ALTERATION OF FREE FATTY ACIDS INDUCED BY BENZODIAZEPINES ADMINISTRATION IN ALBINO RATS

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The benzodiazepines are a class of psychoactive drugs with varying hypnotic and anxiolytic properties. They are used in the treatment of a variety of indications such as seizures, anxiety, and insomnia. The over-prescribing of benzodiazepines on a long-term basis can cause physical dependence and have many adverse effects on health. This work aimed at studying the effect of two drugs of this group, clorazepate and bromazepam, on the concentration of liver and brain free fatty acids in albino rats.

Results showed that, the saturated, monounsaturated and the polyunsaturated fatty acids were reduced in liver tissue by acute and chronic doses of the two drugs except, the content of myristoleic acid (14:1) and palmitoleic acid (16:1) which were increased. On the other hand, the polyunsaturated fatty acids, Linoleic acid (18:2), arachidic (20:2), arachidonic acid (20:4) and docohexanoic acid (22:6) were increased in brain tissue by administration of acute and chronic doses of clorazepate and bromazepam.

Introduction

Benzodiazepines (hypnotic, minor tranquilizers) are now the preferred hypnotics[1]. Benzodiazepines enhance the effect of the neurotransmitter gamma-aminobutyric acid, which results in sedative, hypnotic, anixyolitic anticonvulsant, muscle relaxant and amnesic action. These

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properties make benzodiazepines useful in treating anxiety, insomnia, agitation, seizures and muscle spasms. Two members of this group were chosen in this study. Clorazepare (tranxene) is a member of long acting benzodiazepines, and bromazepam (lexotanil) is a member of short acting benzodiazepines. These drugs possess a muscle relaxant, anticonvulsant, antianxiety and sedative hypnotic effects [2].

However, their adverse effects and their potential for producing dependency is generally conceded to limit their therapeutic use to relatively short periods of time, from 1 to 6 weeks and only for acute anxiety disorders[3]. In rats long administration of clorazepate produced memory impairment[4] and manic reaction[5]. Bromazepam was activating GABA receptor leading to centrally mediated inhibitory effects on ACTH and cortical secretion that could reflect an inhibitory influence on CRH [6]. Long term use of bromazepam is common in drug poisoning suicides in the elderly and should be prescribed with caution for this age group [7].

Clorazepate produced jaundice and hepatic necrosis[8]. Oxazepam (clorazepate metabolite) when administrated in chronic dose, leads to prenecrotic and necrotic changes in liver parenchyma with reduction in liver metal contents (zinc, iron and copper) [9].

Musavi and Kakkar, 2003[10], stated that, a decrease in oxidative decomposition of polyunsaturated fatty acid, was observed on administration of 3mg/ kg diazepam for 21 consecutive days. So this work was conducted to study the alteration of free fatty acids induced by the administration of the chosen benzodiazepines in the brain and liver of albino rats.

Materials and Methods

I- Materials

a- Compounds Studied

1- Clorazepate "tranxene":

The drug obtained as capsules of dipotassium clorazepate from the Nile Co. for pharmaceuticals and chemical industries, Cairo, A. R. E. under the licence from Clin-Midy, Paris.

2- Bromazepam "lexotanil":

The drug obtained as lexotanil tablets from F. Hoffmann La Roche and Co. Ltd, Basle, Switzerland.

b- Animals

48 male rats *"Rattus norvegicus"* weighed (90-120g) were obtained from Experimental Animal House, Helwan, Egypt. Animals were housed in a group of six rats in plastic containers. Food and water allowed *ad. libitum.* All animals were normal and healthy.

The animals were divided into two groups, each comprised 24 rats, for each group, 18 animals were treated and 6 were served as control. Treated animals were divided into:

Clorazepate treated animals

Two acute oral doses (6 animals for each) were administered to the animals. The first dose was 0.135mg/100g body weight, which represents the lowest therapeutic hypnotic dose of the drug (CZI). The second dose was 0.27 mg/ 100g body weight which represents the highest therapeutic hypnotic dose of the drug (CZII).

For chronic treatment: 6 rats received oral doses of clorazepate 0.09 mg/100g body weight which represents the lowest limit of the therapeutic dose for 30 consecutive days (CZIII) [11]. Control animals received 1ml/ saline vehicle daily.

