The effect of co-administration of restraint stress and morphine in prenatal period and re-exposure to stress at the end of infancy on corticosterone blood levels and pentylentetrazol-induced epileptic behaviors in rat

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Abstract

Background & Aims: Stressful events during gestation have important effects on the later physical and mental health of the offspring. The present study aimed to identify effects of co-administration of stress and morphine in prenatal period and re-exposure to stress at the end of infancy on corticosterone blood levels and pentylentetrazol-induced epileptic behaviors in rat.

Materials and Methods: Pregnant rats were divided to six groups of control, stress, saline, morphine, stress-saline and stress-morphine. In the stressed group, rats were stressed and held immobile for three consecutive days started on day 15 of pregnancy. The rats in saline and morphine groups received saline and morphine in the same days. In the morphine/saline-stress groups, rats were exposed to stress and received morphine/saline simultaneously. On postnatal day 22, half of the pups re-exposed to stress, and pentylentetrazol-induced epileptic behaviors of each rat were assessed. Blood samples were collected to determine corticosterone level.

Results: Latency of first epileptic behavior decreased significantly in stress-morphine group compared to other groups. Re-exposure to stress significantly led to a decrease in number of clonic seizure. There was no significant difference between the experimental groups in duration of clonic attacks and mortality rate. The level of corticosterone showed a significant increase in stressed pups and decreased in morphine group.

Conclusion: these results indicated that co-administration of morphine and restraint stress during late pregnancy had profound impact on neurochemical development and might alter vulnerability to PTZ-induced epileptic behaviors. Prenatal stress is more powerful than postnatal stress on influencing neural development and seizure susceptibility in rats.

Keywords: Restraint stress, Morphine, Seizure, Corticosterone, PTZ, Rat

Introduction

Prenatal environmental factors exert a profound influence and leads to severe birth outcomes, including preterm birth, fetal growth retardation, delays in early motor development and behavioral abnormalities(1). Prenatal stress can affect susceptibility to seizures in rats during postnatal development that can persist until adulthood (2). The appearance of such changes depends on the timing of the maternal stress, its intensity and duration and gender of the offspring(3).The major pathway implemented in coordinating the consequences of stress in most mammalian species is the hypothalamic-pituitary-adrenal(HPA)axis.

Corticotrophin releasing factor (CRF) expressing neurons within the parvocellular component of the paraventricular nucleus of the hypothalamus have been identified as one of the key elements in the stress response. The typical biochemical cascade in response to

physiological and psychological stresses involves the release of CRF from paraventricular neurons into the hypophysial portal system that in turn stimulates the release of adrenocorticotrophic hormone (ACTH) into general systemic circulation(4).Circulating ACTH can then interact with adrenal cortex receptors to stimulate the synthesis of steroids (steroidogenesis) as well as causing a marked elevation in plasma glucocorticoids(5).Animal studies indicate that administration of morphine during gestation causes morphological and behavioral aberrations in rat offspring including changes in seizure susceptibility (6-9). Prenatal morphine exposure induces long-term alterations in adult brain and behavior. Many abused drugs, including opiates, can cross the placenta to affect the development of the central nervous system (CNS)(10). Complex effect of morphine on seizure has been reported in terms of type and experimental condition. According to previous reports, the effect of morphine on seizure activity appears to be biphasic, potentiating seizures at doses above 2 mg/kg and inhibiting seizures at lower doses in several seizure models (11-13).Morphine excites dopamine neurons in the ventral tegmental area of the brain through inhibition of gamma-aminobutyric acid (GABA) ergic inhibitory interneurons(14). Pentylentetrazol(PTZ) acts as a GABAA receptor antagonist(15). Therefore, both morphine and PTZ act as GABA receptor inhibitors(16). Intraperitoneal (IP) administrations of PTZ are used to investigate the effects of acute and chronic epileptic seizures in animals (17, 18). Although there are many reports on the effect of prenatal stress on seizure susceptibility of young animals in different types of experimental seizure models, few studies have been accompanied by prenatal stress investigating the pups' seizure vulnerability(19-21). Moreover, there was not any accessible study on directly re-exposing the pups to stress so that they were stressed and exposed to morphine in their prenatal period. Therefore, this study aimed to investigate the effect of co-administration of restraint stress and morphine in prenatal period and re-exposure of stress at the end of

infancy on corticosterone blood levels and PTZ-induced epileptic behaviors in rat.

