

Decreased Serum Glutamate Levels in Male Adults with Internet Gaming Disorder: A Pilot Study

Soo-Hyun Paik, Mi Ran Choi, Su Min Kwak, Sol Hee Bang, Dai-Jin Kim

Department of Psychiatry, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Objective: Alteration in glutamatergic neurotransmission and dopaminergic dysfunction has been implicated in both the initiation and expression of addiction related behaviors. This pilot study was aimed to investigate the serum levels of glutamate and dopamine in adults with internet gaming disorder (IGD).

Methods: We measured serum levels of glutamate and dopamine in male participants with IGD (n=26) and age-matched healthy controls (n=25). Clinical interviews were performed to identify IGD and to rule out psychiatric comorbidities. Serum levels of glutamate and dopamine were examined by enzyme immunoassays using ELISA Kits.

Results: Serum levels of glutamate were lower among IGD than control (IGD: 24.184 ± 12.303 $\mu\text{g/ml}$; control: 33.676 ± 12.413 $\mu\text{g/ml}$; $t=2.742$, $p=0.008$), while levels of dopamine did not differ between. Serum glutamate and dopamine levels did not correlate with gaming hours and exposure to game in the IGD group. But serum glutamate levels were positively correlated with the dopamine levels ($r=0.360$, $p=0.013$).

Conclusion: Our results suggest that altered glutamatergic neurotransmission may contribute to the pathophysiology of IGD.

KEY WORDS: Internet gaming disorder; Glutamates; Dopamine; Serum.

INTRODUCTION

Internet gaming disorder (IGD) is characterized as excessive and uncontrolled gaming behavior which eventually leads to functional impairment or distress.¹⁾ Over the last decade, uncontrolled internet gaming behavior have produced worldwide public health concerns and social problems.¹⁾ Numerous studies have been published regarding the neurobiological underpinning of IGD. Altered reward sensitivity,²⁾ dopaminergic reward system deficiency,³⁾ deficits in cognitive-emotional processing, impulsivity, cue reactivity and impaired decision-making ability that have been proven in neuroimaging and behavioral tasks have been reported to be associated with

IGD.⁴⁻⁶⁾ Nevertheless, the pathophysiology of IGD is poorly understood.

Altered glutamatergic neurotransmission is known to be associated with various psychiatric disorders, such as schizophrenia,⁷⁾ mood disorders,⁸⁾ obsessive-compulsive disorders (OCD),⁹⁾ and addictive disorders.¹⁰⁾ In particular, glutamate plays a crucial role in regulating both the development and expression of addictive behaviors, such as sensitization and drug seeking.¹⁰⁾ Drugs of abuse, including alcohol,¹¹⁾ nicotine,¹²⁾ cocaine,¹³⁾ and opioid,¹⁴⁾ are known to alter glutamate neurotransmission and cause long-lasting neuroadaptation in the abuser's brain. Abnormal glutamatergic neurotransmission have been suggested as a pathophysiological mechanism of pathological gambling,¹⁵⁾ a non-substance addictive disorder which shares similar neurobiological aspects with IGD.¹⁶⁾ Though direct observation of abnormal glutamate transmission was absent in the pathological gambling, treatment of pathological gambling with glutamate modulating agents, such as N-acetylcysteine and memantine, was successful.^{17,18)} To date, however, the role of glutamate transmission has never been studied in IGD.

Received: April 24, 2017 / **Revised:** May 29, 2017

Accepted: June 27, 2017

Address for correspondence: Dai-Jin, Kim, MD, PhD
Department of Psychiatry, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea
Tel: +82-2-2258-7586, Fax: +82-2-594-3870
E-mail: kdj922@catholic.ac.kr
ORCID: <https://orcid.org/0000-0001-9408-5639>

© This is an Open-Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Role of dopamine in reward system has been well established. Addictive behaviors such as excessive and uncontrolled internet use and gaming as well as drugs of abuse change both structural and functional regions within dopaminergic reward system,^{3,5)} which eventually leads to change in behaviors contributing to craving, risk taking, and outcome prediction errors.^{19,20)} Moreover, interaction between dopamine and glutamate is related to drug-seeking behaviors and relapse in an animal study,²¹⁾ and dopamine-glutamate co-transmission seems to occur in reward processing in addiction.²²⁾ In order to elucidate the pathophysiology of IGD, it is important to assess both dopaminergic and glutamatergic dysfunction.

