CYTOCHROME P450 DOWN-REGULATION BY SERUM FROM HUMANS WITH A VIRAL INFECTION AND FROM RABBITS WITH AN INFLAMMATORY REACTION

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ABSTRACT:

Serum from humans with an upper respiratory viral infection (HSURVI) and from rabbits with a turpentine-induced acute inflammatory reaction (RSSTIAR) reduces the activity of hepatic cytochrome P450 (P450) following 4 h of incubation. The aim of the present study was to assess the effect of HSURVI and RSSTIAR on P450 activity and expression following 24 h of incubation with hepatocytes from control (HCONT) and rabbits with a TIAR (HINFLA). RSSTIAR incubated with HCONT for 24 h reduced P450 content and activity, and CYP3A6 by 45%, without changing CYP1A1 and 1A2; when incubated with HINFLA, RSSTIAR decreased P450 content and activity without affecting CYP1A1 or 1A2. HSURVI incubated for 4 h with HCONT decreased P450 activity without affecting the amounts of CYP1A1, 1A2, or 3A6, although when incubated for 24 h, P450 activity and CYP3A6 amount decreased. HSURVI incubated with HINFLA for 4 h reduced P450 content and activity, and incubated for 24 h reduced activity, P450 content, and amount of CYP1A1 and 1A2 proteins. The present study demonstrates that 1) the effect of RSSTIAR and HSURVI depends upon the susceptibility of the hepatocyte, i.e., HCONT or primed HINFLA; 2) P450 down-regulation is preceded by a decrease in P450 activity; 3) the nature of the inflammatory reaction determines the repercussions on P450 activity and expression; and 4) CYP3A6 is more vulnerable than CYP1A1 and 1A2 to the down-regulation provoked by an inflammatory challenge.

In human, viral and bacterial infections as well as influenza and BCG vaccinations decrease the clearance of exogenous substances such as theophylline and antipyrine, secondary to a decrease in activity of multiple isoforms of the cytochrome P450 (P450) (Morgan, 1997). As a consequence, bacterial and viral inflammatory reactions are cause of severe drug toxicity, essentially in pediatric and geriatric populations (Hendeles et al., 1977; Ziment, 1982; Koren and Greenwald, 1985). In animal models, infectious and noninfectious acute inflammatory reactions, such as those induced by endotoxin and turpentine, also diminish the rate of metabolism of xenobiotics (Parent et al., 1992; Morgan, 1997).

In response to viral infections, the concentration in blood of many cytokines is increased (Ramshaw et al., 1997). It has been assumed that in vivo cytokines are responsible for P450 depression because in vitro cytokines can depress multiple hepatic P450 isoforms and their mRNAs. For instance, INF-γ depresses CYP1A2, 2A6, 2B6, and 3A4; IL-6 depresses CYP1A1, 1A2, 2D, 3A4, and 4A1; and IL-1β down-regulates 1A2, 2C11, 2D6, 2E1, and 3A (Fukuda et al., 1992; Trautwein et al., 1992; Donato et al., 1997; Parmentier et al., 1997). Furthermore, it has been reported that INF-α (Stanley et al., 1991), IL-1 (Peterson and Renton, 1986), and TNF-α (Paton and Renton, 1998) can also reduce the activity of several P450 isoforms.

In vitro, following an incubation period of 4 h with hepatocytes, serum from humans with an upper respiratory tract viral infection (HSURVI) and serum from rabbits with a turpentine-induced acute inflammatory reaction (RSSTIAR) decreases the activity of CYP1A1 and 1A2 without affecting the amount of these proteins (El-Kadi et al., 1997). The mediators responsible for the decrease in P450 activity are INF-γ, IL-6, and IL-1β in HSURVI, and IL-6 in RSSTIAR (Bleau et al., 2000), demonstrating that in vivo, infectious, and noninfectious inflammatory reactions generate serum mediators, namely, cytokines, capable to reduce P450 activity.

