Review of Literature
2. REVIEW OF LITERATURE

2.1 Myocardial Infarction

The term "myocardial infarction" focuses on the heart muscle, which is called the myocardium, and the changes that occur in it due to the sudden deprivation of circulating blood. The word "infarction" comes from the Latin "infarcire" meaning "to plug up or cram." It refers to the clogging of the artery, which is frequently initiated by cholesterol piling up on the inner wall of the blood vessels that distribute blood to the heart muscle.

Coronary arteries are blood vessels that supply the heart muscle with blood and oxygen. Coronary atherosclerosis (or coronary artery disease) refers to the atherosclerosis that causes hardening and narrowing of the coronary arteries. Blockage of a coronary artery deprives the heart muscle of blood and oxygen, causing injury to the heart muscle. Diseases caused by the reduced blood supply to the heart muscle from coronary atherosclerosis are called coronary heart diseases (CHD). Coronary heart diseases include heart attacks, sudden unexpected death, chest pain (angina), abnormal heart rhythms and heart failure due to weakening of the heart muscle.

Myocardial infarction results from the blockage of artery due to atherosclerosis, a gradual process in which plaques (collections) of cholesterol are deposited in the walls of arteries. Cholesterol plaques cause hardening of the arterial walls and narrowing of the inner channel (lumen) of the artery. Plaque rupture with subsequent exposure of the basement membrane results in platelet aggregation, thrombus formation, fibrin accumulation, hemorrhage into the plaque and varying degrees of vasospasm. This can result in partial or complete occlusion of the vessel and subsequent myocardial ischemia.
Plaque build up in the coronary artery blocking blood flow and oxygen to the heart.

Damage and death to heart tissue shown in purple.

Fig 2.1.1 Myocardial Infarction
resulting in an acute reduction of blood supply to a portion of the myocardium. Arteries that are narrowed by atherosclerosis cannot deliver enough blood to maintain normal function of the parts of the body they supply. The initial events occur within the few seconds or minutes after total coronary artery occlusion and are associated with reversible changes. Total occlusion of the vessel for more than 4-6 hours results in irreversible myocardial necrosis, but reperfusion within this period can salvage the myocardium and reduce morbidity and mortality.

The severity of myocardial infarction is dependent on three factors: the level of the occlusion in the coronary artery, the length of time of the occlusion, and the presence or absence of collateral circulation. Generally, the more proximal the coronary occlusion, the more extensive is the amount of myocardium at risk of necrosis. The larger the myocardial infarction, the greater is the chance of death due to a mechanical complication or pump failure. The longer the time period of vessel occlusion, the greater the chances of irreversible myocardial damage distal to the occlusion. The extent of myocardial cell death defines the magnitude of the myocardial infarction.

Myocardial infarction is characterized by a reduced production of energy stores (ATP molecules), as the myocyte shifts from aerobic to anaerobic glycolysis and increased glycogenolysis. Enzymes that participate in the breakdown of glycogen such as the phosphorylases are putatively released during this time. In order to conserve energy, there is impairment or failure of the ATP-dependent ion membrane pumps resulting in the release of intracellular electrolytes such as potassium and phosphate. Concomitant to energy deficits is the inability of the heart to remove waste products. This leads to accumulation and release of metabolites such as lactate and adenosine. Low molecular weight proteins may be able to pass through reversibly injured but
reparable membranes. If the affected artery becomes potent during the early time intervals either spontaneously or by pharmacologic (thrombolytic therapy) or surgical (angioplasty or bypass) means, the jeopardized myocytes can fully recover.

Prolonged or permanent occlusion, however, leads to the onset of irreversible damage. The hallmark of irreversible damage is disruption of cellular membranes and release of macromolecules such as enzymes and large molecular weight proteins. The release of mitochondrial proteins in particular, is indicative of cell death and tissue necrosis. Cardiac enzymes and proteins have the advantage of organ specificity, and essentially are only released during irreversible damage. However, they cannot directly pass to the vasculature, and must travel through slow lymphatic drainage. Therefore there is a delay before they appear in the blood. In addition, proteins with low molecular weight will appear in blood sooner than large proteins and enzymes. The size of the protein and its distribution within the cell dictates the appearance rate. Small intracellular proteins (e.g., myoglobin and fatty acid binding protein) appear first, while large proteins (e.g., CK and LDH) and those that are part of the contractile apparatus (e.g., troponin) have a delayed appearance. Strategies for development of early acute myocardial infarction markers should be focused on proteins that are specific to the heart.

Myocardial infarction can be subcategorized on the basis of anatomic, morphologic, and diagnostic clinical information. From an anatomic or morphologic standpoint, the two types of myocardial infarction are transmural and nontransmural. A transmural myocardial infarction is characterized by ischemic necrosis of the full thickness of the affected muscle segments, extending from the endocardium through the myocardium to the epicardium. A nontransmural myocardial infarction is defined as an area of ischemic
necrosis that does not extend through the full thickness of myocardial wall segments. In a nontransmural myocardial infarction, the area of ischemic necrosis is limited to either the endocardium or the endocardium and myocardium. It is the endocardial and subendocardial zones of the myocardial wall segment that are the least perfused regions of the heart and are most vulnerable to conditions of ischemia. If a large amount of heart muscle dies, the ability of the heart to pump blood to the rest of the body is diminished, and this can result in heart failure. The body retains fluid, and organs (for example, the kidneys) begin to fail.

2.1.1 Symptoms

Everyone will experience different symptoms with each heart attack. Heart attacks frequently occur from 4:00 A.M. to 10:00 A.M due to higher adrenaline amounts released from the adrenal glands during the morning hours (Willich et al., 1992; Brezinski et al., 1988) and include the following symptoms - a sensation in the chest that may be felt as choking, numbness, squeezing or pressure. Chest pain behind the sternum is a major symptom of heart attack (Manfredini et al., 2003). But in many cases the pain may be subtle or even completely absent (called a "silent heart attack"), especially in the elderly and diabetics (Jalal et al., 1999). Often, the pain radiates from chest to arms or shoulder, neck, teeth, or jaw, abdomen or back, lasts longer than 20 min. Not fully relieved by rest or nitroglycerine, both of which can clear pain from angina, the pain can be intense and severe or quite subtle and confusing. Other symptoms either alone or along with chest pain include shortness of breath, cough, lightheadedness, dizziness, fainting, nausea or vomiting sweating, which may be profuse, feeling of "impending doom", anxiety, pallor (paleness) and restlessness.
2.1.2 Risk factors

2.1.2.1 Smoking

Prolonged exposure to cigarette smoke, either active or passive, increases the risk of dying from a heart attack or complications arising from atherosclerosis by three to fivefold. Much of the ill-omened health effects related to smoking occur due to an increase in free-radical activity. Unfortunately, as the population of free radicals increases, vitamin C (a powerful antioxidant) decreases in the smoker. The following reactions define the hardship cigarette smoking imposes upon the cardiovascular system, increased heart rate (one cigarette can increase the heart rate 20-25 beats a minute) and disrupted circulation to the legs and feet. It takes 6 h for the circulation to return to normal after just one cigarette.

Data published in the Journal of the American Medical Association (JAMA), indicate that the critical phase of cardiovascular disease is significantly accelerated in smokers. The critical phase is marked by 60% coverage of arterial surfaces with atheromatous materials. Although the ages were hypothetically assigned, a smoker with normal blood pressure and cholesterol levels reaches the critical phase 10 years earlier than the nonsmoker and 20 years earlier if the smoker is also hypertensive (Grundy, 1986).

2.1.2.2 Obesity

Excessive body weight is a risk factor in so many diseases that obesity itself is now regarded as a disease. A troublesome weight problem is no longer just an annoyance but a significant risk for heart disease, both independently and in association with other risk factors such as diabetes, hypertension and dyslipidemia (Rao et al., 2001). The pattern of the fat distribution is another important prognosticator of host vulnerability. Overeating in
the absence of obesity poses a cardiac risk, as well. Reports from patients indicated that unusually heavy meals were often consumed during a 26h period preceding a myocardial infarction (Lopez-Jimenez et al., 2000). Other factors increasing cardiovascular risk, such as excessive fibrinogen, elevated C-reactive protein, and insulin resistance, often shares common denominator obesity. During the American Heart Association's 71st Scientific Session (in 1998), the guidelines for assessing the risks imposed by obesity (as measured by Body Mass Index) were reported. This study was based on data from the Framingham Heart Study (Kagan et al., 1962), Third National Health and Nutrition Examination Survey (Thompson et al., 1998).

