Sialic acid and its analogues as potential neuro anti-inflammatory therapeutic candidates for Alzheimer’s disease

Pazhani Sundaram*
Recombinant Technologies LLC, USA

Abstract
Post-translationally modified human β-amyloid (Aβ) is found to be a potent target for drug development. Implication of glycosylation, more particularly sialylation as identified with tyrosine at position ten (Y₁₀) in the Aβ appears to play a role in pathogenesis of Alzheimer’s disease. Sialylation facilitates Aβ interaction, internalization, and transport to the brain. It is therefore postulated that selective intervention with sialylation is a novel strategy to design drugs against Alzheimer’s disease and many other diseases where similar sialylation is involved. This commentary gives an overview of the impact of the observed sialylation on the structure of Aβ, which could play a role in the pathogenesis in Alzheimer’s disease.

Sialic acid derivatives with α₂-6 linkage and or α₂-8 specific linkage are hypothesized to be ideal drug candidates for AD.

Correspondence to: Pazhani Sundaram, Recombinant Technologies LLC, 1090 Meriden Waterbury Road, Suite 1 Cheshire, Connecticut 06410, USA; Tel: 203 271 3125, Fax: 203 271 3126; Email: contact@recombtech.com

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Glycosylation, a transient regulatory process

APP is best known as the precursor molecule whose proteolysis generates Aβ, a polypeptide containing 37 to 42 amino acid residues whose amyloid fibrillar form is the primary component of amyloid plaques found in the brains of AD patients. APP including Aβ undergoes extensive post-translational modifications including glycosylation, phosphorylation, sialylation, and tyrosine sulfation, as well as many types of proteolytic processing to generate peptide fragments with post-translational modifications [5].

Glycosylation is one of the post-translational modifications that occur in the Aβ portion in APP [6]. A significant correlation between disease states and glycosylation pattern on human proteins has been discussed in the literature [7]. The post-translational modifications including glycosylation are shown in Figure 1.

Glycosylation patterns, including the glycosidic linkage, are considerably altered during disease states. Depending upon the disease state, a specific set of glycosylation enzymes is either up- or down-regulated, which results in the synthesis of the same protein with different types of oligosaccharide and/or with different types of glycosidic linkages [8]. In AD subjects, Aβ, tyrosine at position 10 (Y10) is O-glycosylated. The different glycoforms such as mono-, di-, and tri-sialylated glycoforms are predominantly found to be associated with the site [9].

Biological functions of the N- and O-linked glycosylation are not fully understood. Differences in glycosylation and particularly sialylation create multiple isoforms of Aβ in humans [9]. Aβ isoforms in AD subjects are significantly different and the level of sialylation is found to be significantly higher (~2.5 times) in AD subjects compared to healthy humans [9]. A striking feature observed in cerebrospinal fluid (CSF) of AD subjects is that the amino acid tyrosine in the tenth position on Aβ (Y10) is O-glycosylated with mono-, bi-, and tri-sialic acids as shown below in Figure 2.

Interestingly, they are predominantly in the bi-sialylated glycoform. Though the glycosidic linkage of the bi-sialic acids chain associated with Y10 remains unknown, the bi-sialylated terminals are likely to be linked to each other through α-2,8 linkage. In human brain proteins, α-2,8 linked sialic acids have been found predominantly. For instance, neural cell adhesion molecule (NCAM), and synaptic cell adhesion molecule 1 (SynCAM1) are displayed with α-2,8 linked poly sialic acids (PSA; 3, 4) [10]. In AD subjects, the sialylated structures including lactone

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such modification is expected to reduce the cross-linking and fibril formation that are the hallmark of AD and thus provides a novel strategy to develop new drugs against Aβ and ameliorate AD and many other diseases [19]. The in-silico analysis with sialyllactose, a sialic acid analogue reaffirms this postulation. Therefore, sialyllactose, its derivatives and other sialic acid containing derivatives provide suitable drug candidates to treat AD.

In the 3D structure, Aβ N-terminal region (1-16), as well as amino acids region 26-30, are found to be flexible regions. These flexible regions are involved in inter and intra-amyloid interaction. Figure 3 shows intra-amyloid interactions. Without being held to theory, it is postulated that sialic acid present at Y10 in combination with or without S8 phosphorylation facilitates Aβ interaction, internalization, and transport into the brain.

The P13 region of the Aβ with amino acids (1-17) is not implicated in AD pathogenesis, whereas the Aβ isoforms N-terminal region comprising Y10 may be associated with AD pathogenesis. Thus, the Aβ N-terminal amino acid region 1-16 is considered critical for disease pathogenesis, and therefore is identified as potent target for drug development. Post-translational modifications such as sialylation and phosphorylation create negative charge and influence the pathological properties of Aβ. The negative charge may facilitate Aβ transport across the blood brain barrier.

There appears a sialic acid binding site in Aβ and the N-terminal region 1-11 including Y10 is critical for sialic acid binding. Thus, selective interference of sialic acid binding is expected to interfere with the Aβ interaction, internalization, and transport into the brain. For example, sialyllactose, a sialic acid containing oligosaccharide selectively binds Aβ and will interfere with Y10 mediated transport and plaque formation. Figure 4 shows α2-3 and α2-6 linked sialyllactose. In silico study confirms that these two oligosaccharides are possible drug candidates and can selectively interfere with loop formation and inter- and intra-amyloid cross-linking and subsequent plaque formation. Thus, a 2-3 and a 2-6 linked sialyllactose and n-acetylneuraminic acid (NeuAc) are considered as potential drug candidates.

The sialic acid linkage determines the positive or negative biological properties in humans. For instance, α2-3 linked sialic acid is involved in inflammation while the α2-6 linked sialic acid is involved in anti-inflammation [20]. Thus, without being held to theory, it is believed that the most favorable drug candidate is α2-6 linked sialic acid analogues and or their derivatives. In AD subjects, there appear bi-and tri-sialic acids with or without lactone formation. Sialic acids are linked to the core saccharide or to the terminal sialic acid with α2-8 linkage. Since the AD subjects generate Aβ with α2-8 linkage, the drug candidates may be designed with such α2-8 linkage to effectively inhibit glycosylated Aβs in AD. Additionally, lactone formation occurs likely due to acidification of sialic acid at inflammation sites. The drug candidate with lactone will also be potent in interfering with glycosylated Aβ (Figure 5).

Conclusion

It is very plausible that sialylated Aβ, such as O- glycosylation linked to Y10 as described previously could be effective targets to developing candidates that could inhibit Aβ-induced cytotoxicity. Our laboratory is currently screening and testing several such compounds for AD treatment.

Competing interests

None

Figure 3. Y10 mediated loop formation and cross-linking between intra- Aβ interactions

Figure 4. α2-3 and α2-6 linked sialic acid drug candidates

Figure 5. α2-8 linked Sialic acid drug candidate. (Polysialic acid)

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