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HISTAMINE BIOSENSOR: A REVIEW

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ABSTRACT

Some biogenic amine like Histamine, cadaverine and putrescine have been confirmed as useful chemical indicators to estimate bacterial spoilage of foods, particularly fish and fish products, cheese, meat and fermented foods. Histamine is toxic at high intakes, while cadaverine and putrescine potentiate the effects of Histamine. Histamine has regulated level of 200 mg/kg (200 ppm). Basic principle involved in Biogenic amines biosensor is the action of diamine oxidase (DAO) that catalyzes the oxidative deamination of primary amines to the corresponding aldehydes, hydrogen peroxide and ammonia. Two different approaches for the histamine biosensor design were studied, i.e. the enzyme DAO was directly immobilized on the surface of the oxygen electrode membrane using glutaraldehyde or entrapped in a hydrogel film. In histamine biosensor consisting of diamine oxidase (DAO) and a conventional oxygen electrode transducer was developed and applied for the determination of standard histamine solutions. For immobilisation with glutaraldehyde, the enzyme was cross-linked with glutaraldehyde as a bifunctional reagent on the electrode surface. For entrapment, DAO was entrapped in a polymeric hydrogel film, i.e. poly(hydroxyl ethyl methacrylate) (pHEMA) polymer and deposited onto the teflon membrane of the oxygen electrode. Good linear correlation response obtained of the histamine biosensors with immobilized DAO showed between the changes of oxygen level with changes in concentration of histamine at both high concentration ranges (200-1000 mg/L) and low concentrations (20-100 mg/L). However, the sensitivity of the biosensor response decreased at high concentration range of histamine, for the direct DAO immobilisation with glutaraldehyde. Biogenic amines concentration can be measured by monitoring either the decrease in oxygen or the increase of hydrogen peroxide concentration.

INTRODUCTION: Nature of Biogenic amines is aliphatic, alicylic and heterocylic organic bases of low molecular weight. To estimate bacterial spoilage, biogenic amines, especially putrescine, cadaverine and histamine, have been confirmed as useful chemical indicators [1]. Histamine, putrescine, cadaverine, tyramine and agmatine are produced from the decarboxylation of histidine, ornithine, lysine, tyrosine and arginine respectively. Histamine is associated of scombroid poisoning in conjunction with the ingestion of some fish species such as tuna, mackerel, sardine, herring, and anchovy. The formation of histamine in fish products is directly correlated with the concentration of histidine in the tissue and the level of

microorganisms present in the product, due to bacterial histidine decarboxilase action on histidine [2].

Seafood products are important for nutrition and also as an item of international trade and foreign exchange earner for a number of countries in the world. Unlike other animal products, the quality of seafood products is more difficult to control due to the variations in species, sex, age, habitats and action of autolytic enzymes. Therefore, simple and rapid techniques for the estimation of seafood freshness are important in the seafood industry. During storage, histamine was observed to accumulate in tissues of fish and other seafoods when spoilage by bacteria commenced [3].

Histamine poisoning, also known as 'scombroid fish poisoning', histamine overdose, pseudo allergic fish poisoning or mahi-mahi flush is among the most common toxicities related to fish ingestion. The poisoning directly relates to improper preservation and inadequate refrigeration. In histamine biosensor histamine concentration can be measured by monitoring either the decrease in oxygen concentration or the increase of hydrogen peroxide.

Histamine poisoning, also known as 'scombroid fish poisoning' is an illness that results from eating spoiled fish because of inadequate refrigeration or preservation after it is being caught. It is most commonly reported with fish from Scombridae and Scomberesocidae families. One of the toxic agents implicated in scombroid poisoning is chemical called histamine. For years, studies had been conducted to find the best method to detect and determine the level of histamine in food. This can avoid people from consuming spoiled food, instead of giving them treatment after being poisoned. The enzymes diamine oxidase (DAO) and histamine-N-methyl transferase (HMT) present in intestinal tract of humans convert histamine to harmless degradation products [4].

A biosensor may be broadly defined as any measuring device that contains a biological element (Buerk, 1993) or a device incorporating a biological sensing element connected to a transducer (Eggins, 1996) [5].

A Preliminary Investigation on a Histamine Biosensor most frequent intoxication caused by biogenic amines involves histamine. Histamine is formed mainly through decarboxylation of histidine by exogenous decarboxylase released by microflora associated with the fish or salt-water environment.

Histamine poisoning is known to be associated with the consumption of fish such as tuna and sardines.

Biosensor provides a rapid and simple means of biogenic amine detection without the need of complicated sample pretreatment procedures. However, the successful of a biosensor construction depends heavily on the enzyme immobilization technology. Immobilization not only allows the enzyme to be in close contact with the transducer but also helps in stabilizing the enzyme for repeating usage. Enzyme immobilization can be performed directly on the transducer or in most cases, via a membrane, which can subsequently be attached on the transducer. Enzymes can be immobilized either through adsorption, entrapment, covalent binding, cross-linking or a combination of all these techniques.

Biogenic Amines: They are termed biogenic amines because they are formed in raw food by bacterial action. Biogenic amines may present in various foods, particularly fish and fish products, cheese, meat and fermented foods (Eerola et al., 1993). During storage and processing, if foods are mishandled, certain protein within the foods might break down to free amino acids, which may also be naturally present within the food. If the food is contaminated with bacteria containing decarboxylase enzymes, this free amino acid undergoes decaroxy lation to produce biogenic amine.