Bromazepam treated animals

Animals received two acute oral doses (6 animals for each). The first dose was 0.054mg bromazepam in 1ml saline solution/ 100g body weight, which represents, the lowest therapeutic hypnotic dose of the drug (BZI). The second was 0.11mg/ 100g body weight which represents the highest therapeutic hypnotic dose of the drug (BZII).

For chronic treatment: 6 rats received a daily oral doses of bromazepam 0.027mg/ 100g body weight which represents the lowest limit of the therapeutic sedative dose for 30 consecutive days [12].

Sample Collection and Preparation:

The whole brain and 1g of the liver of all animals were immediately removed after sacrificing, preserved in cold saline solution (10ml), homogenized for 5 minutes by electric homogenizer and centrifuged at 3500 r.p.m for 15 minutes. The pellets were then washed twice with 5ml cold saline, the supernatant was discarded. An equal volume of 10% cold TCA was added and centrifuged for 10 minutes at 600 r.p.m. The residues were then washed twice with 5% ice cold TCA, the supernatants contained the acid – soluble phosphorous was discarded[13]. For lipid extraction, the residue after removal of the acid soluble components was extracted 3 times with a mixture of coloroform: methanol (2: 1, V/V) [14].

II Methods

Parameter Investigated

Identification of liver and brain FFA was carried out according to the method of Farag *et al.*, 1986 [15].

Statistical Analysis

All data were expressed as means + standard deviation.

Data of different groups were compared using student "t" test. Differences at ($P<0.05$) were considered significant [16].

The average of the results of control groups, were used in the statistical analysis, as there are no significant differences between them.

RESULTS

Data in figures (1-3) showed that: The saturated, monounsaturated and polyunsaturated liver free fatty acids were decreased by administration of 0.135 and 0.054 mg/ 100g body weight of clorazepate (CZI) and bromazepam (BZI) respectively compared to control, except the content of myristoleic acid (14: 1) and palmitoleic which (16: 1) were increased.

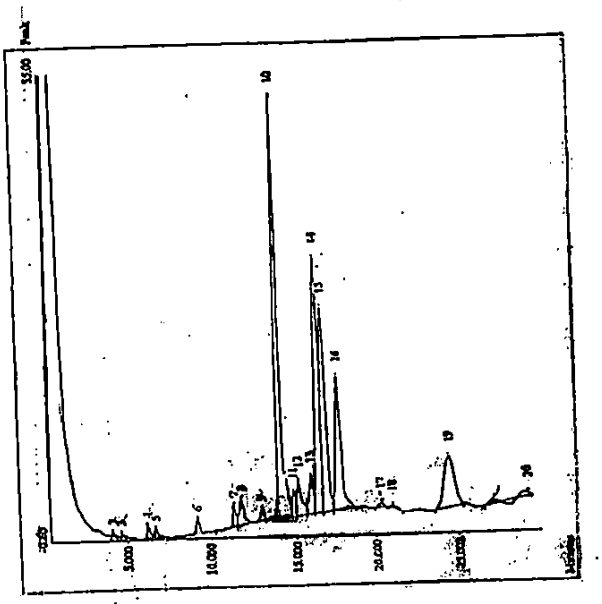
Figures (4-5) indicated that: 0.27 mg/ 100g body weight clorazepate (CZII) and 0.11 mg/100g body weight bromazepam (BZII) moderately reduced all types of liver free fatty acids.

Results shown in figures (6-7) indicated that: chronic administration of 0.09 mg/ 100g clorazepate (CZIII) and 0.027 mg/100g bromazepam (BZIII) also reduced the concentration of saturated, unsaturated and polyunsaturated FFA content of liver. The reduction was highly significant ($P < 0.01 - 0.001$).

On the other hand, data in figures (8-14) indicated that: 0.135 mg/ 100g body weight clorazepate (CZI) slightly increased ($P < 0.05$) the brain content of polyunsaturated free fatty acids. While monounsaturated free fatty acids were unchanged. The administration of 0.054 mg/100g of bromazepam (BZI) showed no effect on the content of brain free fatty acids.

