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Role of S-adenosylmethionine on the hepatobiliary homeostasis of glutathione during cyclosporine A treatment

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The effects of cyclosporine A (CyA) treatment on the hepatic content and biliary output of reduced (GSH) and oxidized (GSSG) glutathione and lipid peroxidation in the liver, and the ability of S-adenosylmethionine (SAMe) to antagonize the CyA-induced alterations were studied in male Wistar rats. To evaluate the efficacy of SAMe, three CyA and SAMe protocols were used: cotreatment with SAMe plus CyA, pretreatment with SAMe before starting cotreatment, and post-treatment with SAMe after beginning treatment with CyA alone. CyA treatment for one and four weeks depleted liver GSH, decreased the GSH/GSSG ratio and significantly reduced GSH and GSSG biliary concentrations and secretion rates. Additionally, long-term treatment enhanced lipid peroxidation. By contrast, when the rats were treated with CyA plus SAMe using any of the administration protocols, SAMe was seen to be efficient in antagonizing the GSH hepatic depletion, the changes in hepatic GSH/GSSG ratio and the increase induced by CyA in lipid peroxidation. Furthermore, SAMe also abolished the effects of CyA on the biliary secretion rates of GSH and GSSG. The efficacy of SAMe was similar, regardless of the administration protocols used. In conclusion, our results clearly demonstrate that SAMe is good for preventing, antagonizing and reversing the CyA-induced alterations in the hepatobiliary homeostasis of glutathione.

Key words: Cyclosporine A, Glutathione, Lipid peroxidation, S-adenosylmethionine.

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The liver is the major site of glutathione synthesis and also the major supplier of plasma and bile glutathione (24, 31). The transport of tripeptide across the canalicular membrane of hepatocytes constitutes the primary osmotic driving force in bile acid-independent bile flow formation (3, 21). In addition to its role in bile formation, the hepatobiliary efflux of glutathione plays another important role since it contributes to hepatic glutathione turnover, the regulation of inter-organ glutathione homeostasis and of the thiol redox status of liver cells, the detoxification of toxins and reactive compounds via its conjugation with reduced glutathione (GSH) and it later elimination into bile. Moreover, biliary glutathione can act - together with other thiols- as a mucolytic agent within the biliary tree, it is able to decrease the probability of bile stone formation and may accelerate the dissolution of cholesterol and pigment stones. Finally, this efflux of glutathione also provides a mechanism for maintaining suitable levels of the tripeptide and its constituent amino acids in ductular and intestinal epithelia (3, 23, 31). In the intestinal tract the principal action of GSH is related to its role as a scavenger of free radicals and toxins ingested with foods or produced in the lumen (23), although the compound also helps to maintain normal redox potentials in enterocytes, improves the action of prostaglandins and stabilizes mucus composition by regulating the thiol/disulphide ratio (23).

The liver is also a target organ for cyclosporine A (CyA), a key immunosuppressive drug in the struggle against rejection in organ transplantation, whose clinical use is limited by its nephrotoxicity, hepatotoxicity and neurotoxicity (5). Regarding hepatotoxicity, it is well known that treatment with CyA produces cholestasis, thus interfering with a major hepatic function, i.e., bile formation (5, 27). Hepatic bile formation involves multiple secretory processes that depend critically on the active transport of osmotically active compounds from hepatocytes into the canalicular lumen. Bile acid and glutathione are considered to be the major osmotic contributors to bile generation in many species (1, 3, 21, 23). Regarding bile acid, it is known that CyA interferes with their hepatobiliary transport, thus reducing bile acid secretion rates and bile acid-dependent bile flow formation (11, 16). Regarding biliary glutathione, our team has observed that a single i.v. dose of CyA markedly reduces the biliary concentration and secretion rates of both forms of the tripeptide, GSH and oxidized glutathione (GSSG), as well as glutathione-dependent bile flow; additionally, when rats were subchronically treated for one week, similar cholestatic and inhibitory effects on the biliary secretion of glutathione were noted both before and after the inhibition of intrabiliary glutathione catabolism (20, 27). In view of all the foregoing, inhibition of the hepatobiliary efflux of glutathione in patients receiving CyA therapy could potentially compromise not only bile formation but also GSH-based detoxification processes in the liver and in the intestinal wall and lumen as well as the rest of the functions of the tripeptide in the biliary and intestinal tracts.

