GluN3A Receptor mRNA Expression in Adolescents Experiencing Nicotine Addiction Disorder and Internet Addiction

Luh Nyoman Alit Aryani[1], Ni Ketut Putri Ariani[2], Cokorda Bagus Jaya Lesmana[3],I.G. Kamasan Nyoman Arijana[4]

[1]Faculty of Medicine, Udayana University, Indonesia. E-mail: alitaryani@rocketmail.com

[2]Faculty of Medicine, Udayana University, Indonesia.

[3]Faculty of Medicine, Udayana University, Indonesia.

[4]Faculty of Medicine, Udayana University, Indonesia.

ABSTRACT

The prevalence of people experiencing substance addiction and behavior addiction disorders is increasing every year. The criteria for addiction are characterized by tolerance (increased dose, withdrawal (withdrawal) and obsessive thoughts about the use of the substance. The most common addictions in adolescents are nicotine addiction and internet addiction, which have several adverse effects on the user. Nicotine as an ingredient.Contained in cigarettes, many cause high addiction rates in adolescents. Internet use is increasing in several levels of society, especially in adolescents. The incidence of internet use causes many problems, especially in cases of internet addiction. behavior has been studied a lot, including many biological factors play a role in the case of addiction. One of them is a disturbance in the neurotransmitter and its receptors. Some of the neurotransmitters that play a role are dopamine, GABA, Glutamate, Serotonin and Norepineprin. Glutamate in cases of addiction. In general, this study aims to determine the expression of Glutamate receptor mRNA in adolescents who experience nicotine addiction and internet addiction.

Method: Analytical research using a cross-sectional design by looking at the expression of mRNA Glutamate receptors in adolescents who experience nicotine addiction and internet addiction were analyzed by proportional difference test.

Discussion: The results found that the expression of GluN3A mRNA in the Nicotine group was lower than the Internet Addiction group with a significant p value of 0.000. The existence of a basic deficiency in the expression of the GluN3A subunit in people prone to addiction could form the basis of further studies with the control group and as a consideration in the choice of therapy.

KEYWORDS

Addiction, Nicotine, Internet, GluN3A.

Introduction

The prevalence of people experiencing addiction disorders is increasing every year, so it is necessary to seek promotional, preventive, and curative actions, both for those without problems or those with problems. There are two treatments that can be done, first, namely pharmacological and secondly non-pharmacological. To be able to provide good treatment, it is necessary to know the factors that cause addiction.

Addiction is usually used in a clinical context and is refined by excessive behavior. The concept of addiction can be applied to a broad range of behaviors, including addiction to substance and information communication technology.[1,16]

The diagnosis in DSM 5 classifies substance dependence into Substance-related and Addictive Disorders. Benchmark criteria can be considered to meet the whole group of control failure (criteria, 1-4) social disorders (criteria 5-7), Indonesian use (criteria 8-9) and pharmacological criteria (criteria 10-11).[2]

Four important initial components proposed to diagnose internet addiction in DSM-5 include, (1) excessive internet use, often associated with loss of sense of time or neglecting basic needs, withdrawal, including feelings of anger, tension, and / or depression when the computer is inaccessible,tolerances, including the need for better computer equipment, more software, or longer usage times, and adverse consequences, including frequent argumentation, lying, poor school performance, fatigue and social isolation.[2,3]

In previous study mentioned that teens who use the internet have been studied in 11 European countries. The prevalence of pathological use was 4.4% and the prevalence of maladaptive use was 14.3%. Pathological internet users use the internet almost twice as much as adaptive users. Most of the pathological users were men, while women

represented the majority of usersmaladaptive. Men spend more time on the internet playing online games, while women use the internet more for social networking and e-mail.[4]

Factors associated with internet addiction include biological factors, family factors (family function and upbringing), socioeconomic factors, personality and gender factors. Socio-economic factors also play a role in the relationship between internet addiction and emotional and behavioral problems. Socio-economic factors include family income, number of family members and occupation of both parents. Children are more likely to turn to the internet if both parents work, this is what can cause internet addiction and psychological problems in children.[5]

Nicotine also increases glutamate release which mediates dopamine release and γ-aminobutyric acid / GABA release (which inhibits dopamine release). Long-term nicotine exposure will result in desensitization of some nicotinic cholinergic receptors. This results in the loss of GABA-mediated inhibitory activity but the glutamate-mediated excitation activity to persist. The net result is increased excitation of dopaminergic neurons and increased response to nicotine. Nicotine lowers the threshold for reward and this effect can last more than 30 days.[6]