For example, lysine is decarboxylated to produce cadaverine, histidine is decarboxylated to produce histamine, while glutamine, agmatine and arginine is decarboxylated to produce putrescine (Halasz et al., 1994). Biogenic amines often appear in conjunction with intoxication. It were generated by microbial spoilage of food which high in protein content or through processing, ripening and storage of fermented foodstuff. Therefore, certain biogenic amines could be used as an indicator for food quality and hygiene during processing (Leuschner et al., 1998). The biogenic amines content of food depends on the biotechnological processes involved in the production procedures. It is influenced by certain factors such as microbial growth, availability of free amino acids, the

presence of decarboxylase enzymes and elevated **(Fig. 1)** temperature conditions (Halasz et al., 1994).

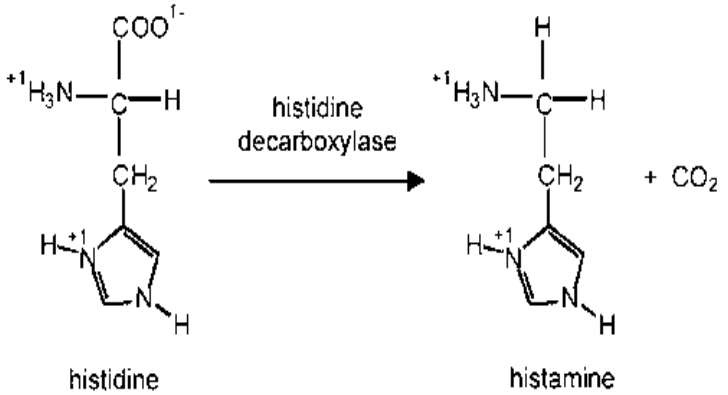

FIG. 1: PRODUCTION OF HISTAMINE FROM HISTIDINE BY THE ENZYME HISTIDINE DECARBOXYLASE

The enzymes that are involved in the production of histamine, histidine decarboxylase, require temperature greater than 15°C and 30°C is the optimum temperature. In tropical areas of the world, fish are often caught in temperature exceeding 20°C. If these fish are not refrigerated immediately, conditions are favorable for biogenic amines production providing bacteria containing decarboxylase enzymes are present. Bacterial growth will cease at temperature lower than 5°C, however enzymatic activity will still continue, resulting in further amine production (Ahmed, 1991).

HISTAMINE: Histamine is an essential biogenic amine present in prokaryotes and tissues of animals and plants. In humans, histamine acts as a neurotransmitter, mediates allergic reactions, plays a role in cell proliferation, and is important in signaling the release of gastric acid into the stomach. Histamine receptors are the targets of drugs that treat allergies and stomach acidity, but there is very little structural information on the histamine-binding sites of these proteins **(Fig. 2)**.

