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The Protective Effects of Acetyl L-Carnitine for The Offspring and Lactating Moms of Rats Received Bromocriptine

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Abstract

MAMMARY glands are only found in mammals and specialize in synthesizing, secreting, and delivering milk to the newborn. The purpose of this study was to investigate protective effect of Acetyl L-Carnitine (ALCAR) on lactating mothers and pups of rats receiving bromocriptine. Female rats(n=24) weighing (200-250g) were divided into four groups, 6 for each group: control group(G1) given distilled water, bromocriptine treated (G2) given orally bromocriptine (4 mg/kg), (ALCAR) treated groups(G3) take orally ALCAR (100 mg/kg) and the co-administrated group (G4) was treated orally with bromocriptine (4 mg/kg) and ALCAR (100 mg/kg) from pregnancy to weaning. Growth and physiological factors of pups; blood samples collection for growth and prolactin hormone estimation using ELIZA technology. At the end of experiments, animals were sacrificed, and mammary glands were processed for hematoxylin and eosin staining. The results showed that the weight of the pups reduced significantly in bromocriptine and ALCAR, but did not differ from the control in 21 days of parturition. G2, G3, and G4 cause an increase in the period it takes for ear lobe, hair, teeth to grow in and eyes to open. Growth and prolactin hormone increase in G2 and increase in G4 in compared to G3. The histological changes of mammary glands showed G2 has atrophy and loss of secretory acini, interlobular ducts, and intralobular ducts. In conclusion, ALCAR moderately rescued the detrimental impacts of a decreased pups' growth and physiological development of the sense and reproductive organs, which can reduce the negative effects of bromocriptine in mammary gland.

Keywords: Acetyl L-carnitine, Bromocriptine, Growth hormone, Prolactin hormone, Rat.

Introduction

The drug bromocriptine, which belongs to the class of medications known as ergot alkaloids, inhibits the production of prolactin, a hormone that is secreted from the pituitary gland [1], The rationale for its medicinal use in the treatment of endocrine and neurological problems is its role as a potent dopamine agonist [2]. A sympatholytic dopamine D2 receptor agonist, bromocriptine has exceptional bioactivities [3]. Its ability to decrease prolactin secretion explains its effectiveness in preventing puerperal lactation and treating pathological hyperprolactinemia that results in galactorrhea, infertility, or hypogonadism [3].

A natural source substance called acetyl-L-carnitine (ALCAR) like beef meat prevents the buildup of long-chain fatty acids by transporting them to the mitochondria, where they are oxidized to produce adenosine triphosphate [4-6]. In a variety of cell types, carnitine prevents mitochondrial damage caused by oxidative stress and mitochondria-dependent apoptosis [7]. L-carnitine has been shown in recent research to have an anti-peroxidative effect on a variety of tissues and may be essential for maintaining oxidative and antioxidative equilibrium [8,9]. L-carnitine (LC) and its acetylated equivalent, acetyl L-carnitine (ALCAR), can control the oxidative stress of the female reproductive system (10). Due to the female reproductive system's susceptibility to free radicals, it is important to utilize the most modern protection methods, The "quasi-vitamins" L-carnitine (LC) and Acetyl-L-Carnitine (ALCAR) alone or in conjunction with other antioxidants can be used to accomplish this [10]. Reducing cellular stress, achieving hormonal

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balance, increasing energy output, maintaining the stability of the oocyte cell membrane through acetylation of phospholipids [11], preventing free radical-induced DNA damage for the storage of adequate acetyl as an energy supply to maintain the health of reproductive cells [10].

The amount of dietary carnitine absorbed and stored depends on the amount of carnitine taken [12], about 54 - 87% of dietary carnitine is absorbed in the rats by their intestine (12) reaching the blood stream and is also excreted in milk [13]. Since the majority of postpartum mothers are given nutritional supplements and medications that can pass through breast milk when the mother is nursing, there are concerns about the safety of newborns. The relative infant dose is an important indicator of the risk of adverse effects after exposure to chemicals in breast milk [14], so pregnancy and offspring outcomes in mice were improved by giving them 0.5 mg/Kg L-carnitine [15]. Drugs may alter the volume and content of milk by altering the hormonal milieu necessary for nursing, the blood supply to the mammary gland, the amount of functional mammary tissue, or by directly or indirectly interfering with the release of nutrients by the mammary epithelium [16]. The study aims to evaluate the protective effects of acetyl L-carnitine on lactating mothers and pups of rats receiving bromocriptine.

Material and Methods

All of the experiment's steps were carried out at the animal house of veterinary medicine at Mosul University.

