EFFECT OF MORPHINE SULPHATE ON TOTAL LIPIDS AND TRIGLYCERIDES CONTENTS IN SERUM AND BRAIN REGIONS OF RAT

OTHMAN A. AL SAGAIR*

SUMMARY : The present work was undertaken to examine the effect of acute (35 mg/kg b.w.) and chronic (15-75 mg/kg b.w.) doses of morphine sulphate as well as withdrawal of the drug on total lipids and triglycerides levels in adult male albino rats (Ratus norvegicus) in an attempt to explore the changes occurring in serum levels and different brain regions.

The data of the present work revealed occurrence of highly significant increases in total lipids of serum and different brain regions after acute and chronic administration of morphine and during drug withdrawal.

The acute administration of morphine and during drug withdrawal led to significant increases in the triglycerides content of serum and in most the studied brain regions. On the other hand, after chronic administration of morphine, levels of triglycerides returned approximately to the normal values in serum, cortex, striatum and pons, while in cerebellum and thalamus- hypothalamus triglycerides level showed significant increases.

Finally, the data presented here illustrate that morphine is capable of having a marked effect on lipids of serum and of different brain regions in rats.

Key Words: Morphine sulphate, total lipids.

INTRODUCTION

Acute and chronic morphinization enhanced the process of gluconeogensis in rat liver *in vivo* (24). This effect may be explained on the basis that morphine enhances lipolysis in rat adipose tissue (25). On the other hand, morphine did not exhibit a lipolytic activity in isolated rat adipocytes (9), while alternation of the membrane lipid phase transition may be flindaniental to the action of morphine in brain mitochondria (10). However, after 36 hours of morphine or stadol administration, drug tolerance seemed to develop by the eventual decline in hepatic total lipids content (7). Lamb and Dewey (12) showed that morphine induced elevations of triglyceride formation correlated well with a rise in microsomal phosphatidate phosphohydrolase activity. Also Bryant *et al.* (5) demonstrated that circulating triglyceride levels were elevated following morphine pellet implantation. Conversely, Ali (1) found that morphine produced dose-dependent and significant decrease in triglycerides concentrations.

Okasha (15) found that administration of morphine leads to increases in total lipids, and triglycerides in rat serum. On the other hand, Selevich and Lelevich (20) found that chronic morphine decreased the levels of total lipids in the cortex of hemispheres. Three days after withdrawal the cerebellum and hemisphere cortex demonstrated a reduced level of total lipids. While, seven days after morphine withdrawal the level of total lipids was

*From Department of Medical Microbiology, Faculty of Science, El Qassim University, El Qassim KSA. P.O. Box 237, Bureida, Saudi Arabia.

diminished in the brain stem. However, Hula *et al.* (11) found that levels of total lipids were diminished in the brain of rats with morphine physical dependence.

The present study was designed to provide more information on the effect of acute and chronic administration of morphine as well as drug withdrawal and its effects on the total lipids and triglycerides contents in serum and specific brain regions of rats.

MATERIALS AND METHODS

Drug

The drug used during the experiments of this study was morphine sulphate, which was obtained from Egypt Company for pharmaceutical drugs, El-Mataria, Cairo, Egypt and diluted by 0.9% NaCl solution. The drug was injected intraperitoneally (i.p.).

