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The Effect of Resveratrol on Anxiolytic and Emotional Memory Impairment Induced by Morphine

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Abstract

Introduction: A body of pharmacological and non-pharmacological studies have been conducted with the purpose of attenuating morphine side effects such as anxiety and memory impairment. It seems that there is a close relationship between resveratrol and morphine according to molecular cell pathway. Thus, the aim of the present investigation was to evaluate the effect of resveratrol on anxiolytic-like behavior and emotional memory induced by morphine.

Materials and Methods: A basic experimental research has been designed for this study. The test-retest protocol of elevated plus-maze (EPM) apparatus was used. The male Wistar rat received subthreshold dose of resveratrol (50 mg/kg), 15 minutes before injection of saline (1 ml/kg) or different doses of morphine (1.25, 2.5 and 5 mg/kg) on the test day. Twenty-four hours after test day, the EPM's parameters was also measured without drug injection. All drugs were injected intraperitonealy.

Results: The data indicated that higher dose of morphine (5 mg/kg) elevated Open Arm Time (%OAT, P<.05) and Open Arm Enters (%OAE, P<.001) on the test day, and also %OAT (P<.05) and %OAE (P<.001) on the retest day, indicating decrease of anxiety and impairment of emotional memory, respectively. Moreover, subthreshold dose of resveratrol (50 mg/kg) restored all parameters induced by higher doses of morphine in the test (P<.05 for %OAT and P<.01 for %OAE) and the retest day (P<.05 for %OAT and P<.001 for %OAE).

Conclusion: The principal findings of this research showed that resveratrol can alter morphine responses on anxiety and emotional memory process. It is also postulated that the resveratrol can decrease the morphine side effects in the people using it.

Keywords: Anxiety, Memory, Morphine, Resveratrol, Rat

1. Introduction

Iran is a major route for substance transport from Afghanistan -as the largest producer opium in the world- to Europe. Rapid prevalence of addiction in Iran has been observed [1]. These rapid changes are having a serious effect on cultural behaviors such as social interaction and aging phenomenon. According to the World Health Organization (WHO), using opium in IRAN is three

times more than other countries in the world [2]. Prior studies have noted morphine as an abuse drug altering cognitive and non-cognitive behaviors. For example, Malboosi et al indicated that injection of morphine impaired spatial memory and altered gene expression of TFAM, PGC-1alpha, Delta fosB and CART in the CA1 region of hippocampus indicating its effect on mechanism of biogenesis of mitochondria and apoptosis in the neurons [3]. Another, Nasehi et al reported that mu opioid receptors of morphine have a critical role in the effect of swimming on scopolamine (as a muscarinic acetylcholine receptor antagonist), inducing impairment of emotional memory.[4]. In 2013, Valizadegan et al. published a paper in which they demonstrated morphine deceased anxiety and emotional memory processing in the same method used in present study [5].

A considerable number of studies have been done to lower morphine's side effects such as anxiety, memory, and decision making. Anvari et al published a paper in which they described using Transcranial Direct Current Stimulation (tDCS) in the acute and subchronic anodal condition, restored morphine effect on analgesia [6]. Moreover, Eslimi and co-workers showed that activation of mu opioid receptors potentiated decreased anxiety caused by cholestasis, while blockade of this receptor altered this phenomenon [7]. Elhampour corroborated the beneficial effect of supplement compound (curcumin) for decreasing the morphine effect [8]. This view is supported by Heshmatzad (2021) who maintained NeuroAid restored the morphine effect on gene expression levels of GluN2A and GluN3A in the hippocampus and striatum of rats [9].

