ETHANOL TOXICITY: LIPID AND CARBOHYDRATE METABOLISM; ETHANOL IN PREGNANCY AND THE FETAL ALCOHOL SYNDROME

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Abstract - Ethanol is absorbed by diffusion across the gastric and intestinal mucosa. Following absorption, ethanol is mainly metabolized in the liver where cytosolic alcohol dehydrogenase and mitochondrial aldehyde dehydrogenase are the principal enzymes of ethanol oxidation. Hepatic metabolism of ethanol leads to an increased formation of NADH and acetaldehyde which are the factors directly responsible for most of the metabolic disturbances produced by ethanol. Almost all lipid metabolism pathways are affected by ethanol, and hyperlipemia and fat accumulation in the liver are the most common disturbances. Several mechanisms contribute to these conditions but the ethanol effects of enhancing the arrival of lipids to the liver and decreasing their further disposition seem to be the most important. Ethanol effects on carbohydrate metabolism are also very diverse, producing either hyperglycemia or hypoglycemia depending on the availability of glycogen stores. Ethanol decreases liver gluconeogenetic activity by siphoning substrates which are converted to their reduced form.

Alcohol ingestion during pregnancy may produce the fetal alcohol syndrome which causes retarded growth and abnormalities in fetal development. Animal models for this syndrome have been developed using different species. In the rat, 25% ethanol in the drinking water during pregnancy provides a daily total caloric intake similar to that of pregnant controls but causes weight reduction in both mother and fetus. Blood glucose levels are preserved in the alcoholic rat mother but liver glycogen is decreased and blood ketone bodies are augmented and these parameters are significantly affected in the fetus.

INTRODUCTION

Alcoholism constitutes one of the major health, social and economic problems in the world. Ethanol-induced effects are very widespread and include cirrhosis, cancer and heart diseases, besides related psychological factors. In the United States, cirrhosis of the liver is the fifth leading cause of death in the general population and about 5% of the population are active alcoholics (Ref. 1). In economic terms, it has been estimated that the alcohol related expenditure for one year in the United States is nearly 43 billion dollars (Ref. 2). In Spain, the mean annual consumption of pure alcohol per inhabitant is 19.0 l (Ref. 3) and today also about 5% of the population suffer from alcohol misuse (Ref. 4).

The individual response to alcohol is variable; for example, although fat accumulation in the liver is the most common metabolic disturbance produced by alcohol (Ref. 5), only 10-20% of all heavy drinkers develop severe liver injury (Ref. 1). The mechanism of this variable response to alcohol remains obscure but it may depend on the factors affecting its absorption, removal and degradation as well as the condition of the receptor subject.

Ethanol is a lipid-soluble nonelectrolyte molecule, and as such it is rapidly absorbed into the circulation by diffusion across the gastric and intestinal mucosa. Ethanol absorption is reduced by factors that decrease gastric motility (including high concentrations of ethanol itself) and by the presence of food in the stomach that acts as a barrier to ethanol's contact with the mucosa (Refs. 6,7). Once ethanol is absorbed, most of it (over 90%) is distributed

among the body tissues where its complete oxidation yields about 7 kcal/g. The remainder is excreted unchanged in the urine, expired air and sweat (Ref. 8).

Whole-body distribution of radioactivity has been measured in various species after labelled ethanol administration (Refs. 9-11), showing that it rapidly accumulates in tissues with high blood flow and water content such as the liver, spleen, brain and lung. Ethanol is mainly metabolized in the liver although the kidney, muscle, lung, intestine and brain may also metabolize small quantities (Ref. 8). The rate of ethanol metabolism may be altered by different approaches (Ref. 13), fructose being the most efficient agent to accelerate its metabolism (Refs. 14,15), while pyrazole (Ref. 16) and 4-methylpyrazole (Ref. 17) are potent inhibitory agents.

While there are many excellent and extensive reviews of the biochemistry and pharmacology of alcohol, some aspects still remain unclear and even controversial, such as those concerning the interrelationships between alcohol and intermediary metabolism, and also the metabolic basis of the fetal alcohol syndrome. Without intending to be an exhaustive review, this presentation summarizes the present state of knowledge of these problems and describes our own contribution to the study of their metabolic aspects in an experimental model of the fetal alcohol syndrome.

