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Anxiogenic Effects of Acute Injection of Sesame oil May be Mediated by β-1 Adrenoceptors in the Basolateral Amygdala

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ABSTRACT

Purpose: A few studies have indicates that the sesame oil influences anxiety, but many reports show that β-1 adrenoceptors (ARs) of the basolateral amygdala (BLA) plays a pivotal role in this regard. Therefore, in this study the effect of acute injection of sesame oil on anxiety-like behavior in the presence and absence of the BLA β-1 ARs in the male Wistar rats were investigated.

Methods: Guide cannulas, for seven groups of rats, were implanted bilaterally into the BLA. Two weeks after the stereotaxic surgery, anxiety-like behaviors (the OAT%, OAE % and locomotor activity) were evaluated by Elevated Plus-Maze (EPM) for all groups. 3 groups received different volumes of sesame oil (i.p.) and they were compared with control group (received saline via i.p.), and the anxiogenic volume of sesame oil (1.5ml/kg) was determined. Then, 3 other groups received constant effective volume of sesame oil (1.5ml/kg) along with 3 different doses of betaxolol, selective β-1 ARs antagonist, intra BLA microinjection in order to be compared with sesame oil group (1.5 ml/kg).

Results: The acute injection of sesame oil with the volume dependent manner showed an anxiogenic effect with reduction of the OAT% and OAE% which the maximum effect of sesame oil was observed in the dose of 1.5mg/kg. Also, betaxolol with dose dependent manner attenuated the anxiogenic effects of sesame oil (1.5mg/kg), but this reduction could not remove the anxiety effects completely.

Conclusion: It seems that the sesame oil acute (i.p.) injection induces anxiety, and this effect is attenuated by inhibition of β-*1ARs in the BLA.*

Introduction

Anxiety is known as a complex and compatible behavior in human and animals.[1] If it exists in the right level, it has appropriate effects on the learning and human's routine activities.[2] Nowadays, it is revealed that the anxiety-like behaviors are affected by the central/peripheral nervous systems (CNS/PNS) and different mediators such as hormones and neurotransmitters.[3-6] For example, high level of norepinephrine in limbic region has anxiety effects on human and animals.[7-10] In this regard, many studies show that the adrenergic/noradrenergic system plays a critical role in anxiety-like behaviors and these effects are mediated by two groups of α and β adrenoceptors (ARs) in different regions of the brain.[11-14] Among the different types of ARs, the regulatory role of β ARs, especially β-1 ARs, is confirmed on the anxiety-like behaviors in many studies.[12,14] For instance, betaxolol, as a selective β-1 ARs antagonist, has been used for treating anxiety disorders.[14] Furthermore it is revealed that the β-1 ARs, in the CNS, have effects on the anxiety-like behaviors.[12,14] Also, many studies show that the selective β-2 ARs antagonists are effective in treating acute anxiety, but they don't have any effects on treating chronic anxiety.[12,14,15] In addition, it is confirmed that the β-1 gene expression in amygdala obviously increases the cocaine-induced anxiogenesis.[14] In the different parts of limbic system such as amygdala and hippocampus, there is a powerful noradrenergic system which imposes effects on anxiety-like behaviors.[12,14] Also, β-1 and β-2 ARs elevation in amygdala, hippocampus and other parts of limbic system has been confirmed in anxiety complications.[16] Mammalians studies revealed that the amygdala complex, especially basolateral amygdala (BLA), has regulatory role via β ARs on anxiety-like behaviors.[12,17] Fu and et al. (2008) confirmed that intra BLA injection of metaproponolol, as a selective β-1 ARs antagonist, attenuates the anxiety.[12] Also, their western blot analyses confirmed that after anxiety condition, the β-1 ARs gene expression significantly increases in the BLA.[12]