Materials and Methods

This research was an experimental trial. All the experimental protocols and procedures were complied according to guide lines of 1975 declaration of Helsinki as reflected in the guidelines of Medical Ethics Committee, Ministry of Health, I.R. Iran. Also, Regional Medical Ethics Committee in West Azarbyjan province, I.R. Iran, approved this study. Male and female Wistar rats (200–250 g) were obtained from the animal facility at Urmia University of Medical Sciences, Urmia, Iran. The rats were 8 weeks old on delivery. They were housed in groups of four per cage, and they were kept in standard conditions as follows: standard 12 h light/dark cycle (light on at 7 am), 22±2°C and food and water ad libitum. When they were 12 weeks old, all the female rats were mated with a sexually experienced male of the same genotype. Each female was paired with one male at 8am and checked for plugs at 3pm. The pregnant rats were immediately moved to new cages in which they were four rats per cage for the entire gestation period. They were divided to six groups (n=9, in each group): control, restraint stress, saline, morphine, stress-saline and stress-morphine. The stressed group was exposed to restraint stressor on gestation days 15, 16 and 17 (GD15, GD16 and GD17, respectively). The morphine group was treated with10, 12 and 15 mg/kg morphine IP at GD15, GD16 and GD17, respectively. The doses for prenatal morphine exposure were chosen according to previously reported studies (22-24). The saline groups received 0.5 ml saline IP on the same days. In the morphine/saline-stress groups, the rats were exposed to stress and received morphine/saline simultaneously. The control rats were transported to the experimental room on GD15, GD16 and GD17, and they were handled similar to the stressed rats, but they were not exposed to stress. This gestational age as "late-gestational period" was chosen because of its importance in developing of opioid system(25), HPA axis and nervous system(26). Prenatal stress, particularly during third weeks of

pregnancy, plays an important role in increasing seizure vulnerability in rat offspring(27).

Restraint stress procedure: For restraint stressed rats, stress involved transporting from the home cage to the experimental room and placing the pregnant female in a restraint chamber (a transparent, plastic, cylindrical chamber, 6 cm in diameter and 16 cm in length) under normal room conditions. The animals were restrained for 120 min twice per day (between 08: 00–10: 00 and 15: 00–17: 00) for 3 consecutive days. This protocol has previously been shown to cause alterations in the regulation of HPA axis in the offspring (1, 28).

Behavioral assessment: After parturition, the pups in each group were mixed and equally divided in the dams incase their birth date was the same. Each dam along with her pups was maintained in the individual cage(27). On postnatal day 22, half of the pups were re-exposed to the stress for one hour. To induce seizure, on P22, PTZ (60 mg/kg) was injected IP to all of the offspring of each group. Following the injection, behavior of each rat was observed and documented for 60 min by a digital camera. The seizure rating was assessed using a previously defined scale(29): 0=normal; 1=immobilization, sniffing; 2=head nodding, facial and forelimb clonus; 3=continuous myoclonic jerk, forelimb clonus, tail rigidity; 4=generalized limbic seizures with violent convulsion; 5=continuous generalized seizures (tonic or tonic-clonic convulsions).In rats, the occurrence of seizures increases during the second and third postnatal week(s) in response to convulsant agents(30-32), and it decreases between postnatal day 30-35, just prior to puberty(33-36).

Sample Collection: One hour after behavioral assessment, the blood samples were collected by cardiac puncture under ether anesthesia. Blood was collected in 1.5-ml EDTA-coated micro-centrifuge tubes, and it was kept on ice, and it was later centrifuged for 15 min at3,

000 rpm at 4˚C. Its plasma was transferred to clean 1.5 ml micro-centrifuge tubes and stored frozen at -80˚C until COS levels were determined. This hormone was measured using a commercial ELISA kit (Rat Corticosterone ELISA Kit, Chongqing Biospes Co. China).

Statistical analyses: Normally distributed data related to COS blood levels were analyzed using parametric techniques. To analyze the data related to COS, two-way ANOVA was performed for two factors of stress and morphine. The data related to epileptic behaviors that were not normally distributed were analyzed using Mann–Whitney U-test and/or Kruskal–Wallis one-way ANOVA. Also, post-hoc analyses were done using Tukey's test. Results were expressed as the mean ± standard error (SE) of the mean. Differences were considered statistically significant at p<0.5.

