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Ethanol Interaction with Drug Acetylation *In Vivo* and *In Vitro*

HARALD OLSEN AND JØRG MØRLAND[1]

Department of Clinical Pharmacology, University Hospital and Institute of Medical Biology, University of Tromsø, Tromsø, Norway

OLSEN, H. AND J. MØRLAND. *Ethanol interaction with drug acetylation* in vivo *and* in vitro. PHARMACOL BIOCHEM BEHAV **18**: Suppl. 1, 295–300, 1983.—The acute effect of ethanol on sulfadimidine or procainamide pharmacokinetics was studied in healthy drug-free volunteers. Ethanol treatment increased the elimination rate, as well as the amount of acetylated drug measured in blood and urine. No changes of apparent volume of distribution or renal drug clearance were found. In three out of seven slow acetylators tested, the rate of acetylation increased so noticeably after ethanol that they would otherwise have been classified as rapid acetylators. Using suspensions of isolated rat liver parenchymal cells, the effect of ethanol, acetate, citrate, pyruvate, and L(−)carnitine on acetylation of sulfanilamide and procainamide was studied. Ethanol treatment enhanced sulfanilamide acetylation, whereas the acetylation of procainamide was unchanged. Acetate, citrate, and pyruvate treatment enhanced the acetylation of both drugs. Acetate treatment increased both K_m and V_{max} of both sulfanilamide and procainamide acetylation. In rat liver homogenates, acetyl-CoA increased the rate of sulfanilamide acetylation in a dose-dependent manner.

Drug acetylation Ethanol Interaction In vivo In vitro

THE acute interaction between ethanol and drugs usually leads to decreased rates of drug metabolism. Both oxidation and conjugation of drugs with glucuronic acid, may be inhibited by ethanol [9, 13, 20, 21]. Theoretically, however, ethanol could have the opposite effect on drug acetylation and enhance the speed of this conjugation reaction since ethanol is metabolised to acetate and may increase the formation and concentration of acetyl-CoA, the acetate donor in the N-acetyltransferase reaction leading to acetylation of drugs [25]. This would require that low concentrations of acetyl-CoA be rate-limiting in this reaction. Also other substances, e.g., pyruvate and citrate, which may enhance the hepatic level of acetyl-CoA should then enhance drug acetylation. For some drugs acetylated; hydrallazine, isoniazid, procainamide, and certain sulfonamides, great interindividual differences in the acetylation rate have been found [10, 16, 18]. Furthermore it has been found that the activity of the enzyme N-acetyltransferase is controlled by genes of large effect in humans and rabbits, and people may thus be classified as slow or rapid acetylators [5, 6, 7].

The hypotesis of a nongenetic regulation of the N-acetyltransferase reaction, by means of substances which may regulate the acetyl-CoA level at the site of reaction, has been tested both *in vivo* and *in vitro*. The results of these experiments have been published in detail previously [15, 16, 18]. This report contains a review of the results.

METHOD

In Vivo *Studies in Man*

Drug-free healthy volunteers took part in two separate cross-over studies. In one [16], sixteen subjects, aged 18–36 years, were given sulfadimidine (10 mg/kg). In the other [18], eleven subjects aged 25–36 years were given procainamide (10 mg/kg). The participants were fasted over-night and at 8 a.m. the drug was given by mouth. Half of the subjects receiving sulfadimidine or procainamide received no further treatment, while the others had ethanol (0.73 g/kg) 1.5 and 2 hr after taking procainamide or sulfadimidine, respectively. Ethanol was then given hourly (0.11 g/kg) until 7.5 or 10 hr after procainamide or sulfadimidine intake, respectively. Usually venous blood samples were collected at 2 hr, and then hourly until 8 hr or 10 hr after procainamide or sulfadimidine intake. Occasionally urine was collected. One week later, the experiment was repeated; the ethanol-treated and control groups were reversed. Thus each subject served as his or her own control.