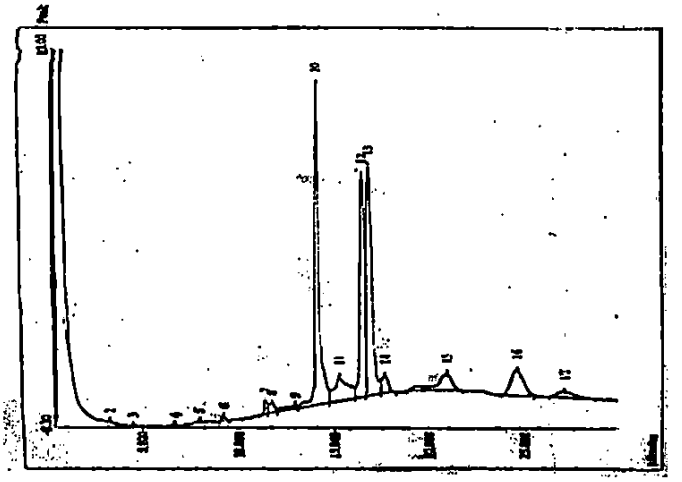
The highest acute dose of clorazepate 0.27 mg/ 100g body weight (CZII) and bromazepam 0.11 mg/100g body weight (BZII) were significantly increased ($P < 0.01$) the concentration of archidonic acid (20:4) and behnic acid (docohexanoic acid) (22:6).

Daily injection of 0.09 mg/ 100g clorazepate (CZIII) and 0.027 mg/100g bromazepam (BZIII) for 30 consecutive days, highly increased ($P < 0.001$) the concentration of saturated, unsaturated and polyunsaturated FFA content of brain, compared to control, especially the concentration of archidonic and behnic acids.



Peak	Name	Peak	Name
2	Hydroxy caprylic-8-	11	Palmitoleic-16:1-
3	Caprylic-8-	12	Palmitolenic-16:2-
4	Hydroxy capric-10-	14	Stearic-18:0
5	Capric-10-	15	Oleic-18:1-
6	Lauric-12-	16	Linoleic-18:2-
7	Hydroxy Myristic -14-	17	Arachidic-20-
8	Myristic-14-	18	Cis 11 Ecosenoic-20:1-
9	Myristoleic-14:1-	19	Arachidonic-20:4-
10	Palmitic-16-		

Fig. (1): Control Liver.



