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Evidence-based modeling of mode-of-action for functional ingredients influencing Alzheimer's disease through neurotrophin pathway

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ABSTRACT

Background: Brain-derived neurotrophic factor (BDNF) is the most widely expressed member of the neurotrophin family in the human brain and is crucially involved in the development of neural circuits, modulation of synaptic plasticity, and regulation of cognitive functions, including learning and memory. Many studies have shown the association of altered BDNF levels with neurodegenerative and neuropsychiatric disorders. However, BDNF is not able to cross the blood-brain barrier and, thus, its delivery to the nervous system is a challenge. Therefore, functional diets with the ability to induce production of BDNF in the brain may offer an alternative route. The objective of this study was three-fold: first, to find out diets that are causally linked to the agonistic activity of BDNF in the neurotrophin signaling pathway; second and mainly, to investigate mode-of-action of these functional diets through systems-based mechanistic modeling in the context of Alzheimer's disease; and third, to demonstrate the proof-of-concept application of systems biology methods, that are well established in the pharmaceutical sector, to the emerging field of functional food.

Methods: In the first step, two cause-and-effect models of BDNF signaling in two states, i.e. normal state and Alzheimer's disease state, were constructed using published knowledge in scientific literature and pathway databases. A "differential model analysis" between the two states was performed by which mechanistic mode-of-action of BDNF in neurotrophin signaling pathway could be explained with a high molecular resolution in both normal and disease states. The BDNF mode-of-action model was further validated using the "biomarker-guided validation" approach. In the second step, scientific evidence on the effect of various functional diets on BDNF levels and BDNF-related biological processes or outcomes was harvested from biomedical literature using a disease-specific semantic search. This information was then added to the mechanistic model of BDNF mode-of-action and used to substantiate the mode-of-action model.

Results: The differential model analysis resulted in a mechanistic mode-of-action model for the effector BDNF signaling pathway through NTRK receptors (Neurotrophic tyrosine kinase

receptor type 2) in neurons. The model revealed an amyloid-mediated neurotrophin switch mechanism by which the amyloid-beta protein competitively blocks BDNF-NTRK2 downstream signaling under Alzheimer's conditions, thereby "switching" the entire pathway from its normal state with neuroprotective effect to the disease state with a strong push towards neuron apoptosis. This hypothetical switch mechanism was validated by expressed biomarkers as well as empirical data obtained from experimentation of BDNF mimetics in animal models. Several functional diets were found in the literature that showed agonistic effects on the effector BDNF pathway. These effects are exerted through increased levels of BDNF and subsequently, activating the BDNF survival pathway, which leads to similar observations that have been made with BDNF mimetics in animal models.

Conclusions: To our knowledge, this is the first study to investigate mode-of-action of functional foods using systems-based modeling approaches. Moreover, such models can answer the question how functional diets can possibly act at the molecular level and interfere with the disease mechanism. Using scientific evidence supporting such models, there is a possibility to introduce new functional formulations by combining functional ingredients of these diets.

Keywords: evidence-based modeling, mode-of-action, functional ingredient, BDNF, Alzheimer's disease