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COMMENTARY

DO CYTOCHROMES P-448 AND P-450 HAVE DIFFERENT FUNCTIONS?

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Recently Ioannides and Parke [1] claimed that the 3-methylcholanthrene-(MC)-inducible cytochrome P-448 isoenzymes are specifically concerned with the activation of chemicals to reactive intermediates, leading to the formation of toxics, mutagens and carcinogens. In contrast, the phenobarbital-(PB)-inducible cytochromes P-450 "generally" direct the overall metabolism of a chemical towards the formation of inactive metabolites and detoxication.

We disagree with this statement and wish to offer our reasons. If on the one hand the cytochrome P-448 binding sites contain a number of hydrophobic aromatic amino acid residues orientated to allow occupation by similar substrates (toxics and carcinogens) containing co-planar aromatic rings only, whereas those (hydrophilic) of the PB–cytochromes P-450 allow attachment to a wide range of compounds (many of them detoxified), on the other hand the large number of chemicals "activated" by cytochromes P-450 stresses the importance of this last set of hemoproteins for human health. In other words, even though for cytochromes P-448 the ratio of metabolized/activated chemicals is close to one, and for cytochromes P-450 this ratio is greater than one, the increased number of cytochrome P-450 substrates that can be activated to highly reactive intermediates suggests that caution should be exercised by the Authors in their assumption.

For example, it is well known that the metabolism of *N*-nitrosamines (the position of which between mutagens and carcinogens is not clear in the review), mainly activated by the PB-induced cytochromes P-450 [2–4] and by the ethanol-induced forms at low substrate concentration [2], gives rise to potent and organothropic carcinogens [5–7]. Some of these are listed in Table 1 [7–21]. The PB-induced cytochrome P-450 isoenzymes are also responsible for the metabolic conversion of olefins into epoxides, or other very reactive intermediates, leading to the formation of toxics, mutagens and carcinogens [22, 23]. The above effects can also be observed after the activation of saturated aliphatic halogenated hydrocarbons by the PB-induced isoenzymes [24]. Some of these carcinogens are listed in Table 2 [25–36], but many others could be cited. Neither olefins nor aliphatic halogenated hydrocarbons are reported in the commentary by Ioannides and Parke.

We suggest not emphasizing unduly the role of the MC-inducible cytochromes P-448 in the bioactivation

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Table 1. Carcinogenic nitrosamines and some nitrocompounds

N-Nitrosomethylbenzylamine	*N*-Nitrosomethylurethane
N-Nitrosodiethylamine	*N*-Nitroso-*N*-methylurea
Dimethylnitrosamine	*N*-Nitrosotrimethylurea
Diethylnitrosamine	*N*-Nitroso-*N*-ethylurethane
Methylethylnitrosamine	*N*-Nitrosopropylmethylamine
Dialkylnitrosamine	*N*-Nitrosoethylmethylamine
N-Nitrosodiethanolamine	Nitrosoepthylmethyl-to
N-Nitroso-*n*-propylamine	Nitrosododecylmethylamine
N-Nitroso-*n*-butylamine	*N*-Nitrosodi-*n*-propylamine
N-Nitrosobutyl-4-hydroxybutylamine	Nitrosodi-*iso*-propylamine
N-Nitroso-*n*-amylamine	Nitrosodibutylamine
N-Nitrosoallylmethylamine	Nitroso-*iso*-butylamine
N-Nitroso-*n*-butylmethylamine	Nitrosomethylneopentylamine
N-Nitrosomethylvinylamine	Nitrosomethyltridecylamine
N-Nitrosomethylphenilamine	Nitrosomethyltetradecylamine
N-Nitrosoethylisopropylamine	Nitrosomethylacethoxymethylamine
N-Nitrosobutylethylamine	Nitrosodi-2-propanolamine
N-Nitrosoethylvinylamine	Nitrosomethylethanolamine
N-Nitrosoethyl-2-hydroxyethylamine	Nitrosopropylpropanolamine
N,N'-Dinitroso-*N,N'*-dimethylethylenediamine	Nitrosopropylethanolamine

Table 2. Carcinogenic olefins and aliphatic halogenated hydrocarbons

1,2-Dibromo-3-chloropropane	1,3-Cyclohexadiene
1,2-Dibromoethane	Isoprene
1,2-Dichloroethane	1-Hexadecene
Hexachloroethane	4-Vinylcyclohexene
1,1,2,2-Tetrachloroethane	Vinyl bromide
Tetrachloroethylene	Butadiene monoxide
1,1,1-Trichloroethane	Ethylene dibromide
1,2-Dichloroethylene	Chloral hydrate
1,1,2-Trichloroethane	3,4-Epoxy-1-butene
Trichloroethylene	1,3-Butadiene
Pentachloroethane	1,3-Dichloropropene
1,1,1,2-Tetrachloroethane	1,2-Dichloropropane
Vinyl chloride	Chlorofluoromethane
Acrylonitrile	2-Chloro-1,1,1-Trifluoroethene
Styrene	Methyl chloride
Vinylidene chloride	Methyl iodide
1,3-Butadiene	1,2-Dibromo-3-Chloropropane
2-Chlorobutadiene	Dichloromethane
Chloroform	Hexachlorobutadiene

of chemicals in toxics and carcinogens, when it is known that other cytochrome P-450 forms, such as cytochrome P-450b (PB-inducible), cytochrome P-450ISF-G (isosafrole-inducible), cytochrome P-450PCN (pregnenolone 16-α carbonitrile-inducible) or cytochrome P-450j (ethanol- and acetone-inducible) are strongly associated with chemical hazards.

A second problem arises from the conclusions of the Authors when they suggest, as a future possibility, the use of nutrients to increase the PB cytochrome P-450-dependent enzymes.

There is no doubt that this suggestion may lead to a magnification of toxic effects for humans. In fact, the induction of this set of cytochrome P-450 isoenzymes could increase the rate of activation of olefins and nitrosamines [37]. Again, the increased levels of a number of enzymes associated with drug metabolism (including the PB-inducible forms of cytochrome P-450 but not the MC-induced cytochromes P-448), being associated with liver-tumor promoting ability, have aroused great interest in recent years as potentially important markers of neoplastic progression [38–41]. Moreover, the use of nutrients that can modulate the PB-induced cytochromes P-450, as well as the use of cytochrome P-448 inhibitors (also proposed by the Authors) without a clear understanding of the possible consequences in the modulation of the other cytochrome P-450 forms (with the implication of endogenous metabolism), seems to be too broad.

Finally, although not all chemicals metabolized by cytochromes P-450 give rise to very reactive intermediates, it should be noted that these intermediates (as well as those obtained in the metabolic activation of barbiturates) may have, at least in some cases, the ability to act as promoters in the initiation/selection processes of experimental hepatocarcinogenesis [42, 43].

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