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Research on Some Aspects of the Cytochrome P450 Proteins

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Abstract: The Cytochrome P450 was first described in 1958 as a brown pigment when carbon monoxide was added to hepatic microsomal preparations, which had been reduced with dithionite or NADH. This hemeprotein had probably arisen very early in chemical evolution (the origin of life). One of its early functions was probably the detoxification of molecular oxygen, which was poisonous to primordial life, which had not evolved other protective mechanisms. Since its initial discovery, it has been identified in a very large variety of animal tissues, plants and microorganisms. It is now known that there are various cytochromes P450, which perform a large variety of enzymatic functions. The cytochromes P450 have among other functions the metabolism or detoxification of 'xenobiotics' or 'foreign chemicals', which include drugs and environmental pollutants. The functioning of the steroid hydroxylases in adrenocortical mitochondria is influenced (regulated) by the dielectric constant in the immediate vicinity of the enzyme. Sodium and potassium ions influence the functioning of these hydroxylases differently in view of the different effect their ionic radii have on the dielectric constant. Spices have been found to bind to cytochrome P450. This may modify the activity of the enzyme. This may account for certain herbal medicinal preparations being effective in members of some communities but not in others, which have different dietary habits or preparations. Spices are also added as a component of some herbal medicinal preparations. More investigations need to be performed to ascertain the effect the consumption of spices may have on the efficacy of medicines in general.

Keywords: Evolution, Herbs, Pharmacology, Steroids, Hormones, Adrenal, Mutagens, Carcinogens

1. Introduction

The first indication of the existence of a family of proteins, which later came to be called the cytochromes P450, was obtained by Garfinkel in 1958 and 1963 and Klingenberg in 1958. They reported the development of a brown pigment when carbon monoxide reacted with hepatic microsomal preparations, which had been reduced with dithionite or NADH. Omura and Sato (1964) and Sato and Omura (1961, 1978) followed up this observation with the determination that the pigment was a hitherto un-described hemeprotein distinct from cytochrome b5. The carbon monoxide-complexed microsomal particles absorbed light strongly at 450 nm. This characteristic led the particle (pigment) to be named cytochrome P450. It was found later that the pigment could be converted to a cytochrome of the b type, the carbon monoxide-complex of which absorbed light strongly at 420 nm. This led to that pigment being named cytochrome P420.

Many of the earliest studies on cytochrome P450 were performed on the hemeprotein found in the micro-organism, Pseudomonas putida, and on mammalian forms present in, for example, the microsomes of mammalian liver and the adrenal cortex. The mitochondria of the cells of the mammalian adrenal cortex, corpus luteum of the ovary, testis and placenta were also found to contain cytochromes P450. The cytochrome P450 of microsomes was associated in its catalytic activity with a flavoprotein. That of the microorganisms, Pseudomonas putida and Bacillus megaterium, and those of the mitochondria required, in addition, iron-sulphur proteins (called adrenodoxin in the case of the adrenocortical mitochondria).

There has been a great deal of research over the years on the cytochromes P450, their distribution in living organisms and their functions. They probably arose in the Early Precambrian and are now found to be widespread in living organisms (i.e. animals, plants and microorganisms). Their functions have also been determined to be correspondingly diverse. Introductions to cytochromes P450 distribution and functions may be referred to in [1-2].

Table 1. *Examples of tissues in which cytochromes P450 have been identified [2].*

