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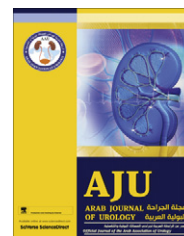


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ORIGINAL ARTICLE

Effect of noise stress on male rat fertility, and the protective effect of vitamins C and E on its potential effect

Ali Fathollahi ^{a,*}, Majid Jasemi ^b, Ghasem Saki ^c

^a Emam Khomeini Hospital, Ahwaz Joundi Shapour University of Medical Sciences, Ahwaz, Iran

^b Urology Ward, Golestan Hospital, Ahwaz Joundi Shapour University of Medical Sciences, Ahwaz, Iran

^c Physiology Research Center, Ahwaz Joundi Shapour University of Medical Sciences, Ahwaz, Iran

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KEYWORDS

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FSH;
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ABBREVIATION

LH, luteinising hormone

Abstract Objective: To evaluate the effect of noise on the fertility of male rats, and to assess the effect of vitamins C and E on its potential effect.

Materials and methods: Forty adult male rats were randomly divided into five equal groups. Group 1 (control) was not exposed to noise. Groups 2–5 were exposed to noise of 90–130 dB and 300–350 Hz from 19.00 to 07.00 h every day for 50 days; group 2 received vitamin C and group 3 received vitamin E. Group 4 received vitamins C and E concomitantly and group 5 received no vitamins. After 50 days, the serum levels of follicle-stimulating hormone (FSH), luteinising hormone (LH) and testosterone were measured. Each rat was then left for 1 week with three female rats, for mating. Pregnant females were killed humanely after 19 days of pregnancy and evaluated for the presence and number of viable, dead and absorbed fetuses.

Results: The mean serum FSH level was statistically significantly different between the control and groups 2 ($P < 0.05$) and 5 ($P < 0.001$). The mean serum LH level differed significantly between the control and groups 2 ($P = 0.05$), 3 ($P < 0.05$) and 5 ($P < 0.001$). The mean serum testosterone level was significantly different between the control and group 5 ($P < 0.001$). Serum FSH, LH and testosterone levels in group 5 were significantly different from all the others ($P < 0.001$).

* Corresponding author. Tel.: +98 9121957991.

E-mail addresses: patronager@yahoo.com (A. Fathollahi), mjasemizergani@yahoo.com (M. Jasemi).

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The pregnancy rates in females mated with groups 1 and 5 were statistically different ($P < 0.05$). Comparing groups 1–4, there was no difference in the occurrence of abnormal pregnancy ($P > 0.05$), but group 5 values were significantly different from the others ($P < 0.001$).

Conclusion: These data strongly suggest that noise stress has a significant effect on the fertility of male rats.

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Introduction

Of all cases of infertility in humans, $\approx 20\%$ are due entirely to a male factor, with an additional 30–40% involving both male and female factors [1]. One of the goals when evaluating an infertile man is to identify reversible conditions that are responsible for infertility. Various conditions can cause infertility. Moreover, there are many controversies about environmental factors and occupational exposure to physical agents that might affect fertility [2]. Exposure to chemical toxins, and the effect of heat and cigarette smoking, have long been studied [3]. However, the effects of noise stress on different systems related to fertility have yet to be elucidated. Some have suggested that the teratogenic action of noise is primarily the result of decreased uroplacental blood flow, resulting in foetal hypoxia, and increased secretion of maternal catecholamines [4]. Geber [4] reported a significantly reduced litter size and a significant increase in the number of resorptions per litter amongst pregnant rats exposed to noise. Others [5] exposed mice to noise at 83–95 dB during gestation, and reported increased pre-implantation mortality, decreased litter size, and decreased embryo size and weight amongst the exposed offspring. There was no significant effect on the number of litter resorptions. However, these data are inconsistent amongst the various experimental conditions [6–8]. These different results might be due to variability in acoustic stimuli, exposure regimens, test species, and other variables [9].

Antioxidants are the main defence against oxidative stress induced by free radicals. There are preventive antioxidants and scavenger antioxidants. Preventive antioxidants, e.g. metal chelates and metal-binding proteins, block the formation of new free radicals, whereas scavenger antioxidants remove the free radicals that have already formed [10].

Oxidative stress can be limited by using chain-breaking antioxidants such as vitamins E and C as drug supplements [11]. More specifically, these vitamins have been shown to have protective effects on the testis and on fertility [3,12].

In the present study we evaluated the effect of noise stress on male rat fertility and administered vitamins C and E to assess any change in the effects of noise.

Materials and methods

This experimental study was conducted in the Physiology Research Centre of Ahwaz Joundi Shapour University of Medical Sciences from September 2010 to December 2010. Male rats (200–250 g) of the Wistar strain (*Rattus norvegicus*) were used, acclimated to $22 \pm 1^\circ\text{C}$ and maintained under conditions of 12-h of light and dark, with free access to tap water and commercial rat food. All procedures were approved by international guidelines and by the Institute Research Ethics and Animal Care and Use Committee of the authors' institution. Every effort was made to minimise the number of animals used and their suffering.

