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Research Article
Association Between Opioid Receptor Kappa 1 Gene Polymorphism, Kappa Opioid Receptor Level and Dynorphin Level with Non-Suicidal Self-Injury

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Abstract

Background and Objective: Non-Suicidal Self-Injury (NSSI) is a mental health threat that is a major concern among adolescents and young adults nowadays. It is assumed that NSSI is involved in the mesocortical dopamine reward system, the endogenous opioid system and the overstimulation of the stress system. This study aims to investigate the correlation between Opioid Receptor Kappa 1 (OPRK1) rs7016778 and rs7824175 gene polymorphisms, Kappa Opioid Receptor (KOR) and Dynorphin level with NSSI. **Materials and Methods:** This research was a cross-sectional comparative study between 84 subjects diagnosed with NSSI and 76 controls. The method used was purposive sampling. The NSSI was determined by using the NSSID and ISAS questionnaire according to DSM-5. The examination of polymorphism of the OPRK-I gene was examined using a Polymerase Chain Reaction (PCR) and the level of KOR and Dynorphin was determined using ELISA. **Results:** The OPRK1 rs7016778 gene polymorphism was more common in the NSSI group. The OPRK1 rs7824175 gene polymorphism was more common in the control group. The KOR and Dynorphin levels were higher in the NSSI group. There were differences in KOR levels between NSSI and the control group. There is a relationship between KOR levels and Dynorphin levels with NSSI. There were no differences in the OPRK1 gene polymorphisms rs7016778 and rs7824175 between NSSI subjects and controls. There was no difference in Dynorphin levels between NSSI subjects and controls. **Conclusion:** The role of the Kappa Opioid Receptor (KOR) and Dynorphin in the pathophysiology of NSSI can be considered.

Key words: Non-suicidal, self-injury, opioid, kappa receptor, dynorphin, gene polymorphism

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Non-Suicidal Self-Injury (NSSI) is a public health problem that is a major concern at the moment and a common mental health threat among adolescents and young adults[1-3]. According to the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders; Fifth Edition), NSSI is defined as the deliberate destruction of body tissue directly, by itself, without suicidal intent, occurring within five days or more in the last year[4].

The prevalence of NSSI was found to be high in adolescents, with a peak at 14-15 years of age. The incidence rate continues to rise every year: 33% in developing countries such as China, Turkey, India and Mexico and 24% in the United States[5]. In Indonesia, according to a survey by Tresno *et al.*[6], 38% of respondents had ever committed NSSI and 21% of them had attempted suicide. Data from outpatients at HB Saanin Mental Hospital Padang showed that 78.8% of patients performed mild self-harm and 21.2% performed severe self-harm[7]. Research by Swannell *et al.*[8] shows that around 17.2% of teenagers have committed NSSI at least once throughout their lifetime.

Continued NSSI action can cause addiction that can lead to disruption in the brain's motivation system, including the mesocortical dopamine reward system and the endogenous opioid system, as well as overactivation of the stress system. Currently, there is no research directly linking the mesocortical reward system and NSSI but there is a hypothesis linking both[9]. Polymorphism KOR gene played a role in the tendency for experimental animals to consume alcohol voluntarily. The KOR gene, recently discovered, has a 36G>T Single Nucleotide Polymorphism (SNP) linked to substance dependence in humans[10].

There is still limited research linking OPRK1 (Opioid Receptor Kappa 1) gene polymorphisms and NSSI. Analysis of the influence of genetic and environmental factors suggests an association between NSSI and candidate polymorphisms of the endogenous opioid system. Genetic polymorphisms of Pro-Dynorphin and OPRK1 can be associated with stages of addiction development[11].

Bresin and Gordon[12] reported that low levels of endogenous opioids may be associated with NSSI, whereas lower levels of β-endorphins (and possibly enkephalins) and relatively normal levels of Dynorphin may cause an imbalance in the opioid system and produce dissociative feelings. This study aimed to investigate the association between Opioid Receptor Kappa1 rs7016778 and rs7824175 gene polymorphism, Kappa Opioid Receptor (KOR) and Dynorphin level with non-suicidal self-injury.

MATERIALS AND METHODS

Study area: This research was a cross-sectional study with a comparative study design. Sampling was collected by purposive sampling at the Psychiatric Polyclinic of Dr. M. Djamil Central General Hospital Padang, Ibnu Sina Islamic Hospital Padang and HB Saanin Padang General Mental Hospital. The research was conducted for two years, starting in 2022 until 2024.

