

## REVIEW PAPER

# Description of schizophrenia and related mechanisms: Oxidative stress and role of ketamine against N-methyl-D-aspartate receptor

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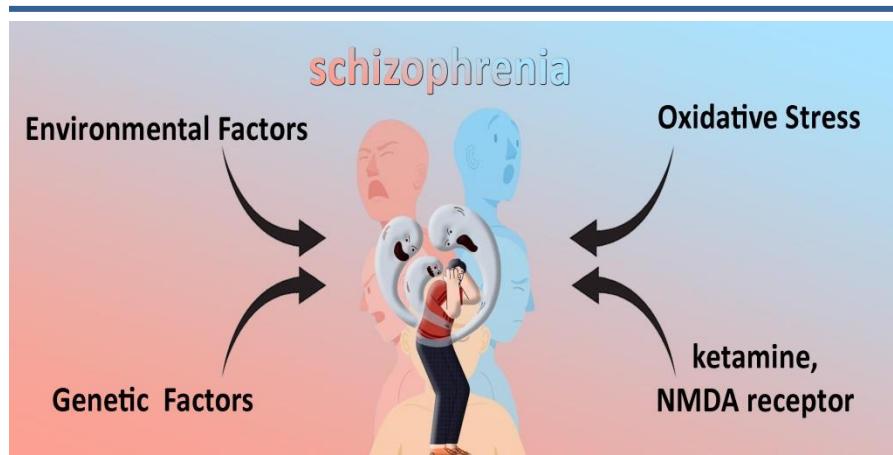
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## Highlights

- Schizophrenia is considered a debilitating and complex mental disease.
- Environmental and genetic factors can affect the development of this disease.
- Oxidative stress and impaired glutaminergic receptors involved in schizophrenia pathogenesis.
- Ketamine contributes to the development of schizophrenia symptoms via NMDA receptors.

## Graphical Abstract



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## Abstract

Schizophrenia is a very violent mental illness with an occurrence of less than 1% in the global population. The disease mainly happens in early adulthood and late adolescence, at which time the symptoms and psychological features of the disease appear and often lead to a difficult and painful life for both the patient and his family. This disorder can be impressed by genetic and environmental factors. Environmental factors including infections, stress, nutrition, etc. can change the risk of developing this disease. Genetic factors such as genes involved in neurological processes can also have a main role in the disease development. Glutamate receptors are accountable for glutamate-mediated postsynaptic stimulation of nerve cells and are essential for learning, memory development, neuron communication, anxiety, pain perception, and regulation of brain function. However, hyperactivity of NMDA receptors is effective in the development of schizophrenia. Non-competitive antagonists or open channels of N-methyl-D-aspartate receptors or NMDARs including low-dose phencyclidine and ketamine lead to schizophrenia-like symptoms and results in GABA impairment. Levels of glutamate in the hippocampus are also increased by ketamine, which corresponds to an increase in glutamate in schizophrenia. This study aimed to description of schizophrenia and related mechanisms by focus on the oxidative stress and role of ketamine against NMDA receptor.



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## Introduction

Schizophrenia is a neurological illness with an occurrence less than 1% in the world's population. The disease is described by signs such as delusional, talking to themselves, engaging with imaginary people, and having movements beyond one's control. Symptoms of this disease are classified into three types: positive signs (mental disorder, delirium, and hallucinations), negative signs (absence of motivation and social isolation) and cognitive signs (impaired attention and conscious memory) (1). Its positive effects are reduced by the use of antidepressants based on the inhibition of dopamine receptor D2. But symptoms such as memory impairment are not eliminated by these drugs because of our restricted knowledge of the disease pathophysiology. The disease usually occurs at a young age and early adulthood. The prevalence of this disease is higher in women than men. In the acute form of the disease, life expectancy decreases (2).

The risk of developing schizophrenia in adulthood is much higher than in peers if the child's childhood is spent mainly playing and experiencing pleasant things, unpleasant and stressful experiences. Inheritance factors have a central role in the development of this disease. Genomic studies have illustrated that the dopamine receptor D2 genetic marker is a cause of the disease and other genes involved in excitability and glutamatergic neurotransmission including subunits of calcium voltage channels and a group of NMDA receptors in schizophrenia are other causes of the disease (3). Of course, some aspects of this disease can also be affected by environmental factors. For example, increased rates of uterine insufficiency (such as certain infections during pregnancy and malnutrition during pregnancy), as well as postpartum complications (such as preterm delivery and pregnancy poisoning), also increase the risk of schizophrenia. Other environmental factors including stress of the mother, childhood trauma, and oxidative stress are involved in the development and spread of the disease (4).

