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Research paper

Ganglioside and related-sphingolipid profiles are altered in a cellular model of Alzheimer's disease

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ABSTRACT

Sphingolipid-related issues are increasingly discussed to contribute to the neuropathological process of Alzheimer's disease (AD). In this study, gangliosides and related-sphingolipids (ceramides, neutral glycosphingolipids and sphingomyelins) were analyzed in neuroglioma (H4) cells expressing the Swedish mutation of the human amyloid precursor protein (H4APPsw) and compared with those of wild-type control H4 cells. These cells were chosen since H4APPsw cells were previously reported to reproduce well some essential features of AD. We found that H4APPsw cells exhibited a striking elevation of the simplest ganglioside GM3, an abnormality that was consistently reported in AD patients and animal models of AD. Concomitantly, the levels of both lactosylceramide (the immediate metabolic precursor of GM3) and ganglioside GD1a increased, suggesting a deregulation in the biosynthesis of gangliosides in the H4APPsw cells. Moreover, while the total ceramide level remained unaltered in H4APPsw cells, a shift in ceramide composition from long chain - to very long chain fatty acid-ceramide species was recorded. Because sphingolipid alterations occurring in H4APPsw cells were similar to those observed in transgenic mice and in human brains, this cellular model might be useful to further explore the complex role of sphingolipids in AD pathogenesis.

1. Introduction

Alzheimer's disease (AD), the most common form of dementia, is characterized by the formation of senile plaques due to aberrant amyloid precursor protein (APP) processing that leads to the deposition of aggregated amyloid-β peptide (Aβ), neurofibrillary tangles composed of hyperphosphorylated tau protein and neuronal loss. Apart from that, dysregulated lipid metabolism may also play an important role in the neuropathological process of this disease [1–3]. Indeed, the brain contains a large amount of lipids, in particular sphingolipids (SLs) such as ceramides, sphingomyelins (SM) and glycosphingolipids (GSLs). In addition to their structural roles, SLs exert a wide range of important biological functions, by modulating the function of several membrane associated proteins, and participating to several signaling pathways [4].

Ceramides (Cer) are the simplest SLs, and are the core constituent of most sphingolipids. For example, Cer can be transformed into sphingomyelins (SM) by SM-synthases by the addition of phosphorylcholine, whereas sphingomyelinases (SMases) catalyze the catabolism of SM into Cer. Ceramide glycosylation leads to the formation of glycosphingolipids such as glucosylceramide (GlcCer) and lactosylceramide (LacCer), which can be further processed to gangliosides, the most complex GSLs containing sialic acid residues. In the brain, the major gangliosides are members of the a-series (GM1 and GD1a) or b-series (GD1b and GT1b), and are synthesized from a common precursor (GM3), itself derived from LacCer (Fig. 1C).

Several studies have revealed quantitative and qualitative changes of SLs in post mortem AD brain tissues. For instance, specific changes in the ganglioside content have been detected in the brain of AD patients, although with regional variations [5–7]. While complex gangliosides (GT1b, GD1b, GD1a and GM1) appeared to be depleted, simple gangliosides, especially GM3, were consistently

