كليّة الصيدلة
Faculty of Pharmacy

Toxic Alcohols and Aldehydes

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Toxic Alcohols

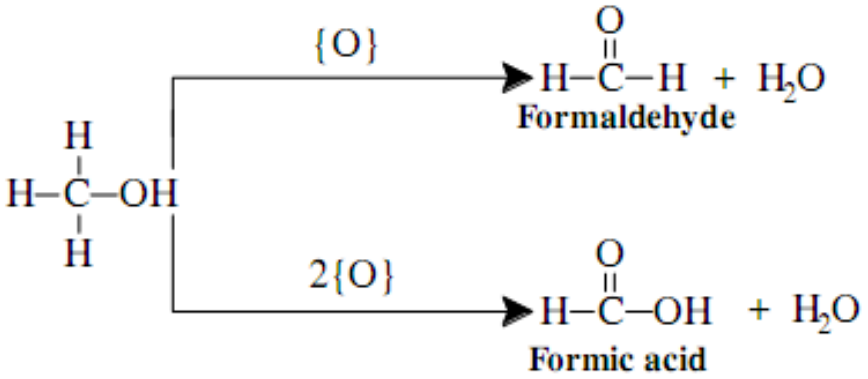
- Alcohols are common types of chemicals, and exposure to alcohols can cause diverse biological effects, either indirectly through metabolic products or directly through the parent with the substrates of biological pathways.
- Ethanol, methanol, Ethylene Glycol and isopropanol are the important alcohols are able to make toxicity in humans.
- Carbon chains with carbonyl groups (H–C=0) are classified as aldehydes
- Among the aldehydes, formaldehyde distributed in the environment , its established carcinogenicity and developmental toxicity in laboratory animals.

Methanol

- Methanol is readily available at various concentrations in numerous industrial and household products, including washer fluid and as a paint thinner.
- It is also used in the manufacture of formaldehyde and methyl t-butyl ether.

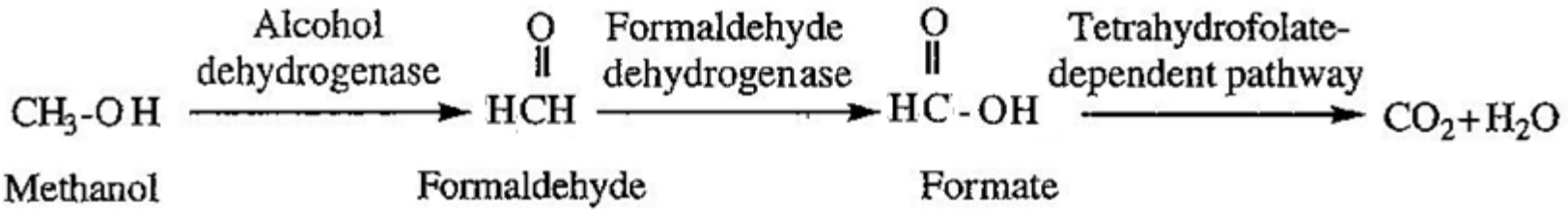
Methanol

- Methanol, also called methyl alcohol and once commonly know as wood alcohol, is a clear, volatile liquid mp, –98°C; bp, 65°C).
- Methanol has been responsible for the deaths of many humans who ingested it accidentally or as a substitute for drink ethanol.
- The fatal human dose is believed to lie between 50 and 250g. In the body, methanol undergoes metabolic oxidation to formaldehyde and formic acid:



Toxicokinetics

- Methanol is readily absorbed via the skin, GI, and respiratory routes.
- When ingested, peak methanol blood levels occur within 30 to 60 minutes.
- Methanol is oxidized in the liver to formaldehyde by ADH, which in turn is converted to formic acid (formate)by the action of formaldehyde dehydrogenase according to the following formula:



Toxicokinetics

- Formation of formic acid is largely responsible for the toxicity of methanol.
- Formate is further eliminated by the action of formyl-tetrahydrofolate-reductase (formyl-THFR) by combining with tetrahydrofolate (THF) to form 10-formyl THF .
- The product is then converted to carbon dioxide and water by the catalytic action of formyl-THF-dehydrogenase (F-THF-DH).
- The elimination half-life of formate is about 3.5 hours.

Toxicokinetics

- Methanol has little toxicity and produces less inebriation than ethanol
  - Ethanol and fomepizole (ADH inhibitor) , can inhibit the metabolism of methanol by, thus delaying its elimination.
  - Formic Acid(format) responsible for Ocular toxicity
  - The formic acid product of this reaction causes acidosis, with major adverse effects on the central nervous system, retina, and optic nerve.