Since in vivo, an inflammatory reaction depresses the expression of multiple isoforms of the P450, it was of interest to establish whether HSURVI and RSSTIAR are capable to down-regulate the expression of selected P450 isoforms in hepatocytes. Specifically, the aims of the present study were 1) to assess the effect of RSSTIAR and HSURVI on the activity and expression of hepatic CYP1A1, 1A2, and 3A6 following 24-h incubation periods; and 2) to compare the differences in effect between RSSTIAR and HSURVI as a function of the source of the hepatocytes, i.e., hepatocytes harvested from control rabbits (HCONT) and hepatocytes from rabbits with a TIAR (HINFLA). The use of HINFLA was justified because the density of surface receptors to...
cytokines is greater than in HCONT (Dinarello, 1994). Theophylline was used to assess the activity of some isoforms of the P450. In the rabbit, theophylline is primarily metabolized by CYP1A2 and CYP1A1, and to a minor degree by CYP3A6; CYP1A1, and CYP1A2 both contribute to the formation of theophylline three metabolites 3-methylxanthine (3 MX), 1-methyluric acid (1 MU), and 1,3-dimethyluric acid (1,3DMU) (Kurdi et al., 1999).

Materials and Methods

Collection of Hepatocytes and Serum from Rabbits. Male New Zealand White rabbits (1.8–2.2 kg) were obtained from Ferme Charles Rivers (St.-Constant, Québec, Canada). A local inflammatory reaction was induced by the s.c. injection of 5 ml of turpentine (Recochem, Montréal, Québéc) distributed into four distinct sites of the back of the rabbits. Forty-eight hours later, blood (20 ml) was withdrawn from the central artery of an ear of the rabbits, controls and with a TIAR; the rabbits were anesthetized, and hepatocytes were isolated. Blood samples were allowed to clot at room temperature for 2 h, centrifuged at 2500 rpm for 5 min, and the serum was decanted and stored frozen at −20 °C in 1-ml aliquots until use. The severity of the inflammatory reaction was assessed by measuring serum concentrations of seromucoids (Parent et al., 1992). All the experiments were conducted according to the Canadian Council on Animal Care guidelines for use of laboratory animals.

Hepatocytes were isolated according to the two-step liver perfusion method of Seglen (1976), with minor modifications (El-Kadi et al., 1997). Viability was over 90% as assessed by trypan blue exclusion, and cell concentration was adjusted to 4 × 10^6/ml with Williams’ medium E supplemented with 10% calf serum. Aliquots of 2 ml of the hepatocytes, i.e., 8 × 10^6 cells, in suspension were transferred into each well of 12-well plastic culture plates (Falcon; Becton Dickinson Labware, Rutherford, NJ) coated with type I rat tail collagen and incubated with serum from control rabbits (RSCONT) and RS TIAR for 4 and 24 h at 37°C in an atmosphere of 95% O_2, 5% CO_2. Cell culture was conducted under sterile conditions.

Collection Serum from Humans. Blood (10 ml) was withdrawn from humans (n = 8) with an inflammatory reaction secondary to an upper respiratory viral infection, at the apex of clinical symptomatology, i.e., 24 h after the appearance of overt manifestations of an upper respiratory tract viral infection, such as rhinorrhea, sneezing, nasal congestion, sore throat, cough, and systemic signs of malaise, including fever, in absence of purulent secretions. Blood samples were allowed to clot at room temperature for 2 h, centrifuged at 2500 rpm for 5 min, and the serum was decanted and stored frozen at −20°C in 1-ml aliquots until use.

Five of the volunteers with an upper respiratory viral infection, once the blood sample was withdrawn, took 300 mg of theophylline orally, and urine was collected for 24 h. At least 2 months later, in absence of any sign of infectious disease, a blood sample of 10 ml was withdrawn from the same five volunteers who subsequently received orally a second dose of 300 mg of theophylline, and urine was collected for 24 h. Serum from healthy volunteers (HS CONT) and HSURVI were incubated with HCONT and HSURVI and its effect on total P450 content and theophylline metabolism was assessed. Theophylline and its metabolites were assayed in the 24-h urine collections.

Cytochrome P450 Content and Activity. The efficacy of the serum to reduce hepatic P450 content was tested by incubating 200 µl of serum with 2 ml/well of HCONT and HSURVI for 4 and 24 h. Hepatic P450 content, evaluated by its ability to bind carbon monoxide, was measured spectrophotometrically as described by Omura and Sato (1964). Protein content in hepatocytes was measured by the method of Lowry et al. (1951).

To assess the effect of serum on the activity of CYP1A1, 1A2, and 3A6 we determined the ability of P450 to metabolize theophylline by measuring the concentration of theophylline metabolites 3 MX, 1 MU, and 1,3DMU generated after 4 and 24 h of incubation (Kurdi et al., 1999). Theophylline was dissolved in serum-free Williams’ medium E, and 100 µl was added to each well containing the hepatocytes to attain a final concentration of 176 µM. After 4 and 24 h of incubation, an aliquot of the medium was collected and frozen at −20°C until analysis of theophylline and its metabolites by high-performance liquid chromatography (da Souich et al., 1989).