Metabolism of ethanol

There is general agreement that alcohol dehydrogenase (ADH) is the major site of initial ethanol metabolism. This enzyme catalyzes the following reaction:

$$\underset{\text{Ethanol}}{CH_3\text{-}CH_2OH} + NAD^+ \rightleftharpoons \underset{\text{Acetaldehyde}}{CH_3\text{-}CHO} + NADH + H^+$$

Most ADH in the body is in the liver although there are small amounts in certain extrahepatic tissues such as the kidney and gastric mucosa (Ref. 18). This distribution makes the liver the main site of ethanol oxidation, as shown in humans (Refs. 19,20) and experimental animals (Refs. 21-23). Cell fractionation studies reveal that ADH is found exclusively in the cytosol of the hepatocytes (Refs. 24,25).

Two other pathways have been proposed for the oxidation of ethanol to acetaldehyde. One of these pathways is a peroxidatic reaction catalyzed by catalase which utilizes hydrogen peroxide (Ref. 26):

$$H_2O_2 + CH_3\text{-}CH_2OH \longrightarrow CH_3\text{-}CHO + 2H_2O$$

This reaction takes place mainly in the liver peroxisomes which contain most of the liver catalase activity as well as the capacity to form hydrogen peroxide, via oxidase reactions (Refs. 27,28). The other pathway is the microsomal ethanol-oxidizing system (MEOS) which requires NADPH and oxygen (Refs. 29,30):

$$NADPH + H^+ + O_2 + CH_3\text{-}CH_2OH \longrightarrow CH_3\text{-}CHO + NADP^+ + 2H_2O$$

The quantitative role of these two pathways in total ethanol metabolism is still controversial but there is general agreement that, under normal conditions, ethanol oxidation proceeds primarily via the ADH pathway. Acetaldehyde is always the first oxidation product of ethanol and is oxidized mainly to acetate by the aldehyde dehydrogenase (ALDH) catalyzed reaction:

$$CH_3\text{-}CHO + NAD^+ + H_2O \longrightarrow CH_3\text{-}COO^- + NADH + H^+$$

Unlike ADH, ALDH is located in virtually every organ in the body (Ref. 31), although it is most active in the liver. It has been proposed that the level of ALDH activity in liver can adequately handle all the acetaldehyde produced from the ethanol-oxidizing systems (Ref. 32). Also unlike ADH, ALDH is found in both microsomes and mitochondria as well as in the cytosol, although the low-Km isoenzyme is found primarily in mitochondria (Ref. 32). Thus acetaldehyde is formed in the liver by oxidation of ethanol in the cytosol but it diffuses into the mitochondria where, in its matrix space, it is oxidized to acetate.

Although the final fate of these metabolites has not been definitely established, the intracellular localization of these reactions indicates their coupling with other related pathways (Fig. 1), resulting in the net production of NADH both in the intra- and extramitochondrial space and the production of acetate. The liver may metabolize acetate (Ref. 33) but most of it seems to be utilized *in vivo* by extrahepatic tissues (Ref. 34).

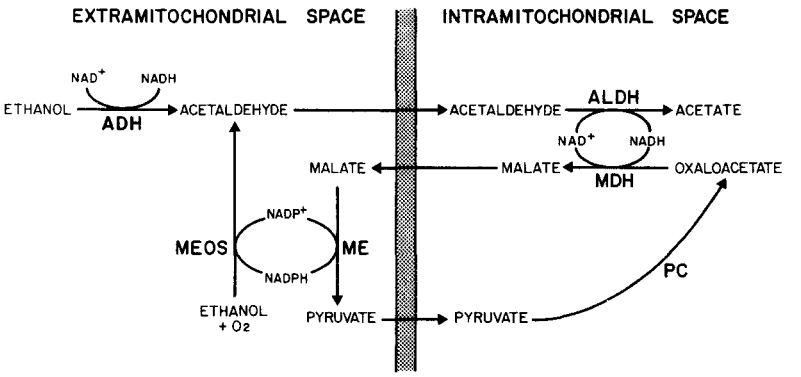

Fig. 1. Coupling of the main ethanol-oxidizing systems with the other pathways in the intramitochondrial and extramitochondrial spaces in the liver cell. ADH = alcohol dehydrogenase; ALDL = acetaldehyde dehydrogenase; MEOS = microsomal ethanol-oxidizing system; PC = pyruvate carboxylase; ME = malic enzyme.