Impaired neurotransmission in systems such as gamma aminobutyric acid, glutamate, serotonin, dopamine, and acetylcholine, and altered brain functions, neural circuits, and signal conduction pathways are involved in schizophrenia. Reactive oxygen species (ROS), inflammatory responses, changes in oligodendrocytes, epigenetic alterations, dysfunction of mitochondria, and imbalances are seen in schizophrenia. Altered the expression of genes contributed to G-protein signaling, energy and metabolism, synapses, neuronal growth, myelination, apoptosis, glial function, apolipoproteins, and sphingolipid metabolism are also seen in disease (5).

Oxidative stress is a sign of nerve disorders including schizophrenia. The mechanism of oxidative damage in this disease is not completely understood, but there is much evidence to support the theory that oxidative damage contributes to the pathology of schizophrenia. Research has shown that in schizophrenia, the level of peroxidation of lipid in the thalamus and hippocampus is meaningfully elevated. High concentration of oxidation in the body undoubtedly damage tissues, which is common pathogenesis of acute schizophrenia (6). Some studies show that the levels of enzymatic antioxidants in schizophrenia patients are lower or higher than in normal subjects. And plasma concentrations of non-enzymatic antioxidants including bilirubin, uric acid, and albumin are lower in schizophrenics than in healthy individuals. Pathological consequences of oxidative stress such as oxidative injury to cellular proteins, lipids, enzymes, carbohydrates and genome content are involved in the development of schizophrenia (7).

The effect of glutamate is regulated by ionotropic receptors such as NMDA and metabotropic receptors. Transporters in plasma membrane, including excitatory and vesicular amino acid transporters, release glutamic acid from the synaptic place. Hyperactivity of NMDARs is effective in the progress of schizophrenia. Non-competitive antagonists or open channels of NMDA receptors such as low-dose phencyclidine and ketamine cause schizophrenia-like symptoms and lead to GABA impairment. Glutamate levels in the hippocampus are also increased by ketamine, which corresponds to an increase in glutamate in schizophrenia (8). This study aimed to description of schizophrenia and related mechanisms by emphasis on the oxidative stress and role of ketamine against N-methyl-D-aspartate receptor.

## Schizophrenia definition and history

Schizophrenia has been widely described for the past two centuries. Because of this, researchers believe that the population has been affected by schizophrenia in the last two centuries, and that some issues, such as population growth, industrialization, and urbanization, may involve in the disease development (9). In the early 1900s, the term schizophrenia was employed by a Swiss psychiatrist, which is based on the Greek word *skhizein* (to split) and *phrēn* (mind). It is a violent mental illness determined by profound impairment of cognition, insufficient emotion, and a disrupted ability to behave appropriately. In the world's population, about one percent of patients suffer from these severe statuses (10). Schizophrenia is still an incurable disorder and its causes are not well understood. In the early twentieth century, it was said that a factor influencing the progress of this disease is genetic factors. Recently, the disease has been referred to as a neurodevelopmental disorder that is long and difficult to diagnose. A person may suffer from this disease for several years before the characteristic symptoms appear. People experience the highest risk of developing the disease between the ages of 15-30. The course of this illness is different in schizophrenia patients. This disorder occurs in acute episodes. This condition may resolve over several periods, and about 30% of people with schizophrenia can return to normal. People with this disease often cannot do their jobs and usually do not have an independent life. People with schizophrenia generally live about 20% shorter lives than healthy people in the community (10). According to Palmer et al., Schizophrenia people are at advanced risk of suicide (11). The incidence of suicide among people with schizophrenia is about 4.9%, which is usually close to the onset of the disease. Causes of suicide in people with schizophrenia are usually due to impaired social life and incapability to manage regular life. The role of the family in returning to normal life is very important in people with schizophrenia. These people should be constantly encouraged in their activities. Despite the many changes in treatment options in recent decades, no significant improvement has been achieved and the improvement rate in this disease is 1 in every seven patients (12). Given the severity of the disease, its subsequences, as well as the unknown cause of the disease, risk factors for the disease should be considered and efforts to prevent the disease should be focused.