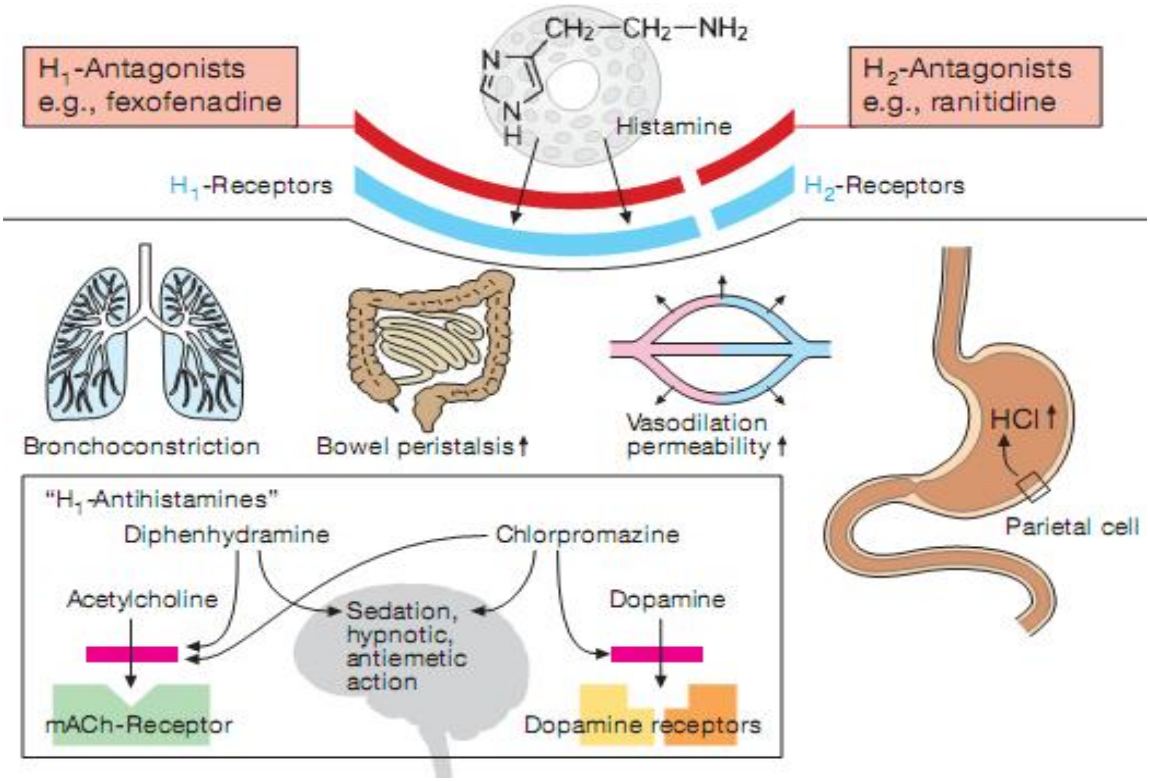

FIG. 2: HISTAMINE ACTIONS ON DIFFERENT TISSUES

Trimethylamine dehydrogenase from *Methylophilus methylotrophus* and the quinoprotein methylamine dehydrogenase from *Paracoccus denitrificans* have been used in general amine-sensing electrodes without the complication of O_2 chemistry, but neither is as effective as histamine sensors. Many biogenic amines have been studied in scientific literature, however diamines such as histamine, putrescine and cadaverine are often documented in clinical studies with histamine being linked to food poisoning and putrescine and cadaverine potentiating the toxicity of histamine (Public Health Division, 2002). Histamine, cadaverine and putrescine have been confirmed as useful chemical indicators to estimate bacterial spoilage. Consumption of high level of histamine can lead to scombrotoxicosis

while the presence of other biogenic amines is described to potentiate the effects.

The significance of histamine is well known. Person being highly sensitive to histamine often develops pseudoallergic symptoms shortly after ingestion. For healthy individuals, the putrescine or cadaverine is not considered to be toxic. In general, dietary polyamines at levels normally present in food are nontoxic, while biogenic amines, particularly histamine is toxic at high intakes.

The Food Standards Code stated that the regulated level for histamine is 200 mg/kg (200 ppm). Histamine itself is not destroyed by cooking, freezing, smoking, curing and canning (Lange and Wittmann, 2001). This is the same histamine that causes problems for some people when high levels are produced in cheese and red wine. Histamine has an important role in human metabolism, such as the release of stomach acid. In small doses it has little effect, but in larger doses it has toxic effects. The intestinal tract of humans contains the enzymes diamine oxidase (DAO) and histamine-N-methyl transferase (HMT) which convert histamine to harmless degradation products.

Putrescine and cadaverine can inhibit these enzymic reactions and are therefore potentiators of histamine toxicity.

Histamine Poisoning: The presence of low levels of histamine, in the diet normally has no toxic effect as humans do not absorb histamine efficiently from the gastrointestinal tract. If a high level of histamine is present in the diet, then the capacity of DAO and HMT to detoxify histamine will be limited and histamine will enter into the bloodstream resulting in histamine poisoning (Taylor, 1986).

The poisoning directly relates to improper preservation and inadequate refrigeration. Histidine decarboxylase (HDC) found in E. coli and in Proteus and Klebsiella species, converts histidine which present in fish tissue to histamine. The bacteria also live on fish tissue. Without adequate cooling, these bacteria multiply; increasing the conversion rate of histidine to histamine, thus increase the histamine levels. Conversion of histidine to histamine by histidine decarboxylase (HDC).