Inebriation: ادمان، مسكر

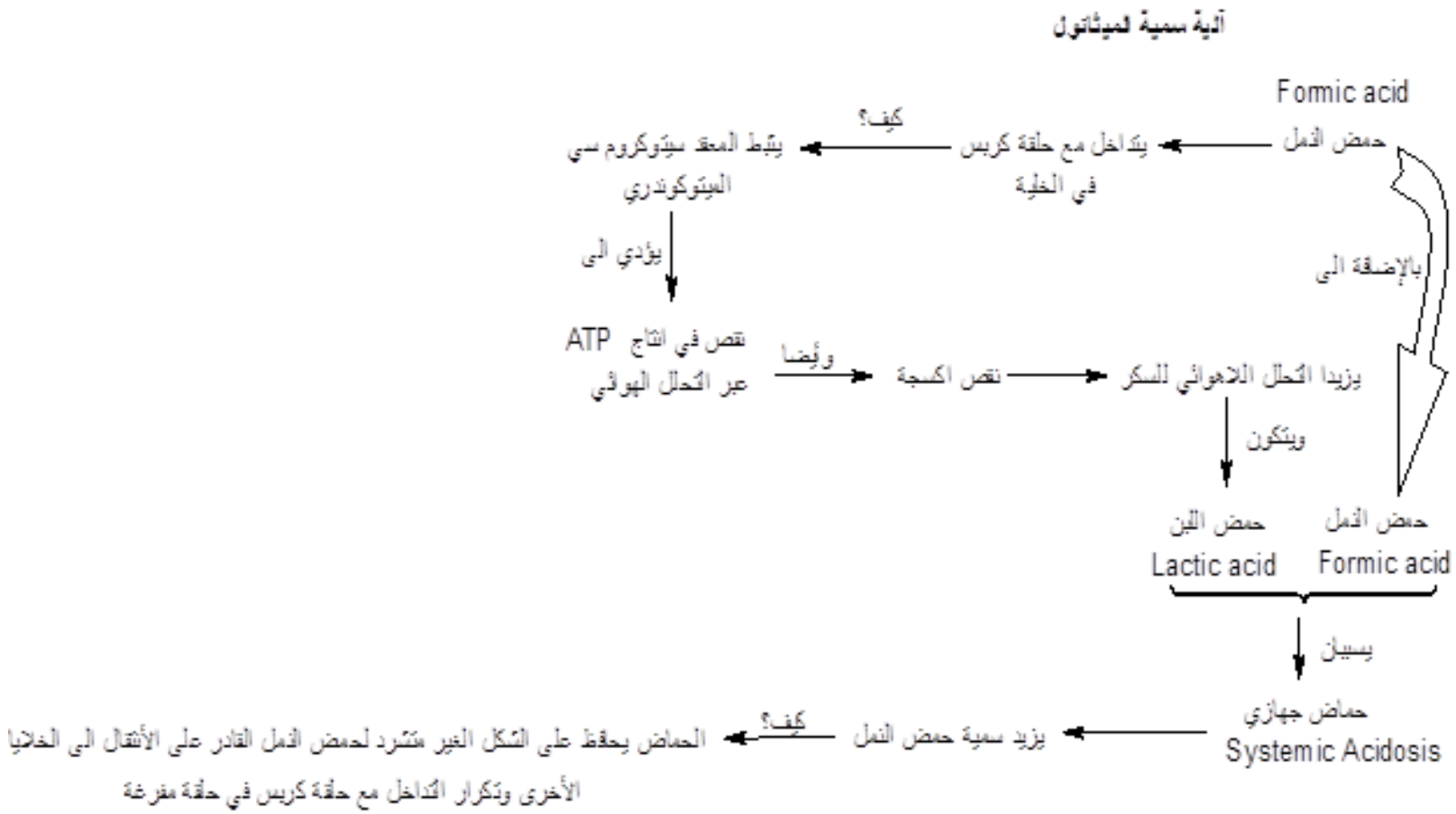
MECHANISMS OF TOXICITY

- Most of the toxic effects are attributed to the formation of formate.
- Formate inhibits the mitochondrial cytochrome c oxidase complex and decreases ATP production, resulting in increased anaerobic glycolysis and production of lactate.
- The accumulation of formate and lactate causes systemic acidosis, which facilitates the formation of nonionized formate, leading to its increased cellular accumulation and cytotoxic effects.

MECHANISMS OF TOXICITY

- In addition, production of hydroxyl radicals and induction of lipid peroxidation may also be implicated in the cellular damage induced by methanol intoxication.
- Ocular tissues such as optic nerve and retina are more susceptible to the toxicity of formate because the retina is able to metabolize methanol to formate, resulting in retinal edema and optic nerve damage.

MECHANISMS OF TOXICITY



Clinical Manifestations of Acute Intoxication

- Methanol primarily affects the nervous, ocular, and GI systems.
- While intoxication symptoms appear within a few hours after methanol intake, they can be delayed to more than 30 hours.
- Among the symptoms induced by methanol, the most typical clinical presentation is visual disturbance, including blurred vision, visual hallucination, and loss of vision.

Clinical Manifestations of Acute Intoxication

- Ocular-Upon eye examination, retinal edema, visual field constriction, and nonreactive pupils (follow-up).
- Nervous System-Nonspecific neurological manifestations, such as headache, vertigo, bradycardia, impaired consciousness, seizures, and coma.
- Others-Abdominal pain, diarrhea, GI hemorrhage, and pancreatitis represent signs and symptoms of GI complications.
- Finally, systemic metabolic acidosis induced by methanol intoxication may also increase the respiratory rate.

Management of Acute Intoxication

- **General Supportive Care**—Respiratory support, cardiac monitoring and circulatory assistance should be established
- **Antidote Therapy** –Ethanol and ADH inhibitor, fomepizole, are used as antidotes in methanol intoxication, They effectively block the metabolism of methanol and reduce its toxic effects.
- fomepizole should be given IV to all patients with methanol intoxication.
- Caution is in order for Et administration since it may cause CNS depression and hypoglycemia.
- However, fomepizole has great efficacy and fewer side effects than Et; hence it is the favored antidote in the treatment of methanol intoxication.

- Fomepizole is an ADH inhibitor that effectively blocks the metabolism of methanol and reduces the conversion of the alcohol to formaldehyde and formic acid

Ethanol

- Ethanol (ethyl alcohol) has been produced from fermented grain, fruit juice, and honey for thousands of years.
- The presence of ethanol in wine, beer, and liquor

and the use of it as a common solvent

- The a abuse of ethanol is not only a serious public health problem but also one of the major social problems, especially in Western countries.

CHEMICAL CHARACTERISTICS

- Ethanol is a colorless aliphatic hydrocarbon molecule.

This weakly polar molecule is both water and lipid soluble.

The average apparent volume of distribution (Vd) of ethanol is about 0.6 L/kg, which is nearly equivalent to that of water.

- Ethanol diffuses across cell membranes easily and is absorbed from the gastrointestinal tract rapidly.
- Ethanol penetrates the blood brain barrier and placenta .

- oxidation of Et yields 7.1 kcal/g, calories obtained from Et alone are insufficient for maintenance of body weight for chronic drinkers.
- However, **starvation** can occur in chronic drinkers due to the absence of other important nutrients, which are present in a normal, complete diet.

