Research Paper

Effect of Intracerebroventricular Morphine Withdrawal on Anxiety Behavior in Male Rats Reared in Social Isolation

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Key words:
Anxiety, Morphine, Social isolation, Rats

ABSTRACT

Aims Narcotics prescription has controversial effects on the occurrence of anxiety processes; however, its acute and chronic effects on behavioral differences in social isolation are unclear in the processes of dependence and withdrawal. The present study aimed to investigate the effects of acute and chronic intracerebroventricular morphine sulfate withdrawal on the fear and anxiety behaviors of male rats reared in social isolation.

Methods & Materials The present experimental study investigated 32 male 21-day-old male weaned Wistar rats that were divided into two groups of saline (control) and morphine receivers (test). They were then divided into acute and chronic subgroups that were reared under social isolation conditions. The rats of the acute daily consumption group received 10 µg/kg of morphine sulfate solution via intracerebroventricular injection for 10 days, but the chronic rats received it for 60 days. After the end of dependence by its withdrawal, the rats were quitted for 5 days, and their anxiety levels were measured using the Elevated Plus Maze (EPM). The obtained data were analyzed in SPSS using One-Way Analysis of Variance (ANOVA), Tukey's posthoc test and Paired Samples t-test.

Findings The research results indicated that the percentage of time and number of open arm entries in rats reared in social isolation significantly decreased during the dependence phase and 5 days after withdrawal in acute and chronic groups ($P<0.001$). Furthermore, their anxiety rate increased compared to the control group. The findings also suggested a higher incidence of anxiety among chronic consumer groups than acute consumer groups after abstinence.

Conclusion The study findings indicated that the discontinuation of morphine consumption in social isolation could increase the incidence of anxiety behaviors in rats. Therefore, negative emotional states associated with acute and chronic morphine withdrawal could lead to anxiety-like behaviors.Keywords: Anxiety, Morphine, Social isolation, Rats.

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Extended Abstract

1. Introduction

Drug addiction is a type of chronic and regressive brain disease characterized by loss of control over medication use, repeated attempts in quitting or reducing drug use, drug use continuation despite negative consequences, reduced engagement in social, occupational, and social activities. They, instead, continue seeking for drug, self-prescription, and the emergence of departure or withdrawal symptoms [1, 2]. Symptoms such as muscle aches, severe muscle irritability, hostility, convulsions, diarrhea, and anxiety become so painful and intolerable that in many cases the patients resume drug use [4, 5].

Part of the soothing effect of opioids is through the predictable reduction of anxiety [6]. Previous studies have shown that morphine dependence in addicted mice causes anxiety-like behaviors [7]. Anxiety is one of the most commonly reported symptoms of quitting a variety of drugs. It is thought that termination of emotional withdrawal symptoms such as anxiety, numbness, agitation, restlessness, and fatigue are to be the drivers of resuming drug use that eventually lead to drug dependence [8, 9]. Discontinuation of opioids is associated with anxiety-like symptoms in humans and animals [9]. Animal models show similarities between drug dependence and sedation at behavioral and neurochemical levels [8].

2. Methods

For this experimental study 32 male Wistar rats that weaned aged 21 days were used. Then each rat was kept in a separate cage measuring 22×25×40 cm, in a state of social isolation. Specific water and food (pellets) were readily available, except during testing. The animals were housed in a 12 h light-dark period (seven in the morning to seven in the night) and 22±2° C without any sound or noise pollution. The experiments were carried out from 9 am to 1 pm.

Rats were randomly divided into four groups, each with eight rats. Rats were divided into control (saline) and Morphine Sulfate (Sigma-Germany) groups, each containing acute and chronic subgroups. In acute groups, the intravenous-cerebral injection was performed for 10 days and in chronic groups for 60 days [7, 19]. Five days after discontinuation of drug use, in the acute groups on days 15 and in the chronic groups on days 65 , the maze tests were performed.

Morphine sulfate was injected intracerebroventricular at a dose of 10 µg/kg. All injections were performed in 100 rg volume and 0.1 ml on body weight.

