small group of PD patients, suggesting the role of DA in maintaining an appropriate anorectal function.\textsuperscript{45} Botulinum causes the inhibition of the contraction of the smooth musculature in the GI system, and has been used successfully in the treatment of anorectal dysfunction in PD.\textsuperscript{2}

Since stimulation of 5-HT\textsubscript{4} receptors enhances the release of ACh and CGRP from stimulated nerve terminals in the GI tract, 5-HT\textsubscript{4} agonists are used to obtain prokinetic effects; therefore, tegaserod (5-HT\textsubscript{4} receptor partial agonist) and mosapride citrate (selective 5-HT\textsubscript{4} receptor agonist) have been used recently in humans.\textsuperscript{46} However, the former has been recently withdrawn from the US Market because it raised the risk of heart attacks and strokes.

The role of DA in the bowel motility, although far from being clear, needs to be considered for potential treatments of GI dysfunction in PD. A decrease in DA levels and in D\textsubscript{1} receptors could be compensated by the administration of selective D\textsubscript{2} agonists which may be more useful than mixed DA agonists. Apomorphine, a mixed agonist stimulating both D\textsubscript{1} and D\textsubscript{2} receptors,\textsuperscript{47} is effective centrally for the treatment of the ‘on-off’ motor syndrome after long-term administration of L-DOPA. At the same time, the mixed agonist action of apomorphine seems to be effective in improving the motility of the gut. Increased levels of DA could also be obtained by the direct infusion of L-DOPA in duodenum.\textsuperscript{48} This route of L-DOPA administration has been used to reduce motor fluctuations in PD patients, since short plasma half-life of L-DOPA and erratic gastric emptying are circumvented. In the duodenal infusion it can be postulated that a ratio of 1 : 10 instead of 1 : 4 of L-DOPA and DOPA decarboxylase inhibitors, would determine higher peripheral levels of DA, that could stimulate all DA receptors.\textsuperscript{49}

It is worth noting that the lack of dopaminergic cells does not merely reflect a lack of DA, but also leads to the loss of a variety of other messenger molecules, including co-transmitters, peptides, and to the loss of uptake sites which may be relevant as modulators of gut activity. These potential targets should be considered in future drug design.

CONCLUSIONS

Most patients with PD experience autonomic dysfunctions involving the GI system, which complicates the clinical management of the disease and lowers the quality of life.
Despite its frequency as an onset symptom of PD, the altered motility of the gut is poorly understood. A few pathological and experimental investigations led to the characterization of DA deficiency and the presence of LB as typical hallmarks of such digestive dysfunction, paralleling what occurs in the central nervous system. Further studies are needed in order to better clarify the peripheral degeneration which is responsible for altered GI motility in PD, and how specific drugs may restore this function. Since current therapeutic strategies offer only a partial symptomatic effect, the development of treatment strategies should also be considered that would delay or prevent the progression of the disease. Given the early onset of the ‘Parkinsonian gastrointestinal dysfunction’, the prompt diagnosis of such a condition might also serve as an early marker to apply neuroprotective strategies intended to delay the onset of the motor symptoms of PD.

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