In Vitro *Studies in Rat*

The acetylation of sulfanilamide and procainamide in the absence and presence of ethanol (33 mM), acetate (0.5–5 mM), citrate (4 mM), pyruvate (4 mM) and L(−)carnitine (2 mM) was studied in suspensions isolated rat liver parenchymal cells [15]. The cell suspensions were prepared from rat livers perfused with CA^{++} free buffer and 0.5% collagenase, according to the method of Berry and Friend [1], as described elsewhere [14].

Additionally, the effect of various acetyl-CoA concentrations (0.05–0.8 mM) on sulfanilamide acetylation in homogenates of rat liver was studied [15].

[1]Present address of both authors: National Institute of Forensic Toxicology, Sognsvannsveien 28, Oslo 3, Norway.

TABLE 1

ETHANOL EFFECT ON SULFADIMIDINE HALF-LIFE AND ACETYLATION* [16]

	N	Half-Life (min)	Acetylation* Hours after sulfadimidine 2	8
Rapid acetylators	9			
Control value		129 ± 12	44.0 ± 30.6	79.3 ± 17.1
After ethanol		99 ± 9†	40.2 ± 25.2	84.7 ± 17.1†
Slow acetylators	7			
Control value		301 ± 53	15.3 ± 11.9	30.0 ± 7.7
After ethanol		250 ± 58‡	17.1 ± 5.0	36.7 ± 20.4†

*N-Acetylsulfadimidine in percentage of the sum of recorded sulfadimidine and N-acetylsulfadimidine.
†$p<0.05$ compared with control value.
‡$p<0.01$ compared with control value.

TABLE 2

ETHANOL EFFECT ON PROCAINAMIDE PHARMACOKINETICS [18]

	N	Control value	After ethanol
$T_{1/2}$ (min)	11	171 ± 41	128 ± 25*
slow acetylators	5	186 ± 38	138 ± 28†
rapid acetylators	6	153 ± 43	120 ± 21†
Cl_T (ml · min^{-1})	11	532 ± 132	711 ± 149*
slow acetylators	5	472 ± 108	719 ± 169‡
rapid acetylators	6	582 ± 138	704 ± 169†
V_β (l · kg^{-1})	11	2.1 ± 0.5	2.0 ± 0.5
slow acetylators	5	1.8 ± 0.2	2.0 ± 0.5
rapid acetylators	6	2.3 ± 0.6	2.0 ± 0.4
Cl_R (ml · min^{-1})			
PA	7	468 ± 148	484 ± 150
NAPA	6	230 ± 147	218 ± 58

*$p<0.01$ compared with control value.
†$p<0.05$ compared with control value.
‡$p<0.05$ compared with control value and with the increase found in the rapid acetylators.

Analytical Methods

Sulfadimidine, sulfanilamide, acetylsulfadimidine and acetylsulfanilamide concentrations were measured by Bratton and Marshall's method [2]. Procainamide and N-acetylprocainamide (NAPA) were measured by gas chromatography [15,18]. Blood ethanol and acetate concentrations were measured as described elsewhere [18].

The formula used for pharmacokinetic calculations are described in the respective papers [16,18]. Abbreviations used are: $T_{1/2}$=elimination half-life, k_{el}=apparent elimination rate constant at first-order kinetics, K=elimination rate constant at zero-order kinetics, Cl_R=renal drug clearance, Cl_T=total body clearance, V_β=apparent volume of distribution.

RESULTS

In Vivo *Studies in Man*

Sulfadimidine. Wide variations in rates of sulfadimidine elimination and acetylation were found among the 16 volunteers. Nine subjects could be classified as rapid acetylators and seven as slow acetylators. In Table 1, the results concerning ethanol effect on sulfadimidine elimination and acetylation are shown. As can be seen, ethanol intake caused a reduction in sulfadimidine half-lives in both rapid and slow acetylators, whereas the percentage of acetylated sulfadimidine increased more between 2 and 8 hours when ethanol was present than without ethanol. In three slow acetylators, the percentage acetylated sulfadimidine measured in blood at eight hours was increased so noticeably after ethanol that they would have been classified as rapid acetylator according to the criteria of Evans [5].