2.1.2.3 Diabetes

The degenerative process that accompanies diabetes significantly affects the heart. Atherosclerosis tends to develop early, progress rapidly, and be more virulent in the diabetic. Data released from the Framingham Study showed a 2.4-fold increase in congestive heart failure in diabetic men and a 5.1-fold increase in diabetic women over the course of the 18-year study (Fein et al., 1994). Diabetics are particularly susceptible to silent myocardial infarctions, that is, an asymptomatic attack that interrupts the blood flow to coronary arteries. More than 80% of people with diabetes die as a consequence of cardiovascular diseases, especially heart attacks (Whitney et al., 1998). High homocysteine levels also play a significant role in diabetes-induced cardiovascular disease.

In fact, hyperhomocysteinemia is considered a reliable predictor of mortality among diabetic patients. The symptoms of hypoglycemia can mimic a heart attack, that is, dizziness, fatigue, sweating, shakiness, lightheadedness, palpitations, and in some cases, unconsciousness. Normal brain function requires 6 g of glucose an hour, which can be
delivered only if arterial blood contains over 50 mg/dl of glucose (Pike & Brown, 1984). Although hypoglycemia is not a heart attack, the stress imposed upon the heart can be significant. Chronic hyperglycemia causes monocytes and adhesion molecules to bind to vessel walls. In turn, cholesterol and other lipids are more easily deposited. Lipids become disorganized, with more of the LDL cholesterol and less of the beneficial HDL cholesterol appearing in the bloodstream (Garg & Grundy, 1990).

2.1.2.4 Hypercholesterolemia

It is established that high cholesterol levels account for about 10-15% of ischemic strokes. When levels of HDL (high density lipoproteins, also known as good cholesterol) are elevated, cardiovascular disease is reduced. The HDL$_2$ sub fraction is even more correlated with cardiac protection and longevity than total HDL cholesterol (Sardesai, 1998). Typically, low triglyceride/LDL levels and high HDL levels place an individual in a better position cardiovascularly. Elevated triglyceride levels usually modulate when less food is consumed, particularly foods causing a rise in blood sugar levels. Too much cholesterol is not good, but too little may not be good either. The American Heart Association announced in 1999 (at the annual Stroke Conference) that people with cholesterol levels less than 180 mg/dl doubled their risk of hemorrhagic stroke compared to those with cholesterol levels of 230 mg/dL, however, the risk of a stroke escalated as cholesterol levels exceeded 230 mg/dl. The National Cholesterol Education Program announced that cholesterol levels of approximately 200 mg/dL appear ideal for stroke prevention (Castelli, 1988).

2.1.2.5 Homocysteine

Homocysteine is a sulfur containing non-essential amino acid produced by the demethylation of the essential amino acid methionine. Because of an increasing
awareness of the risks imposed by newer risk factors, homocysteine is being factored into
the genetic equation. Hyperhomocysteinemia may arise from genetic defects of enzymes
involved in homocysteine degradation and remethylation. With a gene frequency between
one in 70 and one in 200, elevated blood levels of homocysteine may be more common
than previously thought (Berwanger et al., 1995). Canadian researchers estimate the
inherited amino acid disorder (homocysteinemia) is present in approximately 20% of
coronary artery disease patients (Superko, 1995). There are multiple mechanisms
involved in the pathogenesis of hyperhomocysteinemia, including not only
heterozygosity, but dietary factors as well (Kardaras et al., 1995).

2.1.2.6 Stress

More than one-quarter of a million heart episodes occur annually, that is, palpitations,
angina, arrhythmias, and heart attack as a result of a stressful experience. During periods
of mental or emotional arousal, a silent ischemic attack (a decreased supply of
oxygenated blood) can occur. Unlike an angina attack, which is usually prompted by
physical exertion, more than three-fourths of silent ischemic attacks are caused by mental
arousal. There is also a definite link between the hardening of the carotid artery and
higher levels of stress (Barnett et al., 1997). A recent study of 2800 men and women over
55 years of age showed that even minor depression can increase cardiac mortality 60%,
while major depression may actually triple the rate of cardiac-related deaths (Penninx et
al., 2001). When an ailing heart is struggling to keep pace with circulatory demands it is
forced to deal with an emotional provocation. It is reported that an individual who is
prone to anger is about 3 times more likely to have a heart attack or sudden cardiac death
than someone who is the least prone to anger (Williams et al., 2000). Higher levels of
homocysteine are associated with feelings of aggression and rage in both men and women.
(Stoney et al., 2000). Under stress, the sympathetic nervous system is alerted and the release of adrenaline increases, ultimately, one's breathing, heartbeat, and blood pressure also increase.

2.1.2.7 Gender

Studies have demonstrated that heart disease is the number one killer for both men and women (Kagan et al., 1962; Kannel et al., 1998). In both men and women, coronary heart disease has exceeded that of other cardiovascular illnesses, such as stroke or congestive heart failure. While coronary events occurred twice as often in men, with advancing age the incidence of heart disease in women approaches that seen in men (Swahn, 1998). Premenopausal women appear to be somewhat protected from atherosclerosis due to the presence of estrogen, which lowers LDL cholesterol and raises HDL cholesterol, reducing the risk (Wenger, 2003). Menopause appears to be the interval associated with a significant rise in coronary events, as well as a shift to more serious manifestations of the disease.

2.1.2.8 Heredity

The risk is higher if there is a family history of heart diseases and people with such a history should therefore be made aware of the risk of developing heart diseases. Geneticists are looking for mutated genes that may be expressing themselves as contributors to coronary artery disease. For example, 50% of suppressed HDL cholesterol can be linked to genetic factors. A gene (ABC1), when mutated, appears responsible for increasing the risk of heart disease by lowering levels of HDL cholesterol. It is reported that people with defects in ABC1 have just as much risk for heart disease because of too little HDL as individuals with high levels of LDL cholesterol (Marcil et al., 1999).
2.1.2.9 Sedentary lifestyle

Scientists believe that a properly planned exercise program may be the single greatest preventive measure against cardiovascular disease. However, it is extremely important that the individual and the activity be properly matched. Exercise reduces blood pressure and heart rate by influencing sympathetic neural and hormonal activity. As epinephrine (adrenaline) and nor-epinephrine levels are decreased, one's blood pressure and heart rate subsequently decrease (Katona et al., 1982; Duncan et al., 1985; Smith et al., 1989). A regular exercise program reduces the risk of stroke, not only by lowering blood pressure, but also by increasing peripheral circulation and oxygen delivery. C-reactive protein, another of the newer risk factors for cardiovascular disease, also appears lowered by exercise (Szymanski et al., 1994; Ford, 2002). Excessive fibrinogen, a risk factor for cardiovascular disease, is impacted by exercise. Exercise of moderate intensity increases fibrinolytic activity by increasing tissue plasminogen activators, which break down fibrinogen, decreasing the risk of blood clot formation.

2.1.2.10 Newer risk factors

In the last 25 years, the incidence of coronary fatalities has decreased 33%. This is due largely to avoiding the traditional risk factors. An auxiliary list of newer predictive factors may significantly increase the numbers benefiting from 21st century diagnostics and treatment (Ridker, 1999). Those with high levels of fibrinogen were more than twice as likely to die of a heart attack, the risk of a stroke increases as well (Wilhelmsen et al., 1984; Packard et al., 2000). Lipoprotein (a) modulates fibrinolysis, inhibits plasminogen binding to fibrin, and may also inhibit t-Pa, a clot-dissolving substance produced naturally by cells in the walls of blood vessels. The end result is a greater risk of blood clot formation, and thus heart attack and stroke (Loscalzo et al., 1990; Ridker, 2000; Caplice
et al., 2001). Homocysteine is regarded as more dangerous than cholesterol because homocysteine damages the artery and then oxidizes cholesterol before cholesterol infiltrates the vessel (Braverman, 2003). It is now widely recognized by scientists as the single greatest biochemical risk factor for heart disease, estimating that homocysteine may be a participant in 90% of cardiovascular problems. Syndrome X represents clusters of symptoms and includes an inability to fully metabolize carbohydrates, hypertriglyceridemia, reduced HDL levels, smaller and denser LDL particles, increased blood pressure, visceral adiposity, disrupted coagulation factors, insulin resistance, hyperinsulinemia, and often, increased levels of uric acid, a forerunner to heart disease (Reaven, 2000; Fang et al., 2000). C-reactive protein appears intricately involved in the inflammatory process, thus proving to be a potential target for the treatment of atherosclerosis (Pasceri et al., 2000; Alvaro-Gonzalez et al., 2002).