Previous Research has noted the importance of Polyphenolic compounds found in many plants such as resveratrol (as a crucial active ingredient of stilbene phytoalexins) on several brain functions, [10]. These compounds, first extracted from the roots of the oriental medicinal plant Polygonum Capsidatum [10]. It showed that resveratrol induced its effect via different pathways such as neuroprotective, anti-inflammation and anticancer [10]. Some molecular mechanisms were proposed for resveratrol effects. For instance, Kumar and co-workers demonstrated that resveratrol reversed diabetic neuropathy through block of nitric oxide production and TNF-a gene expression in spinal nerve-ligated and diabetic rats [10, 11]. A strong relationship between resveratrol and morphine has been reported in some studies. Tsai in 2012 reported that resveratrol restored interleukin IL-6, IL-1b, TNF-a (a proinflammatory cytokines) and microglia activation following morphine administration [12], thus altered pain perception following tolerance phenomenon induced by morphine [12]. Tsai points out that resveratrol induced its effect via gene expression of HDAC1 of SIRT1. According to the data resveratrol reversed the effect of neuroinflammation caused by morphine HDAC1 gene expression [13] or regulation of analgesia tolerance throughout SIRT1 regulation in the rat spinal cord [13, 14].

In reviewing the literature, no data was found on the association between resveratrol and amnesia induced by morphine. Thus, this paper, using test and retest protocol of elevated plus maze, seeks to address the question if resveratrol affects anxiety and emotional memory impairment caused by morphine in the male Wistar rat.

2. Materials and Methods

A basic experimental research has been designed for this study in cognitive and neuroscience research center (CNRC), Islamic Azad University, Tehran, Iran.

Animals

The 64 male Wistar rats weighing 180-200 g were used in this study without exclusion from the study. All subjects were gained from the Institute for Cognitive Science Studies; Tehran, Iran. They were divided into eight groups (eight rats into each group). For ethical concerns, all standards conditions were met. Among others, room temperature was set up in 22 ± 2°C and light and dark cycle was also set up in 12 hours' light and 12 hours' darkness, turned on at 7:00 A.M. Moreover, in all resting and experimental time the rats had free access to water and water. Each rat was only used once. All experimental interventions have been done in the light phase of circadian rhythms and each subject was applied once. All procedures were approved by the cognitive and neuroscience research center (CNRC), Islamic Azad University, Tehran, Iran.

Drugs

Morphine sulfate was purchased from Temad company, Tehran, Iran, while resveratrol was bought form Sigma-Aldrich, Germany. The normal saline was applied for dissolution of both drugs [4, 5].

Apparatus

The plexiglas elevated plus-maze device used in this study had plus shape with two open- arms (50×10 cm) and two close arms (50×10×40 cm) that oppositely positioned. The open-arms section is safe by 1cm high plexiglas ledge in the surrounding to prevent falls of

animals in this section placed 50 cm above the floor. The device has a center area with 10×10 cm connection for sections [15, 16].

Behavioral testing

To evaluate anxiety and emotional memory, the animals were placed to the elevated plus maze in method of test and retest [17-19]. In general, in this method the responses by animals in the test day indicated anxiety condition of animals, hence decrease in the %OAT [(time in open-arms/300) × 100] and %OAE [(open arms entries/open arms entries + enclosed-arms entries) ×100], showing antigenic-like behaviors and vice versa for anxiolytic-like behaviors. Moreover, because formation of learning and memory occurred in the test day, the %OAT and %OAE will be decreased in the retest day when compared to test day, thus the data for the retest day may showthe emotional memory formation [15, 16, 20]. To show the normal condition of animals, the enclosed arm entrance was assessed as the index of locomotor activity.

Experimental design

The effect of pretest administration of morphine on anxiety-like behaviors and emotional memory

For evaluation of the effect of morphine on anxiety and emotional memory, the animals received saline (1 ml/kg) or different doses of morphine (1.25, 2.5 and 5 mg/kg), 15 minutes before testing day. The treated animals in the previous section were also retested without drug injection in the retest day.

The of effect of resveratrol on anxiolytic-like behaviors and emotional memory deficit caused by morphine

To reveal whether the effects of resveratrol injection could possibly block the morphine responses, the rats received subthreshold dose of resveratrol (50 mg/kg) before saline (1 ml/kg) or subthreshold and effective doses of morphine (1.5, 2.5 and 5 mg/kg), with 5 minutes interval. The EPM's test was carried out 15 minutes after the second injection. Moreover, emotional memory was also assessed in the elevated plus maze in the retest day without drug injection.