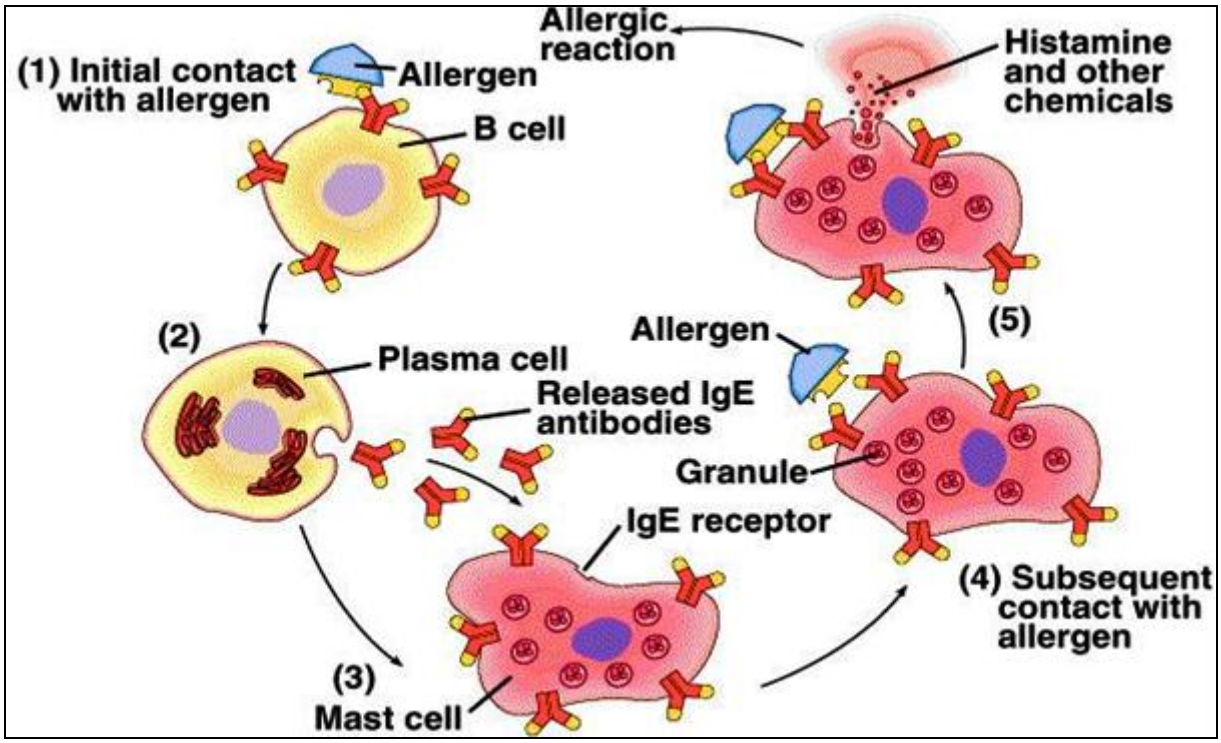

FIG. 3: AN OVERVIEW OF ALLERGIC REACTIONS

Histamine poisoning described as a food-borne chemical intoxication. It is most commonly reported with fish from Scombridae and Scomberesocidae families.

Histamine poisoning can be resulted from inappropriate handling of fish during storage or processing. The poisoning actually is caused by ingestion of the toxins within the fish's tissues.

FIG. 4: THE CONSUMPTION OF TUNA AND SCOMBROID POISONING (HISTAMINE POISONING)

Other chemicals have been found in decaying fish flesh, but their association to scombroid poisoning has not been clearly established. Generally, the symptoms of histamine or scombroid fish poisoning are a `sharp', `metallic' or `peppery' taste while eating the fish, flushing (reddening of the face and sometimes the neck, arms and upper part of the trunk), severe headache, palpitations (rapid heartbeat), stomach cramps and/or diarrhea, itching on the face or around the mouth, a burning sensation in the throat or dryness of the mouth, difficulty in swallowing and/or breathing, muscle weakness and nausea (Wu et al., 1997; Bardocz, 1995; Hughes and Potter, 1991). The toxic levels for histamine are estimated at 200-500 mg/kg (200-500 ppm) (Noltkamper, 2002) while the recent regulated level is 200 mg/kg (200 ppm) **(Fig. 3 & 4)**.

Diamine Oxidase: Oxidative deamination of histamine and other biogenic amines occurred by Diamine oxidase (DAO, EC 1.4.3.6) [amine: O_2 oxidoreductase (deaminating)] is a member of the class of copper-containing amine oxidases. Other names are diamino oxhydrase, histaminase, histamine deaminase, histamine oxidase, amine oxidase, amine oxygen oxidoreductase, Cu-amine oxidase, monoamine oxidase and others. Diamine oxidase was originally called histaminases because characterized as the enzyme degrading histamine. It is characterized by possessing the active-site cofactor topa quinine formed posttranslationally by modification of a conserved tyrosine residue. Although diamine oxidase appears to play an important role in histamine catabolism, the

Enzymes efficiently converts many diamines besides histamine and is expressed in many tissues, suggests that it might have additional function. These ubiquitous soluble enzymes catalyze the oxidative deamination of primary amines to form the corresponding aldehydes, ammonia and hydrogen peroxide (Wilflingseder and Schwelberger, 2000).

$$RCH_2NH_2 + H_2O + O_2 \longrightarrow RCHO + NH_3 + H_2O_2$$

Measurements of the oxygen consumption or the hydrogen peroxide production are commonly used for assays of the enzyme activity (Wimmerova and Macholan, 1999).

Introduction of Biosensor: Biosensors represent a powerful technology development in analytical measurement. Biosensors have the ability to measure the presence, absence, or concentration of specific organic or inorganic substances and to do so accurately, with rapid response time, and with high levels of specificity.

Biosensors find commercial application in the areas of health care, food-quality control, pharmaceuticals, and environmental monitoring and greatest use in health care, especially in patient monitoring. A common requirement of all these applications is on-site analysis, preferably on a real-time basis. The resulting benefits of closer monitoring range from a more efficient industrial productions process to better-informed legislation on safety standards and population exposure to chemical and biological hazards. The apparent opportunities in biosensor commercialization have led to interest by many large electronic and life science companies.

However, without the technical skills, the delivery channels, or a unique, differentiated, biosensor offering, players will have great difficulty entering the market. The biological element involved might be tissue, microorganisms, organelles, cell receptors, enzymes, antibodies ornucleic acids (Rogers and Gerlach, 1996). The sensing element which responds to

the substance being measured is biological in nature. It has to be connected to a transducer of some sort so that a visually observable response occurs. A transducer converts an observed change, physically or chemically into a measurable signal, usually an electronic signal whose magnitude is proportional to the concentration of a specific chemical or set of chemicals. It is an apparently alien marriage of two contrasting disciplines which combines the specificity and sensitivity of biological systems with the computing power of the microprocessor **(Fig. 5)**. Biosensors are generallyconcerned with sensing and measuring particular chemicals which need not be biological components themselves, although sometimes they are. They are referred as the substrate, although the more general term analyte is often used (Eggins, 1996).

