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MECHANISMS OF TOXICITY AND METABOLISM

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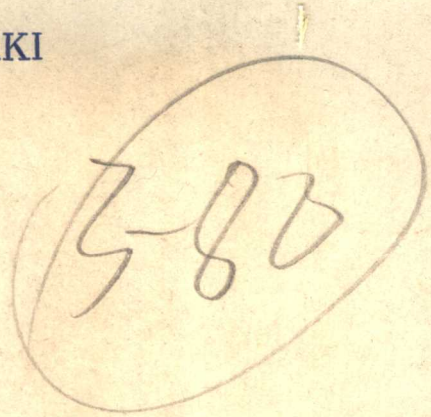

Proceedings of the Sixth International Congress of Pharmacology

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University of Helsinki

VOLUME 6

MECHANISMS OF TOXICITY AND METABOLISM

Supplement to

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Preface

The International Union of Pharmacology (IUPHAR) held the Sixth International Congress of Pharmacology in Helsinki, Finland on 20–25 July 1975. The scientific programme was organised with the help of the International and Scandinavian Advisory Boards and it consisted of 15 invited lectures, 20 symposia, 5 seminars on methods, and volunteer papers, some of them as poster demonstrations. Altogether 1580 communications were delivered by the 2 600 active participants attending the Congress.

The texts of the invited lectures and symposia have been included in the Proceedings of the Congress. It is readily noticeable that all the major areas of pharmacology, including clinical pharmacology and toxicology, are well represented. Special attention has been paid to several interdisciplinary areas which are on the frontiers of pharmacology and have connections with physiology, biochemistry and endocrinology. Many of the topics are of special interest to internists, psychiatrists, neurologists and anaesthesiologists. Chapters on the abuse of alcohol, new teaching methods and the conservation of wild animals reflect the wide scope of the Congress.

One can hardly imagine any other Congress Proceedings where more world-famous authors representing pharmacology and the related sciences have reported the most recent developments in their special fields. The invited lectures give a particularly clear introductions to the areas in question, even for those previously unfamiliar with them.

For the first time the Proceedings of an International Pharmacology Congress have been produced by the photo offset-litho process. This method was chosen in order to publish the volumes in the shortest possible time. It clearly demands the emphasis be placed upon the scientific content of the volumes, possibly at the expense of retaining some infelicities of style or presentation.

We are convinced that these Proceedings present a unique opportunity to keep abreast of the latest developments in pharmacology and related areas of research. Our sincere thanks are due to the authors, the members of the advisory boards and our colleagues of the Programme Committee for making the scientific programme of the Congress so successful and the publication of the Proceedings possible.

The Editors

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Invited lectures

DEVELOPMENTAL ASPECTS OF DRUG METABOLISM

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Developmental aspects of drug metabolism as well of those of other biological phenomena are generally twofold. Development can be described by examining various species of different levels of biological evolution or by studying the ontogenetic evolvement of the features in question in one animal species or groups of related species. In this article the latter approach will be used and the animal species involved are mammals. That the phylogenetic approach is also feasable is evidenced by numerous data on oxidative metabolism mainly of insecticides in birds, fish and insects. A review on diene-organochlorine insecticides by Brooks (6) epitomizes the fact that insects, birds and fish possess the enzymatic mechanisms for epoxidation of these insecticides to only a slightly less degree than do mammals. Thus the ability to oxidize foreign compounds does not seem to be restricted to animals of higher organization, and consequently the key enzyme for hydroxylation, cytochrome P 450, has been found in insect microsomes (28), and binding spectra of pesticide substrates have been measured (30).

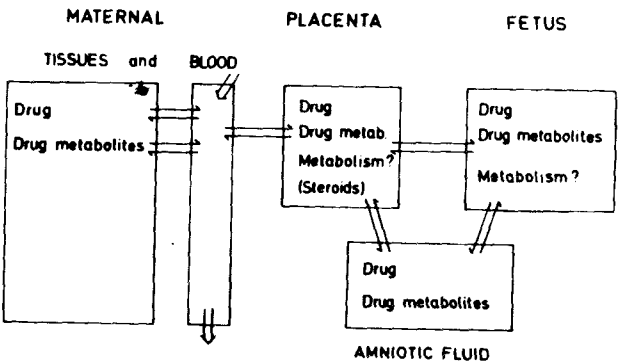
This article shall be concerned with the ontogenetic approach, i.e. with the examination of the development of drug metabolizing systems during the various phases of individual development and growth of mammals. Several recent reviews and monographs deal with perinatal aspects of pharmacology and display a large body of experimental evidence for the fact that there is a development of the oxidative metabolism of drugs and other foreign compounds with increasing age (1, 3, 8, 11, 12, 14, 15, 21, 24, 33, 34, 37, 50, 55, 56). The reviews also show that drugs applied to the maternal organism will penetrate the placenta and reach the fetus. Physiological and other, but not drug metabolic, aspects of perinatal life have recently been summarized (35).