The ethanol dosage regimen used was followed by relatively constant blood ethanol (approximately 1 g/l) and acetate (approximately 0.8 mmol/l) concentrations. However large variations between individuals in blood acetate concentrations was found. When the mean concentration of acetate, measured between four and 10 hours, was plotted against the part of the increase in the amount of acetylated sulfadimidine that could be ascribed to ethanol, a correlation was found which bordered on significance at 5 % level.

Procainamide. Tables 2 and 3 show the results of procainamide elimination (Table 2) and acetylation (Table 3) in absence and presence of ethanol. As can be seen, the half-life was significantly reduced (apparent elimination rate constant increased by 32±12%), and the total body clearance increased (37±27%), while the apparent volume of distribution (V_β) as well as the renal clearance (Cl_R) of both procainamide and N-acetylprocainamide were unchanged when ethanol was present. The relative effect of ethanol on procainamide half-life or apparent elimination rate constant was similar in the slow and rapid acetylators while the relative increase in total clearance was significantly higher in the slow than in the rapid acetylators, 55±26% versus 23±20%. In all subjects, the percentage acetylated procainamide in blood increased with time. This increase was greater when ethanol was present. Also in urine, the percentage of acetylated procainamide was increased significantly when ethanol was present, in both the 0–8 hr and 0–48 hr period. Again, when the individual mean acetate concentration measured between 3 and 8 hr was plotted against the ethanol mediated increase in percentage acetylated procainamide between 8 and 2 hr, a correlation was found ($r=0.753$, $p<0.05$).

In Vitro *Studies in Rat*

The effect of ethanol (33 mM) on sulfanilamide and procainamide acetylation in suspensions of isolated rat liver cells is shown in Table 4. With sulfanilamide as substrate, ethanol treatment increased the elimination (k_{el} increased by 15±9%, $p<0.05$). The level of acetylated sulfanilamide also increased significantly. With procainamide as substrate, the percentage of N-acetylprocainamide and the elimination rate of procainamide was similar in both ethanol treated and con-

TABLE 3

ETHANOL EFFECT OF PROCAINAMIDE ACETYLATION* [18]

	N	Control value	After ethanol
Blood			
whole group			
2 hr	11	18.9 ± 8.3	23.0 ± 7.8
8 hr	11	44.6 ± 14.3	58.0 ± 15.8
Difference		25.7 ± 7.2	32.8 ± 13.9†
slow acetylators			
2 hr	5	12.2 ± 2.2	17.7 ± 5.6
8 hr	5	34.3 ± 8.1	48.0 ± 6.6
Difference		22.1 ± 6.4	30.3 ± 8.2‡
rapid acetylators			
2 hr	6	24.4 ± 7.4	27.5 ± 6.7
8 hr	6	53.2 ± 13.1	66.9 ± 16.7
Difference		28.8 ± 6.9§	39.4 ± 8.2‡
Urine			
0–8 hr	7	16 ± 10	19 ± 8†
0–48 hr	6	26 ± 7	30 ± 8‡

*The figures represent N-acetylprocainamide as percentage of the sum of recorded procainamide and N-acetylprocainamide.

†$p<0.01$ compared with the control value.

‡$p<0.05$ compared with the control value.

§$p<0.05$ compared with the corresponding increase found in the slow acetylators.

TABLE 4

ETHANOL EFFECT ON SULFANILAMIDE AND PROCAINAMIDE ACETYLATION IN SUSPENSIONS OF ISOLATED RAT LIVER PARENCHYMAL CELLS [15]

	N	Control	After ethanol
Sulfanilamide			
$k_{el} \cdot 10^3$	5	3.38 ± 0.70	3.92 ± 1.08*
% acSNA			
0–2 hr	5	32.7 ± 5.1	35.9 ± 5.9*
0–4 hr	5	54.9 ± 7.8	60.2 ± 9.8*
mean pH	5	7.16 ± 0.40	6.85 ± 0.14
Procainamide			
$k_{el} \cdot 10^3$	6	5.72 ± 2.4	5.55 ± 3.77
%NAPA			
0–1 hr	6	8.3 ± 2.6	8.7 ± 2.0
0–2 hr	6	22.6 ± 6.3	24.9 ± 9.7
Mean pH	6	7.34 ± 0.05	7.23 ± 0.09