Animals and experimental design

Twenty-four female rats, each weighing between (200 - 250 g), were employed in this investigation. The rats were kept in cages with free access to food and water (*ad libitum*), a 12-hour cycle of light and darkness, and a constant temperature (18 ±2°C). The four groups of rats were divided at random (6 rats per each group):

1. Control group: rats were given daily oral distilled water from pregnancy to weaning.
2. Bromocriptine treated group: rats were given daily, orally bromocriptine 4 mg/kg B.WT. from pregnancy to weaning [17].
3. Acetyl L-carnitine (ALCAR) from Santa Cruz with number (CAS 3040-38-8) treated groups: rats were given daily orally ALCAR 100 mg/Kg B.WT. from pregnancy to weaning [18,19].
4. Bromocriptine + Acetyl L-Carnitine treated groups: rats were given daily orally bromocriptine 4 mg/kg body weight and ALCAR 100 mg/kg body weight from pregnancy to weaning.

Estrus Cycle Determination

The rats were evaluated for the estrous cycle by taking daily vaginal swabs for eight days before the experiment began. The "Whitten Effect" [20], which causes the synchronization of estrus in females by exposure to male pheromones, was used to create two unique synchronized groups of females according to the various phases of the estrus cycle. They continued to be examined every day to check for pregnancy. Its vaginal examination was performed according to the same protocol as [21], females were held up by their tails while a cotton swab that had been previously soaked with saline was gently introduced into the vagina to obtain cytology by circular motions. In accordance with the method described in [22] each animal's estrus cycle phase was identified by looking at the product under a light microscope (10x objective). The proestrus was defined by the predominance of nucleated or epithelial cells, the estrus by the predominance of cornified or cells devoid of nuclei, the metestrus by the combination of cornified cells and leukocytes, and the diestrus by the predominance of leukocytes [22].

Growth factors

Mothers and puppies were weighed at birth, 7, 14, and 21 days after the birth. Eight pups from each mother showed signs of growth, including eye opening, tooth development, and hair development, which were all signs of growth in newborn rats. and neonatal mortality from birth to weaning, in addition to the study of neonatal physiological factors, which for newborn male include the period from birth until the testicles descend into the scrotum (today); for newborn females, the period from birth until the appearance of the vaginal opening (day); and the distance between the base of the penis and the anus [23].

Collection of blood samples and Histology preparation

Blood samples collection was carried out at end of experiment and obtained from retro-orbital plexus from the eye. Blood sera stored at (-20°C) for biochemical analysis including growth hormone analysis using rat growth hormone Sandwich ELIZA kit (GH) Cat. NO. E-EL-R3003ELISA, and prolactin hormone Sandwich ELIZA kit Cat.NO.E-EL-R3006 were conducted according to the manufacturing company (Elabscience company [24].

The mammary glands were excised, then preserved for 24 hours in 10% buffered formalin (0.2 M NaH2PO4, 0.2 M Na2HPO4, 37% formaldehyde, pH 7.2). Following many iterative ethanol dehydrations, the tissue was cleansed in xylene before being embedded in paraffin. Hematoxylin and

eosin (H&E) were used to cut the 4 mm-thick semi-serial sections. Four equally spaced mammalian slices from each animal were investigated for histological investigation, and the follicular types were categorized in accordance with [25-27].

Statistical analysis

Data of the results are expressed as (Mean ± Standard Error). A one-way ANOVA and Duncan's test were used to compare the control group to other groups in terms of the measured parameters, and an Pups weight

The results showed that there was a significant decrease in pup's weight in the group treated with bromocriptine and ALCAR alone compared with the control group; also, the group treated with bromocriptine and ALCAR showed a significant decrease in the weight of pups compared with the control group, with a significant increase compared with the groups treated with bromocriptine and ALCAR treatment alone (Tab. 2).

Growth factors of pups

Appearance of ear lobe & hair

The group treated with bromocriptine and bromocriptine with ALCAR caused a significant increase $p \leq 0.05$ in appearance time of ear lobe and hair appearance time compared with the control group. The result showed no differences with ALCAR treatment alone compared with the control (Tab.3).

Appearance of teeth &eye opening.

All treatments caused a significant increase $p \leq 0.05$ in teeth time appearance and eye-opening time appearance, with no differences between bromocriptine alone and with bromocriptine and ALCAR. (Tab.3)

Physiological factors of pups

The pup's testicle descent time into the secrotum.

independent-samples T-test was employed to assess the data on fertility. All statistical analysis was performed by SPSS 24 version program. The test of significance was placed at *($p \leq 0.05$)*. [28].