Based on these findings, we hypothesized that alterations in glutamatergic and dopaminergic neurotransmission may play a crucial role in the pathophysiology of IGD either independently or interactively. Since serum levels of glutamate are positively correlated with the cerebrospinal fluid levels of glutamate in humans,²³⁾ altered glutamate neurotransmission in the brain can be inferred from the changes in the serum levels of glutamate. Thus the present pilot study assessed the serum levels of glutamate and dopamine in male adults with IGD without psychiatric comorbidities in comparison with healthy controls.

METHODS

Participants

Thirty-two male adults with IGD were recruited from online advertisements. Diagnosis of IGD was made by clinical interviews conducted by two qualified psychologists who had experiences on internet addiction and IGD. IGD was determined using the research criteria for IGD from Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5).²⁴⁾ The interview also included past and present psychiatric illness history and use of psychotropic medications. Exclusion criteria were current or past axis I or II psychiatric disorders and suspected intellectual disability, determined by the Korean version of the Wechsler Adult Intelligence Scale version IV (K-WAIS-IV). Three participants were excluded due to the psychiatric comorbidity: one with major depressive disorder, one with dysthymic disorder and one with social anxiety disorder. One participant was excluded due to suspected intellectual disability with full scale intelligent quotient (IQ) below 80. In total, 26 male adults with IGD

were included in this study. The age range was 20 to 38 years old and the mean age of the sample was 28.16 (standard deviation [SD], 5.235). Age matched healthy male controls were recruited from online advertisements. All control participants underwent clinical interviews to exclude IGD, psychiatric comorbidities, and suspected intellectual disability.

Exposure to internet gaming by year and time spent on gaming during weekdays and weekends were asked to all participants. Seven participants from control did not answer to the exposure question and one from IGD did not to both the exposure and gaming hour questions. These variables were counted as missing values in the final analyses. Two control participants have never been engaged in internet gaming and thus their variables were counted as 'zero'.

The study protocol was approved by the Institutional Review Boards of Seoul St. Mary's Hospital (IRB number: KC15EISI0103). This study met the ethical standards of the Declaration of Helsinki, including obtaining informed consent from all the participants and adhering to the privacy rights of the participants.

Biochemistry Test

For each participant, 5 ml of venous blood was extracted and stored at -20°C until analysis. Glutamate and dopamine concentrations were measured using Human Glutamate ELISA Kit (ARG80453) and Huma Dopamine ELISA Kit (ARG50450) respectively purchased from Arigo Biolaboratories (Hsinchu, Taiwan). Before each assay, serum was preprocessed by extraction and derivatization according to manufacturer's instructions. One hundred micro millimeters of standards or the preprocessed serum was applied to glutamate-coated microtiter plate and 50 μl of glutamate antiserum was added. The plate was incubated overnight at 4°C . After washing the plate, 100 μl of enzyme-conjugated antibody was added to the plate. TMB reagent of 100 μl was added, followed by incubating for 30 minutes in dark. After adding 100 μl of stop solution, the plate was read at 450 nm to measure serum neurotransmitter concentrations.