Mitochondria	bovine adrenal cortex, bovine testis, bovine corpus luteum, human term placenta, rat adrenocortical carcinoma, duck adrenal, turtle (*Chelonea mydas*) adrenal, shark (*Galeocerdo cuvieri*) adrenal, insect fat body
Steroidogenic microsomes	human adrenal cortex, horse adrenal cortex, guinea pig adrenal, duck (*Anas platyrhynchos*) adrenal, cobra (*Naja naja*) adrenal, skate (*Raja brachyura*) adrenal, pheasant testis, quail testis, frog testis
Hepatic microsomes	baboon, squirrel monkey (*Saimiri sciureus*), cat, bats (several species), raccoon (*Procyon lotor*), armadillo (*Tolypeutes tricinctus*), quokka (*Setonix brachyurus*), vole (*Microtus pinetorum*), turkey, sparrow (*Passer domesticus*), carp, buffalo fish (*Cyprinus carpio*), trout, bass, shark (*Squalus acanthias*), lobster hepatopancreas, crab (*Callinectes sapillus*) hepatopancreas, chick embryo (17-19 days)
Other nonsteroidogenic microsomes	human renal adenocarcinoma, rat kidney cortex, quail kidney, rabbit small intestine, rat lung, quail lung, mouse skin, rat spleen
Cell cultures	mouse fetal microsomes
Microorganisms	*Claviceps purpurea*, *Saccharomyces cerevisiae*, *Candida tropicalis*, *Pseudomonas putida*, *Bacillus megaterium*, *Corynebacterium sp*., *Rhizobium japonicum*
Insects (preparations from whole organisms)	*Drosophila melanogaster*, eye gnats (several *Hippelates spp.*)
Insects (selected body regions or tissues)	housefly, Corn earworm (*Heliothis zea*), Blowfly (*Calliphora erythrocephala*), cockroach, sawfly (*Macremphytus varianus*), Tobacco hornworm, Tobacco budworm, Silkmoth (*Antherae pernyi*), Armyworm (*Prodenia eridania*)
Plants	Echinocystis macrocarpa, Phaseolus vulgaris, Pisum sativum, Zea mais, cauliflower, tulip bulb, Vinca rosea, Avocado

2. Aspects of the Cytochromes P450

The very large amount of research data accumulated by many groups over the years on various aspects (including functions) of the cytochromes P450 make it impractical to cover the material even briefly in this presentation. What will, therefore, be presented will be material in the research on which the author was himself involved and which results are, to the best of his belief and knowledge, still valid.

2.1. Function of Cytochrome P450 in Early Life Forms

When the Earth first formed billions of years ago, it is believed it had a ‘reducing atmosphere’ composed of gases such as hydrogen, hydrogen sulphide, methane etc but no molecular (ie ‘gaseous’) oxygen. Some of the gases combined, due to the energy in strikes of lightning and in volcanic eruptions, to form carbon-containing organic compounds, such as amino acids. Over very long periods of time, some of these organic compounds may have joined up (perhaps, for example, on the surface of catalytic clays found in pools) to form proteins, enzymes etc and eventually primeval organisms. Some of these organisms may, in due course, have commenced photosynthetic activities, which would have released gaseous oxygen into the atmosphere. Gaseous oxygen is poisonous and primitive forms of cytochrome P450, which possibly arose in the Early Precambrian, may, in the absence of other detoxifying mechanisms, have worked to incorporate gaseous oxygen into complex molecules [3]; thereby detoxifying it.

2.2. Mutagenesis and Carcinogenesis

During the enzymatic activity of cytochrome P450, reactive ‘mutagens’ may be released which lead to the appearance of new species. The reactive mutagens may also be effective as carcinogens [4-6].

2.3. Regulation of Steroid Hormone Biosynthesis Using the Dielectric Constant

It has been demonstrated that one mechanism for the regulation of steroid hormone biosynthesis in adrenocortical mitochondria is dependent on the dielectric constant in the immediate vicinity of the cytochrome P450-containing enzyme complex in the mitochondrion.

This may be the first known example of the dielectric constant influencing the rate of an enzymatic reaction. The different effects of the dielectric constant depending on the ionic radius provides a means of differentiating between sodium and potassium ions [7- 8].

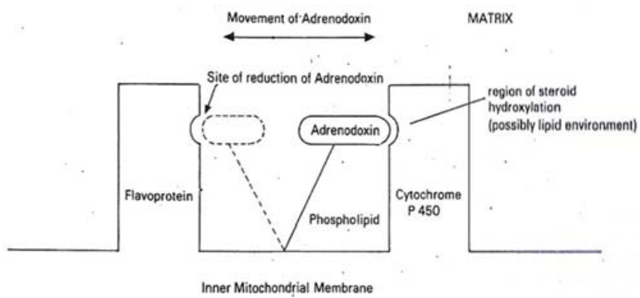

Figure 1. *Scheme of possible interrelationships of components of adrenal cortex mitochondrial steroid hydroxylases (reproduced, with permission, from Cytobios 8, 1973, 81-94).*