Several neurotransmitters play a role in addiction such as dopamine, serotonin, norepinephrine and glutamate. Glutamate, the main excitatory neurotransmitter in the brain, is an important component in the phenomenon of addiction. Neurotransmitters can be found in most parts of the brain, especially the mesocorticolimbus pathway, which is also known as the reward pathway. The receptors are classified as N-methyl-Daspartate (NMDA) receptors, AMPA receptors(a-amino-3-hydroxy-5-methyl-4-isoxazolepropionate)),kainate receptors and metabotropic receptors. Most, if not all, cells in the nervous system express at least one type of glutamate receptor.[7]

The N-methyl-D-aspartate (NMDA) receptor as part of the ionotropic glutamate receptor is a tetramer formed by 3 subunits of different classes: GluN1, GluN2 (GluN2A-D), and GluN3 (GluN3A and B), which can be composed as GluN1 / GluN2 or GluN1 / GluN2 / GluN3.[8]

In the literature it is mentioned, in the brain, basal extracellular glutamate levels are maintained by extracellular cystine and extracellular glutamate which stimulate the mGluR2 / 3 receptor. If we can restore basal extracellular glutamate concentrations we can increase the tonic activation of the mGluR2 / 3 receptor because these receptors are important in the treatment of nicotine dependence. It is equally important to identify genetic factors for nicotine dependence and how genes interact with the environment.[9]

Adolescence is the stage where individuals experience peak physical, cognitive, social and emotional development. The fast and continuous physical development in adolescents causes adolescents to become aware and more sensitive to their body shape and try to compare with their peers. If the changes do not take place smoothly, it will affect the psychological and emotional development of adolescents, and sometimes even anxiety arises, especially if they are not prepared to face them. On the other hand, this situation for parents can lead to conflict if the process of the child becoming an adult is not well understood. Psychosocial changes in adolescents are divided into three stages, namely early adolescent, middle adolescent, and late adolescent.[10]

Previous studies have shown that the expression levels of the subunit GluN3A and GluN3B mRNA in PBLs of online computer game addicts decreased and did not change, respectively, compared with control individuals. This study was conducted to look at the expression of glutamate mRNA receptors in adolescents who experience nicotine addiction and internet addiction, so that they can distinguish mRNA expression in substance addiction, in this case nicotine, compared with behavioral addiction, namely internet addiction.[8]

Methodology

This research is a cross sectional study. The research was conducted at Kerobokan Prison and psychiatric practice in Denpasar, as well as the Biomedical Laboratory of the Faculty of Medicine, Udayana University. Time of study: July to October 2020.

Sampling and Participant

The affordable population of this study were adolescents with nicotine addiction disorders at the Kerobokan Prison Clinic in Denpasar and internet addiction in private psychiatric practices in Denpasar. Inclusion criteria are 12 to 24

years of age and willing to work together to participate in research programs.The first group, subjects were positive for nicotine addiction disorders, with the results of the examination using the Fagerstrom Test For Nicotine Dependence.[11]The subjects in second group were positive for internet addiction disorders, with the results of the examination using the Internet Addiction Test.[12]The exclusion criteria, if they have serious physical illness or severe mental disorders and disabilities.

Procedure and Analysis

The first step was to record patients with addiction disorders according to the inclusion and exclusion criteria. Introduce the patient concerned and provide informed consent about the aims and objectives of the study. After each group was interviewed with a questionnaire, 1 cc of blood was taken by laboratory staff for laboratory examination to evaluate mRNA expression. The examination is carried out by a biomedical specialist. After examining the Glutamate receptor mRNA, it was continued with data analysis by statisticians.

Descriptive statistical test to analyze data about the characteristics obtained from the research results.Categoric Comparison Test in the form of hypothesis test of different proportions of two independent samples is carried out on two groups of samples taken from different populations. The two sample groups are not related, so it is possible that the number of samples taken from the two groups is different. In this proportion difference hypothesis test, the statistical measure tested is the proportion value. The proportion value is the ratio or ratio between an event compared to the total or the entire event.

Results

The mean age of the nicotine addiction group study subjects was 21.7 years which consisted of 100% all males. Most of the subjects of education are high school (70%), followed by junior high school (35%). Most research subjects are employees (30%) who do not work, builders and drivers are equal (20%), traders and students are the same as 1%. The characteristics of first group can be seen in table 1.

