EFFECT OF COCAINE INTAKE ON THE DEVELOPMENT OF FATTY LIVER IN RATS FED A LOW-PROTEIN DIET[1,2]

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SUMMARY

It has been shown that cocaine given in the diet is able to reduce fat accumulation in the liver of protein-malnourished rats (*Arch. Latinoamer. Nutr. 19:* 69-79, 1969). This study was, therefore, designed to approach the probable action of the drug upon the process (increased triglycerides synthesis and normal/decreased capacity for exporting triglycerides from the liver into the blood) which leads to an increased fat accumulation in the liver under this physiological condition. To accomplish this purpose, the total and fractioned lipids in the liver and total lipids as well as lipoproteins in serum were determined in female Wistar rats (120-130 g) fed either a 5% corn protein diet or a 20% casein diet, with and without cocaine (15 mg HCl cocaine/10 g of diet) for 18 days.

The results, aside from confirming the reduction ($p < 0.001$) of fat accumulation in the liver of rats fed on the 5% corn protein diet plus cocaine, revealed that this drug also reduced triglycerides concentration (significantly, ($p < 0.001$, when results were calculated by difference, and slightly reduced them when results were determined) in this tissue. Nevertheless, it increases both total lipids ($p < 0.05$) and trigly-

Manuscrito modificado recibido: 6-3-87.

1 This investigation was supported by the Association of Pharmaceutical Laboratories of Peru, through a grant from the Instituto Hipólito Unanue. Partial support was also obtained from the Organization of American States (OAS).

2 A preliminary report of some of the results of this research work were presented by one of the authors[4], to obtain the title of Pharmaceutical-Chemist at the Programa de Farmacia y Bioquímica, Universidad Nacional Mayor de San Marcos (UNMSM), Lima, Peru.

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cerides-rich pre-beta lipoprotein ($p < 0.10$) levels in the serum of these animals. Otherwise, these lipidic parameters were not modified by cocaine in rats on the 20°/o casein diet, except for the total cholesterol level in liver and the cholesterol-rich beta lipoprotein level in serum. Respectively, these were slightly and significantly ($p < 0.001$) reduced by the drug.

These evidences and their statistical significance suggest that cocaine given chronically with the 5°/o corn-protein diet for 18 days, reduces at least partially (other biochemical event in the liver could have also accounted for its effect at this level) the liver fat accumulation, by increasing the triglycerides output from the liver into the blood. Elsewhere, cocaine appears to be able to induce some metabolic alterations in the hepatic cholesterol of well-nourished rats.

INTRODUCTION

Some years ago we reported (1) that cocaine given a 5°/o corn-protein diet for four weeks to growing rats reduces the accumulation of fat in the liver. The reduction phenomenon of the liver lipids concentration was not seen in animals fed a 20°/o casein diet, plus the drug. In an effort to explain this finding, we searched for a possible association between the metabolism of cocaine after a long-term pretreatment with the drug, and its preventive effect on fat deposition in this tissue *via a de novo* increased synthesis to methyl groups to form choline, the molecule of which has been claimed to hold lipotropic properties (2). Keeping this hypothesis in view, we studied the enzymatic N-demethylation of cocaine which yields formaldehyde and norcocaine and showed that it takes place preferently in the liver (3). Furthermore, we also observed that a long-term pretreatment with the drug induces both much higher increases in the activity of this reaction in rats under a protein-deficiency condition, than in other protein-sufficient ones (4) with no significant increments of the contents of choline isolated from the liver lipids in rats fed a 5°/o corn-protein diet (5). Although these results are consistent with our above-mentioned hypothesis, the latter result –which appears not to offer conclusive evidence for the role of cocaine as a source of methyl groups– suggests, however, that the drug, as inductor of the hepatic drug microsomal enzymatic system when it is given orally (3, 4), might play some role in the hepatic metabolism of phospholipids. This, in turn, would lead to an increased synthesis of intracellular membranes concerned with the lipoprotein synthesis (6).