Statistical Analysis

To compare between the IGD and control groups, independent *t* tests and Mann-Whitney *U* tests were used for normally distributed variables and for nonparametric

Table 1. Comparisons of clinical characteristics and serum neurotransmitter levels

Characteristic	Internet gaming disorder group	Control group	t/U value
IQ			
Full-scale IQ	109.88±11.752	112.64±12.737	t=0.910
VCI	109.92±10.041	111.40±12.705	t=0.465
PRI	109.62±16.879	113.56±14.277	t=0.899
WMI	107.12±13.055	107.16±14.685	t=0.011
PSI	105.73±11.323	108.52±12.797	t=0.825
Exposure to internet gaming (yr)	8.260 (3.00-11.00)	7.760 (0.00-14.00)	U=268.500
Weekday gaming hour	3.208 (2.00-4.00)	1.568 (1.00-2.00)	U=100.500**
Weekend gaming hour	5.17 (3.00-5.00)	3.07 (1.00-3.13)	U=98.500**
Glutamate (µg/ml)	24.18±12.30	33.68±12.41	t=2.742*
Dopamine (µg/ml)	.0471 (.0198-.0835)	.0264 (.0044-.0610)	U=206.000

Values are presented as mean±standard deviation or median (interquartile distance).

IQ, intellectual quotient; VCI, verbal comprehensive index; PRI, perceptual reasoning index; WMI, working memory index; PSI, processing speed index.

* $p < 0.05$, ** $p < 0.005$.

Table 2. Correlations between serum neurotransmitter levels and gaming related variables in internet gaming disorder group

Variable	1	2	3	4	5
1. Serum glutamate levels	1				
2. Serum dopamine levels	0.360*	1			
3. Exposure to internet gaming (yr)	-0.095	0.021	1		
4. Weekday gaming hour	-0.234	-0.126	-0.105	1	
5. Weekend gaming hour	-0.180	-0.105	-0.129	0.505**	1

* $p < 0.05$, ** $p < 0.005$.

variables respectively. The Kolmogorov-Smirnov tests were used to evaluate whether the variables were normally distributed. The data were represented as mean±SD for the t tests and as median and interquartile distance (IQD) for the Mann-Whitney U tests. Correlations between serum neurotransmitter levels and gaming related variables were analyzed by Pearson's correlation coefficients. A p value of less than 0.05 was considered to be statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 24 (IBM Co., Armonk, NY, USA).

RESULTS

Characteristics of the IGD and control subjects were present in Table 1. There were no significant differences between the IGD and control groups with regard to all domains of K-WAIS-IV and full scale IQ. IGD spent more time on internet gaming during weekdays (IGD: 3.208 [IQD, 3.00-8.00], control: 1.568 [IQD, 1.00-2.00]; $U=100.500$, $p=0.000$) and weekends (IGD: 5.17 [IQD,

3.00-5.00], control: 3.07 [IQD, 1.00-3.13], $U=98.500$, $p=0.000$). Exposure to internet gaming by year did not differ between groups.

Glutamate concentrations (µg/ml) were lower in the IGD group than control (IGD: 24.184±12.303, control: 33.676±12.413; $t=2.742$, $p=0.008$), while dopamine serum levels (µg/ml) did not differ between groups (IGD: 0.471 [IQD, .0198-.0835], control: .0264 [IQD, .0044-.0610]; $U=206.000$, $p=0.141$). In the IGD group, serum glutamate and dopamine levels were not correlated to time spent on gaming during weekdays ($r=-0.234$, $p=0.113$) and weekends ($r=-0.180$, $p=0.225$) and exposure to internet gaming ($r=-0.095$, $p=0.511$) (Table 2). However, glutamate concentration was positively correlated with dopamine concentration ($r=0.360$, $p=0.013$). Time spent on gaming during weekdays was positively correlated to time during weekends ($r=0.505$, $p=0.000$).

DISCUSSION

In this study, we demonstrated that serum levels of glutamate in young male adults with IGD were significantly lower than those of the control subjects. To our knowledge, this is the first study that reported decreased serum levels of glutamate in adults with IGD. All participants underwent clinical interviews and objective psychometric tests, and were finally matched as per age and gender to minimize the confounding effects. Carefully selected inclusion and exclusion criteria can serve as a strong methodological strength since the serum glutamate levels vary significantly as per age, gender, intelligence as well as comorbid depressive disorder.²⁵⁻²⁸⁾