The average age of students who were research subjects was 21 years consisting of 25% female and 75% male. Most of the subjects of education are high school (60%), followed by junior high school (35%), bachelor degree (1 person) (5%). Most of the research subjects were students 45%, unemployed (35%), and employees (15%) and 5% students. The characteristics of second group can be seen in table 2.

Table 1. The Sample Characteristics of the Nicotine Addiction Study Group

CharacteristicsN (%)
Age (median).21,7
Sex
Male20 (100)
Female0
Education
ElementarySchool0
Junior High School7 (35)
Senior High School14 (70)
Bachelor0
Profession
Unemployment4 (20)
Student0
College Student1(5)
Employees6(30)
Builder4(20)
Driver4(20)
Trader1(5)

Table 2. Characteristics of the Sample Internet Addiction Research Group

Characteristicsn(%)
Age (median)21
Sex
Male15 (75)
Female5 (25)
Education
Elementary school0
Junior High School7 (35)
Senior High School12(60)
Bachelor1 (5)
Profession
Unemployment7 (35)
Student1 (5)
College Student9 (45)
Employee3 (15)

In the results of the SPSS analysis, the distribution of GluN3A mRNA expression was not normal in both groups, so the Mann-Whitney test was used to compare. The result was that the expression of GluN3A mRNA in the Nicotine group was lower than the Internet Addiction group with a significant p value of <0.001.

Table 3. Comparison of mRNA Expression by Study Group

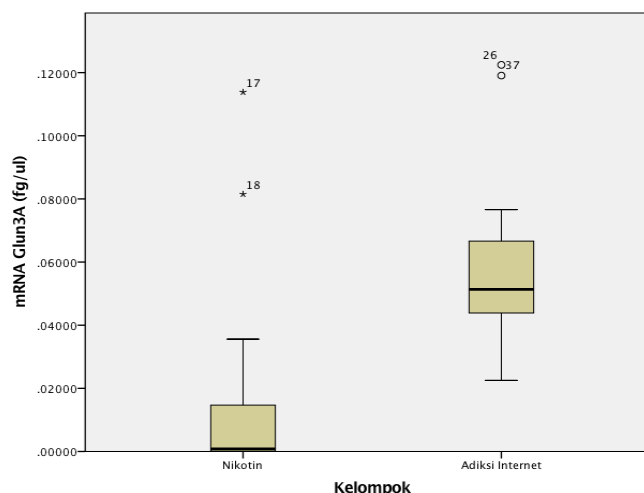| Variable	Nicotine Addiction Group	Internet Addiction Group	pvalue
	Median (IQR)	Median (IQR)	
Ekspresi mRNA	0,000 (0,018)	0,051 (0.024)	<0,001

Figure 1. Expression of mRNA from the GluN3A Subunit (Which is the NMDA Receptor in PBLs of Subjects with Nicotine Addiction and Internet Addiction

Discussion

From the results of this study, the sample characteristics in the internet addiction group were the mean age of 21 years and the nicotine addiction was 21.7 years, which according to the National Family Planning Coordinating Agency(BKKBN) was still a teenager or according to WHO as an young people. For education, most of the samples in both groups were high school graduates, namely 60% on internet addiction and 70% in nicotine addiction. In the nicotine addiction group were all men and in the internet addiction group there were five women. Regarding work, most of the internet addiction group is students (40%) and the nicotine addiction is employees (30%). In accordance with previous research, a survey in Indonesia stated that 35% of adolescents use the internet and as many as 55% are

male adolescents.[13]

Analysis of differences in the expression level of Glutamate GluN3A mRNA in this study from both the nicotine addiction and internet addiction groups showed that the GluN3A mRNA expression in the nicotine group was lower than the Internet addiction group with a significant p value of 0,000. In a previous study, online game addiction and smoking were found, including the mechanism for shifting stress levels in adolescents. Adolescents are unstable individuals who are easily stressed due to modernization. Ineffective adolescent stress management choices such as smoking and playing online games lead to poor body adaptation so that it ends in maladaptive or failure to adapt to the problem at hand.[14]

Previous research showed that the expression level of GluN3A in PBLs of online computer game addicts decreased significantly compared to the control group. In another study found a similar decrease in GluN3A mRNA expression in PBLs of ex-opioid addicts, so, there may be a baseline deficiency in the expression of the GluN3A subunit in people who are prone to addiction and this deficiency improves with substance use, but not with behavioral addicts, such as play computer games.[8]