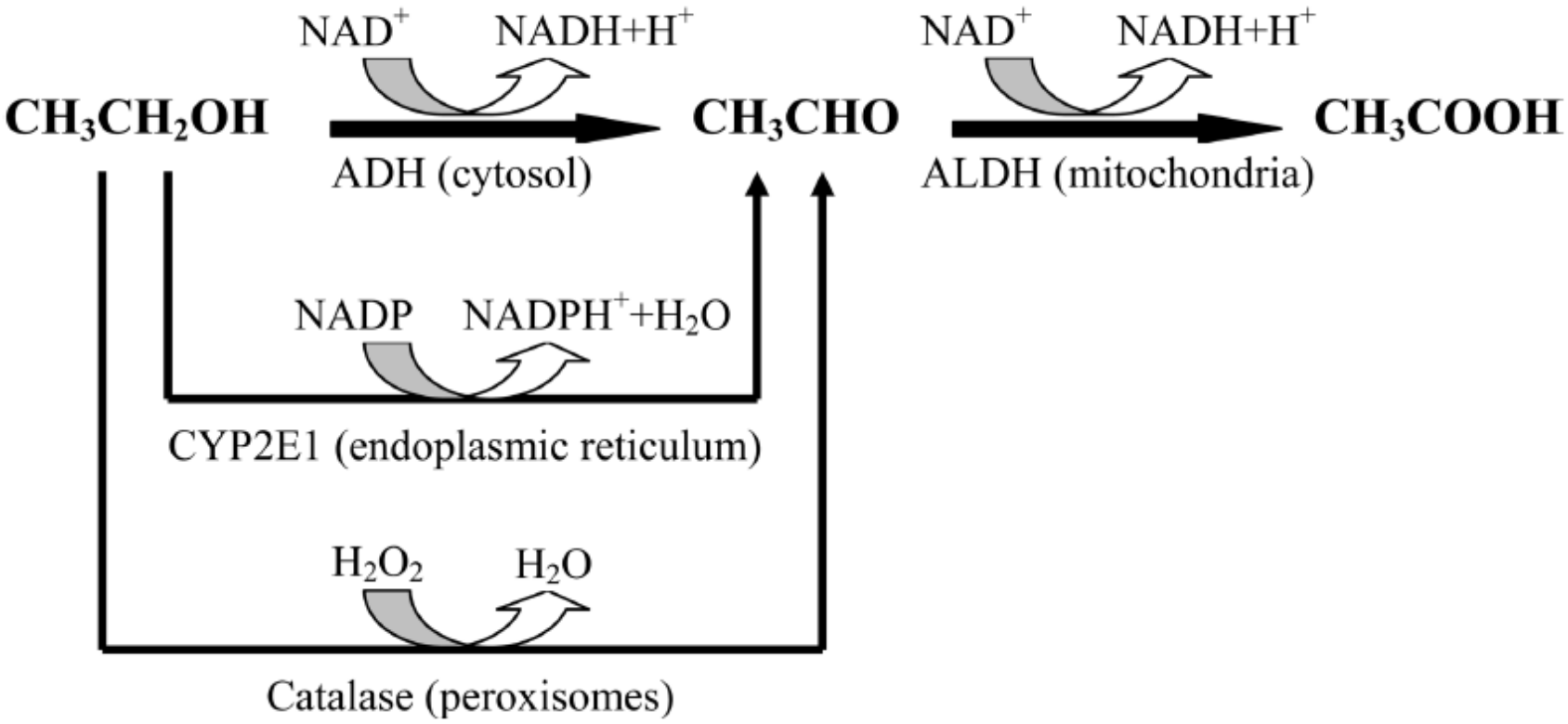
TOXICOKINETICS

The absorption of ethanol from the GI is within 30-60 mn.

- The absorption of ethanol from the GI tract may be delayed by various factors, including co-ingested food, drugs, and medical conditions that inhibit gastric emptying.

More than 90% of the ingested ethanol is oxidized to acetaldehyde by liver (first passes through the liver) and gastric mucosal cells; 5 to 10% is excreted unchanged by kidneys, lungs, and sweat.

Metabolic pathways of ethanol



- For example, some Asian people have a facial flushing reaction when they drink 'alcohol, which is caused by the lower efficiency of their ALDH, leading to accumulated acetaldehyde in blood.

- In addition, ethanol-induced diseases such as pancreatitis, liver cirrhosis and esophageal cancer.

CALCULATION OF BLOOD ALCOHOL CONCENTRATIONS (BAC)

- The blood concentrations of ethanol provides useful information regarding the severity of its intoxication.
- BAC can be calculated according to the following equation, where Vd is the apparent volume of distribution.

BAC (mg/dl) =

[amount of ethanol ingested (mg) /Vd (1/kg)] × body weight (kg) × 10

Mechanisms of toxicity of ethanol

The target of ethanol toxicity:

liver, nervous, gastrointestinal (GI), and cardiovascular (cv)systems .

