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Abd El-Ghany M.A., Hanaa F. El-Mehiry, Nagib, R.M. and Hagar M. El-Sayed
Department of Home Economics, Faculty of specific Education, Mansoura University, Egypt

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Department of Home Economics, Faculty of specific Education, Mansoura University, Egypt

Abstract:

The present study was designed to investigate the Comparison of therapeutic effect between, some sulphur amino acids and drugs Oroxin on β amyloid-induced Alzheimer's in obese rats .Twenty of female rats of Sprague Dawley (weighting 200±10 g) were divided into two main groups Group (1) negative control (-ve) (5 rats). Fifteen rats were fed on the high fat diet and administered aluminum chloride for 6 weeks to induce obesity and Alzheimer and reclassified to three groups (5rats each). Group (2) positive control group (+ ve) Group (3) treated with methionine and cysteine (4.5 g/100 g protein) group (4) treated with orexin drug (OxA) (20 mg/kg b.w.t). The study period was set for ten weeks (six weeks to injury of obesity &Alzheimer's and four weeks for treatment).The results revealed that there was a significant decrease in body weight gain, weight gain percent and FER among all rats group which treated with sulpher amino acids and orexin, in comparing with positive control group. Moreover, The treatment rat groups showed significant decrease in body weight gain, food intake, Food efficiency ratio (FER):, Body mass index (BMI), serum ALT, AST , ALP, Creatinin Uric Acid Urea ,cholesterol, triglyceride, low density lipoprotein cholesterol(LDLc),very low density lipoprotein cholesterol (VLDLc), total lipids (T. Lipids) , phospholipids, brain levels of malondialdehyde (MDA),B-amyloid and serum aluminum chlorid but showed significant increase in serum high density lipoprotein cholesterol (HDLc), brain catalase (CAT), glutathione-S- transferase (GST) and superoxide dismutase (SOD) compared to positive control group. The biochemical analyzes agreed with the histological examination of brain tissue It can be recommendation that the consumption sulphur amino acids could lowering of body weight gain and improvement of biochemical parameters and brain degenerative histopathological changes as the orexin drug

Key words: Methionine, Cysteine, Alzheimer’s Aluminum chloride, Orexin overweight and rats

INTRODUTION

Alzheimer's disease (AD) is the third leading cause of death in these countries according **to Mattson, (2004).** Alzheimer's disease results from an increase in fashioning in indissoluble protein charges as amyloid-β (Aβ) and Protein accumulation leads was synapse dysfunction and neuronal lack of the brain. Various passageways inclusive inflammation, oxidative stress, metal metabolism and mitochondrial dysfunction had proposed to be involved of this operation. However, hyper phosphorylated tau protein for extracellular plaques with intracellular neurofibrillary tangles according **to Cristóvão et al., (2016).** The biggest risk factor for AD is age. The disease is never evident in the young, even in the young with disease-causing mutations that overexpress of amyloid β protein (Aβ) from birth. Aging is also required to observe cognitive loss,pathology, and degeneration in transgenic mice engineered to overexpress multiple disease-causing genes. This means that some phenomenon in the process of aging is required to induce Aβ-mediated neurodegeneration and that Ab expression alone is not a sufficient cause of disease **(Johnson and Johnson. 2012).**Moreover, realization into the mechanisms by which the orexin system is embroiled in feeding may yield new therapeutic options for this corpulence epidemic**. Davies et al., (2015)** Reported that orexin are neuropeptides that regulate the sleep-wake cycle and feeding behavior. QRFP is a newly discovered neuropeptide which exerts similar orexigenic activity, thus playing an important role in energy homeostasis and regulation of appetite. The orexin system leads to an increase of energy expenditure and spontaneous physical activity (SPA) levels. A fundamental point of this review is the evidence that higher orexin signaling provides resistance to the development of obesity and this is possible through different mechanisms like an increase in synthesis or release of orexin peptides or changes in expression of the orexin receptor. It is important to understand the concept of Ox and its role in obesity resistance to find new therapeutic and preventive solutions against the excess body weight, in fact the stimulation of orexin receptors may be a valid therapeutic approach together with appropriate low-calorie diet, frequent physical exercise and psychological proposal in order to build the foundation for preventive and curative therapy against obesity. **Fayez et al., (2019)** declared that vascular dementia is considered a vascular cognitive impairment disease caused by neuronal degeneration in the brain. Several studies have supported the hypothesis that oxidative stress and endothelial dysfunction are the main pathogenic factors in vascular dementia.

