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RESEARCH ARTICLE

Protective Effect of Resveratrol and N-Acetylcysteine Combination Against Locomotor Hyperactivity Induced by MK-801

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ABSTRACT

N-Methyl-D-Aspartate (NMDA) receptors are one of the most important elements of the glutamatergic system. The hypofunction of this receptor causes locomotor hyperactivity. The chemical agent MK-801, which is an NMDA receptor antagonist, also causes locomotor hyperactivity in rodents. In the present study, it is aimed to find the lowest protective dose of neuroprotective resveratrol and N-acetyl-cysteine (NAC) combination on increased locomotor activity using MK-801 in mice. For this purpose, 84 female mice were used and 14 groups of equal number of mice were formed. Locomotor hyperactivity was created in two parts as acute (1 day drug administration) and sub-acute (4 days drug administration) phases. After drug administrations, animals were subjected to open field testing. According to the results, the drug combination was successful in reducing locomotor hyperactivity in the acute phase than in the sub-acute phase. It was observed that the intraperitoneal administration of both low doses of the combination, 40mg/kg resveratrol + 20mg/kg NAC and 20mg/kg resveratrol + 10mg/kg NAC, successfully prevented the locomotor hyperactivity in the acute phase. As a result, it was concluded that the combination of antioxidants has an effect on acutely formed locomotor hyperactivity.
Keywords: Antioxidant, Locomotor Hyperactivity, MK-801, N-acetylcysteine, Resveratrol

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Resveratrol ve N-Asetilsistein Kombinasyonunun MK-801' le İndüklenen Lokomotor Hiperaktivite Karşısında Koruyucu Etkisi

ÖZ

N-Methyl-D-Aspartate reseptörleri glutamaterjik sistemin önemli bir öğesidir. Bu reseptörün hipofonksiyonu lokomotor hiperaktiviteye sebep olur. NMDA reseptörlerinin antagonisti olan MK-801 isimli kimyasal da lokomotor hiperaktiviteye sebep olmaktadır. Sunulan bu çalışmada nöroprotektif özellikleri olduğu bilinen resveratrol ve N-asetilsistein isimli iki antioksidan kombinasyonunun farelerde MK-801'le indüklenen lokomotor hiperaktivite üzerinde etkin olan en düşük dozu araştırılmıştır. Bu amaçla 84 dişi fare eşit olarak 14 gruba bölünmüştür. Lokomotor hiperaktivite akut (1 gün ilaç uygulanması) ve sub-akut (4 gün ilaç uygulanması) faz olmak üzere iki bölümde oluşturuldu. İlaç uygulamalarından sonra hayvanların katettikleri mesafe açık alan test düzeneğinde 10 dakika boyunca kaydedilmiştir. Ölçüm sonuçlarına göre antioksidan kombinasyonunun akut fazda sub-akut faza göre başarılı olduğu gözlenmiştir. Kombinasyonun her iki düşük dozu olan 40mg/kg resveratrol + 20mg/kg NAC ve 20mg/kg resveratrol + 10mg/kg NAC'ın intraperitoneal uygulamalarının akut fazda lokomotor hiperaktiviteyi başarıyla engellediği gözlendi. Sonuç olarak antioksidan kombinasyonunun akut oluşan lokomotor hiperaktivite karşısında etkisinin olduğu sonucuna varıldı.
Anahtar Kelimeler: Antioksidan, Lokomotor Hiperaktivite, MK-801, N-asetilsistein, Resveratrol

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INTRODUCTION

The glutamate is the major neurotransmitter in the brain. The N-Methyl-D-Aspartate (NMDA) receptors are receptors which glutamate binds. Hypofunction of this receptor leads to mental illness such as schizophrenia (McArthur 2012). The hypofunction that has occurred causes an increase in locomotor activity other than schizophrenia. MK-801 is one of the NMDA receptor antagonists and its applications cause compulsive climbing, biting and falling to the side in rodents (Kruk-Slomka et al. 2016, Xiu et al. 2014, 2015, Yu et al. 2011). In addition to these symptoms, increased locomotor activity is also observed (Xiu et al. 2014, 2015, Yu et al. 2011). Since glutamate cannot bind to the NMDA receptor, it begins to accumulate in the extracellular space, thus triggering oxidative stress. The oxidative stress is the abundant production of the reactive oxygen species (ROS) in the tissues. ROS accumulation disrupts the antioxidant system and destroys nerve cells and myelin layer in the brain (Genius et al. 2013, Lin and Lane 2019, Ozyurt et al. 2007).