Statistical analysis

Because the normality of data and two similar behavioral evaluations in the test and retest days for each rat, the raw data were represented as mean±S.E.M and analyzed applying repeated measure analysis. To show the effect of resveratol on the responses induced by morphine, two-way analysis of variance (ANOVA) was also used to compare test days and retest days. Following the significance in the previous analysis, one-way ANOVA and post-hoc analysis (Tukey-test) was done to show the level of significance in an interested comparison between groups. In all statistical analysis, the level of significance was $P<.05$.

3. Results

The result of morphine on anxiety-like behaviors and emotional memory formation

Repeated measure followed by Post hoc evaluation showed that pretest injection of morphine lowered the %OAT (at dose of 5 mg/kg, Figure 1; panel 1A), %OAE (at dose of 5 mg/kg, Figure 1; panel 1B), while it did not change locomotor activity (Figure 1; panel 1C) on test day, suggesting an anxiolytic-like effect by morphine at higher dose used.

In addition, morphine raised the %OAT (at dose of 5 mg/kg, Figure 1; panel 2A) and %OAE (at dose of 5 mg/kg, Figure 1; panel 2B); however, it did not change locomotion (Figure 1; panel 2C) on retest, showing emotional memory impairment by morphine. All statistical analysis results have been summarized in table 1.

The effects of Resveratrol on behaviors induced by morphine

Two-way ANOVA followed by Post hoc analysis indicated that subthreshold dose of resveratrol (50 mg/kg) 15 minutes before morphine lowered %OAT (at dose of 5 mg/kg, Figure 1; panel 3A), %OAE (at dose of 5 mg/kg, Figure 1; panel 3B) but it did not exert any effect on locomotion (Figure 1; panel 3C) when compared to morphine-treated groups on test day, indicating that the resveratrol restored the anxiolytic-like behaviors induced by morphine.

Moreover, similar analysis showed that resveratrol lowered the %OAT (at dose of 5 mg/kg, Figure 1; panel 4A), %OAE (at dose of 5 mg/kg, Figure 1; panel 4B); however, it did not change the locomotor activity (Figure 1; panel 4C) compared to morphine-treated groups in the same day on retest day, indicating that resveratrol is also restored emotional impairment induced by morphine. The statistical analysis results have been summarized in table 1.