## Epidemiological characteristics of schizophrenia

There are studies that show the unequal distribution of schizophrenia in society and its prevalence is higher in lower socio-economic strata. The occurrence of schizophrenia is lower in women than men (13). Studies show the effect of location on the occurrence of schizophrenia (14). The median occurrence of this disease was estimated 15.2/100,000. The incidence of this disease in women compared to men was 1.4: 1. Mortality rates showed that individuals with schizophrenia had a two to threefold elevated risk of death. Other estimates show that the occurrence of schizophrenia is higher in immigrants than in indigenous peoples. Economic status and urbanization can also be correlated with the development of the illness (10). Overall, the occurrence of schizophrenia is assessed at 0.14 to 0.46%. In a review study of Central and Eastern Europe, the incidence of lifelong schizophrenia changes was found to be 0.4% to 1.4% (15). The prevalence of the disease in Finland was estimated at 0.87% (16). Of course, these data are approximate because some factors such as mortality and age-specific migration can distort them.

## Risk factors of schizophrenia

### *Environmental factors*

Although the reason of schizophrenia disorder is not well known, epidemiological and molecular studies have shown the role of several genetic and environmental risk factors in the incidence of the disease (17). Various environmental factors can have a role in changing the risk of the disorder. These include immigration, childhood trauma, infectious agents, urbanization, cannabis use, and psychological factors. These risk factors can be physical, biological, social, or psychological, and may affect different stages of a person's life (early adulthood, adolescence, childhood, and adulthood) (18). People born in late winter and early spring are more prone to schizophrenia (19, 20). There is an outbreak of flu and some other respiratory infections in winter.

These viral infections during pregnancy can cause the brain alteration that increase the risk of developing schizophrenia. Epidemiological data confirm this, but the exact reason is still unknown. Some factors or a combination of them such as temperature, climate, light intensity, nutrition and infectious agents are the most likely explanations for the above issues. Sunlight can be about 90% involved in providing the vitamin D needed by the body. Vitamin D deficiency during pregnancy can negatively affect fetal growth and brain development factors. Both high and low levels of vitamin D in infants elevate the risk of developing schizophrenia (21). Living in urban areas doubles the risk of this disorder. Higher population density equals an elevated schizophrenia risk (22). Also, events in urban life that include noise, stress, crime, pollution, and some other destructive factors can elevate the schizophrenia risk (10).

Some non-genetic complications related to maternal conditions, pregnancy, and birth can affect the development of schizophrenia. The most common complication that can lead to schizophrenia is fetal hypoxia (23). Complications during pregnancy, including preeclampsia, may also elevate the schizophrenia risk (24). Pregnancy stress can also affect the development of schizophrenia in the fetus. Intrauterine bleeding can impair brain development. Complications of labor can also lead to brain ischemia and cranial damage, as well as nerve tissue compression. Therefore, problems during pregnancy and childbirth can be a chief risk factor for the disease. As a result, being aware of the risks and initial therapeutic interventions can be helpful for these individuals (25).

Infectious agents, including viruses, bacteria, and protozoa, can be indirect risk factors for schizophrenia (26). Virus of influenza in pregnancy period is an identified risk factor for neurological disorders such as schizophrenia. This factor can show the greatest effect in the sixth month of pregnancy (27). Influenza A virus can increase the concentration of quinoric acid and impair brain growth and cause cognitive impairment in later developmental stages. Measles is also an infection that has been linked to congenital defects in central nervous system. Early measles infection during pregnancy can elevate the schizophrenia risk in adulthood (10).