We have previously reported that cotreatment with CyA plus S-adenosylmethionine (SAMe) antagonizes the cholestatic effect of CyA, restores the hepatobiliary transport of bile acid, normalizes the biliary excretion rates of cholesterol, phospholipid, biliary proteins and bilirubin, and abolishes CyA-induced changes in several plasma indicators of cholestasis (11, 12, 18). The aims of the present study were on the one hand to

study the effects of short- and long-term CyA treatment on the hepatobiliary handling of glutathione in the rat and, on the other, to evaluate the efficacy of SAMe, administered using different treatment protocols, to prevent, antagonize or restore the CyA-associated disturbances.

Materials and Methods

Animal and experimental procedures.– Adult male Wistar rats weighing 200-250 g b.wt at the start of experiments were housed under standard conditions for 1 week before use. In order to evaluate the efficacy of SAMe to antagonize, prevent or restore CyA-induced alterations, three CyA and SAMe administration protocols were used:1) simultaneous treatment with SAMe plus CyA, or cotreatment; 2) pretreatment with SAMe before starting simultaneous treatment with SAMe plus CyA, and 3) post-treatment with SAMe after beginning treatment with CyA alone. Rats were randomly divided into 8 groups (6-8 animals each) and treated as follows: two groups were treated with the CyA vehicle (olive oil) for one or four weeks and were used as control groups; another two groups were treated with CyA alone for one (CyA-1 group) or four (CyA-4 group) weeks; two cotreated rat groups were simultaneously treated with SAMe plus CyA for one (COT-1) or four (COT-4) weeks; the pretreated rat group (PRET) was given SAMe alone for one week before starting joint administration of SAMe plus CyA for another week; the last group, the post-treated rat group (POST), received CyA alone for one week and were then given SAMe plus CyA for another week.

CyA was administered i.p. at a dose of 10 mg/kg/day; SAMe was administered s.c. at a dose of 10 mg/kg/12 h. Twelve hours after the last dose, a median laparotomy was performed under pentobarbital anaesthesia (50 mg/kg b.wt, i.p.) and the bile duct was cannulated. Losses in body temperature of the animals were prevented using a rectal probe connected to a thermostatically controlled heating lamp. The rats were not starved before surgery. In all animals bile collection was started thirty minutes after finishing the surgical procedure, a time considered to be sufficient to allow bile flow stabilization. To inhibit γ-GT activity, an irreversible inhibitor of this enzyme (acivicin) was administered to all animals after collecting a 15-min baseline bile sample; acivicin, at a dose of 20 μmol/kg b. wt, was administered by retrograde intrabiliary infusion in accordance with previous reports (27). After this, bile was collected for an additional 45 min at 15-min intervals. Bile was collected in pre-weighed tubes on melting ice containing 150 μl of 5% metaphosphoric acid to prevent GSH oxidation. At the end of the assays, the animals were killed by exsanguination. Livers were quickly washed *in situ* with an ice-cold saline solution, removed and weighed. Small pieces weighing 0.5 g were harvested from the liver for biochemical determinations and immediately stored in liquid nitrogen until analysis.

Analytical methods and statistical analyses.– Bile volume was determined gravimetrically without correction for specific gravity. Total glutathione (GSH+GSSG) and GSSG in liver homogenates and bile were evaluated by an enzymatic recycling procedure, according to GRIFFITH (19). GSH concentrations and the GSH/GSSG molar ratio in liver and bile were calculated. Thiobarbituric acid-reactive substances (TBARS), a marker of lipid peroxidation, were determined in liver homogenates according to OHKAWA *et al.* (30).

Data are reported as mean values ± SEM. Significant differences between means were analyzed using ANOVA. When a significant difference was found, means were compared using the Wilcoxon test or the Mann-Whitney U test for paired and unpaired values. P values of 0.05 or less were considered to be statistically significant.

Results

The mean values of the different parameters evaluated in rats treated with CyA vehicle for one and four weeks were similar and within the physiological range for this species (11, 16, 27). Thus, the rat groups treated with CyA vehicle were therefore considered as controls for the rest of the groups.