Experimental design

The rats were randomly divided into five groups of eight each, and thus the fertility of each group was considered comparable to the other groups at the baseline. Group 1 (controls) was not exposed to noise. The rats in groups 2–5 were exposed to noise at 90–130 dB and 300–350 Hz from 19.00 to 07.00 h each day for 50 days. For this exposure the groups were transported to a room of $3 \times 4 \times 3$ m, lined by wood and acoustic segments ('anti-loud' voice), within which 'white noise' was produced [13], and a timer was arranged so that after 1 h of exposure the noise was turned off for 15–60 min before continuing the exposure. This intermittent exposure was to prevent the rats from becoming adapted to the noise. The intensity and frequency of the noise was changed automatically within the range of minimum and maximum every 2–3 min, and this also contributed to preventing adaptation to the noise [14]. The amount and intensity of noise were measured using a noise level meter and the rate and intensity were controlled in this way. Group 2 received vitamin C (125 mg/kg/day) and group 3 received vitamin E (75 mg/kg/day) [3]. Group 4 received vitamins C and E concomitantly. Group 5 received no vitamins.

After 50 days (7 weeks is the time needed for a complete spermatogenesis cycle in male rats) a blood sample was drawn with a syringe from each rat's tail, between 08.00 and 11.00 h, and analysed for serum FSH, LH and testosterone levels using an ELISA technique. As all rats had been assigned randomly to the groups at

the beginning of study, serum levels in the control group were referred to as the normal range and levels in the other groups were compared with those. Each rat was then left with three female rats, for mating, for 1 week. Every morning, females with positive vaginal plaques (pregnant females) were identified and separated. Pregnant females were killed humanely on the 19th day of pregnancy (the duration of normal pregnancy in the rat is 21 days) by cervical dislocation under anaesthesia (an acceptable method of euthanasia of rats used for scientific purposes). Their uteri were then evaluated for the presence and number of viable, dead and absorbed fetuses.

Data are reported as the mean (SD) and percentage, where appropriate. The statistical significance of differences between the control and experimental groups was determined by anova for the hormonal studies. The pregnancy rate and number of dead/absorbed fetuses were compared amongst groups using the chi-square test. Differences between the means were considered to be significant at $P < 0.05$.

Results

Hormones

The mean serum values of FSH, LH and testosterone are shown in Table 1; the difference in mean serum FSH was statistically significant between the controls and groups 2 ($P < 0.05$) and 5 ($P < 0.001$). There was a large difference in serum FSH level between group 5 and all other groups ($P < 0.001$). For LH the difference was significant for the control and groups 2 ($P = 0.05$), 3 ($P < 0.05$) and 5 ($P < 0.001$). Again there was a conspicuous difference between group 5 and all other groups ($P < 0.001$). The mean serum testosterone level was statistically different between the control and group 5 ($P < 0.001$), and again the group 5 values were very significantly different from all the others ($P < 0.001$).

Fertility

Table 1 also gives the pregnancy rates for the five groups. The pregnancy rates amongst the groups were

not significantly different ($P > 0.05$), but the pregnancy rate in groups 1 and 5 were statistically different ($P < 0.05$). The presence and frequency of dead and/or absorbed fetuses in impregnated rats are also given in Table 1. Comparing groups 1–4 with each other, there was no significant difference in the occurrence of abnormal pregnancy outcome ($P > 0.05$). By contrast, the values in group 5 differed significantly from the others ($P < 0.001$).

Discussion

While previous studies had only assessed single hormones, in the present study the complete pituitary–testis hormonal axis of the male rats was assessed after exposure to noise. We also evaluated the possibility of a protective effect of antioxidants on both hormones and fertility.

Noise decreased the serum testosterone level in the present rats but supplementing the rats with either vitamin C or E, or a combination of both, resulted in testosterone returning to the normal range. This result is similar to that reported by Chandrlekha [15], in which male albino rats were exposed to 100 dB of noise for 1 h and 3 h in an acute group, and a daily 1-h exposure for 60 days and 90 days in a chronic group. In that study there was also a significant reduction in serum testosterone levels. Armario and Castellanos [16] also showed that the testosterone response in mice was impaired by water restriction, heat exposure and immobilisation. However, interestingly, an acute noise stress of 80 dB increased the testosterone level. In the present study noise increased the serum FSH levels. By adding vitamin E or vitamins C and E to the regimen, rats exposed to noise were protected from the effect on FSH level. However, vitamin C alone did not compensate for the negative effect of noise stress.

Serum LH level was also decreased by noise to an extent that vitamin C or E could not reverse. However, the combination of vitamins C and E had a protective effect on LH levels against noise stress.

In contrast with previous studies that mainly focused on the effect of noise on female rat fertility, the present

Table 1 Serum FSH, LH and testosterone levels, and pregnancy data, in the five groups.