Therefore, to provide basic information as to the role of cocaine in reducing fat deposition in protein-malnourished rats, we have found it plausible to approach the metabolic condition of lipids in both liver and serum of rats fed both a 5°/o corn-protein diet, and a 20°/o casein diet. In performing the experiments we have taken into account the following fact. Increased triglycerides concentration, the main disturbation of the liver lipid metabolism in rats (7) and humans (8) under protein malnutrition, might be affected, interfering with its metabolism/secretion by cocaine administered chronically and reflected both in its concentration in this tissue, and its mobilization into the blood.

Thus, in this preliminary work we determined total and fractioned lipids in liver and total lipids as well as lipoproteins in serum. Results of

our research work revealed reduction of hepatic triglycerides concentration by cocaine, with concomitant increase of triglycerides-rich pre-beta lipoprotein level in serum. These findings confirm, at least partially, the important role played by cocaine in protecting the liver against fat accumulation in protein-malnourished rats.

MATERIAL AND METHODS

Two groups of Wistar female rats from the animal colony of the Instituto de Bioquímica y Nutrición, with an initial weight of 120-130 g were used. These were housed in galvanized wire-mesh cages in an air-conditioned room with a 12 hr (0.9.00 to 21.00) light-dark cycle. Before experimentation, both groups (n = 12) of rats were allowed free access to either a 5%/o corn-protein diet or a 20%/o casein diet for five days, so they could adjust themselves to the new dietary regime. After this period, each group was divided into two other groups (n= 6) according to whether they were to be fed a 5%/o corn-protein diet with or without cocaine and a 20%/o casein diet with or without cocaine. The composition of these diets has been previously reported (1). However, within a brief term, proteins were provided from a corn meal brand commercially available (corn-protein diet) and from a purified casein protein (Nutritional Biochemicals Co., Cleveland, Ohio, USA) (casein diet). These diets were isocaloric and cocaine hydrochloride (Merck Darmstadt, F.R.G.) (cocaine groups) was added in the proportion of 15 mg/10 g of diet. Both diets and tap water were supplied *ad libitum* for 18 days. Food consumption was registered every two days and the rats weighed simultaneously. On the last day of the experimental period, the diets were removed and the rats were sacrificed by decapitation under a light ether anesthesia. Blood was collected for analysis of serum lipids, protein and lipoprotein. The liver was removed, washed with physiological saline solution (NaCl 0.9%/o), blotted, weighed and frozen at -20°C until the lipids were analyzed. To accomplish this step, a portion of the stored liver tissue was homogenized with ice-cold phosphate buffer (potassium salt) pH 7.4. Determination of total lipids was performed in aliquots of liver homogenate, according to the procedure of Frings and Dunn (9). Triglycerides and organic phosphorus in the liver homogenates were determined according to Bartlet (10) and Soloni (11) methods, respectively. Phospholipids were calculated from P values using a factor of 25. Total cholesterol was measured with a commercially available test (cholesterol enzymatic method, Merckotest, Kit No. 14350, Merck Darmstadt, F.R.G.) (12) according to Richmond's method (13). Lipoproteins in serum were then separated in beta, pre-beta and alpha fractions by electrophoresis on 76 x 25 mm cellulose acetate plates (Titan III-Lipo; Helena Laboratories, Beautmont, Tex. USA) at 250 volts for 25 min, according to a procedure established by the Helena Laboratories (14). Tinction was made with oil red, and evaluation of the percentage of every fraction in a densitometer R-110 (Beckman Inst. Inc. USA). Protein in serum and liver homogenates was determined according to Lowry *et al.* (15). Protein efficiency ratio (PER) or body weight diminution/g of protein consumed, were calculated at 15 days of dietary treatment, according to Osborne, Mendel and

Ferry (16) after determining the N in food by the Kjeldahl method (17).