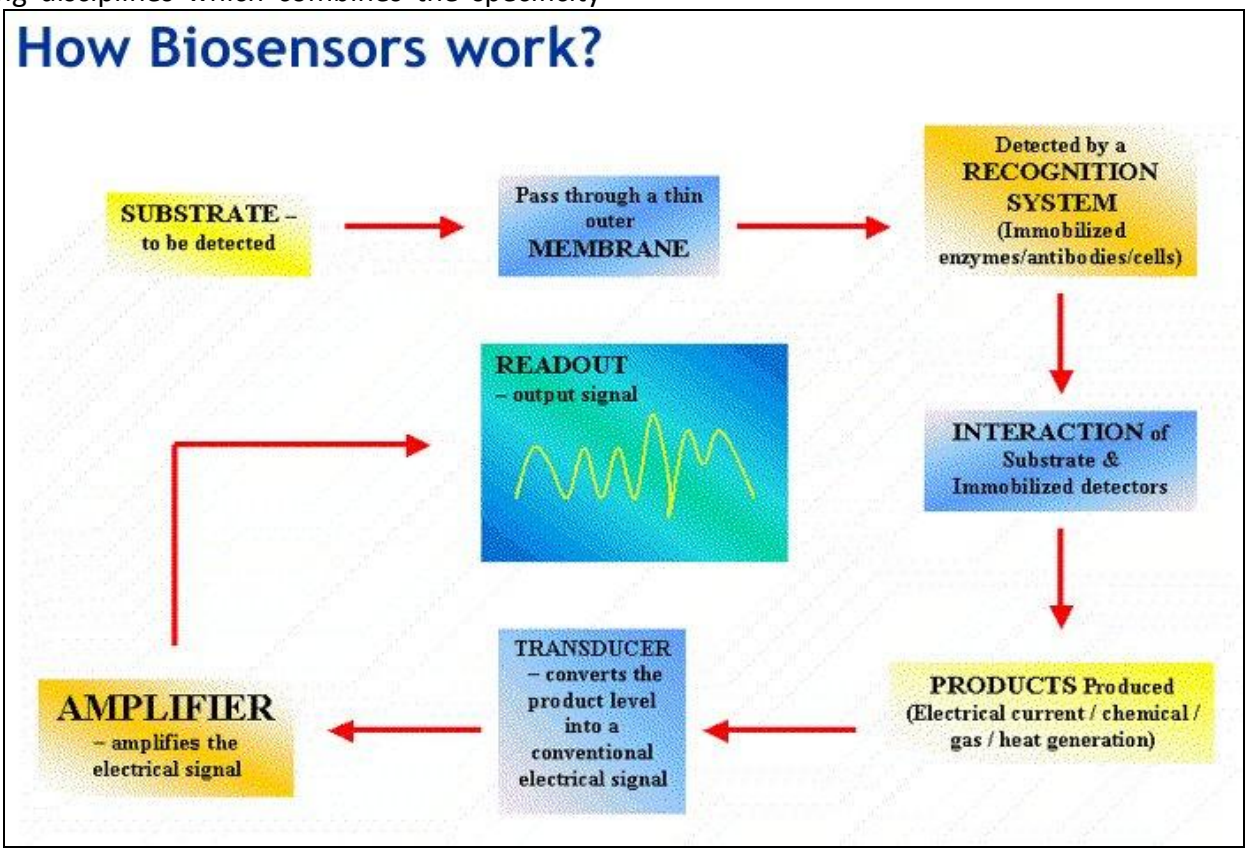

FIG. 5: FIGURE SHOWING WORKING OF BIOSENSORS

A target analyte (illustrated by solid circles) in the external medium must be able to enter the biosensor. The external membrane of the biosensor must be permeable to the analyte, and if possible, exclude other chemical species that the biosensor might also be sensitive to. The biological element inside the biosensor then interacts with the analyte, and responds in the same manner that can be detected by a transducer.

The biological element may convert the analyte to another chemical species (represented by open circles) through a biochemical reaction; produce or release optical, electrical or mechanical properties: or make some other response that can be reliably quantified. There may be another internal membrane near the transducer which might have different permeability properties than the external membrane. The output signal from a biosensor depends on the type of transducer used.

The transducer may be a conventional electrochemical sensor or may be based on another technology (Buerk, 1993).

Chemical Sensor and Biosensor: A chemical sensor is a device that transforms chemical information, ranging from the concentration of a specific sample component to total composition analysis, into analytically useful signal. Chemical sensor usually contains two basic components connected in series that is a chemical recognition system (receptor) and a physicochemical transducer. Biosensors are chemicals sensors in which the recognition system utilizes a

biochemical mechanism. The main purpose of the recognition system is to provide the sensor with a high degree of selectivity for the analyte to be measured. The biological recognition system translates information from the biochemical domain, usually an analyte concentration, into a chemical or physical output signal with a defined sensitivity.

While all biosensors are more or less selective (non-specific) for a particular analyte, some are, by design and construction, only class-specific, since they use class enzymes such as phenolic compound biosensors or whole cells used to measure biological oxygen demand. Because in sensing system presents in living organisms or systems, such as olfaction and taste, the actual recognition is performed by a cell receptor, the word 'bioreceptor' is often be used for recognition system of a biosensor.

The transducer is a part of the biosensor serves to transfer the signal from the output domain of the recognition system to, mostly the electrical domain. A transducer provides bidirectional signal transfer (non-electrical to electrical). The transducer part of sensor is also called a detector or electrode, but the term transducer is often used to avoid confusion.

