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Effects of Mefruside on Renal Hemodynamics

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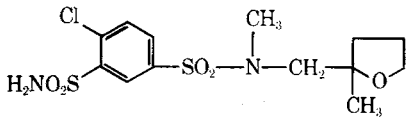
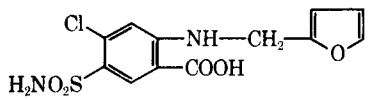
Abstract □ Mefruside, a natriuretic drug similar in structure to furosemide, was examined for activity on renal hemodynamics in the dog. This agent, when administered at 10 mg./kg. i.v., increased renal vascular resistance and decreased renal blood flow. Blood pressure and the rate of glomerular filtration were not affected. Mefruside differs from furosemide in its action on renal hemodynamics, inasmuch as furosemide decreases renal vascular resistance and increases renal blood flow.

Keyphrases □ Mefruside—effects on renal hemodynamics □ Renal dynamics—mefruside, effects

Mefruside {4-chloro-3-sulfonamido-1-[*N*-methyl-*N*-(2′-methyl-2′-tetrahydrofurylmethyl)]-benzenesulfonamide} (I) is a new orally active natriuretic (1). Structurally, this agent is similar to furosemide (II). In



I mefruside



II furosemide

addition to natriuretic activity, furosemide also affects renal hemodynamics to enhance renal blood flow (2–5). The purpose of this study was to determine if mefruside also enhances renal blood flow.

EXPERIMENTAL

Mongrel dogs, weighing 13–16 kg., were anesthetized with sodium pentobarbital, 30 mg./kg. A tracheal cannula was inserted to ensure free passage of air. The kidney to be utilized was exposed by a flank incision, and the renal artery was cleared of the surrounding tissue. A flow transducer (Carolina Medical Electronics model EMP-411, lumen size, 11-mm. circumference) was placed around the exposed renal artery, and renal blood flow was monitored with a square-wave electromagnetic flowmeter (Carolina Medical Electronics model 321). The flowmeter was adjusted to zero flow by briefly occluding the renal artery distal to the flow transducer. Blood pressure was monitored from the carotid artery. Both blood flow and blood pressure were recorded on a Beckman recorder. A solution containing 0.9% NaCl and 0.4% inulin was infused into the right femoral vein at a rate of 0.25 ml./kg./min. for at least 30 min. before and throughout the entire experiment. Mefruside was dissolved in saline using sodium bicarbonate. The drug was given intravenously *via* the right femoral vein.

Urine samples from the exposed kidney were obtained from a renal pelvic catheter introduced into the ureter by way of the retroperitoneal incision. Although urine samples were collected only from the kidney to which blood flow was measured, the other ureter was cannulated *via* a midline incision to ensure free urine flow from the contralateral kidney. Blood samples were obtained from the right femoral artery.

Urine and plasma inulin concentrations were determined by the method of Shreiner (6). Sodium concentrations were determined with a Coleman flame photometer. All data were analyzed with Student's *t* test paired comparisons (7). A *p* value less than 0.05 was used as the level of significance.

Table I—Effect of Mefruside (10 mg./kg.) on Renal Hemodynamics

	Control[a]	Mefruside[b]	Difference[c]
Renal blood flow, ml./min.	174	158	−16 ± 4[d]
Blood pressure, mm. Hg	142	140	−2 ± 2
Renal vascular resistance, mm. Hg/ml./min.	0.84	0.92	0.08 ± 0.02[d]
Sodium excretion, μeq./min.	124	424	300 ± 53[d]
Inulin clearance, ml./min.	30	30	0 ± 3

[a] Control values represent values taken immediately prior to mefruside administration. [b] Mefruside values represent values taken 10 min. after drug administration. [c] Difference from control ± *SE*. [d] Indicates a significant difference, $p < 0.05$, $n = 4$.

RESULTS AND DISCUSSION

Mefruside (10 mg./kg. i.v.) produced a significant decrease in renal blood flow of 16 ml./min. as renal vascular resistance was increased significantly (Table I). These effects were transient. They were maximal about 10 min. after drug administration and returned to control levels by 20 min. after drug administration. Blood pressure was not altered by the drug. Mefruside had no effect on inulin clearance. Sodium excretion was increased from 124 to 424 μeq./min. upon drug administration. The natriuretic action was still present 60 min. after drug administration when the experiments were ended. A lower dose of the drug (2 mg./kg. i.v.) did not produce a significant change in renal vascular resistance or renal blood flow.

