THE ENVIRONMENT AND THE HUMAN BODY

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In 1878, the eminent French savant, Claude Bernard stated in a work entitled " On the Phenomena of Life that "....The constancy of the internal environment is the condition of free and independent life... (maintaining) the constancy of the internal environment demands the development of the organism to a degree that any changes in the external environment be at each moment compensated and equilibrated for. Far, therefore, from the higher animal being indifferent to the world surrounding it, it is, on the contrary, in a narrow and knowledgeable relationship with it, such that its equilibrium results from a continuous and delicate compensation established as by the most sensitive of balances ..... " Given that, in those times, Bernard did not have access to the information and technology available to us today, this was a truly remarkable statement. While it was based largely on intuitive reasoning, the experimental findings in intervening years have given considerable support to his views.

The "internal environment"

The need for mechanisms to regulate the "internal environment" of the body or "homoeostasis" is best understood by considering evolutionary history.

The majority of scientists interested in the investigation of the possible origins of life on earth are of the view that life originated in the marine environment. The arguments leading to this conclusion will not be gone into here, but it may be noted that, (in the short-term) the marine environment has a considerable degree of constancy, not usually being given to rapid and wide fluctuations in composition, temperature etc., In the case of a very small organism with a relatively permeable outer membrane, solutes which do not need active transport across the membrane, water, heat etc., could pass through with relative facility and maintenance of a fairly constant composition within the organism would be less difficult to achieve. This is particularly so since the surface area to volume ratio is high. When the organism increased in size and complexity and, additionally, when it left the marine environment and came to land, however, it had to contend with new challenges such as the elimination of increased quantities of waste and poisonous substances and avoidance of desiccation,, temperature regulation etc., Mechanisms to maintain the constancy of its internal environment had, therefore, to be evolved.

A familiar example of homoeostasis in the human is the regulation of body temperature at a level which is optional for its various components and the activity of its enzymes and other processes. For example, when it is cold, we shiver and generate heat, while, when it is excessively warm, we sweat profusely which, following evaporate loss of heat, has a cooling effect. Other mechanisms of thermoregulation, such as the opening and closing of blood capillaries in the skin are also well known.

These and similar regulatory mechanisms found in present day living organisms are the product of thousands of millions of years of evolution and, in general, are well able to cope with the environmental stresses and challenges an organism would face in nature. However, with the rise of human activities (mostly in the last few hundred years) the environment is presenting or being presented with new challenges which may by termed "unnatural" either quantitatively and/or qualitatively, such as synthetic chemicals whose structures do not resemble any found in nature and which are persistent or only very slowly decomposed under normal conditions.

Cytochrome P-450

One enzyme is very much concerned with the breakdown of toxic chemicals is a protein known as "cytochrome P-450". The protein has been found in a variety of tissues of animals and plants and has also been identified in several micro-organisms. The protein has different roles in the various tissues in which it is found and in the liver, for example, a variety of activities exist side-by-side. Indeed, it has been postulated that the initial activity of cytochrome P-450 in primordial organisms may have been in the detoxification of molecular oxygen.

One important function of cytochrome P-450 in the liver is converting a toxic chemical to a less toxic or a non-toxic species. The characteristic enzymatic activity is termed hydroxylation or the introduction of a hydroxyl (-OH) group into the molecule. Since the substrate chemicals are usually lipid-soluble substances, the introduction of a hydroxyl group renders the molecule more polar. Increasing the polarity of the molecule renders it more water-soluble than it was previously and thus improves the possibility of its being excreted through the kidneys.

The hydroxylation reaction may result in a "reactive group" of the molecule becoming less toxic. Alternatively, however, in some cases a previously non-toxic or slightly toxic chemical may acquire a higher degree of reactivity following enzymatic transformation of the molecule by cytochrome P-450.

A "reactive" molecule may react with one of the components (such as a protein) of the cell. In many cases, this would be of little, if any, material importance. Sometimes, however, the molecule reacts with the DNA (deoxyribonucleic acid) of one of the cell's genes. When this happens, in some cases, a mutation or the development of a cancer may result. It has been found that very often a chemical which is mutagenic (or cancer-causing) and <u>vice versa</u>. This characteristic is made use of in the "Ames Test" to examine rapidly and economically whether a chemical may be cancer-causing. This is carried out by testing if the compound is mutagenic on incubation with a given strain of bacteria, although frequently certain conditions, such as the addition of a cytochrome P-450 containing enzyme preparation for "activation" of the chemical, must be met to optimise the assay.