Experimental animals

Adult male albino rats *(Rattus norvegicus)*, weighing from 120-170 g, were used throughout the experiments. Animals were put on standard diet and water was supplied *ad libitum*. Rats were divided into six main groups each of 5 rats, which were acute, chronic, and withdrawal group. The acutely treated animals received acute dose of morphine sulphate (35 mg/kg body weight). Treated rats were sacrificed by decapitation 2 hrs after injection. In the chronic group, animals received two injections of morphine sulphate per day, commencing with a dose of 15 mg/kg. Each subsequent injection was increased by 15 mg/kg/day until a dose of 75 mg/kg, was attained on the fifth day. This dose was maintained for one additional day thus each rat received a total of 12 injections. Group of these treated animals were sacrificed by decapitation, 2 hrs after the last maintenance dose of morphine was given (chronic group). The other four groups (withdrawal groups) were treated in the same way as chronic group. After drug administration was terminated, animals of four groups were sacrificed at time intervals of 12, 24, 48 and 96 hrs after the last chronic dose. Control group (5 rats) was injected with equivalent volume of 0.9% NaCl (saline). Rats of this group were sacrificed by decapitation 2 hours after injection. Immediately, after sacrifice, brains of all rats were excised from the skulls and placed on iced-glass for dissection into specific regions namely, cortex, cerebellum, striatum, thalamus-hypothalamus and pons. All brain regions were weighed and kept in the deep freezer at -20°C until they were needed for analysis.

Methods

Tissue extracts for lipid species were obtained according to the method of Folch *et al.* (8). Each brain region was homogenized in chloroform: methanol (2:1). Homogenization was carried out using 20 ml of the chloroform: methanol mixture per gram of tissue. The solvent (organic layer) was separated from the homogenized tissue by centrifugation at 2500 r.p.m. for 10 minutes with addition of extra methanol (0.2 ml) to lower the specific gravity of the homogenate. The organic layer was washed with 0.2 ml of saline solution (0.9% NaCl) and then the mixture was separated into aqueous and organic layers by centrifugation at 2000 g for 1-2 min. Then the upper (aqueous) and lower (chloroform) layers were separated. To aid separation of the phases without contamination or loss of the lower phase, after removing the majority of the upper phase, the interface was washed with 1.5 ml of chloroform: methanol: water (3: 48:47) 3 times without mixing. Methanol was then added until the interface become miscible. The chloroform: methanol were evaporated to dryness and reconstituted in 1 ml of chloroform: methanol (2:1) and kept frozen at -20°C until analysis of total lipids and triglycerides.

Total lipids were determined according to the sulfo-phospho-vanillin calorimetric method, using the cal-test diagnostics, Inc. technique. The Cal-test diagnostics were provided by CDI 5751 Chino Avenue, Chino, CA 91710 U.S.A. Triglycerides were determined according to enzymatic colourimetric methods. The reagent enzymatic kits were obtained from Quimica Clinica Aplioada (QCA), S.A. (CN-340, Km 1081 - P.O. Box 20 Spain).

RESULTS

Total lipids

The study of the effects of acute administration of morphine on the total lipids revealed that their levels were significantly increased in cortex, cerebellum, thalamus-hypothalamus and pons ($F=4.94$, $P<0.01$; $F=2.24$, $P<0.05$; $F=3.79$, $P<0.01$ and $F=5.09$, $P<0.001$ respectively). Also the chronic administration of the drug led to highly significant increases in the content of total lipids in the four mentioned brain regions (cortex, $F=7.35$, $P<0.01$; cerebellum, $F=6.72$, $P<0.001$; thalamus-hypothalamus, $F=4.0l$, $P<0.001$ and pons, $F=5.29$, $P<0.01$). However, non-significant increases were recorded in total lipids levels in striatum and serum after acute and chronic administration of the drug. Interestingly, the increases observed after acute and chronic administrations of morphine were maintained during the four days of drug withdrawal especially in serum, cortex, thalamus-hypothalamus and pons. On the other hand, striatal tissues showed non-significant increases during morphine withdrawal except after the fourth day of drug withdrawal, whereas the total lipid content showed significant increase ($F=l.14$, $P<0.05$). However, in cerebral tissue total lipids contents exhibited a highly significant increase ($F=7.47$, $P<0.001$) only after 12 hrs of drug withdrawal (Tables 1 and 2; Figure 1).

Table 1: Effect of acute and chronic administration of morphine sulphate and its withdrawal on levels of total lipids, triglycerides in serum of adult male albino rats.

