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Deficiency of a neuronal growth-sustaining factor in fibroblasts of patients with Alzheimer's disease

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Abstract

A previous report has shown a deficiency of a cholinergic differentiating factor in spent culture media in which Alzheimer's disease (AD) patient fibroblasts were grown (Kessler, 1987). We used a similar approach to investigate whether AD fibroblast-conditioned medium demonstrated central nervous system (CNS) neuronal growth sustaining properties. For these investigations we used cultured fetal murine telencephalic vesicle neurons. Control fibroblast-conditioned medium produced statistically significant neuronal survival as compared to AD fibroblast-conditioned medium or to nonconditioned medium. There was no statistically significant difference between AD fibroblast-conditioned medium and nonconditioned medium results. These results suggest that there may be a deficiency in AD of a CNS neuronal growth-sustaining factor.

Keywords: Alzheimer's disease; Fibroblasts; Growth factor; Tissue culture

1. Introduction

Kessler (1987) investigated the effects of Alzheimer's disease (AD) fibroblast-conditioned medium on the induction of choline acetyltransferase (CAT) in cultured neonatal rat superior cervical ganglion sympathetic neurons. He found that AD-conditioned medium increased CAT activity by only 38% of the control values. He did not observe any difference in neuronal numbers between the AD and control-conditioned mediums. These results indicated a deficiency of a cholinergic differentiating factor in AD.

The primary symptoms of AD are memory loss and cognitive decline due to central nervous system (CNS) neuronal death. Kessler's observations of a deficiency of a cholinergic differentiating factor in AD were based on effects on peripheral, sympathetic neurons, not on CNS neurons. It is important to determine whether in AD there is a loss of a CNS neuronal growth-sustaining factor. For this investigation we used techniques similar to Kessler's, but investigated survival of fetal murine CNS neurons.

2. Materials and methods

After obtaining signed, informed consent, 3-mm punch skin biopsies were aseptically obtained from two AD patients (a 74-year-old female and a 70-year-old male), who satisfied the NINCDS-ADRDA criteria for probable AD (McKhann et al., 1984) and their spouses (a 66-year-old female and a 76-year-old male). In the 74-year-old female AD patient, clinical symptoms had started 3 years previously, and in the 70-year-old male AD patient, 2 years previously. In both cases there was no family history of AD. At the time of biopsy all individuals were healthy and were taking no medications. The biopsy samples were minced with a scalpel into 1-mm fragments and were grown in tissue culture flasks in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal calf serum (FCS). The cultures were incubated at 37°C in a 94% air/6% CO_2 atmosphere. The medium was replaced every 4 days and the spent medium was stored aseptically at 20°C. The number of cells in the AD and control fibroblast cultures was the same. There were no passages of AD or of control fibroblasts.

Pregnant mice were sacrificed by cervical dislocation. Using sterile techniques, E16 normal fetuses were removed from the uterine sacks. Their telencephalic vesicles were

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