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Commentary

Basal Ganglia and Functions of the Autonomic Nervous System

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SUMMARY

1. The aim of this mini-review was to describe an underrecognized but important aspect of the basal ganglia diseases, the dysfunction of the autonomic nervous system that patients suffer owing to the degenerative process affecting these structures, mainly Parkinson's disease.

2. We analyze the most prevalent autonomic abnormalities in these patients from an experimental and clinical point of view.

KEY WORDS: basal ganglia; autonomic nervous system; gastrointestinal functions; salivary glands; cardiovascular functions; bladder; striatum; substantia nigra.

The basal ganglia are nuclei situated deep in the cerebral white matter in the diencephalon and midbrain. The term usually includes caudate nucleus, putamen, globus pallidus and related cell groups closely connected to them, the subthalamic nucleus, and the substantia nigra (Brodal, 1992). In rodents and other animals the caudate and putamen nuclei are not separated structures and collectively termed striatum or neostriatum. For a long time, basal ganglia have been implicated in a wide variety of motor functions since diseases affecting these structures lead to disturbances of movement and muscle tone as important features (Brooks, 1995; Graybiel, *et al.*, 1994; Marsden and Obeso, 1994; Mitchell *et al.*, 1991; Wichmann and DeLong, 1996). However, a growing body of experimental and clinical evidence suggest that the basal ganglia not only play a role in motor functions, but also a role in higher mental process; modulation of pain and control of autonomic activity have been reported (Brown and

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Feldman, 1993; Brown and Marsden, 1990; Kimura, 1995; Pazo *et al.*, 1982; Pazo and Medina, 1983; Quadri *et al.*, 2000; Schultz, 1994). In this review, we address the experimental and clinical data referred to of the most prevalent autonomic manifestations in patients with basal ganglia dysfunctions, mainly Parkinson's disease.

GASTROINTESTINAL FUNCTIONS

The classic monograph of Sir James Parkinson in 1817 (cited by Edwars *et al.*, 1993), described the cardinal features of the disease that now bears his name and reports autonomic gastrointestinal dysfunction associated with motor disturbances, mentioning abnormal salivation, dysphagia, and constipation. Hypersalivation, however, is considered to be the most early and frequent symptom in the 70–78% of the patients (Bardow *et al.*, 2001; Friedman and Potulska, 2001; Korcyn, 1989; Martignoni *et al.*, 1995; Pfeiffer and Quigley, 1999). Subsequent studies found evidences suggesting that patients with PD do not hypersecrete saliva, but the contrary they produce less saliva (Bagheri *et al.*, 1999; Pfeiffer and Quigley, 1999; unpublished observations from authors).

Experimental studies in rats, in this laboratory, have demonstrated that activation of peripheral and central dopamine receptors induce salivary secretion. The peripheral action was mediated by α and β adrenoceptors on the glands (Pazo *et al.*, 1981, 1982). This peripheral effect was not blocked by haloperidol (Fig. 1). The central action of levodopa was suppressed both by sympathectomy and haloperidol administration (Fig. 2). Likewise unilateral lesion of the striatum decreased the salivary secretion induced by levodopa in close correlation with the size of the lesion. The largest damage produced a decrease of 62% of salivary response (Fig. 3). Lesion to the globus pallidus or its output pathways in the H_1–H_2 field of Forel and lesion to the lateral mesencephalic reticular formation also reduced significantly the salivary response to levodopa (Fig. 4). This suggests that outflow from the striatum is mediated by the globus pallidus and fibers in the mesecephalic reticular formation to the sympathetic preganglionic neurons in the spinal cord. The experimental observations support the assumption that activation of central dopamine receptors are involved in salivary secretion, which explains the hyposalivation in Parkinson's disease as a consequence of striatal dopamine deficiency (Friedman and Potulska, 2001; Martignoni *et al.*, 1995). In fact, this symptom has a good response to levodopa administration in PD patients (unpublished observations). However, we could not rule out additional peripheral lesions in autonomic ganglia in these patients.