Drugs can be considered as one of the most common factors in increasing the risk of psychotic diseases. These include phencyclidine, lysergic acid diethylamide (LSD), methamphetamine, opiates, cocaine, tobacco, cannabis, and alcohol. Cannabis, alcohol and tobacco are often abused. The results of studies on cannabis use in adolescence and schizophrenia are contradictory. Some studies also emphasize the role of cannabis in increasing the risk of schizophrenia in susceptible individuals (23). Many patients with schizophrenia become addicted to tobacco (28). In addition, the chemicals in tobacco smoke suppress the symptoms of schizophrenia. For example, nicotine improves memory and information processing. Alcohol is another addictive substance that is abused in fifty percent of people with this disorder (29). Patients' refusal to abstain from alcohol and drugs can lead to a recurrence of schizophrenia.

Prolonged exposure to stress can impair mental health. During the first few weeks of fetal development, fetal mental development can be affected by pregnancy stress and damage. Also, children raised in normal family situations did not have mental health problems, including schizophrenia, compared to poor families. Children who suffer from a lot of stress and have countless negative experiences may develop mental health problems in the future (30). For schizophrenia patients, even a stressful incident can lead to hospitalization. Stress can increase the production of the hormone cortisol, which leads to damage to the hippocampus and exacerbates the course of schizophrenia. Hippocampal volume is reduced in schizophrenics than in normal individuals (10).

### **Genetic and epigenetic factors of schizophrenia**

Many family studies of schizophrenia show that the risk of having children with schizophrenia is about 10 times higher (31). Some studies have suggested that different genes may play a role in changing the risk of schizophrenia. In general, about 30% of the risk of schizophrenia is due to genetic factors. Genomic examinations have revealed that the dopamine 2-receptor gene (DRD2) in schizophrenia is a reason of this illness. Other genes involved in excitability and glutaminergic neurotransmission, including subunits of calcium voltage channels and a group of NMDA receptors in schizophrenia, are other causes of the disease (31, 32).

Genetic disorders, such as the deletion or duplication of certain pieces of DNA, automatically increase the incidence of schizophrenia and occur in 2-3% of people with the disorder. One of the most obvious genetic factors is the deletion of megabases of DNA on the chromosome (22q11), which causes 30-40% of people with this disease (32). The relationship of some single nucleotide variations in different genes with the risk of schizophrenia has been investigated, which are summarized in Table 1. Although efforts have been focused on identifying the genetic or environmental causes of schizophrenia, in some cases molecular factors cannot yet be linked to clinical factors. Epigenetics can explain how environmental parameters affect gene profiles without altering gene sequences. Epigenetic factors include DNA methylation and histone changes (33).

**Table 1.** Some studied polymorphisms in relation with the risk of schizophrenia.

Gene	Variation	Population	Outcomes	References
DRD2	rs1076560	India	There was no association of this SNP with schizophrenia.	(34)
COMT	rs4680		There was no association of this SNP with schizophrenia.	
	rs4680	Poland	It was found significant differences between deficit schizophrenia and nondeficit schizophrenia in COMT-rs4680 genotype distribution.	(35)
	Val158Met	USA	The allele Met was correlated with improved performance in the Processing Speed and Attention domain	(36)
BDNF	rs6265	Poland	No correlation was observed between the BDNF gene polymorphisms and schizophrenia.	(35)
Glutamic acid decarboxylase	GAD65	Canada	They found no true correlation.	(37)
	GAD67		They found no true correlation.	
IFN- $\gamma$	+874T/A	Poland	The of allele A presence at the mentioned polymorphism associates with 1.66-fold higher risk of paranoid schizophrenia development in males.	(38)
IL-6	-174G/C	Poland	The allele C presence at -174 location of IL-6 might associate with the paranoid schizophrenia risk.	(39)
IL-10	-1082G/A		The G allele presence at -1082 location of IL-10 associates with risk of paranoid schizophrenia.	
DRD2	Taq1B	Indian	This variation was not correlated with the risk of schizophrenia.	(40)
	Taq1D		This variation was not correlated with the risk of schizophrenia.	
	S311C		This polymorphism was not associated with the risk of schizophrenia.	
	H313H		Genotype H313HTT was observed to be correlated with schizophrenia	
	Taq1A		This variation was not correlated with the schizophrenia risk.	
IL-1beta	TaqI	China	This variation in IL-1 $\beta$ gene may not confer elevated risk of disease.	(41)



