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IS ALZHEIMER'S DISEASE ASSOCIATED WITH A DECREASED INTRACELLULAR LEVEL OF CALCIUM?

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1. ABSTRACT

Several biochemical events underlying the hallmark lesions of the Alzheimer's disease are calcium-dependent processes, and appear to be inactivated during the disease progression. Therefore, it is reasonable to propose that, contrary to the current beliefs, there is a deficit in the level of intracellular calcium in the early phase of this disease process.

2. DISCUSSION

The etiology of Alzheimer's disease (AD) remains elusive. However, it has been generally accepted that an imbalance of intracellular calcium is a central defect in the disease (1). This would imply that an important clue to AD origin could be related to either high or low calcium level in the neurons of AD patients. Calcium is an important factor which regulates many life processes, including neurotransmission and long-term potentiation (memory formation), functions that are particularly affected in AD. Although it is widely believed that the level of calcium is increased in the brain of the AD patients, (1), the following information suggests that the other possibility should not be ignored.

First, neurotransmitter release and memory formation are both highly calcium-dependent processes (2). As such, the deficit in these processes in AD would point to a decreased rather an increased calcium level. Second, we have proposed that α-secretase, the enzyme responsible for normal processing of ß-amyloid precursor protein, is a calcium-dependent protease (3). This implies that calcium levels, if low, would inactivate this enzyme, thereby overcharging the amyloidogenic pathway to produce excessive Aß. On the other hand, high calcium would overactivate α-secretase and thus would lead to a reduced production of Aß. Third, it has been shown that hyperphosphorylation of tau, the main component of neurofibrillary tangles, is primarily the result of an "inactivation" of protein phosphatases including calcineurin (4). Calcineurin is a Ca^{2+}/calmodulin-dependent phosphatase (5) and it dephospharylates tau in a site-specific manner (including the sites hyperphosphorylated in AD)(4,6). Selective reduction of calcineurin activity results in hyperphosphorylation and accumulation of tau in transgenic mice (7). These findings favor a calcium deficit, particularly in the "early phase" of AD.

On the other hand, many studies have shown that high concentrations of Aß can lead to a rise in calcium level in cells (1). It has also been shown that the calcium-dependent protease, calpain, is overactivated in the postmortem AD brain (8). It should be noted, however, that: (a) high Aß concentration is a characteristic of the late stage of AD, since Aß at physiological concentration in normal individuals does not have any destructive effects; and (b) overactivation of calpain in postmortem AD brain may be due to neuronal death which occurs well before the death of the patient (definition of AD). Therefore, calcium influx into the cytosol after cell death or severe cell damage (calcium gradient collapse) would activate calpain. In other words, these data demonstrate that calcium rise does occur in AD, but more likely in the late stage (high Aß levels) or at the endpoint (postmortem) of the disease.

Perhaps, a "biphasic" scenario for calcium alterations in AD is worth considering. A calcium deficit may occur in the early phase of the disease. This, in turn, could trigger or contribute to the accumulation of both Aß and tau (by inactivating α-secretase and calcineurin). Over time, this would lead to cell damage and death. These latter events would then lead to an increase in intracellular level of calcium.

A calcium deficit early in AD may account for the protective effect of estrogen (9), a potent calcium agonist (10). The memory deficit induced in rodents by the inhibitors of calcium channels may be explained on a similar basis (11,12).

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