RESULTS

The dietary and nutritional parameters after cocaine pretreatment (18 days) of growing female Wistar rats on either 5°/o corn-protein diet or 20°/o casein diet are presented in Table 1.

Other results obtained in the liver (expressed per g of wet tissue or per g of protein) and in serum (expressed per g of serum protein) are shown in Table 2 and Figure 1, respectively. Taken together, these results confirm and extend a previous finding (2), i.e., that cocaine administered to growing rats of both sexes with a 5°/o corn-protein diet, reduces fat accumulation in the liver (Table 2). These findings also demonstrate that there is no significant decrease of the total cholesterol and phospholipids levels in this tissue. With regard to these results, we note both a significant increase ($p < 0.05$) of the level of total lipids and a notorious increase ($p < 0.10$) of the triglycerides-rich pre-beta lipoprotein level in serum (Figure 1). The levels of other lipoproteins, alpha and beta, are not modified by the drug.

Apart from these results, our findings in rats on a 20°/o casein diet, plus cocaine, exhibit a different pattern (Table 2). Thus, concentration of total lipids as well as triglycerides and phospholipids levels of total cholesterol concentration in the liver, is observed. In the same way, neither the total lipids level nor triglycerides-rich pre-beta lipoprotein concentration in serum are changed by cocaine, but cholesterol-rich beta lipoprotein level is significantly decreased ($p < 0.001$).

DISCUSSION

Keeping in mind an early assumption concerning a possible physiological role that cocaine might play in the metabolic economy of human beings who chronically chew coca leaves under poor nutritional conditions, some years ago we carried out several experiments in animals in order to learn more about the biochemical background underlying the effect of the drug. From these studies we must stress the findings already reported (1) and confirmed in the present study, that cocaine, added to a 5°/o corn-protein diet administered to growing rats, counteracts fat accumulation in the liver. In trying to explain this particular finding, however, our new results, herein presented, still do not sufficiently explain the intrinsic mechanism behind this effect, even though we can approach it when we examine the results obtained, in the light of other findings in this respect.

Thus, the effect of cocaine appears not to be due to a reduction of the dietary calories ingested by the animals (Table 1). The data (Table 1, Table 2, and Figure 1) show, in turn, that the effect is due to metabolic events taking place in the liver. Furthermore, they also suggest that in rats, cocaine given chronically with the diet would not be hepatotoxic but, as reported previously (4), it might contribute (e.g. by mediation of

TABLE 1

DIETARY AND NUTRITIONAL PARAMETERS IN GROWING FEMALE WISTAR RATS FED EITHER A 20°/o CASEIN DIET OR A 5°/o CORN-PROTEIN DIET PLUS COCAINE FOR 18 DAYS[1]

Parameters	20°/o Casein diet		5°/o Corn-protein diet	
	Without cocaine (6)	With cocaine[2] (6)	Without cocaine (6)	With cocaine[2] (5)
Initial weight, g	136.9 ± 5.1	127.4 ± 7.5	108.6 ± 8.6	104.2 ±11.4
Final weight, g	183.5 ±13.0	162.9 ± 8.5	96.4 ± 8.8	89.1 ±10.3
Weight change, g	46.5 ± 9.7	35.5 ± 8.1	-12.5 ± 1.9	-14.1 ± 1.3
Food consumed, g	176.8 ±17.3	158.8 ± 8.8	82.5 ± 5.4	76.8 ±10.4
Energy consumed Kcal/ 100 g b.w.	383.8 ±21.3	389.6 ±13.4	298.0 ±19.6	294.5 ±22.0
PER indexes (15 days) or b.w. diminution	1.31 ± 0.16	1.29 ± 0.18	-3.57 ± 0.65	-4.30 ± 0.40
Cocaine, HCl. ingested mg/100 b.w.	—	146.2 ± 8.1	—	129.2 ±17.5

