



# IMMUNE SYSTEM-DRUG METABOLISM INTERACTIONS: TOXICOLOGICAL INSIGHT

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## Abstract

From many years the inflammation is considered as one important determinant of susceptibility to intoxication by xenobiotic exposure. Inflammation and vaccination in most cases are connected with immune system stimulation and release of cytokines, adipokines, reactive oxygen species, nitric oxide, proteases, and lipid metabolites. That was accompanied by different extend of down-regulation of the main xenobiotic/drug metabolizing enzyme system cytochrome P450 (CYP) both in the liver and the adipose tissue. We need more knowledge of possible changes in the pharmacokinetics respectively in effectiveness and side effects of drugs used in chronically ill patients in case of occurrence of acute viral or bacterial infection in them or after the application of different vaccines. This would contribute significantly to the optimization of personal drug therapy avoiding toxicity or lack of effectiveness. Here we tried to summarize some of the main experimental and clinical data of altered drug metabolizing enzyme system in the case of changes in the immune system due to inflammation or vaccination.

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**Key words:** adipose tissue, cytochrome P450, cytokines, interferon, inflammation, toxicity, vaccination

## Introduction

Numerous experimental and clinical data suggest that the major system (host defense) that protects humans from infectious organisms interacts with the principal system that affords protection from chemicals including drugs (drug metabolizing enzymes). This interaction has the potential to produce severe and occasionally life-threatening complications in drug therapy during episodes of infectious disease or other pathological changes of immune system. The loss of cytochrome P450 is now considered to be a multifactorial and frequent consequence of *stimulation* of immune system after infection and inflammation (1-6). In most cases that is accompanied with no other signs of toxicity of affected organs (liver, kidney, brain). Few examples exist for cases with reduced inflammation and *immunosuppression* after induction of cytochrome P450: dioxins (CYP 1A1, CYP 2B1)(7), phenobarbital (CYP 2C, CYP 2B, CYP 3A4) (8,9), rifampicin (CYP 3A4)(10), clofibrate and bezafibrate (CYP 4A) (11).

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## Experimental evidences

In animal models, cytochrome P450 is depressed by various types of: (i) bacterial infections - *Listeria monocytogenes* (12), *Actinobacillus pleuropneumoniae* (13), *Chlamydia trachomatis* (14), (ii) viral infection - *Encephalomyocarditis virus* (15), *murine retrovirus LP-BM5* (16), influenza virus (17), (iii) parasitic infections - *Fasciola hepatica* (18), *Plasmodium berghei* (19), and (iv) *Bacillus Calmette-Guerin* (BCG) (20) and *B. pertussis* (21) vaccines.

Likewise, in experimental diseases such as rat adjuvant polyarthritis (22, 23). Of note, 48 hours after the production of an inflammatory reaction generated by the subcutaneous administration of turpentine in rabbit both hind legs, the tolbutamide total body clearance was markedly decreased due to reduced concentration of hepatic cytochrome P450 (24). Acute adenovirus hepatitis in mice resulted in selective down-regulation of acetaminophen (APAP) metabolizing P450s in liver (CYP 1A2 and CYP 2E1), decreased formation of APAP toxic metabolites and thus decreased the risk of APAP hepatotoxicity (25).

The cytochrome P450 down-regulation is time, dose and immune stimulus dependent. It coincides with the maximum immune response in genetically sensitive animals. Inhibition of drug metabolism appeared mainly after stimulation of cellular immunity and interferon production (26).

