

Prevention of Pyrogen-Induced Renal Hyperemia in the Dog by Dihydroergocornine.* (18096)

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Although the renal hyperemia resulting from the administration of bacterial pyrogens is not prevented by sympathectomy or "virtual denervation" of the kidney(1,2), and is not prevented by antipyretic drugs(3) the possibility remains that the increased blood flow results indirectly from an action of the pyrogens on the central nervous system. Since dihydroergocornine (DHO) is known to interfere centrally with certain autonomic mechanisms(4,5), the experiments reported below were undertaken to determine the effect of this agent on the response of the renal vascular bed to pyrogens.

Methods. Experiments were conducted on trained female dogs without anesthesia or sedation. Glomerular filtration rate and effective renal plasma flow were estimated from creatinine and para-aminohippurate clearances. After a priming dose, these substances were infused at a constant rate in pyrogen-free 5% glucose solution through an intravenous catheter. Urine was collected from a catheter in periods of 15 minutes; the bladder was washed with three 15 cc portions of water and two 20 cc portions of air at the end of each period. Most animals were subjected to "control" runs in which pyrogen alone (2.5 γ total dose) was administered, followed by or preceded by "experimental" runs in which pyrogen was administered 30

minutes after the injection of DHO in a dose of .01 mg per kg intravenously plus .01 mg per kg subcutaneously.† Successive experiments on the same animal were separated by an interval of at least 10 days. Rectal temperatures were recorded in all experiments.

In every experiment 2 or 3 control periods were run on each animal to determine the basic glomerular filtration rate and effective renal plasma flow levels. A pyrogen, derived from the capsule of one of the *Shigella* group of organisms,§ was then injected intravenously in a fixed dose of 2.5 γ per dog. Samples of urine and blood were taken for 6 or 7 additional periods.

Results. In confirmation of numerous previous investigations, it was found that the pyrogen increased renal plasma flow in every animal. The average of maximum responses was 44%, with a range of 27% to 79% (Table I). The renal blood flow increased after a latent period of 30 to 45 minutes, and was usually still elevated at the time collections were discontinued.

No significant changes in glomerular filtration rate were observed, and the creatinine clearance data are consequently omitted from the table.

Rectal temperatures rose in every case, even though some of the animals were hyperthermic at the outset because of high environmental temperatures.

In contrast to the effects of pyrogen in untreated animals, the maximum hyperemic responses after premedication with DHO were greatly diminished (Table I, Fig. 1). The average of maximum responses in 7 animals was +10%, with a range from -4% to +25%. DHO did not alter glomerular filtra-

* Supported by a grant from the Life Insurance Medical Research Fund.

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‡DHO-180 was generously supplied by Sandoz Pharmaceuticals.

§ The pyrogen was prepared and generously supplied by Dr. Herbert Morgan of the University of Michigan School of Public Health.

TABLE I. Effect of Pyrogen on Renal Plasma Flow With and Without DHO Pre-medication.

Dog	Pyrogen alone			DHO-180 + pyrogen		
	R.P.F.			R.P.F.		
	Control, cc/min.	Pyrogen, cc/min.	Change, %	Control, cc/min.	Pyrogen, cc/min.	Change, %
1	200	358	+79	191	239	+25
10	149	226	+52	181	190	+5
13	158	227	+44	134	160	+19
16	175	232	+33	128	123	-4
9	117	148	+27	—	—	—
19	—	—	—	141	147	+4
25	176	239	+36	113	113	0
26	165	228	+38	105	124	+18
Avg			+44.1	Avg		
(S.E. = 6.5; $p = <.001$)				(S.E. = 4.2; $p = <.1, >0.05$)		

tion rate in these experiments, nor did it prevent the hyperthermic response to pyrogen.

Discussion. Though DHO has no significant action on renal plasma flow in the normal or denervated kidney(6), it has been shown to abolish the renal vasoconstriction induced by epinephrine in the dog. This

presumably results from the peripheral "adrenolytic" action of the alkaloid, which action is particularly prominent in the renal vascular tree. The effect of DHO in preventing the renal hyperemia induced by pyrogens can hardly be an adrenolytic action, unless it be assumed that in response to pyrogens adrenergic vasodilatation can occur in the kidney, and that this dilatation can also be prevented by an adrenolytic drug. This seems to us to be an unlikely hypothesis, and it seems more probable that the antagonism between DHO and the pyrogen is a manifestation of a blocking action of the alkaloid in the central nervous system. The data presented in this study do not, of course, prove such a concept, and a peripheral antagonism in the renal vessels remains a possibility.

Summary. Premedication with moderate doses of dihydroergocornine greatly diminished the renal hyperemia produced in the dog by a bacterial pyrogen. No significant change of glomerular filtration rate was observed following administration of either the pyrogen or the alkaloid.

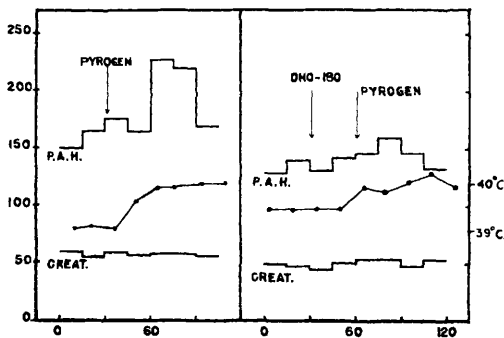


FIG. 1.

Response of renal plasma flow to *Shigella pyrogen*, with and without premedication with dihydroergocornine.

Para-aminohippurate clearance (P.A.H.) and creatinine clearance (Creat.), scale at left in cc/min. Rectal temperature, scale at right. Time in minutes on the abscissa. Dog. #13.

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Received July 14, 1950. P.S.E.B.M., 1950, v75.