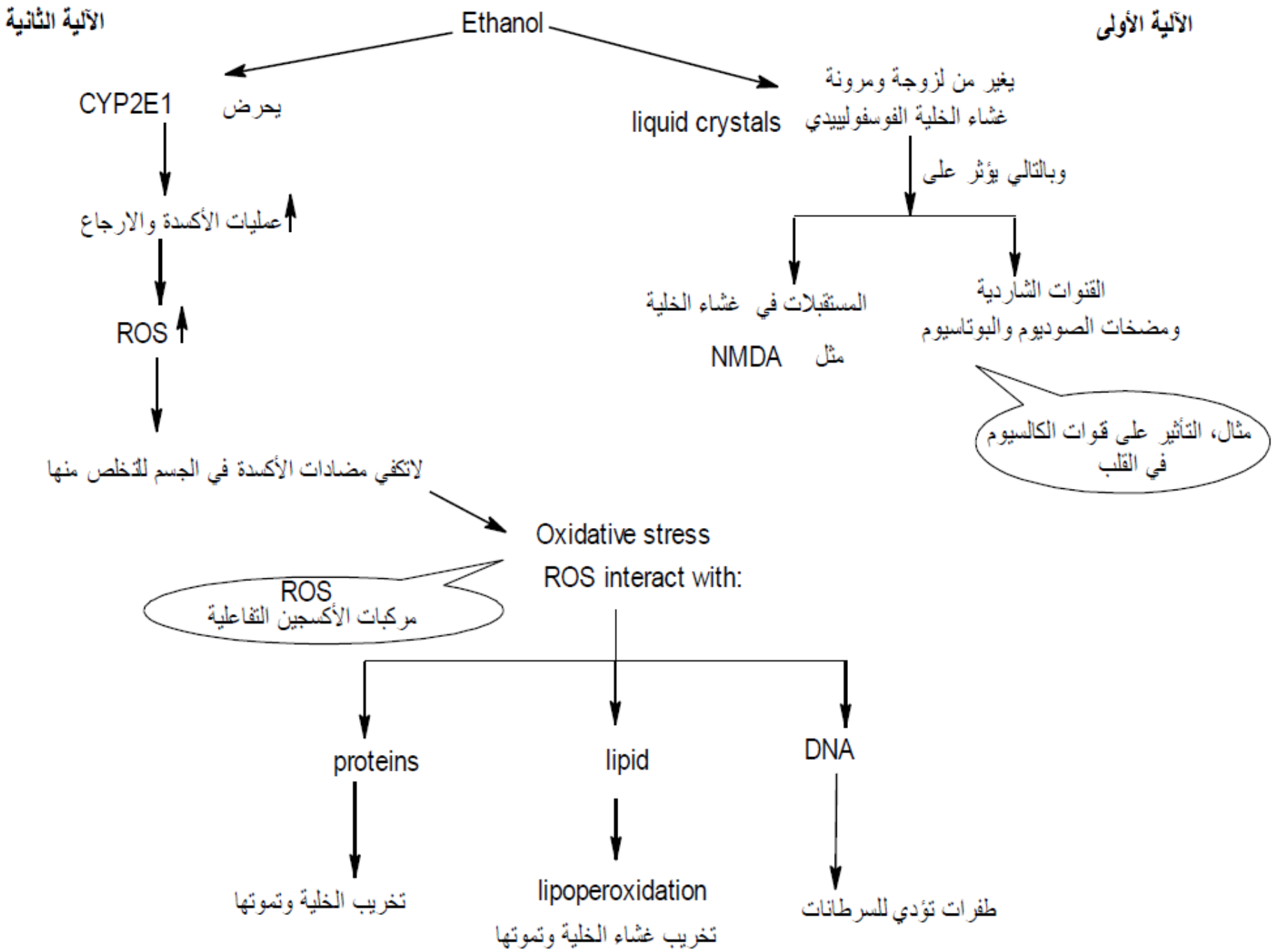
1- Et directly affects cell membrane fluidity and modifies membrane proteins, which may result in alterations in the liquid-crystal state of membranes, membrane ion transport, transmembrane signal transduction [i.e., N-methyl-D-aspartate (NMDA) receptor] activities of membrane enzymes (i.e., Na+-K+-ATPase).

2-The free radicals and reactive oxygen species (ROS) may contribute significantly to ethanol-induced toxicity.

including superoxide, hydrogen peroxide, and hydroxyl radicals. has been shown to result in the formation of 1-hydroxyethyl radicals.

3- Ethanol toxicity is also attributable to the formation of phosphatidyl -ethanol (PE).

(PE) interferes with cell signaling, leading to cell dysfunction ,direct effects on the functions of cell membranes.


الآلية الثانية
Ethanol
الآلية الأولى
CYP2E1
يحرض
يغير من لزوجة ومرونة
غشاء الخلية الفوسفوليبيدي
liquid crystals
عمليات الأكسدة والارجاع
وبالتالي يؤثر على
ROS
المستقبلات في غشاء الخلية
مثل NMDA
القنوات الشاردية
ومضخات الصوديوم والبوتاسيوم
مثال، التأثير على قوات الكالسيوم
في القلب
لاتكفي مضادات الأكسدة في الجسم للتخلص منها
Oxidative stress
ROS interact with:
ROS
مركبات الأكسجين التفاعلية
proteins
lipid
DNA
تخريب الخلية وتموتها
lipoperoxidation
تخريب غشاء الخلية وتموتها
طفرات تؤدي للسرطانات

4-Fatty acid ethyl esters (FAEEs) produced from conjugations of ethanol and fatty acids are also implicated in ethanol mediated toxicity in various organs, including heart, brain, pancreas and liver.

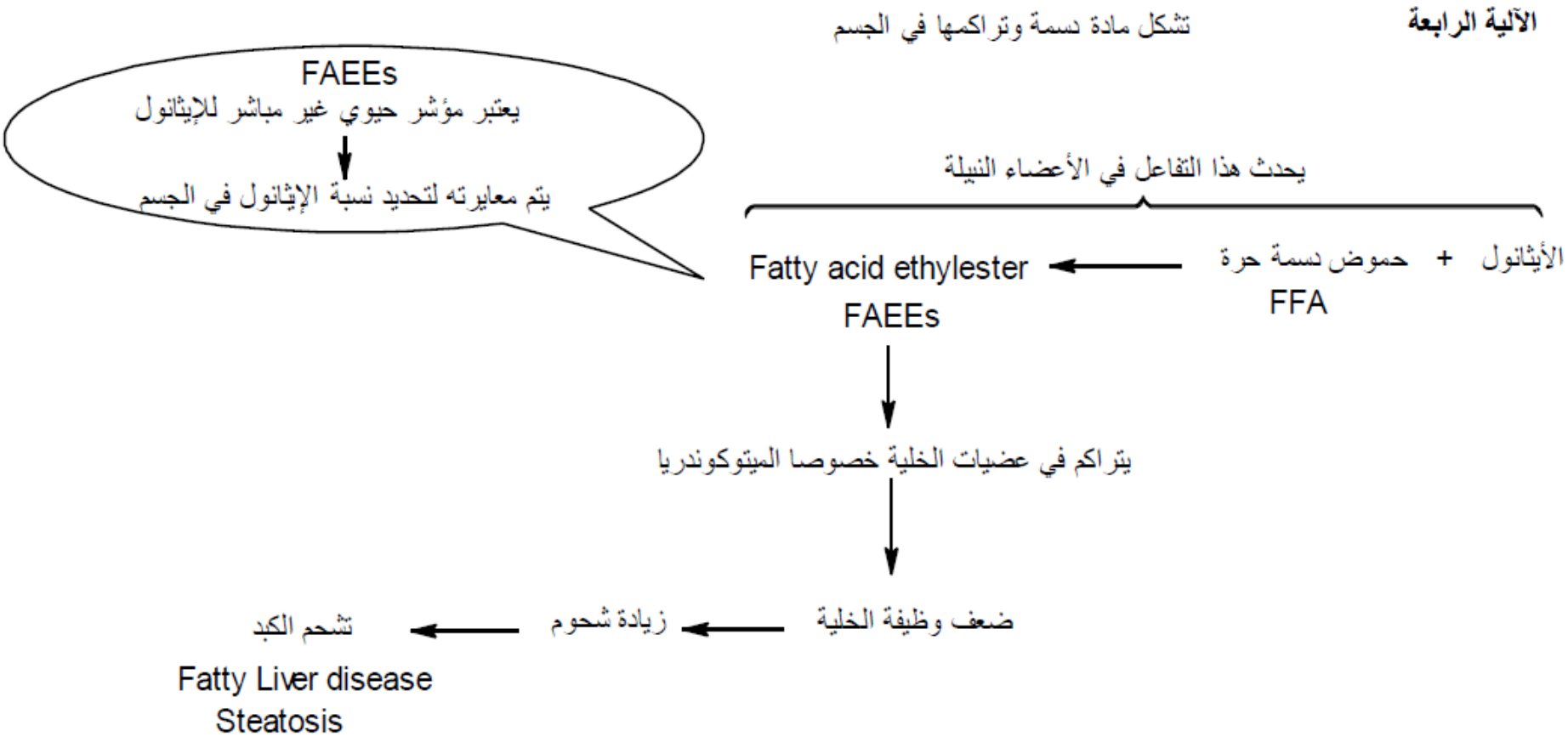
5-Ethanol inhibit the expression of the mitochondrial electron transport chain (METC),sush as NADH dehydrogenase and cytochrome c oxidase and resulting decreased ATP synthesis.