Results

Lactating rats' weight

As shown by the result, in comparison to the control group, the treated mother's weight did not differ significantly (Tab. 1)

Bromocriptine treatment alone and with ALCAR caused significant increase $p \leq 0.05$ in testical descending time compared with control group and ALCAR treatment alone which did not differ significantly differ from control. (Tab.4)

Vaginal opening time in newborn females.

The results of this study showed that there are no significant differences between the control group and any treatment group in terms of the vaginal opening time. (Tab.4)

Effect of ALCAR and Bromocriptine on serum growth hormone level and serum prolactin hormone level:

The results showed that compared to control, bromocriptine treatment alone and bromocriptine combined with ALCAR treatment significantly decreased $p \leq 0.05$ growth hormone and prolactin hormone levels, whereas ALCAR treatment had no significant effect on these levels. (Fig.1,2).

Mammary gland histology

Bromocriptine treatment showed atrophy and loss of the secretory acini, interlobular ducts and intralobular ducts with increase fibrous tissue and thickening in the arterial wall, in addition to necrosis and sloughing of the cells lining ducts. The ALCAR group showing normal and architecture secretory acini, interlobular ducts (Fig. 3,4,5,6,7,8,9,10,11,12).

TABLE 1. Effect of ALCAR and bromocriptine on Lactating rats' weight

Day / Groups	At parturition g/B.W.	At 7 days g/B.W.	At 14 days g/B.W.	At 21 Day g/B.W.
Control	286.25±21.54[a]	250.50±4.90 [a]	249.50±9.53[a]	238.50±22.30 [a]
Bromocriptine	237.60±14.73[a]	234.50±8.64[a]	218.80±17.91[a]	229.40±10.30 [a]
ALCAR	273.00±18.33[a]	251.00±22.19[a]	248.25±12.82 [a]	245.0±8.66[a]
Bromocriptine +ALC	253.00±11.26[a]	256.66±20.93[a]	251.75±11.79[a]	235.25±12.03[a]

Different letters at one column indicate a significant difference between groups at ($P \leq 0.05$).
Means (g/ BW) ± Standard Error

TABLE 2. Effect of ALCAR and bromocriptine on pups' weight (g/B.W.)

Day / Groups	At parturition g/B.W.	At 7 Day g/B.W.	At 14 Day g/B.W.	At 21 Day g/B.W.
Control	7.51±0.18[a]	22.22±0.50[a]	26.19± 0.15[a]	30.24±2.0[a]
Bromocriptine	6.89±0.06[a]	13.00±0.26[c]	15.08±0.36[c]	18.86±0.60[b]
ALCAR	7.71±0.09[a]	12.80±0.30[c]	16.18±0.58[c]	28.40±0.62[a]
Bromocriptine +ALCAR	6.52±0.07[a]	15.02±0.14[b]	18.32±0.32[b]	16.96±0.44[b]

Different letters at one column indicate a significant difference between groups at ($P \leq 0.05$).
Means (g/ BW) ± Standard Error

TABLE 3. The effect of ALCAR and bromocriptine on Growth factor of pups(day)

GF / Groups	Appearance of ear lobe	Appearance of hair	Appearance of teeth	Appearance of eye opening
Control	2.75±0.48[b]	5.50±0.29[b]	8.50±0.29[c]	10.25±0.25[c]
Bromocriptine	4.20±0.37[a]	7.40±0.32[a]	11.80±0.37[a]	14.60±0.24[a]
ALCAR	2.50±0.29[b]	5.75±0.25[b]	10.50±0.29[b]	12.75±0.48[b]
Bromocriptine +ALCAR	4.00±0.41[a]	8.00±0.41[a]	11.75±0.48[a]	13.75±0.63[ab]

Different letters at one column indicate a significant difference between groups at ($P \leq 0.05$).
Means ± Standard Error

TABLE 4. The effect of ALCAR and bromocriptine on Physiological factors of pups(day)

PF / Groups	Decent of testes in to secretum	Appearance of vaginal opening
Control	19.40±0.04[c]	25.1±0.91[a]
Bromocriptine	27.40±0.24[a]	22.1±0.23[a]
ALCAR	19.50±0.56[c]	24.5±1.20[a]
Bromocriptine +ALCAR	24.20 ±0.37[b]	22.9 ±0.94[a]

Means ± Standard Error
Different letters at one column indicate a significant difference between groups at ($P \leq 0.05$).

