

Effect of Noise and Crowding Stresses on Hypothalamic–Pituitary–Gonadal Axis and Protective Effect of Sulpiride Drug in Adult Female Albino Rats

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Abstract

Background: Noise and crowding are the most stressful factors which cause depressant effects on human beings, especially females. Therefore this study was aimed at clarifying their effects on hypothalamus pituitary gonadal axis hormones (luteinizing hormone (LH) and follicle-stimulating hormone (FSH), estrogen (E2) and progesterone as well as prolactin (PRL) and the possible protective effect of antidepressant drug; sulpiride.

Material and Methods: Sixty adult female rats were divided into six groups (10/each):

1- Rats served as control, 2- Rats treated with sulpiride drug only, 3- Rats exposed to noise (90db, 3hr. per day) for 45 days, 4- Rats exposed to noise and treated with sulpiride drug, 5- Rats exposed to crowding and 6- Rats exposed to crowding and treated with sulpiride drug.

Results: Noise and crowding stresses caused a significant decrease of estrogen (E2), progesterone (P), LH and FSH levels and high significant increase in PRL level. Sulpiride drug ameliorated these parameters changes except PRL level which showed a high significant level compared to control group.

Conclusion: it is useful to use antidepressant drug (e.g. sulpiride) with people who are exposing to noise and crowding stress.

Keywords: Noise, Crowding, Sulpiride drug, hypothalamic–pituitary–gonadal axis FSH, LH, PL estrogen, and progesterone.

Introduction

The hypothalamic–pituitary–gonadal (HPG) axis refers to the effects of the hypothalamus, pituitary gland, and gonads as if these separate endocrine glands were a single entity acting as a whole. Since the glands often function in cooperation, endocrinologists and physiologists find it more simple and descriptive to refer to them as a single system. The HPG axis controls reproduction, development, and aging. The hypothalamus produces gonadotropin-releasing hormone (GnRH). The anterior portion of the pituitary gland produces luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and the gonads produce estrogen (E2) and progesterone⁽¹⁾.

Estrogen (E2) is only one of the hormones in the complex milieu that changes across the menstrual cycle; progesterone levels, as well as the ratio of estrogen to progesterone, may have strong influences on fear and anxiety. For example, progesterone has been implicated in neuroimaging studies using emotionally arousing images⁽¹⁾; additionally, its metabolite

allopregnanolone has been associated with impaired fear extinction in rodent models⁽²⁾.

However, **Milad et al.**⁽³⁾ investigated fear extinction with respect to both progesterone and estrogen levels and found that deficits in extinction recall seemed to be more highly associated with estrogen⁽⁵⁾.

Prolactin (PRL) develops the mammary glands and stimulates lactation. Recent evidence shows that PRL plays an important role in the regulatory mechanism of biological responses to several stressors. The increase in peripheral concentrations of PRL is a typical response to physiological and psychological stressors and the response is sometimes used as an index of stress intensity⁽⁴⁾. The physiological meaning of PRL response to stressors remains to be clarified⁽⁵⁾. Many studies have demonstrated that PRL secretion from the anterior pituitary, which is the principal origin of the hormone in circulation, is under regulation by both stimulatory PRL-releasing factors (PRFs) and inhibitory factors,

particularly dopamine (DA) from the tuberoinfundibular dopaminergic neurons (TIDA) ^(5,6).

The HPG axis plays an important role in the development and regulation of a number of the body's systems, such as the immune and reproductive systems. Fluctuating hormone levels cause changes in the hormones that are produced by each gland and as a result have a variety of wide spread and local effects in the body ⁽⁷⁾. Also, the HPG axis can be influenced by lifestyle and dietary factors such as stress ^(8,9) respectively. Therefore, a lack of normal functioning of the female reproductive system impacts a wide variety of other emotional and physical health conditions.

An extensive literature reports that mood disorders are more frequent in women compared with men ^(10,11).