Study design: The study subjects consisted of 84 patients diagnosed with NSSI and 76 healthy controls. The inclusion criteria were age 12-29 years, diagnosed with NSSI or healthy control, never receiving psychopharmacology therapy and willing to be a research subject by filling out informed consent. Meanwhile, the exclusion criteria are being diagnosed with a mental disorder, currently suffering from a physical illness and having a history of serious medical illness such as tuberculosis, cancer, heart disease or congenital abnormalities.

The NSSI diagnoses were determined based on DSM-5 and the behaviour and function of NSSI were determined by the Inventory of Statements About Self-Injury (ISAS) that has been validated in the Indonesian version by Liza *et al.*[13]. The ISAS surveys the lifetime recurrence of 12 distinctive NSSI behaviors performed "intentionally (i.e., for a reason) and without self-destructive expectation (i.e., not for self-destructive reasons)". These behaviors incorporate self-banging/hitting, gnawing, burning, carving, cutting, picking, needling, squeezing, hair pulling, rubbing the skin against harsh surfaces, overwhelming scratching and ingesting chemicals. The 160 blood samples were collected in the clinical pathology laboratory and continued with Polymerase Chain Reaction (PCR) and ELISA examinations at the Biomedical Laboratory, Faculty of Medicine, Universitas Andalas, Padang.

Statistical analysis: The statistical analysis using the Chi-square test, Mann-Whitney test and Spearman-rank correlation with a significance value of $p<0.05$.

Ethical consideration: This research has passed the research ethics review test from the research ethics commission of the Faculty of Medicine, Universitas Andalas, description of ethical approval no: 436/UN.16.2/KEP-FK/2023.

RESULTS

There were 160 participants in the study: 21 male (13.1%) and 139 female (86.9%). The majority of participants were 19 years old 23.8% (minimum 14 years and maximum 28 years of age). Only 1.3% of respondents were married. There were no significant differences in gender, age and marital status between the NSSI and control group (p>0.05), it described in Table 1.

The efficacy of multiple sequence amplification with the BPI-F/R primer combination was seen in Fig. 1. Figure 1a shows the success of multiple alignment of amplified sequences using the OPRK1-F/R rs7016778 primer combination which produces a PCR product of 788 bp and uses reference sequence data with IDE number NC_00008, the position of the rs7016778 mutation, namely nucleotide A, is located at base 11,822. Figure 1b shows the success of multiple alignment of amplified sequences using the OPRK1-F/R rs7824175 primer combination which produces a PCR product of 483 bp and uses reference sequence data with IDE number NC_00008, the position of the rs7824175 mutation, namely nucleotide C, is located at base 5,892.

The results of PCR examination shown in Table 2, can be concluded that the results of the comparison of the Opioid Receptor Kappa I (OPRK1) gene polymorphisms rs7016778 and rs7824175 between subjects with Non-Suicidal Self-Injury (NSSI) and controls are as follows: The OPRK rs7016778 gene found a higher frequency of the AT allele in NSSI (19%), compared to controls (7.9%) while the frequency of the TT allele was found in controls (1.3%) and was not found in NSSI, to investigate the possibility of a relationship between the OPRK1 rs7016778 gene allele and NSSI, a statistical test was

Table 1: Demographic characteristics of participant

Characteristics		NSSI		Control		Total		
		n	%	n	%	n	%	p*
Sex	Male	9	10.7	12	15.8	21	13.1	0.342
	Female	75	89.3	64	84.2	139	86.9	
Age (years old)	14	1	1.2	0	0.0	1	0.6	0.082
M (20.67)	18	7	8.3	7	9.2	14	8.8	
SD (2.06)	19	15	17.9	23	30.3	38	23.8	
Min (14)	20	16	19.0	14	18.4	30	18.8	
Max (28)	21	13	15.5	20	26.3	33	20.6	
	22	13	15.5	6	7.9	19	11.9	
	23	6	7.1	2	2.6	8	5	
	24	5	6.0	3	3.9	8	5	
	25	5	6.0	0	0.0	5	3.1	
	26	2	2.4	0	0.0	2	1.2	
	27	1	1.2	0	0.0	1	0.6	
	28	0	0.0	1	1.3	1	0.6	
Married status	Single	82	97.6	76	100.0	158	98.7	0.176
	Married	2	2.4	0	0.0	2	1.3	

*Chi-square

Table 2: Differences in OPRK1 gene polymorphisms, KOR levels and Dynorphin plasma levels between NSSI and control group