Fig(2):Effects of Acute CZI on Liver FFA

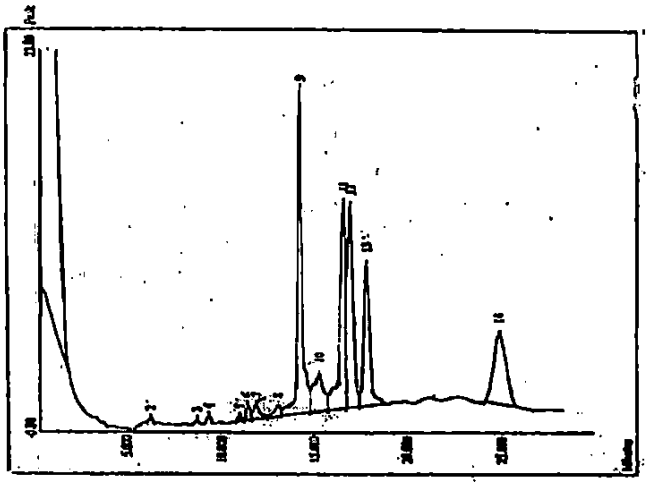


Fig (3):Effect of Acute BZI on Liver FFA

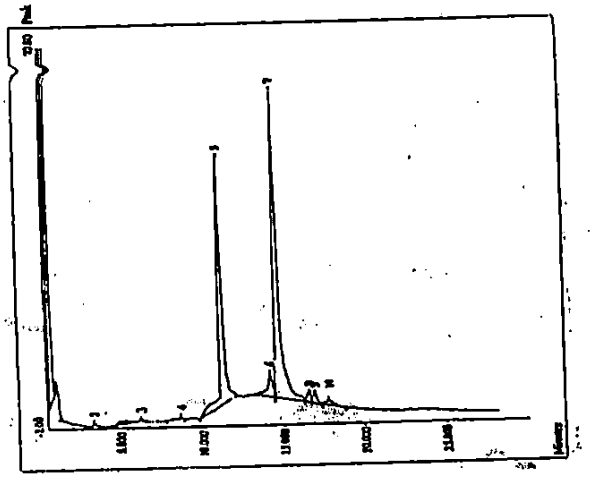


Fig (4):Effect of Acute CZII on Liver FFA

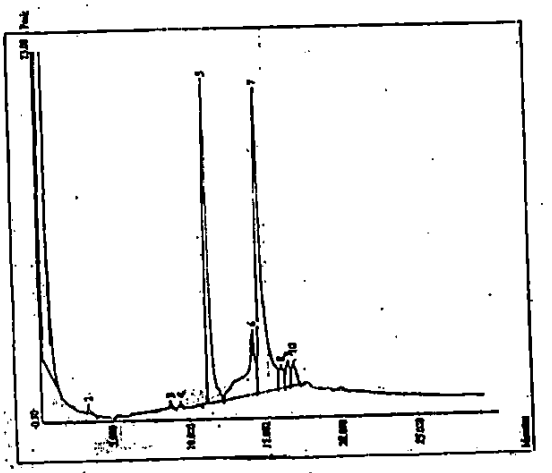


Fig.(5):Effect of Acute BZII on Liver FFA

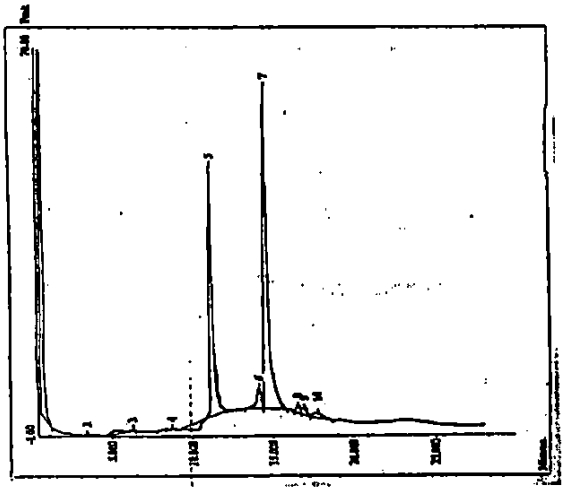


Fig.(6):Effects of Chronic CZIII on Liver FFA

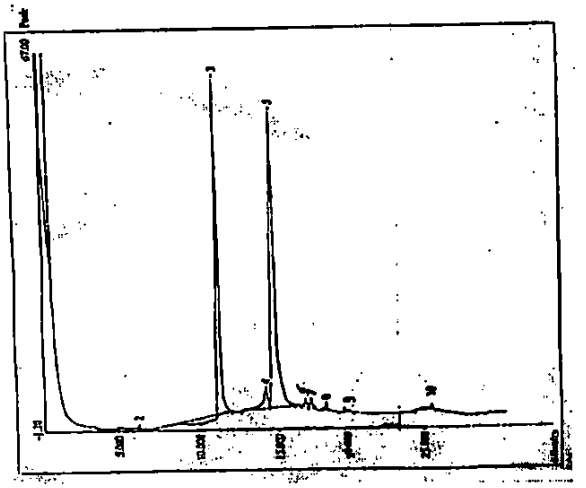
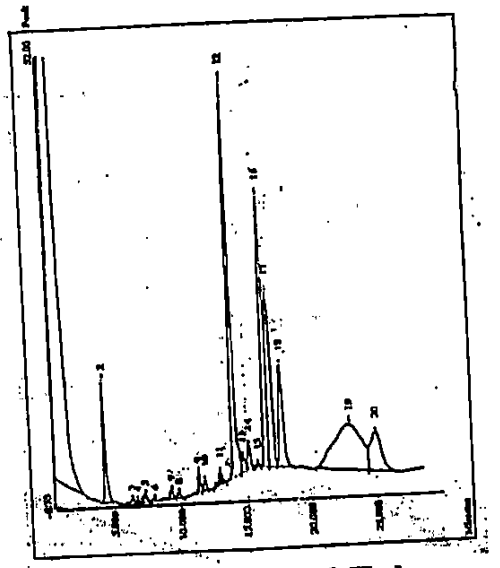


Fig.(7): Effects of Chronic BZIII on Liver FFA



2 -Caprylic-8
4-Capric-10
6-Hydroxylauric-12
8-Hydroxymyristic-14
10-Myristic-14
12-Palmatic-16
14-Palmitolenic-16:2
16-Stearic-18
18-Linoleic-18:2
20-Docohexanoic Acid (22:6)