Noise is an environmental pollutant capable of causing hearing impairment ⁽¹²⁾, behavioral, mental and widespread disturbances at several levels in human organs and apparatus due to chemical and physiological modification of endocrine system ⁽¹³⁾. However, in the modern environment in economically developed countries, noise has become one of the permanent components of the surroundings, which is not prevented even by sleep ⁽¹⁴⁾. Results of numerous epidemiological, laboratories, occupational and environmental studies are evidence of high rate of blood pressure, hypertension and ischemic heart disease, including myocardial infarction, neurosis, different level loss of hearing, ulcer, diabetes, sexual as well as reproductive function disorders in workers of the enterprises with high level of industrial noise and community noise ⁽¹⁵⁾. However, the effects of noise stress on different systems related to fertility have yet to be elucidated ⁽¹⁶⁾. Stress inhibits reproductive functions in different groups of vertebrates ⁽¹⁷⁾. Despite a number of reports on the inhibitory effects of stress on reproduction, the means by which stress influences reproduction is not clearly understood in vertebrates ⁽¹⁸⁾.

Crowding stress is a type of psychosocial stress induced by an increased density of population. Population density may be raised either by increasing the number of species

living in the same area and/or by reducing their living space ⁽¹⁹⁾.

Antidepressant drugs are the most successful drugs in patients with clear vegetative characteristics including psychomotor retardation, stress, sleep disturbance, poor appetite and weight loss. However, a variety of different chemical structures have been found to have antidepressant activity. Their number is constantly growing, but as yet no group has been found to have a clear therapeutic advantage over the others ⁽²⁰⁾.

Antipsychotics are the most common cause of pharmacologic hyperprolactinemia ⁽²¹⁾. Since antipsychotic drugs (e.g. sulpiride) tend to block dopamine D2 receptors, which attenuates the inhibitory effect of dopamine on prolactin release, leading to hyperlactinemia ⁽²²⁾. Sulpiride is the most favorite drug which used to tolerate stress symptom ⁽²³⁾.

So, the present study deals with the possible protective effect of one of the antidepressant drugs (sulpiride) against noise and crowding stresses induced on HPG axis in adult female albino rats.

Material and methods

Sixty female albino rats weighting 150 ± 30 g were purchased from the Department of the Nile Company for Pharmaceuticals. They were kept under observation for one week before the beginning of the experiment to acclimatize to laboratory conditions and fed *ad libitum*, during this time the females showed normal estrus cycle phases by regular vaginal smears. The chosen animals were housed in cages and kept under artificial light for 14 hrs. and in complete darkness for 10 hrs, at normal atmospheric temperature. All animals were fed on standard rodent diet.

Sulpiride administration:

The drug was administered orally by gastric tube at a dose of 0.28mg/100g . body weight/day for 45 days. The dose for the rat was calculated according to the Paget's formula on the basis of the human dose ⁽²⁴⁾.

Application of Noise:

Noise was applied by 5 different sources of enharmonic and high intensity music (90 db).

Application of crowding:

A group of 10 rats were put in a cage with reduced area (20 × 15 × 20 cm).

Animal groups:

Sixty female albino rats were divided into six main groups each one contained ten rats as follow:

Group 1: Normal rats served as control group untreated for a duration of 45 ± 2 days in a standard cage area ($20 \times 45 \times 20$ cm).

Group 2: Rats were treated with the sulpiride drug at a dose of 0.28mg/100mg body weight/day for a duration of 45 ± 2 days in a standard cage area.

Group 3: Rats were exposed to noise (90db, 3hr. per day) for a duration of 45 ± 2 days in a standard cage area.

Group 4: Rats were exposed to noise and treated with the drug for a duration of 45 ± 2 days in a standard cage area.

Group 5: Rats were exposed to crowding only for a duration of 45 ± 2 days in a reduced cage area (1/3 standard cage area) ($20 \times 15 \times 20$ cm).

Group 6: Rats were exposed to crowding and treated with the drug for a duration of 45 ± 2 days ($20 \times 15 \times 20$ cm).