OPRK1 gene polymorphisms, n (%)	NSSI (n = 84)	Control (n = 76)	p-value
rs7016778	-	-	0.076[a]
AA	68 (81.0)	69 (90.8)	
AT	16 (19.0)	6 (7.9)	
TT	0 (0.0)	1 (1.3)	
rs7824175	-	-	0.468[a]
CC	76 (90.5)	66 (86.8)	
AC	8 (9.5)	10 (13.2)	
KOR (nmol/L)	-	-	<0.001[b]*
Mean (SD)	4.24 (3.66)	2.91 (1.61)	
Median (IQR)	2.91 (2.61-3.24)	2.52 (2.34-2.85)	
Min-Maks	2.09-20.16	1.78-13.02	
Dynorphin (ng/L)	-	-	0.375[b]
Mean (SD)	110.41 (99.49)	82.20 (53.93)	
Median (IQR)	70.95 (65.25-91.15)	70.97 (48.05-424.65)	
Min-Maks	48.42-508.09	48.05-424.65	

NSSI: Non-Suicidal Self-Injury, OPRK: Opioid Kappa Receptor, KOR: Kappa Opioid Receptor, [a]Chi-square, [b]Mann Whitney and *Significant p<0.05

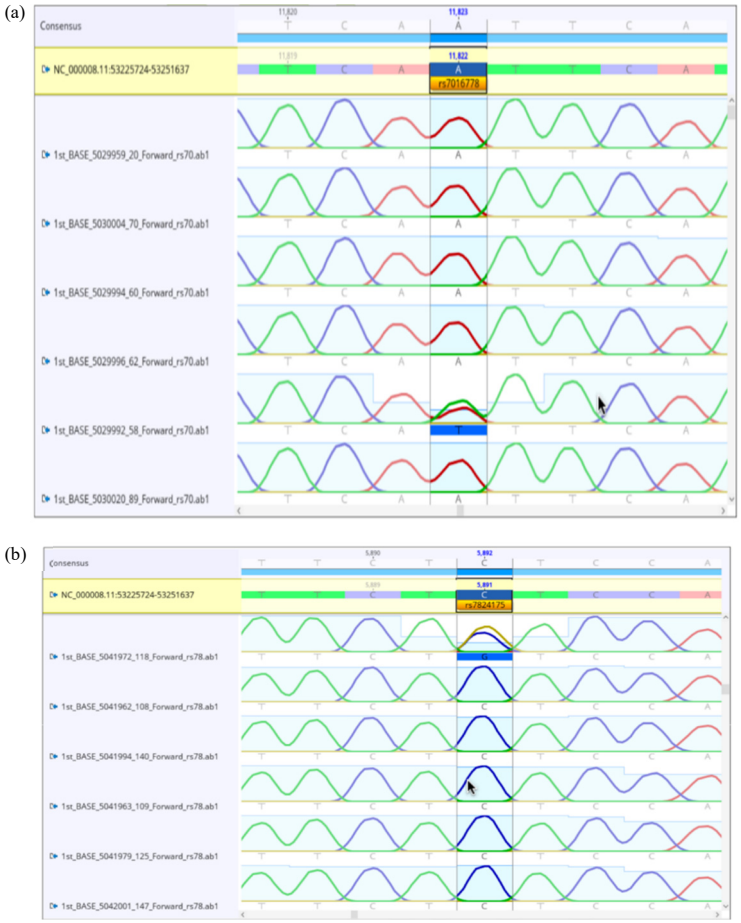

Fig. 1(a-b): Results of multiple alignment sequencing of the OPRK gene (a) SNP rs7016778 and (b) SNP rs7824175

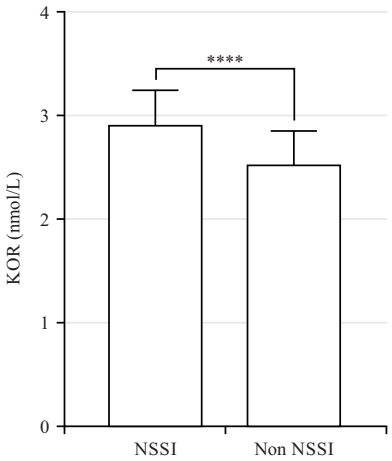

Fig. 2: Differences in KOR levels between Non-Suicidal Self-Injury (NSSI) and control group
****Significant (p: 0.001)

carried out, the p-value was slightly above the significance threshold of 0.076, so that in statistics it seems that there is no significant relationship between the OPRK1 rs7016778 gene allele and NSSI. Meanwhile, for the OPRK rs7824175 gene, there was also no significant difference in allele distribution between the two groups (p = 0.468). The GC genotype was higher in the control group 10 (13.2%) than in the NSSI group 8 (9.5%).