The following translation by myself of an extract from Claude Bernard’s ‘Sur les Phenomenes de la Vie’ published in Paris in 1878 is of interest:

“……The constancy of the internal environment is the condition of free, independent life: ….The constancy of the internal environment depends on the high degree of development of the organism such that external changes are, at each instant, compensated for and equilibrated. The higher animal is not indifferent to its surroundings. On the contrary, it is in a close and responsive relationship with it, in such a manner that its equilibrium is the result of a continuous and delicate compensation established as by the most sensitive of balances. …….".

2.4. Psychiatry

It has been proposed that the effectiveness of the use of lithium in the treatment of certain psychiatric ailments is the consequence of the effect of lithium ions on the biosynthesis of some steroid hormones [9].

2.5. Spices, Herbal Medicines and Cytochrome P450

It has been shown that certain spices may bind to certain cytochromes P450. This could be of importance to drug metabolism in different ways.

2.5.1. Spices and Cytochrome P450

Spices consumed habitually by a given culture on a regular basis may well result in the induction of levels of activity of one or other species of cytochrome P450 or of their inhibition. This could, also, influence the rate of elimination or 'clearance' of the drug from the body.

2.5.2. Medicinal Herbs and Cytochrome P450

This may explain why certain herbal medicines find traditional acceptance in some cultures but not in others [10].

As regards the efficacy of herbal medicines, the National Academy of Sciences of the USA published in Washington, DC in 1975 a report titled 'Herbal Pharmacology in the Peoples' Republic of China', which attempted to identify plant species or phytochemically-related species used by different cultures to treat similar ailments or health conditions. This was in an endeavour to identify plant species which had independently been identified by the different cultures (and ideally in different geographic locations).

The data in the above report was used for comparison with some data available as regards medicinal herbs used in Sri Lanka. References to some of the resulting findings are given below [11-16].

Whilst this line of enquiry was an innovative approach, the extensive journeys of Chinese travelers around the globe should not be overlooked when assessing the value of the findings. Since the above study 'Herbal Pharmacology in the Peoples' Republic of China' was published by the National Academy of Sciences of the US in 1975, there have been several studies and publications by Gavin Menzies and other workers giving in considerable detail accounts of the travels of the ancient Chinese travelers to places near and far around the world [17-20]. It has been reported that these voyages were not merely expeditions of conquest and plunder. The staffing of the ships included scientists specialized in botany, zoology, geology, astronomy etc, in addition to medical specialists. They would have undoubtedly have had a deep and abiding interest in pharmacology and the medicinal properties of the plant species used by the inhabitants of the regions of the world they travelled to. They also brought back to China exotic plants and animals from these regions. (It has been reported that at least one of their ships brought back the gift of a giraffe to China, in addition to other exotic creatures!) The fund of knowledge brought back by the Chinese scientists from the far reaches of the globe to China would undoubtedly have had an influence on the development of the pharmacology and related sciences of the Chinese culture (n.b. Menzies in his extensive writings on the travels of the Chinese voyagers has noted specifically the important place spices played in Ancient Egypt and Italy.)

It must be noted that many (ayurvedic) preparations of medicinal herbs in Sri Lanka include the incorporation of spices. In addition, the patient would usually be consuming spices of one sort or another in his or her customary diet. The influence of these spices on the cytochrome P450 species in the hepatic and other tissues and on drug metabolism need to be assessed in detail.

3. Conclusions

The above brief account presents some of the work on cytochrome P450 with which the author has been associated. The immense amount of research on various aspects of the cytochromes P450 and their activities published in recent years by laboratories around the world renders it impractical to select for discussion many specifics from among them in a relatively brief account. It is especially regrettable as regards the wide ranging work on concerns relating to environmental questions. Very much more research needs to be performed on the influence of the dielectric constant on enzymatic reactions in general. Very much more research also needs to be performed on the effects on health of the consumption of various spices both as a constituent of the normal diet and when taken in combination with medications. It is hoped that the above account will suggest lines for further research on this important family of enzymes.

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