Glutamate Level in Anterior Cingulate Gyrus of Patients with Early Psychosis before and after Electroconvulsive Therapy: A Magnetic Resonance Spectroscopy study

Thesis Submitted in partial fulfillment of the requirements of MD degree in Psychiatry

By
Dr. Mohammed Abd Al-Fattah Khalil
Assistant Lecturer of Psychiatry
Cairo University

Supervised by
Prof. Emad Hamdi Ghoz
Professor of Psychiatry
Cairo University

Prof. Samir Fouad Abo El-Magd
Professor of Psychiatry
Cairo University

Prof. Amany Ahmed Abdou
Professor of Psychiatry
Cairo University

Dr. Lamiaa Ibrahim Abd El-Rahman Metwally
Lecturer of Radiodiagnosis
Cairo University

Faculty of Medicine
Cairo University
2012
بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

"قَالُوا سُبْحَانَكَ
لا عِلْمٌ لَّنَا إِلَّآ مَا عَلِمْتَنَا
إِنَّكَ أَنْتَ الْعَلِيمُ السَّمِيعُ"

صدق الله العظيم

الأية 32 من سورة البقرة
Abstract

Objective: This study verified the relation between glutamate and psychosis together with the effect of electroconvulsive therapy (ECT) on anterior cingulate glutamate in patients with psychosis.

Method: 2 groups were compared in the study: 25 drug naïve patients with early psychotic episode (less than one year duration) and 25 healthy subjects as control. Glutamate was measured by magnetic resonance spectroscopy (MRS) in the anterior cingulate cortex (ACC) in the 2 groups. Patients were examined again after ECT by MRS. Patients were assessed by Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression (CGI) and the Global Assessment of Function (GAF). Cognitive functions were partially assessed by applying the Rey–Osterrieth Complex Figure Test (RCFT).

Results: Patients (before ECT) showed significantly lower glutamate levels than controls. Also patients before ECT showed significantly lower glutamate levels than after ECT. Only total PANSS scores showed statistically significant negative correlation with the glutamate level before ECT.

Conclusion: Glutamate level changes in psychosis and increases after ECT.

Key Words
Psychosis - glutamate - electroconvulsive therapy - magnetic resonance spectroscopy – anterior cingulate cortex.
Acknowledgment

I have the honor to present this work under the supervision of Prof. Emad Hamdi, Professor of psychiatry, Cairo University. Without his guidance and his creative thinking, I could never carry on doing this work.

I feel very grateful to Prof. Samir Abo El-Magd, Professor of psychiatry, Cairo University. His support, patience and guidance were the corner stone for completion of this work.

I am very proud to have Prof. Amany Abdou, professor of psychiatry, Cairo University, supervising this thesis. Without her sincere devotion this work couldn't be accomplished.

I am extremely obliged to Dr. Lamiaa Ibrahim, lecturer of radiodiagnosis, Cairo University, for her invaluable help and precious technical support in the practical part of this work.

I owe a lot to Dr. Sheref Gohar, assistant lecturer of psychiatry, Cairo University, for his precious help.

I am very grateful to the MRI staff in the radiodiagnosis department for their cooperation.

I would like to thank my colleagues, residents and nurse staff in psychiatry department, Cairo University for their effort to help and their patience with aggressive behavior of unmedicated patients.

I must thank all my patients and their families for their patience and time.

Finally yet importantly, I thank my parents and family for their invaluable care and unlimited support.
Index

- List of abbreviations.................................................................(6)
- List of tables..............................................................................(8)
- List of figures............................................................................(11)
- List of statistical charts...........................................................(12)
- Theoretical review....................................................................(13)
- Chapter I: The role of glutamate psychiatry.........................(15)
- Chapter II: Electroconvulsive Therapy (ECT), glutamate and psychosis.........................................................(44)
- Chapter III: Magnetic Resonance Spectroscopy (MRS): A tool for measuring central glutamate levels.................................................................(63)
- Chapter IV: Anterior Cingulate Cortex (ACC): An area for schizophrenia research........(85)