This current study aims to determine the possible neuroprotective effect of methionine & cysteine and drug orexin and the side effects of

aluminium chloride on nutritional status and increase beta-amyloid cause of obesity and Alzheimer's disease in rats

MATERIALS AND METHODS

A-Materials:-

1-Two kinds of sulfur amino acids were used in this study (Methionine and L- Cysteine.) and Aluminium chloride 98% were obtained from El-Gomhoria Company for Chemicals, Egypt.

2-Orexin –A: was obtained from Sigma Peptide Research systemic administration of according to systemic administration of SB at orexin 1 receptor antagonist SB-334867 (SB) 226 relatively low doses (5 or 10 mg/kg) the at 226 relatively low doses (5 or 10 mg/kg)**Richards et al., (2008)**.

3-Experimental animals**:**Twenty rats were purchased from the Agricultural Research Center, Giza, Egypt.The average weight at beginning of experiment was 100±5 g. The animals were kept under observation for five days before experiment and fed on standard diet and water ad libitum. Ethical guidelines of this study was performed based on the guidelines for the use and cares the laboratory animals. Handling and permission was obtained from the concerned Department in Home Economics, Faculty of specific Education, Mansoura University.

4-The standard diet according to **NRC (1995**) comprised of casein (200g/kg), corn starch (497g/kg), sucrose (100g/kg), cellulose (30 g/kg), corn oil (50g/kg), mineral mixture (100g/kg), vitamins mixture (20g/kg) and DL-methionine (3g/kg).

B-Methods*:-*

Experimental design**:** The experimental rats were randomly classified into two main groups as following:

Group (1) (5 rats) was fed on the standard diet daily as a negative control. The second group (15 rats) fed on the high fat diet for 6 weeks to induced obesity **(Abd El-Ghany, 2006 and Daozong Xia et al., 2010)** the induction of Alzheimer's by oral administration of Aluminium chloride 98% at dose (175 mg/kg b.w.t) daily for 25 days to according to **Cao et al.,(2017)** Obese and Alzheimer's main rats group are reclassified into three groups as follows:

Group (2): positive control group fed on high fat diet (HFD) + AlCl3

Group (3): administration of methionine & cysteine orally (4.5 g/100 g protein) in negative saline daily according to **Coates, et al., (1969)**

Group (4): administration of Orexin drug orally (20 mg/kg b.w.t) in negative saline daily according to **Richards, et. al., (2008).**The duration of treated study was four weeks. Food intake was recorded daily. New food was given according to the actual need of each group there meaning diet from the previous day was weighted and food intake was calculated.

Body weight of rats was measured once weekly. Food efficiency ratio was calculated at the end of experiment using the following equation as described, **chapman et al., (1950).**

Anthropometric measurements: as weight and length ,the measurements of all rats were weighed in grams and lengths in cm from nasal to anal were measured at the end of study.The body mass index (BMI) was calculated (by dividing the body weight in kilograms by the length in meters squared).The body weight and body length were measured and used to determine the following equation as **Jeyakumar et al., (2006)**

A-Biochemical analysis of serum:

Serum Aspartate aminotransferase (AST:), Alanine aminotransferase (ALT), lkaline phosphatase (ALP) were performed according to the method of **Devi et al., (2000)**,**Reitman and Frankel, (1957) and Draper and Hadley, (1990)** Serum creatinine, Urea and Uric acid according to **Young, (2001)**, **Patton and Crouch (1977).** and **Barham and Trinder, (1972)**. Serum cholesterol (CHO),triglycerides (TG),high density lipoprotein cholesterol (HDLc) and total lipid content (T. Lipids), were measured according to **Richmond, (1973)**, **Buccolo and David, (1973), Grodon and Amer,(1977**) and **(Haug and Hostmark, 1987)**, respectively but Low density lipoprotein cholesterol (LDLc) very low density lipoprotein cholesterol (VLDLc) and phospholipids were calculated according to **Lee and Nieman, (1996).**Determination of serum aluminum by atomic absorption according to **Kampulainein, (1983)**

B-Tissue examination: Estimation of antioxidant parameters: in brain tissue as Catalase (CAT) , Glutathione (GSH) ,Superoxide dismutase (SOD), Malondialdehyde (MDA) and Beta-Amyloid according to **(Bock et al. 1980 and Lartillot et al. 1988)** ,**(Prins and Losse 1969 and Moron et al., 1979)**,**(Guichardanti et al. 1994 and Misra, and Fridovich, 1972)**,**(Ohkawa et al. 1979 and Guichardanti et al. 1994),** and **(Saido et al.,1995;Thakker, 2009 and Bordji et al.,2010) respectively**

C-Histopathological examination of brain:

The fixed samples of brain in 10 % neutral buffered formalin were cleared in xylol and embeded in paraffin. 4-5 µm thick sections were prepared and stained with Hematoxylin and Eosin (H&E) for subsequent histopathological examination **(Bancroft et al., 1996).**

D-Statistical analysis: were done using "SPSS computer software ver.ll. The majority of the data presented in this study reflect the main I standard deviation (SD) for four determination. One way analysis of variance (ANOVA) followed by LSD test were used the determined the difference

among the means according to **Abou-Allam (2003)**. The significant difference was set at $P < 0.05$

RESULTS AND DISCUSSION

The statistical data in Table 1 presented that, significant body weight gain, weight gain percent and body mass index final among all rats group which treated with**,** methionine & cysteine and orexin but showed significant decrease in food intake and FER in rats group treated with methionine & cysteine and orexin in comparing with Positive control were somewhat in agreement with the results of **Irving et al., (2009)** suggested that increased BMI can be achieved with a specific combination of nutrients, independent of the energy content of the product, in patients with mild AD. **Ylikoski et al., (2000) and Rahmouni et al., (2005)**.They explained that the exact mechanism for the relationship between BMI and reduced cognitive performance remains unknown. Elevated BMI is associated with many pathophysiologic changes with the potential to negatively impact cognitive functioning, including vascular changes, impaired insulin regulation, systemic inflammation, and reduced cardiovascular fitness **Irving et al., (2009)** concluded that an increase in body weight correlated with an increase in Neuropsychiatric inventory (NPi) appetite score, although food intake data were not collected. **Seale, (2011) and Sellayah et al. (2011)** said that orexins are small excitatory neuropeptide hormones that promote wakefulness and stimulate energy expenditure via actions in the brain. Found that Orexin (Ox)-deficient mice became obese despite eating less than their wild-type littermates. While diminished activity and sleepiness presumably accounts for some of the weight gain, Ox-null mice also seem to have an increase in metabolic efficiency**.**

Table (1): Some anthropometric measurement of negative control and obesity with Alzheimer's rats group during the experimental period.

Variables / Groups		Weight Gain (g)	Weight Gain %	Food Intake (g)	(FER)	Initial BMI (g/dl)	Final BMI (g/dl)
Negative control		51.40 ± 2.88 c	25.41 ± 1.68 c	25.69 ± 0.66 c	0.03 ± 0.001 c	5.71 ± 0.10 a	5.29 ± 0.24 b
Ir eat ed	Positive control	127.20 ± 4.76 a	61.87 ± 1.52 a	29.68 ± 1.18 a	0.07 ± 0.001 a	5.38 ± 0.21 ab	6.91 ± 0.08 a
	Treated with Me & C	83.40 ± 2.07 b	40.86 ± 1.57 b	27.62 ± 0.55 b	0.05 ± 0.001 b	5.51 ± 0.17 a	4.68 ± 0.10 c
	Treated with Orexin	37.60 ± 4.27 d	18.57 ± 2.55 d	24.98 ± 0.63 cd	0.02 ± 0.001 cd	5.23 ± 0.40 a	4.55 ± 0.18 c

Values are expressed as mean ± SD, n=5, Mean values in each column having different superscript (a, b,c,..) are significant at $p<0.05$ by different and vice versa. FER: Food efficiency ratio and BMI: Body mass index.