3-Hydroxycapric-10
5-Hydroxylauric-12
7-Lauric-12
9-Hydroxymyristic-14
11-Myristoleic-14:1
13-Palmitoleic-16:1
15-Hydroxystearic-18
17-Oleic-18:1
19-Arachidonic Acid (20:4)

Fig. (8):Control Brain FFA

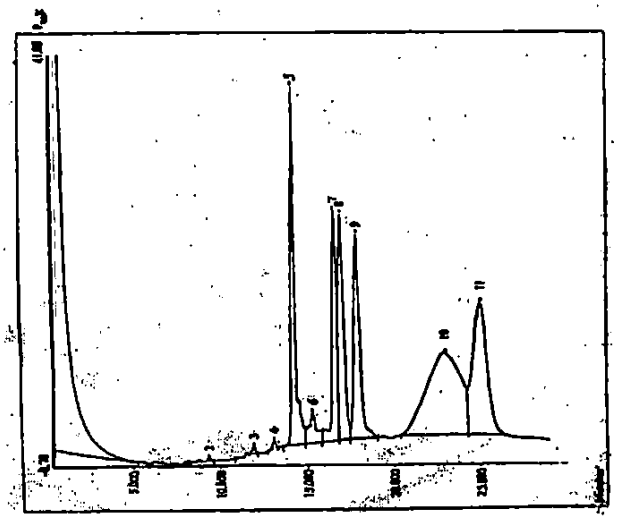


Fig. (9): Effect of acute CZI on Brain FFA

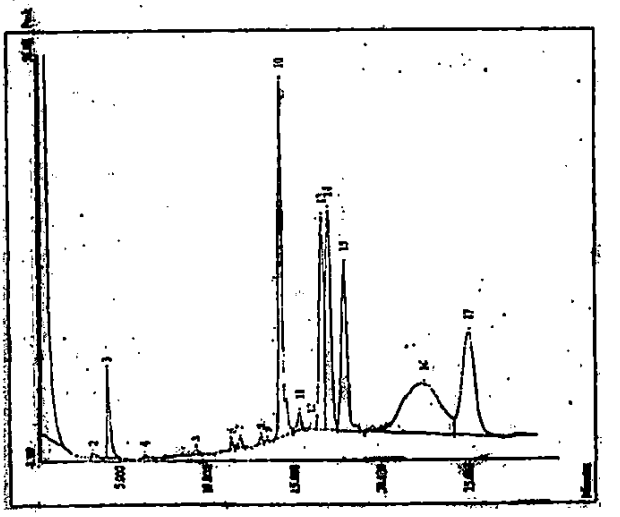
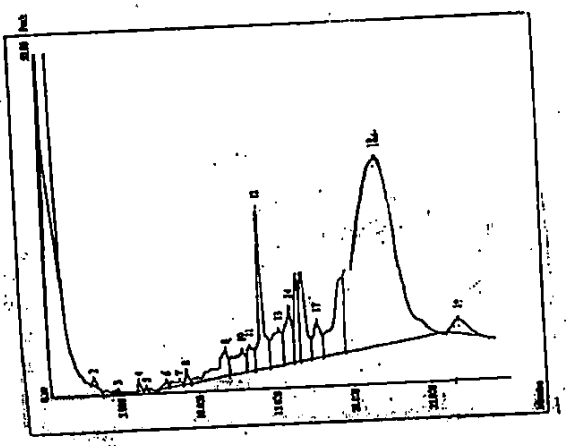