## Clinical evidences

There are many documented examples of compromised drug metabolism in humans with impaired immune system after inflammation (e.g., influenza, adenovirus) or vaccination (27). The magnitude of cytochrome P450 depression in humans is highly variable, and it has been proposed that high initial drug levels may predispose infected individuals to exaggerated pharmacological responses as a result of the down regulation of the drug metabolizing enzymes. These interactions continue to cause problems, such as toxicity, during drug treatment in patients with infections; following vaccination; in cancer patients receiving interferon or cytokine therapy, and in situations where host defense is activated. It is not surprising that the most cases found with impaired drug metabolism after vaccination were patients on chronic anticonvulsant and theophylline treatment where frequent drug monitoring control is obligatory. That concerns incidents of increased carbamazepine (28) and other anticonvulsants toxicity as phenytoin, lorazepam and chlordi-azepoxide (29-31) few days after immunization. In man, acute viral infections of the upper respiratory tract, bacterial pneumonia and BCG vaccination (see Peter Ghenev's *Dance round* in this volume of *Adipobiology*) are able to reduce the clearance

of theophylline by down-regulating multiple isoforms of the hepatic cytochrome P450. Theophylline plasma levels in bronchitis children increased during influenza epidemics. Quinine blood levels (32) as well as the theophylline plasma half-life (33) were increased during *Plasmodium falciparum malaria* infections. HIV infection was related to an increase in variability of drug metabolizing enzymes (34,35). Patients with rheumatoid arthritis showed a three and four fold higher systemic exposure of verapamil and simvastatin compared to healthy volunteers (36).

## Mechanisms of alteration of drug biotransformation during infections and inflammation

When discussing the numerous possible factors responsible for impairment of drug biotransformation and especially of cytochrome P450 system in cases with immunostimulation, it is important to note that (i) the activity and expression of P450 depends on the nature of inflammatory mediators, and (ii) different CYP isoforms are affected to varying degrees by different inflammatory challenge (37).

Mechanisms of cytochrome P450 depression by immunostimulation seems to imply the secretion of pro-inflammatory mediators like cytokines (IL-1, IL-2, IL6, TNF $\alpha$ )(38,39), interferons ( $\alpha$ ,  $\beta$ ,  $\gamma$ ) (6), prostaglandin (PG) E1, PGE2, and PGF2 alpha (40), NF-B by immune cells and bacterial endotoxins (LPS), which contribute for decreased CYP protein synthesis through transcriptional suppression and mRNA destabilization (41). Inflammatory mediators down regulate also inducible P450 expression by influencing different intracellular receptors pathways as aryl hydrocarbon receptor (AhR), PPAR $\alpha$ , the constitutive androstane receptor (CAR) and the pregnane X receptor (PXR). Interleukin-6 is most important of them, down-regulates liver CYP3A4 through translational induction of C/EBP $\beta$ -LIP (liver-enriched transcriptional inhibitory protein), which competes with and antagonizes constitutive C/EBP (enhancer binding proteins) transactivators (39). Gene expression of Cyp3a11 is reduced by activation of Toll-like receptors (TLRs) in mice treated with Gram-negative or Gram-positive bacterial components, LPS or lipoteichoic acid (LTA) respectively (42). Toll-Interleukin 1 Receptor Domain-Containing Adaptor Protein (TIRAP) is involved in TLR2-mediated drug metabolizing enzymes (DME) regulation *in vivo* and in isolated primary hepatocytes, but not in regulation of cytokine expression in the liver (43); for TLR4-resistin interaction, see Gertler's review in this volume of *Adipobiology*. On the other hands the alteration of mouse constitutive CYPs' expression levels during inflammation varies according to the immunostimulation pathway, the anaphylaxis-induced inflammation had less effect than LPS-induced inflammation (44).

With significant importance for safety anticoagulant therapy of millions of patients, were the findings from several control clinical studies, that warfarin kinetics and efficacy were not changed after vaccination with influenza vaccine (45). This findings could be explained with the failure of INF $\gamma$  to decrease mRNA level of CYP2C cytochromes (main enzymes metabolizing warfarin)(46). Immunostimulants would also activate directly or indirectly (*via* MAF secretion) macrophages or Kupffer cells leading to the secretion of reactive oxygen species (ROS) and NO (47,48) and ultimately to the loss of mRNA<sup>CYP</sup> (49). In this context there are some experimental evidences that safer immunostimulator should be a drug with some antioxidant properties (50).

