

## DOCTORAL THESIS

### Glutamate antagonism as a potential treatment of Parkinson's Disease: a study in a rat model

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Glutamate Antagonism as a Potential Treatment of  
Parkinson's Disease: A Study in a Rat Model

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## Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disease and the patients suffer serious motor disorder. Degeneration of dopaminergic neurons is the cause of PD. Glutamate excitotoxicity is known to contribute to the progressive dopaminergic denervation and it is one main cause of motor symptoms of PD. Attenuation of glutamate excitotoxicity may be a valuable mean in both treatment of motor symptoms and neuroprotection of dopaminergic neurons.

In the present study, two different strategies were employed to attenuate glutamate excitotoxicity by the reduction of glutamate receptor, NMDA receptor, overstimulation and the removal of synaptically released glutamate by the upregulation of glutamate transporter. First, a single dose of a small interfering RNA (siRNA) that targets N-methyl-D-aspartate receptor one (NR1) (siRNA-NR1) was employed to reduce the protein expression of functional NMDA receptor in the striatum. After administration of the siRNA-NR1 into normal rats, the NR1 protein was significantly down-regulated in both immunofluorescence experiment and Western blot analysis. After the application of the siRNA-NR1 to the 6-hydroxydopamine- (6-OHDA)-lesioned rat, an animal model of PD, the grip strength and the number of contralateral rotation, which represented motor deficits, were found to be significantly reduced. The siRNA-NR1 was also found to decline the reduction of tyrosine-hydroxylase (TH)-positive cell ratio (lesion vs nonlesion) in SN of the 6-OHDA-lesioned rats.

Secondly, the effects of a neuroprotective antibiotic, ceftriaxone, was examined. Seven-day treatment of ceftriaxone was applied to the rats before the 6-OHDA lesion and five post-lesion time points were selected (day 2, 4, 6, 8 and 10) for analyses. By behavioral tests, ceftriaxone treatments were found to decrease both the grip strength and numbers of contralateral rotations in the 6-OHDA-lesioned rats. In addition, the reduction of tyrosine-hydroxylase (TH)-positive cell ratio (lesion vs nonlesion) in SN of the 6-OHDA-lesioned rats with ceftriaxone treatment was found to be decreased. Application of ceftriaxone enhanced the immunoreactivity and protein expression of GLT1. GLT1 is a major glial glutamate transporter and is responsible for re-cycling of synaptic glutamate. These results indicate that the up-regulation of GLT1 protein by the application of ceftriaxone inert neuroprotection of dopaminergic neurons.

In addition, co-administration of ceftriaxone and siRNA-NR1 was also applied in the 6-OHDA-lesioned rats. Significant reductions in both grip strength and the number of rotation were found in the co-treated animal groups when compared to the saline-treated animals. The degree of neuroprotection was similar between co-treatment and ceftriaxone treatment groups.

In conclusion, the present results as a whole have provided that glutamate antagonism

is beneficial to both amelioration of motor symptoms and neuroprotection of dopaminergic neurons. The present data can provide a basis for future development of non-dopaminergic therapies in treatment of PD.

## Table of Contents

|   |     |
|---|-----|
| <b>Declaration</b>                                      | i   |
| <b>Abstract</b>   | ii  |
| <b>Acknowledgements</b>                                 | iv  |
| <b>Table of Contents</b>                                | v   |
| <b>List of Figures</b>                                  | x   |
| <b>List of Abbreviations</b>                            | xiv |
| <b>Chapter 1 Background and Literature Review</b>       | 1   |
| 1.1 Parkinson's Disease                                 | 1   |
| 1.2 Basal Ganglia                                       | 2   |
| 1.2.1 Anatomical Structure of Basal Ganglia             | 2   |
| 1.2.2 Features of Each Regions Within the Basal Ganglia | 3   |
| 1.2.2.1 Striatum (Str)                                  | 3   |
| 1.2.2.2 Golbus Pallidus (GP)                            | 4   |
| 1.2.2.3 Subthalamic Nucleus (STN)                       | 5   |
| 1.2.2.4 Substantia Nigra (SN)                           | 6   |
| 1.2.3 Functions of the Basal Ganglia                    | 7   |
| 1.2.4 Microcircuitry of the Basal Ganglia               | 7   |
| 1.3 Etiology of PD                                      | 9   |
| 1.4 Glutamate   | 10  |
| 1.5 Glutamate Receptors                                 | 11  |
| 1.5.1 Iontropic Glutamate Receptors                     | 12  |
| 1.5.2 The Mechanisms of Iontropic Glutamate Receptors   | 13  |
| 1.6 Glutamate Transporters                              | 14  |
| 1.7 Glutamate Excitotoxicity                            | 15  |

|   |           |
|---|-----------|
| 1.8 Therapeutical Trend   | 16        |
| 1.9 Animal Model of PD  | 17        |
| 1.10 Objectives of the Thesis   | 19        |
| <b>Chapter 2 Materials and Methods</b>  | <b>23</b> |
| 2.1 Animals   | 23        |
| 2.2 Six Hydroxydopamine Lesion  | 23        |
| 2.2.1 MFB Lesion  | 24        |
| 2.2.2 Striatal Lesion   | 24        |
| 2.3 Apomorphine-induced Rotation Test   | 25        |
| 2.4 Grasping Test   | 25        |
| 2.5 siRNA-NR1 Application   | 26        |
| 2.6 Ceftriaxone Pretreatment  | 26        |
| 2.7 Tissue Preparation  | 26        |
| 2.8 Immunocytochemical Staining   | 27        |
| 2.8.1 Single Immunoreactivity for Immunoperoxidase  | 27        |
| 2.8.2.1 Immunofluorescence Staining   | 28        |
| 2.8.2.2 Processing for Laser Scan Confocal Microscopy   | 29        |
| 2.9 Western Blotting  | 29        |
| 2.10 Semi-quantitative Analysis   | 31        |
| <b>Chapter 3 Effects of Administration of siRNA-NR1 in<br/>Six-hydroxydopamine-lesioned Rat</b> | <b>32</b> |
| 3.1 Introduction  | 32        |
| 3.1.1. Striatum as the Target Region for Treatment of PD  | 32        |
| 3.1.2 NMDA Receptor as the target for Treatment   | 33        |
| 3.1.3 Application of siRNA  | 35        |