Blood collection:

At the end of the last exposure, the animals were sacrificed and about 5 ml of blood was collected from each rat and then centrifuged for 15 minutes at 3000rpm. Sera were collected and kept at -20°C till hormone analysis.

Hormonal analysis: The technique of Enzyme-Linked Immunosorbent Assay (ELISA) was used to determine the levels of E2, Progesterone, LH, FSH and PRL hormones in serum specimens. The ELISA

test was detected using Roche Automated ELISA system.

Data analysis:

The obtained data were statistically analyzed by using the student t-test according to the method of **Snedecor and Cochran** ⁽²⁵⁾, $P \leq 0.05$ considered significant while $P \leq 0.01$ was considered highly significant difference.

Results

Sulpiride administration induced insignificant effect on all tested HGA hormones except PRL which increased significantly compared to normal control group.

There was a highly significant ($P < 0.01$) reductions in serum LH, FSH, E2, and Progesterone levels in noise or crowding exposed female albino rats, while there was a highly significant ($P < 0.01$) increase in serum PRL levels compared to normal unexposed rats (table 1). Treatment of rats with sulpiride exposed to noise or crowding enhanced all measured hormone levels (LH, FSH, E2 and P) except PRL which still highly increased in comparison with normal control rats.

The group treated with the sulpiride drug showed a highly significant increase ($p < 0.01$) in serum PRL when compared with control group throughout the experimental period. Also, there was a highly significant increase ($p < 0.01$) in serum Prolactin of noise, crowding, noise treated with drug and crowding treated with drug groups (table 1).

Groups Parameters		Control	Drug	Noise	Noise + Drug	Crowding	Crowding + Drug
		FSH (mIU/ml)	Mean	23.9	21.9	15.9	19.8
SE±	2.63		0.5	1.7	2.1	2.1	1.89
P			<0.05	<0.01	<0.01	<0.01	<0.01
% of change			2.8	-38.4	-31.1	-44.8	-25.6
LH (mIU/ml)	Mean	26.6	24.8	10.4	19.8	10.4	21.3
	SE±	3.12	1.43	3.54	1.9	3.32	1.4
	P		N.S	<0.01	<0.01	<0.01	<0.01
	% of change		-6.7	-60.9	-25.5	-60.9	-19.9
Prolactin (ng/ml)	Mean	7.2	19.1	21.3	27.4	22.1	25.1
	SE±	1.32	1.1	2.1	1.3	2.21	1.29
	P		<0.01	<0.01	<0.01	<0.01	<0.01
	% of change		165.2	195.8	280.5	206.9	248.6
Progesterone (pg/ml)	Mean	21.6	20.8	10.9	15.8	11.3	15.6
	SE±	0.9	0.89	0.62	1.1	2.0	1.5
	P		N.s	<0.01	<0.01	<0.01	<0.01
	% of change		-3.7	-49.5	-26.8	-47.6	-27.7
Estrogen E2 (pg/ml)	Mean	52.86	52.43	25.7	39.1	27.4	41.3
	SE±	2.44	3.34	1.7	1.0	2.1	1.9
	P		N.S	<0.01	<0.01	<0.01	<0.01
	% of change		-0.81	-51.3	-26.03	-48.1	-21.8

Table (1): FSH, LH, prolactin ,progesterone and estrogen levels of female albino rats after exposure to stress (noise or crowding) and treated with Sulpiride drug.

Each value represents mean ± SE .

P < 0.05 significant difference.

P < 0.01 high significant difference

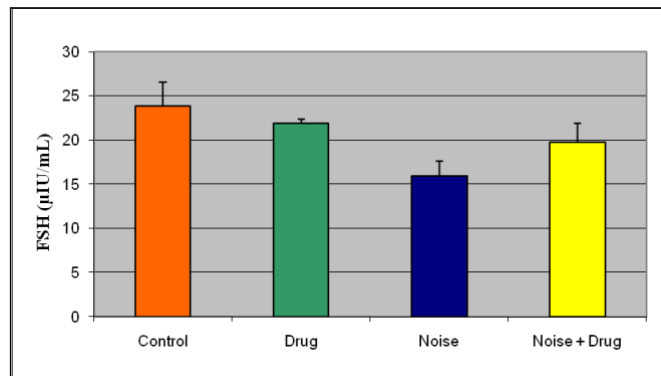


Fig. (1): FSH level in serum of albino rats after exposure to noise and treated with Sulpirid drug and their control.