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On the other hand, the sesame seed and its products such as sesame oil are used in large quantities in medicine and food industries.[18] The sesame oil is mainly composed of stearic and poly unsaturated fatty acids (PUFAs) such as linolenic acid and it has antioxidant effects through containing high levels of vitamin E.[18-21] Also, different studies confirmed that the sesame oil contain metallic ions such as magnesium, copper, calcium, iron, zinc and also vitamin B.[21] Traditional medicine reports explained that sesame oil is a good medicine for treating arthritis romatoid, lung complication, colon cancer, osteoporosis, blood pressure, and migraine.[18] On the other investigations, the effect of sesame oil has been proved on memory and learning.[22] The PUFAs in the sesame oil increases the dendrite branches, number of neural synapses, and synapses efficiency.[23,24] It is believed that neurophysiological effects of sesame oil on the learning process and emotional behavior may be performed through its antioxidant effects on cholesterol and modulation of neurotransmitter systems.[25,26] Also, sesame oil anti-depression characteristics have been confirmed through its effects on plasma cholesterol.[25] The results of many studies show that sesame oil produces low serum cholesterol which changes the plasma cholesterol level in the neurons membrane in certain areas of CNS. It will change production of some neurotransmitter receptors, especially serotonergic receptors, in these areas and which finally changes emotional and anxiety-like behaviors.[27-30] Based on our collected data about sesame oil effects on anxiety and its correlation with β-1 ARs of amygdala, there are very little evidence related to this issue. So, due to the widespread uses of the sesame oil, as a vehicle oil in the many steroid drugs and food industry, our team research conducted this study for discovering the effects of acute i.p. injection of sesame oil on the anxiety-like behaviors and its interaction with BLA β-1 ARs.

Materials and Methods

Animal

This study was conducted using the adult intact male Wistar rats with weight range of 180±20gr and age range of 13±2 weeks in the surgery time. The rats were divided into seven groups. Each group contains 8 animals. The rats were housed four per cage in the colony room with a 12-hour reverse- light/dark cycle (7:00AM-19:00PM light off) at 22±1 °C and relative humidity of 30% to 50%. All the animals one week before the surgery were compatible with conditions and handling was taken 5min daily for all animals. In the study, all of the behavioral sessions were taken in the light period from 9:00 to 14:00 when rats usually have the most activities. Each animal was used once and had stereotaxic surgery.

Surgery

Two week before behavioral testing, rats were implanted with stainless-steel guide cannulas aimed at the BLA. Rats were anesthetized with interperitoneal injection (i.p.) of ketamine hydrochloride (50mg/kg) and xylazine (4mg/kg), and mounted in a stereotaxic instrument (Stalling Co, Illinois, and USA). The scalp was incised and retracted, and the head was positioned to place bregma and lambda in the same horizontal plane. Two small holes were drilled through the skull for bilateral placement of stainless-steel guide cannulas (21gauge; 14mmin length; Samen Mashhad, Iran) into the BLA (2.8mm from Bregma, 5mm lateral, and 6.8mm through the skull surface) along with three jeweler's screws.[31] Cannulas were affixed to the skull, and the scalp incision was closed with dental cement. After surgery, stainless-steel obturators (27gauge; 15mm in length; Samen Mashhad, Iran) were placed in the guide cannulas. The obturators were replaced every other day throughout the experiment.

Drug and injections

The sesame oil approved by Berovich Company (Berovich, Tehran, Iran) with different volume of 0.5, 1, and 1.5 ml/kg per rats were injected interperitoneally (i.p.). Betexolol hydrochloride (Tocris Bioscience, IO Center Moorend Farm Avenue, Bristol BS 11,OL, UK), as a selective β-1 ARs antagonist, was diluted in the normal saline (Samen Mahhad, Iran) to provide appropriate doses of betaxolol (0, 0.025, 0.1 and 0.4 µg/rat) and microinjected intra BLA.[32] For Betaxolol or its vehicle intra BLA microinjection in 60 seconds, a stainless steel needle (15mm stainless steel 27gauge tubing) connected to the Hamilton syringe of 2 µl by a polyethylene tube were placed into guiding cannulas. The volume of all the intra BLA injections into each cannula was 0.5 µl and for complete betaxolol and vehicles diffusion, top of the needle was kept in the cannula for 90 additional seconds. 15min after intra BLA injections saline or different volume of sesame oil: 0.5, 1, and 1.5 ml/kg per rat were injected to animals.

Behavioral testing

The Elevated Plus-Maze (EPM) test was applied to investigate the anxiety-like behavior. The EPM is an unconditional anxiety model which is used for measuring the anxiety like parameters.[33,34] The EPM is consisted of two open arms (50×10 cm, surrounded by a 0.5-cm-high border) and two closed arms (50×10 cm, surrounded by 30-cm-high walls). The apparatus was elevated 50cm above the floor. A 40W red light was placed at the upper part of EPM center in the height of one meter in order to shed light on the arms equally. The test session was initiated by placing the rat on the central platform of the EPM, facing one of the open arms, and letting it move freely. Each

session lasted 5min, being recorded by a high quality Sony handycam (Sony Handycam HDR-CX 110 Camcorder-1080i). All test sessions were carried out under lighting phase between the 9:00 to 14:00. The criterion to determine the rat's entrance to each arm was entering of two rat's hind legs on the arm. The number of entries and the time spend on the open and close arms were recorded and after each test, the EPM was thoroughly cleaned by sterilized cotton and 70% ethyl alcohol. Using the collected data, the percentage of open arms entries to total arms entries (%OAE), the percentage of time spend on the open arm to total spending time on the all arms (%OAT), and the number of total arms entries (Locomotor activity), were evaluated.