Subjects with NSSI had significantly higher KOR levels compared with control group (mean 4.24 nmol/L in NSSI vs 2.91 nmol/L in non-NSSI, p<0.001) Fig. 2. There was a significant difference in plasma KOR levels between subjects with NSSI and control group (p<0.001) Fig. 2. There was no significant difference in plasma Dynorphin levels between subjects with NSSI and control group (p = 0.375). However, the average Dynorphin level was higher in NSSI subjects (110.41 ng/L) compared to the control group (82.20 ng/L) as shown in Fig. 3.

Figure 4 shows the correlation between Kappa Opioid Receptor (KOR) levels and plasma Dynorphin levels in NSSI subjects and controls. This analysis was performed using Spearman's Rank Correlation. Figure 4a shows that there was

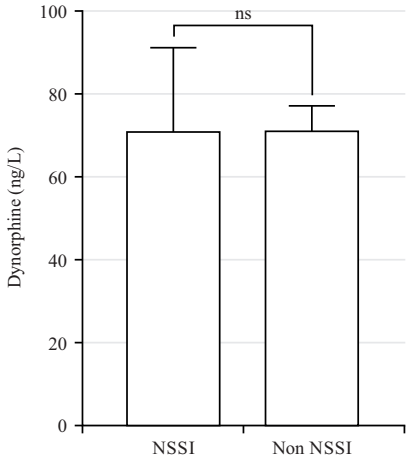

Fig. 3: Differences in Dynorphin levels between Non-Suicidal Self-Injury (NSSI) and control group
ns: Non significant (p: 0.375)

a significant positive correlation between KOR levels and plasma Dynorphin levels (coefficient r = 0.578, p<0.001). This indicated that increased OPRK levels are associated with increased overall plasma Dynorphin levels. Figure 4b shows the correlation in subjects with NSSI: The correlation between KOR levels and plasma Dynorphin levels in subjects with NSSI was stronger (coefficient r = 0.680, p<0.001). This indicates that in subjects with NSSI, increased OPRK levels are more strongly associated with increased plasma Dynorphin levels than in subjects without NSSI. Figure 4c shows the correlation in control subjects: There was a significant positive correlation between KOR levels and plasma Dynorphin levels in control subjects (coefficient r = 0.508, p<0.001). Although the correlation was significant, its strength was lower compared to subjects with NSSI.

DISCUSSION

In this study, PCR examination of the OPRK1 rs7016778 gene found a higher frequency of the A genotype in NSSI patients. The PCR examination of the OPRK1 rs7824175 gene found a higher frequency of the C genotype in controls. There was no difference in the polymorphism of the OPRK1 rs7016778 and rs7824175 genes between subjects with NSSI and controls. The PCR examination was performed on the OPRK rs7016778 and rs7824175 genes based on previous research conducted by Sato *et al.*[14] discovered that muscle pressure pain tolerance varies in relation to OPRK rs7016778 and rs7824175. This Single Nucleotide Polymorphism (SNP) accounted for 43% of the variation in muscle pressure pain sensitivity and this result remained statistically significant even after correcting for multiple testing[14]. The results of the study in the NSSI group showed a higher frequency of the A allele than the control, this can be compared with the study by Sato *et al.*[14], which found a high muscle pressure pain threshold in the group of subjects who had the OPRK rs7016778 gene genotype AA and AT which means those with these alleles have high muscle tension pain threshold. The NSSI patients they tend to do self-harm behavior that will produce pain, but the pain seems to be tolerated and accepted and desired by the individual, as well as OPRK rs7824175 allele C, groups that have many allele C such as genotype GC/CC will have a low pain threshold, in the study it was found that the control group had more allele C than the NSSI group so it can be concluded that the pain threshold of the control group is lower than the NSSI group. From this study, it can be concluded that this genetic variation can affect how a person feels and responds to mechanical pain. This polymorphism is located in the intronic region of the gene, which is not directly involved in protein synthesis but can affect gene expression or protein function through mechanisms such as linkage disequilibrium. That is, this SNP may function as a marker for polymorphisms that affect protein function[14]. Olesen *et al.*[15], did not find a significant association between OPRK gene polymorphism and pain sensitivity.