Parameter	Animal group	Hours of withdrawal	Mean ± S.E as absolute value	Mean ± S.E as % of control	% of control
Total lipids	Control		47.35 ± 3.26	100 ± 6.88	-
	Acute		55.25 ± 3.56	116.68 ± 7.51	116.68
	Chronic		54.03 ± 3.96	114.12 ± 8.36	114.12
	Withdrawal	12	61.81 ± 5.47	130.55 ± 11.56	130.55
		24	81.95 ± 5.14	173.08 ± 10.86	173.08**
		48	74.32 ± 4.22	156.96 ± 8.93	156.96**
		96	86.18 ± 1.45	182.02 ± 3.07	182.02***
Triglycerides	Control		128.57 ± 2.69	100 ± 2.09	-
	Acute		153.41 ± 5.77	119.31 ± 4.49	119.31**
	Chronic		114.94 ± 5.32	89.40 ± 4.13	89.40
	Withdrawal	12	153.84 ± 5.06	119.65 ± 3.93	119.65**
		24	162.63 ± 4.77	126.49 ± 3.71	126.49**
		48	136.55 ± 2.18	106.21 ± 1.69	106.21
		96	141.31 ± 6.00	109.91 ± 4.97	109.91*

Absolute values measured by mg / 100 ml
Number of animals in each group = 5
Non significant (P > 0.05)

* Significant (P < 0.05)
** Highly significant (P < 0.01)
*** very highly significant (P < 0.001)