2.1.3 Signs and tests

Physical examination may show rapid pulse, crackles in the lungs, a heart murmur, or other abnormal sounds. Blood pressure may be normal, high or low. The following tests may reveal a heart attack and the extent of heart damage:

Cardiac enzymes are muscle proteins that are released into the blood circulation by dying heart muscles when their surrounding membranes dissolve. Such enzymes include creatine kinase (CK), special subforms of CK, and troponin (Collinson et al., 2003). The following tests may show the by-products of heart damage and factors indicating a high risk for heart attack,

- Troponin T
- Creatine kinase
- Diagnostic marker enzymes
• Lipid profile
• Homocysteine
• Electrocardiogram (ECG) single or repeated over several hours changes
  (Kennon et al., 2003)
• Echocardiography
• Coronary angiography
• Nuclear ventriculography (MUGA or RNV)

2.1.4 Treatment

The goals of treatment are to stop the progression of the heart attack, to reduce the demands on the heart so that it can heal, and to prevent complications. The immediate goal of treatment is to quickly open the blocked artery and restore blood flow to the heart muscle, a process called "reperfusion". Delay in establishing reperfusion can result in irreversible death to the heart muscle cells and reduced pumping force of the remaining heart muscle (Gersh, 2003; Janousek, 2003). An intravenous line will be inserted to administer medications and fluids. A urinary catheter may be inserted to closely monitor fluid status. Oxygen is usually given, even if blood oxygen levels are normal. This makes oxygen readily available to the tissues of the body and reduces the workload of the heart. Nitrates such as nitroglycerin are given for pain and to reduce the oxygen requirements of the heart. Morphine or morphine derivatives are potent painkillers that may also be given for a heart attack.

If the ECG recorded during chest pain shows a change called "ST-segment elevation," clot-dissolving (thrombolytic, blood thinning medications) therapy may be initiated as an IV infusion of streptokinase or tissue plasminogen activator. Blood clots are a major factor in heart attacks. Anti-clotting agents that inhibit or break up blood clots are used at
every stage of heart disease. They are generally either anti-platelet agents or anticoagulants. It will be followed by an IV infusion of heparin as a blood-thinning agent to prevent blood clots and to maintain an open artery during the initial 24-72 hours (Neri Serneri et al., 1989). Taken orally, warfarin may be prescribed to prevent further clot development.

Thrombolytic therapy is not appropriate for people who have had a major surgery, organ biopsy or major trauma within the past 6 weeks, recent neurosurgery, head trauma within the past month, history of gastrointestinal bleeding, brain tumor, stroke within the past 6 months and current severely elevated high blood pressure. Significant bleeding can complicate use of thrombolytic therapy. A cornerstone of therapy for a heart attack is antiplatelet medication. One antiplatelet agent widely used is aspirin. Aspirin alone has been reported to reduce risk of death from heart attack or stroke by 25% to 50% and to cut risk of non-fatal heart attacks by 34% (Buerke & Rupprecht, 2000). Two other important antiplatelet medications are ticlopidine (Ticlid) and clopidogrel (Plavix). Other medications include β-blockers, ACE Inhibitors and calcium channel blockers.

β-blockers reduce the oxygen demand of the heart by slowing the heart rate and lowering pressure in the arteries. They are now well known for reducing deaths from heart disease by reducing the workload of the heart. They include propranolol (Inderal), carvedilol (Coreg), bisoprolol (Zebeta), acebutolol (Sectral), atenolol (Tenormin), labetalol (Normodyne, Trandate), metoprolol (Lopressor, Toprol-XL) and esmolol (Brevibloc) (Gottlieb & McCarter, 2001). A number of agents are available for lowering cholesterol and other dangerous fat molecules (lipids). They include statins, fibrates and niacin. Statins may have significant benefits for heart patients. ACE Inhibitors includes
(Khattar, 2003; Bauersachs & Fraccarollo, 2003) ramipril, lisinopril, enalapril, or captopril and calcium channel blockers also serves to prevent heart failure.

2.1.5 Surgery and other procedures

Emergency coronary angioplasty may be required to open blocked coronary arteries. This procedure may be used instead of thrombolytic therapy or in cases where thrombolytics should not be used. Often the re-opening of the coronary artery after angioplasty is ensured by implantation of a small device called a stent. Emergency coronary artery bypass surgery may be required in some cases. The different types of laboratory tests (biochemical, immunological and coagulative) now available, should soon allow improvement in the diagnosis and therapy of ischemic coronary diseases.

2.1.6 Prevention

To prevent a heart attack:

- Control blood pressure
- Control total cholesterol levels.
- Stop smoking
- Eat a low fat diet rich in fruits and vegetables and low in animal fat.
- Control diabetes
- Lose weight if overweight.
- Exercise daily or several times a week by walking and other exercises to improve heart fitness. (Consult your health care provider first.)

After a heart attack, follow-up care is important to reduce the risk of having a second heart attack. Often, a cardiac rehabilitation program is recommended to return to a "normal" lifestyle. Follow the exercise, diet, and medication regimen prescribed by the doctor.
2.2 Taurine

Taurine is one of the most common sulfur-containing amino acids found in nature. This non-protein amino acid is present in high concentration in most of the tissues, amounting to about 50-60% of the total free amino acid pool. Tiedemann & Gmelin were the first to isolate taurine from ox bile in 1827, where it was found in high concentration (Huxtable, 1992). Demarcay, in 1838 gave the name taurine to a similar crystalline material obtained from ox bile. The bovine connection (Latin name "bos taurus") clearly explains the descriptive name, "Taurine". However, the name of taurine was credited by Demarcay to Gmelin. In the succeeding years, intensive analytical work produced a vast quantity of information on the distribution of taurine in animal organs.

Taurine is a conditionally essential amino acid involved in a large number of metabolic processes. Its function in the body has been underestimated for a long time. In recent years, it has become clear that taurine is a very important amino acid in the visual pathways, the brain, nervous system and cardiac functions. It is a conjugator of bile acids and hence performs key functions in cholesterol metabolism (Gaull et al., 1985). Basically, its function is to facilitate the passage of sodium, potassium, calcium and magnesium ions into and out of cells, and to stabilize the structural and functional integrity of the cell membranes (Satoh, 1998). It is involved in detoxification of xenobiotics and is also very essential for efficient fat absorption and solubilization (Loria et al., 1997). The requirement of this free amino acid is absolutely indispensable in prenatal and infant development (Chesney et al., 1998). Though absence of taurine does not result in immediate deficiency and disease, long-term deprivation can cause a multitude of health problems. One is not stumbling into the abyss of teleology in thinking
Fig. 2.2.1 Structure of Taurine
that a compound conserved so strongly and present in such high amounts is exhibiting functions that are advantageous to the life forms containing it.

### 2.2.1 Distribution of taurine

Taurine is a phylogenetically ancient compound with a disjunctive distribution in the biosphere. It is present in high concentration in algae and in animal kingdom, including insects and arthropods. It is generally absent or present in traces in the bacterial and plant kingdoms. In many animals, including mammals, it is one of the most abundant low-molecular-weight organic constituents. A 70-kg human contains up to 70 g of taurine. Taurine is found in greater concentrations in all animal products. Meat, poultry, eggs, dairy products, and fish are good sources of taurine. Table: 2.2.1 shows the level of taurine content present in some seafood (ZhaoXi-he, 1994). In plant kingdom, taurine occurs in traces, averaging ~0.01 μmol/g fresh wt of green tissue. This is <1% of the content of the most abundant free amino acids (Huxtable, 1992).