Results

Effects of prenatal morphine and stress exposure on COS blood levels in prepubertal rats:

Data analyzed by two-way ANOVA on corticosterone blood level in offspring showed that: the effect of group was significant (p<0.001), but the effect of gender (p=0.709) and re-exposed-stress (p=0.541) were not significant. The interaction between group *gender (p=0.002), and the interaction of group*re-exposed-stress (p<0.001) were significant, but interaction of sex*re-exposed-stress (p=0.072) showed no significant effect. The interaction between group*sex*re-exposed-stress was not significant (p=0.060). Meanwhile, stress-morphine group has greatest level of corticosterone (7.54±0.51ng/L), and stress-saline group has the least amount of corticosterone (4.17 ± 0.51ng/L) compared to the other groups. Figure 1 shows the results of this analysis.
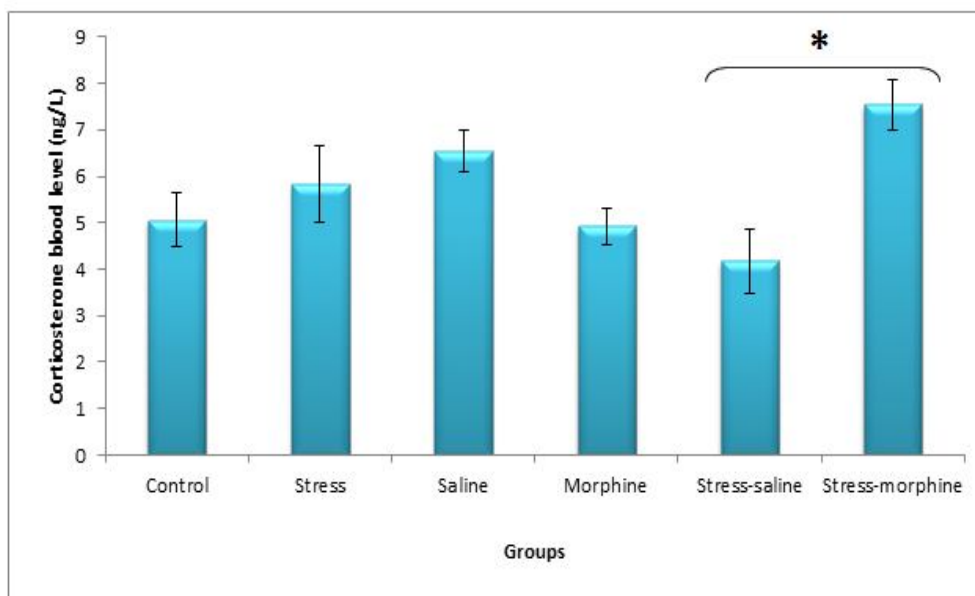
Figure 1. Theeffect of prenatal morphine and stress exposure on COS blood levels in offspring; *Indicates significant difference between stress-morphine and stress-saline group (p<0.001)

The effects of prenatal morphine and stress on latency of first seizure:

The results of the data analysis by two-way ANOVA on the latency of first epileptic behavior showed that: the effect of group was significant (p<0.001), but the effect of sex (p=0.135) and re-exposed-stress (p=0.146) were not significant. The interaction between group *sex (p=0.015) and the interaction of group*re-exposed-stress (p<0.001) were significant, but interaction between sex*re-exposed-stress, was not significant (p=0.072). The interaction between group*sex *re-exposed-stress was significant (p<0.001). The results of this analysis are shown in Figure 2.
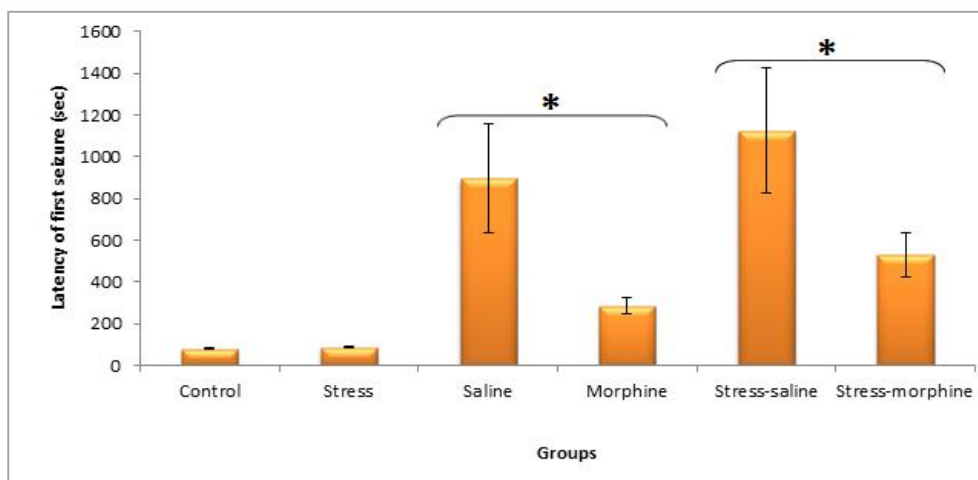