Table 2 shows results significant decrease in ALT, AST , ALP, creatinine, Uric Acid and urea among rats groups which treated with methionine & cysteine and orexin, in comparing with Positive control obesity and Alzheimer's rats group. The results of some liver function parameters were agreed with the results of **Thomas et al. (2004)** and **Yousef (2004)** mentioned that the induction rate in serum bilirubin was associated with free radical production. Also, the elevation in plasma bilirubin concentration could be due to the onset of periportal necrosis. The present results also showed that the activities of AST, ALT and lactate dehydrogenase LDH were significantly increased in plasma of rats treated with AlCl3 and this is an indication to liver damage. , while increased glucose, urea, creatinine and bilirubin as compared to control. The decline in plasma total protein after treatment with AlCl3 was mainly due to the decrease in albumin. The inhibitory effected of AlCl3 on protein profile. **Mahieu et al., (2005**) noted that the elevation in plasma urea and creatinine levels in AlCl3-treated rats is considered as a significant marker of renal dysfunction, who reported that alterations in serum urea may be related to metabolic disturbances.

Table (2): Some liver and renal function parameters of negative control and different experimental obesity with Alzheimer's rats group at the end of the study.

Variables / Groups		AST (µ/L)	ALT (µ/L)	ALP (µ/L)	Creatinin (mg/dl)	Uric Acid (mg/dl)	Urea (mg/dl)
Negative control		38.80 ± 6.76 d	25.84 ± 3.18 d	6.84 ± 0.51 d	0.76 ± 0.11 c	4.30 ± 0.57 bc	41.30 ± 4.57 bc
Treat	Positive control	177.20 ± 7.59 a	195.30 ± 4.89 a	34.20 ± 3.83 a	2.54 ± 0.27 a	8.24 ± 0.03 a	76.04 ± 8.55 a
	Treated with Me &C	126.21 ± 12.63 b	108.15 ± 9.89 b	26.86 ± 1.90 b	1.34 ± 0.09 b	5.88 ± 1.76 b	42.36 ± 6.69 b
	Treated with Orexin	94.60 ± 3.57 c	82.26 ± 4.43 c	15.29 ± 5.64 c	1.38 ± 0.31 b	5.98 ± 1.18 b	43.64 ± 4.29 b

Values are expressed as mean ± SD, n=5, Mean values in each column having different superscript (a, b,c,..) are significant at $p<0.05$ by different and vice versa. AST: Aspartate aminotransferase, ALT: Alanine aminotransferase and ALP Alkaline phosphatase

As seen in Table 3 revealed significant decrease in the serum cholesterol, TG, LDLc, VLDLc and T.Lipid among all rats group in treated groups administrated methionine & cysteine and orexin, But, significant increase in the HDLc, in comparing with Positive control.Also, revealed significant increase in phospholipid in rats group

treated with orexin in comparing with Positive control There results of some serum lipid patterns were agreed with the results obtained from. **Yousef (2004)** indicated that plasma total lipids, cholesterol, triglycerides and LDL-c were significantly increased by AlCl3 treatment, while HDL-c levels were decreased. **Bjelik et al., (2006)** suggested that serum cholesterol level is associated with Aβ expression in the liver. high cholesterol diet is considered as one of the risk factors which can increase Aβ expression levels in the rodent brain. **Mailloux et al., (2007)** estimated that Al is also reported to increase lipid accumulation in hepatocytes in vitro**. Li et al., (2012)** considered that the question of whether a link exists between Al treatment, serum cholesterol levels and Aβ expression in the liver in vivo.