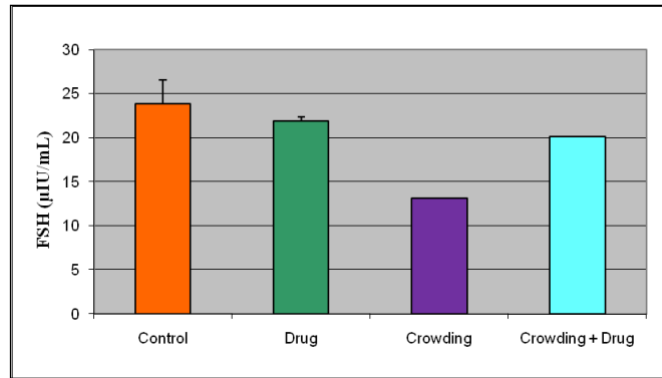


Fig. (2): FSH level in serum of albino rats after exposure to crowding and treated with Sulpirid drug and their control.

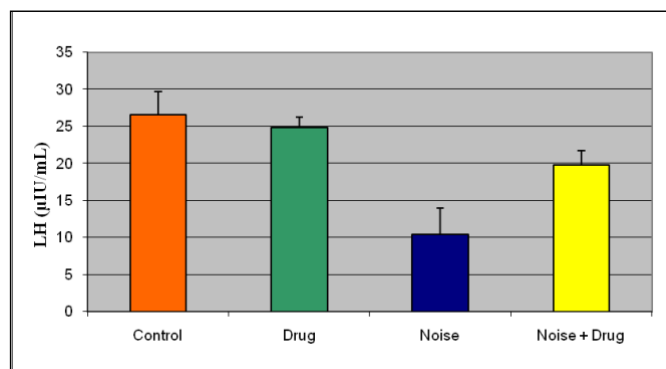


Fig. (3): LH level in serum of albino rats after exposure to noise and treated with Sulpirid drug and their control.

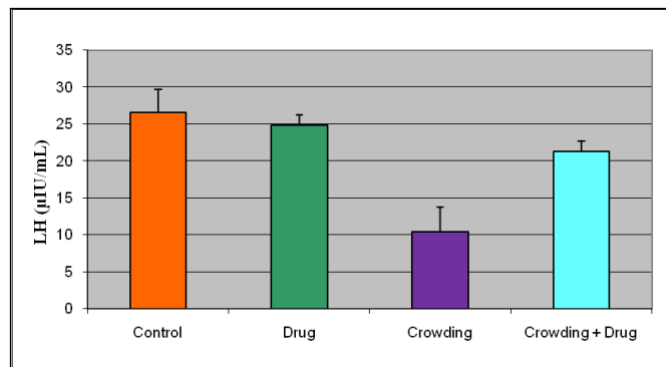


Fig. (4): LH level in serum of albino rats after exposure to crowding and treated with Sulpirid drug and their control.

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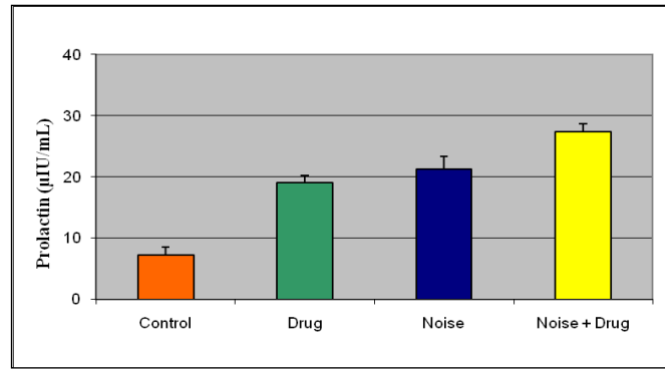


Fig. (5): Prolactine level in serum of albino rats after exposure to noise and treated with Sulpirid drug and their control.