General effects of ethanol on intermediary metabolism

Most of the metabolic effects of ethanol are caused indirectly by the primary products of its oxidation, NADH and acetaldehyde. This means that the hepatic oxidation of ethanol is a prerequisite condition for its metabolic action.

A large proportion of the disturbances produced by ethanol can be attributed to the generation of NADH or, by transhydrogenation, to the formation of NADPH (Refs. 35, 36). The excess of cytoplasmic NADH produced by the ADH reaction in the conversion of ethanol to acetaldehyde has important metabolic consequences due to its independence of the intramitochondrial NAD^+ - NADH pool (Ref. 37). Preexisting hydrogen acceptors must be employed in the cytosol to reoxidize the NADH. The locations of NAD-linked dehydrogenases in different cell compartments (Refs. 37, 38) indicate the disposition of extramitochondrial "reducing equivalents" during the oxidation of ethanol (Ref. 39). Thus, since NADH formed by the oxidation of ethanol to acetaldehyde cannot cross the mitochondrial membrane (Refs. 40, 41), mitochondrial access could be gained via "shuttle" compounds that are reduced by those dehydrogenases. These reduced forms easily cross the mitochondrial membrane and are reoxidized into the mitochondria and then returned to the cytosol without loss of carbon atoms (Fig. 2). By this "shuttling" effect, the reducing equivalents liberated in the cytosolic oxidation of ethanol are made available to the mitochondria and are pooled with those formed intramitochondrially by the oxidation of acetaldehyde. These substances furnish extra fuel for the respiratory chain, decreasing the consumption of physiological substrates such as fatty acids and tricarboxylic cycle intermediates (Fig. 2). Indeed, it has been shown that decreased fatty acid oxidation (Refs. 42,43) and decreased tricarboxylic acid cycle activity (Ref. 44) are two major metabolic alterations induced by ethanol ingestion.

The generation of excess reducing equivalents in cytosol that follows ethanol oxidation may cause further metabolic disturbances. These equivalents may be shunted to the synthesis of fatty acids and α-glycerol phosphate (Refs. 45,46) which are the direct precursors for triglycerides. Augmented cytosolic NADH enhances the conversion of pyruvate to lactate, thereby decreasing the availability of the former for glucose synthesis (Fig. 3) and stimulating the production of lactate which may lead to hyperuricemia (Ref. 47). Similarly, two other gluconeogenetic substrates, triose phosphate (mainly dihydroxyacetone phosphate) and oxaloacetate, are also decreased by this alteration in the pyridine nucleotide redox state (Ref. 48), which forces their respective conversion to α-glycerol phosphate and malate (Fig. 3).

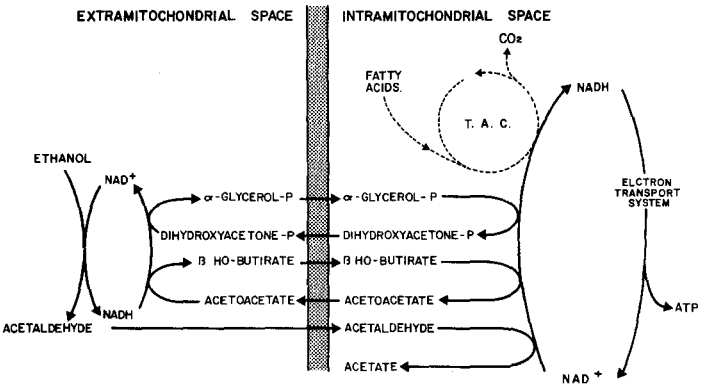

Fig. 2. Disposition of the reducing equivalents formed by the oxidation of ethanol via "shuttle" compounds that are converted into their reduced form and cross the mitochondrial membrane for their reoxidation. This action, together with the NADH formed intramitochondrially by the oxidation of acetaldehyde, decreases (dotted lines) the consumption of physiological substrates such as fatty acids and tricarboxylic acid cycle (T.A.C.) intermediates.