### 2.2.2 Structure of taurine

The structure of taurine was well established by Redtenbacher (1846). Taurine (2-aminoethane sulphonic acid) is a small organic molecule consisting of hydrogen (H), nitrogen (N), carbon (C), sulfur (S) and oxygen (O) (Fig: 2.2.1). It is structurally different from most of the biological amino acids in following ways;

i. It is a sulfonic acid rather than a carboxylic acid

ii. It is a β-amino acid rather than an α-amino acid

iii. It does not have a chiral center and

iv. It does not have an L- or D-configuration.
<table>
<thead>
<tr>
<th>Sea Food</th>
<th>Taurine content</th>
</tr>
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<tbody>
<tr>
<td>Conch (Strombus gigas)</td>
<td>850</td>
</tr>
<tr>
<td>Ink fish</td>
<td>672</td>
</tr>
<tr>
<td>Blood Clam</td>
<td>617</td>
</tr>
<tr>
<td>Clam</td>
<td>496</td>
</tr>
<tr>
<td>Shellfish</td>
<td>332</td>
</tr>
<tr>
<td>Crab</td>
<td>278</td>
</tr>
<tr>
<td>Prawn</td>
<td>143</td>
</tr>
<tr>
<td>Sole</td>
<td>256</td>
</tr>
<tr>
<td>Crucian carp</td>
<td>205</td>
</tr>
<tr>
<td>Silver carp</td>
<td>90</td>
</tr>
<tr>
<td>Hairtail fish</td>
<td>56</td>
</tr>
<tr>
<td>Yellow croaker</td>
<td>88</td>
</tr>
<tr>
<td>Eel</td>
<td>91</td>
</tr>
</tbody>
</table>

Values are mg/100g edible portion (Zhao Xi-he, 1994).
2.2.3 Pharmacokinetics

Though taurine can be synthesized from methionine and cysteine in living beings, it is usually derived from food sources. The average intake of taurine varies widely from 40 to 400 mg per day. Following ingestion, taurine is absorbed from the small intestine, via the β-amino acid or taurine transport system, which is sodium and chloride dependent carrier system located in the apical membrane of intestinal mucosa. Intestinal health is a major factor in the ability to absorb and provide taurine in sufficient amounts for the multitude of biological processes in which it is involved. The absorbed taurine is transported to the liver via the portal circulation, where much of it forms conjugates with bile acids. Taurocholate, the bile salt conjugate of taurine and cholic acid, is the principal conjugate formed by the action of the enzyme choloyl-CoA N-acyltransferase. The taurine conjugates are excreted through the biliary route. Taurine that is not conjugated in the liver is distributed from the systemic circulation to various tissues in the body. It is not usually completely reabsorbed by the kidneys and some fraction is excreted in the urine (Hayes & Sturman, 1981). Reports by Barada et al. (1997) indicated that the intestinal capacity to absorb taurine decreased with aging.

2.2.4 Taurine metabolism

The body synthesizes taurine from the amino acids methionine and cysteine. Vitamin B-6 (pyridoxal-5' phosphate) is a key cofactor in this process. From cysteine, hypotaurine (an intermediary product in the metabolic process) is produced. Its turnover into taurine occurs rapidly thereafter. Taurine synthesis is regulated by the enzyme cysteine sulfenic acid decarboxylase (CSAD). CSAD is activated under conditions that promote protein phosphorylation (a specific step in the conversion of amino acids into protein). Membrane changes initiated via glutamate or potassium promote CSAD activity, which implies an
Fig. 2.2.2 Metabolism of Taurine

www.genome.jp/kegg/pathway.html

1. EC 4.1.1.15: glutamate decarboxylase
2. EC 4.1.1.29: L-cysteinesulfinic acid decarboxylase (CSAD)
3. EC 1.13.11.19: cysteamine oxygenase
4. EC 1.13.11.20: cysteine dioxygenase
5. EC 1.8.1.3: hypotaurine dehydrogenase
6. EC 2.3.2.2: gamma-glutamyltransferase
7. EC 4.4.1.10: cysteine lyase
8. EC 2.7.3.4: taurocyamine kinase
9. EC 2.3.1.65: glycine N-choloyltransferase
10. EC 2.6.1.55: taurine-2-oxoglutarate transaminase
11. EC 1.4.99.2: taurine dehydrogenase
12. EC 4.4.1.12: sulfoacetaldehyde lyase
anti-excitotoxic role of taurine. There is evidence that taurine is converted into five other compounds in biological systems. It is converted either to inorganic sulfate and carbamyltaurine or to taurocyamine and phosphotaurocyamine. It can also be converted into isothionic acid, or conjugated with bile acid which is the major route. Three different types of reactions, transamination, oxidation and oxygenation initiate taurine degradation. In the first two cases, sulfoacetaldehyde is an intermediate, whereas in the third case, taurine is converted to sulfite and aminoacetaldehyde (Fig: 2.2.2).

2.2.5 Properties of taurine

2.2.5.1 Physico-chemical properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Details</th>
</tr>
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<tbody>
<tr>
<td>Molecular formula</td>
<td>$\text{C}<em>{21}\text{H}</em>{17}\text{NO}_3\text{S}$</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>125.15</td>
</tr>
<tr>
<td>Physical state</td>
<td>Tetragonal needle shaped crystals.</td>
</tr>
<tr>
<td>Colour</td>
<td>Colorless</td>
</tr>
<tr>
<td>Odor</td>
<td>Odorless</td>
</tr>
<tr>
<td>Solubility</td>
<td>Soluble in water (10.48 g/100ml at 25 °C) and insoluble in absolute alcohol.</td>
</tr>
<tr>
<td>Melting point</td>
<td>328 °C (decomp.)</td>
</tr>
<tr>
<td>pH (0.5M in water, 25 °C)</td>
<td>4.5-6</td>
</tr>
<tr>
<td>Optical rotation</td>
<td>Nil</td>
</tr>
</tbody>
</table>

2.2.5.2 Physiological properties

(i) Antilipidemic effect of taurine

Taurine has been reported to attenuate the elevation in total and LDL cholesterol levels in people consuming high fat/ high cholesterol diet. Recently, physicians have
adopted 2:1 as the ideal ratio of total cholesterol to HDL and prescribed taurine to reach that magical lipids ratio (Mizushima et al., 1996). Reports by Murakami et al. (1999) indicate that the administration of taurine lowers serum LDL and VLDL by 44% and elevates HDL by 25% in experimental mice. Taurine conjugates have been reported to suppress very low-density lipoprotein (VLDL) secretion. VLDLs are produced through a series of reactions of proteins with aldehydes. Researchers have demonstrated that taurine exhibits a high reactivity with aldehydes, thus it acts to inhibit protein modification to LDL. With regard to HDL, taurine enhances serum HDL concentration in a dose-dependent manner. High fat diets produce hypercholesterolemia (elevated cholesterol), atherosclerosis, and accumulation of lipids on the aortic valve of the heart. The taurine supplementation to the cholesterol-free diet has also been reported to produce 43% reduction in hepatic triglycerides content (Park & Lee, 1998). The antilipidemic and cholesterol-lowering action of taurine may lie in its ability to promote the degradation of potentially detrimental cholesterol to relatively harmless bile acids.

(ii) Antidiabetic effect of taurine

In both forms of diabetes, insulin dependent (Type 1) and non-insulin dependent (Type 2), taurine exerts a multitude of beneficial actions. Supplementation of taurine has been reported to prevent the triggering of platelet aggregation in Type 1 diabetes, a major risk factor of cardiovascular diseases (Franconi et al., 1995). Administration of taurine has also been found to normalize the adverse blood lipid profile associated with the diabetic condition. Reports (You & Chang, 1998) indicate that administration of taurine can counteract the elevated plasma triglycerides and LDL cholesterol in diabetics with no adverse effect on serum glucose levels. This effect is largely due to a correction of vascular endothelial vasodialation characteristic of the diabetic state (Kamata et al.,
In Type 2 diabetics, the impaired glycemic control is largely due to peripheral insulin resistance, hepatic insulin resistance, and a failure of β-cell function. Recently, taurine as well as the more established natural agents, has found a role in correcting the metabolic anomalies in vascular smooth muscle produced by Type 2 diabetes (McCarty, 1997).

In models of diabetic mice, researchers found that taurine supplementation yields specific beneficial effects on levels of malondialdehyde (MDA), a marker of lipid peroxidation resulting from free radical damage. Dietary supplementation of taurine is able to correct abnormal elevations of MDA and thus to prevent depletion of glutathione in diabetics (Lim et al., 1998). Diabetes is notable for its impact on eyesight and to produce a generalized decline in the content of free amino acids in the retina and retinal pigment epithelium of the eye. Taurine supplementation has been reported to reduce the deleterious action of diabetes on amino acid transport systems, which results in alteration of the cellular amino acid balance. It has also been found as an effective method for correcting the antioxidative imbalances that produce diabetic cataracts (Obrosova et al., 1999).