Ethics of Animal Care and Use

In the present study, all experiments and methods were carried out in accordance with the Institutional Guidelines for Animal Care and Use of Laboratory Animals, and approved by the Biology Department of Shahid Chamran University (Ahvaz, Khuzestan Province, Iran).

Experiment I: Effects of sesame oil acute injection alone on the anxiety-like behaviors

Four rat groups received saline (1ml/kg rat), as betaxolol vehicles, intra BLA (1 µl/rat). After 15min, each group received saline or different volume of sesame oil: 0.5 ml/kg, 1 ml/kg and 1.5 ml/kg via i.p. respectively, and constitutes Control, Sesame 0.5, Sesame1, and Sesame 1.5 groups. The behavioral test session was performed 45min after the i.p. injection and the percentage of open arm time (%OAT), the percentage of open arm entries (%OAE) and locomotors activity were assessed (Figure 1).

Experiment II: Effects of betaxolol against anxiogenesis effects of sesame oil acute injection in the Experiment I

Three groups of rats received different doses of betaxolol: 0.025, 0.1, and 0.4 µg/rat intra-BLA, After 15min, the effective volume of sesame oil on the anxiety in the experiment 1, 1.5 ml/kg, i.p., was applied and injected into the all groups and constitute: bet. 0.025, bet.1 and bet.4 groups, respectively, and it was compared with control and Sesame 1.5 groups, as mentioned earlier. The behavioral test session was performed, using the EPM, 45min after the i.p. injection and the percentage of open arm time (%OAT), the percentage of open arm entries (%OAE) and locomotor activity were assessed (Figure 2)

Cannula verification

The animals were immediately killed with chloroform after the completion of the two experiments. Subsequently, 0.5µl per cannula of ink (0.1% aquatic methylene blue) was injected intra-BLA by a 15mm stainless steel 27gauge. Following that the animals' brain was removed and fixed in 10% formalin two weeks before sectioning. All sections were examined to determine the location of the cannula aimed for the BLA. The cannula placement was verified using the Atlas of Paxinos and Watson (1998).[31] The data from rats with cannula placement outside the BLA were excluded from the analyses.