Fig. 1 shows the changes elicited in hepatic glutathione levels, and the GSH/GSSG ratio by CyA alone and SAMe plus CyA in rats treated with the different protocols used in this study. As can be seen, significant decreases of 41% in glutathione hepatic concentrations were already detected after CyA treatment for one week and this depletion was not more pronounced when treatment was prolonged for four weeks. Moreover, CyA treatment reduced the GSH/GSSG ratio in the two groups of rats treated with CyA alone and increased hepatic TBARS levels, although only when the long-term treatment was applied (Table I). The liver GSSG concentration was not altered in CyA treated rats. By contrast, when the animals were treated with SAMe plus CyA using any of the administration protocols, SAMe was seen to be efficient in antagonizing the glutathione depletion caused by CyA administration. In addition, the GSH/GSSG ratio was totally normalized regardless of the type of administration protocol used, except the short-term cotreatment group. Finally, the increase induced by CyA in lipid peroxidation, which was only observed in the CyA-4 group, was also completely abolished when the long-term cotreatment was used.

Table I. *Effects of SAMe administration on GSSG and TBARS hepatic levels.*
Values are given as means ± S.E.M. from CyA-vehicle treated rats (Control) and rats treated with CyA alone for one (CyA-1) and four (CyA-4) weeks, or CyA plus SAMe (Pretreatment, Posttreatment and Cotreatment groups). n = 5-6 animals per group. $p < 0.05$, significantly different from controls (*) or CyA treated groups (#).

	GSSG (μmol/g liver)	TBARS (nmol/g liver)
Control	0.053 ± 0.002	21.3 ± 1.8
CyA-1	0.045 ± 0.003	23.6 ± 2.9
CyA-4	0.056 ± 0.003	32.1 ± 3.4*
Pretreatment	0.047 ± 0.007	20.5 ± 1.6
Posttreatment	0.048 ± 0.007	24.4 ± 2.8
Cotreatment-1	0.048 ± 0.001	19.3 ± 1.0
Cotreatment-4	0.049 ± 0.004	23.0 ± 1.2#

CyA treatment also caused a significant decrease in glutathione biliary concentrations and secretion rates, both before (Table II) and after (fig. 2) acivicin administration. Evidently, after inhibition of γ-

Table II. *Effects of SAMe administration on glutathione biliary concentration and secretion before γ-GT inhibition.*
Results and symbols as in Table I

	Concentration (mM)	Secretion (nmol/min/g liver)
Control	2.23 ± 0.21	3.94 ± 0.36
CyA-1	1.57 ± 0.25	2.52 ± 0.51*
CyA-4	1.14 ± 0.16*	1.61 ± 0.30*
Pretreatment	2.87 ± 0.20#	4.10 ± 0.25#
Posttreatment	1.91 ± 0.28	3.45 ± 0.51
Cotreatment-1	2.27 ± 0.39	3.44 ± 0.70
Cotreatment-4	2.84 ± 0.42#	4.28 ± 0.71#

GT activity, glutathione concentrations and output increased significantly in all experimental groups, although the mean values of glutathione concentrations and output continued to be lower in the groups treated with CyA alone. By contrast, when CyA and SAMe were administered using the previously described protocols, the effects of CyA on both the biliary concentrations and secretion rates of glutathione were totally abolished. The beneficial effects of SAMe were more marked after inhibition of γ-GT activity, since in some groups the biliary output of glutathione was even greater than in untreated rats.

Regarding changes in GSSG biliary secretion, the effects of SAMe were also observed in all the experimental groups, both under basal conditions and after inhibition of the intrabiliary catabolism of the tripeptide (Table III). CyA treatment