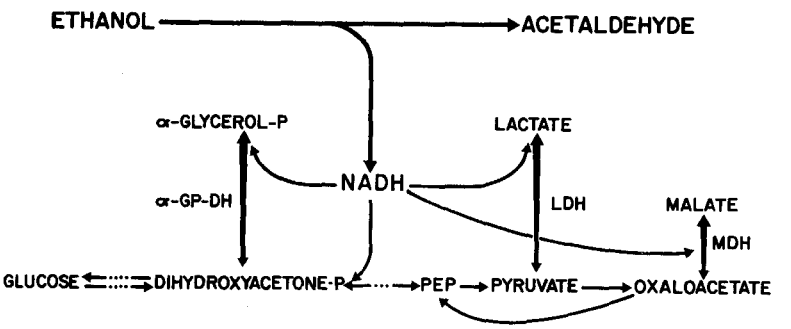

Fig. 3. The excess of reducing equivalents in the form of NADH in the cytosol as a consequence of ethanol oxidation decreases the availability of gluconeogenic substrates (dihydroxyacetone phosphate, pyruvate and oxaloacetate) due to their reduction by means of the respective NAD-linked dehydrogenases. GP-DH = α -glycerol phosphate dehydrogenase; LHD = lactate dehydrogenase; MDH = malate dehydrogenase. ——...—— = Intermediate reactions of the gluconeogenic or glycolytic pathways.

Acetaldehyde, the other product of the primary oxidation of ethanol, also seems responsible for many of the alterations observed after alcohol consumption (Ref. 49). Acetaldehyde has been reported to inhibit protein synthesis (Ref. 50) and mitochondrial fatty acid oxidation and ketogenesis (Ref. 51) and to impair glycoprotein metabolism (Ref. 52).

Effects of ethanol on lipid metabolism

Hyperlipemia and accumulation of fat in the liver are the most common disturbances of lipid metabolism produced by ethanol (Ref. 5). These effects are striking and interrelated. It has been shown (Refs. 53,54) that chronic alcohol consumption augments postprandial hyperlipemia and that after the administration of a fat containing meal, alcoholics with fatty liver develop a higher and more prolonged elevation of serum triglycerides than do subjects with cirrhosis or than nonalcoholics. Thus hyperlipemia is more pronounced in alcoholics with fatty liver than in patients with well established cirrhosis (Refs. 55,56). Alcoholic hyperlipemia corresponds to an elevation in plasma of the three main lipid classes: triglycerides, cholesterol and phospholipids, but the particulate fat shows an elevation of the triglyceride-rich lipoproteins, namely very low density lipoproteins (VLDL) (Ref. 57) and chylomicrons (Ref. 58), although both low density lipoproteins (LDL) and high density lipoproteins (HDL) are also augmented (Ref. 57). The elevation of circulating triglycerides seems primarily correlated with alcohol ingestion since after its withdrawal, triglyceride clearance is much faster than that of cholesterol and phospholipids (Ref. 59).

Mechanisms of the alcoholic fatty liver

Several mechanisms may contribute to the ethanol-induced fatty liver, although their relative importance varies with factors such as the duration and size of ethanol doses and diet: (a) Enhanced triglyceride breakdown in peripheral fat deposits which produces an increased mobilization of free fatty acids; (b) Increased uptake of fatty acids by the liver; (c) Decreased fatty acid oxidation in the liver; (d) Enhanced supply of lipids from the small intestine; (e) Increased fatty acid synthesis and esterification for the formation of triglycerides; and (f) Decreased secretion of lipoproteins by the liver and decreased hydrolysis of fatty acid esters in the liver.

The increased mobilization of fatty acids from adipose tissue with ethanol requires the administration of stressful doses (Ref. 60), while more moderate doses produce the opposite antilipolytic effects, as shown by reductions of circulating FFA (Ref. 61) and glycerol (Ref. 62) levels. The stimulatory effect has been interpreted as secondary to the catecholamine release produced by stress, while the inhibitory effects seems to be mediated by acetate (Ref. 63), the main final product of ethanol oxidation. In any case, the uptake of fatty acids by the liver is consistently increased by even moderate alcohol doses (Ref. 64), probably as a consequence of the stimulating effects of ethanol on hepatic blood flow (Refs. 65,66).