- Generally, women have a higher peak ethanol concentration than men if exposed to the same amount of ethanol, due to their lower body water content and the lower level of ADH in gastric mucosal cells.
- ADH, ALDH, and CYP2E1 display genetic polymorphisms.
- Polymorphisms of these alcohol-metabolizing enzymes may lead to alterations in the ethanol elimination rate.

Mechanisms of Organ-Specific Toxicity

Liver:

- The increased NADH levels resulting from Et oxidation not only reduces gluconeogenesis but also accelerates triglyceride synthesis from free fatty acids, which leads to steatosis(accumulation of fat in liver parenchyma).

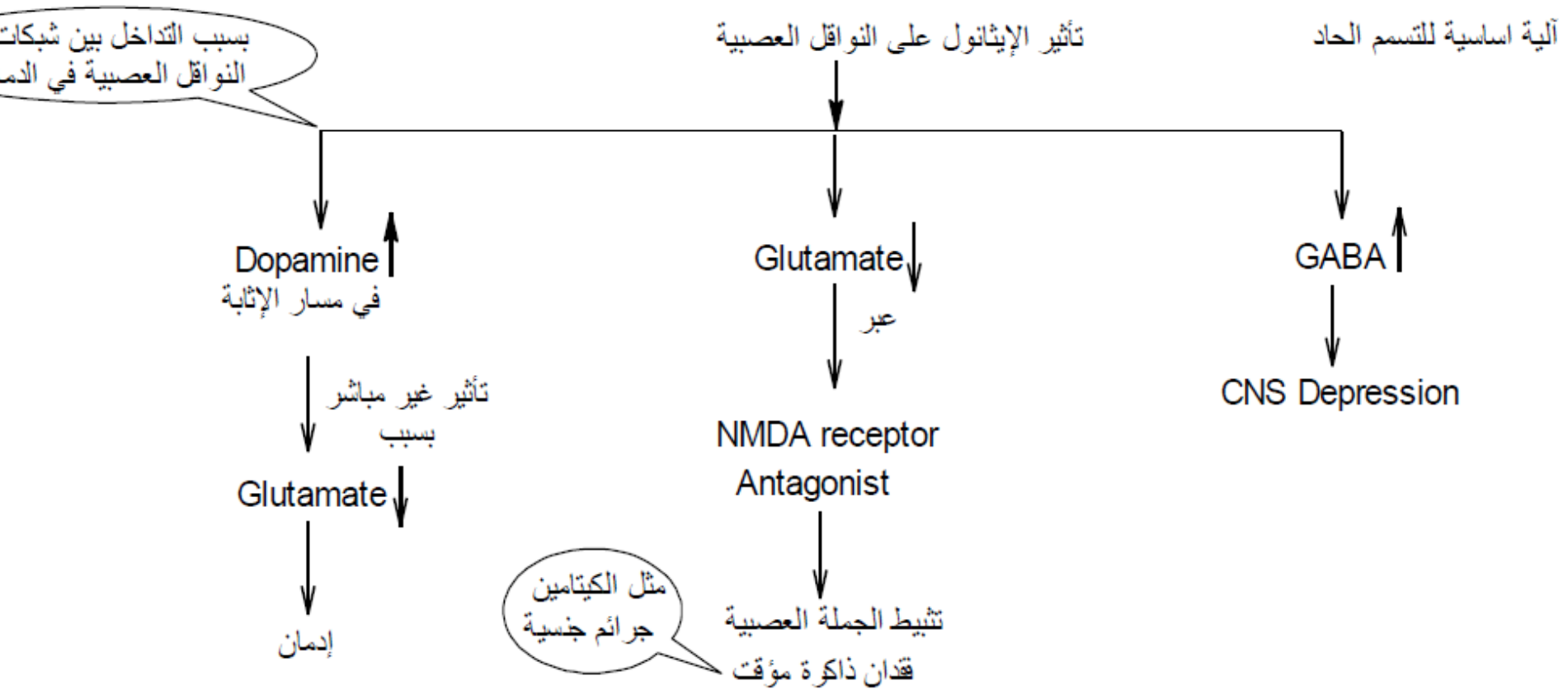

الآلية الرابعة
تشكل مادة دسمة وتراكمها في الجسم
FAEEs
يعتبر مؤشر حيوي غير مباشر للإيثانول
يتم معايرته لتحديد نسبة الإيثانول في الجسم
يحدث هذا التفاعل في الأعضاء النبيلة
الأيثانول + حموض دسمة حرة
FFA
Fatty acid ethylester
FAEEs
يتراكم في عضيات الخلية خصوصا الميتوكوندريا
ضعف وظيفة الخلية
زيادة شحوم
تشحم الكبد
Fatty Liver disease
Steatosis

- Acetaldehyde interacte with cellular macromolecular ,leading to the formation of protein and enzyme inactivation, and stimulate collagen synthesis by liver cells induced liver cirrhosis.
- Ethanol stimulates release of endotoxin by Gram- negative bacterriain the gut and inters the liver induces liver toxicity.

central nervous system:

- As a central nervous system (CNS) depressant, Et alters neurotransmission by interfereing with G protein–regulated, and voltage-sensitive channels, as well as its interaction with glutamate and g-aminobutyric acid (GABA)- neurons.