<u>Xenobiotic metabolism</u>

The many possible substrates of hepatic cytochrome P-450 include "xenobiotics" (foreign chemicals) such as pesticides, hydrocarbons, cannabinoids and medicinal drugs. Interestingly, different species of cytochrome P-450 appear to be present in the liver and the activity of these species towards a given substrate may differ one from the other. Also, cytochrome P-450 species are frequently highly inducible and this may occur selectively for a given species.

While it has long been known that cytochrome P-450 enzymes are frequently involved in the metabolism of medicinal drugs such as phenobarbitone and of perticidal chemicals, more recent researches are extending our understanding of the various processes involved. Thus, some chemicals, such as piperonyl butoxide, which are termed "synergists", are known to improve the effectiveness of pesticide formulations. It is now known that many of these act by blocking the "active site" of the cytochrome P-450 and thus hindering the breakdown of the pesticidal active agent. Similarly, any chemical which induces or suppresses the biosynthesis of the cytochrome P-450 containing enzyme system may also alter the rate at which the chemical is metabolised and thus its activity.

Ayurvedic medicines

In this connection, it has been proposed that such phenomena may provide an explanation as to why certain traditional or ayurvedic medicines may be effective only among certain peoples and not among others. It was postulated that factors such as the regular comsumption of spices in the diet may prepare the body in such a way as to make it possible for the active ingredient(s) in the ayurvedic preparation to be effective.

Regulation of steroid hormonal biosynthesis

In addition to its presence in the liver, cytochrome P-450 is also found in other tissues such as those producing the steroid hormones. In the human, these tissues include the adrenal cortex, ovary, testis and placenta, while the steroid hormones produced include the mineralocorticoids, glucocorticoids, androgens, estrogens and progestins.

The various steroid hormones have different (though sometimes overlapping) functions controlling many very important physiological functions including some of those concerned with maintaining the constancy of the "internal environment". These hormones may be effective ("potent") in their effects at even small concentrations and it is, therefore, vitally important that their biosynthesis and secretion is strictly regulated to be at levels optimal for the needs at any given time. One such regulatory mechanism which is discussed below as an example concerns the biosynthesis of the mineralocorticoid hormones and involves the operation of a feedback control mechanism.

The mineralocorticoid hormones have among their functions the control of level of sodium ions in the blood plasma and the relative proportions of sodium to potassium ions in the blood. Two hormones with mineralocorticoid properties, called aldosterone and deoxycorticosterone, are produced by the adrenal cortex. More than one mechanism has been known or suspected for the control of the biosynthesis and secretion of these steroids.

An interesting mechanism of control of the biosynthesis of mineralocorticoid hormones relates to the influence of the dielectric constant in the immediate vicinity of a cytochrome P-450 containing enzyme complex on the rate of the necessary hydroxylation reactions.

This effect of dipolar ions (which affect the dielectric constant) has been experimentally demonstrated on the rate of the over-all hydroxylation reaction. In other experiments, it was also found that sodium, potassium and some other monovalent ions also had an effect on the rate of hydroxylation and, interestingly, that the extent of the various effects appeared to be related to the (different) ionic radii of the ions examined. It has been postulated that these observations may be related to the effect of the ionic radius on the dielectric constant a (minute) distance away from the ion.

Therefore, the dielectric constant in the vicinity of these steroid hydroxylases can be influenced either by changes in (sodium) ion content or by changes thus lead to changes in the rate of biosynthesis of mineralocorticoid hormones which in turn lead to effects designed (through the kidneys etc.,) to correct the levels of sodium and potassium ions. This entire feedback control mechanism is thus a fascinating example of devices in the body which act continuously to main: ·the constancy of the internal environment.

Conclusion

The foregoing account has touched very briefly on the concept of the "internal environment" proposed by Claude Bernard and on examples which have a bearing on this concept. Physiologists, biochemists and scientists in other disciplines will be aware of numerous other examples of the maintenance of the constancy of the "internal environment". Indeed, even a schoolboy engaged in a 100 metre-dash, could reflect that the panting and sweating he was experiencing would serve not only to increase his intake of oxygen but also to dispose of the excess carbon dioxide, water and heat produced during the "combustion" within his body of carbohydrates etc; to provide the energy requirements for the excercise. While even the examples given above have been dealt with only very superficially due to the customary constraints, more detail is given in the references listed below.

One aspect of the above discussion has, therefore, been to emphasize that, while the body cannot cope very well with "unnatural" or excessive abuses or assaults on it such as by certain synthetic chemicals or certain types of radiation, it is not entirely defenceless and, indeed, has a host of mechanisms to enable it to meet the normal challenges of living. Desirable practices to be followed by society in general and in our day-to-day lives would appear to be those which would reduce or prevent our exposure to such "unnatural" or excessive challenges.