UTTAR PRADESH JOURNAL OF ZOOLOGY

42(24): 470-474, 2021
ISSN: 0256-971X (P)

EFFECT OF KETAMINE HYDROCHLORIDE ON OVARIAN AND UTERINE ACTIVITIES IN ALBINO RATS

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AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

Editor(s):
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Received: 01 October 2021
Accepted: 03 December 2021
Published: 17 December 2021

Original Research Article

ABSTRACT

Ketamine hydrochloride at the dose levels of 1mg and 3mg/100 g body weight was administered to normal cycling rat for 20 days through intraperitoneal routes. At autopsy on 21st day significant reduction in the ovarian and uterine weight was observed. Histological observations showed decrease in the number and size of graafian follicles, corpora lutea and increase in the atretic follicles in the ovary. The uterus showed absence of endometrial glands, decrease in the height of myometrium, endometrium and its epithelial cells. The total protein and glycogen content of the ovary and uterus is decreased whereas the cholesterol content is increased. This action of ketamine hydrochloride to gonadotrophins is discussed.

Keywords: Ketamine hydrochloride; atretic follicles; ovarian steroids.

1. INTRODUCTION

Ketamine is a subject of intense study and fascination in perioperative pain [1], depression [2], nociplastic [3] and neuropathic pain [4]. It is general anesthesia agent approved as anesthesia combining with other medicinations or either alone. It acts as a super drug used in short-term medical procedures that do not require the relaxations of skeletal muscles [5-8].

In pharmacology, ketamine regulates the neurotransmission of N-methyl-D-aspartate(NMDA) receptors [9]. Thereby reducing pain perception, inducing sedation. Ketamine appears to non-

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competitively block NMDA receptors, thus induces dissociative anesthesia [10].

Ketamine acts as a neuroleptic anesthetic agent used since its discovery in 1962 and extensively used drug, particularly by medical professionals. Ketamine is used for recreational purpose, since its synthesis and produces addiction in humans and animals [11]. The misuse of ketamine is spread beyond this group to the community-at-large. Majorly it was associated with "rave" dance subculture of the 90's in United States followed by other countries of the world. Ketamine is known as "angel dust", special K, cat valium, "K", or "Kit Kat" [12].

At low doses, ketamine influences distortion of space and time, hallucinations and mild dissociative effects. At high dose ketamine influences severe dissocation known as "K-hole", the abusers experiences intensively detached to the point that their perceptions entirely divorced from their previous reality [13]. In rats, acute subanesthetic doses of ketamine produce a schizophrenia-like symptomatology including hyperlocomotion, enhanced stereotyped behaviours, cognitive and sensorimotor gating deficits, and impaired social interactions [14]. It is important to mark that drug abuse generates toxic effects in different organs, which depends on the administration pathway used by the abusers [15]. Long-term ketamine intake has several harmful effects, includes neurodegeneration, intracranial hypertension and a decrease in the grey matter of brain. Ketamine can alter cardiac functions in the form of tachycardia, hypertension and cardiac muscle damage [16]. In addition ketamine can evoke hepatorenal injury. It is well known to produce uropathy [17].

2. MATERIALS AND METHODS

Normal cycling healthy female albino rats of wistar strain were maintained at room temperature of 28 ± 2°c with lighting schedule of 12 hours light and 12 hours darkness. They were grouped in individual cages, each containing six animals. They were fed with a standard pellet diet (VRK Nutrition, Pune) and water *ad libitium*. The animals were divided into the following groups:

Group 1- Received 0.2ml saline interaperitonally for 20 days and served as control group.
Group 2- These rats received ketamine hydrochloride 1 mg/100 g body weight interaperitonally for 20 days.
Group 3- These rats received ketamine hydrochloride 3 mg/100 g body weight interaperitonally for 20 days.

The treatment was started from estrous phase only as the ovarian and uterine activities changed markedly from one phase to another phase. The treatment was given once a day between 10:00 AM to 11:00 AM for 20 days, all the experimental rats were sacrificed by decapitation on 21st day 24 hours after the final dose.

The body weight was recorded, ovary and uterus were dissected out, freed from adherent tissue and weighed on Anamed electronic balance. The number of graafian follicle, atretic follicle and corpora lutea was made from randomly choosen 20 sections from each group. Ovarian Follicular Kinetics- Morphometric analysis(ovarian follicular kinetics) of the ovary was made according to established methods [18]. Histological stained serial sections of ovary were used. Follicular diameter and morphology was the criteria to classify the follicles as follows.

Class I : Small preantral follicles (SPAF) (<90 µm)
Class II:Large preantral follicles (LPAF) (91-260 µm)
Class III: Small antral follicles (SAF) (261-350 µm)
Class IV: Medium size antral follicles (MSAF) (351-430 µm)
Class V: Large size antral follicles (LSAF) (431-490 µm)
Class VI: Graafian follicles (GF) (>491µm)

2.1 Histometry

Micrometric measurements such as diameter of uterus, thickness of myometrium, endometrium and epithelial cell height were also made from randomly selected 20 sections which appeared round in cross sections from each group. Micrometric measurements were made by using stage and ocular micrometer.

Protein content of ovary and uterus was estimated by Lowry's method [19] to estimate the amount of protein. Cholesterol content of ovary and uterus was estimated by Liberman and Burchard's reaction as described by Peter and Vanslyke [20]. The glycogen content of ovary and uterus was estimated by Carrol et al. [21].