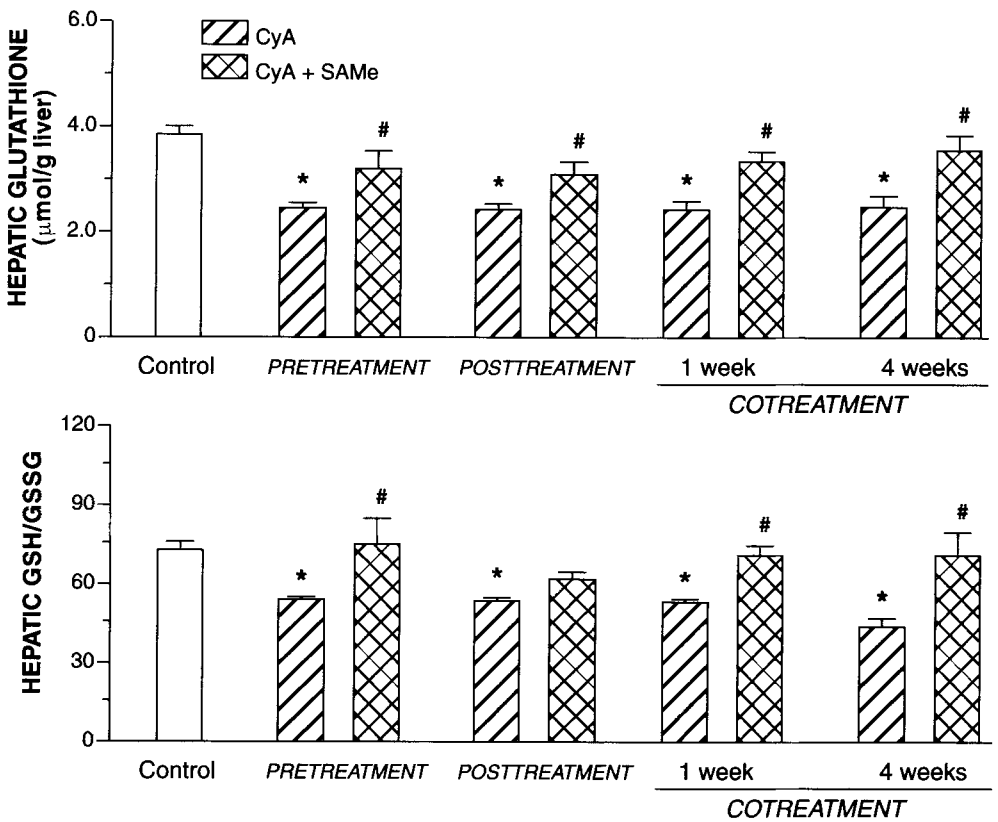

Fig. 1. *Effects of treatment with CyA alone and treatment with SAMe plus CyA on hepatic glutathione and GSH/GSSG hepatic ratio using the different protocols.*

Rats treated with CyA-vehicle were used as controls. CyA (i.p.) and SAMe (s.c.) were administered at doses of 10 mg/Kg per day and 10 mg/Kg every 12 hr, respectively. Data are given as mean values (±S.E.M.) for 5-6 rats in each group. * and #, means different from Controls and CyA groups, respectively ($p < 0.05$).

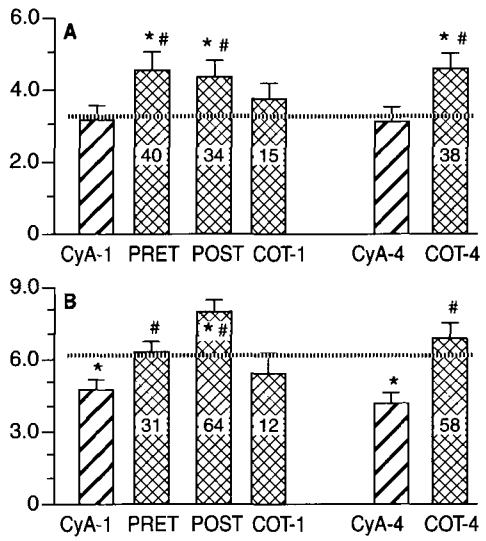

Fig. 2. *Comparison of the effects of SAMe treatments on glutathione biliary concentrations (mM, A) and secretion (nmol/min/g liver, B) after acivicin administration.*
CyA was administered alone over one or four weeks (▨) or with SAMe (▩), following the protocols used. Data are given as mean values (± S.E.M.) for 5-6 rats in each group. The number inside each bar represents the relative increase with respect to the groups treated with CyA alone (=100%). Rats treated with CyA-vehicle (▭) were used as controls. CyA (i.p.) and SAMe (s.c.) were administered at doses of 10 mg/Kg per day and 10 mg/Kg every 12 h, respectively. * and # means different from control and CyA groups, respectively ($p < 0.05$).

reduced GSSG biliary output and treatment with both drugs markedly increased or normalized this parameter before and after γ-GT inhibition, respectively.