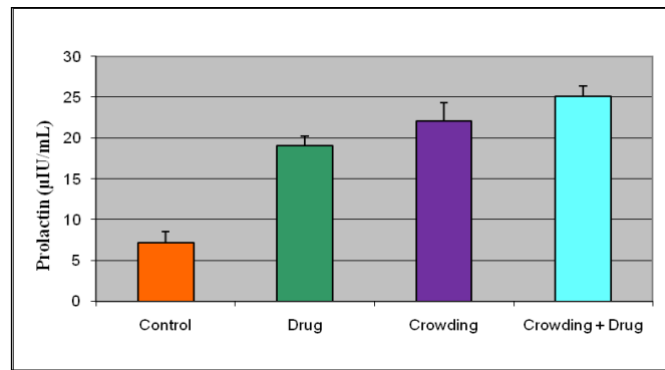


Fig. (6): Prolactine level in serum of albino rats after exposure to crowding and treated with Sulpirid drug and their control .

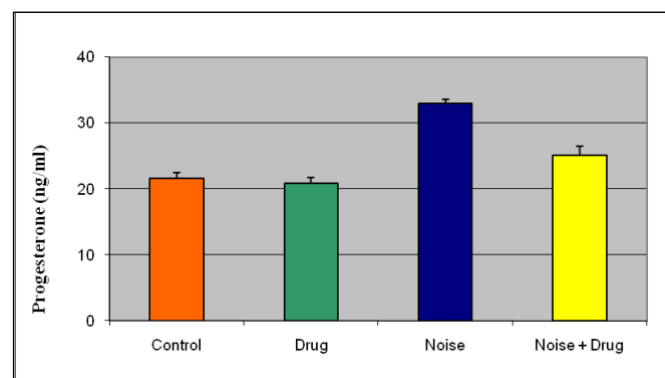


Fig. (7): Progesterone level in serum of albino rats after exposure to noise and treated with Sulpirid drug and their control .

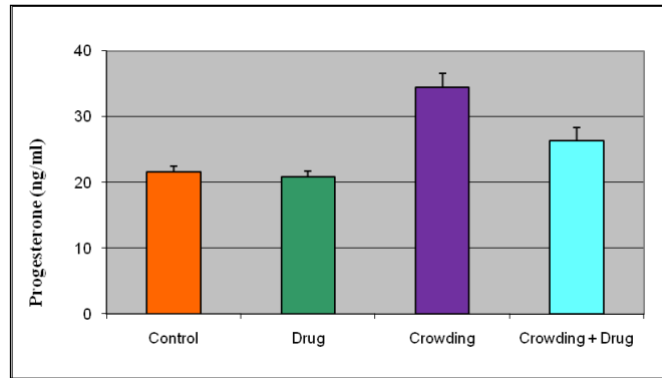


Fig. (8): Progesterone level in serum of albino rats after exposure to crowding and treated with Sulpirid drug and their control .

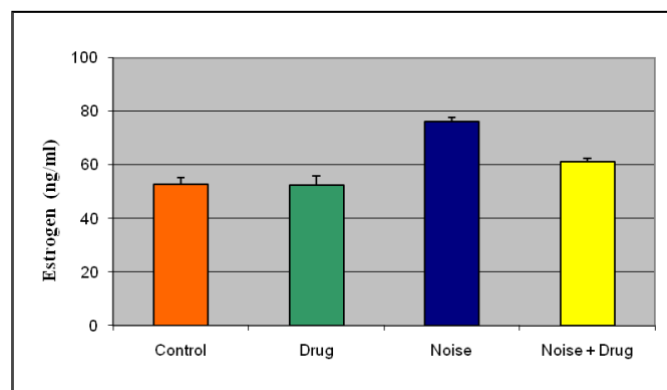


Fig. (9): Estrogen level in serum of albino rats after exposure to noise and treated with Sulpirid drug and their control .

