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Effect of 2-Dimethylaminoethanol on Renal Hemodynamics.* (23920)

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Recently Pfeiffer *et al.*(1) reported that 2-dimethylaminoethanol (DMAE) may act as a possible tertiary amine precursor of acetylcholine. This observation associated with its possible therapeutic effects on the central nervous system led to this study. If DMAE acts as a precursor it might be expected to produce changes in urine flow and renal hemodynamics similar to those noted with acetylcholine. This report is concerned with the effect of DMAE† on urine flow in dogs and rats as well as hemodynamic changes in dogs.

Methods. Male and female rats weighing between 240 and 400 g receiving no food and water for 18 hours were used. Prior to experiment 25 ml of tap water/kg body weight was administered *via* stomach tube to each animal. The compounds to be tested were dissolved in water immediately before hydration. The rats were placed in metabolism cages, 2/cage, and urine collected 5 hours. Urine measurements were made on control rats administered only water as well as rats given DMAE and choline chloride in varying doses. In addition, the effect of DMAE on renal hemodynamics were carried out on trained unanesthetized female dogs in the postabsorptive state. One hour before each experiment the dogs were hydrated with 25 ml of water/kg of body weight. Inulin and para-aminohippurate (PAH) clearances were used as a measure of glomerular filtration rate (GFR) and renal plasma flow (RPF) respectively. Inulin was analyzed according to the method of Roe, Epstein and Goldstein(2) and PAH according to the method of Smith *et al.*(3). Throughout the experiment glucose 5% in water was infused at constant rate of 3 ml/min. Following 2 control periods, DMAE was infused for 1 hour followed by one hour during which time 2 more clearance samples were taken. Doses of DMAE infused were 1.0, 1.5, 2.5, 5.0 and 7.5 mg/kg.

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† Supplied by Dr. C. C. Pfeiffer, Emory University.

TABLE I. Effect of DMAE on Water Excretion in the Rat.

Rat No.	Water adm. (ml)	% of load excreted	Rat No.	Water adm. (ml)	% of load excreted
A. 25 ml water/kg			B. Choline, 75 mg/kg		
1, 22	14.35	72	15, 19	14.40	55
43, 4	16.00	68	42, 32	7.90	62
7, 11	9.50	43	15, 20	14.30	28
8, 19	7.83	51	1, 2	14.85	64
21, 22	16.30	62	8, 18	14.35	29
45, 26	15.85	47	10, 4	16.15	38
33, 41	17.00	38	15, 19	14.40	49
11, 13	14.30	63	42, 60	8.68	53
2, 19	13.80	58	4, 5	17.49	46
19, 43	15.40	71	4, 11	17.05	27
51, 32	12.60	42	2, 18	15.00	38
20, 30	9.50	58	8, 18	14.35	29
Avg % excreted of total load		56.08 ± 11.7			43.17 ± 13.5
C. DMAE, 50 mg/kg			D. DMAE, 75 mg/kg		
1, 3	16.00	22.5	8, 9	14.90	42
11, 13	15.70	53.4	2, 3	14.90	42
19, 18	14.85	43.7	1, 15	14.60	14
7, 8	15.55	38.5	40, 39	13.05	20
9, 10	12.00	48.0	34, 33	12.50	16
14, 15	13.50	8.1	35, 36	14.25	22.3
17, 20	12.30	23.6	1, 10	14.95	6.7
6, 17	10.80	20.3	14, 19	13.30	5.1
16, 20	11.25	40.0	8, 9	11.95	40
			8, 3	14.95	37
			48, 49	8.20	46
			53, 37	8.12	45
			9, 8	14.60	32
			4, 5	15.93	29
			18, 1	15.40	28
			19, 8	16.20	18
Avg % excreted of total load		33.12 ± 15.06			26.57 ± 13.0

	Diff. between means	t for diff.	P
Water—Choline	12.91	2.49	<.05
" —DMAE 50	22.96	3.93	<.001
" — " 75	29.51	6.20	<.001
Choline—DMAE 50	10.05	1.61	>.1
" — " 75	16.60	3.29	<.01
DMAE 50—DMAE 75	6.55	1.14	>.2