IGD was associated with decreased peripheral glutamate levels, implicating altered glutamate neurotransmission. Glutamate signaling has been implicated as important in addictive disorder. In substance addiction, drugs of abuse alter glutamate transmission²⁹⁾; nicotine enhances extracellular levels of glutamate,³⁰⁾ opiate reduces synaptic overflow of glutamate,³¹⁾ and alcohol has mixed effect on extracellular levels of glutamate.¹¹⁾ In addition to these direct effects, glutamate regulates dopaminergic activity and thus modulates dopaminergic reward processing via incentive arousal for drug-related cue.^{23,32)} Conditioned drug-related cue elicits a phasic increase in the firing of ventral tegmental area dopamine neuron and eventually lead to the co-release of dopamine and glutamate in prefrontal cortex and the nucleus accumbens.²²⁾ Glutamate is involved in the learning and memory processes via N-methyl-D-aspartate (NMDA) receptors.³³⁾ Altered glutamate transmission has been considered to play a role in reconsolidation of drug-associated memories and thus in relapse of addictive disorder.²⁹⁾ Moreover, glutamate excitotoxicity was implicated in motivational processes and reduced the capacity of prefrontal cortex to provide executive control over drug seeking.^{34,35)} As in substance addictions, alteration in glutamate neurotransmission may modify dopaminergic reward processing and reconsolidate addictive behavior-related memories in IGD.

Another explanation can be drawn from the pathophysiology of OCD. Altered glutamate neurotransmission in corticostriatal-thalamocortical (CSTC) circuitry has been proposed to be involved in the OCD.⁹⁾ Within the CSTC circuits, glutamate plays a key role in the direct

pathways, which induce thalamic stimulation of cortex. Preclinical and clinical trials have demonstrated that glutamatergic modulating agents such as riluzole and memantine targeted obsessive-compulsive symptoms and impulsivity in OCD.³⁶⁾ Considering compulsive and uncontrolled gaming behaviors observed in IGD,³⁷⁾ glutamate may alter the CSTC circuit of individuals with IGD and result in excessive preoccupation and compulsive gaming behaviors.

In this study, serum dopamine levels did not differ between groups. Though serum dopamine does not cross the blood-brain barrier and serum homovallinic acid (HVA) levels did not correlate with HVA levels in the cerebrospinal fluid,²³⁾ serum dopamine levels have been suggested to reflect dopamine levels in the striatum.^{38,39)} In this sense, our results did not reflect previous studies reporting alterations in dopaminergic transporters and receptors in the striatum of IGD.^{40,41)} However, serum dopamine levels were positively correlated with glutamate levels in this study. Since dopamine and glutamate are co-transmitted in the addict's brain when he or she is engaged in a drug-related behavior,²²⁾ the correlation reported in this study might reflect the co-transmission of glutamate and dopamine in IGD.

We could not find the correlation of serum glutamate levels with exposure duration with the internet gaming and gaming hours. The results suggested that glutamate dysfunction may serve as a biomarker that occurs in the early stage of the disorder and is maintained through the course, as shown in the study of adults with autism.²⁸⁾

The following limitations should be addressed. First, the sample size was too small to draw final conclusions. However, carefully matched control subjects would minimize the influence of various confounding factors. Further research with a larger sample is needed to validate the preliminary results. Second, causal inferences could not be made from the results because of the lack of longitudinal data. Third, we did not assess the severity of IGD by quantitative scales such as Young's internet addiction tests, thus were unable to investigate the correlation between serum neurotransmitter levels and the disease severity.

In conclusion, the present pilot study suggested that alteration in glutamatergic neurotransmission may contribute to the pathophysiology of IGD. Abnormal glutamate transmission may moderate drug-related learning and

memory, contribute to the obsessive and compulsive gaming behaviors, or indirectly modulate dopaminergic reward system. Further researches using the magnetic resonance spectroscopy would be necessary to investigate glutamate dysfunction in the brain of IGD, especially in the striatum and the CSTC circuits.

■ Acknowledgments

This research was supported by the Brain Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (NRF-2014M3C7A1062893).