Western Blot Analysis. Proteins were separated by SDS-polyacrylamide gel electrophoresis (7.5% polyacrylamide) under nonreducing conditions (Smith, 1994). Proteins were electrophoretically transferred to a nitrocellulose membrane using a semidyfer transfer process (Bio-Rad, Hercules, CA). CYP1A1 and 1A2 proteins were detected with a polyclonal anti-rabbit CYP1A1, and visualized with an alkaline phosphatase-conjugated secondary goat antibody using nitro blue tetrazolium as the substrate (Kruger, 1994). CYP3A6 protein was detected with a monoclonal anti-rat CYP3A1 and a horseradish peroxidase-conjugated secondary antibody; chemiluminescence was visualized by autoradiography (Thorpe et al., 1985). The intensities of the bands were measured with a software Un-Scan-It-Gel (Silk Scientific Inc., Orem, UT).

Drugs and Chemicals. The Percoll gradient, Williams’ medium E, calf serum, type I rat tail collagen, NaCl, KCl, KH_2PO_4, HEPES, EGTA, glucose, theophylline, 3 MX, 1 MU, and 1,3DMU were purchased from Sigma (St. Louis, MO) and insulin was from Roche Molecular Biochemicals (Mannheim, Germany).

Statistical Analysis. All data are reported as means ± S.E. The comparison of the results from the various experimental groups and their corresponding controls was carried out using a one-way analysis of variance followed by Newman-Keuls post hoc test. The effect of RS TIAR and HSURVI on the amount of CYP1A1, 1A2, and 3A6 (densitometry values) was compared with the effect of RSCONT and HSURVI by using a paired t test. The differences were considered significant when p < 0.05.

Results

Effect of a TIAR on P450 Content, Activity, and Amount of P450 Approteins. Total P450 content in HCONT was 0.284 ± 0.014 nmol/mg of protein, a value that was reduced to 0.152 ± 0.012 nmol/mg of protein in HINFLA (p < 0.05). Compared with HCONT, when theophylline was incubated for 4 h with HINFLA, the formation of 1,3DMU, 3 MX, and 1 MU was reduced by 43, 85, and 43%, respectively (p < 0.005), reflecting essentially a decrease in CYP1A1 and 1A2 activity (Table 1). After 24 h of incubation, the formation of 1,3DMU, 3 MX, and 1 MU was reduced by a percentage similar to that reported after 4-h incubation (data not shown). Compared with HCONT, the TIAR diminished the amount of CYP1A1 by 47%, i.e., densitometry values were 391,687 ± 41,243 in HCONT and 207,492 ± 30,617 in HINFLA (n = 3, p < 0.05). CYP1A2 densitometry values were 309,098 ± 57,205 in HCONT and 205,618 ± 35,456 in HINFLA (n = 3, p > 0.05). The amount of CYP3A6 apoprotein was reduced to an undetectable level (Fig. 1).

Effect of RSCONT and RS TIAR on P450 of HCONT Following 4 and 24 h of Incubation. Incubation of RSCONT with HCONT for 4 h did not modify P450 content and ability to biotransform theophylline (n = 7) (Table 1). Compared with RSCONT, RS TIAR did not modify P450 content, and did not reduce the formation of 3 MX, 1 MU, and 1,3DMU (p > 0.05) (Table 1). Neither RSCONT nor RS TIAR affected the amount of CYP1A1, 1A2, and 3A6 apoproteins in HCONT (data not shown).

After a 24-h period of incubation with HCONT, compared with RSCONT, RS TIAR did not modify P450 content, but reduced the formation of 1 MU and 1,3DMU by 27 and 28%, respectively (p < 0.05, n = 8) (Table 1). Following 24 h of incubation with RS TIAR, the amount of CYP1A1 and 1A2 remained unchanged, i.e., densitometry values for CYP1A1 were 283,835 ± 17,818 incubated with RS CONT and 327,771 ± 27,457 with RS TIAR (p < 0.05). CYP1A2 densitometry values were 305,303 ± 60,486 with RSCONT and 327,771 ± 79,745 with RS TIAR. On the other hand, by reference to RSCONT (densitometry value 492,585 ± 98,749), CYP3A6 decreased by 45% when HCONT was incubated with RS TIAR (284,232 ± 68,265) (n = 4, p < 0.05) (Fig. 2).