Electrochemical Biosensor: A biosensor with an electrochemical transducer is called an electrochemical biosensor. It is an integrated receptor-transducer device, which is a capable of providing selective quantitative or semi-quantitative analytical information using a biological recognition element. A biosensor can be used to monitor either biological or non-biological matrices. Non-electrochemical transducers are used within biosensors, these includes piezoelectric, calorimetric (thermistor) and optical (planar wave guide, fiber optic) **(Table 1)**.

TABLE 1: DIFFERENT TYPES OF ELECTROCHEMICAL TRANSDUCERS

Measurement	Transducer	Transducer Analyte
Potentiometric	Ion Selective Electrode (ISE), Glass Electrode, Gas Electrode, Metal electrode	K^+, Cl^-, $Ca2^+$, FH^+, Na^+ , CO_2, NH_3, Redox Species
Amperometric	Metal or Carbon electrode chemically modified electrodes (CME)	O2, sugars, alcohols, phenols, etc.
Conductometric	Interdigitated electrode, Metal electrode	Urea, oligonucleotides, charged species
Ion charge or field effect	Ion-sensitive field-effect transistor, Enzyme FET	H^+, K^+

The First Biosensor: These were first described by Clark and Lyons (1962) for the determination of glucose and often called enzyme electrodes. This is by far the most studied and developed biosensor application.

Glucose is of special importance because of its involvement in human metabolic processes. In particular sufferers from diabetes mellitus do not produce sufficient insulin in their pancreas to control adequately the level of glucose in their blood.

Fundamental of Amperometric Biosensor: Amperometric measurements can be measured when a defined potential is applied at a working electrode with respect to the reference electrode. This result current that can be related to the concentration of an electroactive substance in the solution. At low current densities, it is sufficient for most of elementary electrochemical setup to have two electrodes, which are working electrode (WE) and reference electrode (RE). However, at higher current densities, the potential of reference electrode may change with current, so it is not possible to obtain reproducible determination of analyte.

To avoid this problem, a third electrode is required (three-electrode setup) which is known as counter electrode (CE). For the three-electrode setup, current is measured between working and counter electrodes, while potential is measured based on reference electrode. The measured current is directly related to the rate of the overall process in the electrochemical cell (Wagner and Guilbault, 1994).

An amperometric system based on screen-printed electrodes would allow the production of simple, inexpensive and portable devices for rapid seafood and fish product freshness and spoilage determination. Amperometric biosensors measure the electron flow of the oxidation or reduction of an electro-active species. The steady state current is proportional to the concentration of the electro-active species. In the field

of enzyme electrodes, the most widely use enzymes are oxidases that produce electro-active hydrogen peroxide, which can be measured by a current signal (Willner et al., 2000) or direct electrochemical communication of a substrate with the enzyme.

Amperometric biosensors have been found to overcome most of the other types of biosensor disadvantages. The amperometric biosensors can be operated in turbid media, have comparable instrument sensitivity and are more amenable to miniaturization (Chaubey and Malhotra, 2002).

Histamine Biosensor: Seafood and fish products are important for their nutritional value and also as item of international trade and foreign exchange earnings for a number of countries in the world. Unlike other animal products, the quality of seafood and fish products are more difficult to control due to their variations in species, sex, age, habitats and the action of their autolytic enzymes (Venugopal, 2002). The levels of histamine have been suggested as rapid seafood and fish products spoilage indicators (Male et al., 1996; Tombelli and Mascini, 1998; Patange et al., 2005). Histamine was observed to accumulate in seafood and fish tissues when bacteria spoilage commenced during storage of the products (Male et al., 1996) without altering the seafood and fish normal appearance and odor (Lehane and Olley, 2000). Therefore, simple and rapid techniques for determining the levels of histamine in seafood and fish products are in great demand by the food industry in order to estimate the products freshness.

However, chromatographic methods are generally complicated and require long analysis time and expensive instrumentation. Biosensors such as electrochemical enzyme probes, based on oxygen electrodes using monoamine oxidase (MAO) and diamine oxidase (DAO) were developed for biogenic amine detection.

Other biosensors that utilized plant tissue was also reported.

Biosensor provides a rapid and simple means of biogenic amine detection without the need of complicated sample pretreatment procedures. However, the successful of a biosensor construction depends heavily on the enzyme immobilization technology. Immobilization not only allows the enzyme to be in close contact with the transducer but also helps in stabilizing the enzyme for repeating usage. Enzyme immobilization can be performed directly on the transducer or in most cases, via a membrane, which can subsequently be attached on the transducer. Enzymes can be immobilized either through adsorption, entrapment, covalent binding, cross-linking or a combination of all these techniques.

In histamine biosensor, the basic principles are the same as the principles of the glucose biosensor. The basic underlying chemistry is the action of diamine oxidase (DAO) that catalyzed the oxidative deamination of histamine to imidazole acetaldehyde, hydrogen peroxide (H2O2) and ammonia (NH3). The reaction involved is shown in **Figure 6** (Niculescu et al., 2001).