CARDIOVASCULAR FUNCTIONS

The prevalence of cardiovascular dysfunctions in PD patients is less frequent than gastrointestinal dysfunctions. Some studies have described heart rate variability, however, the most frequent disturbance is impairment in blood pressure regulation, manifested as postprandial hypotension, which is frequently associated with orthostatic hypotension (Golstein *et al.*, 2002; Kallio *et al.*, 2000; Senard *et al.*, 2001). The reduced sensitivity of the baroreceptor reflex has been suggested to be the

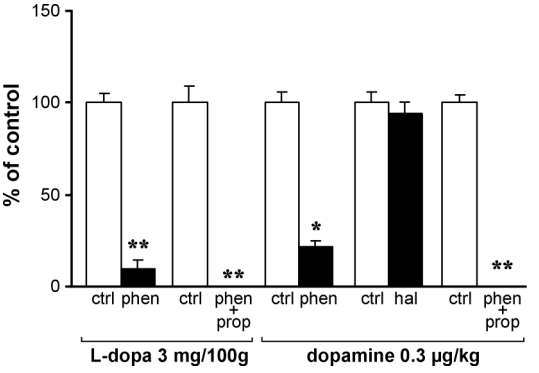

Fig. 1. Secretory responses to L-dopa and dopamine as percent of control values. Pretreatment with phentolamine (3 mg/kg, i.v.) plus propranolol (1 mg/kg, i.v.) blocked the secretory response, while pretreatment with phentolamine alone reduced the response. Haloperidol (0.3 mg/kg, i.v.) produced no effect. Data are the means ± SEM of at least five observations. $^{*}p < 0.01$; $^{**}p < 0.001$ as compared with controls, paired t-test. Abreviations: ctrl = controls; phen. = phentolamine; prop. = propanolol; hal. = haloperidol. Modified from Pazo *et al.*, 1981.

causative factor (Floras *et al.*, 1988; Gribbin *et al.*, 1971; Loew *et al.*, 1995), although central mechanisms are probably also involved (Loew *et al.*, 1995).

Experimental observations suggest that the extrapyramidal system could be implicated in the regulation of the cardiovascular system. Electrical or chemical

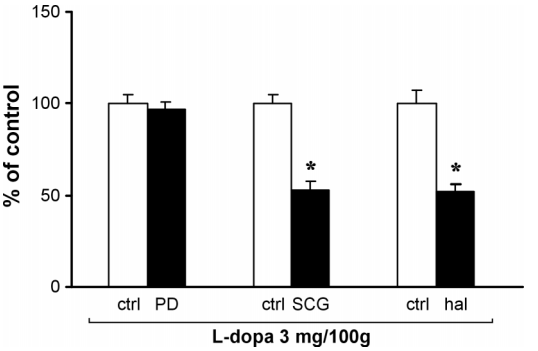

Fig. 2. Secretory responses to L-dopa as percent of control values. Parasympathetic decentralization (PD) did not modify the secretory response to L-dopa while superior cervical ganglionectomy (SCG) reduced the response in about a 50%. Similar results are observed after i.v. administration of haloperidol (hal). Controls (crtl) are the secretion of contralateral submandibular gland. Data are means ± SEM of at least five observations. $^{*}p < 0.05$ when compared with controls, paired t-test . Modified from Pazo *et al.*, 1981.

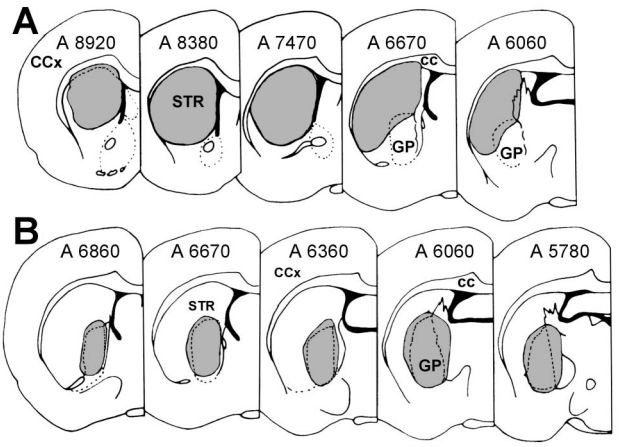

Fig. 3. Schematic drawing of striatal lesions (grey areas) in (A) and globus pallidus in (B) that produced a significant reduction of salivary secretion in response to L-dopa. For (A) 62.4 ± 4.9, $n = 5$, $p < 0.02$ and for (B) 65.8 ± 2.3, $n = 5$, $p < 0.01$, when compared with the contralateral side (100%), paired t-test. Outlines and levels adopted from Koning and Klippel, 1963. Modified from Pazo *et al.*, 1982.