The decreased fatty acid oxidation produced by ethanol (Refs. 42,43) actively contributes to the deposit in the liver of dietary fat and/or the fatty acids derived from endogenous synthesis (Ref. 5). The supply of dietary and nondietary lipids from the intestine is augmented by ethanol consumption, the effects being mainly determined by a stimulating action on splanchnic circulation (Ref. 66) and mesenteric lymph flow (Ref. 67). The conversion of ethanol to liver fat is limited, but ethanol enhances the incorporation of acetate and pyruvate into fatty acids (Refs. 68,69). This lipogenetic effect of ethanol seems to be both directly and indirectly related with the excess formation of reducing equivalents which results from ethanol oxidation. In its direct way, the action may be exerted throughout the positive effector role of NADPH (besides being its unique coenzyme) on the fatty acid synthase complex (Ref. 70) (Fig. 4). Indirectly, the increased NADH formed by oxidation of ethanol favors the production of α-glycerol-phosphate from dihydroxyacetone-phosphate (Ref. 71), resulting in accelerated hepatic fatty acid esterification for synthesis of glycerides (triglycerides, phosphatidylcholine and phosphatidylethanolamine (Ref. 72) Fig. 4). This effect should reduce the pile up of free fatty acids (and their acyl-CoA derivatives) in the hepatocyte and consequently reduce their inhibitory effects on liver lipogenesis (Ref. 73) (Fig. 4).

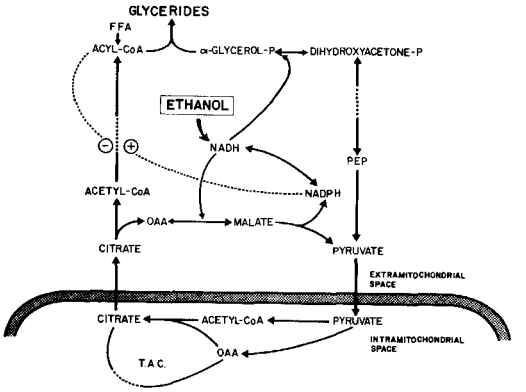

Fig. 4. The theoretical mechanism for the ethanol effect of enhancing liver lipogenesis. The NADH formed from ethanol oxidation is converted into NADPH by direct transhydrogenation or by the coupling of malate dehydrogenase (OAA ⟷ Malate) and malic enzyme (malate ⟷ pyruvate) reactions. The increased NADH formed favors conversion of dihydroxyacetone-P into α-glycerol-P, resulting in accelerated synthesis of glycerides. This effect reduces the intracellular concentration of FFA and their acyl-CoA derivatives, thus reducing their inhibitory effect on fatty acid synthesizing enzymes (acetyl-CoA carboxylase and fatty acid synthase).

The decreased hepatic lipoprotein secretion as a factor in ethanol-induced fatty liver is still unresolved. Although hepatic lipoprotein secretion decreases after high ethanol doses (Ref. 74), augmented liver production of serum lipoproteins in alcohol-containing diets has also been reported (Ref. 75). Since this situation coincides with the maintenance of fatty liver condition, the secretion of lipoproteins by the alcoholic liver may be reduced in proportion to the increase in lipids ready to be exported. The inability of the liver to eliminate its fat has been linked to associated effects of ethanol which diminish the secretion of exportable proteins (Ref. 76).

Decreased hydrolysis of fatty acid esters (triglycerides, phospholipids and cholesterol esters) in the liver has also been proposed as a factor in the development of fatty liver after alcohol ingestion (Ref. 5). This hydrolysis is predominantly catalyzed by lysosomal acid lipase and esterase. Although it is not yet known how the activity of these enzymes is affected by ethanol, it has been reported that the hydrolysis of cholesterol esters decreases after chronic ethanol administration (Ref. 77).

Mechanism for alcoholic hyperlipemia

Alcoholic hyperlipemia is also caused by multiple factors. As already mentioned, the net production of serum lipoproteins by the gut and liver, together with the increased release of free fatty acids from adipose tissue, are the main factors contributing to the greater infiltration of lipids into the blood. This greater infiltration is opposed by an unchanged or even reduced removal of lipids from circulation (Refs. 5,78). The activity of extrahepatic lipoprotein lipase can be either decreased (Ref. 79), unchanged (Ref. 80) or even enhanced (Ref. 81) after ethanol ingestion. However, hepatic triglyceride lipase activity is consistently reduced in alcoholic patients with liver damage (Refs. 82, 83). This may diminish the removal of serum lipids by the liver, actively contributing to maintenance of hyperlipemia.