Taurine supplementation has also been reported to prevent diabetic nephropathy, which is the leading cause of end-stage renal disease in over half of Type 1 diabetics. Reports by Trachtman et al. (1995) indicated that taurine supplementation is able to exert beneficial changes in the kidneys of diabetic rats, specifically reducing proteinuria and albuminuria by nearly half. This effect is attributed to the ability of taurine to decrease lipid peroxidation and reduce accumulation of advanced glycosylation end products within the kidney. Nandhini et al. (2004) have reported that taurine can be used as a therapeutic supplement for the prevention of diabetic pathology.
(iii) Anticancer properties of taurine

Taurine has been found to inhibit tumors and extend the survival period of tumor induced experimental mice. Zhang et al. (1997) observed that, tumor cell membrane fluidity was much improved with taurine treatment. The calcium homeostatic mechanism is one of the critical features involved in the anti-cancer functions of taurine (Finnegan et al., 1998). Also the oral administration of taurine has been found to reduce the degree of membrane damage and to activate glutathione antioxidant system in rats exposed to carcinogens. Reports by You and Chang, (1998b) suggested that taurine inhibited hepatocarcinogen-induced lipid peroxidation by operating the tissue antioxidant defense status at a higher level in the liver of experimental animals. Taurolidine, a derivative of taurine produced a significant reduction in the growth of both tumor cells and intraperitoneal tumors (Jacobi et al., 1997). Taurine level in serum and other tissues is a useful marker for providing valuable prognostic information in cancer patients (Scioscia et al., 1998; Vecer et al., 1998).

(iv) Taurine and detoxification

Taurine and to a lesser extent glycine are the major amino acids associated with the removal of toxic chemicals and metabolites from the body (Birdsall, 1998). Low taurine levels are important in chemically sensitive individuals, particularly to chemicals such as chlorine, chlorite (bleach), aldehydes, alcohols, petroleum solvents and ammonia. It has also been found that reactive unstable aldehyde compounds are formed in states of taurine deficiency (Kozumbo et al., 1992). Reports by Timbrell et al. (1995) indicate that taurine deficient individuals are more prone to xenobiotics-induced tissue damage. In the liver, taurine administration has been reported to inhibit the toxic effects of high fructose feeding, alcohol, acetaminophen, and thioacetamide in rats (Dogru et al., 2001).
kidneys, taurine has been proved to protect against cisplatin toxicity and to prevent salt feeding induced renal damage in salt-sensitive rats (Saad et al., 2002). Taurine also protected against ulcers caused by monochloramine, a toxin associated with *Helicobacter pylori* infection (Kodama et al., 2000). Supplementation of taurine has been found to inhibit intestinal endotoxin translocation and subsequent hepatic injury (Roth et al., 1997; Wang, 1995). Accumulation of heavy metals exhibits a variety of toxic effects, and taurine reduces the damage caused by excess levels of cadmium, copper, and lead in rats (Hwang et al., 1998; Hwang et al., 2001; Gurer et al., 2001). Taurine also reduced the toxic effect of oxidized fish oil in rats (Hwang et al., 2000).

(v) Antioxidant effect of taurine

Free radicals are particularly detrimental to tissues which contain high concentration of lipids (fat molecules) like LDL, which free radical atoms readily attack. Physicians now regularly recommend the use of antioxidant vitamins (A, beta-carotene, C and E) and the mineral selenium as counter-measures to free radicals. Recently, the value of taurine as a potent antioxidant has been discovered. If present in sufficient concentration, taurine protect against oxidative cellular damage (Aruoma et al., 1988). Reports indicate that taurine administration effectively counter the stimulation induced by excitatory agents in cerebella neurons. Taurine modulates cell viability, which is an important alternate protective mechanism to offer protection against free radical damage. The antioxidant properties of taurine are also seen in its ability to inhibit neutrophil burst and subsequent oxidative stress, which results in reperfusion injury to heart tissue (Raschke et al., 1995). Taurine prevents the inactivation of superoxide dismutase by $H_2O_2$ (Pecci et al., 2000). It also acts as an antioxidant by preventing changes in the levels of non-enzymatic free radical scavengers (Tadros et al., 2005).
(vi) Role of taurine on cellular tonicity

Tonicity (synonymous with osmolarity) is a term that describes the status of cell fluid volume in relation to its external medium. Taurine plays an important role in maintaining the delicate balance of tonicity in animal cells (Pasantes-Morales et al., 1998). Cells demonstrate an ability to change their concentration of taurine, in response to how plumped or shrunken in volume they become. Taurine, as an important amino acid osmolyte, helps to regulate osmolarity without causing additional perturbations of cellular tonicity. When cells are hypo-osmotic during hyponatremia, they would normally swell and could lyse if the hyponatremic state continued. Taurine is thus extruded to help prevent such severe osmolar changes. In hypernatremia, cells are usually shrunken or "crenated" and have a reduced fluid volume, taurine uptake is thus increased to help regulate osmolarity and avert severe osmolar changes associated with possible cell death (Trachtman et al., 1990). Under hyper osmolar conditions, net taurine production increases in cells so that they may maintain high intracellular levels. The pathway for taurine efflux also serves to conduct ions (potassium and chloride) from the cells as well. When researchers cultured astrocyte cells under hypo-osmolar conditions, the cells lost 88% of their taurine contents (in addition the amino acids alanine and aspartate) while restoring their normal volume (Olson, 1999). This study suggests that loss of taurine is a major factor in the process of volume regulation.

(vii) Cytoprotective effect of taurine

Taurine is able to resist the action of free radical damage that would otherwise be caused by radioactive substances (Song et al., 1998). Its suppression of transcription counters the production of collagen and elevations of hydroxyproline in pulmonary tissue, serving to protect against radiation-related pulmonary injury. Taurine has been found to
attenuate apoptosis due to oxidative stress and endothelial cell necrosis is halted with similar efficacy (Wang et al., 1996). It is also found that taurine is effective in inhibiting liver fibrosis in experimental model (Refik Mas et al., 2004). Reports by Hilgier et al. (1999) indicated that taurine's role in cell volume regulation and neuro-protection may be particularly valuable in those suffering from hepatic encephalopathy. Supplementation of taurine ameliorates ischemic damage of the liver by increasing its biliary, serum and liver calcium concentrations (Ono et al., 1998). Taurine supplementation has benefit as an adjunct therapy in fatty liver associated with simple obesity (Obinata et al., 1996). The protective action of taurine against cyclosporineA-induced hepatotoxicity suggested that taurine may find clinical application against a variety of toxins during occurrence of cellular damage as a consequence of reactive oxygen species (Hagar et al., 2004). These functions are due, in large part, to its antioxidant activity and regulation of intracellular calcium flux, which has great implications for the therapeutic value of taurine (Wang et al., 1996).

(viii) Anti-inflammatory effect of taurine

In inflammatory disease, plasma taurine becomes depleted, signifying a greater demand by the body in this state. Taurine prevents the tissue damage resulting from inflammation. The mechanism involves taurine monochloramine, a product formed through a series of reactions based in the leukocytes (white blood cells) (Nagl et al., 1998). In a dose-dependent manner, taurine monochloramine inhibits the production of substances that promote inflammation, such as nitric oxide, prostaglandin PGE2, and tumor necrosis factor. Thus, taurine itself counters the inflammatory response by reducing the expression of nitric oxide synthase and cyclooxygenase-2 (COX-2), not unlike the role of the new COX-2 specific inhibitor drugs celecoxib and rofecoxib (Barua
et al., 2001). Taurine monochloramine reduces the toxicity of free radical oxidants, serving to decrease the production of tissue-damaging inflammatory substances and regulate the function of neutrophils to promote their protective effect (Nakamori et al., 1990). Taurine also works cooperatively with the cysteine pool to lessen the depressive impact of tumor necrosis factor on cells of the lung. Son et al. (1998) reported that taurine ameliorates inflammatory bowel disease by increasing the ability of the colon to defend against oxidative damage. By inhibiting neutrophil (white blood cell) activation and lipid peroxidation, taurine prevents the adhesion of neutrophils to the gastric lining (Son et al., 1996). Taurochenodeoxycholic acid (TCDCA) is reported to attenuate raise in the hydrophobicity of the bile and to reduce the intestinal inflammation (Uchida et al., 1997). Combined treatment of taurolin with vitamin E has been shown to effectively decrease oxidative stress during peritonitis, an inflammation of the membrane lining in the abdominal cavity (Konukoglu et al., 1999). Magnesium taurate may become a valuable drug to reduce migraine incidents (McCarty, 1996).