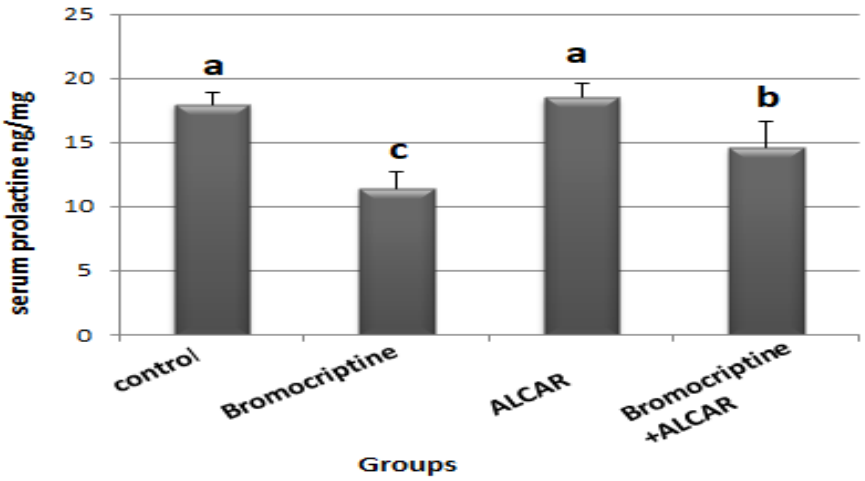

Fig.1. The effect of ALCAR and Bromocriptine on serum growth hormone level and serum Prolactin hormone level

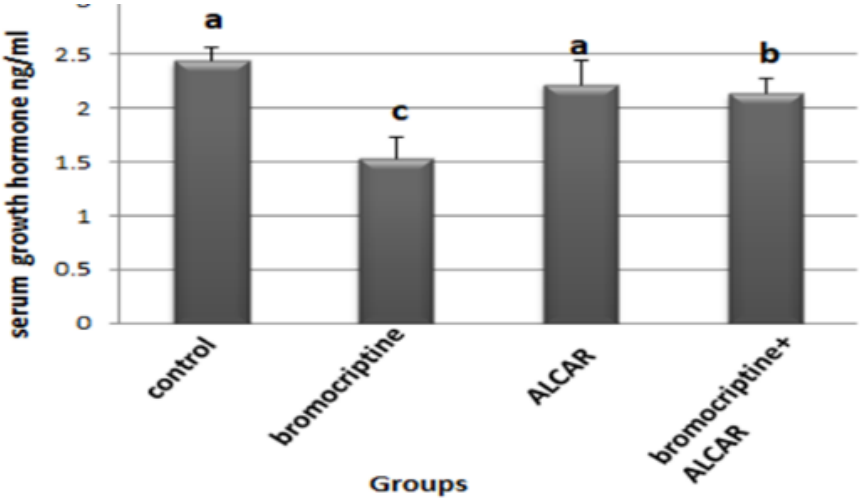

Fig. 2. Effect of ALCAR and bromocriptine on serum growth hormone

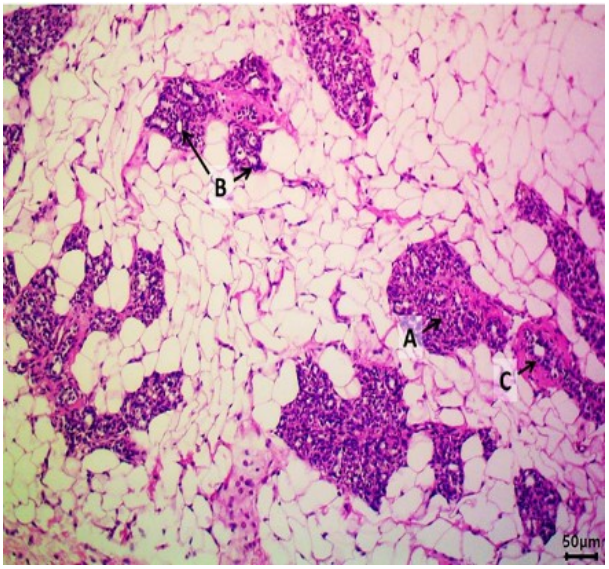

Fig. 3. Rat mammary gland of the control group showing normal architecture of the secretory acini (A), intralobular ducts (B) and interlobular ducts (C). H&E stain