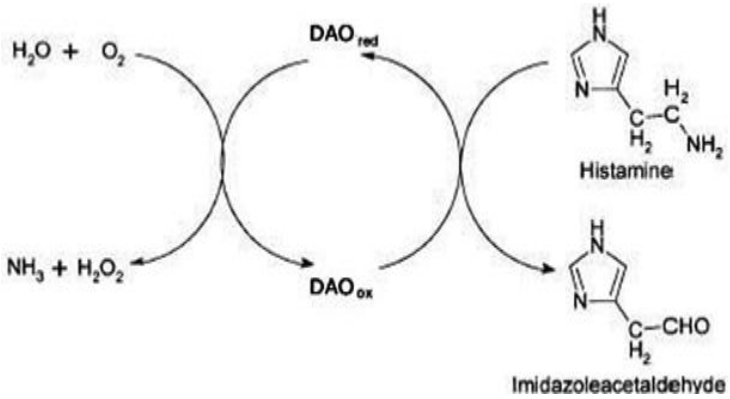

FIG. 6: OXIDATIVE DEAMINATION OF HISTAMINE TO IMIDAZOLEACETALDEHYDE, HYDROGEN PEROXIDE AND AMMONIA BY DIAMINE OXIDASE [17]

The reaction will become rate limited if either histamine or oxygen concentration is too low. Histamine concentration can be measured by monitoring either the decrease in oxygen concentration or the increase of hydrogen peroxide, as the reaction proceeds (Lange and Wittmann, 2001). For oxygen-based histamine sensor, since oxygen is consumed during the reaction, oxygen concentration in the diamine oxidase membrane will be a linear function of histamine concentration.

The oxygen concentration can be measured by coupling the immobilized diamine oxidase membrane to an electrochemical oxygen sensor. Since oxygen is

also available in the sample, a similar reference oxygen sensor without the enzyme needs to be incorporated in the system. The signal current is then subtracted from the reference electrode and gives the result of histamine dependent difference current. The advantage of this type of sensor is that it has low electrochemical interference due to the use of a nonporous hydrophobic membrane. This membrane only allows gaseous molecules to reach the electrode and also can provide information on oxygen variations in the system. The immobilization of diamine oxidase will help prolong the working lifetime of diamine oxidase as catalase promotes the degradation of hydrogen peroxide to oxygen and water.

The hydrogen peroxide-based histamine sensor has found wide application in the development of such a sensor, especially an implantable version, due to its simple sensor configuration that facilitates ease of miniaturization. Unlike oxygen, hydrogen peroxide is not present in the sample to be analyzed. This make no differential setup needed. However, it suffers from an intrinsic problem, the interference from small endogenous analytes, which may be electro-active at the detection potential of hydrogen peroxide which is quite high (Azila Abdul Aziz, 2001).

Those two types of sensors mentioned above are known as the first generation amperometric biosensors. The second generation of histamine biosensors makes use of mediators to shuttle electrons from the enzyme to the electrode, instead of oxygen, which are reversible, had appropriate oxidation potentials and whose concentration could be controlled. If the system is oxygen, the biosensor will become insensitive to histamine, thus will only respond to changes in oxygen concentration. As oxygen remains in the system, the mediator must be able to compete effectively for the electrons (Azila Abdul Aziz, 2001).

The use of mediator in determining the content of histamine and other biogenic amines has been studied by Tombelli and Mascini (1998), compared to a single enzyme sensor and a flow system based on hydrogen peroxide generated by enzymatic reaction. A bi-enzyme FIA system with amperometric detection was used based on the following enzyme reactions, with ferrocene carboxylic acid (Fc-COOH) as the mediator facilitating the electron transfer between the electrode and horseradish peroxidase (HRP).

Pea seedling amine oxidase (PSAO) catalyses the oxidation of the amine and subsequently the co-substrate, molecular oxygen, is reduced to hydrogen peroxide. Hydrogen peroxide is then expends in the following peroxidase catalyzed reaction using Fc-COOH as the mediator. The amperometric signal is monitored reductively at the electrode. Figure illustrated the basic principle of the electron **(Fig. 7)** transfer during measurements (Wimmerova and Macholan, 1999).

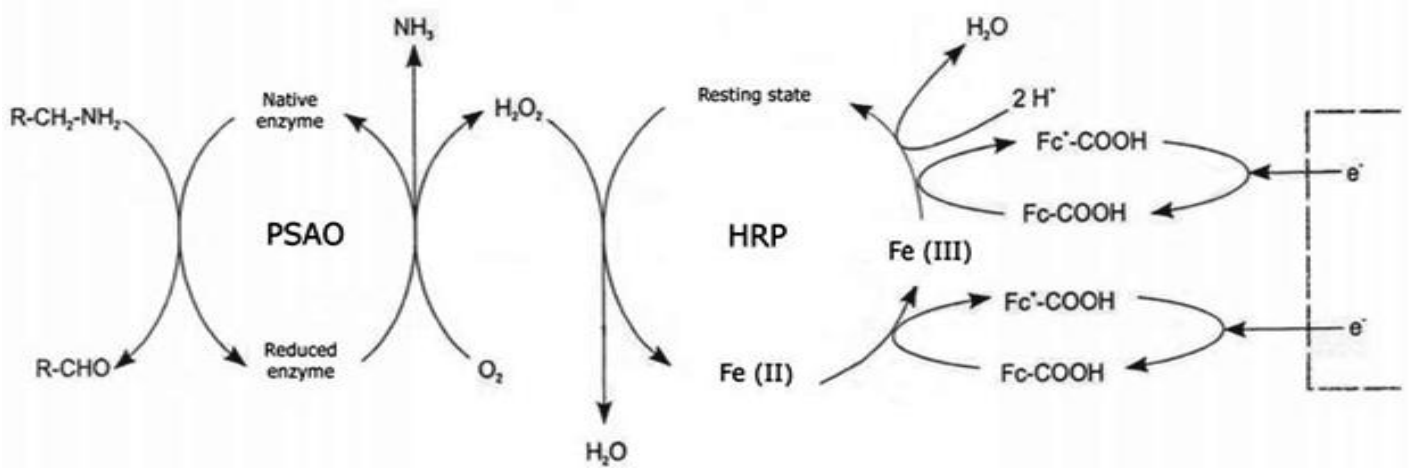

FIG. 7: THE BASIC PRINCIPLE OF THE ELECTRON TRANSFER DURING MEASUREMENTS IN AMPEROMETRIC BI-ENZYME SYSTEM [17]

