Ganglioside catabolism is altered in fibroblasts and leukocytes from Alzheimer's disease patients

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GANGLIOSIDE CATABOLISM IS ALTERED IN FIBROBLASTS AND LEUKOCYTES FROM ALZHEIMER'S DISEASE PATIENTS

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COMMENT

The paper by Pitto et al. entitled «Enhanced GM1 catabolism in cultured fibroblasts from Alzheimer patients» was recently published in Neurobiology of Aging [19]. This very interesting paper draws attention to the alterations of glycosphingolipid (GSL) metabolism in peripheral tissue (skin fibroblasts) derived from patients with diagnosis of Alzheimer's disease (AD). The authors suggest that found biochemical alterations could serve as a peripheral hallmark of the disease. This paper, amongst many others, presents additional evidence supporting the theory that AD is either a systemic disease or at least has numerous systemic implications which may be recognized and used for diagnostic purposes. In available literature there have been only a few data referring to glycosphingolipid metabolism in AD peripheral cells. However, it has to be pointed out that the observations on glycosphingolipid metabolic alterations not only in AD but also in Down's syndrome (DS) peripheral tissues have been previously published by other groups [9] and [17], in addition to the paper by Pitto et al [19].

The biological roles of glycosphingolipids have been extensively studied and their involvements in key cellular events as well as their particularly important functions in animal brain tissue are well known [8], [15], [20] and [24]. The idea that there are alterations in glycosphingolipid metabolism in Alzheimer's disease arose from biochemical studies of brain gangliosides pattern [1], [11], and [20]. These studies established that specific changes of content and composition of brain gangliosides may serve as stage specific markers of brain development and aging [12] and [21]. Also, it was shown that ganglioside pattern is altered in AD brains [5], [13] and [14]. Specific changes in content and composition of gangliosides and other membrane lipids in AD brain regions were documented by several groups and finally most systematically presented by Svennerholm's group in 1994 [22]. Mentioned specific changes of ganglioside content and composition were mostly discussed as a consequence of

neuronal cell degeneration, demyelination and gliosis, which was the most logical explanation. However, a tempting speculation that observed biochemical alterations of gangliosides are due to the accelerated lysosomal degradation of gangliosides in AD brain tissue was in fact proposed by Kračun et al. in 1990 and 1992 [13] and [14]. This hypothesis was supported by immunohistochemical studies of Cataldo and colleagues, showing both abnormal distribution and colocalization of several lysosomal hydrolases and proteases (β-hexosaminidase A, α-glucosidase, catepsin D) with β–amyloid in diffuse plaques in cerebellum and striatum in AD and Down's syndrome (DS) brain tissue [2] and [3]. A documented increased expression of lysosomal hydrolases in neuronal populations affected by amyloid pathology was explained as a proof for up-regulation of endosomal-lysosomal systems and was proposed to be an early marker of metabolic dysfunction related to primary AD etiopathogenesis [2] and [3]. It was a logical step further to analyze glycosphingolipid metabolism in peripheral cells. In 1994 and 1995, Maguire and colleagues showed decreased activity of GSL biosynthetic enzymes (sialyltransferases) in serum [16] and brain tissue [17] in AD and DS as compared with control samples. In our study published in 2002, the activity of several enzymes involved in ganglioside and sulfatide catabolism (β–galactosidase, β-hexosaminidase, β-hexosaminidase A and arylsulfatase A) was analyzed in leukocytes and skin fibroblasts derived from individuals with Alzheimer's disease and Down's syndrome [9]. Our results showed statistically significant increase in β–galactosidase activity in AD and DS leukocytes in comparison with age-matched control leukocytes ($P<0.01$ and $P<0.05$, respectively; Student's t-test). Also, increased activity of β–galactosidase and β–hexosaminidase was observed in AD and fetal DS skin fibroblast cell line and age-matched controls obtained from commercial sources (AD line obtained from Coriel Cell Repositories, and fetal DS line from European Collection of Animal Cell Cultures), as well as in several DS and age-matched control skin fibroblast cultures established in our laboratory. The number of

examined cell cultures was too small for statistical analysis, and these data were not quantitatively shown in the paper (as suggested by reviewer) but were discussed in one paragraph in section Discussion. Our results were the ones which indicated that acceleration of at least some lysosomal catabolic pathways of gangliosides, i.e. significantly increased activity of β–galactosidase is present in AD and DS nonneural cells (leukocytes and skin fibroblasts). In 2003 an another important paper also reported increased activity of β-galactosidase, β-hexosaminidase and α-mannosidase in human AD skin fibroblasts [7]. In this paper, Ras activation was suggested to play a role in transcriptional up-regulation of analyzed lysosomal glycohydrolases in AD skin fibroblasts.

It has to be noted that increased activity of majority of lysosomal enzymes also accompanies normal aging. In the study by Dimri et al [6], β-galactosidase has been identified as a biomarker of senescence in human skin fibroblasts and in aging skin *in vivo*. In that study, three- to five-fold higher expression of lysosomal β–galactosidase mRNA was observed in senescent cells [6]. In our study, increased activity of β–galactosidase and β–hexosaminidase in control peripheral cells was observed to accompany aging [9]. However, this increase was found to be significantly more pronounced in leukocytes and skin fibroblasts derived from patients with AD and DS, disorders in which some kind of pathological aging process occurs. These findings raise several interesting questions: first, whether detected changes of glycosphingolipid metabolism in peripheral cells may present as markers for pathological aging in AD and DS; second, is there a change in transcriptional regulation of analyzed enzymes; third, are there mutations in biosynthetic/catabolic enzymes which may contribute to complex AD pathogenesis; fourth, which other (epigenetic) events modify and cause altered enzyme activities in AD and DS.

It is not surprising that glycosphingolipids are involved in neurodegeneration as they are present in highly organised and functionally essential lipid domaines (lipid rafts) of

membranes, together with cholesterol and phospholipids. As physicochemical properties of membranes are altered during aging and neurodegeneration, it is clear that any imbalance of proportion of lipids in membranes and/or changed ratio of membrane lipids may contribute and further complicate AD pathology [18]. Indeed, there have been a lot of studies so far which provided the data on possible roles of cholesterol and APP processing in lipid domaines in AD pathology [10]. Also, several other studies revealed that GM1 ganglioside may act as an endogenous seed for amyloidogenesis, interacting with amyloid protein [4] and [23]. Mentioned biochemical imbalances in membrane composition in brain resulting from/leading to neurodegeneration are expected if we deal with the brain. However, very similar biochemical alterations observed in peripheral tissues are not so easily understood and explained. Thus they deserve our attention and investigation, especially bearing in mind probable systemic nature of Alzheimer's disease.

We may conclude that firm data support the hypothesis on alteration of glycolipid metabolism in peripheral cells in both Alzheimer's disease and Down's syndrome. Namely, the alterations concerning both biosynthetic and catabolic pathways of nonneural glycosphingolipids (skin fibroblasts, leukocytes, serum) in AD and DS have been observed and published by several groups [7], [9], [17] and [19]. Most recent results on increased β–galactosidase activity in AD skin fibroblasts [19], based on somewhat different experimental approach, nicely confirm the observations and conclusions of other studies dealing with glycosphingolipid metabolism in AD peripheral cells. Taken together, all those studies and results indicate that further investigations are needed to clarify the role of glycosphingolipids in neurodegeneration, in order to find specific biochemical markers and develop practical diagnostic approaches directed to easily obtained peripheral tissues (i.e. leukocytes and skin fibroblasts).

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