Elevated Histidine Decarboxylase Activity in the Kidney of the Pregnant Mouse

It has been found in this laboratory that the histamine-forming capacity is increased in certain kinds of normal and malignant rapid tissue growth[1-4]. Rat foetuses, particularly, exhibit very high levels of histidine decarboxylase activity.

The present results in mice reveal a new relationship between histamine metabolism and pregnancy. Adult mice weighing about 30 g were killed by decapitation and the kidenys examined for histidine decarboxylase activity by procedures developed by SCHAYER et al.[5] and described in detail by WHITE[6]. The results are summarized in the Table in which for comparison values from some of the richest known sources of mammalian histidine decarboxylase are included.

From the Table it is seen, first, that in the kidney of the non-pregnant female the enzyme level is about twenty times higher than in that of the male. Further, and most striking, in pregnancy the kidney enzyme level is elevated to about fifty times the non-pregnant values. This activation during pregnancy can hardly be due to differences in endogenous amounts of the coenzyme pyridoxal-5-phosphate, because addition of this compound to non-pregnant kidney mince during incubation with ^{14}C-histidine did not cause a significant increase in the rate of formation of ^{14}C-histamine.

The physiological significance of the increased histamine forming capacity in the mouse kidney during pregnancy is open to speculation. SCHAYER[7] demonstrated the existence of at least two varieties of mammalian histidine decarboxylase. It remains to characterize more specifically the nature of the female mouse kidney enzyme and to see to what extent the enzyme and its increase during pregnancy is species specific.

Zusammenfassung. Die Fähigkeit, ^{14}C-Histamin aus ^{14}C-Histidin zu bilden, steigt in der Niere der schwangeren Maus enorm an. Dieses Organ ist deshalb eine der reichsten Quellen von tierischer Histidindecarboxylase.

The histidine decarboxylase activity of kidneys in male, pregnant and non-pregnant mice. Each figure represents the observation from one mouse. For comparison the activity of rat gastric mucosa and rat foetal liver are shown.

Species	Tissue	Histamine formed (ng/g/3 h)
Mouse	male kidney	4
		8
		14
		58
		80
Mouse	female kidney, non-pregnant	120
		310
		390
		660
		1 880
Mouse	female kidney, pregnant	20 800
		26 500
		32 300
		38 900
		43 400
Rat	gastric mucosa	1 010
		1 340
		1 430
		1 540
Rat	foetal liver	21 400
		23 300
		37 000
		54 200

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Experimental Hypertension Elicited by Injections of Methyl Cellulose[1]

It has been shown that when various animal species are injected with methyl cellulose, storage cell macrophages and vascular endothelial cells incorporate the material thereby being converted into 'foam cells'[2-4], resembling the intravascular lipid-filled foam cells which occur in certain forms of human cardiovascular[5] and renal[6] disease. Kidney glomeruli are transformed into structures which have been likened to 'grape clusters' because of the marked and extensive endothelial swelling. Recent examination, in our laboratory, of histological material from rats which had been the recipients of hormone solutions containing methyl cellulose as a suspending agent, revealed that the glomerular capillaries were so occluded by endothelial swelling as to severely curtail the circulation of blood through them. Because of the relationship between 'renal ischemia' and hypertension[7,8] it seemed worthwhile to investigate the effect which such restriction of intraglomerular circulation might have on the blood pressure.

Method. 20 immature female rats of the Holtzman strain weighing 70–90 g were unilaterally nephrectomized and placed on a 1% NaCl intake, procedures which are known to facilitate induction of hormonal hypertension[9]. Ten of them received daily subcutaneous injections of a methyl cellulose solution which ranged between 1% and 0.25% concentration. Those which survived the full period of treatment received a total of 106 mg of the polysaccharide. The remaining ten received no injections. Blood pressures were measured periodically on unanesthetized animals by a tail-plethysmograph. The experiment was concluded on the 32nd day, surviving animals being killed with ether. Organs and tissues from them and those which died intercurrently were taken for weight and microscopic examination.