### Which CYP isoforms are more affected after immune stimulation?

Decreased activities of liver CYP 1A1 (51), 1A2, 2A6, 2B6 and 3A4 are the most affected in infected rats. In humans CYP2A6, CYP2A7, CYP2C19 and CYP3A4 (52) were down-regulated in HBV- and/or HCV-infected livers compared with normal livers. Influenza virus vaccination down regulate CYP 1A2 expression (29). In human immunodeficiency virus-positive patients CYP 2D6 expression was also decreased (53). Some liver enzyme activities as CYP 2E1 and CYP 4A, alcohol dehydrogenase and N-acetyltransferase were even found to be increased (54) and some subfamily (CYP 2B and 3A) to be decreased (55) in AA or LPS treated rats. LPS treatment induced renal CYP 4A mRNAs in mice and rats (thus increased the levels of  $\omega$ -hydroxylated products of fatty acids) and hepatic CYP4A in rats only (56,57). Increased CYP3A4, CYP3A5, and P-gp mRNA expression levels were also detected in Crohn disease (CD) noninflamed duodenal biopsies which lead to elevated first-pass metabolism of drugs thus explained high inter-individual differences in CD pharmacotherapy (58).

### Novel immunotherapeutics and CYP-mediated metabolism

Cytokines or agents known to modulate cytokines should be evaluated in in vivo studies with relevant CYP substrates, particularly when used in combination with small molecules, and most importantly, with small molecules with narrow therapeutic indexes. The same is true for the promising novel anticancer agents that up regulate immune responses. These agents, either alone or in combinations, may cause systemic immune-related adverse events, with potential clinical implications for use of concurrent agents metabolized by CYP and other pathways (59).

### Obesity, immune system and drug toxicity

Today, the link between obesity, immunity and inflammation is well documented (60, 61). Likewise, various CYPs were found to be expressed in the adipose tissue which appears to be a “post-liver” major organ involved in the activity of xenobiotic/drug metabolizing enzymes (62-64). Impaired immune response in animals and humans affected by obesity, leading to increased risks of infection. Population studies have shown the same things. For instance, hospitalized patients affected by obesity are more likely to develop secondary infections and complications, such as sepsis, pneumonia, bacteremia, and wound and catheter infections. Overall, it appears that obesity may increase risk for bacterial and viral infections. Mortality of obese patients with severe sepsis was also higher than non-obese patients. In many cases, the basis for these differences is the different degrees of gene expression. Thus, analysis of gene expression in brains of lean and obese mice after intraperitoneal injection with LPS demonstrated more than 10 times differences in lipid transport, insulin receptors and cytochrome P450 enzymes proteins between both groups (65). An important parallel between obesity related pathology of adipose tissue and liver pertains to the emerging role of macrophages (66). It is well known that the phagocytic activity and secretory capacity of Kupffer cells were highly correlate with increased immune reactions and down regulated expression of some liver cytochrome P450's. In the same time the inhibition of Kupffer cell by GdCl<sub>3</sub> (gadolinium chloride ) exerted antiobesity effects in high fat-fed mice (67). All this shows that obese persons are not only more susceptible to infections, but with greater risk for adverse drug reactions due to impair drug metabolism and kinetics.

### Concurrent inflammation as a determinant of susceptibility to toxicity from xenobiotic agents

Concurrent inflammation should be considered as a potentially important determinant of susceptibility to intoxication from environmental chemicals, drugs and other xenobiotic agents. That is, when exposure to certain xenobiotics coincides with a period of inflammation, an individual may be at greater risk for adverse effects (68).

### Conclusion

We need more knowledge of possible changes in the pharmacokinetics respectively in effectiveness and side effects of medicines used in chronically ill patients in case of occurrence of acute viral or bacterial infection in them or after the application of different vaccines. This would contribute significantly to the optimization of personal drug therapy avoiding toxicity or lack of effectiveness.

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