Effects of ethanol on carbohydrate metabolism

The effects of ethanol on blood glucose levels have been the subject of much controversy (Ref. 84) as well as research, as ethanol may produce either hyperglycemia or hypoglycemia. These opposite responses seem dependent on hepatic carbohydrate stores because when they are adequate, ethanol induces hyperglycemia, whereas when they are low it induces hypoglycemia. The hyperglycemic effect of ethanol may be secondary to the release of catecholamines (Ref. 85)

which are known to have both glycogenolytic (Ref. 86) and gluconeogenetic (Refs. 87,88) effects on the liver and thus to enhance the net production of glucose. Two products of ethanol oxidation, acetaldehyde and acetate, have hyperglycemic effects because they increase the liver's glycogenolytic activity (Ref. 89) by an as yet unidentified mechanism which is not mediated by catecholamines.

When liver glycogen concentration is low, the catecholamine mediated glycogenolytic effect of ethanol cannot be sustained due to lack of substrate. In this condition, gluconeogenesis is inhibited by the action of ethanol, providing the major alteration leading to hypoglycemia (Ref. 84).

The mechanism of gluconeogenesis inhibition by ethanol is not yet clear (Ref. 90), although one explanation (Refs. 18,39) has been consistently supported by most investigators: when glycogen stores are diminished and the amino acids available for glucose synthesis also reduced, lactate becomes the main substrate for gluconeogenesis. For this to happen, lactate must be oxidised to pyruvate (Fig.3) through the lactate dehydrogenase reaction:

$$\underset{\text{Lactate}}{CH_3\text{-}CHOH\text{-}COO^-} + NAD^+ \rightleftharpoons \underset{\text{Pyruvate}}{CH_3\text{-}CO\text{-}COO^-} + NADH + H^+$$

Ethanol oxidation increases the $NADH/NAD^+$ ratio, as explained above, and this effect not only inhibits the conversion of lactate to pyruvate but also enhances the reverse. By a similar mechanism, two other substrates are also pushed off the gluconeogenetic pathway: dihydroxyacetone-phosphate which is converted to α-glycerol phosphate, and oxaloacetate which is converted to malate (Fig. 3). It has been shown that these two gluconeogenetic substrates are decreased by enhancing the $NADH/NAD^+$ ratio (Ref. 48).

Ethanol in pregnancy. The fetal alcohol syndrome.
Chronic ethanol ingestion during pregnancy in humans produces a syndrome of retarded growth and abnormalities in fetal morphology known as the fetal alcohol syndrome (FAS) (Refs. 91,92). Actually the adverse effects on offspring of ethanol consumed during pregnancy have been recorded since the time of Aristotle (Ref. 93). In 1899, Nicloux first demonstrated that ethanol ingested by the mother reaches the fetus in concentrations close to those in maternal circulation (Ref. 94). The rate of ethanol metabolism in the fetus is slower than in the mother because, although ADH is present in the human fetal liver after the 8th week of gestation, its activity is very low (Ref. 95) and at birth has reached 18% of the level in adults. Acetaldehyde administration to the mother has important teratogenic effects on the fetus (Ref. 96), but its transfer from the mother's to the fetus' blood is negligible (Refs. 97,98) probably due to its oxidation by the placenta (Ref. 99). Thus most of the negative effects of maternal ethanol ingestion in the offspring may be secondary to metabolic alterations in the mother rather than direct consequences of fetal ethanol oxidation or of the toxic action of acetaldehyde crossing the placenta.

It is not yet known whether there is a specific critical period of pregnancy when the fetus is most vulnerable to alcohol ingestion by the mother, nor is there an effective therapeutic (and/or preventive) treatment to protect the fetus from this injury. All these uncertainties and the ethical issues that preclude human experimentation lay more stress on the selection of proper experimental models to resolve these questions.

Animal models of fetal alcohol syndrome
There is a long history of animal models of FAS, starting with the work of Combemale in 1888 (Ref. 100) who exposed a pregnant bitch to ethanol and reported that of the six pups, three were stillborn and three were of "weak intelligence and defective to be mated with normal studs." In other early animal models of FAS, non-mammalian species were used such as fish (Refs. 101,102) but recent research has been mainly focussed on mice and rats (Ref. 103).