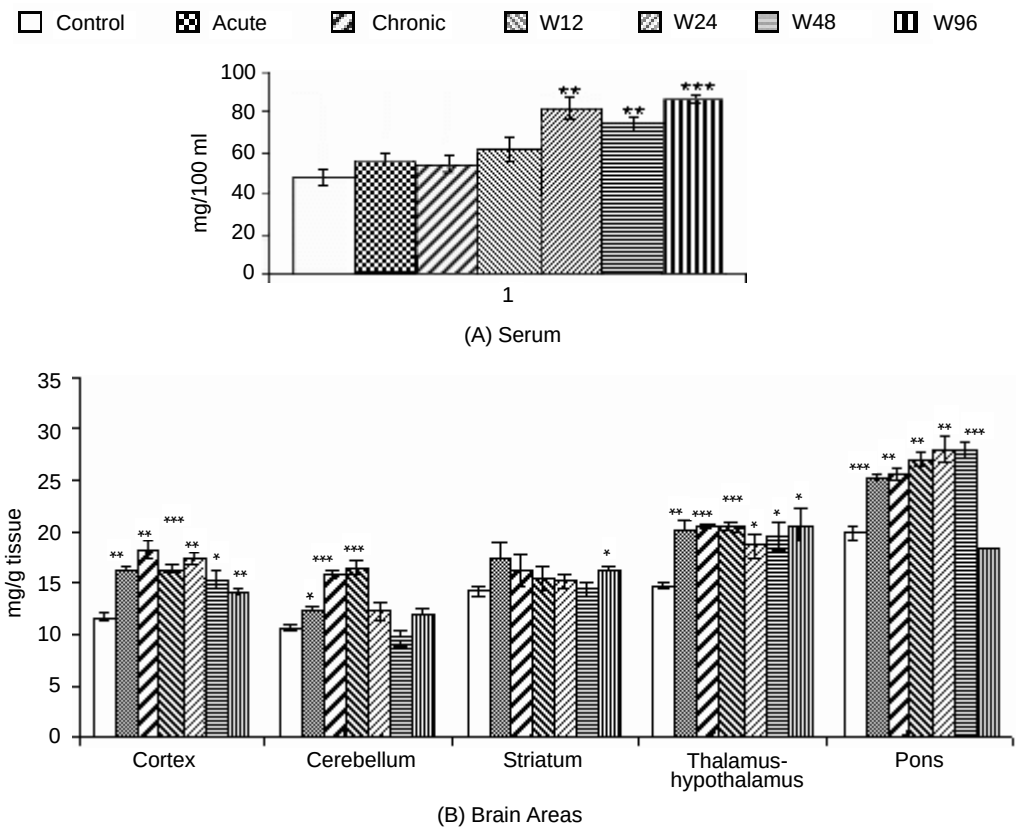
Triglycerides

Examination of triglycerides levels after acute administration of morphine revealed significant increases in serum and different in at brain regions except in striatum where the increase in the triglycerides contents were non-significant. On the other hand, after chronic administration of the drug, animals developed tolerance to the drug as indicated by triglycerides levels bringing then values approximately to the normal in serum, cortex, striatum and pons. However, tolerance which developed after chronic administration of morphine was incomplete, in cerebral and thalamic-hypothalamic tissues, where the triglyceride levels showed significant increases (F=2.90, P<0.01 and F=3.30, P<0.01 respectively). The data also indicated that triglycerides were significantly increased in serum after 12 (F=3.76, P<0.01), 24 (F=5.07, P<0.01) and 96 (F=1.90, P<0.05) hrs of drug withdrawal. In the brain regions, this increase was only significant in the cortex (F=5.19, P<0.01 and F=4.57, P<0.01) and pons (F=2.21, P<0.05 and F=9.32, P<0.01) after 12 and 24 hrs respectively of morphine withdrawal and in thalamus-hypothalamus after 24 (F=5.69, P<0.01), 48 (F=3.90, P<0.01) and 96 (F=10.55, P<0.001) hrs of drug withdrawal. On the other hand, non-significant changes were recorded in the triglycerides contents of cerebral and striatal tissues during all periods of drug withdrawal. However, the non-significant changes in the cortex and pons after 48 and 96 hrs of drug withdrawal and in striatum and cerebellum through the period of drug withdrawal indicated signs of tolerance to the drug (Tables 1 and 3, Figure 2).

DISCUSSION

Although the literature contains many references on the effect of morphine and other narcotics on the lipid metabolism (3-5,7,11,12,15,20), few direct estimates of the effect of morphine on brain regions total lipids and triglycerides have been reported before. The present data revealed occurrence of significant increases in total lipids contents in most studied brain regions after acute and chronic administration of morphine, while non-significant increases were recorded in the total lipids level of serum and striatal tissue. Supporting evidence in favor of the

Figure 1: Effect of acute and chronic morphine sulphate administration and its withdrawal on the level of total lipids (A) serum and (B) brain areas of adult male albino rats. Each bar represents mean of absolute value ±S.E. of ten rats per group. Statistically significant from control *P < 0.05, **P < 0.01, ***P < 0.001.



increase recorded in total lipid levels after morphine administration, which might reflect increased accumulation of lipids, is supplied by Thureson-Klein *et al.* (22), Okasha (15) and El Daly (7). Morphological findings have also demonstrated that liver is filled with round lipid droplets after morphine administration (14, 22). Thureson-Klein *et al.* (22) also observed a large increase in lipid droplets in hepatocytes after morphine treatment. Lipid droplets accumulation was thought to be due mainly to the increase in the triglycerides level within the hepatocytes (21). The last authors also indicated that, morphine disrupts cellular membranes by interacting with membrane components and altering membrane phosphoglyceride content which may suggest a morphine-dependent rise in membrane phosphoglyceride biosynthesis. Presumably this might reflect the attempt of the hepatocyte to repair injured membranes by generating new membrane phosphoglyceride components.

These observations suggest that there may be several biochemical changes that can lead to lipid accumulation in the different brain regions after acute and chronic morphine administration as occurred in the present work. It was demonstrated that adrenergic stimulation of the central or sympathetic nervous system might increase the mobilization of free fatty acids from peripheral depots. At the same time, there may be increased synthesis of triglycerides and decreased ability to mobilize triglycerides from brain tissues.

Conversely to the present investigation, Selevich and Lelevich (20) indicated that chronic morphine sulphate administration (for 7 days in increasing doses of 20 to 40 mg/kg body weight) decreased the level of total lipids in the cortex of the hemisphere in rats. The reduction in total lipids content of the brain was also confirmed by Hula *et al.* (11); who stated that the level of total lipids was diminished in the brain of rats with morphine dependence. This may

Table 2: Effect of acute and chronic administration of morphine sulphate and its withdrawal on the level of total lipids in different brain regions of adult male albino rats.