(ix) Protective effect taurine on pulmonary function

The depletion of taurine is particularly harmful to pulmonary tissue. Alveolar macrophages reside on the surface of lung alveoli. Their main purpose is to ingest inhaled particular matter to dispose of it. Alveolar macrophages become more susceptible to reactive forms of oxygen when deprived of the antioxidant protective capacity that taurine provide (Giri & Wang, 1992). Taurine is useful as an adjunct therapy for the management of cystic fibrosis patients experiencing complications of fat malabsorption and essential fatty acid deficiency because taurine supplementation provides a more healthy profile of triglyceride absorption and fatty acid composition of chylomicrons (Belli et al., 1987; Smith et al., 1991). Hence taurine is a novel and valuable aid for cystic fibrosis treatment.
Both taurine and niacin are reported to down-regulate genetic actions that express lung fibrosis (Giri et al., 1994). Taurine and niacin completely or partially, ameliorated pulmonary fibrosis of a chemical origin (Gurujeyalakshmi et al., 1998; Wang et al., 1992). Taurine exerted a protective antioxidant effect in the prevention of damage from acute ozone exposure, especially in the bronchioles (Gordon et al., 1998).

(x) Taurine in kidney function

Taurine is necessary for the proper functioning of the kidney as an organic osmolyte. Absence of taurine resulted in diminished renal function such that the process of excretion of unwanted substances from the blood is grossly impaired. Depending on the concentration of the final urine emerging from the kidney, the medulla area will deliberately modify its own tonicity. When the fluid in medulla is hypertonic, its cells accumulate taurine and similar osmolytes, thus exerting a conservatory effect (Trachtman et al., 1992). Thus, the kidney exercises self-preservation by modulating the volume of its cells to promote its functions. This osmotic response results from an increased activity of specific sodium-coupled transporters. Supplementation of taurine prevented glomerular hypertrophy, diminished glomerulosclerosis, tubulointerstitial fibrosis and diabetic nephropathy by reducing renal oxidant injury possibly through its antioxidant effects (Chiba et al., 2002; Sener et al., 2005).

(xi) Taurine and membrane stabilization

Taurine's ability to stabilize cell membranes may be attributed to several events. Taurine has been shown to regulate osmotic pressure in the cell, maintain homeostasis of intracellular ions, inhibit phosphorylation of membrane proteins, and prevent lipid peroxidation. As an osmotic regulator, it has been suggested that taurine, along with
glutamic acid, is instrumental in the transport of metabolically-generated water from the brain (Van Gelder, 1990). Taurine acts as an antioxidizing agent and a membrane stabilizer to maintain the functions of membrane-bound protein enzymes. It is of particular value to the preservation of erythrocytes. Nandhini & Anuradha, (2003) have reported that taurine lowers glucose-induced lipid peroxidation, protein glycosylation and Na\(^+\)/K\(^+\) and Ca\(^{2+}\) -ATPase activities in red blood cells. It is suggested that the effect of taurine on lipid peroxidation could be due to its antiacidotic action as well as to its membrane stabilizing activity.

(xii) Taurine in fetal development

Taurine is critical during fetal development to produce normal fetal β-cell function (Cherif et al., 1998). According to Dhillon et al. (1998), the decrease in taurine levels in whole blood is speculated to assist with the maturation and efficiency of auditory synapses in full-term infants (Tyson et al., 1989). Reduction in the activity of placental taurine transporters resulted in low plasma taurine concentrations, with subsequently compromised availability of the amino acid for cellular processes (Norbreg et al., 1998). Taurine is now added to many infant formulas to provide improved nourishment because of its ability to improve fat absorption in pre-term infants and in children with cystic fibrosis and its beneficial effects on auditory response development (Gaull, 1989).

(xiii) Effect of taurine on alcoholism

Some of the most novel applications for taurine result from studies of its role in alcoholism. Taurine can either promote or repress the reward effects associated with alcohol consumption, the delineating factor being the amount of alcohol consumed. In a study designed to assess the preference of rats to alcohol coupled with an odor stimulus, the group that did not receive supplemental taurine became conditioned for either a
significant aversion for the stimulus (prompted by high doses of alcohol) or no reaction (prompted by lower doses). When ethanol in a 2.0 g/kg dose was given to rats pretreated with oral taurine, they responded with a reduced aversion for a particular odor stimulus when paired with alcohol consumption. This may provide important insight into the modulation of the reward effect of alcohol (Quertemont et al., 1998). Previous studies had found that while taurine does not interact with alcohol to produce an effect on alcohol consumption, its major metabolite taurocholic acid is responsible for the metabolic conversion of alcohol (Spanagel & Ziegglansbereg, 1997). Alcohol-induced fatty liver was prevented in animals receiving taurine supplementation. The protective effect of taurine is attributed to the potential of taurine conjugated bile acids (particularly taurocholic acid) to inhibit adverse enzymatic functions associated with alcohol consumption (Kerai et al., 1998).

(xiv) Taurine in vision

In the healthy eye, taurine is found in very high concentration. Nutritional factors including taurine are now recognized as important factors in the reversal of retinitis pigmentosa (Allen & Lowry, 1998). Fletcher & Kalloniatis (1997) suggest that amino acid neurochemistry may have an underlying metabolic role in the onset and progress of retinitis pigmentosa. A combination of taurine with vitamin E, vitamin C, and alpha lipoic acid has been shown to protect against radiation-associated protein leakage and may become important for the prevention of damage to the vision of people involved in radiation associated occupations (Bantseev et al., 1997). Taurine is important for the regeneration of damaged cells in the retina. Taurine activity implies a critical and changing role in the development of vision (Nag et al., 1998).
(xv) Anti-aging properties of taurine

Dawson et al. (1999) reported that the impairment in spatial learning ability of older rats was correlated to the reduction in taurine in the striatum of the brain and decline in taurine levels of the spleen, kidney, eye, cerebellum, and serum are associated with age in rats. Taurine administrated to experimental animals has been able to increase the level of acetylcholine in the brain, which is abnormally low in Alzheimer's disease (Tomaszewski et al., 1982; Csernansky et al., 1996). Taurine, along with magnesium, may target the channels of energy metabolism to reduce the risk of Alzheimer's (McCarty et al., 1998). Taurine also improved the mechanical threshold for contraction, shifting it toward the normal value (Pierno et al., 1998). The observed age related decline in taurine in L-cysteinesulfinic acid decarboxylase and cysteine dioxygenase activities in F344 rat hepatic tissue suggests that the observed decrease in tissue taurine levels might be associated with a reduction in taurine biosynthesis (Eppler & Dawson, 1999).

(xvi) Taurine and dermatological disorders

Psoriasis of a chronic, plaque-type nature has been correlated to marked depression of neutrophil taurine levels. Stapleton et al. (1996) and Yamaguchi et al. (1998) have demonstrated that the taurine conjugated bile acid taurine ursodeoxycholic acid exerted a growth suppressive effect on keratinocytes, and thus its presence may be of importance in skin conditions. Previous reports (Degim et al., 2002; Farriol et al., 2002) indicate that administration of taurine improves recovery from burn-injured skin and a topical taurine gel accelerates wound healing in mice. As an osmolyte, taurine helps maintain hydration in the epidermis when it is exposed to a dry environment (Jaeke et al., 2003).
Antimicrobial effect of taurine

The taurine derivative N-chlorotaurine is a weak oxidant produced by leukocytes in response to bacterial and fungal exposures and it destroys pathogens incurred as a result of inflammatory reactions (Nagl et al., 1998). This may become an important addition to the list of substances that are useful as antiviral agents. By virtue of its detergent activity, taurolithocholic acid 3-sulfate demonstrates excellent anti-pathogen activity against chlamydia, herpes simplex (types 1 and 2), gonorrhea, and human immunodeficiency virus. It is also less cytotoxic than other agents used. Taurolithocholic acid 3-sulfate may be a valuable topical microbiocidal agent against sexually transmitted diseases (Herold et al., 1999). The amino acid taurine, down regulates polymorphonuclear neutrophil cell death and preserves function in the urine, suggesting taurine as a therapeutie option for urinary tract infection (Condron et al., 2004). Taurolin, a derivative of taurine is a potent chemotherapeutic agent that mobilizes anti-microbial activity against bacteria, yeast, and mycetes (fungi). Jurewitsch et al. (1998) reported that low daily doses of taurine instilled in conjunction with the parenteral infusion has been shown to successfully reduce catheter-related bloodstream infections.