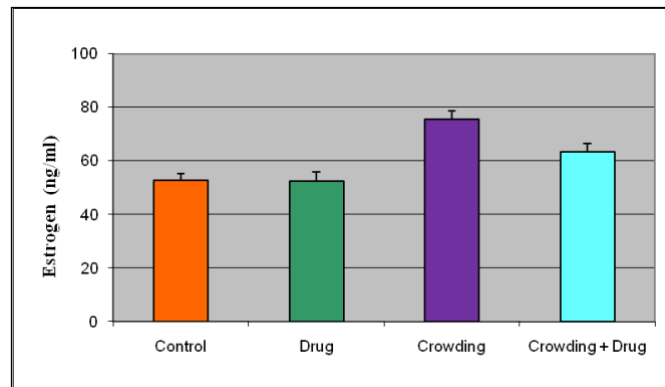


Fig. (10): Estrogen level in serum of albino rats after exposure to crowding and treated with Sulpirid drug and their control .

Discussion

The physiological mechanisms contributing to social stress induction of reproductive dysfunction include activation of the adrenal axis, increased secretion of endogenous opioids, increased prolactin release, and changes in sensitivity to gonadal steroid hormone feedback. Reproductive dysfunction is caused by various forms of physical stress: energy restriction, temperature stress and environmental stress: crowding and noise stress⁽⁹⁾. As regard to the effect of chronic noise and crowding stresses on the pituitary-ovarian axis of the adult female albino rats, the present study showed a significant decrease ($P < 0.01$) in serum estradiol, progesterone, LH and FSH, with a highly significant increase ($P < 0.01$) in prolactin as compared to those of control group.

Shannon and John⁽²⁶⁾ suggested that various stressors, including infection, malnutrition, anxiety and depression, trigger a rise in glucocorticoids that suppress reproductive functions along the hypothalamo-pituitary-gonadal (HPG) axis^(27, 28). At the level of the hypothalamus, glucocorticoids inhibit the release of gonadotropin-releasing hormone (GnRH) release^(29, 30). The effect of glucocorticoids in the pituitary is secondary to its effect on GnRH secretion but results in a decline in circulating luteinizing hormone (LH) levels⁽³¹⁾. At the cellular level, glucocorticoids exert their effects through binding the glucocorticoid receptor (GR), a member of the nuclear steroid receptor superfamily that functions as a ligand-dependent transcription factor to regulate the expression of glucocorticoid-responsive genes⁽³²⁾. GR regulates expression of genes either positively and negatively depending on the glucocorticoid response element sequence, promoter context, or alternatively, binding DNA indirectly through other transcription factors. The localization of the GR to specific cell types within the testis and ovary suggest a direct influence on reproductive function at the gonadal level^(33, 34). Glucocorticoids act directly at the level of the testis or ovaries through inhibition of steroid hormone production or glucocorticoid-induced apoptosis^(35, 36).

In harmony with our results, **Young and Korszun**⁽³⁷⁾ clarify that interaction between stress and decreased serum progesterone may

be due to increase in secretion of stress hormone particularly corticosteroids. This interferes with the reproductive process and is considered a major cause for infertility and miscarriages. Recently, it has been reported that noise and crowding stresses leads to desquamation, produced elevation of stress hormones .ACTH, which stimulates secretion and growth of zone fasciculata and zone reticularis of adrenal gland and stimulates the secretion of cortisol which may cause whole body activation that called fight and flight response. This is a normal biochemical process The problem is that in order to synthesize cortisol, adrenal glands need progesterone that acting as stress hormone. The adrenal glands cannot synthesize cortisol without progesterone. Often referred to as the progesterone steal. So, the body will steal however much progesterone it needs to make cortisol.