Silent polymorphisms of the OPRK gene do not seem to impact mRNA transcription, but post-transcriptional mechanisms such as mRNA stability, translation efficiency and regularity could affect the function of the KOR system and potentially increase vulnerability to substance abuse or addiction. Different types of opioid receptors may be responsible for causing addiction. Kappa Opioid Receptor (KOR) seems to be involved in stress reactions, opioid withdrawal and psychostimulant reactions through the inhibition of mesolimbic dopamine[10].

In this study, levels of Kappa Opioid Receptor (KOR) and Dynorphin (DYN) were examined in two treatment groups, namely the NSSI group and the control group. The results obtained showed that KOR and Dynorphin levels were found to be higher in the NSSI group compared to the control group. Although only the difference in KOR levels was statistically significant (p<0.000), Dynorphin levels in the NSSI group were higher than those in the control group. Neuropeptides, including opioids, oxytocin and vasopressin, play an important role in regulating affiliative behavior[16]. This is in accordance with research by Stanley *et al.*[17], which also found no difference in Dynorphin levels between NSSI patients and controls; however, Dynorphin was examined in cerebrospinal fluid.

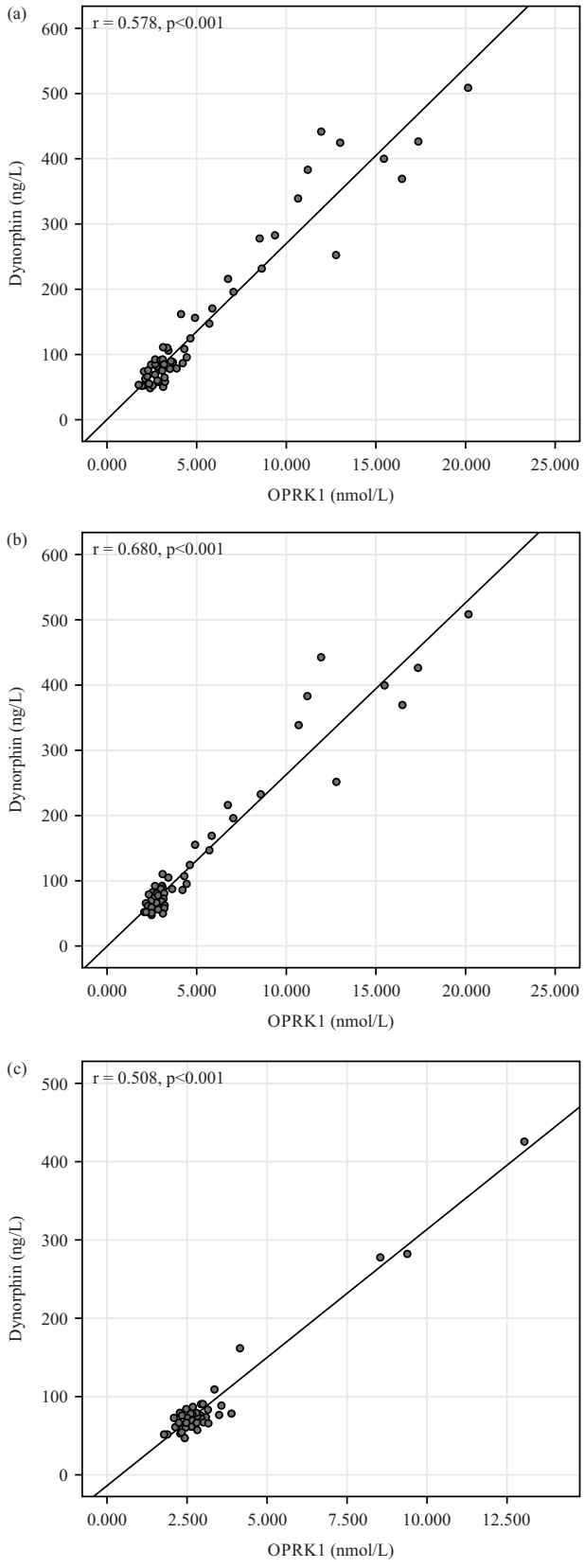

Fig. 4(a-c): Scatterplot of KOR levels and plasma Dynorphin levels in subjects with NSSI and control, (a) Correlation in all subjects, (b) Correlation in subjects with NSSI and (c) Correlation in control subjects

Because the Kappa Opioid Receptor (KOR) binds to Dynorphin, the higher the KOR levels, the less Dynorphin. Meanwhile, Dynorphin levels were higher in NSSI patients than in controls because stress is most often associated with unpleasant circumstances. It rapidly induces the release of hormones and neuropeptides, including Dynorphin, which activates Kappa Opioid Receptors (KOR) in the central and peripheral nervous systems[18].

