

EFFECTS OF DIURETIC DRUGS ON RENAL FUNCTION IN *Squalus Acanthias*

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The diuretic drugs, furosemide and ethacrynic acid, generally considered to affect diuresis through alteration of sodium reabsorption, were studied in the spiny dogfish, *Squalus acanthias*. The effect of these agents on renal function in an elasmobranch is of interest because of the major role that active urea reabsorption by the kidney of these species plays in osmoregulation. In addition, the complex structure of the nephron and its remarkable counter-current mechanism offer further attraction for altering renal function by pharmacological agents.

Recently captured female dogfish weighing between 3 and 7 Kg were studied in the free-swimming state in running sea water at about 13° C. Urine was quantitatively collected through an inlying catheter in the urogenital papilla. Blood samples were obtained through an inlying arterial catheter. Standard clearance techniques were used. Inulin, 15 ml of 3-1/3% solution in dogfish Ringers, was injected intravenously 12 to 16 hours prior to 2 control clearance periods. Blood and urine were assayed for inulin, urea, sodium, potassium, magnesium, calcium and total osmolality. After the two control periods, furosemide 20 mg (3 fish), or 40 mg (6 fish), or ethacrynic acid 50 mg (3 fish) were injected intravenously and from 2 to 5 further clearance periods were obtained. For comparison, a group of 7 fish were studied using the same protocol except that epinephrine 3 mgm was injected intra-muscularly. Two additional dogfish were used as controls and received no pharmacological agent.

The experimental data are given in the table.

RENAL RESPONSE IN SQUALUS ACANTHIAS TO DIURETIC AGENTS

Values except for ratios expressed as unit / hour / Kg and given as mean \pm standard deviation

	Control Fish		Furosemide		Ethacrynic Acid		Epinephrine	
	Control	0 Drug	Control	Drug	Control	Drug	Control	Drug
Volume	0.80 \pm 0.30	0.82 \pm 0.28	0.55 \pm 0.22	1.54 \pm 0.56	0.36 \pm 0.17	1.32 \pm 0.38	0.64 \pm 0.30	1.21 \pm 0.53
C _{In} ml	3.51 \pm 0.49	3.39 \pm 1.32	2.46 \pm 1.39	2.25 \pm 1.29	1.84 \pm 0.96	2.08 \pm 0.60	3.02 \pm 1.51	4.10 \pm 2.70
U _{Na} ^V mEq	0.224 \pm .059	0.22 \pm .076	0.151 \pm .060	0.420 \pm .155	.098 \pm .056	0.369 \pm .115	0.126 \pm .050	0.268 \pm .119
C _{Na} /C _{In}	0.35 \pm 0.07	0.26 \pm 0.08	0.24 \pm 0.06	0.70 \pm 0.17	0.21 \pm 0.06	0.69 \pm 0.08	0.18 \pm 0.07	0.29 \pm 0.10
U _{urea} ^V mM	66 \pm 49	61 \pm 36	39 \pm 22	284 \pm 140	25 \pm 16	244 \pm 83	49 \pm 25	178 \pm 95
C _{urea} /C _{In}	0.08 \pm 0.07	0.07 \pm 0.07	0.05 \pm 0.02	0.40 \pm 0.15	0.05 \pm 0.02	0.43 \pm 0.07	0.06 \pm 0.03	0.17 \pm 0.07
C _{osm} ml	0.59 \pm 0.22	0.62 \pm 0.20	0.40 \pm 0.17	1.42 \pm 0.58	0.25 \pm 0.13	1.26 \pm 0.39	0.42 \pm 0.20	0.94 \pm 0.47
C _{H₂O} ml	0.20 \pm 0.10	0.20 \pm 0.10	0.15 \pm 0.08	0.12 \pm 0.09	0.11 \pm 0.07	0.07 \pm 0.04	0.17 \pm 0.07	0.27 \pm 0.08
Osm U/P	0.75 \pm 0.06	0.76 \pm 0.04	0.72 \pm 0.06	0.91 \pm 0.07	0.70 \pm 0.15	0.95 \pm 0.03	0.69 \pm 0.09	0.76 \pm 0.07
U _K ^V mEq	28 \pm 14	54 \pm 22	28 \pm 22	25 \pm 14	8 \pm 8	23 \pm 14	48 \pm 67	63 \pm 84
U _{Mg} ^V mEq	13 \pm 3	16 \pm 7	13 \pm 8	10 \pm 8	6 \pm 4	7 \pm 6	16 \pm 5	18 \pm 6
U _{Ca} ^V mEq	6.6 \pm 0.7	5.4 \pm 1.3	4.4 \pm 2.6	8.0 \pm 3.2	2.5 \pm 1.8	6.8 \pm 2.7	5.2 \pm 3.1	9.2 \pm 4.0

Furosemide in either dose and ethacrynic acid produced a three-fold increase in urine volume. Epinephrine caused a lesser diuresis (two-fold). Inulin clearance was unaffected except by the epinephrine which resulted in a 1.3 fold increase ($p = 0.04$). Osmolar clearance increased under the influence of all agents and proportionately greater than the augmentation of urine volume. With furosemide and ethacrynic acid, the ratio of urine osmolality to that of plasma regularly exceeded 0.9 and in many instances approached unity. This increased osmolar output under the influence of diuretics was contributed to heavily by urea and sodium ion. Urea excretion increased 8 to 9 fold on the average with furosemide or ethacrynic acid in contrast to a 4-fold increase with epinephrine. Urea excretion relative to its filtered load changed from 6% to over 40% with furosemide and ethacrynic acid, and from 6% to 17% with epinephrine. Plasma urea concentration decreased only slightly in all experimental groups.

A moderate but regular (about two-fold) increase in calcium excretion was observed with both the diuretic drugs and epinephrine. Magnesium excretion was unchanged. In some studies potassium output was increased but this was irregular and requires further study.

The diuretic drugs, furosemide and ethacrynic acid, have dramatic effects on urea and sodium excretion in *Squalus acanthias*. There is no alteration in rate of glomerular filtration, and interference with active tubular reabsorption of urea and sodium is proposed. Epinephrine also produced increased excretion of urea and sodium but this is moderate and associated with a mild increase in glomerular filtration.

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CARDIOVASCULAR RESPONSES TO SPINAL CORD STIMULATION IN THE DOGFISH

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The spinal cord was stimulated in 22 anesthetized dogfish (20 mgm/Kgm pentobarbital intrarterially) in which the cord had been transected at the spino-medullary junction. In five fish the brain was also removed. Blood pressure was recorded from a catheter inserted into the dorsal aorta. Rectangular stimuli were delivered for not less than 30 seconds at a variety of voltages (5-25) and frequencies (5-50 Hz). Stimulation at distances 1-8 cm caudal to the transection site caused complete cardiac inhibition or marked slowing either with or without an intact brain (Figure 1). Blood pressure elevated abruptly with the onset of stimulation even though the heart stopped completely. It then declined exponentially until the heart resumed beating. The blood pressure then increased, sometimes to greater than control level, but decreased to control value before the cessation of stimulation. During the second rise of pressure (after the resumption of the heart beat) the pulse pressure was increased. Cardiac inhibition was rarely observed when the cord was stimulated more than 12 cm caudal to the transection site. Blood pressure sometimes increased and then decreased abruptly simultaneously with the onset and cessation of stimulation (Figure 2A and B).