### Schizophrenia and oxidative stress

Increasing the reactive species levels and decreasing the concentration of antioxidants cause oxidative damage to cells. Studies display that oxidative damage are present in schizophrenia (5, 6). Although oxidative damage may not be a major cause of schizophrenia, there is some evidence that it might have a role in the poor outcomes of schizophrenia. Assessing oxidative stress in the brain is very hard and there is no suitable method to measure this factor in living tissue in humans. Various methods have already been used to measure oxidative stress in this disease. Recently, various studies have examined some parameters related to oxidative stress, including the levels of antioxidant. Glutathione and total levels of antioxidant have been revealed to be lower in the serum of people with schizophrenia (6, 42). Also, increased concentrations of ROS have been observed in schizophrenics, along with decreased levels of SOD and GPx. In addition, glutathione levels were assessed after death and evidence showed a decrease in glutathione levels in the brains of schizophrenia patients, followed by an elevation in oxidative stress (43, 44). In schizophrenia, redox impairment and consequent oxidative damage might be seen in some patients. They show decreased concentrations of polyunsaturated fatty acids (PUFAs) in red blood cells at certain phases of the disorder (45). Genetic studies have revealed a correlation of gene variants involved in oxidative damage and the disease. Occurrence of a specific genotype in the catalytic unit of glutathione cysteine ligase can impair GSH synthesis capacity. Genomic studies have identified the *cacna1c* gene as a strong risk factor for emotional impairments. This gene has been shown to be associated with the function of mitochondria and its oxidative damage, and might play a major role in pathogenesis of schizophrenia (46, 47).

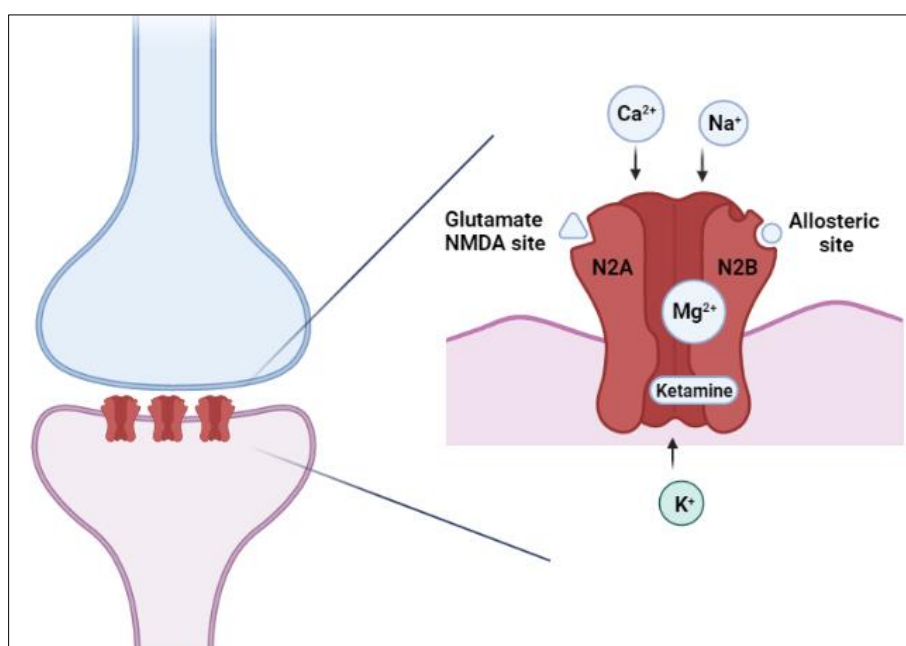
### NMDA receptor and the ketamine effects in schizophrenia