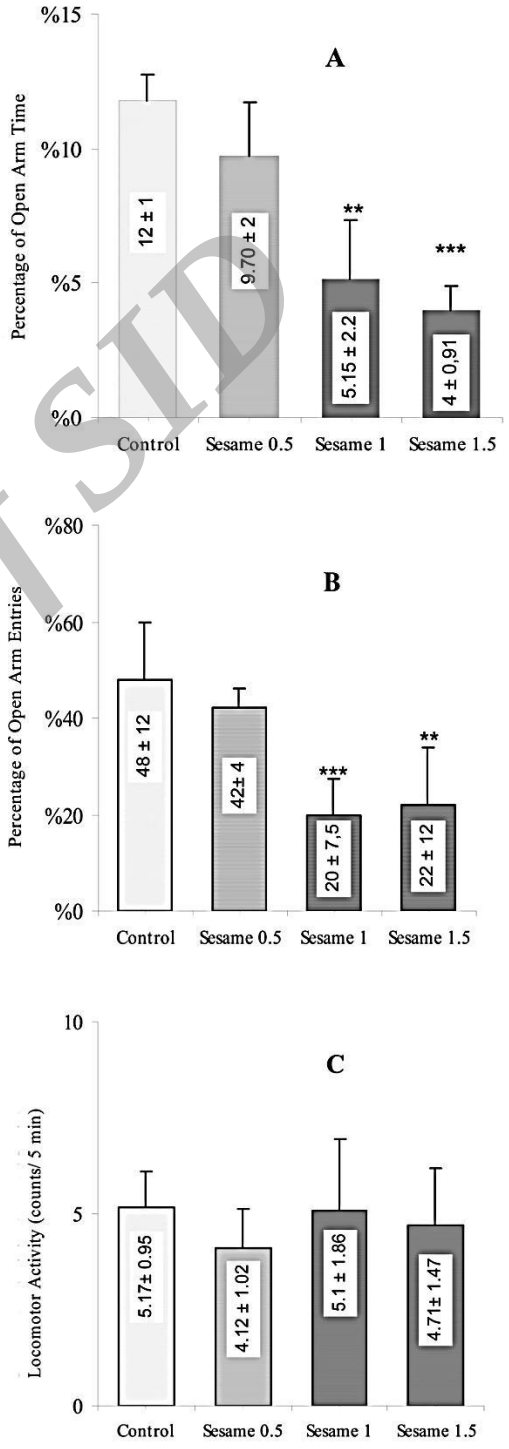

Figure 1. The effects of different volume of sesame oil on the anxiety like behaviors in the EPM: (A) OAT%, (B) OAE% and (C) locomotor activity. **p<0.01 ***p<0.001

Statistical analyses

Statistical analyses were performed using SPSS software (SPSS-PC, version 15. SPSS, Inc., Chicago, IL). Graphical data are expressed as means±SEM. The data analysis for the experiments 1 and 2 was performed by one-way analysis of variance (ANOVA) followed by Tukey test for assessing specific group comparisons. The differences between the experimental groups at each point were considered as statistically significant (P <0.05).

Results

Effects of sesame oil acute injection alone on the anxiety-like behaviors in the EPM

Figure 1, shows the comparison between measurement anxiety behaviors in four groups: control (saline), Sesame 0.5, Sesame 1, and Sesame 1.5. As it can be seen in Figure 1A regarding OAT%, there was a significant difference with p<0.01, and p<0.001 between control group and two groups of sesame 1 and sesame 1.5. Also, regarding the number of rats` entering into open arms (%OAE), there was a significant difference, p<0.001, p<0.01, between control group and sesame 1, and sesame 1.5 (Figure 1B). But, as Figure 1C shows, there was not any significant difference among four groups in regard to locomotor activity. So, the sesame oil with volume dependent manner increases anxiety in the adult male rats.

Effects of betaxolol (B) on anxiogenesis effects of sesame oil acute injection in the EPM

Figure 2, Part A, B and C, shows the anxiety assessment behaviors in each group of: sesame 1.5, B 0.025, B 0.1, B 0.4 and control. As mentioned earlier regarding the control and sesame 1.5, the sesame oil in the maximum volume, regarding the Experiment I, was injected to the three groups of: B 0.025, B 0.1, and B 0.4, but they had received different doses of betaxolol intra-BLA. As the Figure 2A, there was a significant difference with p<0.01, p<0.001, and p<0.001 between OAT%, of sesame 1.5 with OAT% of: B 0.1, B 0.4 and control group, respectively. Also, a significant difference, p<0.01, p<0.001, was observed in regard to %OAE among sesame 1.5 group with control and B 0.4 groups, respectively (Figure 2B). In the Figure 2C, there was not seen any significant difference between sesame 1.5 with control group and any other groups. Figure 2 contains the analyses of control group in the first step of the study to assure the effect of sesame oil on anxiety. It should be noted that, although rats had received different doses of betaxolol, but the anxiogenesis effect of sesame oil was not completely removed even in maximum dose of betaxolol.