|   |           |
|---|-----------|
| 3.1.4 Mechanism of siRNA in the Down-regulation of Protein Expression   | 36        |
| 3.2 Objectives  | 37        |
| 3.3 Materials and Methods   | 38        |
| 3.4 Results   | 39        |
| 3.4.1.1 The Effect of siRNA-NR1 on Rotation Tests   | 39        |
| 3.4.1.2 Effects of siRNA-NR1 on Motor Strength  | 40        |
| 3.4.2 Change in TH Immunoreactivity After siRNA-NR1 Administration  | 40        |
| 3.4.3 Change in NR1 Immunoreactivity After siRNA-NR1 Administration in Normal Animals   | 41        |
| 3.4.3.1 Change in NR1 Immunoreactivity After siRNA-NR1 Administration in 6-OHDA-lesioned Rats After siRNA-NR1 Treatment             | 41        |
| 3.4.4 NR1 Protein Expression in Normal Rats After siRNA-NR1 Treatments  | 42        |
| 3.4.5 NR1 Protein Expression in Lesion Animals After siRNA-NR1 Treatments   | 42        |
| 3.5 Discussion  | 43        |
| 3.5.1 siRNA Affects Glutamatergic Transmission  | 43        |
| 3.5.2 siRNA Affects NMDA Receptor Functions   | 44        |
| 3.5.3 siRNA Brings Neuroprotection of Dopaminergic Neurons  | 47        |
| 3.5.4 Glutamate and Dopamine Interactions   | 47        |
| 3.5.5 Unleash the Power of siRNA Therapy  | 48        |
| <b>Chapter 4 Ameliorations of Motor Symptoms and Neuroprotective Effects of Ceftriaxone in the Six-hydroxydopamine-lesioned Rat</b> | <b>69</b> |
| 4.1 Introduction  | 69        |
| 4.2 Objectives  | 72        |
| 4.3 Materials and Methods   | 73        |

|  |     |
|--|-----|
| 4.4 Results  | 74  |
| 4.4.1 Effects of Ceftriaxone Pretreatment on Muscular Rigidity and<br>Contralateral Rotation in 6-OHDA-lesioned Rats                 | 74  |
| 4.4.2 Tyrosine Hydroxylase Labeling in the Str and SN  | 75  |
| 4.4.3 Effects of Ceftriaxone Treatments on GLT1 Immunoreactivity   | 75  |
| 4.4.4 Changes in the Protein Expression of TH and GLT1 After<br>Ceftriaxone Treatment  | 76  |
| 4.5 Discussion   | 77  |
| 4.5.1 GLT1 Levels and Neuroprotection  | 77  |
| 4.5.2 Up-regulation of GLT1  | 78  |
| 4.5.3 GLT1 Protein Level and Activity  | 80  |
| 4.5.4 Possible Mechanisms of GLT1 Up-regulation  | 80  |
| 4.5.5 Ceftriaxone May Mediate Other Forms of Neuroprotective Effects   | 82  |
| 4.5.6 Applicability of Ceftriaxone   | 82  |
| <b>Chapter 5 Co-administration of siRNA-NR1 and Ceftriaxone in the<br/>Six-hydroxydopamine-lesioned Rat: Synergism in Treatment?</b> | 102 |
| 5.1 Introduction   | 102 |
| 5.2 Objectives   | 104 |
| 5.3 Materials and Methods  | 105 |
| 5.4 Results  | 106 |
| 5.4.1 Co-administrations of siRNA-NR1 and Ceftriaxone on Motor<br>Behaviors  | 106 |
| 5.4.2 Neuroprotective Effect on the TH-positive Neurons in the SN  | 106 |
| 5.4.3 Changes in NR1 and GLT1 Immunoreactivity After<br>Co-administration  | 107 |



|   |     |
|---|-----|
| 5.4.3.1 Down-regulation of NR1 After Administration of siRNA-NR1  | 107 |
| 5.4.3.2 Up-regulation of GLT1 After 7 days Administration of Ceftriaxone  | 107 |
| 5.5 Discussion  | 108 |
| 5.5.1 Co-administration of siRNA-NR1 and Ceftriaxone Offers Synergism<br>in Amelioration of Motor Symptoms and Neuroprotection? | 108 |
| 5.5.2 Interaction Between NMDA Receptors and GLT1 Protein Expression  | 109 |
| 5.5.3 NMDA Receptor Activation and Glutamate Transporters   | 111 |
| <b>Chapter 6 Summary and Conclusion</b>   | 126 |
| 6.1 Introduction  | 126 |
| 6.2 Other Possible Targets for Glutamate Antagonism   | 126 |
| 6.3 The Present Results May Path Novel Drugs for Treatment of PD  | 127 |
| 6.4 Further Investigations  | 127 |
| 6.5 Conclusion  | 129 |
| <b>List of References</b>   | 130 |
| <b>Appendix I</b>   | 156 |
| <b>Appendix II</b>  | 157 |
| <b>Appendix III</b>   | 158 |
| <b>Curriculum Vitae</b>   | 162 |