Table (3): Fasting levels of some serum lipid patterns of negative control and obesity with Alzheimer's rats treated by sulphur amino acids and Oroxin at the end of the study.

Variables / Groups		CHO (mg/dl)	TG (mg/dl)	HDLc (mg/dl)	LDLc (mg/dl)	VLDLc (mg/dl)	T.Lipid (mg/dl)	PL (mg/dl)
Negative Control		**85.38 ± 9.38 d**	**57.70 ± 6.23 d**	**37.79 ± 3.71 a**	**36.05 ± 2.78 c**	**11.54 ± 1.24 d**	**349.66 ± 45.40 d**	**206.58 ± 10.99 cd**
Positive control		**251.90 ± 9.05 a**	**245.76 ± 23.82 a**	**17.36 ± 3.46 c**	**185.38 ± 6.97 a**	**49.15 ± 4.76 a**	**720.48 ± 13.13 a**	**222.82 ± 39.85 b**
Treated with	Treated with Me and C	**114.64 ± 10.05 b**	**133.90 ± 9.16 b**	**27.02 ± 4.03 b**	**60.84 ± 5.25 b**	**26.78 ± 1.83 b**	**466.85 ± 59.59 b**	**218.31 ± 41.86 bc**
	orexin	**94.46 ± 6.33 c***	**104.32 ± 5.21 c**	**36.34 ± 4.26 a**	**37.26 ± 6.71 c**	**20.86 ± 1.04 c**	**455.62 ± 55.23 bc**	**256.83 ± 36.91 a**

Values are expressed as mean ± SD, n=5, Mean values in each column having different superscript (a, b,c,) are significant at $p<0.05$ by different and vice versa. CHO: Total Cholesterol, TG: Triglycerides, HDL-c: High density lipoprotein, LDL-C: Low density lipoprotein, VLDL-c: Very low density lipoprotein and PL: Phospholipid

The statistical data in Table 4 presented that, revealed significant increase in brain antioxidant enzymes as Catalase, glutathione peroxidase GSH and superoxide dismutase SOD among all treated rats group with methionine & cysteine and orexin in comparing with Positive control. But, showed significant decrease in brain MDA, Aβ and serum Aluminum among all

rats group which treated with methionine & cysteine and orexin in comparing with Positive control the results of some antioxidant indicators were agreed with the results of **Nehru & Anand (2005) and Li et al., (2012)** proved that aluminum chloride-induced free radicals by inhibited of the antioxidants enzymes defense, as SOD, catalase, GST and glutathione peroxidase GSH-Px, which function as blockers of free radical processes. We observed a significant decrease in the enzymes in all tested tissues of treated rats, who observed a significant decrease in the activities of SOD and catalase in brain after aluminium treatment, the levels of thiobarbituric acid reactive substances TBARS were found to be elevated but the activities of glutathione S-transferase GST, SOD, CAT and GSH-Px were decreased in brain compared to negative control group. **Damante et al., (2009) and Abd El-Ghany et al., (2016)** found that the mechanism of Al induced Aβ expression in brain. by increased levels of lipid peroxidation (MDA.The significant increases of MDA contents were observed the rats treated of AlCl3, and the brains suggesting that Al may contribute to the increase of oxidative stress products. Activity and decrease of oxidative enzymes activities.Total superoxide dismutase and (GSH-Px) activities enhanced significantly in AlCl3 treated brains .The serum level of aluminum shows significant decrease among rats group treated with methionine &cysteine and orexin, in comparing with Positive control .The high levels of Al in their drinking water did increase the number of amyloid plaques or amount of over-phosphorylated tau in their brains may offer an explanation as to why Aβ deposition is apparent in AD-affected neocortex

Table (4): Brain antioxidant enzymes, β-amyloid and serum Aluminum of Negative control and different experimental obesity with Alzheimer's rats group at the end of study.

