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LEVODOPA'S EFFECTS ON ANORECTAL CONSTIPATION IN DE NOVO PARKINSON'S DISEASE PATIENTS: THE QL-GAT STUDY

Hypothesis / aims of study

Gastrointestinal tract (GIT) dysfunction is common in Parkinson's disease (PD) patients. However, it remains unclear whether levodopa affects GIT function in PD. We aimed to perform an open study of levodopa's effects on ano-rectal constipation in *de novo* PD patients by the quantitative lower-gastrointestinal autonomic test (QL-GAT).

Study design, materials and methods

Nineteen unselected *de novo* PD patients (10 men, 9 women; mean age, 66 years; mean duration of the disease, 2.2 years) were recruited in the study. All but except for one patient had constipation according to a questionnaire on pelvic organ function. These patients were treated with 200 mg/day of levodopa with 20 mg/day of carbidopa for 3 months. Pre- and post-treatment, objective parameters in the QL-GAT that comprised colonic transit time (CTT) and rectoanal videomanometry were obtained. Statistical analysis was made by Student's *t*-test.

Results

Levodopa was well tolerated by all patients. Most patients reported subjective improvements in bowel frequency and difficult defecation. Levodopa did not change significantly CTT of the total colon or any segment of the colon. During rectal filling, levodopa significantly lessened the first sensation ($p<0.05$). It also tended to augment the amplitude in SPRC, though these changes did not reach statistical significance. During defecation, levodopa significantly lessened the amplitude in paradoxical sphincter contraction upon defecation (PSD) ($p<0.01$). It also tended to augment the amplitude in rectal contraction, lessen the amplitude in abdominal strain, though these changes did not reach statistical significance. Overall, levodopa significantly lessened post-defecation residuals ($p<0.05$).

Interpretation of results

The QL-GAT in the present study showed for the first time that levodopa, a precursor of dopamine, augmented rectal contraction, lessened PSD, and thereby ameliorated ano-rectal constipation in *de novo* PD patients without serious adverse effects. The underlying mechanism is complex. The strength of cholinergic transmission in the enteric nervous system (ENS) is thought to be regulated by opposing receptors; serotonin 5-HT4 receptor-mediating excitation and dopamine D2 receptor-mediating inhibition, based on evidences of knock-out mice [1]. However, a number of studies have also demonstrated increased motility in the colon (scarce in dopamine receptors), not in the stomach (rich in dopamine receptors), in response to externally-administered dopamine, presumably mediated by other receptor populations such as adrenergic or serotonergic receptors, or by central nervous system (CNS) mechanisms [2]. While dopamine cannot penetrate the blood-brain barrier, levodopa can reach the CNS. Electrical stimulation or microinjection of dopamine into the striatum inhibits upper-GIT motility. However, under stress conditions, intra-cerebroventricular administration of dopamine facilitates colonic spike bursts presumably via the hypothalamus [3]. Considering the above evidences, in our *de novo* PD patients, levodopa might have acted on the lower-GIT function by both the ENS and CNS mechanisms.

Concluding message

The QL-GAT in the present study showed for the first time that levodopa augmented rectal contraction, lessened PSD, and thereby ameliorated ano-rectal constipation in *de novo* PD patients without serious adverse effects.

	total colon (hours)	right (hours)	left (hours)	rectosigmoid (hours)
before	**49.3**	**10.0**	**12.5**	**26.6**
after	**56.7**	**9.7**	**15.4**	**31.6**
paired t-test	**NS**			

Table 1 Results of colonic transit study.
NS: not significant

	anal manometry at rest				rectoanal videomanometry							
	anal pressure (cmH2O)		abdominal pressure (cmH2O)		storage phase (ml)		(cmH2O)		defecation phase (cmH2O)			(ml)
	rest	Squeeze	cough	strain	first sensation	rectal capacity	SPRC	anal pressure	rectal pressure	anal pressure	Abdominal pressure	post defecation residuals
before	**66.0**	**69.1**	**66.0**	**31.6**	**178.6**	**372.8**	**8.2**	**18.0**	**4.4**	**29.7**	**39.4**	**142.2**
after	**62.6**	**71.7**	**71.1**	**36.3**	**121.3**	**316.1**	**10.2**	**9.2**	**7.3**	**-7.1**	**31.5**	**53.9**
paired t-test					**p<0.05**					**p<0.01**		**p<0.05**

Table 2 Results of anorectal videomanometry.
SPRC: spontaneous phasic rectal contraction

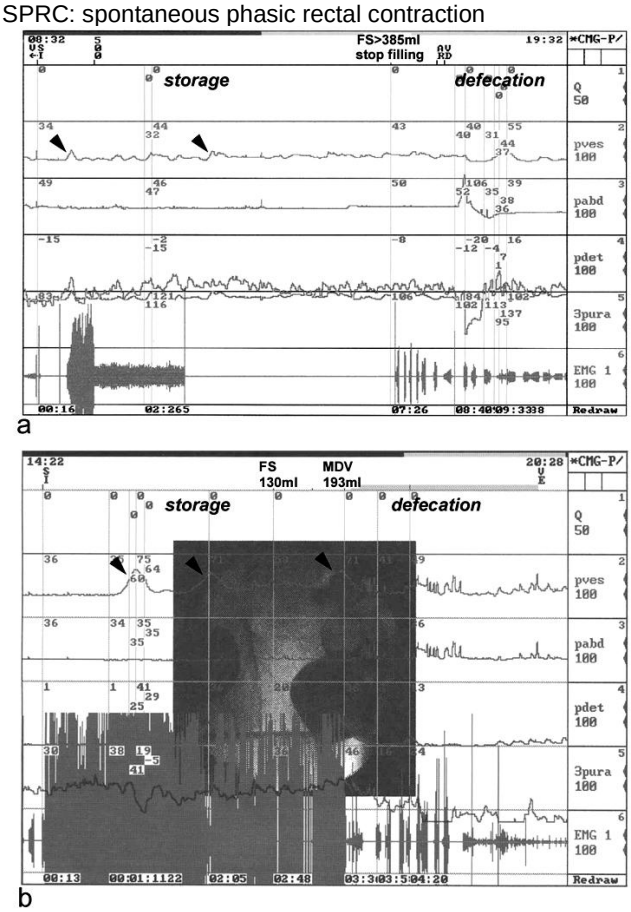

Figure 1 Representative case of anorectal videomanometry.
The spontaneous phasic rectal contraction (SPRC) of the patient (68-year-old man with PD) was small (arrows), and we stopped filling at the volume of 385 ml because of leaking, whereas he did not have rectal sensation at all (a.Pre). After levodopa, his SPRC increased (arrows), and he became to have a normal first sensation of 130 ml and a rectal capacity of 193 ml (b.Post). Sphincter EMG was not properly recorded.

Q: fecal flow, pves: naïve rectal pressure, pabd: abdominal pressure, pdet=rectal pressure (pves – pabd), pura: anal pressure, EMG: anal sphincter EMG, SI: start of rectal infusion, FS: first sensation, MDV: maximum desire to void (rectal capacity), VD: defecation

References
1. J Neurosci (2006) 26: 2798-2807.
2. Am J Physiol Regulatory Integrative Comp Physiol (2000) 279: R599–R609.
3. Brain Research Bulletin (1992) 29: 135-140.

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Was this study approved by an ethics committee?	**Yes**
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Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**