*$p<0.05$ compared with control value.

trol cells. Addition of ethanol to the cell suspensions caused a more pronounced decline of the medium pH than observed in the control (Table 4). Since pH variations of the incubation medium may change the acetylation rate [15,17] it seems necessary to have close pH control when studies on drug acetylation in isolated rat liver cells are performed. Due to the findings that both procainamide and sulfanilamide acetylation are pH dependent [15,17], the decreased medium pH caused by ethanol treatment may probably abolish a stimulating effect of ethanol or ethanol metabolites. Table 5 shows the effect of various acetate (0.5–5 mM) concentrations on sulfanilamide and procainamide acetylation in cell suspensions. Acetate concentrations of 1.0 mM and higher increased the relative acetylation of both drugs, and concentrations of 2.0 mM and higher increased the rate of disappearance of parent drug (Table 5). In separate experiments [15], the acetylation rate at various sulfanilamide and procainamide concentrations was studied in the absence and presence of 4 mM acetate. By means of double-reciprocal plots (Lineweaver-Burk plot) it could be calculated that V_{max} increased by 77% and 70% and K_m by 78% and 70% for sulfanilamide and procainamide acetylation, respectively, in the acetate treated cells. In Table 6, the effects of equimolar concentrations (4 mM) of acetate, citrate, and pyruvate alone and combined with L(−)carnitine (2 mM) on sulfanilamide and procainamide acetylation are shown. With sulfanilamide as test substance, acetate, citrate, and pyruvate treatment caused increased acetylation, and combined with L(−)carnitine, the effect of each of the precursors of acetyl-CoA was further enhanced (Table 6). It is, however, perceivable that sulfanilamide acetylation changed from zero- to an apparent first-order kinetics in the cells treated with acetate or pyruvate combined with L(−)carnitine. With procainamide as test drug, acetate and pyruvate treatment enhanced the elimination of procainamide as well as the percentage acetylated drug, while citrate treatment enhanced the percentage acetylated drug only (Table 6). However, the effect of pyruvate treatment was significantly stronger than that caused by acetate treatment ($p<0.05$). Combining L(−)carnitine with each of the precursors of acetyl-CoA enhanced the percentage N-acetylprocainamide further in pyruvate and citrate treated cells, whereas the elimination rate was further enhanced in the pyruvate treated cells only.

Figure 1 shows the effect of various acetyl-CoA concentrations on the rate of sulfanilamide acetylation in homogenates of rat livers. As can be seen, the rate of sulfanilamide acetylation increased with increasing acetyl-CoA concentrations, indicating that an experimental V_{max} value of the enzyme may also be dependent on the cofactor concentration.

DISCUSSION

Our studies showed that in humans, acute administration of ethanol enhanced the elimination of both sulfadimidine and procainamide. The enhanced elimination could have been caused by more extensive distribution, increased metabolism (caused, e.g., by enhancement of either enzyme activity or cofactor level or more drug available for the enzyme), and/or enhanced excretion. Since we found that both the renal clearance and the apparent volume of distribution of sulfadimidine and procainamide were similar in both controls and after ethanol treatment, the most likely explanation of our findings seem to be increased acetylation. The increased percentage of acetylated drug measured in both blood and urine after ethanol treatment supports this assumption. Reduced protein binding during ethanol treatment could have made more drug available to the enzyme, and thereby enhanced the rate of acetylation of the drugs. However, a displacement effect of ethanol on protein binding is doubtful [9]. Displacement from tissue binding sites or

TABLE 5

ACETATE EFFECT ON SULFANILAMIDE AND PROCAINAMIDE ACETYLATION IN SUSPENSIONS OF ISOLATED RAT LIVER PARENCHYMAL CELLS* [15]