1 Before the 18-day-experimentation, both groups of rats were fed their corresponding diets without cocaine for 5 days.

2 During experimentation, cocaine hydrochloride was given in proportion of 15 mg/10 g of diet. The results are expressed as mean values ± s.e.m. for the number of animals, given in parenthesis. Protein (N x 6.25),PER indexes and b.w. diminution were determined as described in *Material and Methods.*

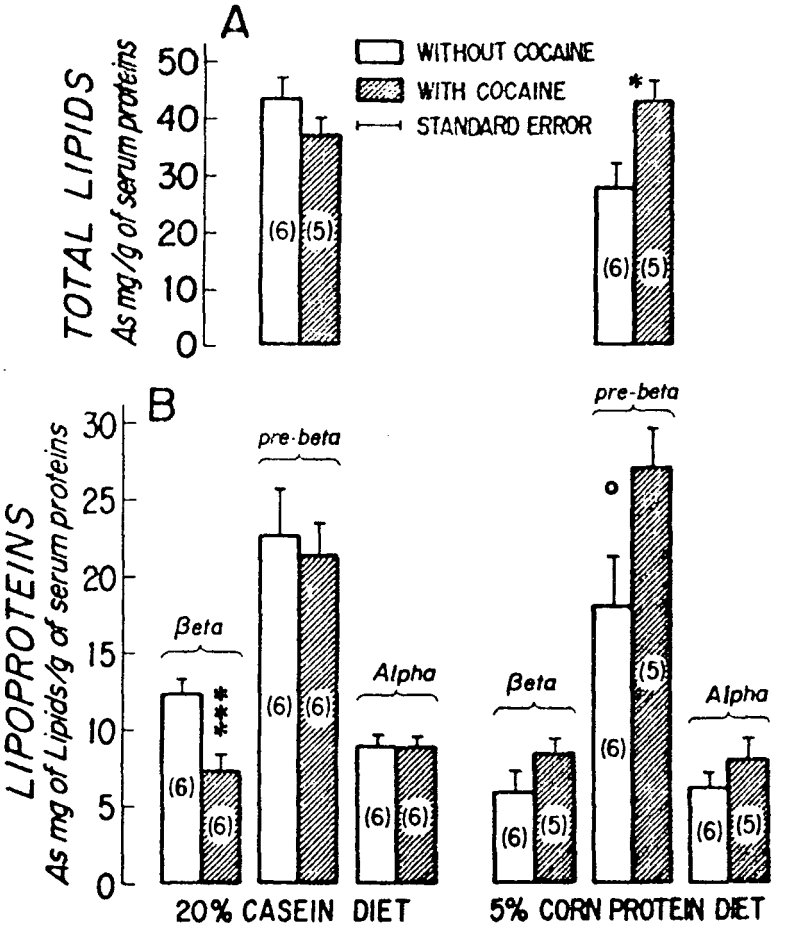

FIGURE 1

Serum total lipids level (A) and serum lipoproteins concentration (B) in rats fed either a 20°/o casein diet without (a) and with (a1) cocaine, or a 5°/o corn protein diet without (b) and with (b1) cocaine, for 18 days. Cocaine was given in proportion of 15 mg/10 g of diet. Results are expressed as mean values ± s.e.m. for the number of animals given in parenthesis. Levels of lipids (averages, mg°/o: a) 319.5, a1) 303.5, b) 204.4, b1) 281.3), proteins (averages, g°/o: a) 7.4, a1) 8.1, b) 6.8, b1) 6.5) and lipoproteins fractions (averages, °/o: a) beta = 28.5, pre-beta = 50.7, alpha = 20.8; a1) beta = 20.5, pre-beta = 56.2, alpha = 23.5; b) beta = 20.2, pre-beta = 58.4, alpha = 21.5; b1) beta = 19.7, pre-beta = 61.7, alpha = 18.6) were determined as described in *Materials and Methods*, and used to calculate the results.