Effect of RSCONT and RS TIAR on P450 of HINFLA Following 4 and 24 h of Incubation. Following 4 h of incubation, and compared with RSCONT, RS TIAR did not reduce P450 content in HINFLA, but reduced the formation of 1 MU and 1,3DMU by 34 and 26%, respectively (p < 0.005, n = 7) (Table 2). On the other hand, the
Following 24 h of incubation with RS TIAR, the amount of CYP1A1 and 1A2 remained unchanged, i.e., densitometry values for CYP1A1 were 204,011 ± 15,777 with RS CONT and 201,612 ± 19,225 with RS TIAR, and for CYP1A2 densitometry values were 218,437 ± 27,978 with RS CONT and 228,921 ± 40,541 with RS TIAR (n = 4). Since in RS INFLA, the amount of 3A6 apoprotein was not measurable, it was not possible to assess the effect of RS TIAR (data not shown). The percentage of reduction for each metabolite is greater at 24 h than at 4 h (p < 0.05).

**In Vivo Effect of an URVI on Metabolism of Theophylline in Human Volunteers.** During the symptom-free period in five control volunteers, the 24-h urinary recovery of theophylline and its metabolites accounted for 69% of the dose administered, of which 13.3% was 3 MX, 20.3% 1 MU, and 52.5% was 1,3DMU. While the volunteers presented symptoms of URVI, the 24-h urinary recovery of theophylline and its metabolites decreased to 58% (p < 0.05). Compared with the control period, recovery of 3 MX, 1 MU, and 1,3DMU was decreased by 30, 29, and 14% (p < 0.05), respectively (Fig. 3).

**Effect of HS CONT and HS URVI on P450 of H CONT Following 4 and 24 h of Incubation.** Incubation of HS CONT with H CONT for 4 and 24 h did not change hepatic P450. In contrast, following 4 h of incubation, HS URVI did not modify total P450 content but decreased the formation of 1 MU and 1,3DMU by 28 and 32%, respectively (p < 0.05) (Table 3). The amounts of CYP1A1, 1A2, and 3A6 were not affected (data not shown).

Following 24 h incubation of H CONT with HS URVI, P450 content did not change, but the concentration of 3 MX, 1 MU, and 1,3DMU decreased by 27, 38, and 36% (p < 0.05), respectively (Table 3). Under these experimental conditions, incubation with HS URVI, the amount of CYP1A1 and 1A2 remained unchanged, i.e., densitometry values for CYP1A1 were 234,567 ± 15,777 incubated with RS CONT and 204,011 ± 15,777 with RS TIAR, and for CYP1A2 densitometry values were 218,437 ± 27,978 with RS CONT and 228,921 ± 40,541 with RS TIAR (n = 4). Since in HS INFLA, the amount of 3A6 apoprotein was not measurable, it was not possible to assess the effect of RS TIAR (data not shown). The percentage of reduction for each metabolite is greater at 24 h than at 4 h (p < 0.05).

**Effect of H CONT and H INFLA on P450 of H CONT Following 4 and 24 h of Incubation.** Incubation of H CONT with H CONT for 4 and 24 h did not change hepatic P450. In contrast, following 4 h of incubation, H INFLA did not modify total P450 content but decreased the formation of 1 MU and 1,3DMU by 28 and 32%, respectively (p < 0.05) (Table 3). The amounts of CYP1A1, 1A2, and 3A6 were not affected (data not shown).

**Effect of RS CONT and RS TIAR on P450 of H INFLA Following 4 and 24 h of Incubation.** Incubation of HS URVI with H INFLA for 4 h decreased total P450 content from 0.140 ± 0.013 nmol/mg of protein to 0.101 ± 0.011 nmol/mg of protein (p < 0.05). HS URVI lowered the concentration of 1 MU and 1,3DMU by 42 and 32%, respectively (Fig. 4).

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**Fig. 1.** Effect of a turpentine-induced inflammatory reaction on the amount of CYP1A1, 1A2, and 3A6 apoproteins in hepatocytes from control (H CONT) and rabbits with a turpentine-induced inflammatory reaction (H INFLA) 48 h after the injection of turpentine.

Numbers indicate densitometry values.

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</table>

**Fig. 2.** Effect of serum from control (RS CONT) and rabbits with a turpentine-induced inflammatory reaction (RS INFLA) on the amount of CYP1A1, 1A2, and 3A6 apoproteins in hepatocytes from control rabbits (H CONT) and rabbits with a turpentine-induced inflammatory reaction (H INFLA), after a 24-h period of incubation.