According to Tombelli (1998) by using second enzymatic reaction and a mediator, two distinct advantages are obtained. First, it allows low potential detection (0.00 mV) of substrates, hence avoiding interferences from electroactive species which enhances the specificity of the assay. Second, the assay sensitivity is enhanced by increasing the efficiency of the electrochemical detection.

The third generation amperometric biosensors are based on the use of conducting organic salts or polymers. These conducting salts can be built into electrodes in three ways; as single crystals, as pressed pellets or as a paste with graphite powder (Eggins, 1996). The films are grown electrochemically and enzyme is entrapped in the membranes.

The advantage of this system is that manipulation of the electropolymerization can give a film that extends the linear range for substrate detection and reduces oxygen dependence.

Immobilization of Diamine Oxidase (Cross-Linking Method): Enzyme By entrapment and crosslinking in a poly (vinyl alcohol) (PVA) membrane cross-linked with glutaraldehyde Diamine oxidase (DAO) membrane was prepared. The cross-linking ratio (CR) is defined as moles of glutaraldehyde per moles of PVA repeat unit (CR = moles glutaraldehyde/moles PVA). The PVA concentration and the cross-linking ratio was varied between 5 – 15% for PVA concentration and 0.02 – 0.12 for cross-linking ratio to determine the optimum parameter for enzyme immobilization.

Immobilization Methods in Constructing Histamine Biosensor: For improvement in the sensitivity of biosensors there are many methods of immobilization have been used and investigated. Lange et al. (2001) were firstly used 20% of transglutaminase solution for immobilization of diamine oxidase, plasma amine oxidase and tyramine oxidase. IMMOBILIZATION technique provides good result with sensor. It improved the sensitivity of sensor, but unfortunately, when lots of transglutaminase was finished, difficulties occurred with the regular quality (sensor reproducibility was low).

Therefore, they investigated the conventional immobilization method, which was based on glutaraldehyde-albumin cross-linking. In their research, they compared the results obtained (to determine biogenic amines: specifically histamine and tyramine) between enzyme sensor array and high performance liquid chromatography (HPLC). From the results, it can be concluded that by using enzyme sensor array, less time was required to conduct experiments and was not tedious as when handling HPLC, but still the reproducibility, data validity, detection limit and so on were still poor. Glutaraldehyde was always chosen as the cross-linking agent to entrapped diamine oxidase.

Tombelli and Mascini (1998) used glutaraldehyde solution on cellulose acetate membrane to immobilize diamine oxidase on a platinum electrode. It was also helped Bouvrette et al. to develop their membranes. Poly (vinyl alcohol) is a non-toxic water-soluble synthetic material that has good film forming properties, resulting in tough membranes. Glutaraldehyde, a bifunctional agent that can react with organic hydroxyl groups, was used as the cross-linking agent. Glutaraldehyde can also react with the lysine amino acid residues in the enzyme.

The cross-linking process overcomes the loss of enzyme activity due to diffusional loss, which is a prevalent problem for enzyme immobilized in physical entrapment. PVA can stabilize the activity of various enzymes such as horseradish peroxidase. The stabilization effect is achieved through the inhibition of the formation of non-functional conformations due to the extensive hydrogen bonding between the H-atoms of the alcohol groups in PVA and the O-atoms of the carbohydrate groups in diamine oxidase. These properties make PVA an appropriate matrix for diamine oxidase immobilization.

RESULT AND CONCLUSION: Biosensor provides a rapid and simple means of biogenic amine detection without the need of complicated sample pretreatment procedures. However, the successful of a biosensor construction depends heavily on the enzyme immobilization technology. Immobilization not only allows the enzyme to be in close contact with the transducer but also helps in stabilizing the enzyme for repeating usage.

In the presence of DAO enzyme, histamine is converted to various products with the consumption of oxygen according to the following equation:

$$RCH_2NH_2 + O_2 + H_2O \rightarrow RCHO + NH_3 + H_2O_2$$

When the concentration of histamine increases, the amount of oxygen consumes will be higher and thus a larger difference in the reduction of oxygen (in arbitrary unit) will be observed.

For the direct immobilization procedure, although the responses of the biosensor are linear even at higher concentrations of histamine, i.e. from 200-1000 mg/L, the sensitivity has decreased considerably when compared to low histamine concentration range. In comparison, the reduction in sensitivity at high levels of histamine is more pronounced for the free DAO.

Such a reduction in the response of the biosensor at high level of histamine (>10,000 mg/L) is attributed to the inhibitory effect of the enzyme by histamine and this was reported for both free and immobilized DAO.

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