	Control	Acetate 0.5 mM	Acetate 1.0 mM	Acetate 2.0 mM	Acetate 5.0 mM
Sulfanilamide					
K (μM/min)	0.35 ± 0.09	0.44 ± 0.13	0.43 ± 0.07	0.44 ± 0.10†	0.49 ± 0.13†
% acSNA					
0–2 hr	8.6 ± 2.4	12.3 ± 5.8	12.0 ± 2.6†	14.0 ± 3.4†	13.3 ± 5.0†
0–4 hr	19.9 ± 5.5	24.5 ± 7.2	23.9 ± 3.6	24.9 ± 5.5	26.8 ± 7.5†
Procainamide					
$k_{el} \cdot 10^3$	5.3 ± 1.3	5.1 ± 0.6	6.1 ± 1.5	6.9 ± 2.2†	6.6 ± 2.1‡
% NAPA					
0–1 hr	8.1 ± 1.8	8.5 ± 2.4	9.9 ± 2.4	10.9 ± 1.9†	12.2 ± 2.2‡
0–2 hr	25.3 ± 2.7	27.6 ± 1.0	32.4 ± 5.6†	35.0 ± 7.8†	35.7 ± 7.1‡

*The results are means ± SD of five experiments, except in the procainamide treated cells combined with 5.0 mM acetate which represents mean of four experiments ± SD.

†$p<0.05$ compared with control value.

‡$p<0.05$ compared with control value (Wilcoxon-Mann-Whitney test).

TABLE 6

EFFECT OF VARIOUS ACETYL-CoA PRECURSORS ON SULFANILAMIDE AND PROCAINAMIDE ACETYLATION IN SUSPENSIONS OF ISOLATED RAT LIVER PARENCHYMAL CELLS* [15]

	Sulfanilamide		Procainamide	
	K	% acSNA	$k_{el} \cdot 10^3$	% NAPA
Control	0.39 ± 0.11	13.1 ± 4.3	4.5 ± 1.2	25.8 ± 6.9
Citrate	0.45 ± 0.09†	15.1 ± 2.9‡	4.8 ± 1.3	28.6 ± 8.6‡
Acetate	0.46 ± 0.09‡	15.6 ± 3.2‡	5.5 ± 1.3‡	30.9 ± 8.0‡
Pyruvate	0.46 ± 0.10‡	15.5 ± 3.6‡	6.6 ± 1.5‡	39.3 ± 15.8‡¶
Carnitine				
Citrate	0.61 ± 0.16‡	21.2 ± 6.1‡§	5.7 ± 1.7‡	36.3 ± 10.5‡§
Acetate	1.7 ± 1.2 $\cdot 10^{-3}$†	22.0 ± 2.7‡§	6.5 ± 2.2‡	38.5 ± 16.1‡
Pyruvate	1.9 ± 0.2 $\cdot 10^{-3}$†	24.6 ± 3.2‡§	8.1 ± 3.9‡§¶	47.7 ± 17.6‡§¶

*The cells were incubated for 3 hours with sulfanilamide and 2 hours with procainamide as substrate. The results are means ± SD of five experiments.

†The elimination changed from zero to apparent first order kinetics, and the apparent elimination rate constant (k_{el}) is given.

‡$p<0.05$ compared with control value.

§$p<0.05$ compared with the values obtained with the corresponding precursor alone.

¶$p<0.05$ compared with the acetate treated cells or acetate plus carnitine treated cells.

increased distribution would probably have caused changes of the apparent volume of distribution [26]. Enhanced enzyme concentration as a consequence of acute ethanol intake seems unlikely, whereas enhanced enzyme activity due to ethanol (e.g., allosteric effects on the enzyme leading to enhanced activity) can not be ruled out as an explanation. However, since the level of acetyl-CoA in the environment of the enzyme is partly rate limiting for the acetylation process ([25], Fig. 1), and since ethanol may increase the cellular level of acetyl-CoA [8,22] it seems more reasonable to explain our results as a consequence of an enhanced availability of acetyl-CoA at the site of drug acetylation caused by ethanol metabolism. This assumption was supported partly by the finding of some correlation between the individual blood acetate level and the increase in percentage of acetylated drug [16,18].