We shall concentrate here on three different aspects of drug handling during pregnancy and early life, namely a) drug distribution, b) the development of the mixed function oxidase during ontogeny, and c) the interaction of drugs with microsomes from human placenta.

Drug distribution

In addition to the normally relevant compartments for drug distribution, such as blood and various tissues, the number of drug compartments is increased by those of the placenta, the fetus itself and the amniotic fluid. Fig. 1 shows this situation in a diagrammatic way. A given

DRUG COMPARTMENTS IN PREGNANCY



drug that enters the blood stream will be distributed more or less rapidly between maternal tissues and the feto-placental unit. Since biological membranes represent a barrier for penetration, there will be a time lag before the drug enters the more remote compartments. When the maternal elimination rate exceeds that in the feto-placental unit higher concentrations in the fetus than in the maternal blood can result towards the end of the elimination phase. This illustrates that in fetal plasma or even more so in the amniotic fluid given drugs or their metabolites may reach their peak levels later than in the maternal blood and therefore may be found in relatively higher concentrations than in the maternal blood during the elimination phase. These pharmacokinetic parameters could furnish a partial explanation for the delayed action of drugs on the fetus or newborn. Examples for this type of drug distribution during pregnancy in humans are the results of Good and Johnson (13) on kanamycin and of Bray et al. (5) on ampicillin. 500 mg of kanamycin were injected intramuscularly to 27 women with uncomplicated pregnancies and deliveries and samples were taken from the amniotic cavity by catheter before and from cord blood immediately after delivery. At the time of delivery (about 6 hours after injection) levels were the same in all three compartments, while kanamycin in the maternal serum had reached its maximum 1 - 2 hours after injection.

To reach the fetus drugs have to penetrate the placental membrane. This occurs for practically all drugs by passive diffusion, whereby the penetration rate is determined by the concentration gradient and by the lipid solubility of the respective substances. The penetration rate is also governed by the placental surface area available for transport. According to earlier electron microscopic studies (48) only about 5 - 10 per cent of the placental surface area consists of epithelium which allows a relatively easy penetration. Thus only a fraction of the total area seems to be suitable for the exchange of solutes and gases. Furthermore penetration is determined by the dissociation constant (and thus the pH of the solution) and the lipid solubility of the undissociated compound (see 12). This explains the rapid entry of substances with a high oil/water partition coefficient at pH 7.4 e.g. general anaesthetics. On the other hand, highly polar compounds such as succinyl choline, decamethonium or d-tubocurarine have a comparatively slower penetration rate (34). The great majority of therapeutics ranges between the two extremes. Since placental and fetal membranes do not seem to have other physicochemical properties as do other biological membranes, no specific exclusion or accumulation is to be expected for the feto-placental unit and has not been demonstrated so far, i.e. there does not seem to be a "fetus-specific" drug. An interesting exception could possibly be the accumulation of ethanol in monkey fetal pancreas 90 minutes after ethanol injection (18).

In addition to the outlined pharmacokinetic aspects a possible difference in drug binding between fetal and adult plasma proteins could be of relevance to the distribution of drugs. Attempts to assess this possibility (27) show that certain differences in binding of e.g. phenytoin can occur. It will require further work, however, to judge the importance to overall drug distribution within the feto-placental unit.

Ontogenetic development of drug metabolism

Development of drug oxidizing capacity in laboratory animals.

Before developmental aspects are discussed the main features of the drug oxidizing enzyme system shall be briefly outlined, and only a general reference is given (4) for documentation of the properties of the microsomal monooxygenase system. The incorporation of oxygen into the drug substrate molecules is catalysed by a complex mixed function oxidase that reduces one atom of the oxygen molecule to water thereby gaining the chemical energy for the incorporation of the other. The central catalyst is a carbon monoxide sensitive hemoprotein, cytochrome P 450, which strongly absorbs light at 450 nm when its reduced form (Fe^{++}) is combined with carbon monoxide. It is located mainly in the membranes of the smooth endoplasmic reticulum of the liver cells. The substrate specificity of this system is very low and such diverse reactions as the hydroxylation of saturated and unsaturated hydrocarbons, O- and N-dealkylations, epoxidation of unsaturated hydrocarbons etc. are catalysed. The reaction cycle begins with the binding of the substrate by the oxidized form of cytochrome P 450. This binding process leads to spectral changes which produce a difference