Fig. (10): Effect of Acute BZI on Brain FFA



Fig(11): Effect of Acute CZII on brain FFA

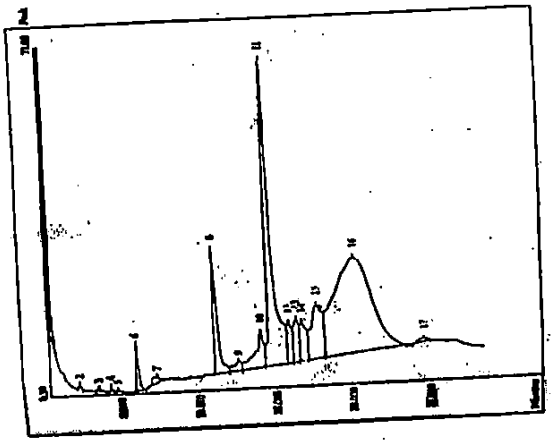
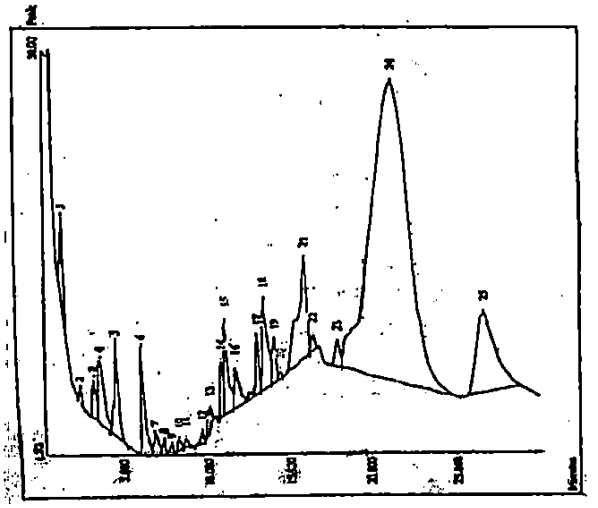
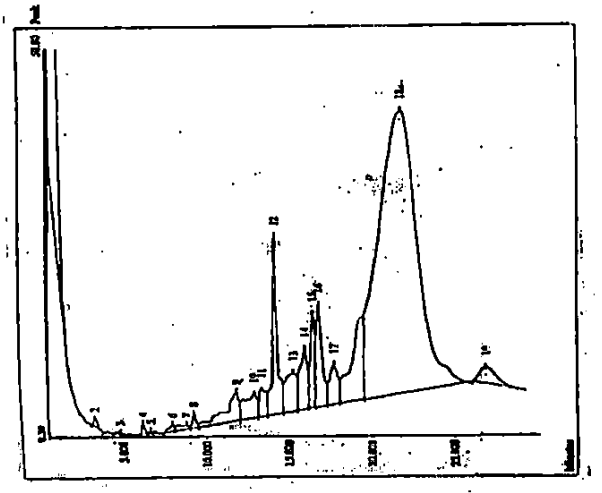


Fig. (12): Effect of Acute BZII on Brain FFA



Fig(13): Effect of chronic CZIII on brain FFA



Fig(14):Effect of Chronic BZIII on Brain FFA

DISCUSSION

Lipid metabolism is of particular interest due to its high concentration in CNS. The importance of lipids in cell signaling and tissue physicology is demonstrated by many CNS disorders and injuries that involve deregulated metabolism [17].

The present study sheds light on some of the biochemical effects of two benzodiazepines named clorazepate and bromazepam on lipid metabolism. Data in figures (1-7) showed that, acute and chronic administration of clorazepate and bromazepam significantly reduced saturated and unsaturated free fatty acids content in liver with a predominant increase in myristoleic (14:1) and palmitoleic acids (16:1).

The present results were in accordance with Molochkina *et al.*, 2005, Zanger *et al.*, 2007 and Vourvahis and Kashuba, 2007 [18]. They reported that, the biotransformation of drugs are presented as an enzyme complex. The drug combines with the oxidized cytochrome P450 to from cytochrome drug complex. This complex is then reduced and combines with molecular oxygen to form oxygenated intermediates, many of which can undergo a cycling process between oxidation and reduction. This process can cause oxidative stress in cells. Such oxidative stress can result in several adverse consequences such as lipid peroxidation. Lipid peroxidation not only destroys lipids in cellular membranes but also generate endogenous toxicants as free radical and electrophils [19]. This byproduct of lipid peroxidation results in the inhibition of several cytochrome P450 isoenzymes and depletion of total lipids and fractions [20].

The depletion of liver free fatty acids after acute and chronic administration of clorazepate and bromazepam may be attributed to the observed increase of liver total lipids and fractions [21].

Antonenkov *et al.*, 2006 [22] stated that, administration of drugs caused marked reduction in the liver isoform of fatty acid binding protein (L-FABP), which facilitates the cellular uptake, transport and

metabolism of fatty acids. Therefore, a marked reduction in fatty acid uptake from plasma and a decrease in intracellular triglyceride level were detected in mice.