The combination of resveratrol and N-acetylcysteine (NAC) is known to build a defence mechanism against oxidative stress (García-Alcántara et al. 2018). The resveratrol is an organic and polyphenol non-flavonoid antioxidant. It is found in the vegetables and fruits (Gupta 2016). Since the brain contains high amounts of fat and needs oxygen, it is highly likely to be affected by oxidative stress. (Rege et al. 2013, Venturini et al. 2010). Resveratrol crosses the blood brain barrier and increases the release of endogenous antioxidant enzymes that maintain the oxidation balance within the cell (Bastianetto et al. 2015, Gerzson et al. 2014, Venturini et al. 2010). It is known that the resveratrol increases the neuronal plasticity, strengthens the memory, and improves the macular degeneration, stroke and dementia in the elderly (Bastianetto et al. 2015, Monserrat et al. 2016). However, resveratrol acts as a neuroprotector against various toxins that affect the brain and cause Alzheimer's and Parkinson's disease (Giovinazzo and Grieco 2015, Jeon et al. 2012, Pasinetti et al. 2014, Rege et al. 2013).

Besides the resveratrol, the NAC is also quite effective on the brain (Dean et al. 2004, 2011). The NAC also crosses the blood-brain barrier, protects the nerve cells and improves the demyelination (Adair et al. 2001, Dean et al. 2004, 2011, Farr et al. 2003). Immediately after intraperitoneal (i.p.) administration, NAC reaches high values in the brain and continues this for 48 hours (García-Alcántara et al. 2018). It neutralizes and reduces the ROS by boosts the endogenous antioxidant mechanism (Tardiolo et al. 2018). NAC has a healing and protective role in mental illnesses such as schizophrenia and Alzheimer's (Adair et al. 2001, Lin and Lane 2019, Dean et al. 2011, Farr et al. 2003). It also plays a role in NMDAR recovery (Himi et al. 2003, Janaky et al. 2007, Varga et al. 1997). Recent human trials of NAC have shown that it has a curative effect on the negative symptoms of schizophrenia. (Bulut et al. 2009).

In the present study, a positive control group was also formed. Clozapine used in the positive control group is an atypical antipsychotic drug. The use of this drug is in the treatment of anxiety-induced psychological illnesses. However, it is known that clozapine has an inhibitory effect on the locomotor hyperactivity initiated by NMDA receptor antagonist (Gattaz et al. 1994, Gururajan et al. 2012, Pinar et al. 2015).

In the present study, the open field test was used to determine the degree of locomotor activity in mice (Akillioglu et al. 2012, Pinar et al. 2015). The effect of antioxidants on the locomotor hyperactivity induced by MK-801 has been demonstrated in previous studies. However, no study was found to obtain a low protective dose by combining antioxidants. Therefore, the aim of this study is to try to find the lowest useful dose of antioxidant combination by inducing locomotor hyperactivity in mice.

MATERIAL and METHODS

The trial was performed on the 84 female balb/c mice. All mice were obtained from the Experimental Animal Unit of Afyon Kocatepe University after approval of the Ethical Committee for Experimental Animals of the same university (AKUHADYEK-55–18).

First, all mice were evenly divided into 14 groups and kept in quarantine for one week before the trial. They were fed ad libitum with commercial rat feed and tap water. All mice in the control group were received 10ml/kg saline intraperitoneally (i.p.) (As drugs are dissolved in this liquid). The doses of the resveratrol, NAC, clozapine and MK-801 in this study were selected from the previous studies (Atalay et al. 2017, Fukami et al. 2004, Gattaz et al. 1994, Xiu et al. 2015). The groups created are shown in Table 1.

Table 1: Information about groups and drugs. IP: intraperitoneally.