In order to compare the efficiency of the different administration protocols of SAMe against CyA, the relative increases seen in the biliary output of glutathione after acivicin with respect to the data obtained in CyA groups (100%) were calculated. As can be seen in the top panel of fig. 2, the effects of SAMe on glutathione biliary concentrations were similar in the pretreatment, post-treatment and long-term cotreatment groups, this efficacy being greater than that seen in the one-week cotreatment group. In the case of biliary secretion (lower panel), the efficacy of the administration of SAMe was similar when it was administered following the post-treatment and long-term cotreatment protocols, and considerably higher than that observed when the pretreatment and short-term cotreatment protocols were used.

Discussion

Hepatic glutathione homeostasis is extremely important in liver physiology

Table III. *Effects of SAMe administration on GSSG biliary concentration and secretion before and after γ-GT inhibition.*
Results and symbols as in Table I

	Concentration (mM)		Secretion (nmol/min/g liver)	
	Before	After	Before	After
Control	0.11 ± 0.02	0.19 ± 0.02	0.22 ± 0.05	0.40 ± 0.08
CyA-1	0.13 ± 0.02	0.16 ± 0.03	0.17 ± 0.04	0.26 ± 0.05*
CyA-4	0.08 ± 0.03	0.13 ± 0.03	0.11 ± 0.03*	0.19 ± 0.02*
Pretreatment	0.20 ± 0.05	0.22 ± 0.04	0.32 ± 0.10*#	0.34 ± 0.07
Posttreatment	0.20 ± 0.03*	0.25 ± 0.02#	0.36 ± 0.07*#	0.44 ± 0.05#
Cotreatment-1	0.25 ± 0.05*#	0.28 ± 0.05#	0.37 ± 0.09*#	0.40 ± 0.07#
Cotreatment-4	0.20 ± 0.05#	0.22 ± 0.05	0.30 ± 0.07*#	0.36 ± 0.06#

and liver plasma membrane (LPM) functions, and increases in the formation of GSSG and TBARS are indicators of free radical formation and accelerated lipid peroxidation (2, 40). In this regard, MADESH *et al.* (25) have indicated that the intracellular glutathione status plays an important role in the lipid composition of the cells (GSH depletion increases cholesterol and reduces phosphatidylcholine), and it is also well known that i) oxidative stress and excess free radical formation lead to membrane lipid and protein-SH oxidation (2, 40), ii) that both effects alter LPM composition and fluidity and, iii) that changes in LPM fluidity can influence carrier-mediated transport processes and membrane-bound enzyme activities (17, 28, 35, 36). Moreover, CyA increases H_2O_2 and free radical formation in the liver (10, 42) and we have observed that CyA, as well as reducing liver GSH, also reduces the GSH/GSSG molar ratio and increases TBARS levels. Finally, it has been indicated that CyA alters the composition and lateral organization of lipids in *in vitro* models (37). Also, we have recently observed that the drug not only alters LPM composition but also fluidity and Na^+,K^+-ATPase activity (17). Taken together, all these findings clearly suggest that CyA might induce changes in the functional integrity of LPM, thus altering the canalicular and basolateral efflux/transport of glutathione.

The nature of the canalicular transporter/s of GSH and GSSG is currently uncertain, but it seems that the active secretion of GSH and GSSG into the canaliculus is largely dependent on the ABC transporters (ATP-binding cassette proteins) (3, 29, 39, 41). One of these transporters, the canalicular multispecific organic anion transporter (cMoat/mrp2), has long been recognised as the main carrier for GSSG and glutathione-conjugated compounds (1, 3, 29, 39), and it has recently been demonstrated that the cMoat also transports GSH (3, 39, 41). CyA is a potent inhibitor of multiple canalicular transport systems, and inhibitions of the cMoat/mrp2, bile acid export pump (cBaep), potential-dependent bile acid carrier, and other ATP-dependent export carriers have been reported (4, 9, 33). This inhibitory activity could account for the low biliary output of substrates that use either cMoat -such as GSSG, glutathione- and glucoronate-conjugates, i.e. BSP, bilirubin or leukotrienes-, the cBaep -such as bile acid- or the multidrug resistance carriers -such as phospholipids or colchicine- (18, 33, 38). Although the mechanism is obscure, it is likely that the CyA-induced inhibition of the canalicular transporter of GSH and GSSG could be caused/mediated by CyA-induced alterations in the hepatic homeostasis of glutathione and in the functional integrity of LPM.

