EFFECTS OF GDNF AND OVEREXPRESSED BACE ON APP PROCESSING IN LUHMES CELLS AS HUMAN NEURONAL MODEL OF ALZHEIMER’S DISEASE

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Introduction: Alzheimer’s disease (AD) exists most commonly as sporadic form without genetic background, where particularly the level/activity of β-secretase (BACE) is elevated. Investigations on this AD type with the currently available in vitro systems are often difficult to perform due to limited cell supply, lack of neuronal properties, etc. As new approach, we here describe the usage of human neurons, differentiated from the conditionally-immortalized and non-transformed cell line LUHMES.

Aims: We evaluated the LUHMES cells regarding the endogenous expression and interaction of AD-relevant proteins and as model of sporadic AD with exogenous BACE expression.

Methods: We applied state-of-the-art methods like immunochemistry, qPCR, ELISA and lentiviral transduction.

Results: We found that levels of the amyloid precursor protein (APP), BACE and γ-secretase increased during the differentiation of LUHMES cells, leading to an enhanced processing of APP into extracellularly measurable sAPPβ and Aβ. This enhancement was to a great extent dependent on the presence of glial cell derived neurotrophic factor (GDNF) in the culture medium and could be stimulated or abolished within 24 hours by addition or withdrawal of GDNF. Stable LUHMES lines, overexpressing BACE above a certain threshold, surprisingly generated less Aβ than wildtype cells despite increased β-cleavage of APP. Treatment with moderate concentrations of BACE inhibitors led to an unexpected rise in Aβ.

Conclusions: In summary, our studies suggest that neuroprotective factors and pharmacological treatments might also have adverse effects regarding Aβ generation, and that the LUHMES system is well suited to study these effects on a human neuronal background.