Behavioral scientists believe that any entity capable of stimulating a person is addictive; and whenever a habit turns into an obligation, it can be considered an addiction. Previous researchers also believed that there were a number of similarities as well as some differences between diagnostic symptomsof drug addiction and behavior.[15]The difference in the results of this study between the two groups may be due to several confounding factors that must be considered or need to be compared with healthy controls.The results of this study can also support the idea that manipulation of the glutamatergic system with a special focus on the NMDA receptor GluN3A subunit is an effective way of approaching behavioral and substance addiction management.

Conclusion

The most characteristics of those experiencing nicotine addiction and internet addiction are 21 years of age, male and high school education, and most jobs in the internet addiction group are students and in nicotine addiction are employees. The expression level of GluN3A mRNA found in the Nicotine group was lower than the Internet Addiction group. Future studies need to use healthy controls so that they can evaluate the differences in outcomes between the two groups and healthy controls. It is necessary to develop further research on risk factor mechanisms. Seeing the dangers of nicotine and internet addiction among adolescents (causing psychiatric disorders and physical disorders), it is hoped that prevention can be carried out more actively by the government, society and health workers.

References

[1] Sadock BJ. *Kaplan & Sadock's Synopsis of psychiatry.* 11th ed. Philadelphia: Lippincott Williams & Wilkins; 2015.

[2] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorder-5 Washington DC: American Psychiatric Publishing*, 2013.

[3] Weinstein A, Feder LC, Rosenberg KP, Dannon P. Internet Addiction Disorder: Overview and Controversies. *Behavioral Addiction.* 2014; 10(1016): p. 99-117.

[4] Sinkkonen HM, Puhakka H, Meriläinen M. Internet Use and Addiction among Finnish Adolescents (15–19 Years). *Journal of Adolescence.* 2014; 37: p. 123-131.

[5] Kayri M, Gunuc S. Comparing Internet Addiction in Students with High and Low Socioeconomic Status Levels. *Addicta: The Turkish Journal on Addictions.* 2016; 3(2): p. 177-183.

[6] Sargo SS, Subagyo R. *Drug and Drug Abuse Pharmacotherapy.* 1st ed. Surabaya: Airlangga University Press; 2014.

[7] Zhou Y, Danbolt NC. Glutamate as a neurotransmitter in the healthy brain. *Journal of neural transmission.* 2014; 121(8): p. 799-817.

[8] Shirazi M. Expression of NMDA Receptor Subunits in Human Blood Lymphocytes: A Peripheral

Biomarker in Online Computer Game Addiction. *Journal of Behavioral Addictions.* 2018; 7(35).

[9]   Kleinjan M. Predicting nicotine dependence profiles among adolescent smokers: the roles of personal and social environmental factors in a longitudinal framework. *BMC Public Health.* 2012.

[10] Batubara JR. Adolescent Development (Youth Development). *Sari Pediatrics.* 2016; 12(1): p. 21-29.

[11] Nasution REP. Your Level of Addiction to Nicotine. Fagerstrom test: White Coat Hunter; 2017.

[12] Faraci P, Craparo G, Messina R, Severino S. Internet Addiction Test (IAT): Which is the Best Factorial Solution? *Journal of Medical Internet Research.* 2013; 15(10).

[13] Fitri E, Erwinda L, Ifdil I. The Concept of Online Game Addiction and Its Impact on Adolescent Mental Emotional Problems and the Role of Guidance and Counseling. *Journal of Counseling and Education.* 2018; 6(3): p. 211-219.

[14] Gewab BT, RIsanti ED, Herawati E, Mahampang N. The Relationship of Online Game Addiction and Smoking with Stress in Adolescents. *Biomedicine.* 2020 Aug; 12(2): p. 117-123.

[15] Alavi SS, Ferdosi M, Jannatifard F, Eslami M, Alaghemandan H, Setare M. Behavioral addiction versus substance addiction: Correspondence of psychiatric and psychological views. *International journal of preventive medicine.* 2013; 3(4): p. 290.

[16] Nyandra, M., Kartiko, B.H., Susanto, P.C., Supriyati, A., Suryasa, W. (2018). Education and training improve quality of life and decrease depression score in elderly population. *Eurasian Journal of Analytical Chemistry, 13*(2), 371-377.