PACAP/VIP Glycopeptide Agonists as Neuroprotective Therapies for Parkinsons Disease

https://www.neurodegenerationresearch.eu/survey/pacap-vip-glycopeptide-agonists-as-neuroprotective-therapies-for-parkinsons-disease/

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Country

USA

Title of project or programme

PACAP/VIP Glycopeptide Agonists as Neuroprotective Therapies for Parkinsons Disease

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,864,181.65

Start date of award

30/09/2015

Total duration of award in years

4

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

pituitary adenylate cyclase activating polypeptide, Vasoactive Intestinal Peptide, Glycopeptides, neurorestoration, PACAP27

Research Abstract

? DESCRIPTION (provided by applicant): Parkinson’s disease (PD) is the 2nd most common neurodegenerative disorder, affecting over 1 million people in the US. PD causes difficulties with movements such as walking, writing, and speaking that occur because of deficits in the chemical dopamine in the brain due to dopaminergic neuron death. Current therapies for PD only treat the symptoms and do not reverse underlying disease processes that cause dopamine-producing brain cells to die. This situation has led to widespread interest in new strategies of neuroprotection or neurorestoration. The most promising approaches to modifying the disease process in the laboratory have relied on endogenous brain chemicals known as “”growth factors.”” Several growth factors have demonstrated the ability to reverse the disease process in animal models of PD. A few of these growth factors have shown sufficient promise that they have been tested in clinical trials in humans with PD. One promising set of such growth factors are the peptide “”secretins”” Vasoactive Intestinal Peptide (VIP) and Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP), which play important roles in neuronal survival, neuroprotection, inflammation and immunomodulation. PACAP is protective against the loss of dopaminergic neurons in rodent models of PD, but only after being injected directly into the brain. We propose to circumvent this difficulty by creating PACAP/VIP glycopeptides, which are surfactants, possess extended half-lives in vivo, and can efficiently cross the blood-brain barrier (BBB). We have developed a new technology platform to develop these glycopeptide analogues that show increased stability, maintain potent binding and efficacy at the desired receptor(s), and that penetrate the BBB. We will synthesize a series of novel glycopeptides based on PACAP and VIP, screen for activity at the PAC1, VPAC1 and VPAC2 receptors expressed in CHO cells, and test the most promising compounds in animal models of PD for neuroprotective and neurorestorative activity after systemic administration. We will further refine our drug development by “”shotgun”” microdialysis to efficiently quantify brain levels of our drugs over time, allowing direct measurement of drug stability in vivo. This is accomplished by multiple collision-induced fragmentation mass spectroscopy (MSn). In this way we hope to produce one or more drug candidates for further development, ultimately leading to approval for human use and clinical application in the treatment of PD.

Lay Summary

PUBLIC HEALTH RELEVANCE: Parkinson’s disease (PD) is the 2nd most common neurodegenerative disease in the US. The incorporation of carbohydrates into endogenous peptide neurotransmitters (neuromodulators, neurohormones) provides new glycopeptide therapeutics with enhanced properties for drug design, and which have activities similar to the endogenous peptides. Microdialysis methods combined with MS measurement of BBB penetration will permit the development of glycopeptide drugs that are active in the CNS after peripheral administration.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Parkinson's disease & PD-related disorders

Years:
2016

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N/A

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