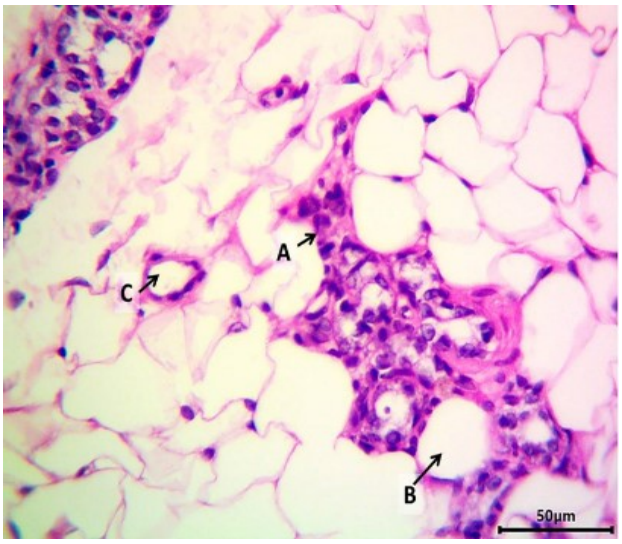

Fig. 4. Rat mammary gland of the control group showing normal architecture of the secretory acini (A), intralobular ducts (B) and interlobular ducts (C). H&E stain, 400X.

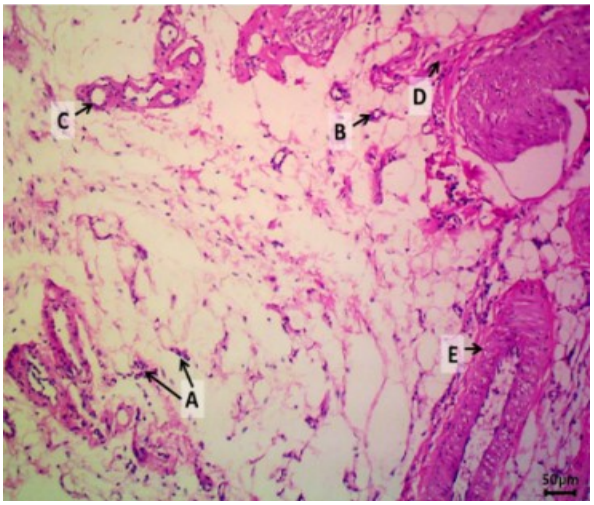

Fig. 5. Rat mammary gland of the bromocriptine treated group showing atrophy and loss of the secretory acini (A), intralobular ducts (B) and interlobular ducts (C) with increase fibrous tissue (D) and thickening in the arterial wall (E). H&E stain, 100X.

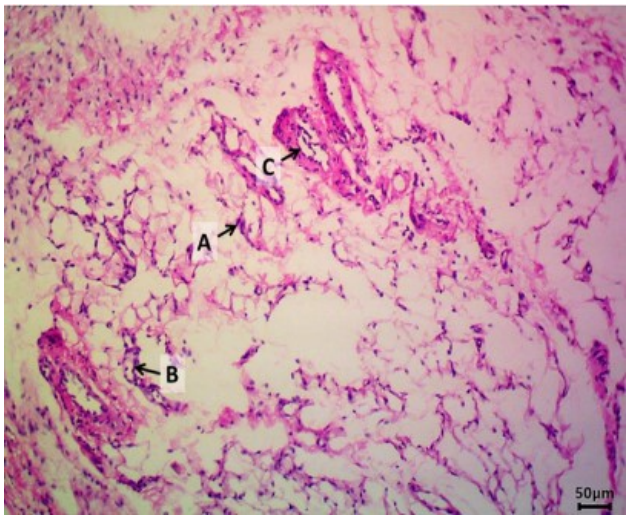

Fig. 6. Rat mammary gland of the bromocriptine treated group showing atrophy and (necrosis) loss of the secretory acini (A), intralobular ducts (B) and interlobular ducts (C). H&E stain, 100X.

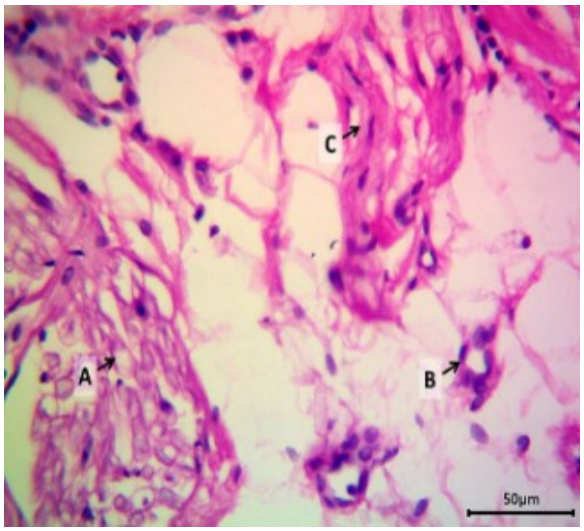

Fig. 7. Rat mammary gland of the bromocriptine treated group showing necrosis of the secretory acini (A), atrophy of the intralobular ducts (B) and increase fibrous tissue (C). H&E stain, 400X.