Figure 2. The effect of prenatal morphine and stress exposure on latency of first seizure in offspring; *Indicates significant difference between morphine and saline group (p=0.029), and between stress-morphine and stress-saline group (p=0.036).

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Effects of prenatal morphine and stress exposure on number of clonic seizure:

The results of the data analysis by two-way ANOVA on number of clonic seizure showed that: the effect of group (p<0.001) and re-exposed-stress (p=0.02) were significant, but the effect of sex was not significant (p=0.435). The interaction between group *sex was not significant (p=0.254), whereas the interaction of group*re-exposed-stress (p=0.024) and interaction between sex *re-exposed-stress (p=0.011) were not significant. The interaction between group* sex *re-exposed-stress was significant (p<0.001). The results of this analysis are shown in Figure 3 (A and B).
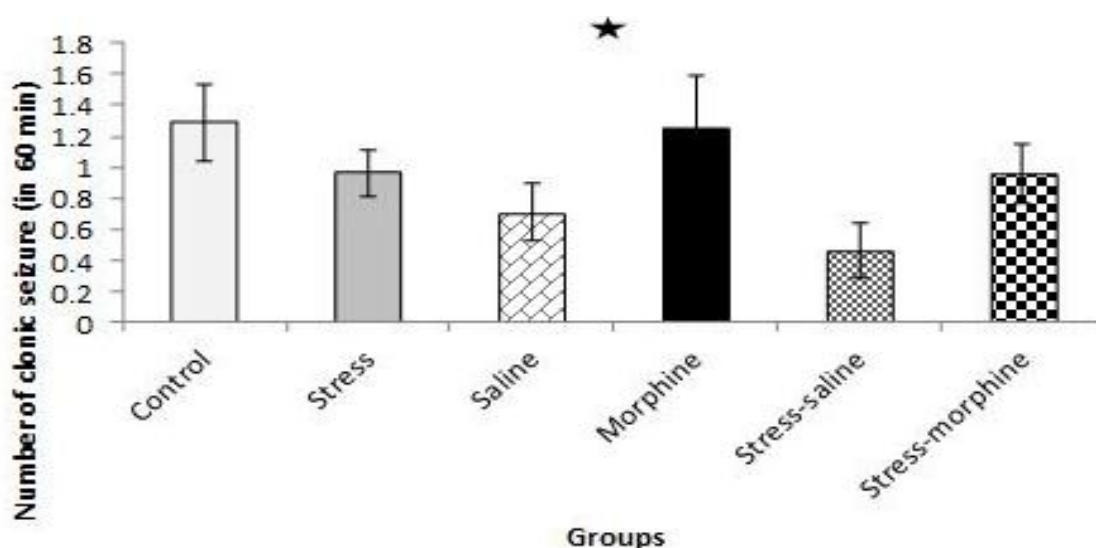

