Cholinergic approaches to the treatment of progressive supranuclear palsy

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Summary. In spite of the severe loss of cholinergic neurons in the brains of patients with progressive supranuclear palsy (PSP), marginal or null benefits are seen in clinical trials after the administration of physostigmine, a cholinesterase inhibitor, or RS-86, a cholinergic agonist. The possible role of cholinergic therapy in PSP is reevaluated.

It has been shown that several cholinergic regions are affected in progressive supranuclear palsy (PSP): the basal forebrain, basal ganglia, mediodorsal thalamic nuclei, midbrain and pontine areas (Brandel et al., 1991; Hirsch et al., 1987; Juncos et al., 1991; Kish et al., 1965; Malessa et al., 1991; Ruberg et al., 1985; Tagliavini et al., 1983). Lesions in particular structures may result in specific neurobehavioral deficits; e.g. lesions in the basal forebrain and mediodorsal thalamus may lead to the memory deficits seen in PSP. Involvement of the mesencephalic and pontine nuclei (rostral interstitial nucleus of the medial longitudinal fasciculus, superior colliculus and laterodorsal tegmental nucleus) may result in supranuclear ophthalmoplegia. The affected striatum and pedunculopontine nuclei may contribute to the motor deficits exhibited by PSP patients. These brain-behavior correlates prompt the question: Could cholinergic stimulation improve the neurobehavioral abnormalities seen in PSP patients?

The rationale for cholinocceptive treatment of the memory and cognitive disorders found in these patients is as follows: in PSP, the mediodorsal and basal forebrain cholinergic nuclei are affected, but the cortical neurons (Hauw et al., 1990) and the noradrenergic, dopaminergic and serotonergic subcorticocortical pathways are relatively spared (Agid et al., 1986; Ruberg et al., 1992). This differentiates PSP from Alzheimer’s disease (AD) which has severe cortical pathology, and from Parkinson’s disease (PD) which also has severe subcortical pathology. Therefore, the relative selectivity of the cholinergic lesions found in PSP makes it an ideal condition for treatment with cholinergic agents.

In contrast to patients with PD, motor function in PSP patients does not change after treatment with oral or intravenous physostigmine (Duvoisin, 1967; Litvan et al., 1989, in preparation). This differential response may be
attributed to degeneration of cholinergic striatal interneurons and the pedunculopontine nuclei. Thus, in addition to the nigral degeneration, also seen in PD, the degeneration of these cholinergic neurons might contribute to the interruption of the nigrostriatocortical pathways and explain why PSP patients do not respond to dopaminergic therapy. Degeneration of the pedunculopontine nuclei also seen to a lesser degree in PD patients might explain the failure of dopaminergic agents to improve the balance disorder often seen in these patients (Hirsch et al., 1987; Jellinger, 1988; Koller et al., 1989).

To date, only two cholinergic agents have been used to treat PSP. Foster et al. (1989) evaluated the effects of RS-86, an M1–M2 muscarinic agonist, on motor and cognitive function in 10 PSP patients. No effects were found with regard to either cognitive tasks or motor functions. However, there were changes in two measures of REM sleep which are typically sensitive to cholinergic treatment (increase in total, and percentage of, REM sleep and decrease in REM latency).

Litvan et al. (1989) administered oral physostigmine to 8 PSP patients at an “optimal” dose while evaluating a wide range of cognitive and motor abilities. The “optimal dose” was selected by titrating physostigmine on consecutive days from 0.5 mg to 2 mg every 2 hr, 6 times a day, using the total number of words recalled on the Selective Reminding Test as the dependent variable (Buschke et al., 1974). In this test, patients had to recall a list of 12 words. Before each trial, the subject is reminded of the words that he/she did not recall on the previous trial. Both short- and long-term explicit memory can be measured with this test. The group mean dose curve (Fig. 1) indicates that we successfully found an optimal dose for each patient in the open study. The effects of physostigmine were marginal (in the double-blind, controlled phase) on two measures of secondary memory: long term memory (the ability of the subject to recall a word on two consecutive trials without being reminded) and consistent long term memory (the capacity to recall a word consistently through the end of the test) (Fig. 2). Similar results were found on two indices of forgetting from the Brown-Peterson paradigm (Brown, 1958). In this paradigm, patients were given three words, and after interference-filled intervals of different durations (3–36 sec), they were asked to recall the originally presented words. Only two patients showed any consistent (improvement in all 4 outcome measures) positive effects (Fig. 2). The pattern of results was similar to those found with physostigmine treatment of AD (Thal et al., 1983).

In another experiment, Kertzman et al. (1990) evaluated spatial attention in the same group of PSP patients. The task used was designed by Posner who with Rafal had originally shown that PSP patients had difficulty with spatial attention (Rafal et al., 1988). In this task, the subject fixates on a spotlight and presses a button as soon as a target light appears. A cue stimulus precedes the target and cues the subject to look toward the same or opposite spatial location of the subsequent target (valid or invalid condition, respectively) (Fig. 3). The subjects’ reaction times were measured from target onset to button press for all the conditions. The validity effect