TABLE 2

LIVER LIPIDS COMPOSITION IN FEMALE WISTAR RATS FED EITHER A 20o/o CASEIN DIET OR A 5o/o CORN-PROTEIN DIET PLUS COCAINE POR 18 DAYS[1]

Parameters	20o/o Casein diet		5o/o Corn-protein diet	
	Without cocaine (6)	With cocaine[2] (6)	Without cocaine (6)	With cocaine[2] (5)
Liver weight, g/100 g b. w.	3.68 ± 1.33	3.93 ± 0.18	3.79 ± 0.24	3.79 ± 0.24
Lipids, mg/g wet tissue				
Total lipids	80.21 ± 3.61	78.65 ± 5.82	108.59 ± 6.10*	73.95 ± 2.54**
Total cholesterol	16.33 ± 1.11	15.54 ± 0.88	11.00 ± 0.58	11.64 ± 1.58
Phospholipids	5.25 ± 0.25	5.75 ± 0.75	6.00 ± 0.25	5.50 ± 0.25
Triglycerides (determined)	61.18 ± 2.82	62.99 ± 7.29	77.12 ± 2.54	71.95 ± 8.13+
Triglycerides (calculated)	58.63 ± 3.64	57.39 ± 5.74	91.60 ± 6.52	56.80 ± 3.44**
Lipids, mg x 10^3/mg protein				
Total lipids	555.00 ± 31.00	512.00 ± 52.00	781.50 ± 126.00°	528.80 ± 25.00++
Total cholesterol	114.40 ± 12.29	100.05 ± 5.84	75.93 ± 5.34	83.88 ± 12.52
Phospholipids	36.25 ± 2.75	37.00 ± 4.75	41.75 ± 3.75	39.75 ± 3.75
Triglycerides (determined)	422.23 ± 24.68	410.51 ± 51.21	549.70 ± 71.82	519.98 ± 73.39+
Triglycerides (calculated)	402.72 ± 24.09	370.57 ± 52.71	668.66 ± 122.50	405.11 ± 23.88**

1 The results are expressed as mean values ± s.e.m. for the number of animals, given in parenthesis.

2 Cocaine hydrochloride was given in proportion of 15 mg/10 g of diet. Levels of lipids (above) and proteins (averages, mg/g wet tissue, casein 20o/o: *without cocaine* 146.6; *with cocaine*, 156.1; corn protein 5o/o: *without cocaine* 149.0, *with cocaine* 140.9) were determined as described in *Materials and Methods*. * $P < 0.005$ (vs. 20o/o casein diet without cocaine). ** $P < 0.001$ (vs. 5o/o corn-protein diet without cocaine). + $P < 0.60$ (vs. 5o/o corn-protein diet without cocaine). ++ $P < 0.20$ (vs. 5o/o corn-protein diet without cocaine). ° $P < 0.20$ (vs. 20o/o casein diet without cocaine).

some factor/by inducing adaptive responses in the body/through more direct action on the liver) to favor its own metabolism in this tissue and, therefore, its elimination from the body. Any of these conditions (or all of them together) induced by cocaine could have had a special meaning in protein-malnourished rats, where the drug appears to be acting against the induction of fatty liver. In partial support of this suggestion are previous laboratory findings (2-4) which show no apparent damage of the liver (as determined each by macroscopic examination, fat concentration and activity of the glutamic pyruvic transaminase, the latter considered to be an adequate marker for hepatocellular damage) caused by cocaine in both well-nourished and malnourished rats, but an increase of the liver cocaine N-demethylation, depending upon changes in the body (decrease of PER indexes/body weight values) induced by the drug. In like manner, results from other investigators (18, 19) show no injury and injury (fat accumulation, necrosis and increase glutamic pyruvic transaminase activity) in the liver of rats and mice, respectively, as a consequence of the different hepatic metabolism of norcocaine (N-demethylated metabolite of cocaine) between these two animals species (20).

