Immunization with Cholinergic Cell Bodies Induces Histopathological Changes in Rat Brains

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Received December 12, 1990; Accepted May 31, 1990

ABSTRACT

We have previously shown that sera from patients with Alzheimer's disease (AD) contain antibodies to the cell bodies (perikarya; PK) of purely cholinergic Torpedo neurons, and that repeated immunization of rats with this neuronal preparation for over a year induces learning and memory impairments. In the present study, we examined the brain morphology of cholinergic PK immunized rats relative to controls. Immunohistochemical studies of the brains of these rats revealed the accumulation of IgG in specific areas, such as, the hippocampus. Parallel histochemical studies demonstrated significant changes in the hippocampus, and in white matter areas. They included large vacuoles and necrotic nuclei in the granular layer of the dentate gyrus, tangle-like appearance in some pyramidal neurons of the hippocampus, and vacuolar degeneration accompanied by oligodendroglia hypertrophy in white matter tracts, such as, the corpus callosum and fimbria. In contrast, immunization with Torpedo cholinergic nerve terminals, that has no cognitive effects on the rat,

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Molecular and Chemical Neuropathology Vol. 13 © 1990 by the Humana Press Inc.
also did not induce brain morphological changes. These findings suggest that the learning and memory deficits induced by immunizing rats with cholinergic PK are related to the observed brain morphological changes, and support the hypothesis that the antibodies to cholinergic neurons found in the sera of AD patients may play a role in neuronal degeneration in this disease.

**Index Entries:** Alzheimer's disease; antibodies; histology; hippocampus; acetylcholine; rat; *Torpedo.*

**INTRODUCTION**

The cognitive impairment in Alzheimer's disease (AD) is associated with degeneration of cholinergic neurons in the basal forebrain that provide most of the cholinergic input to the cortex and hippocampus, (Blessed et al., 1968, Coyle et al., 1983, Sims et al., 1983). Although the etiology and pathogenesis of the cholinergic degeneration in AD are not known, several reports implicate immunological mechanisms (Ichii and Hage, 1976, McGeer et al., 1987 Nandy, 1985, Singh et al., 1987). We have previously shown that sera of AD patients contain antibodies (IgG) that bind to specific constituents of cholinergic neurons, and that these IgG bind to cholinergic cell bodies but not to cholinergic nerve terminals (Chapman et al., 1986, 1988). This study employed as antigen the purely cholinergic electromotor neurons of the electric fish *Torpedo* that are chemically homogeneous and contain many constituents that cross-react antigenically with human and other mammalian cholinergic preparations (Kushner, 1984, Patrick and Lindstrom, 1973, Richardson et al., 1982). These findings and the observation that AD sera and cerebrospinal fluid contain IgG that bind to mammalian cholinergic neurons and immunolyse them (Fillet et al., 1985, Foley et al., 1988, McRae-Degueurce et al., 1987), suggest that the cholinergic degeneration in AD is associated with the production of antibodies to these neurons.

The anticholinergic AD antibodies may be a secondary phenomenon resulting from the destruction of cholinergic neurons in AD, and have no role in triggering this process. However, once formed, they may contribute to the pathogenesis of cholinergic neuron degeneration. In order to study this possibility, we recently immunized rats repeatedly for over a year with isolated cell bodies (perikarya; PK) of *Torpedo* cholinergic neurons, that are recognized by AD sera, and with their nerve terminals, that are not recognized by AD sera (Chapman et al., 1986), and examined the effects of these treatments on their behavior. These studies revealed that the cholinergic PK immunized rats were impaired in spatial learning and memory tasks (T-maze alternation and Morris swim tests), and displayed a significant deficit in short-term memory, whereas the cholinergic synaptosomes immunized rats showed no such deficits (Chapman et al., 1989).