Parameter	Brain regions	Animal group	Hours of withdrawal	Mean ± S.E as absolute value	Mean ± S.E as % of control	% of control
Total lipids	Cortex	Control		11.65 ± 0.42	100 ± 3.57	-
		Acute		16.13 ± 0.63	138.39 ± 5.45	138.39**
		Chronic		18.31 ± 0.81	157.13 ± 15.53	157.13**
		Withdrawal	12	16.43 ± 0.49	140.99 ± 4.17	140.99***
			24	17.42 ± 0.55	149.47 ± 4.75	149.47**
			48	15.34 ± 0.99	131.64 ± 8.48	131.64*
			96	14.11 ± 0.34	121.14 ± 2.95	121.14**
	Cerebellum	Control		10.51 ± 0.14	100 ± 1.31	-
		Acute		12.27 ± 0.52	116.81 ± 4.99	116.81*
		Chronic		15.91 ± 0.36	150.43 ± 3.46	150.43***
		Withdrawal	12	16.60 ± 0.70	158.05 ± 6.64	158.05***
			24	12.38 ± 0.73	117.80 ± 6.91	117.80
			48	9.74 ± 0.69	92.68 ± 6.58	92.68
			96	12.02 ± 0.50	114.42 ± 4.80	114.42
	Striatum	Control		14.19 ± 0.43	100 ± 3.04	-
		Acute		17.67 ± 1.31	124.53 ± 9.23	124.53
		Chronic		16.26 ± 1.49	114.59 ± 10.49	114.59
		Withdrawal	12	15.46 ± 1.25	108.95 ± 8.78	108.95
			24	15.23 ± 0.65	107.33 ± 4.61	107.33
			48	14.39 ± 0.70	101.41 ± 4.97	101.41
			96	16.17 ± 0.50	113.92 ± 3.55	113.92*
	Thalamus-hypothalamus	Control		14.83 ± 0.27	100 ± 1.79	-
		Acute		20.27 ± 0.88	136.65 ± 5.92	136.65**
		Chronic		20.60 ± 0.24	138.84 ± 1.60	138.84***
		Withdrawal	12	20.51 ± 0.35	138.24 ± 2.36	138.24***
			24	18.61 ± 1.17	125.44 ± 7.90	125.44*
			48	19.50 ± 1.45	131.41 ± 9.80	131.41*
			96	20.64 ± 1.65	139.11 ± 11.09	139.11*
	Pons	Control		19.91 ± 0.71	100 ± 3.55	-
		Acute		25.32 ± 0.35	127.18 ± 1.75	127.18***
		Chronic		25.53 ± 0.61	128.24 ± 3.07	128.24**
		Withdrawal	12	27.07 ± 0.65	136.00 ± 3.25	136.00**
			24	28.03 ± 1.35	140.80 ± 6.81	140.80**
			48	28.02 ± 0.79	140.76 ± 3.93	140.76***
			96	18.42 ± 0.30	92.57 ± 1.51	92.57

Absolute values measured by mg / g. tissue
Number of animals in each group = 5
Non significant (P > 0.05)

* Significant (P < 0.05)
** Highly significant (P < 0.01)
*** very highly significant (P < 0.001)