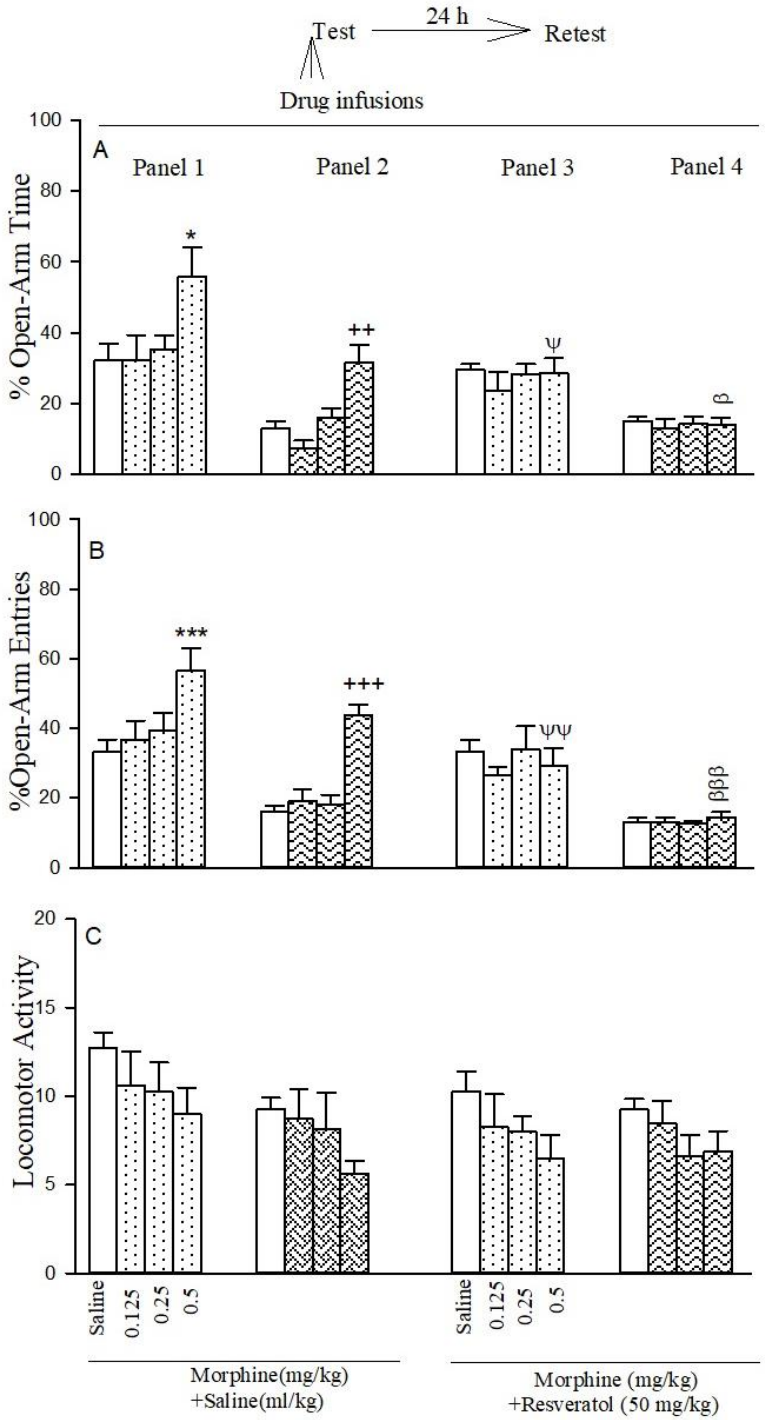

Figure 1. evaluation of three parameters of EPM apparatus following pretest injection of resveratrol 15 min before different doses of morphine In the next day, all interventional animals were also evaluation in the elevated plus maze without drug injection. That panels A, B and C represents %Open-Arms Time; %Open-Arms Entries and Locomotor Activity, respectively. Each bar is represented as mean±S.E.M (eight rats in each group). *P<0.05 and ***P<0.001 showing the different from saline group on the test day as control group. ++P<0.01 and +++P<0.001 different from control saline groups on retest day. ψP<0.05 and ψψP<0.01 different from the test groups as compared to respective groups in the panel 1. βP<0.05 and βββP<0.001 as compared to respective control group in the panel 2.

Table 1. summarized of data analysis in the experimental groups

Experiments	Behaviors	Inter-group		Intra-group		Inter-Intra group	
Repeated measure analysis for morphine between panel 1 and 2 Figure 1.		F(1, 48)	P	F(3, 48)	P	F(3, 48)	P
	%OAT	3.05	P<0.05	3.5	P<0.05	2.58	P<0.05
	%OAE	2.98	P<0.05	3.01	P<0.05	3.04	P<0.05
	LOCOMOTION	1.54	P>0.05	2.01	P>0.05	1.89	P>0.05
Two-way ANOVA analysis results for the effect of resveratol injection on exploratory-like behaviors induced by morphine in the test day (Between panel 1 and 3 of Figure 1.		F(1, 56)	P	F(3, 56)	P	F(3, 56)	P
	%OAT	6.35	P<0.001	4.9	P<0.001	8.25	P<0.001
	%OAE	4.28	P<0.01	5.01	P<0.001	4.5	P<0.01
	LOCOMOTION	2.86	P>0.05	2.34	P>0.05	1.89	P>0.05
Two-way ANOVA analysis results for the effect of resveratol injection on exploratory-like behaviors induced by morphine in the retest day (Between panel 2 and 4 of Figure 1.		F(1, 56)	P	F(3, 56)	P	F(3, 56)	P
	%OAT	5.89	P<0.001	4.78	P<0.001	3.9	P<0.01
	%OAE	2.8	P>0.05	3.96	P<0.05	3.87	P<0.05
	LOCOMOTION	1.72	P>0.05	2.87	P>0.05	2.03	P>0.05