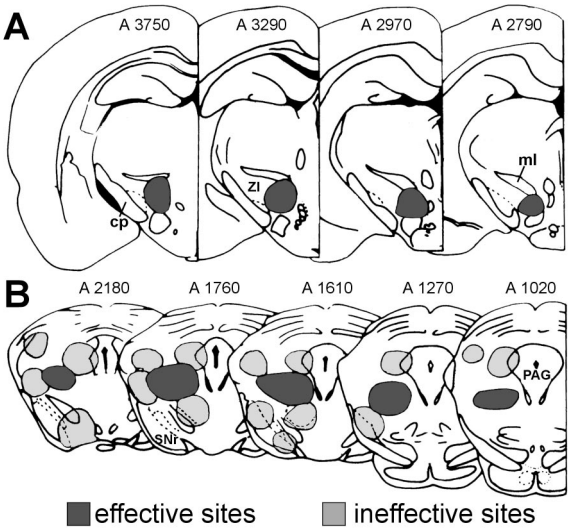

Fig. 4. Schematic drawing of the lesioned effective sites that produced a significant reduction of the salivary secretion in response to L-dopa. In (A) the fields of Forel and in (B) the lateral reticular formation. Grey light areas are examples of some lesions that left salivary response unmodified (ineffective). For (A) 58.8 ± 3.9, $n = 4$, $p < 0.02$ and for (B) 53.9 ± 6.9, $n = 8$, $p < 0.01$. Outlines and levels adopted from Köning and Klippel, 1963. Modified from Pazo *et al.*, 1982.

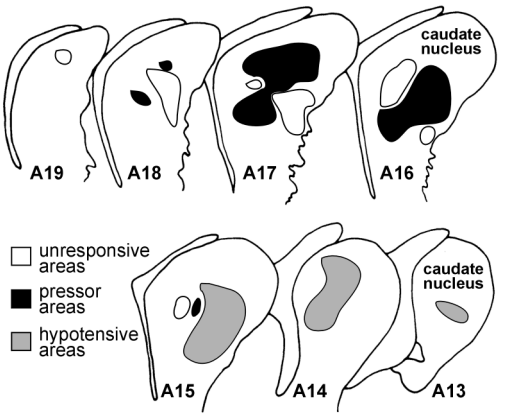

Fig. 5. Schematic representation of the areas explored with microinjections (10 μg/0.5 μL) of carbachol within the caudate nucleus of the cat. The rostral areas produce elevation of the blood pressure while the caudal areas reduce the blood pressure. Outlines and levels were adopted from Snider and Niemer, 1961. Modified from Pazo and Medina, 1983.

stimulation of the substantia nigra pars compacta in rats enhanced dopamine release in the striatum and elicited proportional hypertension and tachycardia. This effect was blocked by intrastriatal microinjection of haloperidol (Lin and Yang, 1994; Linthorst *et al.*, 1990). Similar results were observed in awake cats (Ångyan, 1991). A relationship has also been described between activity of nigrostriatal pathway and arterial baroreceptors (Yang and Lin, 1993). Deafferentation of baroreceptors decreased striatal dopamine concentration and tyrosine hydroxylase activity (Alexander *et al.*, 1984). In rats spontaneously hypertensive, the microinjection of apomorphine, an agonist of dopamine receptors, facilitated reflex bradycardia elicited by systemic injection of adrenaline. The striatal lesion inhibited this reflex (Lin *et al.*, 1982; Wu *et al.*, 1984). Studies in our laboratory, in cats locally anesthetized and paralyzed, microinjections of a cholinergic agonist, carbachol, into the striatum produced biphasic effects on blood pressure. When the injections were made in the rostral aspect of the nucleus hypertension was induced, whereas injections in the caudal parts of the striatum induced hypotension (Pazo and Medina, 1983; Fig. 5). The above experimental evidence supports a direct association between nigrostriatal system and cardiovascular functions. It could be the basis on blood pressure alterations in Parkinson's disease as the result of changes in the sensibility of arterial pressoreceptors and blood pressure lability (Golstein *et al.*, 2000).