To study the maternal-fetal metabolic interactions during chronic alcohol ingestion during pregnancy, we used the rat as an experimental model of FAS. From the day of mating, half of the mothers received 25% ethanol in their water while the other half received tap water and were used as controls. This treatment was maintained until the 21st day of gestation when the animals were killed. Both groups of animals were allowed a purina chow diet "ad libitum." As shown in Fig. 5, both the mean daily volume of liquid drunk and of food taken by the mothers under alcohol treatment were significantly lower than in their controls, but the daily total of ingested calories was similar in both groups. This finding validates the experimental design although the control animals were not supplemented with an extra caloric intake to compensate for the calories ingested by the alcoholic rats in the form of ethanol. In some chronic ethanol

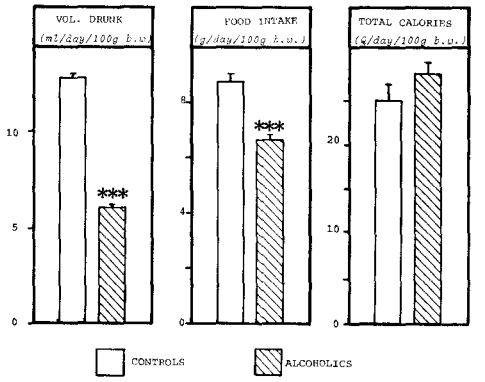

Fig. 5. Daily intake of liquid and food in alcoholic (25% ethanol in drinking water for 21 days) pregnant rats. P vs controls: *** = $P < 0.001$. n = 8-10 rats/group.

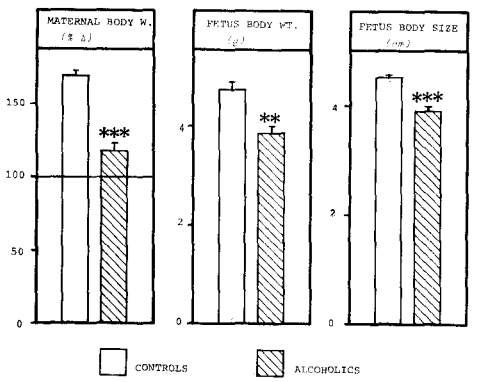

Fig. 6. Percent of body weight increase during 21 days of pregnancy in alcoholic rats (25% ethanol in drinking water) and body weight and size of their fetuses. P vs. controls: ** = $P < 0.01$; *** = $P < 0.001$. n = 8-10 rats/group.

experiments, control animals have been treated with sucrose, glucose or fructose, but it is known that these sugars alter metabolic parameters that are also affected by ethanol (Refs. 104-106) and their use in controls for chronic ethanol experiments has recently been criticized (Ref. 107).

Despite a similar caloric intake, the weight gain in alcoholic rats during pregnancy was much less than the gain in controls (Fig. 6). This reduced body weight in the alcoholic pregnant rats is due in part to a significant reduction in the weight and size of their fetuses, as compared with fetuses of normal pregnant controls (Fig. 6).

The evaluation of metabolic parameters in mothers and fetuses was performed according to our methodology used in pregnant rats (Refs. 108,109). Blood glucose levels are lower in the normal pregnant rat (Ref. 108) probably due to increased utilization of maternal glucose by the fetus more than to an impaired gluconeo-

genesis which may be normal or even augmented (Refs. 108,110). Blood glucose levels were unchanged in alcoholic mothers as compared with their controls (Fig. 7), coinciding with a significant reduction in liver glycogen content in the mothers (Fig. 7). Thus, as gluconeogenesis is probably limited in the alcoholic mother due to the ethanol effects on this pathway described above, her normal glycemia seems to be maintained at the expense of enhanced liver glycogenolytic activity. Both blood glucose and liver glycogen concentrations are greatly reduced in the fetuses of alcoholic mothers (Fig. 7). These two parameters in the fetus must necessarily come from maternal glucose production because the capacity of the fetus to synthesize glucose is limited (Refs. 111, 112). The present findings may be interpreted as the result of an impaired transfer of maternal glucose through the placenta or as a rate of glucose utilization by the fetal tissues of alcoholic mothers which may be greater than the rate of its availability. The latter possibility seems less likely since, if the fetus reacted in a manner similar to the alcohol fed nonpregnant rat, it would manifest a potential decrease in glucose utilization (Refs. 113,114) rather than an augmented one. In any case, the reduced carbohydrate stores in the fetus of an alcoholic mother must endanger the maintenance of blood glucose levels during the first hours after birth, since the newborn blood glucose levels are initially dependent on the use of glycogen stored in the liver during the last phase of intrauterine life (Refs. 115-117).