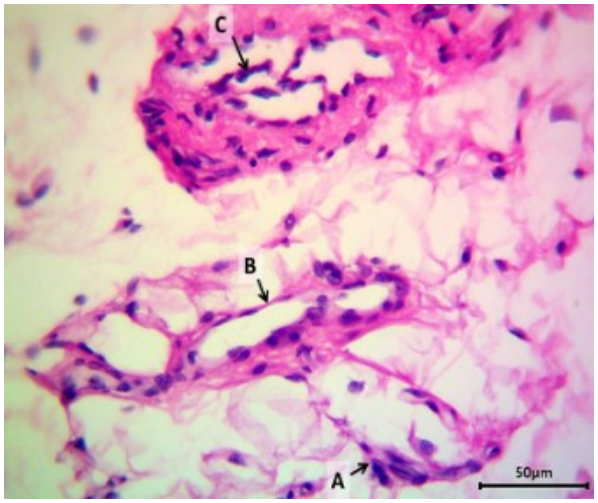

Fig. 8. Rat mammary gland of the bromocriptine treated group showing atrophy of the secretory acini (A), necrosis of the intralobular ducts (B) and sloughing of the cells lining ducts (C). H&E stain, 400X.

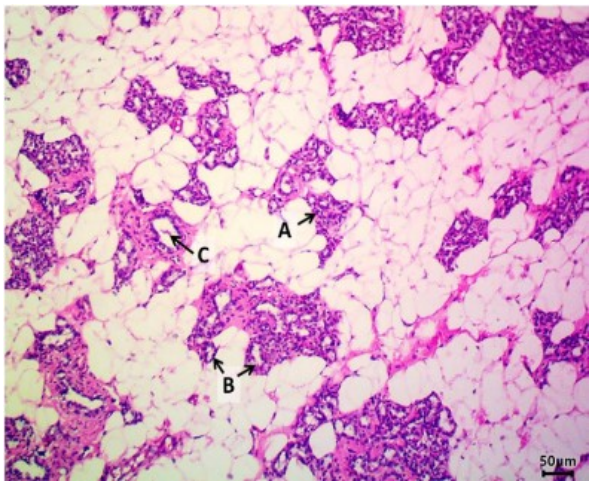

Fig. 9. Rat mammary gland of the ALCAR treated group showing normal architecture of the secretory acini (A), intralobular ducts (B) and interlobular ducts (C). H&E stain, 100X.

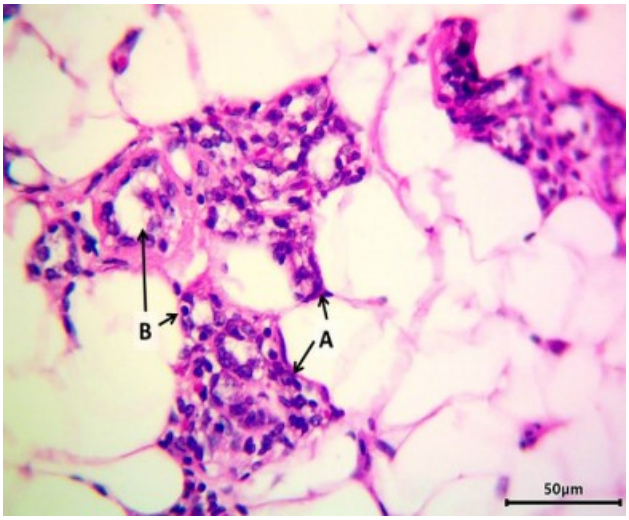

Fig. 10. Rat mammary gland of the ALCAR treated group showing normal architecture of the secretory acini (A) and intralobular ducts (B). H&E stain, 400X.

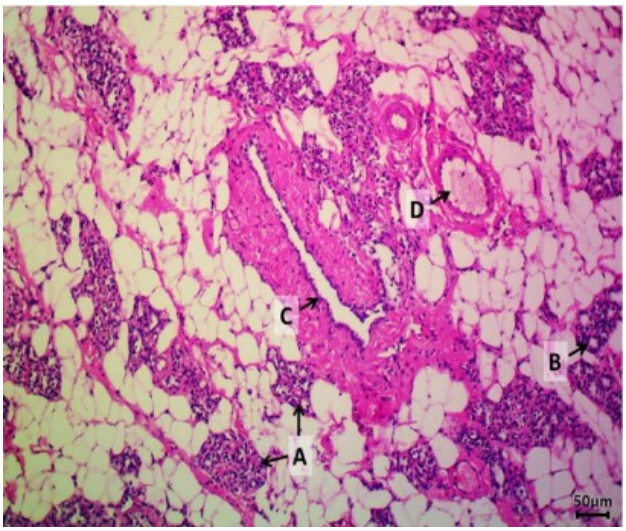

Fig. 11. Rat mammary gland of the ALCAR and bromocriptine treated group showing normal architecture of the secretory acini (A), intralobular ducts (B), interlobular ducts (C) and blood vessels (D). H&E stain, 100X.

