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Master's Thesis

to earn the

Master of Science in Molecular Medicine

Characterizing the Role of a GLUT1 Mutation in GLUT1-deficiency Syndrome

Presented by

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Abstract

As the primary glucose transporter across the endothelial cells of the blood-brain barrier, the GLUT1 protein plays a central role in the regulation of brain energy metabolism and maintenance of central nervous system homeostasis [1]. GLUT1 has 492 amino acids, many of which have been reported to be susceptible to missense mutation that causes GLUT1-deficiency syndrome, a genetic disease characterized by impairment of glucose transport into the brain [1, 2]. One of the clinically identified missense mutations is a Pro485-to-Leu substitution (GLUT1P485L) located in the cytoplasmic carboxyl tail of GLUT1 [1, 3].

Contents

List of Figures

List of Tables

Introduction

As the primary glucose transporter across the endothelial cells of the blood-brain barrier, the GLUT1 protein plays a central role in the regulation of brain energy metabolism and maintenance of central nervous system homeostasis [1]. Human GLUT1 has 492 amino acids, many of which have been reported to be susceptible to missense mutation that causes GLUT1 deficiency syndrome (G1DS), a genetic disease characterized by hypoglycorrhachia (low glucose concentration in the cerebrospinal fluid), seizures and delayed neurological development [1, 2]. GLUT1 mutations in G1DS patients impair glucose transport into the brain across the blood-brain barrier, resulting in the disease phenotypes.

One of the clinically identified missense mutations in GLUT1 is a Pro485-to-Leu substitution ($GLUT1^{P485L}$) located in the cytoplasmic carboxyl tail [1, 3]. However, the molecular mechanisms by which the mutation causes the disease remains elusive. In a previous proteomic screen study to investigate the impact of disease-causing mutations, the $GLUT1^{P485L}$ mutation was found to lead to an increased binding of clathrins. Sequence analysis revealed that the mutation creates a dileucine motif known to mediate clathrin-dependent endocytosis ([D/E]XXXL[L/I]) in the cytoplasmic tail [4, 5].

Based on these findings, it is hypothesized that the $GLUT1^{P485L}$ mutation causes clathrin-mediated endocytosis and possibly subsequent degradation of GLUT1, leading to the development of GLUT1-deficiency syndrome. The hypothesis will be further investigated in this master thesis.

Materials and methods

List of Abbreviations

LAH **L**ist **A**bbreviations **H**ere
WSF **W**hat (it) **S**tands **F**or

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