Variable	Group				
	1	2	3	4	5
FSH	2.24	3.23 [†]	2.60	2.36	9.04 [‡]
LH	2.11	2.85	3.45 [‡]	2.26	7.51 [‡]
Testosterone	8.89	7.89	8.36	8.49	3.49 [‡]
Pregnancy rate, n/N (%)	23/24 (96)	20/24 (83)	18/24 (75)	20/24 (83)	16/24 (67)
Frequency of dead and/or absorbed fetuses in impregnated mates, n/N (%)	2/23 (9)	2/20 (10)	2/18 (11)	2/20 (10)	10/16 (63)

[‡] $P < 0.001$, vs. group 1.

[†] $P < 0.05$, vs. group 1.

study assessed the fecundity of the male rat. In a study by Kimmel et al. [6] pregnant mice were exposed to 100 dB of noise on days 3–6, 7–10 or 11–14 of gestation. There were significantly increased resorption rates and fewer live fetuses per litter in each of the treated groups. We also had similar results, as there were more pregnant rats containing any dead and/or absorbed fetuses than in those that had mated with noise-exposed male rats. Moreover, in females mating with noise-exposed males who had received vitamins, either alone or in combination, this effect was corrected.

Nawrot et al. [7] exposed mated female mice to either semi-continuous 126-dB low-frequency noise, intermittent 110-dB mid-frequency noise, or semi-continuous, very high-frequency (18–20 kHz) 113-dB noise on days 1–6 or 6–15 of gestation. There was significantly greater embryo and foetal mortality, decreased foetal weight, and a decreased pregnancy rate amongst the exposed mice. The negative effect of noise was also reported by Cosa and Cosa [8], who reported abnormalities in reproduction, and a significant decrease in pregnancy rate and lethal effect in mice embryos exposed to high frequencies of noise. Again, in the present study, on assessing the pregnancy rate, overall there was no significant difference, except when comparing rats in the control group with noise-exposed rats, when the difference was significant; this is in line with previous results.

In a follow-up study, Nawrot et al. [17] exposed mated female mice to high-frequency 110-dB noise on days 6–15 of gestation. There was a lower pregnancy rate and mean foetal weight, and increased foetal mortality, amongst the exposed mice. As in the earlier study [7], there was no significant effect on the frequency of foetal malformation or litter resorption amongst the mice exposed to noise. By contrast, we found noise stress to predict a higher occurrence of abnormal pregnancy, defined as foetal resorption and/or death.

However, vitamin supplementation could potentially prevent these effects. This might be interpreted as a more teratogenic or detrimental effect of noise stress on male fertility rather than on the female reproductive state. Vitamin C neutralises hydroxyl, superoxide and hydrogen peroxide radicals, and prevents sperm agglutination [11]. Lewis et al. [18] found reduced levels of vitamin C in the seminal plasma of infertile men. Akmal et al. [19] showed that vitamin C supplementation in infertile men might improve the sperm count, sperm motility and sperm morphology. As in previous studies, we showed that vitamin C had a protective effect on the fertility rate and foetal abortion and death; however, its effect on FSH and LH was not significant.

In a randomised cross-over study, vitamin E improved sperm function, as assessed by the zonal binding test [20]. In the present study, vitamin E could prevent the negative effect of noise on the pregnancy rate and the rate of foetal death and abortion. Like vitamin C,

it had no protective effect on the level of LH, but the FSH level was improved. Likewise, a combination of vitamins C and E normalised the pregnancy rate and the rate of foetal abortion and death. Importantly, the combination normalised the FSH and LH levels. However, according to Agarwal et al. [11], many studies failed to examine the effect of antioxidants on a specific group of infertile patients with high oxidative stress.

Last, we did not conduct a histological evaluation, but considering the large changes in the hormonal milieu, it could be assumed that noise would cause structural changes leading to abnormalities in FSH, LH and testosterone levels. Our data are in contrast with those in the study by Gunther [21], who examined the effect of noise on the fertility of 21 male guinea pigs. Noise at 110 dB lasted 3–5 h daily over 22–31 days. Histological examination of the testicular tissue showed no disorders of spermatogenesis. Nevertheless, Gunther noted that the negative result was attributed to failings in the test arrangement. Exposure to noise only lasted for at most 31 days, but the duration of spermatogenesis in guinea pigs is ≈ 40 days. Moreover, the exposure was only 5 h/day, yet the recovery took 4–5 times longer every day. Consequently, the daily short-term depression of the neuroendocrine system affected gonadotrophin secretion in a similar pattern to the daily biorhythmic variation. Therefore, the expected inhibition of fertility by the neuroendocrine route could not be confirmed.

In conclusion, the present data strongly suggest a negative role for noise stress on the fertility of the male rats. However, these results should be further assessed in humans (e.g. factory workers, those living near airports, etc.). It is also recommended that the effect of noise on testicular size, weight and histology be evaluated in other studies.

Conflict of interest

This project was financially supported by the research deputy of Ahwaz Jundi Shapour University of Medical Sciences (AJUMS).

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None.

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