Figure 3 A. Effect of prenatal morphine and stress exposure on number of clonic seizure; ★ indicates significant difference between saline and morphine, and between stress-saline and stress-morphine groups.
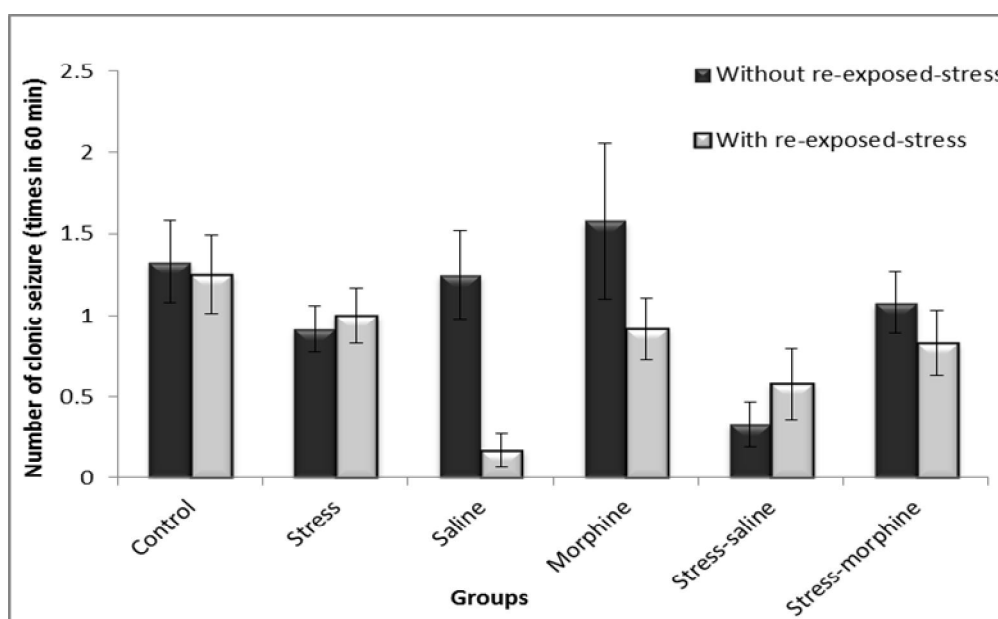

Figure 3 B. Effect of re-exposure to stress in rat pups that treated with morphine and stress during prenatal period on the number of clonic seizure; According to data analysis by Two way ANOVA, the effect of re-exposure to stress were significant(p=0.02).

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The effect of prenatal morphine and stress on duration of clonic seizure:

The results of the data analysis by Kruskal-Wallis test for duration of clonic seizure indicated no significant difference between groups (Figure 4).
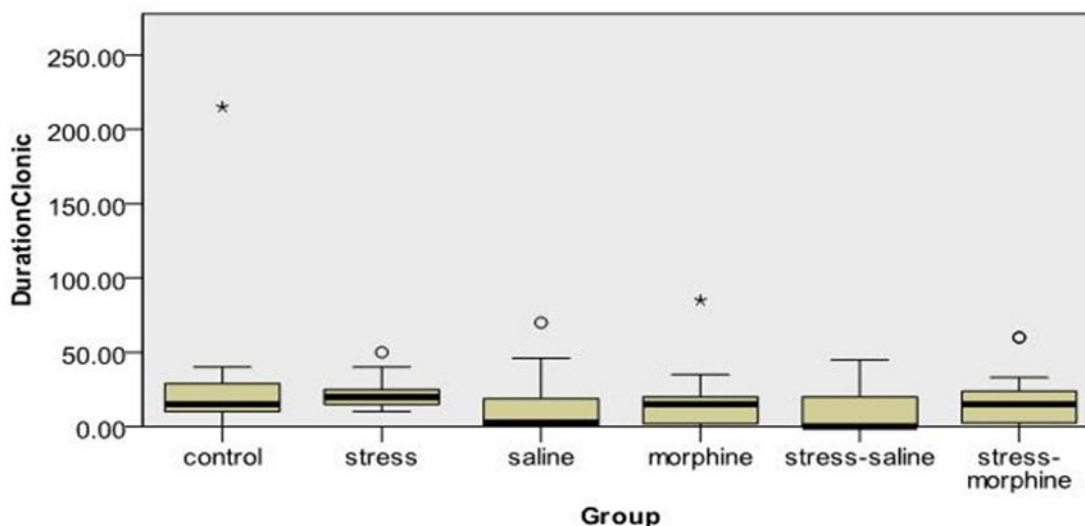

Figure 4: Theeffect of prenatal morphine and stress on the duration of clonic seizure. There was no significant difference between groups. This figure was created by SPSS software, and the signs (* and o) inside the figure do not indicate a significance difference. They are symbols for uneven data distribution.