spectrum characteristic of either of two groups of substrates, which are classified as type I and type II. Type I substrates seem to bind to a lipophilic binding site on the cytochrome, while type II substrates bind to or to the neighbourhood of the heme site. After the drug substrate is combined with cytochrome P 450 the latter is reduced to the ferrous state by a NADPH dependent reductase, which also is able to reduce cytochrome c, if present (therefore NADPH-cytochrome c-reductase). This reductase is also present in the enzyme complex and can be measured separately by adding oxidized cytochrome c. The next step in the reaction sequence is the addition of one molecule of oxygen which interacts with the heme iron to finally become "activated" and incorporated into the substrate. Before this can occur the intermediate complex, which absorbs light at 440 nm and which has been postulated recently, must undergo a second reduction step, which seems to be catalysed by cytochrome b_5 that is also present in microsomal membranes. There is a preference for NADH over NADPH for this reaction, hence a synergistic effect of NADH on the steady state reaction rate maintained by NADPH. This sequence of uptake of oxygen first and then the second electron has been debated recently. The reaction cycle is terminated by the seperation of the oxidized product from the ferric cytochrome P 450 after rearrangement. This reaction scheme calls for a 1 : 1 : 1 stoichiometry for substrate (product), NADPH and oxygen. Thus in characterizing the age dependent development of the hepatic drug oxidizing activity various parameters of the system are measured by most authors such as product formation, cytochrome P 450 concentration, NADPH-cytochrome c-reductase, NADPH-cytochrome P 450-reduction, cytochrome b_5 and substrate binding spectra. Repeated administration of a large number of different drugs and other foreign compounds such as barbiturates, polycyclic hydrocarbons and insecticides induce the formation of the mixed function oxidase and thus increase the drug metabolic activity. Two classes of inducers can be distinguished. Phenobarbital represents an inducer that increases cytochrome P 450 and NADPH-cytochrome c-reductase, while the carcinogenic polycyclic hydrocarbon 3-methylcholanthrene increases a slightly different form of the central cytochrome, the carbon monoxide complex of which will absorb not at 450 but at 448 nm, hence P 448. This latter mode of stimulation leads to large increases in activity towards e.g. 3,4-benzpyrene but not towards substrates like hexobarbital or ethylmorphine. These considerations are of importance with respect to the induction of enzyme activities in utero or postnatally.

The first recognition of a perinatal development of the drug oxidizing activity came in 1958 with the observation (20) that newborn mice and guinea pigs are unable to demethylate monomethyl-4-aminoantipyrine, dealkylate phenacetin and oxidize the side chain of hexobarbital. Also the glucuronidation of phenolphthalein was lacking in these in vitro experiments. These experiments could be verified in vivo by measuring the sleeping time in mice of various ages with the result that immediately after birth the sleeping time was very much longer than in adults. It was concluded that newborn animals lack the respective enzymatic activity and this conclusion was tacitly applied also to humans. Subsequently (10) se-

veral mechanisms for the lack of drug oxidation in rabbit liver preparations were discussed such as absence of the active protein, lack of cofactor or endogenous inhibitors. Combination experiments led to the conclusion that an endogenous inhibitor seemed present in the nuclear or mitochondrial fraction of baby liver homogenates. A similar finding was reported for rats (25). In concordance with this it was reported (26) that in cultures of chick embryo liver the development of glucuronyl transferase is delayed by the presence of fetal bovine serum and enhanced by the presence of adult serum. The postnatal development of hexobarbital metabolism could also be retarded in rats by the implantation of a growth hormone producing pituitary tumor (55). Thus growth hormone can possibly lead to the impairment of drug metabolizing activity.

However the assumption of a fetal inhibitor was seriously modified by the electron microscopic finding (7) that the fetal hepatocyte possesses only a very poorly developed endoplasmic reticulum and that this is increased in parallel with a steep postnatal increase of NADPH-cytochrome c-reductase. The latter reaches its maximal value about one day after birth, while the other components of the mixed function oxidase show a much slower increase. Interestingly a microsomal marker enzyme, glucose-6-phosphatase, shows a very steep postnatal increase. Presumably the steeply rising enzymes are synthesized in the rough portion of the endoplasmic reticulum. Closer examination (31) revealed that both type I and type II substrates show the postnatal increase in their metabolism reaching adult levels at about 3 - 5 weeks. In males the maturation of drug oxidation followed most closely the increasing mean specific activity of NADPH-cytochrome P 450-reductase while in females there was a closer relationship to the increase in NADPH-cytochrome c-reductase. In both sexes the correlation between drug oxidative activity and increasing concentration of cytochrome P 450 was poor. Basically the same observation of a concomitant increase in mixed function oxidase components and drug metabolism was made in guinea pigs (29) and in swine (51). In the latter animal also ethyliso-cyanide spectra have been measured in different age groups with the result that also this parameter, which is clearly discernible already in fetal life, gradually increases with postnatal age. It did not become evident from the spectra, if cytochrome P 450 might exist in a different conformational configuration in fetal liver.