In addition to the efficiency of its canalicular transport systems, the efflux rate of glutathione from the liver into bile is known to depend mainly on the hepatic content of the tripeptide (3, 21, 24, 31). Thus, the CyA-induced hepatic depletion of GSH observed by us and/or the inhibition of the canalicular transport of GSH and GSSG by the drug, as indicated above, could explain, at least theoretically, the lower release of glutathione into bile in the CyA rat groups. These hypotheses and others that might also help to explain the CyA-induced falls in biliary glutathione have recently been discussed by our team (17, 27). In brief, the CyA-induced hepatic depletion of GSH might be due: a) to increases in both the sinusoidal efflux and extrahepatic utilization of GSH and, b) to compromised synthesis

and/or increased intrahepatic glutathione utilization, as proposed for other hepatotoxins. However, other mechanisms must also be involved since when a single i.v. dose of CyA was given to anaesthetized rats, the biliary output of GSH and GSSG was also rapidly reduced whereas the hepatic contents of the tripeptide remained unaffected (27). A reflux of the tripeptide from the intrabiliary space into the hepatic circulation -secondary to changes in the permeability of the paracellular pathway- can also be ruled out as a possible causative mechanism of the CyA-induced falls in biliary glutathione levels since the drug did not modify hepatobiliary [^{14}C]sucrose clearance in the rat (27). Possible CyA-induced changes in γ-GT activity do not seem to be the cause either, since the biliary output of glutathione in CyA treated rats was lower than in untreated rats, both before and after hepatic γ -GT activity had been inhibited. Accordingly, our findings on biliary glutathione in the CyA-treated rats might be due to: 1) a sustained depletion of the hepatic pool of glutathione and, 2) an inhibition of its biliary secretion due, in turn, to inhibition of the carriers that transport GSH and GSSG from inside hepatocytes to bile.

It is well known that SAMe, the only natural sulphonium compound present in mammals, has a good capacity to antagonize the hepatotoxic effects of many toxins, and it has been successfully used to treat liver cell injury, including alcoholic liver diseases, cholestasis of pregnancy and recurrent intrahepatic cholestasis, as well as in many experimental models of cholestasis and hepatotoxicity induced by a variety of agents. In such disorders, SAMe has been shown to be able to reduce liver injury, improve the biochemical parameters of cholestasis, palliate cholestasis and normalize the hepatic levels and redox status of glutathione (12, 13, 15, 22, 26, 32). The beneficial effects of SAMe on hepatic and biliary glutathione observed by us could be related to its role in preserving LPM fluidity and functions through its participation in transmethylation reactions (13, 15, 22, 26, 36) and to the capacity of the compound to promote transulphuration reactions and glutathione biosynthesis.

Transmethylation with SAMe as a methyl donor is one of the preferred pathways used by hepatocytes to preserve LPM functions. Through methylation of phosphatidylethanolamine (PE) to produce phosphatidylcholine (PC), SAMe modulates membrane fluidity and functions (14, 15, 17, 28, 35, 36). In this context, it has been observed that SAMe depletion is associated with phospholipid depletion in LPM (6), with decreases of rat LPM fluidity (35), with an inhibition of Na^+,K^+-ATPase activity and an exacerbation of the liver membrane injury associated with ethanol (32), CCl_4 (7) or ethynylestradiol (14). By contrast, cotreatment with exogenous SAMe and ethanol (32), or ethynylestradiol (14), or chlorpromazine (15) normalizes PC contents, the PC/PE ratio and LPM fluidity in rat liver, which in turn normalizes the sodium pump and Na^+/H^+ antiport activities in rats intoxicated with these drugs (14, 36). In this regard, we have recently reported that cotreatment with SAMe plus CyA for one week antagonizes the CyA-induced alterations in LPM composition and fluidity and the activity of several transport and enzymic proteins (17). Accordingly, it is probable that, by restoring the hepatic pool of SAMe, SAMe preco- and post-treatment normalizes the methylation flux of membrane phospholipids, in turn helping to protect the liver

against CyA-induced GSH depletion, oxidative stress and lipoperoxidation and to normalize LPM fluidity and the activity of the canalicular transporters of glutathione.