- Methodology............................................................................(98)
- Results....................................................................................(125)
- Discussion................................................................................(173)
- Summary................................................................................(196)
- Conclusions and future directions.................................(205)
- References..............................................................................(207)
- Appendices.............................................................................(235)
- Arabic summary......................................................................(243)
List of abbreviations

5HT: serotonin
ACC: anterior cingulate cortex
AMPA: quisqualate/α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ASC-T: alanine-serine-cysteine transporter
CGI: Clinical Global Impression
cho: choline
CSTC: cortico-striatal-thalamic-cortical
cr: creatine
DLPFC: dorsolateral prefrontal cortex
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition
EAAT: excitatory amino acid transporter
ECT: Electroconvulsive therapy
GABA: gamma amino butyric acid
GAF: Global Assessment of Function
Gln: glutamine
Glx: glutamate + glutamine
ICD 10: International classification of diseases, tenth edition
lac: lactate
LGICs: ligand-gated ion channels
MCI: mild cognitive impairment
mGluRs: metabotropic glutamate receptor
ml: myo-inositol
MRS: Magnetic Resonance Spectroscopy
NA: nucleus accumbens
NAA: N-acetylaspartate
NE: norepinephrine
NMDA: N-methyl-D-aspartate
PANSS: Positive and Negative Syndrome Scale
RCFT: Rey–Osterrieth Complex Figure Test
SCID: Structured Clinical Interview for DSM-IV
S.D.: standard deviation
SNAT: specific neutral amino acid transporter
VGICs: voltage-gated ion channel
VGLUT: Vesicular glutamate transporters
VTA: ventral tegmental area
List of statistical tables

Table (1): Comparison between ages of patients versus control group
Table (2): gender distribution in patients and controls.
Table (3): age difference between male and female patients.
Table (4): marital states of patients
Table (5): levels of education of patients
Table (6): differences in education between cases and controls.
Table (7): nature of occupation of patients
Table (8): diagnostic breakdown of patients according to DSM IV.
Table (9): diagnostic breakdown of patients according to ICD 10.
Table (10): frequency of different types of schizophrenia.
Table (11): shows frequency of family history
Table (12): baseline PANSS, CGI and GAF results
Table (13): post ECT PANSS, CGI and GAF results
Table (14): duration of illness (DUP)
Table (15): baseline RCFT results
Table (16): post ECT results of RCFT
Table (17): compares patients versus missed patients
Table (18): Glutamate level in anterior cingula patients (before ECT) versus controls regarding glutamate in anterior cingulate cortex
Table (19): Glutamate level in ACC of patients (after ECT) versus controls regarding glutamate in anterior cingulate cortex
Table (20): compares patients before ECT versus patients after ECT regarding glutamate
Table (21): glutamate and PANSS subscales, total PANSS, GAF and CGI
Table (22): correlations between changes in cingulate glutamate levels and changes in PANSS (total and subscales)
Table (23): correlation between age of patients and glutamate in ACC
Table (24): correlation between age of controls and glutamate in ACC
Table (25): male versus female patients before and after ECT as regard glutamate

Table (26): correlation between DUP and glutamate before ECT, glutamate after ECT and glutamate change

Table (27): correlation between glutamate before ECT and RCFT (copy, 3 min. recall and 30 min. recall) before ECT.

Table (28): correlation between glutamate change and RCFT (copy, 3 min. recall and 30 min. recall) changes.

Table (29): difference between before and after ECT regarding positive symptoms subscale in PANSS

Table (30): difference between before and after ECT regarding negative symptoms subscale in PANSS

Table (31): difference between before and after ECT regarding general psychopathology subscale in PANSS

Table (32): difference between before and after ECT regarding total PANSS

Table (33): difference between before and after ECT regarding RCFT (copy)

Table (34): difference between before and after ECT regarding RCFT (3 minutes recall)

Table (35): difference between before and after ECT regarding RCFT (30 minutes recall)

Table (36): differences between males and females regarding PANSS (total and subscales) before ECT.