The results show that mefruside does possess renal hemodynamic properties but that they are not similar to the renal hemodynamic properties of furosemide. Furosemide decreases renal vascular resistance and thereby enhances renal blood flow (2–5). In contrast, mefruside (10 mg./kg. i.v.) increases renal vascular resistance and thereby decreases renal blood flow. The effect of mefruside on renal blood flow is more like that of the thiazide agents which also increase renal vascular resistance and decrease renal blood flow (2, 8).

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1-(3,4-Dimethoxyphenyl)-2-propanol Effect on Conditioned Avoidance Response in the Rat

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Abstract □ The compound, 1-(3,4-dimethoxyphenyl)-2-propanol, was found to prolong latency times initially in a conditioned avoidance response test in rats. It was found to be a CNS depressant in mice. The structural implications of this action, plus the relationship between 1-(3,4-dimethoxyphenyl)-2-propanol and psychotomimetic amphetamines, are discussed.

Keyphrases □ 1-(3,4-Dimethoxyphenyl)-2-propanol—effect on conditioned avoidance response, rat □ Psychotomimetic agents—3,4-dimethoxyamphetamine oxygen analog, pharmacological screening

The literature contains a report indicating that the oxygen analog of mescaline, namely, 3,4,5-trimethoxyphenylethanol (TE), may be psychotomimetic (1). TE was isolated as a product of mescaline metabolism. When it was injected intravenously into rabbits, a mild mescalinelike action was observed.

In structure–activity relationship studies on mescaline, certain methoxylated amphetamines were found to be more potent than mescaline (2). If conversion from β-phenylethylamine to phenylisopropylamine can enhance the potency of psychotomimetics, then a similar logic possibly could be applied to the oxygen analogs of these psychotomimetics. One could anticipate that any mescalinelike actions would be more pronounced in 1-phenyl-2-propanols than in 2-phenylethanols. This paper reports the results of a study on the effect of 1-(3,4-dimethoxyphenyl)-2-propanol (DP), which is the oxygen analog of the psychotomimetic agent 3,4-dimethoxyamphetamine, on conditioned avoidance response (CAR) in the rat.

RESULTS AND DISCUSSION

Although the synthesis of DP was reported in the literature (3), no pharmacological information on the compound could be found. Initially the effect of DP on CAR in rats was studied. The evaluation of drug action on CAR has been exploited widely. This technique has been especially valuable for the evaluation of psychotomimetics (4).

To determine whether DP is producing an effect similar to mescaline or 3,4-dimethoxyamphetamine (3,4-DMA), the effects of these drugs at various dosages on a running response in conditioned male rats were determined. Each drug was given in three dosage levels ("effective dose," one quarter the effective dose, and four times the effective dose) to groups of six rats. Figures 1 and 2 show the mean reaction time for each trial during the drug sessions for each dosage level of mescaline and 3,4-DMA. That the profile of 3,4-DMA is not completely analogous to mescaline may be due to the amphetamine structure present in 3,4-DMA. CNS stimulation caused by amphetamine would be expected to counteract the increased reaction times. Figure 3 shows the enhanced performance caused by amphetamine sulfate relative to placebo. The lower dose was more effective.

Since 3,4-DMA is expected to be a poorer stimulant than amphetamine itself (*i.e.*, require a much larger dose to cause the same effect), the greatest variation from the mescaline profile would be expected at the higher doses. The large variation between reaction times of adjacent trials is observed in both mescaline and 3,4-DMA, which suggests that this is a characteristic feature of the behavior disruption caused by these agents.

Figure 4 shows the effects of DP. The overall profile of the drug session is substantially different from any of the other drugs tested. When it became clear that DP was different, it was subjected to a more conventional pharmacological screening. In mice intraperitoneally it was a CNS depressant [ED_{50}(sleep) = 150 mg./kg; LD_{50} = 650 mg./kg.] (5). This pharmacological action of DP is not unexpected in light of the report that acetophenones and other phenones and their corresponding alcohols exhibit depressant effects (6). Thus, DP may be viewed as a structural isomer of these phenones and alcohols.

The data presented here suggest that a reevaluation of the pharmacological effects of TE is required.[1] A detailed study of the structure–activity relationships and the mechanism of action of ring-substituted phenyl-2-propanols, phenyl-2-propanones, and chemi-

[1] Preliminary, unpublished studies indicate that TE has a CNS-depressant effect, ED_{50}(sleep) > 650 mg./kg. i.p. in mice.