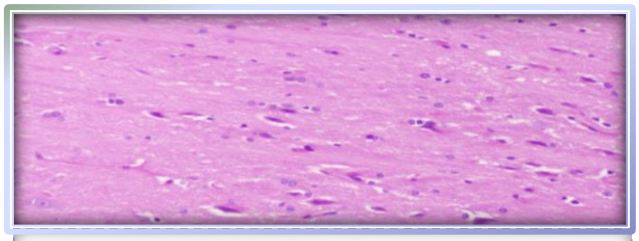
Variables / Groups		Catalase (µ/L)	GSH (µ/L)	SOD (µ/L)	MDA (n moles/ml packed cells)	β-amyloid (pg/ml)	Serum Aluminum (mcg/dl)
Negative control		61.25 ± 8.23 a	32.83 ± 2.01 a	44.55 ± 3.27 a	17.13 ± 4.45 d	5.04 ± 1.88 d	5.02 ± 0.52 d
Positive control		12.20 ± 2.37 e	10.79 ± 1.97 d	10.06 ± 1.24 d	57.03 ± 6.32 a	77.00 ± 7.32 a	48.76 ± 5.73 a
Treated with	Methionine and cysteine	29.20 ± 3.17 d	26.81 ± 4.40 b	27.61 ± 1.23 b	23.14 ± 3.83 bcd	23.35 ± 2.94 b	24.84 ± 1.62 b
	Orexin	37.05 ± 6.71 cd	27.01 ± 0.81 b	19.69 ± 2.07 c	30.61 ± 5.86 b	19.04 ± 2.30 bc	16.44 ± 1.35 c

Values are expressed as mean ± SD, n=5, Mean values in each column having different superscript (a, b,c) are significant at $p<0.05$ by different and vice

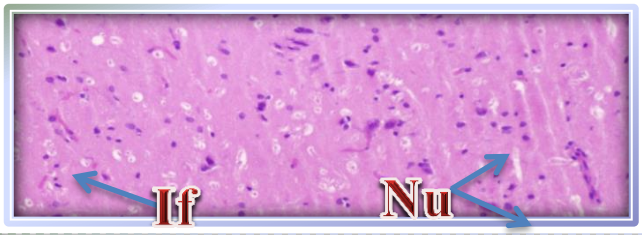
versa GSH: Glutathione, SOD: Superoxide dismutase and MDA: Malondialdehyde

Histopathological Results of brain:

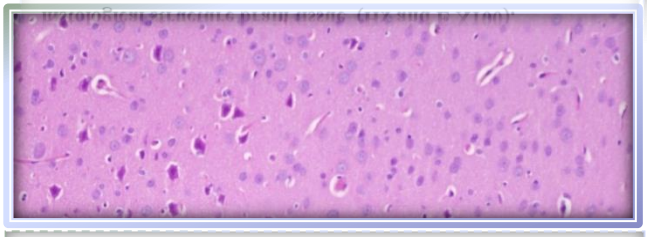
Microscopically, of rat from the negative control group revealed the no histological structure of brain tissue (Pict. 1). Examines sections from the Positive control group showed marked interstitial inflammation edema with hyper chromatic nuclei in pyramidal cells4 (Pict. 2). Other section, from group treated with methionine & cysteine revealed near negative apart from very mild interstitial edema (Pict 3). But section group treated with orexin near negative brain no significant changes (Pict. 4) **Abd El Dayem et al., (2012)** revealed that the micrograph of brain section of negative control group showing negative morphological structure of the hippocampus (Hx & E ×40).but shows the micrograph of brain section of positive control group showed the micrograph of brain various sizes of amyloid plaques formation (arrow) in the cerebral cortex and hippocampus (Hx & E ×40). shows the section of brain tissue of all rats treated showed the presence of focal gliosis in the cerebrum associated with the disappearance of amyloid plaques.