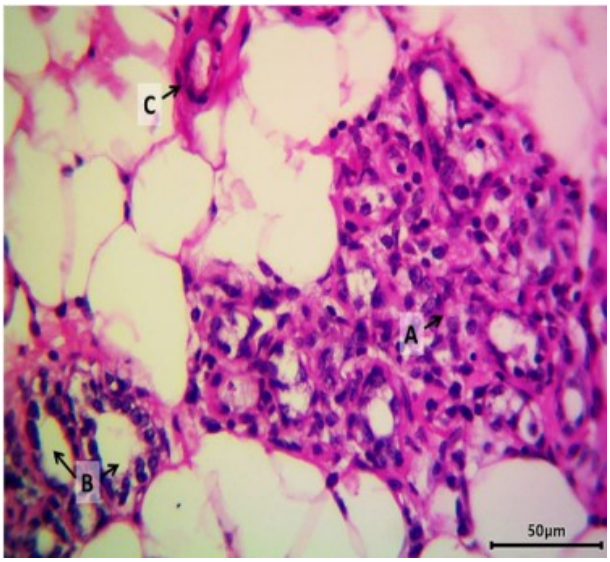

Fig. 12. Rat mammary gland of the ALCAR and bromocriptine treated group showing normal architecture of the secretory acini (A), intralobular ducts (B) and blood vessels (C). H&E stain, 400X.

Discussion

According to the present results, young rat weights significantly decreased with bromocriptine treatment. However, L-carnitine caused an increase in weight compared to the control group, and the weight loss associated with bromocriptine is likely due to a decrease in growth hormone [29]. Bromocriptine alone has also been shown to increase the time it takes for growth factors to appear, as represented by prolonging the number of days until the emergence of ear pinna, hair, teeth, and eye openness, in addition to other physiological factors. Such as the descent of the testes in young rats, but bromocriptine and carnitine together were given to nursing mothers, which led to a shorter period of time in some factors compared to treatment with bromocriptine alone, and bromocriptine significantly reduced the level of the prolactin hormone, or, in other words, reducing the amount of milk and also reducing the level of growth hormone, and as a result, caused a significant decrease in birth weights in periods 7, 14, and 21. And time of testicular descent increased significantly compared to the control group because bromocriptine is a dopamine agonist that controls the release of prolactin, which in turn regulates breastfeeding by preventing prolactin from being secreted, thereby preventing or inhibiting milk production [30]. In contrast, there was no significant difference in the level of prolactin and growth hormone after treatment with carnitine, which was reflected in the absence of a delay in the number of days of descending the testicles and the appearance of the vaginal opening compared with control. However, carnitine did not completely reverse the effect of bromocriptine, and hormone levels did not return to control levels. Treatment with L-carnitine increased birth weights as well as reduced the period of onset of developmental signs because acetyl-L-carnitine (ALCAR) is a carnitine derivative that interacts with the mitochondrial membrane and is essential for mitochondrial fatty acid oxidation and cellular energy generation [31]. Furthermore, carnitine contributes to the energy production processes of the branched-chain amino acids valine, leucine, and isoleucine [32], as well as ketone metabolism [33]. In addition, the distribution of carnitine may be affected by sex hormones. Significantly higher levels of plasma carnitine concentration were found in the liver compared to male rats [34].