Other properties

Nitric oxide and nitric oxide generating compounds (L-arginine, potassium, antioxidants and fish oil) promote N-methyl-D-aspartate activity and releases taurine (Albrecht, 1998). Taurine modification of the polyurethane heart valves, improves their durability by promoting and prolonging the flexing capacity over long-term usage (Bernacca et al., 1998). The taurine-conjugated bile salt taurochlorate, exerting a detergent-like activity, markedly inhibits occlusive action encountered in enteral feeding (Yeoh et al., 1996). A hormone called glutataurine was discovered in the parathyroid
gland of rats. Feuer et al. (1983) found that this peptide had highly selective action on adrenal hormones, which are involved in the body's response to stress. Glutataurine has vitamin A-like effects and it antagonizes cortisone and thyroxine and increases the development of the thymus. Lampson et al. (1983) have found that taurine increases some of the effects of insulin.

2.3 Isoproterenol

2.3.1 Chemistry

Chemically, isoproterenol is an L-β-(3,4-dihydroxyphenyl)-α-isopropyl amino ethanol hydrochloride with a molecular formula of C_{11}H_{17}NO_{3}.HCl. Its molecular weight is 247.7. The hydrochloride salt of isoproterenol is a white to off-white crystalline powder of melting point 170-171 °C. It is soluble in water and ethanol (Fig: 2.3.1).

2.3.2 Mechanism of action and biological effects of isoproterenol

Isoproterenol is a synthetic β-adrenergic agonist and have been used for the induction of myocardial infarction. The pathophysiological changes associated with myocardial infarction induced by isoproterenol mimics to a greater extent with those occurring in humans (Ravichandran et al., 1990). Isoproterenol is a β-adrenergic receptor agonist that increases cytosolic cAMP. In the case of β-adrenergic agonist action, the circulating hormones or drug is the first “messenger”, interacting with β-adrenergic receptor on the external surface of the target cells (Rendon & Lopez, 2001). The drug hormone receptor complex activates the enzyme adenyl cyclase on the internal surface of the plasma membrane of the target cells. This accelerates the intracellular formation of cyclic adenosine monophosphate (cyclic AMP), the second “messenger” which then stimulates...
Fig. 2.3.1 Structure of Isoproterenol
or inhibits various metabolic or physiological processes (Robison et al., 1968; Motulsky & Insel, 1982).

Isoproterenol induces MAP (mitogen activated protein) kinase activation and cardiomyocyte hypertrophy through two different G proteins, Gs and Gi. cAMP-dependent protein kinase A (PKA) activation through Gs phosphorylates β-AR, leading to the coupling of the receptor from Gs to Gi. The activation of MAP kinase through Gβr, Sre family tyrosine kinase leads to the formation of She-Grb2-Sos complex, Ras and Raf-I kinase (Yamazaki & Yazaki, 2000). Thus isoproterenol increase the activities of Raf-I kinase and MAP kinase, which accelerate phenylalanine incorporation into proteins (Yamazaki et al., 1997), leading to cardiomyocyte hypertrophy (Zou et al., 1999).

It has been shown that isoproterenol induces myocardial cell injury similar to that reported for myocardial infarction, myocardial ischemia, cardiac stress and Chagasic cardiacmyopathy (Rona et al., 1983; Cebelin & Hirsch, 1980). Several studies have investigated the molecular and cellular mechanism of isoproterenol-induced cell injury of the myocardium (Chagoya De Sanchez et al., 1997; Curti et al., 1990; Capozza et al., 1992; Rendon & Lopez, 2000; Kondo et al., 1987). Among these, the investigation by Chagoya De Sanchez et al. (1997) establishes a long-term, integrated model of isoproterenol-induced myocardial cell damage encompassing structural, biochemical and physiological aspects.

The enhanced adenylate cyclase activity as result of isoproterenol induction increases cAMP formation, which in turn would have lead to the higher lipid accumulation in the myocardium (Subhash et al., 1978). Isoproterenol is reported to increase lipolysis (Mohan & Bloom, 1999) and this may play a role in isoproterenol-induced myocardial necrosis. Hypertriglyceridemia and high levels of ester cholesterol in serum and heart tissue are the
major factors responsible for the altered cardiovascular functions during isoproterenol-induced myocardial infarction (Freedmann et al., 1988). Accelerated degradation of membrane phospholipids by phospholipase and lysophospholipase has also been proposed to be related to membrane dysfunction and irreversible ischemic injury (Farber & Young, 1981). The administration of isoproterenol increases the activities of myocardial cholesterol ester synthetase and triglyceride lipase with simultaneous decline in the activities of cholesterol ester hydrolase and lipoprotein lipase.

Accumulation of ester cholesterol occurs when the rate of esterification by cholesterol ester synthetase exceeds the rate of hydrolysis, which in turn results in myocardial membrane damage. Peroxidation of endogenous lipid is a major factor in the cytotoxic action of isoproterenol (Namikawa et al., 1992). A growing body of evidence is emerging which suggests that reactive oxygen-derived free radicals play a crucial role in the pathogenesis of isoproterenol-induced myocardial infarction (Nirmala & Puvanakrishnan, 1994).

2.3.3 Ultrastructural features in isoproterenol-induced myocardial infarction

Histopathological studies of the heart show that, isoproterenol results in extensive necrosis extending from the apex to the left ventricle and into the portion of right ventricle and the severity is proportional to its dosage. Myocardial infarction induced by isoproterenol results in the loss of normal convergence of the cardiac cell plates to the ventral veins. Neighboring myocytes shows nuclear and cytoplasmic variations in size and shape. Cells with swollen or even "ballooned" cytoplasms are frequent. Various sizes of necrotic foci of cardiac cells appear, and infiltration of mesenchymal cells to these areas is seen (Fukuda, 2002). Most of the myocytes are eosinophilic in their cytoplasm and the nuclear chromatins appear to be irregularly arranged and endoplasmic reticulum
particularly clumped (Meyer et al., 2001). Periportal fields show enlargement and show inflammatory infiltration (Cortinovis et al., 1993). The rough surfaced endoplasmic reticulum is dilated and detached ribosomes are seen (Takahama & Barka, 1967). The nucleolus appears to be fragmented and dispersed (Alliende & Esponda, 1988). Ballooned cardiac cells and free acidophilic bodies resembling “multivesicular bodies” frequently appear. Moreover, in a few cells, concentric whorls of endoplasmic reticulum appear and numerous vesicles of smooth-surfaced endoplasmic reticulum containing small lipid droplets within their cisternae and U-shaped forms of mitochondria are frequently seen (Lewczuk & Przybylska-Gornowicz, 1997).

2.3.4 Structural and functional changes induced by isoproterenol in heart

Myocardial infarction induced by isoproterenol has been reported to show many metabolic and morphologic aberrations in the heart of experimental animals. It induces myocardial necrosis by a multiple step mechanism (Wexler, 1973; Ravichandran et al., 1991). Isoproterenol has been reported to cause oxidative stress in the myocardium, which results in infarct like necrosis of heart muscle (Nirmala & Puvanakrishnan, 1994).

Administration of isoproterenol induces a significant elevation of the ST-segment elevation with an enhancement in ventricular wall motion (Yamamoto & Katori, 1995). It also elevates mean heart rate with an imbalance in autonomic regulation of cardiac automaticity, which accounts for the 27% incidence of arrhythmias in rats (Rote & Connor, 1992). A progressive enlargement of the LV cavity that is out of proportion to mass, similar to that observed in discrete myocardial infarction also commonly occurs in isoproterenol-induced myocardial necrosis (Teerlink et al., 1994). A drastic decrease in left ventricular pressure and shortening of the arterio-ventricular interval also occur (Chagoya De Sanchez et al., 1997).
Injection of isoproterenol stimulates the development of left ventricular hypertrophy (LVH) with an increase in relative left ventricle weight, LV protein content and LV beta-myosin heavy chain levels. The severity of isoproterenol-induced myocardial fibrosis is in correlation with a high LV ACE activity and ACE mRNA levels, which in turn lead to the parallel development of LVH (Ocaranza et al., 2002). It also increases heart rate by 60% and lowers the blood pressure, resulting possibly in a functional ischemia (Chagoya de Sanchez et al., 1997). The enhancement in heart rate is achieved by shortening the action potential duration (Dorian et al., 2002). There is some functional alterations also induced in the isolated mitochondria such as decrease in oxygen consumption, respiratory quotient, ATP synthesis, protein synthesis and, membrane potential. In isoproterenol-induced myocardial infarction, the energy imbalance is reflected by a decrease in energy charge and in the creatine phosphate/creatinine ratio.