Effect of prenatal morphine and stress on mortality rate:

The pups were also monitored for lethal effect of PTZ-induced seizure for 120 min after PTZ injection. The results of the data analysis by Kruskal-Wallis test for mortality rate indicated no significant difference between the groups.

Discussion

In the present study, COS blood levels and PTZ-induced seizures were investigated on the rats exposed to restraint stress, morphine or both in prenatal period. In addition, the effect of re-exposure to the stress at the end of infancy was studied on these parameters.

Effects of co-administration of restraint stress and morphine on COS blood level (CBL):

This study (Figure1) demonstrated that prenatal stress increased (non-significantly) CBL compared to control group. In contrast, exposure to prenatal morphine decreased (non-significantly) CBL compared to the

saline group. In addition, co-administration of restraint stress and morphine during pregnancy increased CBL in offspring compared to stress-saline. According to the previous studies, prolonged exposure to stress during pregnancy increases the level of CRH, ACTH and COS and alters brain development (37). Chronic stress causes an imbalance in regulation of the HPA axis, and changes feedback regulation of this axis, that lead to an increase in secretion of CRF(38). CRF and glucocorticoids show pro-convulsant effects in pups and are known to decrease seizure threshold, and cause alterations in fetal CNS (39-41). The present findings were consistent with these data. Meanwhile, it has been also reported that exposure to morphine reduces levels of ACTH induced by stress in both diestrus and estrus in females. This might indicate that prenatal exposure to morphine can affect HPA axis and regulates stress response (42). Chronic exposure to morphine in male rats increases concentration of COS binding globulin in the blood, and in turn, appears to dramatically decrease the amount of COS available to

intracellular receptors(43). The results confirm the findings of other investigators in this context.

Interaction between prenatal morphine and restraint stress on PTZ-Induced seizure:

Studies have shown that exposure to stressful situations can lead to profound changes in the electrical properties of neurons, which in turn, can increase the sensitivity of neurons to induce epileptic activity(44). Studies have also shown that the effects of stress on the severity of neonatal seizures are age dependent. So that according to one report, prenatal forced-swim stress potentiates seizure in 15-day-old pups, but seizure severity was not significantly different in 25-day-old pups between groups(45).The current study was conducted on 22-day-old offspring, and found that epileptic behaviors were not significant between stress and control groups. This finding may indicate that the effect of prenatal stress is more severe in younger offspring. Results of previous studies report that exposure to opioids in prenatal period may affect development of CNS and change number of opioid receptors(46). Morphine has a dose-dependent biphasic effect on seizures(47, 48), potentiating seizures at high doses and show antiepileptic effect at lower doses(13).In current study, co-administration of restraint stress and morphine in prenatal period caused earlier onset of first seizure, and increased seizure vulnerability in pups more severely compared to their effects individually. To explain this effect, it was hypothesized that co-administration of morphine with stress, not only did not offset the effects of prenatal stress, but also stabilized the impact of prenatal stress on offspring at least in early lifetime (at the end of infancy).

Impact of re-exposure to stress on PTZ-induced seizure:

Findings of the current study indicated that effect of re-exposure to stress was significant in some epileptic behaviors, and interaction between group* re-exposure to stress was significant on almost all PTZ-induced epileptic behaviors. Confirming this, It has been reported that when animals are subsequently re-exposed to stressors, even if they are different from the original challenge, neurochemical changes occur more readily and the magnitude of the changes is more pronounced(49). Indeed, the initial stressor exposure may have stimulated the sensitization of processes that are responsible for the elevated response to the later stressor experience(50). It has been reported that these sensitized effects may increase susceptibility to psychological disturbances, such as depression, anxiety (51)and epilepsy. Our data is in agreement with existent literatures.

In conclusion, these results indicated that co-administration of morphine and restraint stress during late pregnancy had profound impact on neurochemical development, and it might alter vulnerability to PTZ-induced epileptic behaviors in young animals. In addition, prenatal stress is more powerful than postnatal stress (at least re-exposure to stress at the end of infancy) on influencing neurochemical development and seizure susceptibility in rats.

Ethical approval:

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Acknowledgments

Conflicts of Interest:

The authors declare no conflict of interest.

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