Acetylation of Sulfisoxazole by Isolated Perfused Rat Kidney

Keyphrases □ Sulfisoxazole—renal metabolism to N^4-acetyl metabolite using the isolated perfused rat kidney □ Metabolism, renal—sulfisoxazole, acetylation by the isolated perfused rat kidney

To the Editor:

Although the kidneys contain many metabolizing enzymes of the liver (1), renal drug metabolism has received limited attention, due partially to the relegation of the kidneys to organs of excretion. The isolated perfused kidney is a useful technique for studies of the renal disposition of drugs. In many cases, experiments with the isolated perfused kidney give results that are consistent with data obtained from *in vivo* studies and more clearly define the role of the kidneys in the overall disposition of a drug. In our laboratory, the isolated perfused kidney has been used in renal clearance studies of several compounds (2, 3) as well as in studies of renal metabolism and interconversion of salicylic and salicyluric acids (4).

Since sulfisoxazole (I) is eliminated largely by renal excretion, it can be influenced by protein binding, urinary pH, and the urine flow rate (5, 6). Studies in our laboratory on the renal clearance of sulfisoxazole by the isolated perfused kidney indicated that rat kidneys metabolize this drug to its N^4-acetyl metabolite (II).

Male Sprague–Dawley rats, 350–375 g, were used in the isolated perfused kidney experiments. The surgical technique and experimental details were reported previously (2–4). Sulfisoxazole (6.5 mg) was administered to attain an initial concentration of ~100 μg/ml, and perfusion was continued for 90 min. The experimental time was divided into nine 10-min urine collection periods. Urine samples were assayed for sulfisoxazole and N^4-acetylsulfisoxazole by a modified high-performance liquid chromatographic assay (7).

The mean urinary excretion rates for N^4-acetylsulfisoxazole and sulfisoxazole from five perfusion experiments are presented in Table I. Although the amounts of N^4-acetylsulfisoxazole excreted in the urine were low, they accounted for 5–7% of the total drug excreted as sulfisoxazole plus N^4-acetylsulfisoxazole during the 90-min experiment. Previous *in vivo* experiments on elimination of sulfisoxazole in the rat indicated that, of the total drug excreted in the urine, 12% is excreted as the N-acetyl metabolite (8). The present results thus indicate that half of the excreted N-acetyl metabolite is due to renal metabolism and that, in the rat, the kidneys contribute significantly to the metabolic disposition of sulfisoxazole.

Table I—Urinary Excretion Rates of N^4-Acetylsulfisoxazole (II) Formed by the Perfused Rat Kidney following Administration of 6.5 mg of Sulfisoxazole (I)

Minutes	Urinary Excretion Rate, μg/10 min	
	II	I
10	0.87 ± 0.25[a]	11.12 ± 4.24[a]
20	1.16 ± 0.62	18.78 ± 10.02
30	1.08 ± 0.57	18.40 ± 5.72
40	1.74 ± 0.55	27.98 ± 12.82
50	1.58 ± 0.48	31.13 ± 18.28
60	1.45 ± 0.47	34.70 ± 18.21
70	1.58 ± 0.38	28.30 ± 8.42
80	1.53 ± 0.19	27.30 ± 6.09
90	1.43 ± 0.27	28.38 ± 7.08
Total	12.06	226.02

[a] Mean ± *SD*, $n = 5$.

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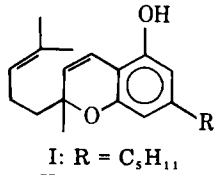
Anti-Inflammatory Activity of Cannabichromene Homologs

Keyphrases □ Anti-inflammatory activity—evaluation of cannabichromene homologs □ Cannabichromene homologs—evaluation for anti-inflammatory activity

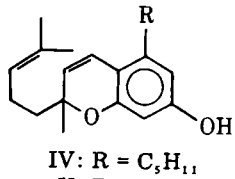
To the Editor:

As part of our continuing study of the cannabinoids, we recently reported that cannabichromene has anti-inflammatory activity. The two tests used to show this activity were the carrageenan-induced rat paw edema test and the red cell stabilization assay (1). To determine the effect of changing the length and position of the side chain of cannabichromene on its anti-inflammatory activity, four homologs were prepared and tested.

Cannabichromene-C_5 (I), cannabichromene-C_1 (II), and cannabichromene-C_0 (III) were prepared following the procedure outlined previously (2), starting from olivetol, orcinol, and resorcinol, respectively. The yield of I was



I: R = C_5H_{11}
II: R = CH_3
III: R = H



IV: R = C_5H_{11}
V: R = H

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