Although SAMe is widely distributed throughout body tissues and fluids, its synthesis, from methionine and ATP, occurs mainly in the liver through the intervention of a methionine adenosyl transferase (MAT) (22, 26, 34). In this sense, a marked reduction in the rate of synthesis and use of SAMe as a consequence of decreases in MAT activity occurring in liver diseases has been described (8). The activity of MAT is subject to redox regulation by the hepatic levels of glutathione (26, 34), and inactivation of this enzyme has been reported after treatment with GSH-depleting drugs and during conditions that induce oxidative stress and/or increase GSH utilization (7, 22, 26), thus reducing the intrahepatic levels of SAMe and glutathione (8, 24, 26). By contrast, exogenous SAMe supplementation is able to: i) prevent carbon tetrachloride- and ethanol-induced MAT inactivation (7), ii) restore glutathione depletion induced by GSH-depleting drugs and hepatotoxins (13, 15, 22, 28) and, iii) minimize CyA-induced injury and lipid peroxidation in isolated and perfused rat liver models (10). Thus, the CyA-induced hepatic GSH depletion and oxidative stress observed by us could cause SAMe depletion (by impairing MAT activity?), thus reducing hepatic GSH levels and hence promoting membrane injury and impairment of the hepatobiliary transport of glutathione. Were this the case, through the administration of exogenous SAMe, the deficit in endogenous SAMe synthesis might be corrected, thus enabling reconstitution of the hepatic pool of SAMe and glutathione and in turn helping to protect the liver against CyA-induced oxidative stress, lipoperoxidation and GSH depletion.

In sum, although further studies should be carried out our results clearly demonstrate that exogenous SAMe administration is good for preventing, antagonizing and reversing the CyA-induced alterations in two of the major functions of the liver, bile formation through glutathione secretion and its contribution of glutathione to the intestine.

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A. I. GALÁN, M. E. MUÑOZ, J. PALOMERO, C. MORENO y R. JIMÉNEZ. *S-adenosilmetionina y homeostasis hepatobiliar del glutatión durante el tratamiento con ciclosporina A.* J. Physiol. Biochem., **56** (3), 189-200, 2000.

Se estudian los efectos del tratamiento con ciclosporina A (CyA) sobre el contenido hepático y la concentración y secreción biliar de glutatión reducido (GSH) y oxidado (GSSG), y los niveles hepáticos de TBARS, y la capacidad de la S-adenosilmetionina (SAMe) para antagonizar las alteraciones inducidas por la CyA en ratas Wistar. Con objeto de evaluar la eficacia de la SAMe, se han utilizado tres tipos de protocolos de administración: cotratamiento o tratamiento simultáneo con CyA y SAMe, pretratamiento con SAMe antes de iniciar el cotratamiento, y post-tratamiento con SAMe después de iniciar el tratamiento con CyA. El tratamiento durante un periodo corto (una semana) o largo (cuatro semanas) con CyA depleciona el GSH, disminuye la relación GSH/GSSG y reduce significativamente la concentración y secreción biliar de GSH y

GSSG. Además, el tratamiento largo aumenta la peroxidación lipídica. Por el contrario, cuando los animales se tratan con CyA y SAMe siguiendo cualquiera de los protocolos de administración, la SAMe muestra ser eficaz para antagonizar la depleción hepática de GSH, normalizar la relación GSH/GSSG y suprimir el incremento inducido por la CyA sobre la peroxidación lipídica. Además, la SAMe normaliza los efectos de la CyA sobre la secreción biliar de GSH y GSSG. La eficacia de la SAMe es similar en todos los tipos de protocolos de tratamiento utilizados. En resumen, nuestros resultados demuestran claramente que la SAMe es eficaz para prevenir, antagonizar y revertir las alteraciones inducidas por la CyA en la homeostasis hepatobiliar del glutatión.

Palabras clave: Ciclosporina A, Glutatión, Peroxidación lipídica, S-adenosilmetionina.

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