In this context, our present results (Table 2 and Figure 1) appear in line with the above-mentioned facts, and the study of their biochemical background allowed us to observe after cocaine pretreatment, patterns of lipid distribution in liver and serum which are opposed to those claimed to take place under protein malnutrition following the administration of either vegetable protein diets (21, 22) or an unbalanced amino acid mixture (23). After these dietary treatments, a feature of fatty liver, different from those features obtained by administration of different chemicals (CC14, ethanol, phosphorus, puromycin, orotic) or by feeding a choline-deficient diet, is obtained. In the former cases, normal/decreased (by diminution of pre-beta apolipoprotein(s) synthesis) capacity for exporting triglycerides-rich pre-beta lipoprotein with increased triglycerides synthesis has been suggested (8, 21-23) while in the latter two, some researchers have suggested a block in the secretion of triglycerides into the blood (24-26), as the pathogenic factor for inducing fatty liver. Nevertheless, an increased concentration of triglycerides is the common response of the liver to these injuries (27, 28).

From these facts we can draw the suggestion that the effect produced by cocaine in protecting the liver against fat deposition in rats which received a choline-supplemented 5o/o corn-protein diet (Table 2) (1), could have been accomplished by an increased secretion of hepatic triglycerides (as pre-beta lipoprotein) into the blood (triglycerides account for about 60o/o of the pre-beta lipoprotein mass, and for about 10-15o/o of each protein, cholesterol and phospholipids) (29), even though it could have also been theoretically accomplished by other means (e.g. inhibition of free fatty acids output from adipose tissue, increased fatty acids oxidation in the liver or decreased hepatic triglycerides synthesis). Of these possibilities, the former appears to be consistent with our findings (Table 2), showing a decrease of the liver triglycerides concentration either determined or calculated (by difference between [the total lipids content and the contents of both total cholesterol and phospholipids (averages; *without cocaine*, 91.6o/o mg/g wet tissue, 668.6 mg x 10^3/mg protein; *with cocaine*, 56.8 mg/g wet tissue, 405.1 mg x 10^3/mg protein)] and

concomitant increases of both the level of total lipids ($p < 0.05$) and the level of triglycerides-rich pre-beta lipoprotein ($p < 0.10$) in the serum (Figure 1) of these animals. However, the significance of some of these changes (significant reduction—caused by cocaine—of the amount of liver triglycerides when assessed by calculation, but only a slight reduction when experimentally determined, as well as the notorious increment of the serum triglycerides-rich pre-beta lipoprotein, the significance of which is not as high as the increments of total lipids level determined in the same fluid) prompt us to think that their dissimilar values are probably dependent on the reliability of the techniques used. Despite this, findings reveal a similar meaning and, according to the interpretation, this means that the increased secretion of triglycerides-rich pre-beta lipoprotein could have accounted for avoiding fat accumulation in the liver.

Concerning the cause of this increased secretion, we must say that it is not immediately known. Nevertheless, when this effect is discussed taking into account some experimentally well-established facts regarding induction of the drug-metabolizing-enzymatic system by certain drugs (including cocaine) (3, 4, 30), as well as evidence (some already mentioned above) showing and/or suggesting that some chemical/physiological factors other than dietary protein [e.g. increased contents of protein and phospholipids in the liver cell membranes, efficient hepatic reutilization of the greater flow of aminoacids from the peripheral tissues (muscles)] caused by malnutrition (31) but magnified by the drugs (4, 32) (e.g. phenobarbital, cocaine), account for some adaptive responses in the liver of rats on protein-deficient diets -plus either plenobarbital (33) or cocaine (4) (increased N-demethylation of ethyl-morphine and cocaine)- we must suppose that this drug administered with the diet to protein malnourished rats could have also induced [like the N-demethylation reaction in protein (casein)-deficient rats] an increase of the triglycerides-rich pre-beta lipoprotein secretion by increasing the synthesis of pre-beta apolipoprotein(s) in the liver. This, in turn, could have led to an increased assembling of both triglycerides and cholesterol to the phospholipid-apolipoprotein(s) complex in the endoplasmic reticulum of parenchimal cells.