Results. Table I indicates the effect of DMAE and choline chloride on urine flow in rats. Results are expressed as percent excreted of total amount of water administered. Compared to water, choline chloride produced a significant decrease in urine flow, ($P<0.05$). DMAE at both dosage levels caused a greater decrease in urine flow ($P<0.001$). In addition, it can be noted that choline chloride and DMAE (50 mg/kg) produced similar changes whereas DMAE (75 mg/kg) caused a significant decrease compared to choline chloride. These results indicate that in rats DMAE in doses employed, produced a significant antidiuresis. Whether DMAE *per se* inhibited water excretion through liberation of the antidiuretic hormone or DMAE acted as a precursor of acetylcholine which then either released antidiuretic hormone or caused hemodynamic changes can not be ascertained from this study.

Since a decrease was noted in rats, it was anticipated that a similar action would occur in dogs if this were a specific effect of DMAE. Table II illustrates experiments employing 5.0 and 7.5 mg/kg doses to indicate lack of effect of DMAE on renal hemodynamics. Ten mg/kg of DMAE produced central nervous system effects of tremors, muscular twitching, emesis and defecation which limited studies

TABLE II. Effect of DMAE on Renal Hemodynamics.

Dog No.	Urine flow, ml/min. C	I	R	G. F. R., ml/min. C	I	R	R. P. F., ml/min. C	I	R	Dose, mg/kg
1	2.41	2.88	3.08	58.5	62.2	56.0	195	209	185	5
2	4.00	3.47	2.72	71.0	59.0	67.1	238	198	190	5
3	2.71	2.76	3.04	48.8	48.3	47.2	138	121	113	5
3	3.64	2.33	2.45	58.6	44.3	49.5	125	115	134	5
2	3.03	3.15	2.95	68.0	66.2	69.1	215	225	214	7.5
2	4.31	3.95	4.12	64.0	67.3	65.2	231	240	229	"
3	2.95	3.08	3.30	54.2	53.4	58.6	140	131	135	"
4	4.00	3.90	3.98	59.0	54.0	61.2	195	208	212	"
5	3.60	3.80	3.51	53.0	56.0	54.2	185	190	178	"

at this concentration. On the basis of these results in dogs it would appear that DMAE in doses that are well tolerated does not have any specific effect on the kidney in acute experiments. No changes in sodium, potassium or chloride excretion were noted in these experiments.

Summary. Renal effects of DMAE were determined in rats and dogs. In high doses an antidiuretic effect was noted in rats. Dogs that had been administered DMAE in maximal tolerated doses exhibited no changes in urine flow nor renal clearances. There were no indications that this compound had any toxic effect on the kidney.

Statistical analysis kindly performed by E. H. Jenny, Emory University.

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Metabolism of Cortisol by Loose Connective Tissue *in vitro.* (23921)

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Extensive transformation of progesterone (1) and cortisol(2) (4-pregnene-11-beta, 17-alpha, 21-triol, 3, 20-dione, or hydrocortisone) to a series of metabolites by eviscerated rats has been demonstrated. These metabolites represent a pool of steroids which have been transformed by a variety of tissues. The extent to which each tissue adds to the pool of steroid products is being investigated. Connective tissue obtained from mice was incubated *in vitro* in the presence of cortisol-4-C^{14}. Histological examination of this tissue has shown that 90% of the cells are fibroblasts(3).

Various products were isolated from these incubations and the following 5 compounds were identified: 4-pregnene-11-beta, 17-alpha, 20-alpha, 21-tetrol, 3-one (20-epi substance "E" of Reichstein); 4-pregnene 17-alpha, 21-diol, 3, 11, 20-trione (cortisone); pregnane 11-beta, 17-alpha, 21-triol, 3, 20-dione (dihydrocortisol); 4-pregnene 11-beta, 21-diol, 3, 20-dione (corticosterone) and 4-androstene 11-beta-ol, 3, 17-dione.

Materials and methods. Fourteen mice (AK) were killed by decapitation and the connective tissue collected as described previously(4). The areolar tissue was placed in 8 incubation flasks immediately after collection. Each flask contained 0.3-0.6 g of tissue in 10 ml of 0.1 M phosphate buffer, pH 7.4 and cortisol 4-C^{14} (25,000 cpm; Specific Activity 1.467 mc/mole). Incubation was carried out in shaking water bath at 37°C for a total of