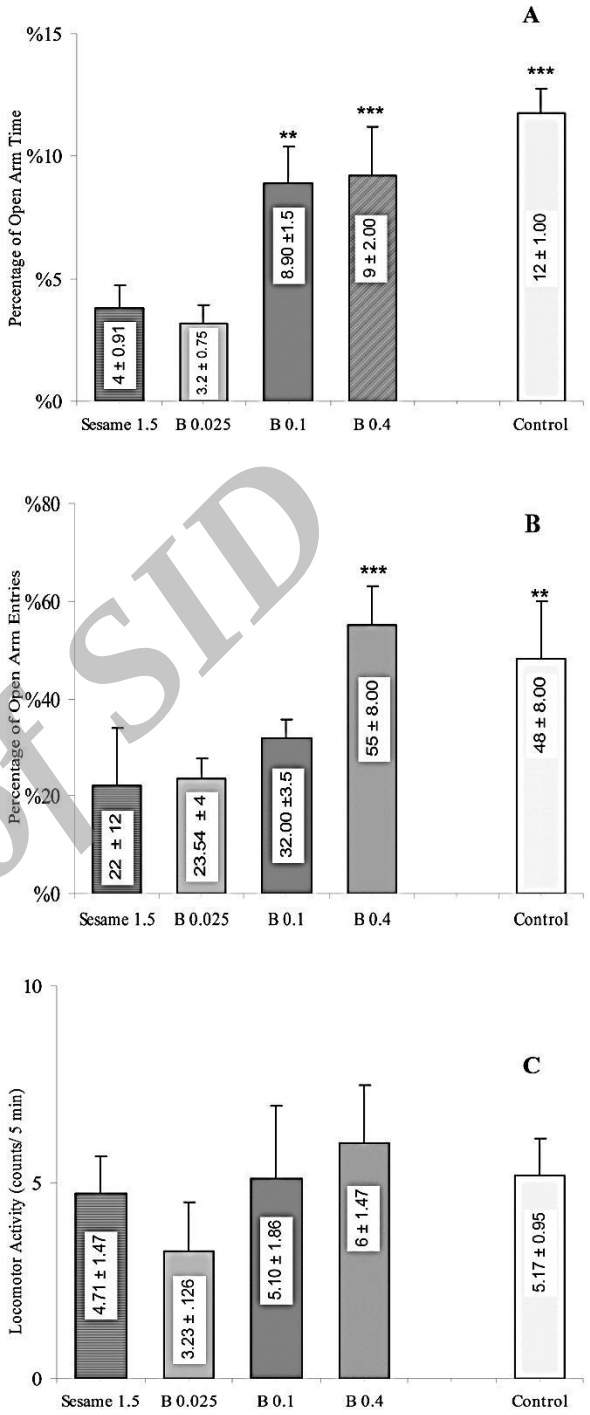

Figure 2. The comparison between anxiogenesis effect of sesame oil (1.5 ml/kg) in the presence and absence of different doses of betaxolol (0.025, 0/1, 0.4 µl/rat) on the anxiety like behaviors in the EPM: (A) OAT%, (B) OAE% and (C) locomotor activity. The significant value is showed comparing the Sesame 1.5 group. **p<0.01 ***p<0.001

Discussion

In the present work, our data revealed the anxiogenic effects of acute injection of sesame oil using the EPM. Our findings clarified reduction of the OAT% and OAE% by sesame oil volume dependent manner and showed it has significant anxiogenic effects. Also, these acute injections didn't impose meaningful effect

on the rats' locomotor activity. So, this note show that the sesame oil anxiogenesis effects was not due to reduction of the rats' locomotor activity.

The results of other studies support the neurophysiologic and antioxidant effects of sesame oil.[18] These activities could be the result of sesame oils' poly unsaturated fatty acids (PUFAs).[18-20] The previous studies confirmed that the sesame oil is enrichment of PUFAs such as linoleic acid. PUFAs can be effective on the neurophysiological processes e.g. learning and memory processes.[18,19,22] Also, other studies show that the unsaturated fatty acids such as oleic acid, other chemical compound in sesame oil, can change in membrane fluidity by reduction in dendrites' plasma membrane cholesterol level.[25] They showed that there is a negative correlation between cholesterol level with emotional disorders such as anxiety and depression.[35-38] Therefore, the evidences have supported significant relationship between anxiety/stress with lipids reduction e.g. cholesterol reduction.[35-38] Herstin and et al. found that females who have total cholesterol lower than 4.7mM/L shows the depression symptoms 2-fold more than others.[39] Also, there are some hypothesis to support the effect of cholesterol level in plasma and neural membrane on anxiety-like behavior.[30,40] The first hypothesis suggests that anxiety can leads to decrease in appetite, and this will cause losing weight and decrease in level of cholesterol, therefore, the anxious individuals have hypocholestermia.[30] But, other studies rejected this possibility.[40] The second hypothesis is about the cholesterol impact on the anxiety and stress and its role in changing serotonergic receptors activities and their down regulation, and finally decreasing in serotonergic system in CNS.[35] According to this theory, serotonin system down regulation leads to the decrease of neurons` activities in this area.[35] In this regard, many studies confirmed the hyperserotonemia in anxious individuals.[41-44] So, these studies revealed that the hypocholestermia may be mediated by down-regulation of serotonin receptors.[40,44] Perhaps, these anxiogenic effects of sesame oil in our experiment caused by reduction of the lipids content of the neurons and then serotonergic system down regulation in CNS. Also, another study confirmed that monkeys which received foods with lower level of cholesterol showed more invasive behaviors where similar cases have been observed in human studies.[28] Further, it is proved that patients whom received anti-cholesterol drugs, revealed much anxiety and depression.[45] In the present study, also, it seems that sesame oil can lead to cholesterol reduction by affecting the blood cholesterol and following that, it will affect some tissues such as CNS and BLA cholesterol contain. Considering the relationship between serotonin and level of cholesterol, it seems that part of its effect is because of the increase of the blood serotonin which finally leads to the increase of anxiety.