The objective of these estimations is to know the biochemical parameters which are vital for protein, carbohydrates and steroid metabolism and biosynthesis. Stastical analysis was carried out by using student "t" test.

3. RESULTS AND DISCUSSION

3.1 Body Weight

There is no significant change in the body weight of the treated rats, compared to control group.

3.2 Estrous Cycle

Length of the estrous cycle in controlled is 5 days, whereas in treated rats 9 to 10 days, with animals in prolonged diestrus phase.

Table 1. Effect of Ketamine hydrochloride on gravimetric and biochemical of ovary in albino rats

	Weight (mg/ 100 g body wt.) Ovary	Cholesterol (µg/mg) Ovary	Protein (µg/mg) Ovary	Glycogen (µg/ mg) Ovary
Saline	58.83±2.01	4.45±0.02	5.21±0.04	2.03±0.03
1 mg Tramadol	53.57±2.06*	5.71±0.03*	4.66±0.06*	1.63±0.02*
3 mg Tramadol	48.66±1.05**	6.98±0.04**	3.19±0.04**	1.55±0.06**

M±S = Arithemetic Mean ± Standard Error
**P<0.01; **P<0.001 compared to respective control*

3.3 Gravimetric Changes

The ovarian and uterine weights of the intraperitonally treated rats showed significant decrease (P<0.01) compared to that of control the same was seen in the group that received ketamine hydrochloride.

3.4 Biochemical Changes

Highly significant (P<0.01) increase in cholesterol content of ovary was seen in rats treated with ketamine hydrochloride intraperitoneally. Whereas, the protein and glycogen content of the ovary decreased (P<0.001) significantly as compared to control group of rats.

Due to ketamine hydrochloride administration, the number of healthy follicles decreased in both 1mg and 3 mg showing significant decrease in class I to class VI follicles.

3.5 Biochemical Changes

Highly significant (P<0.01) increase in cholesterol content of uterus was seen in rats treated with ketamine hydrochloride intraperitoneally. Whereas the protein and glycogen content of the uterus decreased (P<0.001) significantly as compared to control group of rats.

3.6 Histological and Histometric Changes in Uterus

There was significant shrinkage in the diameter of uterus, thickness of endometrium and myometrium (P<0.01) in ketamine hydrochloride treated groups compared to control group. A reduced secretion of endometrial gland was observed.

Table 2. Effect of Ketamine hydrochloride on Ovarian components in albino rats

Treatment	Class I SPAF	Class II LPAF	Class III SAF	Class IV MSAF	Class V LSAF	Class VI GF
Saline	55.32±1.04	46.01±0.17	10.09±0.48	5.28±0.51	3.42±0.33	2.66±0.47
1 mg Ketamine	37.50±1.12**	39.78±0.51**	8.76±0.13**	4.40±0.09**	2.68±0.28**	1.96±0.32**
3 mg Ketamine	31.66±1.03**	29.64±1.34**	5.88±0.06**	3.10±0.06**	1.20±0.31**	0.98±0.49**

*M±S = Mean ± Standard Error; *P<0.01; **P<0.001; compared to respective control*

Table 3. Effect of Ketamine hydrochloride on uterine gravimetric and biochemical parameters in albino rats

	Weight (mg/100 g body wt.) Uterus	Cholesterol (µg/ mg) Uterus	Protein (µg/mg) Uterus	Glycogen (µg/mg) Uterus
Saline	217.12±3.91	3.63±0.07	7.32±0.04	1.79±0.04
1 mg Tramadol	201.53±2.45*	3.97±0.04*	5.16±0.05*	1.56±0.02*
3 mg Tramadol	182.25±2.14**	5.51±0.05**	4.87±0.04**	1.40±0.03**

*M±S = Arithemetic Mean ± Standard Error; *P<0.01; **P<0.001 compared to respective control*

Table 4. Effect of Ketamine on histometric changes of uterus in albino rat

	Diameter of uterus (µm)	Thickness of myometrium (µm)	Thickness of endometrium (µm)	Height of epithelium (µm)
Saline	2241.66±8.12	253.08 ± 3.13	441.03±2.18	36.17±1.08
1 mg Tramadol	2072.15±7.29**	191.04±2.67**	357.23±3.09**	25.21±2.02**
3 mg Tramadol	1854.28±5.32**	179.11±3.54**	326.16±5.89**	17.11±1.03**

*M±S = Mean ± Standard Error; *P<0.01; **P<0.001; compared to respective control*

It is known fact that hypothalamus regulated rhythmic release of FSH, LH and Prolactin through neuroendocrine stimulation to GnRH. Investigations on ketamine hydrochloride shows that ketamine being CNS influencing drug inhibits the release of gonadotrophins. Decreased level of protein in ketamine treated rats indicates hampered growth. Decreased level of glycogen indicates reduced source of energy. Increased levels of cholesterol indicated hampered steroidogenesis.

4. CONCLUSION

In this study there was reduction in the weight of ovary and uterus, changes in biochemical estimation of ovary and uterus was also seen. The reduction in diameter of uterus, thickness of endometrium, myometrium and epithelial cell height may imputing to non- availability of steroids necessary for uterine growth caused by decreased levels of gonadotrophins in ketamine hydrochloride treated rats.

ETHICAL APPROVAL

Approval at the Institutional Animal Ethics Committee (IAEC) of Luqman College of Pharmacy, Gulbarga was taken for conducting experimental activities.

ACKNOWLEDGEMENT

We extremely thank Dr. Syed Sanaulla, Principal Luqman college of Pharmacy, Kalaburagi for providing facilities for conducting experiments.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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