الآلية السادسة



Myocardium

- Chronic Et intoxication induces cardiotoxicity by interfering with myocardial stores of catecholamines and by decreasing synthesis of cardiac contractile proteins, leading to depression of myocardial contractility.

GI effects:

- GI effects of Et ingestion in acute intoxication impair the gastric mucosal barrier and increase gastric and pancreatic secretions. Commonly, Et irritates the GI tract and associated diseases of the stomach and intestinal tract.

MANAGEMENT OF ACUTE INTOXICATION

- The severity of acute alcohol intoxication is dependent on the blood ethanol concentration.

- In the management of acute ethanol intoxication, the important goal is **to prevent** the severe **respiratory depression** and the **pulmonary aspiration of vomitus that occurs.**

- Respiratory and cardiovascular systems must be supported by protecting airway and establishing ventilatory and circulatory assistance.
- Glucose is administered to treat the hypoglycemia and ketosis.
- An electrolyte solution should be given to alcoholic patients who are vomiting and dehydrated.

- Severe vomiting causes the loss of potassium; thus supplementation of potassium is required if renal function is to remain normal.
- Moreover, for chronic drinkers, nutrients such as thiamine, folate, and magnesium should be given.

Clinical Manifestations of Chronic Toxicity

- In the U.S., the level for ethanol intoxication is defined as 80 to 100 mg/d1 in most of the states. 400 mg/dl is the average lethal blood concentration
- Long-term consumption of the organ systems and chronic alcoholic addiction sustains twice the risk of death than that of nondrinkers.
- The higher risk is principally due to the greater incidence of alcoholic liver cirrhosis, infections, cancers, and CV diseases.

Clinical Manifestations of Chronic Toxicity

- Chronic Et consumption affects the (CNS) and peripheral nervous system (PNS).
- CNS damage in chronic alcoholics often presents signs and symptoms corresponding to the Wernicke–Korsakoff syndrome.

This condition is classically characterized by a triad of

1. paralysis of external eye muscles,
2. cerebellar ataxia, and
3. mental confusion.

Major Systemic Effects of Chronic Et Consumption

Liver: Alcoholic hepatitis,Cirrhosis and Liver cancer

CV system: Alcoholic cardiomyopathy,Cardiac arrhythmias and Hypertension

CNS: Wernicke–Korsakoff syndrome, Dementia ,Tolerance, dependence, and withdrawal

Major Systemic Effects of Chronic Et Consumption

GI system

- Gastritis
- Mala bsorption
- Pancreatitis
- Cancer of mouth, pharynx, esophagus

Major Systemic Effects of Chronic Et Consumption

Endocrine and metabolic systems

Hypoglycemia

- Alcoholic ketoacidosis
- Hypomagnesemia
- Hypokalemia
- Malnutrition
- Menstrual cycle abnormalities
- Impotence

Major Systemic Effects of Chronic Et Consumption

Hematologic system

- Iron, folate, B12 deficiency - anemias
- Leukopenia

Management of Chronic Intoxication

- The drugs are designed to interfere with Et metabolism.
- **Disulfiram (tetraethylthiuram)** is the most commonly used drug to prevent drinking. Disulfiram is an inhibitor of ALDH and causes the accumulation of acetaldehyde.
- Disulfiram is understood to inhibit the metabolism of other therapeutic agents such as phenytoin, isoniazid, and oral anticoagulants.
- Is becoming less favored in alcoholism therapy.

Management of Chronic Intoxication

- **Naltrexone**, the opioid receptor antagonist, has high oral bioavailability and a long duration of action.
- The basis for incorporation of an opioid antagonist for the treatment of chronic alcoholism .
- opioid receptor antagonists can reduce the cravings associated with alcohol drinking.

Management of Chronic Intoxication

- Adverse effects include nausea, dizziness, and headache, but an overdose of both naltrexone and disulfiram can result in severe liver damage, acute hepatitis, and liver failure.
- Due to the potential hepatotoxicity for both drugs, the combination of naltrexone and disulfiram should be avoided.

Management of Chronic Intoxication

- **Nalmefene** was also developed as an opioid antagonist.
- it has some advantages over naltrexone,
- including greater oral bioavailability, longer duration of action, and lack of dose dependent liver toxicity.

Fetal alcohol syndrome (FAS)

- The typical features of FAS include retarded body growth, craniofacial abnormalities, and CNS dysfunction.
- The mechanism underlying the teratogenic effects caused by chronic ethanol abuse remains uncertain.

Tolerance, Dependence, and Withdrawal

- **Addiction** the uncontrollable drive to drink alcohol is necessary to maintain an optimum state of well-being.

Tolerance, Dependence, and Withdrawal

- ***Tolerance*** refers to the situation where a higher dose of ethanol to elicit the same behavioral or physiological response.
- ***Dependence*** is defined as a uncontrollable desire to avoid the appearance of withdrwal syndrome when ethanol ingestion is ceased.
- ***Withdrwal syndromeconsists*** of sleep disruption, naxiety, sweating, tremors, even seizure and hallucinations.

Methods of Detection

- Blood alcohol levels can be determined accurately by immunoassay or gas chromatography, but it takes longer to obtain these results than from other methods.
- An electrochemical meter has been applied to test alcohol concentration in venous blood, and this method has *high sensitivity but poor specificity*.
- Breath alcohol analyzers (breathalyzer) are widely used as alcohol-screening tools, especially by law enforcement agencies.

Breathalyzer

- The calculation of the BAC depends on the constant vapor pressure (volatility) of Et, the distribution of Et between blood and pulmonary air spaces.
- This test is performed by microprocessors and infrared spectral analysis with good accuracy.
- The test relies on the oxidation of any alcohol with oxidizing substrates and the production of a green reaction product.