Also, Ugawa *et al.*, 2003 [23] stated that, the interaction of these drugs with some enzymes present in the microsomal part of the endoplasmic reticulum NADPH- cyt P450 mixed function oxidases which oxidize these drugs into active compounds. This oxidation is a necessary step in the metabolism of these drugs which convert the enzyme into inactive form and hence many hydroxylation reactions are inhibited (eg. hydroxylation of free fatty acids inhibited FFA and triglycerides biosynthesis in rats and hamsters). This is in agreement with the present results.

However, the increase of liver myristoleic acid (14:1) and palmitoleic acid (16:1) can be explained by the results obtained by Gnerre *et al.*, 2005 [24] who revealed that, interaction of these drugs with liver microsomal cytochrome P450 leads to diminishing the activity of the NADPH-cyt P450 and b5. The b5 enzyme catalyzes the elongation process of palmitic acid (the end product of fatty acid synthetase system to other longer chain fatty acid). Also cytochrome b5 catalyzed the desaturation process of saturated fatty acids which can be oxidized and inhibited free fatty acid and triglycerides biosynthesis.

Data in figures (8-14) showed that, acute and chronic administration of cloazepate and bromazepam significantly increased saturated and unsaturated free fatty acids especially archidonate (20:4) and behenic acid (docohexanoic acid 22:6). The increased concentration of unsaturated fatty acids especially archidonate are in accordance with those of Olimpia *et al.*, 2005 and Hok *et al.*, 2005[25]. They reported that, in hypoxia, the concentration of free unsaturated fatty acids increased rapidly in brain and the main increase was seen in unsaturated fatty acids: Oleate (C18: 1) and archidonate (20:4).

However, the increase of brain archidonic acid can be explained by Gnerre *et al.*, 2005 [26] who revealed that, interaction of these drugs with brain microsomal cytochrome P450 leads to diminishing of the activity of the NADPH. cyt P450 and b5. The b5 enzyme calalyzes the elongation process of archidonic acid to other longer chain fatty acids.

The accumulation of archidonic acid in brain tissue can also be explained by Andrew *et al.*, 2007 [27] who stated that, archidonic acid can initiate an important cascade of biochemical events leading to the production of eicosanoids (i.e. Prostaglandins, thromboxanes and leukotriens). In absence of oxygen, the enzymes responsible for the catabolism of archidonic acid is nil, leading to its accumulation in tissue.

Also, the increase in archidonic acid can be explained by Simmons *et al.*, 2004 [28] who stated that, in oxidative stress, the activity of enzymes primarily responsible for the catabolism of archidonic acid (cyclooxygenase and lipooxygenase is inhibited, leading to its accumulation in tissue.

Jianfei and Grigor, 2004 and Alexander *et al.*, 2007 [29] reported that, the polyunsaturated fatty acids linoleic acid (18: 2), linolenic acid (18:3), and arachidonic acid (20:4) are increased by superoxide and membrane lipid oxidation caused brain swelling. The increase of brain unsaturated fatty acids and reduction of liver free fatty acids can be explained by Adibhatla and Hatcher, 2007[30] who reported that, oxidative stress, results when generation of Ros (reactive oxygen species) exceeds the cell's capacity to detoxify them. The brain is believed to be particularly vulnerable to oxidative stress as it contains high concentration of polyunsaturated fatty acids that are susceptible to lipid peroxidation consumes relatively longer amounts of oxygen for energy production and has lower antioxidant defenses compared to other organs as liver.

Disturbance in free fatty acids are known to have a variety of detrimental effects on brain structure and function primarily due to

their ability to disrupt cell membranes, in addition to the adverse effect of free fatty acids on cell membranes, potential damage also follows the intracellular accumulation of their metabolites[31].

Pilitsis *et al.*, 2002[32] also explained the increase in brain FFA by benzodiazepines administration as a result of inhibition of mitochondrial Na+/ Ca2+ exchange, prevented the activation of phospholipases and FFA efflux. Also, Schnell *et al.*, 2007 [33] stated that, the G protein coupled receptor (GPR40) can be inhibited by benzodiazepines which has a role in generation of the medium and long chain FFA. These results are in line with the present results.