Also the N-oxidation of N,N -dimethylaniline, which is not mediated by cytochrome P 450, shows a postnatal increase in rats which is distinguished by the occurrance of an initial peak at about three days, a subsequent minimum and a final peak after 25 days (52).

The question whether fetal, neonatal and adult hydroxylases are of the same conformational structure has recently been approached in two ways. In humans, where there is fetal activity, kinetic studies on amino-pyrine-N-demethylation, aniline-p-hydroxylation and 3,4-benzpyrene hydroxylation have yielded mostly linear kinetic plots with fetal and non-

linear ones with adult liver. This is interpreted as showing the presence of one form in fetal and two forms in adult life for the reactions studied (40). Using the inhibitor of 3,4-benzpyrene hydroxylase 7,8-benzoflavone in young rats a twofold effect was seen. During the period of six days postpartum until weaning the enzyme activity is greatly increased while after weaning (day 20) it is inhibited to about 50 per cent of the control value in inhibited adults. In female rats the enzyme remains more sensitive to 7,8-benzoflavone inhibition (54). It is concluded that there are two forms, one which is stimulated and another that is inhibited by the same compound.

An important feature of drug monooxygenases is their inducibility by a number of different chemical compounds. Thus the question of the possibility of induction during the perinatal period has been raised soon after the recognition of the developmental aspects of drug metabolism. In rabbits the administration of the inducer phenobarbital to mothers did not cause enzyme induction in the fetus until just before birth (16). Various reasons were discussed for this lack in inducibility such as a defect in enzyme synthesizing mechanisms or their endogenous stimulation. This area became especially interesting when it was shown that in cultures of hamster embryos the induction of 3,4-benzpyrene hydroxylase by the substrate itself was possible (36). This discrepancy can perhaps find its explanation in recent studies on the inducibility of various drug metabolic enzyme activities in the guinea pig (29). It was found that the application of 100 mg/kg of phenobarbital to pregnant animals resulted in an increase of p-chloro-N-methylaniline demethylation, cytochrome P 450 reduction and cytochrome P 450 concentration only shortly before parturition. But 3,4-benzpyrene hydroxylase was markedly stimulated already much earlier in pregnancy (day 33). This shows a) that small but measurable activities are present at least from day 33 to 63 of gestation and b) that one of the two postulated forms of hydroxylases (namely 3,4-benzpyrene hydroxylase, cytochrome P 448) is inducible at an earlier stage. A similar example has been given in rats, where not only phenobarbital but also 3-methylcholanthrene and 3,4-benzpyrene itself were shown to induce the 3,4-benzpyrene hydroxylation transplacentally at day 20 of gestation (38). The epoxide hydratase is increased by 50 per cent under these conditions by phenobarbital only and not by the other inducers. This points to different trigger mechanisms for the biosynthesis of the two enzymes. The increases in benzpyrene hydroxylation are very large (about 30 fold), possibly because the control activities are very low. Interestingly the inducibility by 3-methylcholanthrene in these fetal livers remains almost constant (30 fold) from day 15 to 20 indicating a relatively early onset of sensitivity to inducers. These results have specific relevance for the potential carcinogenic action of epoxides produced intracellularly in greater amounts by an induced monooxygenase and not inactivated by the (non-inducible) epoxide hydratase.

Development of drug oxidizing capacity in humans.

For many years it was assumed that also human fetuses would be deficient or nearly deficient in drug metabolic activity. This extrapolation