Group	Agent+Dosage	Drug Administration (Day)	Administration Way	Administration
1	Control-saline (10 ml/kg)	1	IP	Acute
2	Clozapine (5mg/kg)	1	IP	Acute
3	MK-801 (1mg/kg)	1	IP	Acute
4	Clozapine (5mg/kg) / MK-801 (1mg/kg) Positive control	1	IP	Acute
5	Resveratrol (50mg/kg)	1	IP	Acute
6	NAC (100mg/kg)	1	IP	Acute
7	Resveratrol (50mg/kg) + NAC (100mg/kg) / MK-801 (1mg/kg)	1	IP	Acute
8	Resveratrol (40mg/kg) + NAC (80mg/kg) / MK-801 (1mg/kg)	1	IP	Acute
9	Resveratrol (20mg/kg) + NAC (40mg/kg) / MK-801 (1mg/kg)	1	IP	Acute
10	Resveratrol (10mg/kg) + NAC (20mg/kg) / MK-801 (1mg/kg)	1	IP	Acute
11	Resveratrol (50mg/kg) + NAC (100mg/kg) / MK-801 (1mg/kg)	4	IP	Sub-acute
12	Resveratrol (40mg/kg) + NAC (80mg/kg) / MK-801 (1mg/kg)	4	IP	Sub-acute
13	Resveratrol (20mg/kg) + NAC (40mg/kg) / MK-801 (1mg/kg)	4	IP	Sub-acute
14	Resveratrol (10mg/kg) + NAC (20mg/kg) / MK-801 (1mg/kg)	4	IP	Sub-acute

The injections were administered to the 1, 2, 3, 5, 6th groups in the morning and after 30 minutes, they were subjected to open field testing. In the 4th group, the clozapine was injected late in the morning and the MK-801 early in the afternoon and the open field test was performed after 30 minutes. 7, 8, 9 and 10th groups received the resveratrol with NAC combination late in the morning and MK-801 early in the afternoon and they were subjected to open field testing after 30 minutes. These groups were terminated on the same day. 11, 12, 13 and 14th groups were also received resveratrol with NAC combination late in the morning and MK-801 early in the afternoon for 4 days and after the final MK-801 injection all mice were tested in the open field device.

After drug administrations all mice were placed in the open field device. This device is made of stainless steel and measures 60cmx60cmx24cm. The basement of the device was divided into 36 equal squares and the movements of the mice were recorded by video camera for 10 minutes. The motor activity degree of the mice were determined by counting the squares passed by the animal (Akillioglu et al. 2012, Al-Amin et al. 2000, Furuie et al. 2013, Kocahan et al. 2012, Xiu et al. 2014, 2015).

The data obtained from experimental animals were evaluated and analysed by SPSS 21.0 by using one-way analysis of variance (ANOVA) and was expressed as means and standard deviations. The LSD and non-parametric Kruskal-Wallis tests were performed for the analysis. A difference in the mean values of $P < 0.05$ was considered to be significant for both tests.

RESULTS

When the data of the MK-801 applied group were analysed, it was seen that MK-801 caused locomotor hyperactivity ($P < 0.05$). It was observed that the movements of the mice in the clozapine (group 2), resveratrol (group 5) and NAC (group 6) groups did not differ from the control group ($P > 0.05$). It was observed that clozapine suppressed the locomotor hyperactivity initiated by MK-801 in the group in which MK-801 was injected with clozapine (Group 4) ($P < 0.05$) (Table 2).

It was observed that the combination of antioxidants suppressed locomotor hyperactivity in groups in which MK-801 was acutely applied (groups 9 and 10) ($P < 0.05$). Especially in the 9th group, the locomotor hyperactivity value was very close to the controls. It was found that the antioxidant combination was particularly effective against acute applications of MK-801. The antioxidant combination was quite effective even at low doses (Table 2).

However, the effect of the combination was not at the desired level against sub-acute applications of MK-801 ($P > 0.05$). The values of the 11, 12 and 13th groups were better than the 14th group. However, the data of the last group was very close to that of the MK-801 group (Table 2).

Table 2: Groups and means of squares passed in open field test.