Table (37): differences between males and females regarding PANSS (total and subscales) and CGI (global improvement and efficacy index) after ECT.

Table (38): differences between males and females regarding RCFT (copy, 3 min. and 30 min. recall) before and after ECT.

Table (39): differences between male and female patients regarding clinical and MRS changes following the ECT.
Table (40): correlation between ages of patients and severity of illness before ECT measured by PANSS (total and subscales), CGI and GAF
Table (41): Spearman correlation between ages of patients and severity of illness after ECT measured by PANSS (total and subscales).
Table (42): correlation between ages of patients and change in PANSS (total and subscales) caused by ECT.
Table (43): correlation between age of patients and RCFT (copy, 3 min. recall and 30 min. recall) before ECT.
Table (44): correlation between age of patients and RCFT (copy, 3 min. recall and 30 min. recall) after ECT and changes in RCFT caused by ECT.
Table (45): correlation between PANSS (total and subscales) and RCFT before ECT.
Table (46): correlation between changes of PANSS (total and subscales) and changes RCFT (three scales) after ECT.
Table (47): correlation between DUP and PANSS scores, CGI severity and GAF before ECT
Table (48): correlation between DUP and change in PANSS scores.
Table (49): correlation between DUP and RCFT scores before ECT & changes
List of figures

Figure (1): glutamate recycle and regeneration (part 1).
Figure (2): glutamate recycle and regeneration (part 2).
Figure (3): glutamate recycle and regeneration (part 3).
Figure (4): glutamate recycle and regeneration (part 4).
Figure (5): types of glutamate receptors.
Figure (6): ionotropic and metabotropic types of glutamate receptors.
Figure (7): NMDA and non NMDA ionotropic receptors.
Figure (8): glutamate tracts in the brain.
Figure (9): MRS curve.
Figure (10): MRS concentrations of particular metabolites marked by colour.
Figure (11): Anatomy of ACC.
Figure (12): The figure used in the RCFT.
Figure (13): The localization of the voxel.
List of statistical charts

Chart (1): gender distribution in patient group.
Chart (2): frequency of marital state of patients
Chart (3): levels of education of patients
Chart (4): nature of occupation of patients
Chart (5): diagnostic breakdown of patients according to DSM IV.
Chart (6): diagnostic breakdown of patients according to ICD 10
Chart (7): frequency of different type of schizophrenia.
Chart (8): pie charts shows frequency of family history
Chart (9): patients (before ECT) and controls regarding glutamate in ACC.
Chart (10): patients (after ECT) and controls regarding glutamate in ACC
Chart (11): patients before and after ECT as regard glutamate
Chart (12): correlation between glutamate and total PANSS before ECT.
Chart (13): comparison between male versus female patients before and after ECT as regard glutamate in ACC
Chart (14): comparison between patients before and after ECT regarding positive symptoms scale of PANSS
Chart (15): comparison between patients before and after ECT regarding negative symptoms scale of PANSS
Chart (16): comparison between patients before and after ECT regarding general psychopathology symptoms scale of PANSS
Chart (17): comparison between patients before and after ECT as regard total score of PANSS
Chart (18): comparison between patients before and after ECT regarding RCFT copy.
Chart (19): comparison between patients before and after ECT regarding RCFT 3 min. recall.
Chart (20): comparison between patients before and after ECT regarding RCFT 30 min. recall.
Theoretical Review
Introduction

This work aims at studying the relation between psychosis and glutamate together with the electroconvulsive therapy (ECT) effect on glutamate.