This is one of the primary reasons some women having a hard time with infertility and miscarriages; they donot have enough progesterone available to conceive or maintain a pregnancy⁽³⁸⁾.

The constant demand for cortisol is going to reduce levels of progesterone. Inadequate levels of progesterone not only interfere with the reproductive process, but also is another reason for many women struggling with hot flashes, and night sweats, progesterone is being stolen away to make cortisol. The progesterone steal causes a deficiency, and also affects the balance of progesterone to estrogen⁽³⁹⁾

These results are also compatible with those of **Shannon and John**⁽²⁶⁾ who demonstrated that, during stress there is a decrease in releasing of gonadotropin releasing hormone (GnRH), which in turn leads to decrease of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary. The decreased amount of these hormones makes the ovaries less stimulated to release estrogen.

Typically stress, particularly if psychological, is transmuted by the brain into signals that communicate with the body and it does this by eliciting a cascade of physiological responses. Some of these responses are beneficial, enabling fight or flight, return to homeostasis and psychological

stress coping; others are detrimental, especially if repeated or prolonged. The biological definition of stress is increased hormone secretion from the neuroendocrine hypothalamo-pituitary-adrenal (HPA) axis after acute stress, HPA axis hormones rapidly return to pre-stress levels, but chronic stress precipitates sustained responses which have adverse consequences, including mental or physical disorders⁽³⁹⁾.

These were in agreement with those some researchers, **Diab *et al.***⁽⁴⁰⁾ who reported that exposure to chronic noise and crowding stress the pituitary-ovarian axis of the adult female albino rats with decreased in serum estradiol and progesterone and decrease in serum LH and FSH, moreover, an ovarian histological changes were detected in the form of cystically dilated follicles lined by granulosa cells separated by normal ovarian stroma. This indicate failure of ovulation and are similar to those of polycystic ovarian syndrome, which may be attributed to adrenocorticotrophic hormone-stimulated secretion of dehydro-epiandrosterone from the adrenal cortex. Dehydro - epiandrosterone was used for the induction of an experimental model to assess polycystic ovarian syndrome.⁽⁴¹⁾ The noise stress results in stimulation of adrenocorticotrophic hormone, adrenal hyperactivity and increased corticosterone secretion with LH reduction and this may be one of pathophysiological mechanisms involved in follicular cyst pathogenesis. **kondoh *et al.***⁽⁴²⁾, They concluded that the intermittent sonic stress can cause decreased uterine receptivity through an ovarian independent pathway and may be attributed to stress - induced increase in the secretion of cortico-releasing hormone, adreno-corticotrophic hormone, glucocorticoids, urocortins, endorphins and orexin. Chronic noise stress - induced hypoinsulinemia may lead to upregulation of the expression of 11 β -HSD enzyme, which may cause alteration in cortisol metabolism, which may be one of the etiologies of polycystic ovary encountered in the study of **Uran *et al.***⁽⁴³⁾

Noise and crowding stresses resulted in serum LH, FSH, E2, and progesterone reduction levels and sulpiride drug could reverse this effect except PRL which increased significantly. This may be one of pathophysiological mechanisms involved in

follicular cyst pathogenesis. Thus, the stress disturb natural fertility through the inhibition of hypothalamic - pituitary-gonadal axis^(41,44). Recent studies on rats have shown that a variety of stressors induced a stress response with an increase in plasma corticosterone levels and this may affect gonadal function, reproductive behavior and egg - laying success⁽⁴⁵⁾.

Noise and crowding decreased the serum E2 and progesterone levels in the present female rats. Also, women under stress had low E2 levels⁽⁴⁰⁾. Low E2 may increase the sensitivity to stressors. Since, **Walf *et al.***⁽⁴⁶⁾ demonstrated that females in the proestrus phase of their cycle (marked by high estrogen levels) show less fear- and anxiety related behaviors relative to females in the metestrus or diestrus phases (lower estrogen levels).

