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# O-GlcNAcylation increases non-amyloidogenic processing of the amyloid- $\beta$ precursor protein (APP)

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## Background

The amyloid- $\beta$  precursor protein (APP) has been extensively studied, due to its role in Alzheimer's disease (AD). Sequential proteolytic processing of APP, catalyzed by  $\beta$ - and  $\gamma$ -secretase, generates the neurotoxic peptide amyloid- $\beta$  (A $\beta$ ), which accumulates in the brain and cause progressive neurodegeneration. However, APP is mainly processed through another pathway, where APP is cleaved by  $\alpha$ - and  $\gamma$ -secretase, generating the secreted sAPP $\alpha$  fragment. Stimulation of  $\alpha$ -secretase processing of APP constitutes an important therapeutical strategy, not only since it precludes the formation of A $\beta$ , but also because the sAPP $\alpha$  fragment has been shown to have neuroprotective properties [1]. APP was the first plasma membrane protein shown to be O-GlcNAcylated [2], a dynamic post-translational modification involving the attachment of  $\beta$ -N-acetylglucosamine (GlcNAc) catalyzed by O-GlcNAc transferase and O-GlcNAcase. However, the consequences of APP O-GlcNAcylation have so far not been investigated.

## Material and methods

We have used siRNA and pharmacological inhibitors directed against O-GlcNAcase and O-GlcNAc transferase to determine these enzymes regulate O-GlcNAcylation of APP. O-GlcNAcylated proteins were immunoprecipitated from cell-lysates using an O-GlcNAc antibody, and APP was then detected by western blot using. The levels of sAPP $\alpha$  and A $\beta$  in the cell medium were analyzed using western blot and ELISA. The studies were mainly performed in human SH-SY5Y neuroblastoma cells, but other cell-lines were used as well as a comparison.

## Results

Here, we show that O-GlcNAcase and O-GlcNAc transferase regulate the level of APP that is immunoprecipitated with O-GlcNAc antibody in human neuroblastoma SH-SY5Y cells. We also show that O-GlcNAcylation increases  $\alpha$ -secretase processing, resulting in increased levels of the neuroprotective sAPP $\alpha$  fragment and decreased A $\beta$  secretion. The proteolytic processing of the APP homologue, APLP2, remained unchanged in response to increased O-GlcNAcylation. Furthermore, the effect of O-GlcNAcylation on APP processing seems to be specific for neuron-like cells, since the levels of sAPP $\alpha$  from the human embryonic kidney cell-line HEK293 remains unchanged in response to inhibition of O-GlcNAcase, whereas the neuroblastoma cell-line SK-N-AS show increased sAPP $\alpha$  levels, but not to the same extent as in SH-SY5Y cells.

## Conclusions

We conclude that increased O-GlcNAcylation selectively affects APP processing in neuro-like cells. Our results implicate O-GlcNAcylation as a potential therapeutic target for Alzheimer's disease

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## References

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