Groups	Mean	Coefficient of error	P_1; P_2
1	178.67 c	21.849	
2	175.50 c	29.095	
3	514.17 a	122.526	
4	229.17 c	53.398	
5	144.33 c	41.185	
6	128.17 c	27.952	0.000*
7	300.67 bc	72.980	0.000*
8	300.17 bc	20.243	
9	208.33 c	50.038	
10	264.17 c	52.811	
11	365.67 ab	55.892	
12	344.00 ab	65.248	
13	428.83 ab	88.521	
14	504.33 a	68.576	

[a,b,c]: In the same column values with different letters show statistically significant differences ($P < 0.05$).
P_1 is the importance level for the varians analyse.
P_2 is the importance level for the Kruskal-wallis.

DISCUSSION

The most important finding of this study was that the antioxidant combination tested was effective on locomotor hyperactivity created by using MK-801 in mice even at low doses in the acute phase. Since the accumulation of MK-801 in the body increased in the subacute phase, the effect of the antioxidant combination was weakened. In a presented study, the protective effect of caffeic acid phenethyl ester (CAPE), which is a very powerful antioxidant produced from propolis, on locomotor hyperactivity using MK-801 on rats was tested. In that study, it was observed that CAPE application suppressed locomotor hyperactivity formed in rats (Ozyurt et al. 2007). In another study, the effectiveness of melatonin hormone against increased locomotor activity using MK-801 was investigated. As it is known, melatonin hormone is a very powerful antioxidant that is secreted from the pineal gland at night and protects the tissues against oxidative stress. In that study, using the melatonin hormone showed a suppressive effect on the increased locomotor activity by MK-801 (Ozyurt et al. 2014).

1-Methyl-1,2,3,4-tetrahydroisoquinoline is a substance produced in the brain and the regulator of the dopaminergic system. The protective property of this substance, which is also a powerful neuroprotective, against the locomotor hyperactivity created by MK-801, was tested. According to the results of the open field test, it was found that this substance also had a suppressive effect on locomotor hyperactivity (Pietraszek et al. 2009). In another study presented, the protective effect of caffeine administration on the locomotor hyperactivity induced by MK-801 was observed. In that study, different doses of caffeine were tried in mice and it was observed that a dose of 1mg/kg improved locomotor hyperactivity and the symptoms completely disappeared after 1 week (De Oliveira et al. 2005).

Apart from antioxidants, regular exercise has benefits on locomotor activity. Exercise is also an important form of treatment for neurological diseases. In a study conducted to understand this, a voluntary wheel was placed in mouse cages for two weeks and it was found that exercise attenuates the locomotor hyperactivity effect created by MK-801 (Kim et al. 2014).

Clozapine, used as a positive control in this study, is an important drug used in neural diseases. Ventral hippocampus defects in newborns can cause symptoms similar to schizophrenia. To test this, MK-

801 was applied to young rat pubs with induced defects in their ventral hippocampus, and severe hyperlocomotion was observed. In this case, clozapine administration reduced the resulting hyperlocomotion to the level of the control group (Al-Amin et al. 2010).

Moreover, the resveratrol has a protective effect on the excitotoxicity induced by the NMDAR. Repeated doses of resveratrol have a curative effect on the locomotor hyperactivity induced by methamphetamine (Miller et al. 2013). Apart from the resveratrol, NAC also has an ameliorative effect on glutamatergic dysfunction. The administration of various doses of NAC has a dose-dependent suppressive effect on methamphetamine-induced acute hyperlocomotion (Fukami et al. 2004). In addition, the combination of resveratrol and NAC improved ototoxicity in the cochlea. The 5 days administration of 10 mg/kg resveratrol + 400 mg/kg NAC has the inhibitory effect on the secondary effect of the aminoglycosides in the ototoxicity (García-Alcántara et al. 2018).

CONCLUSION

In conclusion, in this study, it was tried to create locomotor hyperactivity by administrating MK-801 and the protective effect of antioxidant combination on the locomotor hyperactivity was investigated. It was determined that the combination of antioxidants applied had a protective effect against acutely induced locomotor hyperactivity at both low doses (40mg/kg resveratrol + 20mg/kg NAC and 20mg/kg resveratrol + 10mg/kg NAC). However, the combination was found to have no protective effect against MK-801 administered sub-acutely for 4 days. For the sub-acute and more advanced stages, the dose of the combination can be increased or different antioxidant combinations can be tried. As a result, it was concluded that the combination of antioxidants has an effect on acutely formed locomotor hyperactivity.

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Conflict of Interest: The authors declare that they have no conflict of interest.

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