The *in vitro* study showed that ethanol treatment of isolated rat liver cells may increase the rate of sulfanilamide acetylation (Table 4), whereas procainamide acetylation and elimination were unchanged. Because of ethanol mediated reduction of cell medium pH, these observations were difficult to interpret. It therefore became of importance to study the effect of other substances which could enhance the cellular concentration of acetyl-CoA without changing the medium pH.

Treatment of the cell suspensions with acetate enhanced

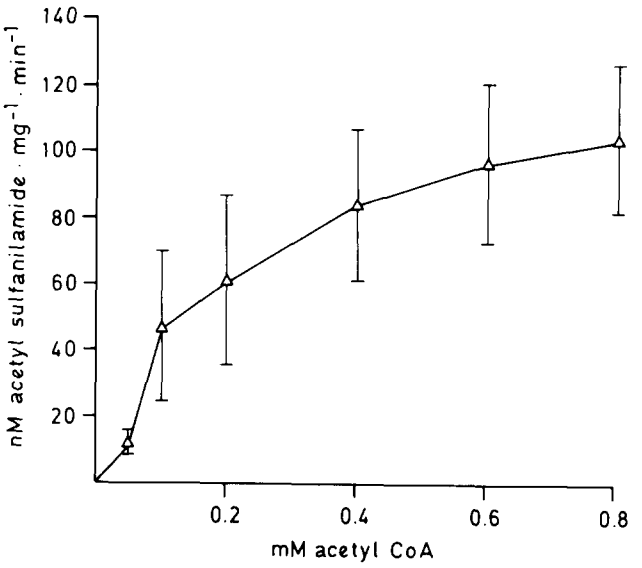

FIG. 1. Effect of increasing concentrations of acetyl-CoA on the rate of sulfanilamide acetylation in rat liver homogenates. Each point represents mean of four experiments ±SD [15].

the acetylation of both procainamide and sulfanilamide at acetate concentrations comparable with those found in humans after ethanol ingestion [16,18]. If the acetate-mediated increase in drug acetylation was caused by enhancement of cellular concentrations of acetyl-CoA, acetate treatment should, according to [25], enhance both K_m and V_{max} of the reaction. This was indeed the case for both sulfanilamide and procainamide (see Results section). Also, other precursors of acetyl-CoA; citrate and pyruvate, enhanced the acetylation of the two drugs. L(−)carnitine has been reported to be linked to the transport of acyl- and acetyl-CoA across the mitochondrial membrane [3, 11, 19, 24]. Combining L(−)carnitine with acetate, citrate or pyruvate enhanced sulfanilamide acetylation more than acetate, citrate or pyruvate did alone (Table 6). With procainamide as test drug, a further increase of the acetylation rate was found when L(−)carnitine was added together with citrate or pyruvate. In rat liver homogenates, acetyl-CoA increased the sulfanilamide acetylation in a dose-dependent manner. Our present conclusion is, therefore, that the concentration of the cosubstrate, acetyl-CoA, might be rate limiting in drug acetylation reactions. It is further indicated that ethanol can increase the rate of such reactions by enhancing the availability of acetyl-CoA for such reactions. This might influence the outcome of treatment with drugs that are acetylated with regard to effects and side-effects [10] when drug and ethanol are combined. The observation that isoniazid hepatotoxicity occurs more frequently when the rate of acetylation is high may be particularly interesting in this respect. Some carsinogens will become more rapid metabolically activated in organisms with a high rate of drug acetylation. Future epidemilogic and experimental studies might reveal whether ethanol-mediated enhanced acetylation is of importance to such biological consequences and other clinical states that have been reported to be linked to rapid acetylation.

Our findings that the rate-limiting factor for drug acetylation may not be the enzyme per se, but rather the amount of cofactor in the intact cell system, seem to be valid for other cytosolic conjugation reactions also. Others have shown that the factors limiting choline acetylation [4] and sulphate conjugation [12,23], may be the amount of cofactor.

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