REFERENCES

- Kuss DJ. *Internet gaming addiction: current perspectives. Psychol Res Behav Manag* 2013;6:125-137.
- Dong G, Hu Y, Lin X. *Reward/punishment sensitivities among internet addicts: implications for their addictive behaviors. Prog Neuropsychopharmacol Biol Psychiatry* 2013;46:139-145.
- Zhu Y, Zhang H, Tian M. *Molecular and functional imaging of internet addiction. Biomed Res Int* 2015;2015:378675.
- Meng Y, Deng W, Wang H, Guo W, Li T. *The prefrontal dysfunction in individuals with Internet gaming disorder: a meta-analysis of functional magnetic resonance imaging studies. Addict Biol* 2015;20:799-808.
- Zhang Y, Ndasauka Y, Hou J, Chen J, Yang LZ, Wang Y, et al. *Cue-induced behavioral and neural changes among excessive internet gamers and possible application of cue exposure therapy to internet gaming disorder. Front Psychol* 2016;7:675.
- Kim YJ, Kim DJ, Choi JS. *The cognitive dysregulation of Internet addiction and its neurobiological correlates. Front Biosci (Elite Ed)* 2017;9:307-320.
- Coyle JT. *Glutamate and schizophrenia: beyond the dopamine hypothesis. Cell Mol Neurobiol* 2006;26:365-384.
- Sanacora G, Treccani G, Popoli M. *Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. Neuropsychopharmacology* 2012;62:63-77.
- Wu K, Hanna GL, Rosenberg DR, Arnold PD. *The role of glutamate signaling in the pathogenesis and treatment of obsessive-compulsive disorder. Pharmacol Biochem Behav* 2012;100:726-735.
- Kalivas PW, Lalumiere RT, Knackstedt L, Shen H. *Glutamate transmission in addiction. Neuropsychopharmacology* 2009;56 Suppl 1:169-173.
- Dodd PR, Beckmann AM, Davidson MS, Wilce PA. *Glutamate-mediated transmission, alcohol, and alcoholism. Neurochem Int* 2000;37:509-533.
- Liechti ME, Markou A. *Role of the glutamatergic system in nicotine dependence: implications for the discovery and development of new pharmacological smoking cessation therapies. CNS Drugs* 2008;22:705-724.
- Kalivas PW. *Glutamate systems in cocaine addiction. Curr Opin Pharmacol* 2004;4:23-29.
- Ho IK, Feng YZ, Tokuyama S, Hoshi K, Rockhold RW. *Glutamate in opioid dependence. Nihon Shinkei Seishin Yakurigaku Zasshi* 1997;17:175-180.
- Potenza MN. *The neurobiology of pathological gambling and drug addiction: an overview and new findings. Philos Trans R Soc Lond B Biol Sci* 2008;363:3181-3189.
- Fauth-Bühler M, Mann K. *Neurobiological correlates of internet gaming disorder: Similarities to pathological gambling. Addict Behav* 2017;64:349-356.
- Grant JE, Kim SW, Odlaug BL. *N-acetyl cysteine, a glutamate-modulating agent, in the treatment of pathological gambling: a pilot study. Biol Psychiatry* 2007;62:652-657.
- Grant JE, Chamberlain SR, Odlaug BL, Potenza MN, Kim SW. *Memantine shows promise in reducing gambling severity and cognitive inflexibility in pathological gambling: a pilot study. Psychopharmacology (Berl)* 2010;212:603-612.
- Cooper S, Robison AJ, Mazei-Robison MS. *Reward circuitry in addiction. Neurotherapeutics* 2017;14:687-697.
- Yuan K, Yu D, Cai C, Feng D, Li Y, Bi Y, et al. *Frontostriatal circuits, resting state functional connectivity and cognitive control in internet gaming disorder. Addict Biol* 2017;22:813-822.
- Taepavarapruk P, Butts KA, Phillips AG. *Dopamine and glutamate interaction mediates reinstatement of drug-seeking behavior by stimulation of the ventral subiculum. Int J Neuropsychopharmacol* 2014;18:pyu008.
- Lapish CC, Seamans JK, Chandler LJ. *Glutamate-dopamine cotransmission and reward processing in addiction. Alcohol Clin Exp Res* 2006;30:1451-1465.
- Alfredsson G, Wiesel FA, Tylec A. *Relationships between glutamate and monoamine metabolites in cerebrospinal fluid and serum in healthy volunteers. Biol Psychiatry* 1988;23:689-697.
- American Psychiatric Association. *Diagnostic and statistical manual of mental disorders, 5th ed: DSM-5. Washington, DC:American Psychiatric Publication;2013.*
- Evers LJ, van Amelsvoort TA, Bakker JA, de Koning M, Drukker M, Curfs LM. *Glutamatergic markers, age, intellectual functioning and psychosis in 22q11 deletion syndrome. Psychopharmacology (Berl)* 2015;232:3319-3325.
- Shimmura C, Suda S, Tsuchiya KJ, Hashimoto K, Ohno K, Matsuzaki H, et al. *Alteration of plasma glutamate and glutamine levels in children with high-functioning autism. PLoS One* 2011;6:e25340.
- Kim JS, Schmid-Burgk W, Claus D, Kornhuber HH. *Increased serum glutamate in depressed patients. Arch Psychiatr Nervenkr (1970)* 1982;232:299-304.
- Shinohe A, Hashimoto K, Nakamura K, Tsujii M, Iwata Y, Tsuchiya KJ, et al. *Increased serum levels of glutamate in adult*

