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Calcium Responses in Fibroblasts from Asymptomatic Members of Alzheimer's Disease Families

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We have previously identified alterations of K^+ channel function, IP_3-mediated calcium release, and Cp20 (a memory-associated GTP binding protein) in fibroblasts from Alzheimer's disease (AD) patients vs controls. Some of these alterations can be integrated into an index that distinguishes AD patients from controls with both high specificity and high sensitivity. We report here that alterations in IP_3-mediated calcium responses are present in a large proportion of AD family members (i.e., individuals at high risk) before clinical symptoms of Alzheimer's disease are present. This was not the case if such members later "escaped" AD symptoms. This preclinical calcium signal correlate of later AD does not reflect, however, the presence of the PS1 familial AD gene.

Key Words: **Alzheimer's disease; calcium; fibroblast.**

INTRODUCTION

Fibroblasts of patients suffering from Alzheimer's disease (AD) exhibit alterations at the cellular and molecular level (Baker *et al.,* 1988; Peterson *et al.,* 1988; Govoni *et al.,* 1993; McCoy *et al.,* 1993; Scott, 1993; Etcheberrigaray *et al.,* 1993, 1994; Huang *et al.,* 1994, 1995; Ito *et al.,* 1994; Kim *et al.,* 1995; Gibson *et al.,* 1996a,b; Hirashima *et al.,* 1996; Scheuner *et al.,* 1996). Despite the lack of complete agreement—particularly in relation to the regulation of intracellular calcium (Borden *et al.,* 1991; Huang *et al.,* 1991; McCoy *et al.,* 1993; Matsuyama *et al.,* 1995; Tatebayashi *et al.,* 1995; Gibson *et al.,* 1996a)—and the lack of methodological standardization, most studies do identify significant cellular and molecular alterations in fibroblasts from AD patients. More recently, we have identified potassium channel dysfunction and alterations of IP_3-mediated calcium release in AD fibroblasts. Patch-clamp techniques revealed the functional absence of an ≈113-pS tetraethylammonium (TEA)-sensitive K^+ channel (Etcheberrigaray *et al.,* 1993). It was also established that intracellular calcium elevations in response to TEA resulted from blockade of functional TEA-sensitive K^+ channels and subsequent depolarization. In consequence, TEA-induced Ca^{2+} elevations were primarily observed in control cell lines and were

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