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Results. By the third week of treatment six of the nine animals remaining were hypertensive, with blood pressures ranging from 156 to 206 mm Hg, one having died prior to this. By the 27th day two others had died and all of the surviving methyl cellulose-treated rats were hypertensive, with pressures ranging 168–234 mm Hg. None of the controls became hypertensive. In the last week of treatment four of the injected rats died with severe ascites, edema, pleural effusion, or a combination of these. A typical example of severe edema is shown in the Figure. At autopsy the hearts were noted to be enlarged and showed small surface scars. The kidneys were yellowish, usually moderately enlarged, and had an irregular surface.

Hypertensive rats had marked cardiac hypertrophy, their hearts being significantly heavier than controls ($P < 0.001$), due chiefly to thickening of the left ventricular wall. The adrenal glands and spleens were not enlarged, being if anything slightly reduced in size. The data on blood pressure and organ weights are given in the Table. Vascular lesions of the type associated with hypertension observed in various organs, and 'foam cell' transformation of glomerular endothelial elements, were both evident on microscopic examination. They are under current study and will be the subject of a later communication.

Severe edema in a rat which had received methyl cellulose for 32 days. Weight 212 g, blood pressure 210 mm Hg. The animal also had marked ascites.

Principal findings in methylcellulose-treated and control rats

Data			Methylcellulose-treated	Controls
Body weight g	Initial		83 ± 2[a]	83 ± 2
	Final		179 ± 11	183 ± 4
Blood pressure	Day 21		157 ± 14	120 ± 3
mm Hg	27		197 ± 12	121 ± 2
	32		200 ± 10	124 ± 2
Organ weights	Adrenals	mg	48.1 ± 3.0[b]	62.1 ± 2.4
	Spleen	mg	467 ± 74[b]	602 ± 24
	Heart	mg	788 ± 29[b]	585 ± 19
	Kidney	g	2.00 ± 0.12[b]	1.88 ± 0.21

[a] Mean ± S. E. of mean.
[b] Based on 3 animals killed and 4 which died in the same week.

Discussion. The physical manifestations of methyl cellulosis include edema, ascites and pleural effusions and, as this experiment shows, arterial hypertension, cardiac enlargement and vascular lesions. The concomitant morphologic transformation of the glomeruli into enlarged 'foam cell' laden structures makes it seem likely that the cardiovascular effects are the sequelae of reduced intrarenal circulation. In contradistinction to other methods of interfering with kidney blood flow and thereby causing hypertension (such as partial occlusion of the renal arteries or the investment of kidneys in a semi-rigid capsule) the present method appears to depend, at least initially, upon impairment of circulation at the glomerular level.

The appearance of the transformed glomeruli as published by others[3,4] and observed by us, is somewhat reminiscent of that sometimes seen in lipoid nephrosis[5] and certain other forms of glomerulonephrosis, excepting that in methyl cellulose thesaurosis the endothelial cells contain the macromolecular polysaccharide instead of lipid. The occurrence of hypertension and edema both in the human and experimental conditions would suggest the possibility that the physiological aberrations in each are evoked by a closely related if not identical mechanism. This would seem to be dependant upon both reduced intrarenal circulation and direct impairment of glomerular filtration. Although in the present study the animals were sensitized to hypertension by uninephrectomy and the imposition of a high NaCl intake, recent experiments in this laboratory indicate that neither is essential to the production of experimental hypertension by this means. Further studies are in progress to elucidate the nature of the mechanism which leads to the development of hypertension.

Résumé. Des injections sous-cutanés d'une solution de méthyl-cellulose provoquent dans la rate une vraie hypertension artérielle maligne. Les animaux utilisés eurent fréquemment des œdèmes et des ascites et toujours des lésions artérielles dans le cœur, les reins et ailleurs.

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Isolation of 5-Hydroxytryptamine from the Skin of the Toad *Bufo arenarum* Hensel

B. arenarum Hensel is the widest spread species of toad in Argentina and has been in common use in this country for physiological and pharmacological work.

From the dried paratoid secretion, usually called venom, bufotenine and dehydrobufotenine[1]; adrenaline[2], bufothionine[3], and from the dried skins, bufothionine, bufotenine and dehydrobufotenine[4a] were obtained. The secretion also contains several bufogenines, which have been recently identified[5]. We now record the isolation of 5-hydroxytryptamine from the dried skins of *B. arenarum*, a compound which has been detected in several species of toad[6].

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