This review provides an updated theoretical background to the practical part of the thesis. These data would cover the main target neurotransmitter: glutamate, the therapeutic intervention: electroconvulsive therapy, the method of measuring the glutamate: magnetic resonance spectroscopy and the area in the brain that will be studied: anterior cingulate cortex

It includes four chapters that cover the following entities:

Chapter I: The role of glutamate in psychiatry

Chapter II: Electroconvulsive Therapy (ECT), glutamate and psychosis therapy

Chapter III: Magnetic Resonance Spectroscopy (MRS):

A tool for measuring central glutamate levels

Chapter IV: Anterior Cingulate Cortex (ACC):

An area for schizophrenia research
CHAPTER I

The role of glutamate in psychiatry
The role of glutamate in psychiatry

This chapter aims at providing a general idea about the neurotransmitter glutamate. It begins with an introduction about this neurotransmitter. Then it includes data about chemistry of the neurotransmitter and its synthesis and metabolism. Receptors and tracts of glutamate in the brain are also illustrated in this chapter. Then this chapter focuses on the role of glutamate in aetiology of different psychiatric disorders. A more detailed section discusses the glutamate theory of schizophrenia and possible treatments of psychosis that act on glutamate.

Introduction

Glutamate is the main excitatory neurotransmitter in the mammalian central nervous system (CNS) and sometimes is considered the "master switch" of the brain, since it can excite and turn on virtually all CNS neurons. The synthesis, metabolism, receptor regulation and key pathways of glutamate are therefore critical to the functioning of the brain. Its effects are mediated through a large variety of ionotropic and metabotropic receptors abundantly expressed along the whole extent of the neuraxis (Schmidt and Reith 2005).

Abnormal regulation of glutamatergic transmission is, therefore, a key factor that underlies the appearance and progression of many neurodegenerative and psychiatric diseases.
Although the importance of glutamatergic transmission in the modulation of neuronal activity has long been established, the complexity of the neuronal pathways involved combined with the multiple effects glutamate could mediate via pre- and postsynaptic interactions with various receptor subtypes, have led to important controversies regarding the exact role glutamate plays in psychiatric diseases (Schmidt and Reith 2005).

In a trial to understand this role, first we have to know more about chemistry of glutamate, tracts in the brain that convey its action and about receptors upon which glutamate acts.

**Biochemistry of glutamate**

Glutamate or glutamic acid is a neurotransmitter that is an amino acid. Its predominant use is not as a neurotransmitter but as an amino acid building block for protein biosynthesis.

When used as a neurotransmitter, it is synthesized from glutamine in glial cells, which also assist in the recycling and regeneration of more glutamate following glutamate release during neurotransmission. Thus, glutamate is first released from synaptic vesicles that store this neurotransmitter in glutamate neurons and secondly taken up into neighboring glial cells by a reuptake pump known as an excitatory amino acid transporter (EAAT).
Glutamate is converted into glutamine inside glial cells by an enzyme known as glutamine synthetase. Glutamine is released from glial cells via reverse transport by a pump or transporter known as a specific neutral amino acid transporter. Glutamine may also be transported out of glial cells by a second transporter known as a glial alanine-serine-cysteine transporter or ASC-T. When glial specific neutral amino acid transporter (SNAT) and ASC-Ts operate in the inward direction, they transport glutamine and other amino acids into the glial cell. Here, they are reversed, so that glutamine can get out of the glial cell and hop a ride into a neuron via a different type of neuronal SNAT operating inwardly in a reuptake manner (Stahl, 2008).

Once inside the neuron, glutamine is converted into glutamate by an enzyme in mitochondria called glutaminase. Glutamate is then transported into synaptic vesicles via a vesicular glutamate transporter where it is stored for subsequent release during neurotransmission. Once released, glutamate’s actions are stopped not by enzymatic breakdown, like in other neurotransmitter systems, but by removal by EAATs on neurons or glia, and the whole cycle is started again (Stahl, 2008). The following figures (1,2,3,4) illustrate these processes.
Figure (1): glutamate recycle and regeneration (part 1)

Figure (2): glutamate recycle and regeneration (part 2)
Figure (3): glutamate recycle and regeneration (part 3)

Figure (4): glutamate recycle and regeneration (part 4)