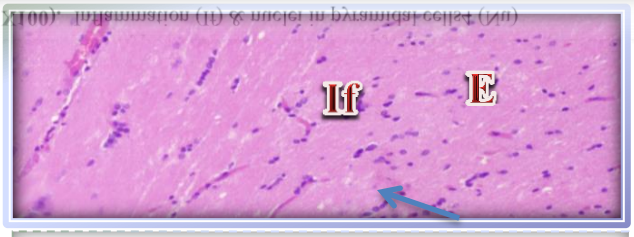
Pict.(1): Photomicrography histological finding in brain of rat from the negative control group revealed the normal histological structure brain tissue (Hx and E X100).



Pict. (2): Photomicrography histological finding in brain of rat from the positive control group showed marked interstitial inflammation edema with hyper chromatic nuclei in pyramidal cells4. (Hx and E X100). Inflammation (If) & nuclei in pyramidal cells4 (Nu)



Pict.(3): Photomicrography histological finding in brain of rat from the group treated with Me + cysteine revealed near normal apart from very mild interstitial edema (Hx and E X100).



Pict.(4): Photomicrography histological finding in brain of rat from the group treated with orexin revealed near normal brain no significant changes (Hx and E X100).

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الملخص البحث:

صممت الدراسة الحالية لمقارنة التأثير العلاجي لبعض الأحماض الأمينية الكبريتية ودواء **الأوريكسين** في علاج مرض الزهايمر الناتج عن ارتفاع البيتا أميلويد في الفئران البدينة حيث اجريت الدراسة علي عشرون من الفئران البدينة التي يتراوح وزنها ٢٠٠ ± ١٠ جم وقسمت الي مجموعتين رائستين المجموعة (١) الكنترول السالبة تحتوي علي خمسة فئران والتي تغذت على الوجبة القياسية والمجموعة الثانية تحتوي علي خمسة عشرة من الفئران والتي تغذت علي وجبة عالية الدهون مع كلوريد الألومنيوم لمدة ٦ أسابيع للاصابة بالسمنة ومرض الزهايمر ثم أعيد تقسمها إلى ثلاث مجموعات.كالاتي المجموعة (٢) مجموعة الكنترول الموجبة المجموعة (٣) المعالجة بالميثيونين والسيستين 4.5 جم / ١٠٠ جم والمجموعة (٤) المعالجة بدواء الأوركسين 20 مجم / كجم من وزن الجسم واستمرت فترة العلاج لمدة اربع أسابيع وأظهرت النتائج ان هناك انخفاض معنوي في كل من زيادة وزن الجسم والمتناول من الطعام وزيادة معنوية في نسبة كفاءة الطعام في جميع مجموعات الفئران المعالجة بالأحماض الأمينية الكبريتية ودواء الأوريكسين بالمقارنة بمجموعة الكنترول الموجبة كما أظهرت نتائج التحاليل البيوكميائية ان هناك انخفاضً معنويً في كل من وظائف الكبد والكلي و كوليسترول الدم ، والدهون الثلاثية، وكوليسترول البروتين الدهني منخفض الكثافة (LDLc) وكوليسترول البروتين الدهني منخفض الكثافة جدًا (VLDLc) والدهون الكلية و كلوريد الالمونيوم و مستويات انسجة المخ من المانولدهيد (MDA) و البيتا اميلويد B-amyloid وارتفاع معنوي في كوليسترول البروتين الدهني مرتفع الكثافة (HDLc) ومستوي خلايا المخ من الانزيمات المضادة للاكسدة كالكتاليز والجلوتاثيون-S -ترانسفيراز (GST) والسوبر اكسيد ديسموتاز (SOD) وذلك بالمقارنة بالمجموعة الكنترول الموجبة.كما اتفقت التخليل البيوكيميائية مع الفحص النسيجي لأنسجة المخ لتاكيد العلاج بالاحماض الامينية الكبريتة والأوركسين و توصي الدراسة بضرورة استهلاك الأحماض الأمينية الكبريتية التي تقلل من الزيادة في الوزن وتحسين المعايير الكيميائية الحيوية والتغيرات النسيجية التنكسية في الدماغ مع دواء الأوركسين

الكلمات المفتحية: ميثيونين ، سيستين ، كلوريد ألومنيوم ألزهايمر ، أوركسين زيادة الوزن ، الفئران