The apolipoprotein(s) is (are) synthetized in the rough endoplasmic reticulum (8), and the triglycerides-rich pre-beta lipoprotein is assembled and packed in the smooth endoplasmic reticulum and Golgy apparatus, respectively (34, 35) and both reticula, rough and smooth, although the latter in major degree, are newly synthetized by the inductive phenomenon resulting from the drug action at this level (36). Therefore, through its effect of inducing both its own hepatic-N-demethylation and the decrease of body weight [and perhaps favoring so the enzymatic induction in the liver by increasing the muscle protein catabolism, as has been suggested previously (4) and commented above], cocaine could also have been responsible for increasing the apolipoprotein(s) (by enhancement of its synthesis and/or the synthesis of membranes of the endoplasmic reticulum) available for assembling the particles of pre-beta lipoprotein in the smooth reticulum.

Even though we still must provide evidence for this assumption neither can we discard another early suggestion about a probable and additional contribution of the cocaine N-methyl groups (through the formaldehyde produced by the N-demethylation reaction of the drug

which is ingested repeatedly and in great amount by the animals under these experimental conditions) to increase the rate of synthesis/turnover of some phospholipids (e.g. phosphatidylcholine) required for the inductive phenomenon (6) in the liver cells.

Among other ways by which the phenomenon of fat accumulation reduction in the liver could have also taken place, as well as regarding the results which show an increase of the serum triglycerides-rich pre-beta lipoprotein level, the possibilities that both an inhibition of the free fatty acids output from adipose tissue, and a decreased removal of that lipoprotein from plasma by cocaine, could have accounted for the effect of the drug in the liver and plasma, respectively, appear not to be consistent with facts showing reduced triglycerides concentration in the liver and hyperlipemia by cocaine (Table 2). We must note, however, that we have not determined the free fatty acids level in serum.

Concerning the other possibility, i.e. that a decreased hepatic triglycerides synthesis could have also been involved in the preventive phenomenon by cocaine, we must comment on the probable diversion of the NADPH equivalents from triglycerides synthesis (fatty acids synthesis) to the N-demethylation reaction of the drug in the liver.

Although in the present study we have not approached the metabolism of cocaine, this suggestion is supported by facts showing the requirement of NADPH by both processes (3, 36, 37) and the characteristics of one of them (N-demethylation of cocaine) which is significantly stimulated in rats fed on protein (casein)-deficient diets plus cocaine (4). Aside from this fact, the striking finding showing a significant ($p < 0.001$) reduction of the cholesterol-rich beta lipoprotein in the serum of rats fed the 20% casein diet, with concomitant slight decrease of total cholesterol in the liver, constitutes a relative support for our assumption that the availability of NADPH for synthetizing both triglycerides (reductive steps for fatty acid synthesis) and cholesterol (reductive steps and demethylation) in each physiological case (malnourished and well-nourished animals respectively), could have diminished by increasing the metabolism of a foreign chemical compound such as cocaine. These probable metabolic influences of cocaine are now being tested in our laboratory. Nevertheless, whatever the mechanism(s) (increased output of pre-beta lipoprotein/increased output of this lipoprotein plus either diversion of the NADPH from triglycerides synthesis to N-demethylation of cocaine or other additional metabolic event) for reversing the protein malnutrition-induced fatty liver, all the results in this respect constitute clear evidence for supporting the assumption of the physiological role for cocaine in those organisms which ingest the drug chronically (coca chewers, human beings/animals, experimentally). Even more, these findings and others already cited (3, 4), allow us to stress the influence of the physiological status upon the metabolic effect of cocaine, probably via the metabolism (N-demethylation) of the drug. This is important to emphasize, because reasonable influences of this metabolism upon relevant metabolic pathways in the liver (according to nutritional status) may occur when we take into account the structure (N-methyl groups), site of biotransformation (mainly in the liver), route and frequency of the doses (orally and repeatedly) and the cellular/physiological influences of cocaine.