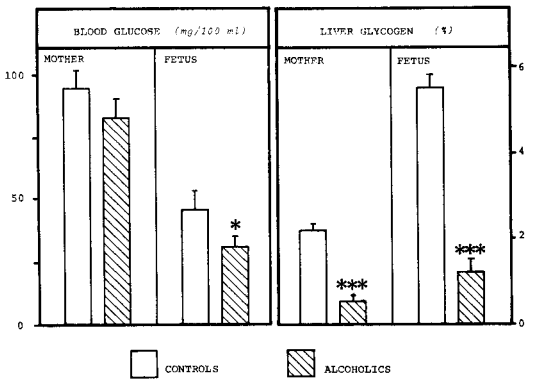

Fig. 7. Blood glucose and liver glycogen concentrations in 21 day pregnant alcoholic rats (25% ethanol in drinking water) and their fetuses. P vs. controls: * = $P < 0.05$; *** = $P < 0.001$. n = 9-10 rats/group.

Survival of the offspring of an alcoholic mother must be sustained by fuels other than glucose. As it has been shown that fetal tissues, including the liver, may use ketone bodies as extra-fuel (Refs. 118,119), both acetoacetate and β-hydroxybutyrate levels in blood were evaluated in mothers and fetuses (Fig. 8). Blood β-hydroxybutyrate, but not acetoacetate levels, appeared elevated in alcoholic mothers while both metabolites were significantly augmented in their fetuses as compared with controls. The origin of these augmented levels of ketone bodies in alcoholic mothers and their fetuses remains to be established but some hypotheses may be proposed. Since the fetus is unable to make ketogenesis (Ref. 120), its ketone bodies must come from the mother. It has been shown that the placenta is permeable to ketone bodies (Refs. 121,122) and ketoacidosis has been observed following alcohol treatment during reduced food intake (Refs. 123,124). Under conditions of reduced carbohydrate stores (due to voluntary limitation of food intake, as in our alcoholic rats and as it normally occurs in alcoholic pregnant women), ketogenesis is enhanced in the mother to preserve its own glycemia and to contribute with this extra-fuel to support the developing fetus. The association of decreased liver glycogen concentration and enhanced ketogenesis has already been suggested in other conditions (Refs. 125,126) and in the case of alcoholics, it must be further facilitated by the augmented availability of lipids in the liver to support such a pathway with enough substrates. Further studies are required to substantiate this hypothesis.

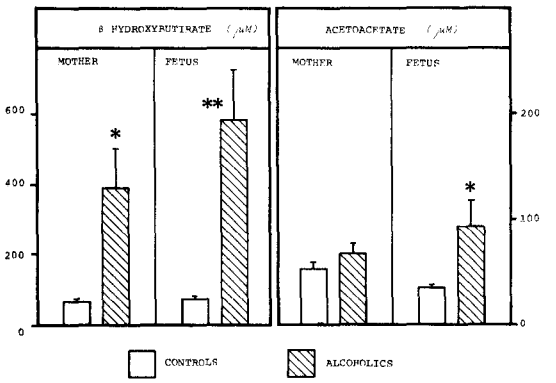

Fig. 8. Concentration of blood ketone bodies in 21 day pregnant alcoholic rats (25% ethanol in drinking water) and their fetuses. P vs. controls: * = P< 0.05; ** = P< 0.01. n = 9 rats/group.

Final comments

Many questions about the effects of ethanol on metabolism still remain to be solved, and they are of decisive importance during gestation. The complex correlations between alcohol abuse, smoking, drug consumption, poor nutrition and other sociological factors still remain unsolved and require both basic and clinical research on the pathophysiology of alcoholism and the pharmacology of ethanol. Scientific knowledge contributing to prevention of the fetal alcohol syndrome would benefit all the population but in particular our future generations.

Acknowledgments

The authors wish to express their gratitude to Drs. M. Salinas, M.A. Mena, A. García and M. Nieto for their help in performing some of the reported experiments, and to Caroline S. Delgado for her editorial help.

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