Platelet phospholipase A$_2$ activity in Alzheimer’s disease and mild cognitive impairment

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Received January 28, 2003; accepted September 29, 2003

Summary. Phospholipase A$_2$ (PLA$_2$) controls the metabolism of phospholipids in cell membranes. In the brain, PLA$_2$ influences the processing of the amyloid precursor protein (APP) and thus the production of the amyloid-beta peptides (A$_\beta$), which are the major components of the senile plaques in Alzheimer’s disease (AD). Reduced PLA$_2$ activity has been reported in brain and in platelets of AD patients. In the present study we investigated PLA$_2$ activity in platelets from 21 AD patients as compared to 17 healthy elderly controls and 11 individuals with mild cognitive impairment (MCI). Subjects were cognitively assessed by the Mini-Mental State Examination (MMSE) and the CAMDEX schedule. Platelet PLA$_2$ activity was determined by radio-enzymatic assay, which mainly detected a calcium-independent form of the enzyme present also in the brain (iPLA$_2$). PLA$_2$ activity was significantly lower in AD than in controls ($p < 0.001$). Mean PLA$_2$ activity in MCI individuals was between the values of AD patients and controls, with a subgroup showing PLA as low as the lowest AD patients, but the differences from MCI were not significant from AD and control groups. Lower PLA$_2$ activity was significantly correlated with a worse cognitive performance both at the MMSE ($p = 0.001$) and the cognitive sub-scale of the CAMDEX inventory ($p = 0.002$). Our data replicate previous findings of reduced platelet PLA$_2$ activity in AD. Both reduced PLA$_2$ activity and the correlation with impaired cognition were also reported in brain tissue of AD patients, suggesting thus that the present determinations in platelets may be related to a reduction in the brain. In the brain the inhibition of PLA$_2$ inhibits the physiological secretion of the APP, a mechanism that increases A$_\beta$ formation. Further longitudinal studies should investigate whether those MCI individuals with the lowest PLA$_2$ values in platelets would be at a higher risk to develop AD during a longitudinal follow up.

Keywords: Dementia, Alzheimer’s disease, mild cognitive impairment, brain phospholipids, phospholipase A$_2$, PLA$_2$, platelets.
Introduction

Phospholipases A₂ (PLA₂) are a super-family of enzymes that participate in a wide variety of physiological processes, including phospholipid metabolism, remodeling of cell membranes, and intracellular signaling. In most cell types, PLA₂ contributes to the release of arachidonic acid from membrane phospholipids, which is a fundamental step in the synthesis of major mediators of the inflammatory response. In cholinergic neurons, particularly, the cleavage of membrane phosphatidylcholine by PLA₂ has an additional role in release of choline, the main precursor for the synthesis acetylcholine (Blusztajn et al., 1987). PLA₂s have a preferential affinity for the cleavage of arachidonyl tails at the sn-2 position of phospholipid molecules (Clark et al., 1991). Abnormal regulation of highly unsaturated fatty acid metabolism by PLA₂ may result in modifications of the neuronal membrane structure and fluidity, and affect intracellular signalling and neurotransmitter- and ion channel-related functions (review in Horrobin, 1998).

Data suggesting increased PLA₂ activity in schizophrenia (Gattaz et al., 1987, 1990, 1995; Noponen et al., 1993; Ross et al., 1997) have raised the attention to the role of membrane abnormalities in neuropsychiatric disorders. Disordered PLA₂ metabolism has also been described in multiple sclerosis (Woelk et al., 1974), temporal-lobe epilepsy (Simonato, 1993; Visioli et al., 1994) and dyslexia (MacDonell et al., 2000).

In Alzheimer’s disease (AD) there have been reports of decreased brain and platelet PLA₂ activity (Gattaz et al., 1995b, 1996). Within AD brains, reduced activity of the enzyme in the frontal and parietal cortex was related to earlier onset of dementia, earlier age at death, and higher counts of senile plaques and neurofibrillary tangles (Gattaz et al., 1996). In addition, ³¹P-spectroscopy studies of AD patients have suggested decreased membrane phospholipid turnover in temporoparietal areas (Brown et al., 1989), which is compatible with the findings of decreased PLA₂ metabolites in the parietal cortex of AD brains (Skinner et al., 1989). At last, in vitro studies have implicated PLA₂ in the regulation of amyloid precursor protein (APP) processing in cell cultures (Emmerling et al., 1993). Taken together, evidence drawn from experimental and clinical studies support the hypothesis that abnormalities in membrane phospholipid metabolism, secondary to reduced PLA₂ activity, might play a role in the pathogenesis of AD.

In the present study we investigated PLA₂ activity in platelets of a larger sample of AD patients as compared to healthy elderly controls, and extended the investigation to a subgroup of non-demented individuals with mild cognitive impairment (MCI). Platelets are frequently used as peripheral markers for neurons because they share some common membrane and receptor properties, providing thus an interesting model for the investigation of metabolic abnormalities in Alzheimer’s disease (Zubenko et al., 1999). In a second step, we attempted to characterise the subtype of PLA₂ detected by our assay in platelets.

Methods

Patients and controls

Twenty-one patients with probable (n = 17) or possible (n = 4) AD according to NINCDS-ADRDA criteria (McKhann et al., 1984), 11 subjects with evidence of mild cognitive...