from the low values found in animals seemed to be justified as long as pertinent experiments on human fetal liver tissue had not been done. However, in 1970 it was found that human fetal liver microsomes did indeed show some metabolic activity (57). In five out of ten livers oxidative demethylation of aminopyrine could be found, while 3,4-benzpyrene was not affected. What is possibly more important, cytochrome P 450 could be found, even if in amounts about 10 times lower than in adults, and an increase could be seen with increasing gestational age from the 14th to the 25th week. Likewise NADPH-cytochrome c-reductase activity was measurable. Furthermore typical substrate-induced difference spectra could be obtained for aminopyrine, testosterone and laurate. Thus the human fetal liver seemed to possess the necessary constituents and properties for oxidation of exogenous and endogenous substrates. These findings quite elegantly agree with simultaneous observations (41, 43) that revealed metabolism of chlorpromazine, 3,4-benzpyrene and N-methylaniline by these preparations, in addition Michaelis constants could be determined. This was followed by the demonstration of cytochrome P 450 in human fetal liver preparations (42). Subsequently it was shown that also other substrates such as ethylmorphine and aniline are metabolized, whereby the reaction rates corresponded to about 35 to 40 per cent of those in adult human liver (45). It is noteworthy that the centrifugal localization of the respective activities is different from the situation in adults. The largest activity was found in the 200 x g pellet i.e. in a relatively crude fraction, whereas the specific activity was highest in the usually washed 105.000 x g fraction (see also 46). This effect may be due to different behaviour during homogenization leading to only partial conversion of the endoplasmic reticulum to uniform microsomes. The remaining cisternae plus intact hepatocytes and nuclei are supposed to form the low speed-fraction containing considerable drug metabolic activity. In electron microscopic studies (58) the development of human hepatocytes was examined between the 7th and 20th gestational weeks with special reference to the endoplasmic reticulum. Initially it consists of ribosome-studded membranes which around the 12th week show a marked increase in smooth reticulum, the locus of cytochrome P 450 containing drug enzymes. In accordance with the observations (52) on postnatal development of N-oxidation in rats it was found that also human fetal liver microsomes catalyse this reaction in the same manner as animal microsomes have been shown to do. This reaction has been found (44) to be independent of cytochrome P 450 and insusceptible to carbon monoxide inhibition. This proves that the flavine containing N-oxidizing fraction is also present in microsomes from immature liver tissue.

A comparison of fetal with adult metabolic activities revealed (39) that on a protein basis between 3 (3,4-benzpyrene hydroxylase) and 15 per cent (aniline hydroxylase) of adult activity were found in the fetuses, while cytochrome P 450 and NADPH-cytochrome c-reductase were 30 - 35 per cent. Spectral changes coincide except that aminopyrine (adult: modified type I) shows type II characteristics.

In view of the above described fetal drug metabolizing ability it is not surprising that the human neonate immediately after birth is quite well able to handle drugs and environmental toxicants to a considerable degree. When applying suitably sensitive and specific analytical methods a great number of drug metabolites can be identified in newborns (see 17). Along these lines is the observation (47) that babies born to epileptic mothers on carbamazepine eliminate the drug equally as fast as adults.

In this situation of an apparent disparity between laboratory animals and man it is difficult to extrapolate from animal results in man. This makes predictions on the e.g. carcinogenic or teratogenic risk of certain compounds almost impossible. Therefore, the observation that a primate species shows the same behaviour is of exceptional importance. Recently it has been found that the metabolism of ethylmorphine, cytochrome P 450 content and NADPH-cytochrome c-reductase activity in man and the stumptail monkey (Macaca arctoides) are the same in fetuses of both species. Thus this monkey may prove to be a useful animal model for fetal drug metabolism studies (9). Very recently a report has appeared, however, that sheds a very different light on the situation (53). In three rabbits on the 30th day of gestation fetal and maternal drug metabolizing activities were compared and it was found that fetal p-nitroanisole demethylation was 30 per cent of maternal, while 3,4-benzpyrene hydroxylation was 5 per cent, NADPH-cytochrome c-reductase 37 and cytochrome P 450 content about 20 per cent of maternal. If this observation is confirmed, the hypothesis of a qualitative difference between laboratory animals and man with respect to fetal hydroxylase activity may have to be modified.

Drug metabolism in the human placenta

Besides its nutritive functions the placenta is also an organ of potential significance for "protecting" the fetus from harmful compounds by "detoxifying" them (37). This may be particularly important in view of the steroids which reach the feto-placental unit during pregnancy. Following the description of cytochrome P 450 in human placental microsomes (32) many attempts have been made to determine the ability to oxidize foreign compounds. But only insignificant capacities in a limited number of substrates have been found. This is probably due to three different reasons:

a) the cytochrome P 450 content is very low in comparison with adult liver
b) the cytochrome P 450 enzyme is of different configuration
c) it does not seem to possess the broad unspecifity towards a host of substrates and thus does not even bind common drug substrates (2).

In comparison with rat (22) or human (2) liver human term placenta contains about 20 and 3 times less cytochrome P 450, respectively, and this is further complicated by the presence of hemoglobin. Interestingly, however, the ratio cyt P 450/ cyt b5 is the same, namely about 1 : 1. In contrast the NADPH-cytochrome c-reductase activity is almost comparable to the adult situation. The only substrate that is appreciably metabolized