BLADDER FUNCTIONS

Clinical studies have indicated that neurogenic bladder dysfunction may occur in patients with extrapyramidal disease, particularly Parkinsonism, however its

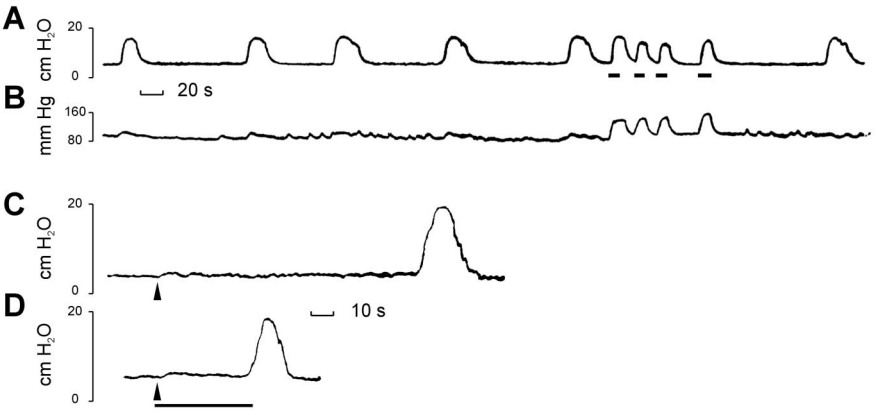

Fig. 6. Cystometrogram (A) of spontaneous contraction of the bladder before and during electrical stimulation (55 μA, 100 Hz) of the dorsomedial striatum (bars beneath the record). Note the induced contractions of the bladder when the striatum was stimulated. Record (B), mean blood pressure. In (C) and (D) cystometrograms of the micturition reflex obtained by infusion of saline solution into the bladder before (C) and during (D) electrical stimulation (line below the record) of the dorsolateral striatum (55 μA, 100 Hz). Head arrows indicate start of the infusion that finished when the bladder began contraction. Note the increased excitability of the micturition reflex (bladder hyperreflexia) by stimulation of the striatum. Modified from Pazo, 1976.

incidence is low (Murnaghan, 1961; Porter and Bors, 1971). The most frequent micturition disturbance is urgency and few cases of urinary incontinuence. Urodynamic studies in these patients have revealed involuntary contraction of the bladder during filling (Bonnet *et al.*, 1997; Murnaghan, 1961; Sakakibara *et al.*, 2001). This detrusor hyperreflexia (Martignoni *et al.*, 1995; Pavlakis *et al.*, 1983) causes urgency and frequency of micturition or incontinence (Chaudhury, 2001; Klutzow *et al.*, 1989). Experimental studies suggest that the basal ganglia are related to bladder contraction. Electrical stimulation of the substantia nigra, subthalamic nucleus, and globus pallidus in the cat inhibits the micturition reflex (Lewin *et al.*, 1967; Lewin and Porter, 1965; Porter *et al.*, 1971). In the rat, electrical stimulation of the dorsomedial striatum elicited vesical contractions and increased excitability of micturition reflex (bladder hyperreflexia; Pazo, 1976; Fig. 6), whereas stimulation of the ventromedial striatum and globus pallidus inhibits detrusor contractions and increases micturition reflex (Fig. 7). Similar results were reported in the cat (Gogate *et al.*, 1974). Bladder hyperreflexia was also observed in marmosets and monkeys made parkinsonian by systemic administration of MPTP (Albanese *et al.*, 1988; Yoshimura *et al.*, 1998). In these monkeys the administration of dopamine D_1agonist SKF 38393 suppressed detrusor hyperreflexia, whereas D_2 agonist bromocriptine augmented the micturition reflex (Yoshimura *et al.*, 1998). This was confirmed with experiments in which the inhibition of bladder contraction induced by substantia nigra stimulation was suppressed by intracerebroventricular administration of D_1antagonist SCH 23390 and the inhibition of bladder contraction was facilitated by intraventricular application of SKF 38393 (Yoshimura *et al.*, 1992).