Numbers indicate densitometry values.
(p < 0.05) (Table 3), without affecting the amount of CYP1A1 and 1A2 (data not shown).

Incubation of HS URVI with H INFLA for 24 h decreased total P450 content from 0.135 ± 0.011 nmol/mg of protein to 0.079 ± 0.009 nmol/mg of protein (p < 0.05) (n = 7), and lowered the concentration of 3 MX, 1 MU, and 1,3DMU by 40, 55, and 39%, respectively (p < 0.05) (n = 7) (Table 3). Following incubation with HS URVI, the amounts of CYP1A1 and 1A2 were reduced by 33 and 22% (p < 0.05), respectively, i.e., densitometry values for CYP1A1 were 193,520 ± 12,936 incubated with H CONT and 125,503 ± 10,377 with HS URVI, and for CYP1A2 densitometry values were 188,124 ± 17,748 with H CONT and 141,281 ± 10,405 with HS URVI (n = 4) (Fig. 4).

Considering the five volunteers who received 300 mg of theophylline, incubation of HS URVI with H INFLA for 4 h reduced theophylline biotransformation and P450 content (data not shown), decrease that was not associated with the decrease in 24-h urinary recovery of 3 MX, 1 MU, and 1,3DMU (Fig. 3). However, the in vitro reduction in P450 content was directly associated (r² = 0.9101) with the in vivo decrease in urinary recovery of the total amount of theophylline metabolites, i.e., 3 MX + 1 MU + 1,3DMU, supporting that the in vivo repercussions of a viral infection on drug metabolism are associated with the ability of the serum of these volunteers to reduce P450 activity.

Discussion

The present study demonstrates that RS TIA R does not affect P450 amount or activity when incubated for 4 h with H CONT, however, it decreases P450 activity in H INFLA. When RS TIA R is incubated with H CONT for 24 h, P450 activity is reduced, as well as the amount of CYP3A6 protein. Incubation of RS TIA R with H INFLA for 24 h decreases total P450 content and activity, without affecting CYP1A1 or 1A2. Keeping in mind that theophylline is primarily biotransformed by CYP1A2 (Kurdi et al., 1999), these results show that RS TIA R elicits a dual effect on P450: it reduces the activity of CYP1A1 and 1A2, and down-regulates CYP3A6. RS TIA R effects on P450 depend upon the length of incubation, and the state of the hepatocytes, i.e., control or primed.

The RS TIA R-induced decrease in P450 activity could be a general phenomenon since the down-regulation of P450 isoforms by lipopolysaccharides is preceded by their inactivation (Sewer et al., 1998). Nitric oxide may have a pivotal role in P450 inactivation by both, the turpentine induced inflammation (El-Kadi et al., 2000), and lipopolysaccharide-induced endotoxemia (Sewer et al., 1998; Takemura et al., 1998). The fact that the biotransformation of theophylline and total P450 content in H INFLA are reduced by RS TIA R without changes in the amount of CYP1A1, 1A2, and 3A6 proteins, further supports that nitric oxide contributes to the reduction in P450 activity. As discussed, upon binding to Fe²⁺ and Fe³⁺-heme, nitric oxide impedes O₂ binding and as a consequence, it reduces theophylline biotransformation. In parallel, nitric oxide binding to Fe²⁺-heme impedes the binding of carbon monoxide used for the spectrophotometric deter-

![Fig. 3. Amount of 3 MX, 1 MU, and 1,3DMU recovered in a 24-h urinary collection from five volunteers with and without an upper respiratory viral infection after oral intake of 300 mg of theophylline.](Image)

**TABLE 2**

Effect of serum from rabbits with an inflammatory reaction on P450 content and ability to biotransform theophylline incubated for 4 and 24 h with hepatocytes from rabbits with a turpentine-induced inflammatory reaction

Hepatocytes from rabbits with a turpentine-induced inflammatory reaction (H INFLA) (n = 7) were incubated with serum from control rabbits (RS CONT), and serum from rabbits with an inflammatory reaction (RS TIA R) (n = 7) for 4 and 24 h. Data are means ± S.E.