In this study, a significant relationship was found between KOR levels and Dynorphin. Two main groups of stress neuropeptides that play a role in this mechanism are corticotropin-releasing factor (CRF, also known as corticotropin-releasing hormone, CRH) and Dynorphin. Subsequently, it was discovered that Dynorphin plays a role in modulating the antinociceptive reaction. The pharmacological level has also well described the Kappa Opioid Receptor (KOR)/Dynorphin system. The KORs, present in many areas of the brain, spinal cord and peripheral tissues, are G Protein-Coupled Receptors (GPCR). The potent endogenous opioid peptide or Dynorphin specifically activates KOR, with each opioid or Dynorphin having unique structural characteristics that determine KOR selectivity. The ion channel in neurons is modulated by KOR in a way that inhibits cell firing and reduces neurotransmitter release. All three opioid systems have shown a stress-induced release of opioid peptides, such as β-endorphin, enkephalin and Dynorphin and this release is linked to stress-induced pain relief in rodents. Moreover, stress has been demonstrated to elevate Dynorphin levels. Combined, these studies indicate that stress may result in higher levels of naturally occurring opioid peptides being released, with Dynorphin being a key peptide released during this process[19].

There is an interaction between CRF and the neuropeptide/Dynorphin circuit that is integral to understanding how the stress response is encoded. Since CRF and KOR lead to HPA activation, it is crucial to also take into account the role of glucocorticoids in Dynorphin/KOR-induced behavior. Some evidence indicates that Dynorphin/KOR activity may be linked to corticosterone levels, as studies revealed that corticosterone levels rose faster after stress in Dynorphin-deficient mice; nevertheless, researchers did not observe any distinct variation in corticosterone levels following stress or non-stress situations between wild-type animals and Dynorphin knockout animals. Moreover, Dynorphin gene disruption or KOR antagonism does not affect stress-induced corticosterone levels, as reported in other countries[19].

Self-harming behaviors will elicit unpleasant stimuli. It is now generally acknowledged that DYN/KOR expression in a number of brain regions-including the thalamus, amygdala, hippocampus, cortex and basal ganglia-as well as the monoaminergic midbrain and brainstem structures linked to motivation, pain and itch processing, are implicated in mental illnesses[20]. Opioids control numerous brain functions related to addiction, such as reward, reinforcement, mood and psychomotor stimulation. More precisely, activation of Kappa Opioid Receptors (KOR) decreases the release of dopamine in the nucleus accumbens of rats and leads to a negative emotional state. Thus, KOR plays a role in addiction, pain, reward, mood, cognition and perception as well. The neuropeptide Dynorphin plays a crucial role in the analgesic and tolerance effects by activating KOR[21]. This limitations were only examined the OPRK gene polymorphisms rs7016778 and 7824175. The study could not directly assess the relationship between opioids and the onset of addiction that may be the basis for the onset of NSSI disorders. Further research is needed to assess this relationship. This is the first study to assess the role of OPRK gene polymorphisms, Kappa Opioid Receptors (KOR) and Dynorphin with non-suicidal self-injury. This study proves the role of Kappa Opioid Receptors (KOR) and Dynorphin in non-suicidal self-injury.

CONCLUSION

This study is the first study to assess the role of OPRK1 gene polymorphism, Kappa Opioid Receptor (KOR) and Dynorphin with non-suicidal self-injury. This study proves the role of Kappa Opioid Receptor (KOR) and Dynorphin in non-suicidal self-injury. Overall, the study of OPRK1 rs7016778 and rs7824175 is expected to provide important insights into how genetic variations can affect individual pain sensitivity, which may have implications for the development of more personalized NSSI therapies in the future.

SIGNIFICANCE STATEMENT

The objective of this study was to determine the relationship between OPRK1 gene polymorphisms rs7016778 and rs7824175, Kappa Opioid Receptor (KOR) levels and Dynorphin levels with nonsuicide self-injury. The results of the study can determine a person's vulnerability to NSSI behavior and determine the risk factors for the emergence of non-suicidal self-injury disorders. The results of the study can be used as a reference for the advancement of science to increase the treasury of science, especially in the field of mental health. This study proves the role of Kappa Opioid Receptor (KOR) and Dynorphin in non-suicidal self-injury. These findings propose the development of opioid-based therapies for NSSI and the development of more personalized NSSI therapies in the future.

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