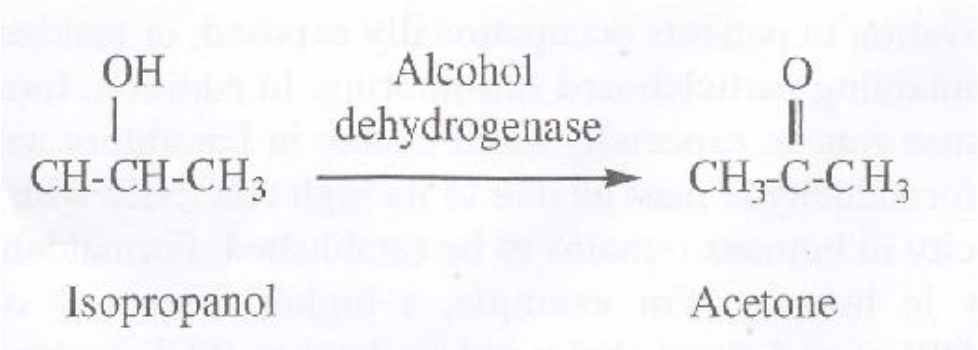
$$K_2Cr_2O_7 + CH_3 - CH_2 - OH + H_2SO_4 \rightarrow CH_3 - COOH + K_2SO_4 + Cr_2(SO_4)_3 + H_2O$$

Isopropanol

- Isopropyl alcohol is a colorless and volatile alcohol with fruity odor and a slight bitter taste.
- It may be ingested accidentally by non alcoholics and by design by alcoholics.
- Fatalities are usually associated with chronic alcoholics with mixed ingestions
- Less toxic than methanol or ethylene glycol

TOXICOKINETICS

- Isopropanol can enter the body **by ingestion**, inhalation of the vapors, or through the skin.
- Isopropanol reaches peak blood levels 30 minutes after ingestion.
- It is metabolized by hepatic ADH of which 80% is converted to acetone :



- Acetone is excreted primarily through the renal route (20% unchanged)
- A small amount through lungs, saliva, and gastric juices.
- The range of elimination half-life for isopropanol is 2.5 to 6.6 hours and 10 to 31 hours for acetone.

.

Mechanisms of Toxicity

- Because acetone cannot be further converted to an acid, isopropanol intoxicationis not considered to cause metabolic acidosis.
- The metabolite, however, is a potent **central nervous system depressant** and **about twice as toxic as Et.**
- Potentially lethal dose is 150 to 240 mL (2 to 4 mL/Kg).

Clinical Manifestations of Acute Toxicity

- The presentation of CNS depression with isopropanol intoxication includes inebriation with drowsiness, incoordination, staggering gait, and slurred speech, as well as sweating, stupor, coma, and death due to respiratory depression.
- GI responses such as nausea, vomiting, and abdominal pain and hemorrhage into the bronchi.

Clinical Manifestations of Acute Toxicity

- In addition, the patient displays an acetone odor in the breath.
- In severe intoxication, myocardial depression and severe hypotension.
- For young children with isopropanol ingestion, irritability, hypotonic, and seizures may be indicators of intoxication.

Management of Acute Intoxication

- Respiratory support and cardiac monitoring are required in the treatment of isopropanol toxicity.
- Patients who demonstrate respiratory depression require :

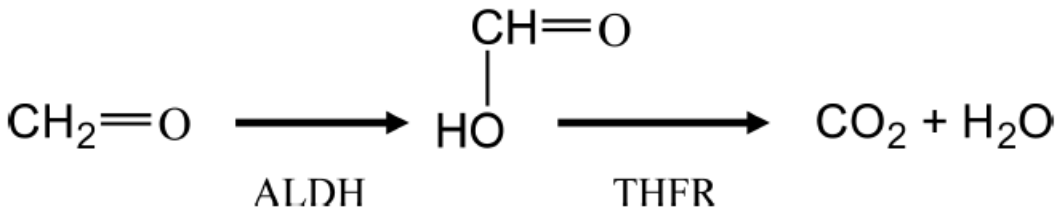
ventilatory support, gastric lavage, and hemodialysis.

Formaldehyde

- Formaldehyde is a nearly colorless gas with a pungent irritating odor.
- It dissolves easily in water and is found in formalin (formaldehyde+methanol). Formaldehyde is used as a preservative, a reducing agent, a corrosion inhibitor, a sterilizing agent ,and a histological preservative.

Toxicokinetics

- Formaldehyde can enter the body by inhalation, ingestion, or skin contact.
- Formaldehyde is readily absorbed via the respiratory and GI routes.
- Dermal absorption of formaldehyde appears to be very slight.
- In the systemic circulation, formaldehyde is rapidly metabolized to formate (CHOOH) by a glutathione-dependent formaldehyde dehydrogenase, the product of converted to carbon dioxide and water



Toxicokinetics

The formic acid may enter the one-carbon cycle and may be incorporated as a methyl group into nucleic acids and proteins.

- Metabolites of formaldehyde are mainly excreted through respiratory and renal routes.

Mechanisms of Toxicity

- Formaldehyde toxicity causes multi organ damage on either acute or chronic exposure.
- Acute toxicity is largely attributable to its irritating and corrosive properties.
- The binding of formaldehyde to endogenous proteins may result in the formation of neoantigens, which can elicit an inflammatory immune response.

Mechanisms of Toxicity

- This mechanism may account for the occurrence of asthma associated with formaldehyde exposure.
- long-term exposure to formaldehyde is associated with the formation of formaldehyde-albumin adducts, autoantibodies, and immune activation in patients occupationally exposed or residents of mobile homes .

Mechanisms of Toxicity

- formaldehyde is a known carcinogen in humans(high reactivity with DNA.
- The ability of formaldehyde to increase the frequency of DNA-protein cross-links (DPCs) and sister chromatid exchanges.(SCEs) in humans has been reported as its potential carcinogenic mechanism.

Clinical Manifestations of Acute Intoxication

- Formaldehyde primarily affects the mucous membranes of the upper airways and eyes. The manifestations include watery eyes, burning sensations in the eyes and throat, nausea, breathless, coughing, chest tightness, and difficulty in breathing at elevated levels (above 0.1 ppm).
- Drinking formalin can cause severe burns to the throat and stomach and 30 ml can cause death.

Management of Acute Intoxication

- There is no antidote for formaldehyde poisoning.
- Supportive care constitutes the primary management of patients with acute formaldehyde intoxication.