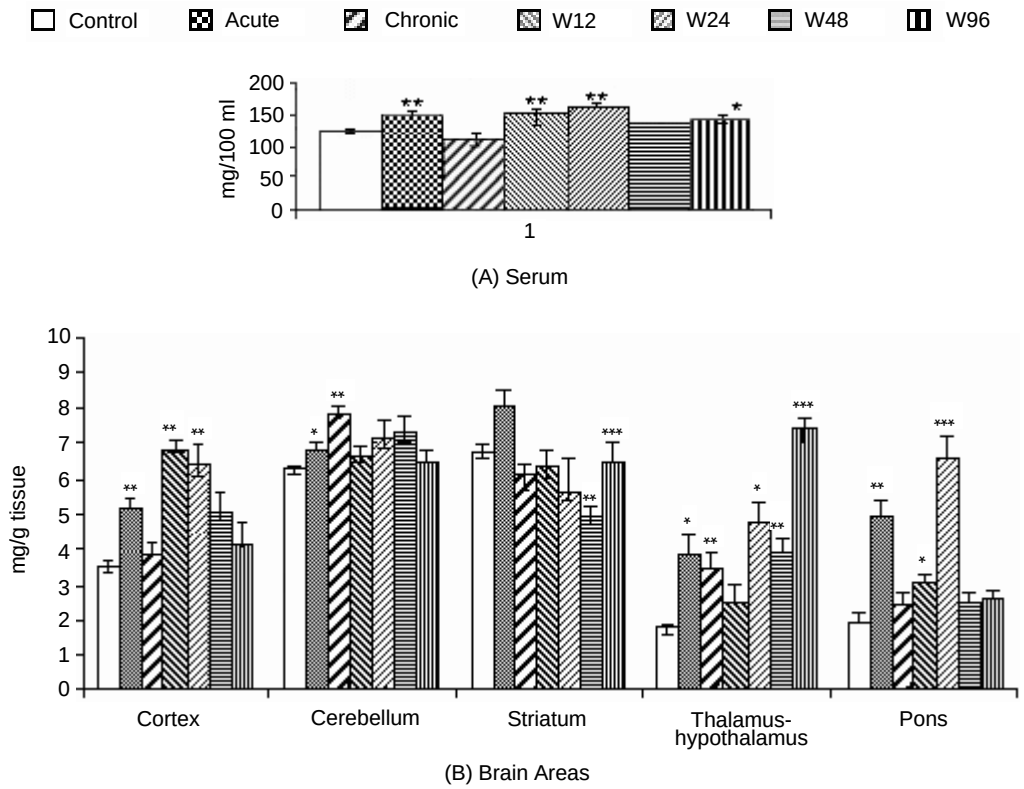
Table 3: Effect of acute and chronic administration of morphine sulphate and its withdrawal on the level of triglycerides in different brain regions of adult male albino rats.

Parameter	Brain regions	Animal group	Hours of withdrawal	Mean ± S.E as absolute value	Mean ± S.E as % of control	% of control
Triglycerides	Cortex	Control		3.62 ± 0.15	100 ± 4.13	-
		Acute		5.27 ± 0.29	145.66 ± 8.01	145.66**
		Chronic		3.91 ± 0.29	107.96 ± 8.01	107.96
		Withdrawal	12	6.84 ± 0.42	189.25 ± 11.66	189.25**
			24	6.46 ± 0.55	178.66 ± 15.21	178.66**
			48	5.03 ± 0.62	139.08 ± 17.07	139.08
			96	4.13 ± 0.55	114.23 ± 15.22	114.23
	Cerebellum	Control		6.28 ± 0.11	100 ± 1.81	-
		Acute		6.77 ± 0.22	107.85 ± 3.49	107.85*
		Chronic		7.76 ± 0.28	123.71 ± 4.42	123.71**
		Withdrawal	12	6.63 ± 0.33	105.69 ± 5.29	105.69
			24	7.18 ± 0.57	114.45 ± 9.11	114.45
			48	7.30 ± 0.50	116.35 ± 7.97	116.35
			96	6.40 ± 0.30	102.00 ± 4.85	102.00
	Striatum	Control		6.75 ± 0.13	100 ± 2.82	-
		Acute		8.09 ± 0.61	119.78 ± 9.04	119.78
		Chronic		6.13 ± 0.26	90.86 ± 3.81	90.86
		Withdrawal	12	6.34 ± 0.43	93.89 ± 6.34	93.89
			24	5.66 ± 0.89	83.84 ± 13.18	83.84
			48	4.92 ± 0.33	72.89 ± 4.85	72.89**
			96	6.43 ± 0.68	95.26 ± 9.98	95.26
	Thalamus-hypothalamus	Control		1.83 ± 0.14	100 ± 7.73	-
		Acute		3.90 ± 0.60	213.87 ± 33.15	213.87*
		Chronic		3.57 ± 0.29	195.83 ± 16.04	195.83**
		Withdrawal	12	2.54 ± 0.37	139.49 ± 20.11	139.49
			24	4.84 ± 0.50	265.14 ± 27.39	265.14**
			48	3.89 ± 0.26	213.25 ± 14.10	213.25**
			96	7.42 ± 0.25	406.37 ± 13.46	406.37***
	Pons	Control		2.03 ± 0.20	100 ± 9.79	-
		Acute		4.95 ± 0.45	243.88 ± 22.14	243.88**
		Chronic		2.43 ± 0.30	119.70 ± 14.55	119.70
		Withdrawal	12	3.13 ± 0.14	154.27 ± 7.02	154.27*
			24	6.67 ± 0.63	328.35 ± 30.88	328.35***
			48	2.41 ± 0.29	118.86 ± 14.55	118.86
			96	2.51 ± 0.19	123.46 ± 9.41	123.46