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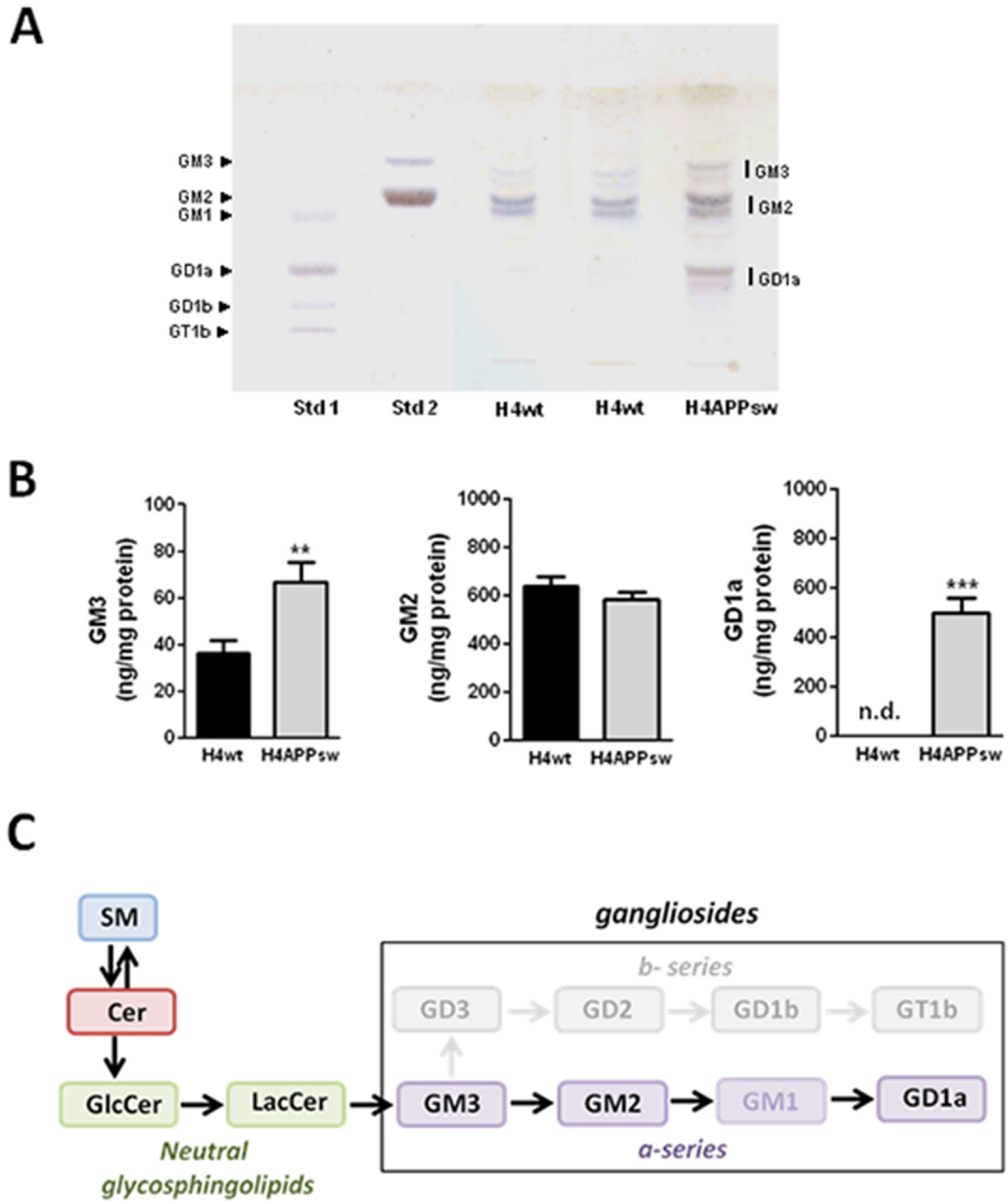

Fig. 1. Ganglioside composition of wild-type and APPsw-transfected H4 cells. **(A)** Typical HPTLC profiles of gangliosides isolated from H4wt and H4APPsw cells. The equivalent of 0.8 mg of cellular protein was applied on each lane. Std1, ganglioside mixture from bovine brain consisting of GT1b, GD1b, GD1a and GM1; Std2, mixture of GM3 and GM2. **(B)** Levels of GM3, GM2 and GD1a isolated from H4wt and H4APPsw cells, respectively; n.d., not detectable. Values are the means ± SEM of 6–8 independent experiments. $^{**}p < 0.01$, $^{***}p < 0.001$ compared to the H4wt values, respectively. **(C)** Schematic drawing of the ganglioside biosynthesis. Cer, ceramides; GlcCer, glucosylceramides; LacCer, lactosylceramides; SM, sphingomyelins.

found to be increased. These alterations were more profound in brain tissues from severely affected AD patients. Since gangliosides showed a strong affinity for Aβ peptide [8], they could be involved in conformational changes of Aβ and the formation of toxic Aβ fibrils [9]. For this reason, ganglioside metabolism has been considered to be closely associated with AD pathogenesis [10].

In addition to gangliosides, other classes of SLs are altered during AD progression. Ceramide levels were found to be elevated in specific AD brain regions [11–14]. The most prominent changes appeared to be in very long chain C24:0 and C24:1 Cer species which tended to accumulate. In contrast, findings about SM level were less consistent since different studies found its content either unchanged [14], increased [11] or decreased [13,15]. Although there is increasing evidence linking these SL abnormalities to other AD-relevant features, in particular to APP processing [1,3], the precise mechanisms governing the involvement of these lipids remain unclear.

During the last few years, we and others showed that some of the lipidic changes found in human AD brain can be recapitulated in various transgenic AD mice [12,16–20], suggesting that these animal models may be appropriate for investigating some aspects of AD-connected lipid disturbance. However, to explore the mechanisms involved in AD pathology and also for screening potential therapies, cellular models may represent an interesting alternative