These present results are also in agreement with the findings of **Knox *et al.***⁽⁴⁷⁾ who reported that a variety of stressors will induce a stress response with an increase in plasma corticosterone levels and that increase in corticosterone may affect gonadal function, reproductive behavior, pregnancy and egg laying success, survival and other aspects of fitness. These results are also compatible with those of **Thorsell**⁽⁴⁸⁾ who concluded that the intermittent sonic stress can cause decreased uterine receptivity through an ovarian independent pathway and may be attributed to stress - induced increase in the secretion of cortico-releasing hormone, adreno-corticotrophic hormone, glucocorticoids, urocortins, endorphins and CRH, which is known to suppress FSH-stimulated estrogen production from rat granulosa cells, decreases the sensitivity of granulosa cells to FSH⁽⁴⁹⁾, suppresses basal estrogen production from luteal cells, and could act to decrease progesterone concentration in sera. On the other side, CRH inhibits LH and FSH secretion, suggesting that its deleterious effects on reproductive functions are exerted through brain sites⁽⁴⁹⁾.

The present results revealed that Sulpiride significantly increased ($p < 0.01$) prolactin in adult female rats in comparison with control group throughout the experimental period. Antipsychotic are a heterogeneous of drugs that have been used in the treatment of schizophrenia, other psychotic disorders, tics, chorea, vomiting⁽⁵⁰⁾.

Long-term administration of neuroleptics causes hyperprolactinemia induced by dopamine blockade in the anterior pituitary (51).

Theisen *et al.* (52) suggested that neuroleptic-induced hyperprolactin reversed might impair ovarian estradiol synthesis, which in the long-term can lead to obesity.

Virkkunen *et al.* (53) suggested that increase of prolactin under neuroleptic treatment might be related to the drug induced hyperprolactinemia. The effects of prolactin on female have been attributed to its ability to decrease and increase respectively the gonadal synthesis of estradiol and progesterone.

Acute sulpiride administration in the perifornical lateral hypothalamus significantly increased food intake and water intake. In addition, systemic sulpiride injections acutely elevated the dopamine metabolites dehydroepiandrosterone-sulfate and homovanilic acid. These results of acute sulpiride administration confirm that this agent is active in the lateral hypothalamus, which is a brain area where blockade of dopamine D2 receptors is known to stimulate increase prolactin in rats (54).

Sulpiride increased PRL significantly in patients with schizophrenia after treatment for 12 month and E2 was significantly lower than that before treatment (19).

The present study also evaluated the possibility of the protective effect of antidepressant drug (sulpiride) on these hormones.

Supplementing the rats with sulpiride resulted in amelioration of the levels E2 and progesterone.

The stressors induced persistent increase in PRL secretion in female rats. This result was consistent with previous reports showing that psychological stress stimulates PRL release in humans (55), and rats (56,57). Stress induces PRL release without changes in TIDA activity (58). These authors suggested that the increase in PRL after restraint in rats is possibly caused by PRL-releasing factors (PRFs), but specific factors were not identified. It has been suggested that various neuroendocrine regulatory mechanism are involved in PRL response to stressors and that the main regulatory route may differ with the type of stressor (59).

Stressed rats treated with sulpiride drug led to an amelioration of hormones of

hypothalamic–pituitary–gonadal axis The long-term administration of sulpiride at the daily dose 4mg/kg is effective in animal models of depression (60).

Sulpiride selectively blocks the above-mentioned types of dopaminergic receptors. It is an exceptionally hydrophilic drug and not lipophilic as most drugs of this type are. It causes no strong extra pyramidal symptoms which could result from D2 receptor blocked in the corpus striatum and which are the equivalent of catalepsia in animals (60).

In conclusion ,In conclusion, continuous exposure to noise stress may have many adverse effects on some of vital physiologic functions in which the alteration in the levels of these hormones may play a significant contributory role, i.e. chronic exposure to high level of noise may be detrimental to ovarian function. This study recommended use sulpiride to ameliorate the effects of stresses. Other studies must be done to evaluate other psychotropic drugs which may not affect prolactin level. Also, other doses of drugs and period of treatment must be tested.

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