3. Results

The results of this study showed that five days after discontinuation of intracerebroventricular administration of morphine, the attendance percentage in the open arm of

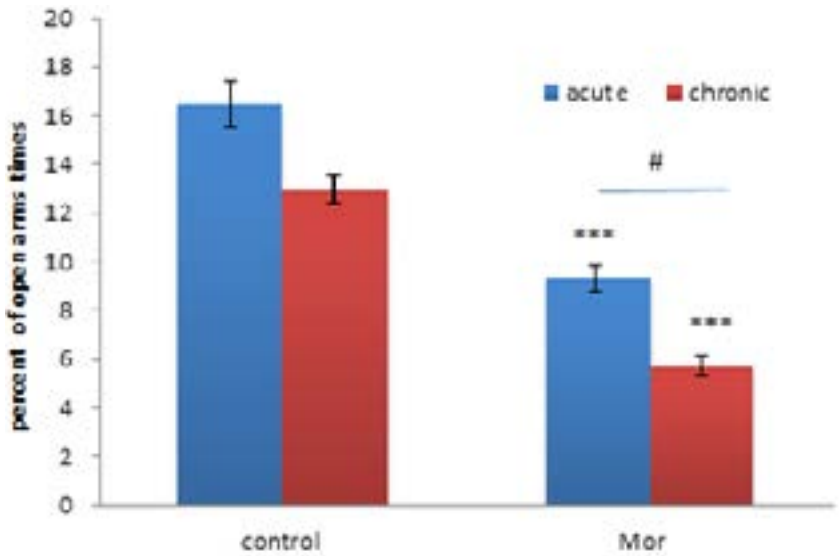

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Figure 1. Mean±SD of the effect of discontinuation of use of intracerebroventricular morphine (10 µg/kg, Mor) in precentage of presence in open arm in plus maze in rats under social isolation compared to control. P<0.05: significant difference with control group receiving saline. : # P<0.05 significant difference between acute and chronic groups

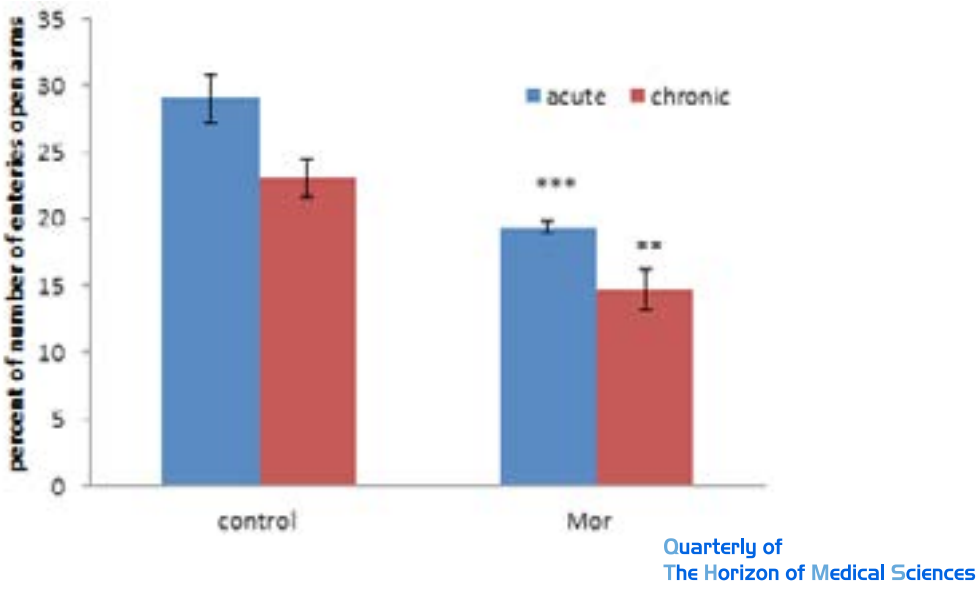

Figure 2. Mean±SD of the effect of discontinuation of use of intracerebroventricular morphine (10 µg/kg, Mor) in precentage of presence in open arm in plus maze in rats under social isolation compared to control.

*** P<0.01 **, P <0.001: Significant difference with control group receiving saline. P <0.05. #: Significant difference between acute and chronic groups

Equine Protozoal Myeloencephalitis (EPM) was significantly decreased in acute and chronic groups compared to the control group (P<0.001) (Figure 1) . The percentage of the entrance to the open arm of EPM in the acute and chronic groups was significantly reduced compared to the control group (P<0.001) (Figure 2). However, there was no significant difference in the entrance percentage in the closed arm of EPM compared to the control group (Figure 3).

The comparison between acute and chronic groups showed a significant decrease in the attendance percentage in EPM in the chronic groups compared to the corresponding acute group (P<0.05) (Figure 1), but the percentage of open and closed arm entrance and the association between acute and chronic groups was not significant (Figures 2 and 3).