Finally, apart from the striking effect of cocaine in reducing the level

of cholesterol-rich beta lipoprotein in serum of rats fed a 20°/o casein diet, the magnitude of the other cocaine-induced changes suggests, among other things, that further experimentation and usage of either long cocaine pretreatment or younger rats than those used in the present study must be done, in order to obtain more conclusive results. Formerly we reported (1) a very significant reduction in liver lipids accumulation in growing rats (46 g b.w.) after 28 days-cocaine pretreatment, which showed signs of severe protein malnutrition.

ACNOWLEDGEMENT

The authors express their appreciation to Dr. Marino Villavivencio, Director of this Center (Centro de Investigación de Bioquímica y Nutrición), for his valuable suggestions.

RESUMEN

EFECTO DE LA INGESTA DE COCAINA EN EL DESARROLLO DE HIGADO GRASO EN RATAS ALIMENTADAS CON UNA DIETA BAJA EN PROTEINA

Se ha demostrado que la cocaína que se administra oralmente con la dieta es capaz de reducir los niveles de acumulación de grasa hepática en ratas con malnutrición proteínica (*Arch. Latinoamer. Nutr. 19:* 69-79, 1969). Por consiguiente, el presente estudio fue diseñado para tratar de determinar la acción de la droga sobre el proceso (aumento de la síntesis de triglicéridos en el hígado y capacidad normal o disminuida para liberar estos triglicéridos al plasma) que induce la acumulación de grasa en el hígado bajo esta condición fisiológica. Para lograr este propósito, se determinó lípidos totales y fraccionados en el hígado, y lípidos totales, así como lipoproteínas en el suero de ratas Wistar hembra (120-130 g) alimentadas con cada una de las dos dietas siguientes: una con 5°/o de proteína de maíz, y la otra, con 20°/o de caseína sin y con cocaína (15 mg HCl cocaína/10 g de dieta) durante 18 días.

Además de confirmar el hallazgo previo de reducción ($P < 0.001$) del valor de grasa acumulada en el hígado de las ratas integrantes del grupo con malnutrición proteínica, que recibieron la dieta con 5°/o de proteína de maíz más cocaína, los resultados también muestran que esta droga disminuye la concentración de triglicéridos (significativamente, $P < 0.001$, cuando el resultado se obtiene por cálculo y, ligeramente, cuando este resultado se obtiene experimentalmente) en el tejido hepático, y aumenta los niveles de lípidos totales ($P < 0.05$) y de la lipoproteína pre-beta rica en triglicéridos en el suero de estos animales ($P < 0.10$). Por otro lado, estos parámetros no fueron modificados por la cocaína en el grupo de ratas alimentadas con caseína al 20°/o, excepto en lo concerniente al colesterol hepático total y a la lipoproteína beta, rica en colesterol, en el suero. Estos valores fueron ligera y significativamente ($P < 0.001$) reducidos por la droga, respectivamente.

Las evidencias en cuestión y sus significancias estadísticas sugieren que la cocaína administrada en forma crónica con la dieta de proteína de maíz al 5°/o por 18 días, disminuye —al menos parcialmente— (otros procesos bioquímicos en el hígado pudieron también haber contribuido en alguna forma al efecto producido en este tejido) la acumulación hepática de grasa, al incrementar la secreción de triglicéridos desde el hígado al plasma. En otro sentido, parece ser que la cocaína es capaz de inducir también ciertas alteraciones metabólicas del colesterol, en el hígado de ratas bien nutridas.

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