2.3.5 Metabolic changes during isoproterenol-induced myocardial infarction

The isoproterenol-induced alterations in experimental animals includes increase in heart weight, marked electrocardiographic changes, increase in the level of serum marker enzymes and lipid peroxides and decrease in the levels of antioxidants (Manikandan et al., 2002). Isoproterenol administration produces a marked increase in CPK, LDH, phospholipase and significant decrease in cardiac glycogen, ATP, creatine phosphate and phospholipid level (Kaul & Kapoor, 1989).

Injection of isoproterenol administration causes a dose dependant increase of lysosomal enzyme activity in vitro and in vivo (Macickova et al., 1999). The increase in the serum lysosomal hydrolase activities in isoproterenol treated rats is mainly due to the decreased stability of the membranes, which is usually reflected by the lowered activity of cathepsins D in mitochondrial and microsomal fractions (Nirmala & Puvanakrinan,
During isoproterenol-induced myocardial infarction the cytoplasm of cardiac myocytes becomes more acidic due to lactate accumulation. The infiltration of inflammatory cells at the infarct regions and altered lysosomal fragility are responsible for the increased activity of these enzymes (Ravichandran et al., 1991).

A considerable body of clinical and experimental evidence now exists suggesting the involvement of free radical mediated oxidative process in the pathogenesis of isoproterenol-induced myocardial infarction (Nirmala & Puvanakrishnan, 1996b). Alterations in tissue defense systems including chemical scavengers or antioxidant molecules and the enzymes catalase, superoxide dismutase, and glutathione peroxidase have been reported in isoproterenol-induced myocardial infarction (Sathish et al., 2003; Sasikumar & Devi, 2000). The administration of isoproterenol produces necrotic lesions in the myocardium and increases lipid peroxidation in the cardiac tissue, which plays a significant part in the pathogenesis of myocardial infarction (Noronha-Dutra et al., 1985; Singal et al., 1982 &1983). A significant depletion of cardiac glutathione (GSH) has been reported in isoproterenol-induced myocardial infarction in rats (Nirmala & Puvanakrishnan, 1996a; Hagar, 2002). Depletion of GSH is known to result in enhanced lipid peroxidation and excessive lipid peroxidation can cause increased GSH consumption and increase the susceptibility of the myocardial cells to reactive oxygen metabolites (Meister, 1988). GSH and GSH-dependent antioxidant enzyme systems are directly related to the pathogenic mechanism of isoproterenol-induced myocardial infarction (Remiao et al., 2000).

There is an early degradation of collagen immediately occurring after isoproterenol-induced myocardial infarction (Ravichandran & Puvanakrishnan, 1993). Ornithine decarboxylase (ODC) is an initial rate-limiting enzyme in the synthesis polyamines
(putrescine, spermidine and spermine). They play a role in cell growth and differentiation. Isoproterenol induces an increase in ODC activity and putrescine and spermidine level in the heart. These polyamines are one of the intracellular factors that contribute to cardiac injury (Tipnis et al., 2000). Elevation in the level of metallothionein production is induced in heart cells during experimentally induced myocardial condition for the protection of myocardial cells from injury (Namikawa et al., 1993). The cardiotoxic effect of isoproterenol is associated with calcium overload. Injection of isoproterenol leads to an increase in Ca and water content and to a reduction in the levels of Zn, Cu and Mg in heart cells (Namikawa et al., 1991 & 1993; Brembilla et al., 1993).

2.3.6 Cardioprotective agents and isoproterenol-induced myocardial infarction

Studies of Remla et al. (1991) on the effect of coconut oil and safflower oil on lipids in isoproterenol-induced myocardial infarction indicates that safflower oil exerts better protection than coconut oil by reducing the levels of cholesterol and triglycerides in heart and aorta. AO-8, a poly herbal formulation has been reported to prevent isoproterenol-induced myocardial infarction in experimental animals by counteracting the isoproterenol-induced free radical formation by its antioxidant property and membrane stabilizing action (Mitra et al., 1999). α-Tocopherol intake has been reported to be cardioprotective against experimentally induced myocardial infarction by inhibiting lipid peroxidation and by maintaining the tissue antioxidant status normal levels (Ithayarasi et al., 1996).

Reports by Manjula et al. (1992) have shown that, aspirin treatment counteracts the effects of isoproterenol on lipid peroxide formation and associated enzymes changes in serum and heart. Earlier the administration of potassium channel opener cromakalim has been reported to have less myocardial degenerative changes on histopathological
examinations when compared with those treated with isoproterenol alone (Aghi et al., 1992). Nirmala & Puvanakrishnan (1996) have studied the protective effect of curcumin against isoproterenol-induced myocardial infarction. The curcumin administration reduces the myocardial damage caused by isoproterenol by maintaining the levels of lysosomal enzymes at near normal. Hashimoto & Ogawa (1981) have stated that premeditation of sulfapyrazone and propranolol reduce cardiac necrosis and hypertrophy induced by isoproterenol, but aspirin did not have such cardioprotective effects.

Studies by Djandjighian et al. (2000) on the hemodynamic and anti adrenergic effects of dronedarone and amiodarone in animals with a healed myocardial infarction indicate that both dronedarone and amiodarone significantly reduces the exercise-induced tachycardia and at the highest dose, decreases the isoproterenol-induced tachycardia. The administration of Ca\(^{2+}\) sensitizer levosimendan has been reported to exert dose- and time-dependent positive inotropic and lusitropic effects on the post-ischemic myocardium, lending support to the hypothesis that Ca\(^{2+}\) desensitization of myofibrils is involved in myocardial stunning (Kristof et al., 1999).

Karthekeyan et al. (2003) have shown that, chronic administration of alcoholic extract of Terminalia arjuna prevents the isoproterenol-induced myocardial ischemic reperfusion injury by a dose dependent modulating effect on the antioxidant milieu of the heart. It is reported to enhance myocardial endogenous antioxidants without producing any cytotoxic effects. Dantrolene, a blocker of sarcoplasmic reticulum Ca\(^{2+}\) release channel has a significant effect in the protection of heart against myocardial infarction induced by isoproterenol on the rat myocardium (Acikel et al., 2005). Vimal & Devaki (2004) have reported that oral treatment of marmesinin exerts protective action against isoproterenol-induced myocardial injury. It inhibits the release of enzymes from nuclear, mitochondrial,
lysosomal and microsomal fractions which could be due to the stabilizing effect of marmisinin on the membrane.

Pretreatment with an ethanolic extract of calotropis procera significantly reduced the elevated marker enzyme levels in serum and heart homogenate in isoproterenol-induced myocardial infarction (Ahmed et al., 2004). Garlic oil is reported to produce a marked reversal of the metabolic changes related to myocardial infarction induced by isoproterenol, by modulating the lipid peroxidation and enhancing antioxidant and detoxifying enzyme systems (Saravanan & Prakash, 2004). Reports by Sathish et al. (2003^a & 2003^c) have shown that the pretreatment with nicorandil and amlodipine could preserve lysosomal integrity and hence established the cardioprotective effect of the combination against isoproterenol-induced myocardial infarction. Yogeetha et al. (2006) have reported the protective effect of ferulic acid and ascorbic acid on lysosomal hydrolases and membrane-bound phosphatases during isoproterenol-induced myocardial necrosis in rats. Farvin et al. (2006) have shown that cardioprotective effect of squalene is probably related to an inhibition of lipid accumulation by its hypolipidemic properties and/or its antioxidant properties. Kumar & Anandan (2007) have reported that treatment with glutamine exerted protective action against isoproterenol-induced myocardial injury by decreasing lipid peroxidation and enhancing antioxidant status.