4. Discussion

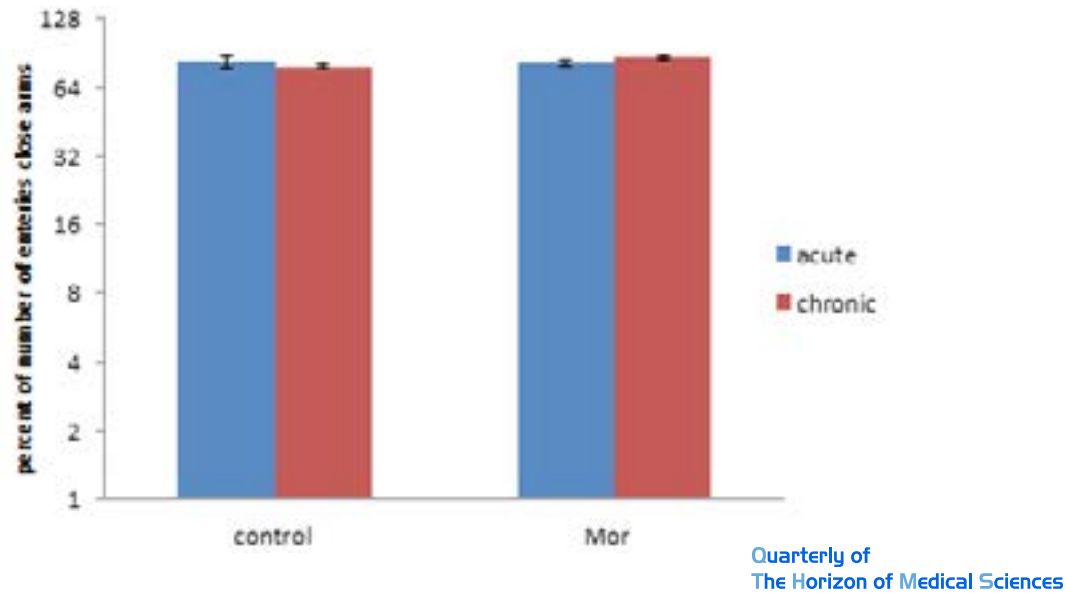

Figure 3. Mean±SD of the effect of discontinuation of use of intracerebroventricular morphine (10 µg/kg, Mor) in precentage of presence in closed arm in plus maze in rats under social isolation compared to control. P<0.05: Significant difference with control group receiving saline. : # P<0.05 significant difference between acute and chronic groups

The results showed that intracerebroventricular morphine-treated groups in acute and chronic conditions in rats cultivated under social isolation, five days after quitting morphine sulfate, compared to control groups, the percentage, and the number of the entrance to open arm of EPM declined.

Compared between the acute and chronic groups, in the chronic groups, after quitting, the percentage reduction of the entrance to EPM was higher but not significant; thus, morphine dependence and also quitting it can affect the rate of the rats' anxiety.

The acute and chronic administration of morphine was significantly different between the groups receiving morphine and the control group, indicating a type of morphine dependence and addiction in mice. Our findings indicate that quitting or dependent morphine-treated rats are more anxious than the control group; this mode in chronically addicted rats is often higher than in acute-treated rats.

5. Conclusion

The results of this study showed that discontinuation of acute and chronic intracerebroventricular administration of morphine under social isolation can increase the mode of anxiety behavior in rats. The rate of anxiety behavior in rats in acute administration was lower than in chronic administration at the time of dependence and after quitting. In summary, negative affective states associated with acute and chronic morphine quitting comprised anxiety-related behavior.

Animal models of negative affective consequences of opioid quitting should be useful in outlining the neurochemical and neuro-anatomical substrates of brain circuits related to stress, affective states, and brain reward. The use of social isolation after weaning among rats is useful for creating behavioral outcomes similar to the results of unpleasant experiences of isolation in humans and is the potential to provide preclinical findings that may turn into clinical research.

Since few studies have been performed on female mice, it is suggested to investigate the effect of acute and chronic morphine sulfate quitting on fear and anxiety behavior in female rats in social and non-social contexts, according to different injection methods.

Ethical Considerations

Compliance with ethical guidelines

This study has obtained its ethical approval from the Research Ethics Committee of Islamic Azad University of Damghan Branch (code: IR. REC. 1396.1544). All experiments on animals in this study was according to the Guide for the Care and Use of Laboratory Animals.

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Authors' contributions

Conceptualization, methodology, and investigation by Ghasemali khodabandeh; writing by Gholamhassan Vaezi; writing, methodology and data analysis by Vida Hojati; consulting by Sharam Sharafi.

Conflicts of interest

The authors declare no conflict of interest related to the present manuscript.

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