- patients with autism. *Prog Neuropsychopharmacol Biol Psychiatry* 2006;30:1472-1477.
29. Gass JT, Olive MF. *Glutamatergic substrates of drug addiction and alcoholism. Biochem Pharmacol* 2008;75:218-265.
 30. Reid MS, Fox L, Ho LB, Berger SP. *Nicotine stimulation of extracellular glutamate levels in the nucleus accumbens: neuropharmacological characterization. Synapse* 2000;35:129-136.
 31. Aghajanian GK, Kogan JH, Moghaddam B. *Opiate withdrawal increases glutamate and aspartate efflux in the locus coeruleus: an in vivo microdialysis study. Brain Res* 1994;636:126-130.
 32. Di Chiara G, Bassareo V. *Reward system and addiction: what dopamine does and doesn't do. Curr Opin Pharmacol* 2007;7:69-76.
 33. Riedel G, Platt B, Micheau J. *Glutamate receptor function in learning and memory. Behav Brain Res* 2003;140:1-47.
 34. Kalivas PW, Volkow ND. *The neural basis of addiction: a pathology of motivation and choice. Am J Psychiatry* 2005;162:1403-1413.
 35. Chambers RA, Taylor JR, Potenza MN. *Developmental neuro-circuitry of motivation in adolescence: a critical period of addiction vulnerability. Am J Psychiatry* 2003;160:1041-1052.
 36. Pittenger C, Krystal JH, Coric V. *Glutamate-modulating drugs as novel pharmacotherapeutic agents in the treatment of obsessive-compulsive disorder. NeuroRx* 2006;3:69-81.
 37. Young KS. *Internet addiction: the emergence of a new clinical disorder. Cyberpsychol Behav* 1998;1:237-244.
 38. Strafella AP, Ko JH, Monchi O. *Therapeutic application of transcranial magnetic stimulation in Parkinson's disease: the contribution of expectation. Neuroimage* 2006;31:1666-1672.
 39. Khedr EM, Rothwell JC, Shawky OA, Ahmed MA, Foly N, Hamdy A. *Dopamine levels after repetitive transcranial magnetic stimulation of motor cortex in patients with Parkinson's disease: preliminary results. Mov Disord* 2007;22:1046-1050.
 40. Tian M, Chen Q, Zhang Y, Du F, Hou H, Chao F, et al. *PET imaging reveals brain functional changes in internet gaming disorder. Eur J Nucl Med Mol Imaging* 2014;41:1388-1397.
 41. Kim SH, Baik SH, Park CS, Kim SJ, Choi SW, Kim SE. *Reduced striatal dopamine D2 receptors in people with Internet addiction. Neuroreport* 2011;22:407-411.