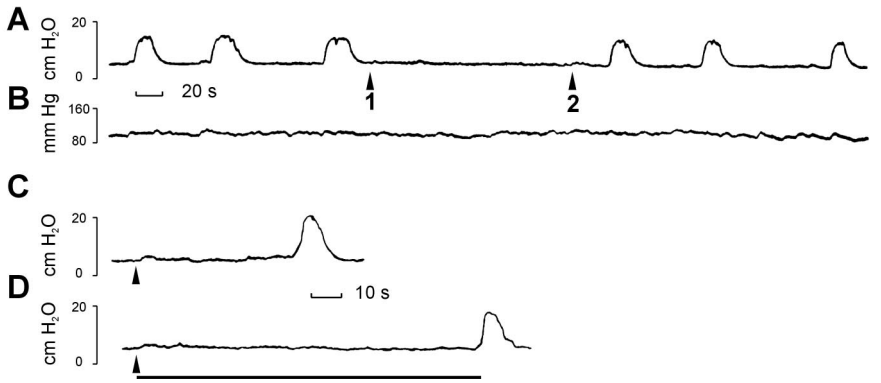

Fig. 7. Cystometrogram (A) of spontaneous contraction of the bladder before and during electrical stimulation (55 μA, 100 Hz) of the ventromedial striatum. Stimulation started at 1 and finished at 2. Note the inhibition of bladder contraction during stimulation. Record (B), mean blood pressure. Cystometrograms of micturition reflex, in (C) micturition reflex before striatal stimulation and (D) during electrical stimulation of the ventromedial striatum (line below the record). The infusion (arrow head) of saline solution into the bladder started at the arrow head and finished when the bladder began contraction. Note the inhibition of the detrusor contraction when the striatum was stimulated. Modified from Pazo, 1976.

Studies performed in patients with Parkinson's disease and urinary symptoms found a correlation between urinary dysfunction and the reduction in the dopamine binding of transporter in both striatum, as determined by SPECT. The decrease was more marked in the caudate nucleus (Sakakibara *et al.*, 2001). These experimental and clinical findings support the assumption that detrusor hyperactivity is due to decrease of D_1dopamine receptors stimulation in the striatum as consequence of the degenerative process in the substantia nigra pars compacta.

THERMOREGULATION

Clinical reports in idiopatic Parkinson's disease have shown abnormal thermoregulation, which consists of heat intolerance and hypothermia (Appenzeller and Goss, 1971; Gubbay and Barwick, 1966) and it was attributed to dysfunction of the autonomic nervous system. The underlying basis were defective thermoregulatory mechanism in PD patients, such as reduced or absent sweating response when their core temperature was increased or peripheral vasodilatation reflex impairment when the skin was heated (Appenzeller and Goss, 1971; Fischer *et al.*, 2001). The somatosympathetic reflex, a sweating reflex associated with thermoregulation, was also found to be abnormal. Its latency was prolonged and its amplitude reduced. On the basis of these clinical findings, it has been postulated an inappropiate activation of the sympathetic nervous system as the cause of the thermoregulation disability in PD patients (Djaldetti *et al.*, 2001; Fischer *et al.*, 2001)

Nevertheless, there are no data on experimental studies in animals about the possible role of the basal ganglia on thermoregulatory functions. However, it was recently reported a significant decrease in the metabolic rate in the striatum of volunteers

during systemic hypertermia (Nunneley *et al.*, 2002). While the functional importance of this finding still has to be determined, it provides a link between basal ganglia and mechanisms of thermoregulation, which could be affected in PD patients.

CONCLUSION

Dysfunction of the autonomic nervous system is an underrecognized but important aspect of the basal ganglia disease. Clinical and experimental evidences support the involvement of these structures in the regulation of some autonomic functions. In Parkinson's disease, the best studied disease, the most frequent autonomic dysfunctions are those affecting the gastrointestinal, cardiovascular, urinary, and thermoregulatory systems. Gastrointestinal manifestations, mainly salivary secretion, reflect a failure of the sympathetic nervous system, according to experimental and clinical observations. Cardiovascular abnormalities are considered to be a sympathetic neurocirculatory failure from generalized sympathetic denervation. This abnormal sympathetic function is believed to be also responsible for the thermoregulation impairment observed in PD patients. Urinary dysfunction could probably be the result of direct action of the basal ganglia on micturition centers in the midbrain according to experimental and clinical findings.

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