Absolute values measured by mg / g. tissue
Number of animals in each group = 5
Non significant (P > 0.05)

* Significant (P < 0.05)
** Highly significant (P < 0.01)
*** very highly significant (P < 0.001)

Figure 2: Effect of acute and chronic morphine sulphate administration and its withdrawal on the level of triglycerides (A) serum and (B) brain areas of adult male albino rats. Each bar represents mean of absolute value ± S.E. of ten rats per group. Statistically significant from control *P < 0.05, **P < 0.01, ***P < 0.001.



be due to the fact that the doses of morphine were different than those we have used and which suggest that the effect of morphine on total lipids content may be dose related.

Alternatively, morphine may influence serum total lipids production in an indirect manner since evidences (25) suggest that morphine doses increase the lipolytic activity in rat adipose tissue and also the drug increase the amount of fatty acid release from isolated epididymal fat pads of rats by a direct effect on adipose tissue. Therefore, the morphine-dependent release of fatty acid (25) and alteration of the membrane lipid phase transition in the brain mitochondria (10) may partly explain the morphine-induced rise in serum total lipids levels.

Interestingly, the elevation of fatty asids thus observed after acute and chronic administration of morphine was maintained during the four days of drug withdrawal in serum and most studied brain regions.

Two explanations could be proposed for the action of morphine on lipid metabolism in rat. Firstly, previous experiments *in vitro* by Sablé-Amplis *et al.* (19) showed that morphine reduces the lipolytic activity of adipose tissue and this might explain the lowering of free fatty acids induced by morphine *in vivo*. In chronically treated rats, morphine *in vitro* does not reduce the lipolytic activity. *In vivo,* tolerance was noted towards the depressive effect of the drug on the level of plasma free fatty acids. Finally, the action of morphine on plasma free fatty acids might result from this direct effect on adipose tissue cells (19). Secondly, the changes in plasma free fatty acids levels could be partially linked to the action of morphine on the adrenals in the case of acutely or chronically treated animals. Indeed, in acutely or chronically morphinized rats Sablé-Amplis *et al.* (18) have noticed an increase in the secretion of corticosterone and this agrees well with the immediate effect of the drug on plasma free fatty acids and with the fact that in chronically treated rats the level of free fatty acids was significantly lower than in normal rats. But this relation does not appear very clear after withdrawal because in abstinent

rats a new dose of morphine stimulates free fatty acids mobilization and simultaneously induces an increase in plasma corticosterone concentration (19).

To conclude, the effects of morphine on plasma lipids may be explained by a direct depressive effect of the drug on the lipolytic activity of the adipocytes and partly the changes occurring in the secretory activity of adrenals (19).