It should be noted that there are contradictory studies regarding the effects of serotonergic system on anxiety.[35,41,42,43,46] De-Almeida and et al (1998) suggested that the low serotonin level would cause to the increase of anxiety.[46] But, many studies approved anxiogenic effects role of high level of serotonin in CNS.[35,41,42,43]

Basically, due to the increase of β-1 and β-2 ARs in amygdala, hippocampus and other parts of the limbic system during anxiety conditions,[47,48] and the controlling role of β-1 receptors in the BLA on decreasing the anxiety behaviors,[12,14] our team research, as other alternative procedure, applied the EPM and then injecting the sesame oil in presence and absence of β-1 ARs into BLA to find another possible interaction between the sesame oil with β-1 ARs in this area.

The results showed that β-1 ARs in the BLA would cause to the attenuation of sesame oil anxiety effects, with different doses of betaxolol, in maximum volume of sesame oil. In this study, interaction between anxiogenic effects of sesame oil and β-1 ARs in the BLA can be seen. Besides, the findings show that microinjection of betaxolol in the maximum dose can't remove the anxiogenic effect of sesame oil completely (Figure 2).

The studies somewhat reconfirmed that the BLA noradrenergic system is mostly innervated from other brain nucleus, especially locus coeruleus,[49,50] and when these postsynaptic neurons discharge in the BLA, they can leads to anxiety-like behavior.[51] Although there are a powerful evidences related to the neurons discharge of locus coeruleus and anxiety in the BLA, but the results state that noradrenergic has a controlling role on BLA.[12,14] Fu and et al. (2008) and other researcher confirmed the anxiolytic effects of β-1 ARs antagonist administration in the BLA.[12,14] Also, their study showed that the β-1 ARs in BLA in anxiety conditions were elevated, and the inhibition of β-1 ARs, by selective β-1 ARs antagonist, metoprolol, would relieve anxiety in anxiety conditions.[12] In their study the up regulation of β-1 ARs in the BLA after the anxiety condition was confirmed by Western Blot analysis.[12] The inhibition of β-1 ARs in the BLA by another selective β-1 antagonist, betaxolol, was also confirmed in other studies.[14] Our result showed that in the absence of β-1 ARs, the sesame oil could not impose anxiety-like effects, in other words, for execution of these effects, β-1 ARs in the BLA is needed.

As we discussed the probability of anxiogenic effects of sesame oil by hypocholestermia earlier, it didn't seem that the sesame oil impose its effects directly via β-1 ARs in the BLA, because the previous studies confirmed that hypercholesterolemia leads to up-regulation of β-1 ARs in the other organs and therefore hypocholestermia, by this mechanism, must be leads to down-regulation of the β-1 ARs.[52] Furthermore, the studies on marmosets maintained on a high cholesterol diet showed 3-fold increase in the β-1 ARs mRNA in endothelial cells, but hypocholestermia made contradiction results.[52] On the other hands, the higher

membrane cholesterol levels led to a decrease in Na/K-ATPase activity and other membrane bounded enzymes,[53] therefore, perhaps down regulation of plasma membrane cholesterol level with sesame oil effects, in the BLAs' neurons, causes anxiogenic effects, as a mentioned earlier.

However, due to the dyssynchrony between intra BLA injection of betaxolol and i.p. injection of sesame oil and then test session in the present study, it is impossible that the sesame oil hasn't enough time to change the level of plasma cholesterol to affect the target β-1 ARs in the BLAs' neurons and other receptor systems such as serotonin or GABA and etc in this area. So, more studies should be done to confirm the precise anxiogenic mechanism of acute injection of sesame oil, but our study revealed the anxiogensis effects of acute injection sesame oil and the existence of unknown interaction between sesame oil and BLA β-1 ARs. In the future studies, research teams can change the administering procedure of sesame oil in order to consider its effect by inhibiting β-1 ARs and serotonin receptors in the appropriate methods.

Conclusion

The present study suggests that the sesame oil i.p. acute injection induces anxiety, and this anxiogenic effect of sesame oil is attenuated by inhibition of β-1 ARs in the BLA, but this reduction could not remove the anxiety effects completely. Therefore, sesame oil and β-1 ARs have an unknown precise interaction in the BLA.

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Conflict of Interest

The authors report no conflicts of interest.

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