Ethylene Glycol

- HO-CH2-CH2-OH
  - تستعمل كمانع تجمد للسيارات
  - الأطفال عرضة للتسمم بالايتيلين غليكول لأن طعمه حلو ورائحته مقبولة و مستساغ
  - مادة تستخدم للانتحار بشكل شائع في الدول الغربية

الأعراض المرافقة للتسمم

1. Metabolic acidosis
2. Renal failure

Ethylene Glycol metabolism

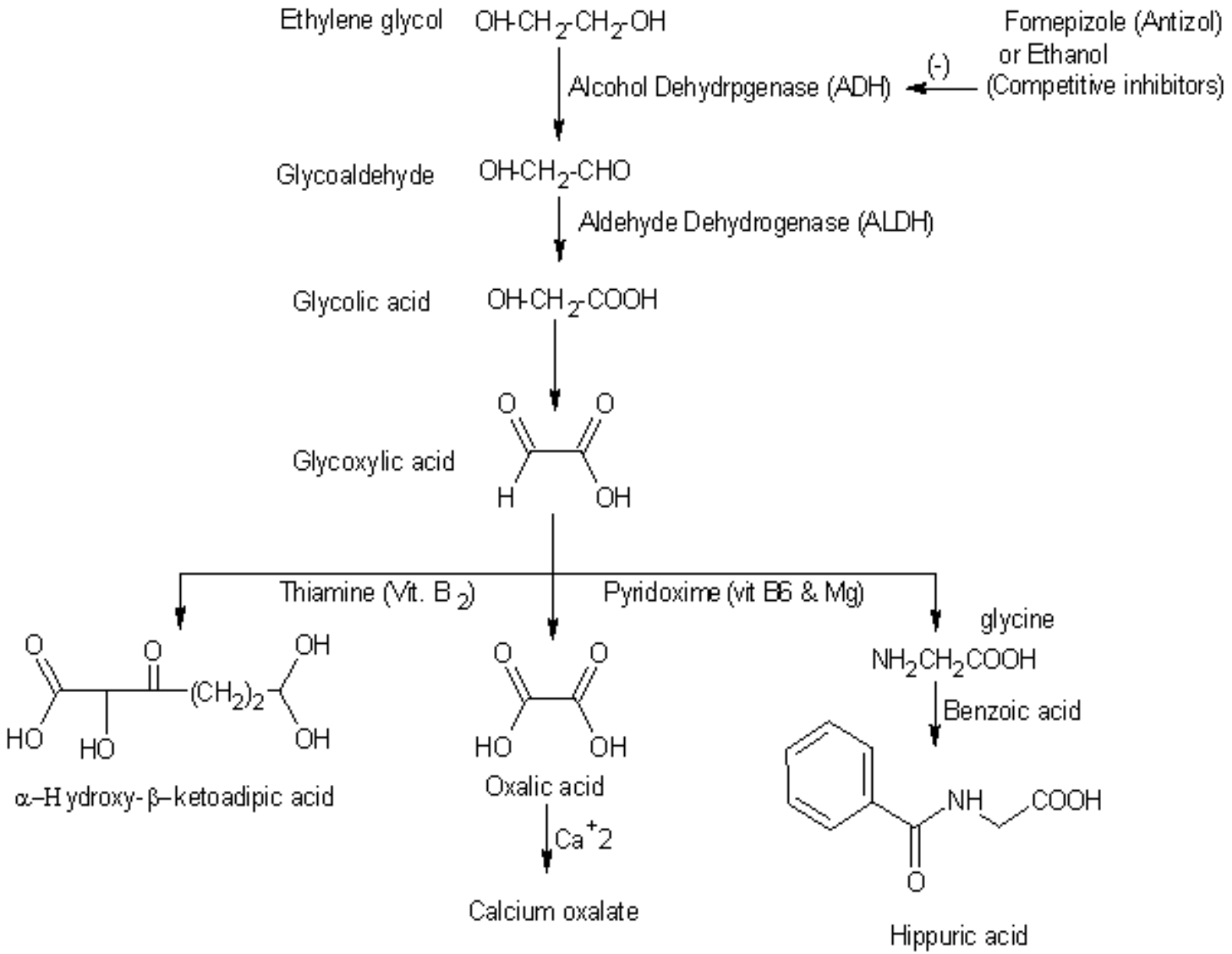
الإيتيلين غليكول يتحول بأنزيم ال ADH إلى غليكو ألدهيد Glycoaldehyde والذي يتحول بدوره إلى Glycolic Acid (GLycolate) بوجود أنزيم الALDH

ثم يتحول ال Glycolic Acid إلى Glycoxylic Acid والذي يعطي ثلاث مركبات:

- (a) الغليسين الذي يتحول بوجود البنزوئيك أسيد إلىHippuric Acid
- (b) الأوكزاليك أسيد Oxalic Acid والذي يتحول بوجود شوارد الكالسيوم إلى أوكزالات الكالسيوم وهي حصى بلورية تترسب في الكلية وتسد النبيبات الكلوية لذلك قلنا أن الإيتيلين غليكول يسبب فشل كلوي، هذا العرض يسمى آفة كلوية انسدادية Obstructive nephropathyوهي تظهر مباشرة عند التسمم الحاد.
- α –Hydroxy-βKetoadipic acid (C)

نلاحظ أن جميع المركبات الناتجة عن إستقلاب الإيتيلين غليكول هي حموض ونتيجة لذلك يعاني المتسمم من حماض استقلابي.

Ethelene glycol metabolism



Management of Acute Intoxication

- سمية الإيتيلين غليكول عائدة إلى مستقلباته أي أن تثبيط الاستقلاب يزيل السمية وبالتالي فإن العلاج يتم باستخدام أحد الترياقين أو كلاهما
- 1) **الإيتانول** :الذي يتنافس مع الإيتيلين غليكول على أنزيم ال ADH ويشغل الأنزيم(استقلاب الإيتانول بال ADH أسرع أيضاً من استقلاب الإيتيلين غليكول)وبالتالي يؤخر استقلاب الإيتيلين غليكول ويؤخر السمية(ولكنه لا يزيل السمية كلياً)
- **2) Fomepizole** يثبط أنزيم ال ADH فيمنع استقلاب الإيتيلين غليكول وبالتالي يزيل السمية.

THE END!!!