The mammary gland tissues were affected by bromocriptine in a number of ways, including necrosis and erosion of the cells lining the ducts, atrophy and loss of the secretory acini, interlobular ducts, and intralobular ducts, as well as an increase in fibrous tissue and thickening of the arterial wall, through D2-receptors that are released at the terminal buttons of the neurons, dopamine acts on lactotrophic cells by controlling intracellular signaling and decreasing prolactin synthesis. In the absence of breastfeeding in sexually mature females or pregnancy (high estrogen levels), dopamine suppresses prolactin in a constitutive manner. Prolactin affects hundreds of physiological processes, but its two major functions are to stimulate milk production and the development of mammary glands within breast tissues. Mammary gland growth is promoted by prolactin. Dopamine antagonists or infundibulum compression can impair prolactin synthesis, which leads to hyperprolactinemia. In contrast, dopamine agonists like bromocriptine, which is used to treat disorders linked to hyperprolactinemia, reduce the amount of prolactin that is produced [35,36]. While treatment with carnitine alone or with carnitine and bromocriptine restored the normal structure of secretory acini, intralobular channels, channels between lobes, and blood vessels, the amino acid carnitine is essential for both cellular proliferation and apoptosis due to its stimulating effect on mitochondria and inhibition of TNF and other anti-proliferative molecules [37]. According to [38] it appears that ALCAR reduced the amount of cytochrome C in the cytosol, which in turn activated caspase-3 [38,39] and protected cells from lipid peroxidation and mitochondrial membrane collapse under stressful circumstances [40,41]. Carnitine has antioxidant qualities, as shown by numerous research. Carnitine regulates the intramitochondrial acetyl CoA/CoA ratio by regulating the supply of acetyl-CoA from the PDH complex and fatty acid oxidation [42]. Additionally, it is essential for protecting DNA from free radical damage, preserving cell membrane stability, and controlling pro-inflammatory cytokines to have an anti-inflammatory effect [13].

Conclusion

We can conclude that ALCAR moderately rescued the detrimental impacts of decreased pups' growth and physiological development of the sense and reproductive organs and can reduce the negative effects of bromocriptine in mammary gland.

Acknowledgment

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and the required facilities.

Conflict of interest

The author declares no conflict of interest.

Ethical approve

The experimental methodology and animal welfare were approved by the institutional animal care and use committee (ref; UM.VET.2022.052), College of Veterinary Medicine, University of Mosul.

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التأثيرات الوقائية للاستايل ل-كارنتين على امهات الجرذان المرضعة وصغارها: دور البروموكربتين

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الخلاصة

توجد الغدد اللبنية فقط في اللبائن، وتتخصص في تصنيع وافرز وتوصيل الحليب الى المواليد. كان الغرض من هذه الدراسة هو دراسة التأثير الوقائي للاستايل ل-كارنتين على الامهات المرضعة التي تتلقى البرموكربتين وصغارها. تم تقسيم اناث الجرذان (عددها=24) بوزن (200-250 غرام) الى اربع مجاميع (عدد كل منها =6).تلقت مجموعة السيطرة الماء المقطر ، المجموعة الثانية (المعاملة الاولى)البرموكربتين عن طريق الفم (4ملغم/كغم)، المجموعة الثالثة (المعاملة الثانية) عن طريق الفم الاستايل ل-كارنتين (100 ملغم/كغم)،المجموعة الرابعة(المعاملة الثالثة) عن طريق الفم البرموكربتين(4 ملغم/كغم) مع الاستايل ل-كارنتين (100ملغم/كغم) من الحمل وحتى الفطام. درست عوامل النمو والفسيولوجية لصغار الجرذان.جمعت عينات الدم لتقدير هرموني النمو والبرولاكتين باستخدام تقنية الاليزا .في نهاية التجربة قتلت الحيوانات وعولجت مقاطع الغدد اللبنية للصبغ بالهيماتوكسلين والايوسين لدراستها نسيجيا . اظهرت النتائج ان وزن صغار الجرذان انخفض معنويا في مجموعتي المعاملة بالبروموكربتين والاستايل ل-كارنتين ،لكنها لم تختلف معنويا عن مجموعة السيطرة في 21 يوم من الولادة. سببت المعاملة الاولى والثالثة زيادة في الفترة الزمنية التي يستغرقها نمو الشعر،فتح صيوان الاذنتين ،نمو الاسنان وفتح العينين.سببت المعاملة الاولى والثالثة زيادة في مستوى هرموني النمو والبرولاكتين بالمقارنة مع المعاملة الثالثة.اظهرت التغييرات النسجية للغدد اللبنية في المعاملة الاولى ضمورا وفقدان العقد الافرازية والقنوات بين الفصوص وداخل الفصوص الافرازية . بالخلاصة فقد اظهر الاستايل ل-كارنتين القدرة بشكل معتدل على تغيير التاثيرات السلبية لانخفاض نمو صغار الجرذان والتطور الفسيولوجي للحواس والجهاز التناسلي ويمكن ان يقلل من التاثيرات السلبية للبروموكربتين على الغدد اللبننية.

الكلمات المفتاحية: اسيتايل ل كارنتين، بروموكربتين، هرمون النمو ، هرمون البرولاكتين ، جرذان.