<table>
<thead>
<tr>
<th>Cytchrome P450</th>
<th>3 MX</th>
<th>1 MU</th>
<th>1,3DMU</th>
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<tbody>
<tr>
<td>4-h Incubation</td>
<td></td>
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</tr>
<tr>
<td>H CONT + RS CONT</td>
<td>0.164 ± 0.021</td>
<td>0.011 ± 0.003</td>
<td>0.053 ± 0.005</td>
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<td>H INFLA + RS CONT</td>
<td>0.125 ± 0.021</td>
<td>0.008 ± 0.002</td>
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<tr>
<td>H CONT + RS TIA R</td>
<td>0.135 ± 0.014</td>
<td>0.069 ± 0.007</td>
<td>0.079 ± 0.012</td>
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<td>H INFLA + RS TIA R</td>
<td>0.086 ± 0.007</td>
<td>0.044 ± 0.007</td>
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<td>24-h Incubation</td>
<td></td>
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<tr>
<td>H CONT + RS CONT</td>
<td>1,3DMU</td>
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<tr>
<td>H INFLA + RS CONT</td>
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<td>1,3DMU</td>
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**TABLE 3**

Effect of serum from control subjects (HS CONT) and volunteers with an upper respiratory tract viral infection reaction (HS URVI) on the ability of hepatocytes from control rabbits (H CONT) and rabbits with a turpentine-induced inflammatory reaction (H INFLA) to biotransform theophylline after a 4- and 24-h period of incubation

Results are means ± S.E.

<table>
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<tr>
<th></th>
<th>3 MX</th>
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<td>4-h Incubation</td>
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<td>H CONT + HS CONT</td>
<td>0.075 ± 0.006</td>
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<td>H CONT + HS URVI</td>
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<td>H INFLA + HS CONT</td>
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<td>H INFLA + HS URVI</td>
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<td>H CONT + HS URVI</td>
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*a p < 0.05 compared with H INFLA + HS CONT.

*a,b p < 0.05 compared with H CONT + HS CONT and H INFLA + HS CONT, respectively.
Following 24 h of incubation, HS_{URVI} down-regulates CYP1A1/2 in H_{INFLA} but not in H_{CONT}, where only CYP3A6 is down-regulated. Possibly several factors associated to the density of surface receptors, the kind of cytokines stimulated by influenza, and the ability of these cytokines to depress selective P450 isoforms contribute to explain these differences. In H_{INFLA} primed by the TIAR, the density of surface receptors to IFN-γ, IL-1β, TNF-α, and IL-6 could be increased, since not only inflammatory stimuli increase the density of surface receptors but also higher levels of circulating cytokines produce the same effect (Volpes et al., 1991; Dinarello, 1994). In humans, influenza increases the concentration of cytokines known to down-regulate P450 isoforms, such as IL-1β, IL-6, TNF-α, and IFN-γ (Han and Meydani, 2000). The ability of these cytokines to depress CYP3A isoforms is greater than that to down-regulate CYP1A1/2 (Abdel-Razzak et al., 1993; Muntané-Relat et al., 1995). These differences may be explained in part by the mechanism through which a cytokine depresses the expression of an isoform. For example, IL-1β promotes a pretranscriptional repression, while IFN-γ exerts a post-transcriptional suppressive effect on CYP3A6 expression (Calleja et al., 1998), and a pretranscriptional down-regulation of CYP1A2 (Abdel-Razzak et al., 1993), however, its effect is weak compared with IL-1β (Calleja et al., 1997). IL-6 is a stronger pretranscriptional repressor of CYP3A4 mRNA than IL-1β and TNF-α, but TNF-α appears to elicit a stronger pretranscriptional effect on CYP1A1/2 than IL-1β and IL-6 (Muntané-Relat et al., 1995). We may postulate that CYP3A6 expression is more sensitive to the effect of cytokines because IL-1β, IL-6, TNF-α, and IFN-γ down-regulate CYP3A6 expression through pre- and post-transcriptional mechanisms, and CYP1A1/2 only by a pretranscriptional repression mechanism.

In conclusion, the present study demonstrates 1) that the effect of RS_{TIAR} and HS_{URVI} depends upon the susceptibility of the hepatocyte (H_{CONT} or primed H_{INFLA}) emphasizing the importance of the model for an accurate interpretation of the results; 2) that P450 down-regulation is preceded by a decrease in P450 activity; 3) that the differences between RS_{TIAR} and HS_{URVI} are primarily dependent upon the mediators contained in the serum, indicating that the nature of the inflammatory reaction is of importance to determine the repercussions on P450 activity and expression; and 4) the present results confirm that CYP3A6 is more vulnerable than CYP1A1 and 1A2 to the down-regulation provoked by an inflammatory challenge, a fact that may have practical consequences when it is taken into account the relevancy of this isoform in drug metabolism.

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References
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