Glutamate receptors are synaptic and non-synaptic receptors that are mainly positioned in the cell membrane of neuron and glia. Glutamate receptors are responsible for glutamate-mediated postsynaptic stimulation of nerve cells and are essential for communication of neuron, learning, formation of memory, anxiety, pain perception, and regulation of brain function. There are two types of receptors in the membrane; metabotropic and ionotropic (48). Ionotropic receptors are divided into three types, NMDA, AMPA, and kainate, depending on the compound to which they are attached. All three types of channels are also opened by glutamate. Ionotropic receptors cause rapid ion infiltration in response to glutamate and form the gateway for excitotoxicity. They contain a site for extracellular glutamate binding and a membrane ion channel (49). NMDARs, the most complex ionotropic glutamate receptors, respond to slow synaptic responses, and these receptors play important roles in brain development, learning, and memory. Therefore, ionotropic receptors could be classified into two NMDAR types and non-NMDA receptors. At rest, the pores of NMDAR channels are usually inhibited by Mg ions. When glutamate is released from presynaptic sites, active AMPARs cause partial depolarization in the postsynaptic membrane, which is sufficient to remove Mg<sup>2+</sup> from NMDARs. NMDARs are then activated, transporting Ca<sup>2+</sup> and Na<sup>+</sup> to the cell. The Ca<sup>2+</sup> influx through NMDARs is important for normal physiological processes in neurons (50). In excitotoxicity, overexpression of glutamate leads to over-activation of NMDARs and overloads calcium inside nerve cells, leading to a range of pro-death signaling events such as activation. Calpain produces ROS and mitochondrial damage that ultimately results in cell necrosis or apoptosis (51). Hyperactivity of NMDA receptors is effective in the development of schizophrenia (52).

More than half a century ago, the exploration for a low-risk but effective sedative led pharmacists to the CI-400 and CI-395 phencyclidines. Although these two were reliable sedatives, the hallucinogenic impacts that patients experienced after consciousness were intense, so the search for phencyclidine-related compounds began with less hallucinogenicity. Finally, ketamine (CI-581) was discovered as a safer substance, first produced by Calvin Stevens at Parke-Davis in 1962. Ketamine is often defined as a unique drug because it has hypnotic, analgesic, and amnesic effects, and having these three properties together is almost unique (53, 54). Ketamine causes a state of anesthesia called dissociative anesthesia, which causes pain, changes in consciousness and

perception, but is not hypnotic or sedative (55). Ketamine appears to selectively block the system of thalamocortical, and the patient quickly enters a trance-like state with the eyes wide open. In this case, the patient is unconscious and completely numb (56, 57). His respiratory system is completely open and only a few pharyngeal-laryngeal reflexes are preserved. This dissociative anesthesia is the result of decreased activity in the structures of thalamocortical system and elevated action in the limbic and hippocampal systems (58). Ketamine is quickly distributed in the brain and other tissues highly perfused. The onset of the first effects is within a few seconds after intravenous injection, 1 to 5 minutes after intramuscular injection, and 15 to 20 minutes after oral administration (54).

The psychiatric impacts of ketamine are detected at doses sub anesthesia (59, 60), which is likely to be achieved in the micromolar range (very low), although the actual concentration is unclear (61, 62). At low  $\mu\text{Mol}$  levels, ketamine prevents only a portion of NMDARs and removes a substantial fraction of NMDARs at the peak of drug action (63, 64). The ketamine effects on NMDAR are illustrated in Figure 1. Ketamine is a non-competitive NMDAR antagonist (65) that acts by a mechanism of open channel block (66). Therefore, ketamine does not attach to closed form of channels of NMDAR (66). Ketamine, similar to its analogues, MK-801 and phencyclidine, forms an open channel block in which the drug attaches to a region electrically deep in the ion channel, blocking the ions flow via the open form channel. Depolarization of the block membrane is likely to decrease with increasing drug detachment rate, but the exact mechanism of the voltage dependence is unknown and does not seem to be completely explained through a model of electrostatic (66).



**Figure 1.** Effects of ketamine on the NMDA receptor. Within the NMDAR channel, ketamine could link to it and actually it is a non-competitive antagonist for NMDAR. The NMDAR inhibition could affect the ions influx and prevent the depolarization of cell membrane.

## Conclusion

Schizophrenia is considered as a severe and debilitating illness with high psychological, social and economic consequences. Numerous genetic and environmental factors can affect the development of this disease. For example, genes involved in neurological processes as well as environmental factors such as lifestyle and stress, etc. can be involved in the development of this disease. Oxidative stress is involved in the development of schizophrenia. Deficiency of antioxidants and increase of oxidative factors are evident in this disease. Impairment of NMDA glutaminergic receptors is also involved in the development of this disease, and ketamine can result in the development of schizophrenia symptoms by acting on these receptors. Given the

great financial and psychological burden that this disease can impose on society, recognizing the pathological aspects of this disease can be useful in providing appropriate treatment strategies.

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