The increase in concentration of docohexanoic acid 22:6 (DHA) by administrating of drugs can be explained by Marcheselli *et al.*, 2003 and Kim, 2007 [34] who stated that, DHA, is the most abundant polyunsaturated fatty acid in the brain and is concentrated in aminophospholipid of cell membrane and increased in brain by oxidative stress. Also, Belayev *et al.*, 2005 [35] reported that, oxidative stress results in rapid accumulation of free fatty acids, including archidonic acid (20:4) and docohexanoic acid (22:6), through the cyclooxygenase/ lipoxygenase (Cox)/ Lox), pathways. Archidonic acid is metabolized to pro inflammatory and vasoactive eicosanoids (Prostaglandins, leukotriens, thromboxanes). It is also metabolized to anti-inflammatory lipoxins through the Lox pathway. DHA is metabolized by Cox/Lox into neuroproctin Dl which has a brain neuroprotective role. Inhibition of Cox/ Lox by drugs result in a rapid accumulation of free fatty acid archidonic acid and DHA [36].

Also, Andrew *et al.*, 2007 reported that inhibition of the catabolism of archidonic acid (20:4) and docohexanoic acid (22:6) increased the atherogenic, carcinogenic and inflammatory properties, as it metabolized into three important compounds, prostaglandin,thromboxanes and leukotrienes which play an important role as a defense mechanism preventing free radicals or active oxygen species formed from drug complex as a normal byproduct from accumulating

in brain tissue, so the role of these compounds in protecting the brain is threatened by drug administration[37].

In conclusion

The two studied drugs share their effects on the central nervous system as they act at a GABA/ benzodiazepine/ barbiturate receptor complex.

The toxicity of the two drugs is generally associated with their bioactivation, the initial step of which is epoxidation by cytochrome P450.

Clorazepate is more toxic than bromazepam as it is converted in the body to oxazepam (which has a carcinogenic effect).

Abuse of clorazepate and bromazepam altered free fatty acids metabolism which believed to be a key event contributes to CNS injury.

Clinically, caution must be taken in the use of these drugs to prevent the undesirable effects and it should not be used without medical prescription.

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التغيرات التى تحدث فى الأحماض الدهنية نتيجة تعاطى عقاقير البنزوديازيبينات فى ذكور الجرذان البيضاء

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تهدف الدراسة إلى تقييم بعض التأثيرات الكيميائية الحيوية لمجموعة البنزوديازيبينات على الأحماض الدهنية الحرة فى كبد ومخ ذكور الجرذان البيضاء . وقد تم اختيار عقارين من هذه المجموعة هما عقار الكلورازيبات ممثلا لمجموعة البنزوديازيبينات طويلة المفعول ، وعقار البرومازيبام ممثلا لمجموعة البنزوديازيبينات قصيرة المفعول لإجراء هذه الدراسة .

تم تقسيم الجرذان البيضاء إلى مجموعتين رئيسيتين ، كل منها قسمت إلى ٤ مجموعات ، ثلاثة منها لمعالجتها بالعقاقير (تم فيها حقن الجرذان البيضاء بجرعتين حادتين وجرعة مزمنة) والمجموعة الرابعة استخدمت كمجموعة ضابطة .

وكان من أهم نتائج الدراسة : أن وجد أن إساءة استخدام عقارى الكلورازيبات والبرومازيبام وخاصة فى الجرعات المزمنة أدى إلى انخفاض تركيز الأحماض الدهنية الحرة (المشبعة وغير المشبعة) فى كبد الجرذان البيضاء . وقد اختلف تأثير هذين العقارين فى مخ الجرذان البيضاء ، حيث أدى حقن كل من الجرعات الحادة والمزمنة منهما إلى زيادة تركيز الأحماض الدهنية الحرة - خاصة الأحماض الدهنية غير المشبعة - نتيجة لتثبيط الإنزيمات المسئولة عن هدم هذه الأحماض . أدى ذلك إلى حدوث خلل فى عملية هدم وبناء الأحماض الدهنية ، مما يسبب حدوث تشوهات فى مخ وكبد الجرذان البيضاء . حيث إن هدم هذه الأحماض يؤدى إلى منع تكوين بعض المركبات البيولوجية الهامة (مثل البروستاجلاندين ، والليكوترين ، والثرومبوكسان) والتى تحمى الجسم من بعض الالتهابات والأورام وحدوث الجلطات .