4. Discussion

The most striking result to emerge from the data is that morphine lowered anxiety-like behaviors and emotional memory in the test and retest protocol. This finding is in agreement with other findings showing morphine causes anxiolytic-like behaviors in the elevated plus maze apparatus via cholinergic and glutamatergic systems [21-23]. In support of the data for morphine effect on emotional memory, several possible explanations are proposed. Bajic et al suggested that prolonged administration of morphine elevated amount of apoptotic cells in cortex and amygdala while they did not change in the hippocampus, hypothalamus, or periaqueductal gray of neonatal rats [24]. Another, Erbs (2016) concluded that chronic treatment with morphine lowered delta receptor of opioids in critical regions of hippocampus including dentate gyrus, CA1 and CA3 without altering GABAergic populations distribution that mainly express delta receptors [25]. Garcia-Garmona et al highlighted a critical role of corticotropin-releasing factor receptors in morphine related behaviors [26]. However, in contrast to our results, Valizadegan (2013) revealed that intraperitoneal injection of morphine (6 mg/kg) caused anxiolytic-like behaviors and memory improvement [5]. It seems that the doses used have critical role in this.

With respect to the second research question, it was found that subthreshold dose of resveratrol restored decease of anxiety and emotional memory caused by morphine. In accordance with the present results, prior data demonstrated that resveratrol induced analgesia effect via mu opioid receptor inasmuch as blocked of theses receptors by naloxone prevented analgesia-induced by resveratol [27]. Han et al. reported that resveratrol decreased morphine dependency through inhibiting microglial activation by AMPK signaling [28]. An interesting article showed that resveratrol restored morphine dependency via upregulating gene expression of SIRT1 in the spinal dorsal horn [14]. As another possible mechanism of resveratrol, Song et al demonstrated that resveratrol has a critical role in adenosine monophosphate-activated kinase dependent manner. This study showed that resveratrol lowered phosphorylation of mitogen-activated protein kinases and reduced proinflamentory cytokines production. Thus, proinflammatory cytokines induced by acute pain could block by resveratrol [29]. This finding was also reported by other studies suggesting that resveratol changed the stability of scaffolding postsynaptic density-95 protein via down-regulation of NMDAR gene expression in the post-synaptic membrane such as NR1 and NR2B subunit [12]. This also partially accords with earlier observations which showed that resveratol induced epigenetic effect. Tsai and co-workers revealed that a critical mechanism for morphine induced antinociception through increase of necrosis factor-alpha receptor (TNFR) gene expression, and resveratol restored this phenomenon via bock of morphine-induced histone deacetylase 1

(HDAC1) overexpression [13].Other possible explanations for resveratrol effect were proposed via opens of small and large conductance Ca^{2+}-activated K^+ channels that elicits its peripheral antinociceptive effect [30]. A limitation of this study is about molecular technique. More information on molecular mechanism of resveratrol would help us establish a greater degree of accuracy on this matter. A case in point is investigation of proteins that regulate apoptosis and mitochondria biogenesis.

5. Conclusion

One of the strengths of this study is the comprehensive examination of the effect of resveratrol on morphine responses on anxiety and emotional memory. Returning to the question posed at the beginning of this study, it is now possible to state that resveratrol can alter morphine induced effect on anxiolytic-like behaviors and emotional memory.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles were considered in this study. No human was enrolled. Animals were treated in compliance with the guidelines established by cognitive and Neuroscience Research Center (CNRC), Islamic Azad University Tehran, Iran.

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Author's contributions

The authors equally contributed to this article.

Conflict of interest

The authors declare no conflict of interest.

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