Studies performed by Selevich and Lelevich (20) indicated that three days after the withdrawal of morphine, the cerebellum and the hemisphere cortex showed a reduced level of total lipids. On the other hand, our study showed that serum and most brain regions total lipids content exhibited significant increase after withdrawal of morphine. These findings suggest that the effect of morphine withdrawal is dependent on the dose of the drug used to produce chronicity. It is difficult to estimate the mechanism of effect of morphine withdrawal especially to conclude that the secretion of corticosterone in adrenals by morphine (19) have contributed to the stimulatory and inhibitory effects on total lipid synthesis, or that morphine reacts indirectly with total lipids synthesis in the brain (11, 20). It has been indicated in the light of the present observations as well as of those reported in the literature, fluctuations occurring in the total lipid concentrations in serum and brain after withdrawal of morphine may be related to the dose of chronicity and the time of drug withdrawal.

The occurrence of marked elevations in triglycerides' levels reported in the present study in blood and different brain regions after morphine administration and during drug withdrawal especially after 12 and 24 hrs are concordant with the findings of several authors (5,6,12,15,21,22). Bryant *et al.* (5) demonstrated that circulating triglycerides levels were elevated following morphine pellet implantation. Okasha also, (15) indicated that the triglycerides levels in serum showed highly significant increases after 1, 12 and 24 hrs of either morphine or stadol administration. However, the last author reported that the triglyceride content of serum showed non-significant changes after 36 hrs of both drugs injection.

Sun *et al.* (21) suggested that morphine may disrupt hepatocellular membrane function (triglyceride transport) by binding to membrane components (phosphoglycerides) and inhibitory oleoyl CoA: 1-acyl-glycerophosphocholine, a key enzyme in the metabolism of membrane phosphoglycerides.

ElDaly (7) revealed that morphine or stadol injection alters hepatic triglyceride metabolism and content in a manner similar to other liver toxins (13). These observations suggest that morphine and stadol may be hepatotoxic to rats (7). This hypothesis is supported by the observation that morphine injection rapidly elevates rat serum GOT and GPT levels (7,15). Therefore, the abnormally high levels of serum transaminases in morphine exposed men (17) may reflect a hepatotoxic effect of morphine.

Lamb and Dewey (12) showed that morphine induced elevation in triglycerides formation correlated well with a rise in microsomal phosphatidate phosphohydrolase activity. In this regard, phosphatidate phosphohydrolase is unique since its reaction product, diglyceride, is utilized for both triglyceride and phosphoglyceride biosynthesis under various conditions or by an indirect manner by increasing glycocorticoids, which leads to increase the activity of phosphatidate phosphohydrolase enzyme.

Deficiency of thyroid hormones was shown to affect triglyceride transport leading often to hypertriglyceridemia (2). It was also indicated that thyroid hormones greatly affect enzymes involved in the fatty acid and glycerolipid synthesis in tissues (16). The effect of morphine T_3 and T_4 levels were further demonstrated in experiments carried out by Okasha (15). Their data revealed that these hormones, are decreased, which may support the increase in triglycerides content in serum and brain regions observed in this work.

On the other hand, the non-significant changes or decreases recorded in the present work after chronic morphine administration or drug withdrawal in the triglyceride content exhibiting a level almost matching that of control animals in serum and different brain regions may indicate that tolerance might have developed. In support of these observations, Lamb and Dewey (12) indicated that decreases in the formation and level of liver triglycerides in morphine implanted mice that received two daily i.p. doses of morphine (100 mg/kg) might suggest morphine tolerance development with respect to liver fat content and production. Also, Okasha (15) and El Daly (7) indicated that the triglycerides content showed non-significant changes after 36 hrs of morphine or stadol injection exhibiting a level almost matching that of control animals which might suggest the development of tolerance.

Finally the data presented here illustrate that morphine is capable of having a marked effect on serum and brain total lipids and triglycerides (1,11,15,20).

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Correspondence:
Othman A. Al Sagair
Medical Microbiology Department,
Faculty of Science,
El Qassim University,
El Qassim KSA. P.O. Box 237,
Bureida, SAUDI ARABIA.
e-mail: othman133@hotmail.com