

DOCTORAL THESIS

Therapeutic effect of cyanines in an alzheimer's disease model in vitro and in vivo

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Date of Award:
2020

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ABSTRACT

Alzheimer's disease is the most common neurodegenerative disease in the elderly. Senile plaques and nerve cells in the fiber entanglement [neurofibrillary tangle (NFT)] are the significant pathological features. Currently, clinical drugs cannot effectively treat AD and reverse its pathogenesis. Therefore, it is of great importance to research and development of new AD therapy drugs. Carbazole-based cyanine is a type of synthetic small molecule compound that shares a common base with different functional groups; for example, SLOH, SLM, and SLCOOH. They exhibited selective binding to A β peptides and showed strong inhibition of A β peptide aggregation.

It was found that one of the cyanines, SLOH, could significantly improve the cognitive ability of 3 \times Tg-AD mice treated for 40 days from the age of 4 months. *In vivo*, SLOH reduced A β levels and decreased hyperphosphorylation of tau both in the hippocampus and cortex by downregulating the activity of Akt/GSK3 β and protein phosphatase 2A, SLOH can also activate the calcium pathway through activating CAMKII and cAMP-response element-binding (CREB).

SLM significantly improved cognitive deficits in AD mice both in AD mice aged 4 months and 8 months. Both oligomeric A β and phosphorylated tau were decreased, and this was due to the activation of autophagic flux.

The other cyanine compound SLCOOH also exhibited significant improvement in the cognitive ability of 4-month 3 \times Tg-AD mice after two months of treatment. There was significantly reduced A β deposition, decreased total tau, and reduced tau hyperphosphorylation by inhibiting the activities of glycogen synthase kinase-3 β in 4-month 3 \times Tg-AD mice. SLCOOH treatment cleared A β

and tau by upregulating the autophagy pathway, which inhibited the activity of mTOR/p70S6K. Moreover, SLCOOH structurally restored synapses and spines and regulated the Ca^{2+} /CaMKII/CREB signaling pathway, leading to enhanced synaptic plasticity and cognitive ability in AD mice. Furthermore, we found SLCOOH ameliorated synaptic deficits by downregulating N-methyl-D-aspartate receptors (NMDAR), thereby modulating intercellular calcium ion (Ca^{2+}) loading and upregulating neuronal calcium dependent signaling.

Thus, our results demonstrated that these three carbazole-based cyanines mitigated cognitive decline by targeting $\text{A}\beta$ and tau pathology in 3 \times Tg-AD mice. Those data strongly support that these three carbazole-based cyanines as a potent therapy for AD.

TABLE OF CONTENTS

DECLARATION	i
ABSTRACT.....	ii
ACKNOWLEDGEMENTS.....	iv
TABLE OF CONTENTS	v
LIST OF FIGURES	viii
LIST OF ABBREVIATION.....	xiii
CHAPTER 1. INTRODUCTION	1
1.1 Alzheimer’s disease	1
1.2 The pathogenesis of AD.....	2
Genetic studies in AD.....	2
The amyloid cascade hypothesis	4
The tau hypothesis.....	5
Autophagy dysfunction.....	8
Synapses in Alzheimer’s disease	11
1.3 Drug Development for Alzheimer's Disease.....	16
1.3.1 Therapies targeted at β -amyloid	16
1.3.2 Therapies Targeted at Tau	18
1.3.3 Drugs targeting the cholinergic system.....	19
1.4 Carbazole-based cyanine	20
1.4.1 SLOH and SLM.....	20
1.4.2 SLCOOH	21
CHAPTER 2. METHODS AND MATERIALS.....	22
2.1 Animals	22
Animal models.....	22
Treatment of animal models	22
2.2 Behavioral test	23
Morris water maze (MWM) test.....	23
T-maze	25
2.3 Cell culture.....	26
Primary neuron culture	26
Cell line culture	27
2.4 Gel electrophoresis and immunoblotting.....	28

2.5 Immuno-staining	30
Immunofluorescent staining	30
Immunohistochemical staining.....	30
2.6 Electrophysiology	31
2.7 Transmission electron microscope (TEM).....	32
2.8 Golgi staining.....	33
2.9 Tandem Mass Tag (TMT)	35
2.10 Statistics	36
CHAPTER 3. RESULTS AND DISCUSSION	37
3.1 SLOH.....	37
3.1.1 SLOH inhibited A β generation by reducing BACE1 in primary neurons	37
3.1.2 SLOH decreased apoptosis level and improved synaptic damage by regulating Ca ²⁺ /CaMKII/CREB in AD neurons	37
3.1.3 SLOH revised cognitive deficits of 3 \times Tg-AD mice.....	41
3.1.4 SLOH reduced the level of A β , but not APP and BACE1 proteins	43
3.1.5 SLOH reduced Tau and its hyperphosphorylation.....	48
3.1.6 SLOH decreased phosphorylated tau by activating Akt and PP2A	48
3.1.7 SLOH upregulated CAMKII and CREB to activate the calcium pathway <i>in vivo</i> .	54
Discussion.....	57
3.2 SLM	61
3.2.1 SLM in 4-month of 3 \times Tg-AD mice.....	61
3.2.2 SLM in 8-month of 3 \times Tg-AD mice.....	72
Discussion.....	76
3.3 SLCOOH	78
3.3.1 SLCOOH restored cognitive impairment of 3 \times Tg-AD mice	78
3.3.2 SLCOOH reduced the A β level of AD mice.....	80
3.3.3 SLCOOH reduced tau and its phosphorylation in AD mice model	82
3.3.4 SLCOOH reduced tau phosphorylation via inhibiting activity of GSK3 β but not PP2A in AD mice model.....	85
3.3.5 SLCOOH treatment promoted clearance by upregulating the autophagic pathway but had no influence on the ubiquitination pathway <i>in vivo</i>	87
3.3.6 SLCOOH treatment improved the structural plasticity of synapses and dendritic spines <i>in vivo</i>	90
3.3.7 SLCOOH treatment enhanced synaptic plasticity by activating the postsynaptic signaling pathway in 3 \times Tg-AD mice	98
3.3.8 SLCOOH treatment reversed the calcium overload via downregulating NMDA	

receptors in 3× Tg-AD mice.....	102
3.3.9 Effect of SLCOOH on the proteome of the hippocampus in AD mice model	105
Discussion.....	114
CHAPTER 4. CONCLUSION	122
REFERENCE.....	123
LIST OF PUBLICATION.....	151
CURRICULUM VITAE	152