Discovery of the Renomedullary System of Blood Pressure Control and Its Hormones

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I worked with Arthur Grollman for 3½ years (and 12 scientific publications) beginning in 1947. Arthur was Chairman of the Department of Experimental Medicine, and I became Chairman of the Department of Pathology at Southwestern Medical School in Dallas. Grollman inoculated me with his concept of a “nonexcretory antihypertensive function of the kidney”, “incretory” he termed it. For some time, he insisted that this function was a cortical one, gainsaying a medullary one. However, toward the end of his career, he conceded the cellular source of this function as controversial, quoting our position. Several key experiments in our laboratory pointed toward a renomedullary antihypertensive function. Jerry Stirman (a surgeon), Bennie Brooks, my research assistant for 39 years, and I began by transplanting whole kidneys into dogs with sustained renoprival hypertension. These kidneys lowered the blood pressure of the hypertensive recipients rapidly, despite the maintenance of a fluid load that was not overcome by diuresis-natriuresis. Thus, the antihypertensive effect resulted from a function unrelated to volume depletion—a finding consistent with the incretory concept. Next, I discovered that renoprival hypertension of the dog was potentiated by a mixture of saline intravenously and protein by mouth. This combination caused what became known as “accelerated renoprival hypertension” (blood pressure elevation of 30–40 mm Hg within 3–4 days). Anastomosing the ureter to the inferior vena cava prevented this type of hypertension whereas ureteral ligation did not. A major morphological disparity between the kidneys of these two states was noted. Uretero-caval anastomosis was attended by an intact and hypertrophied renal medulla, and ureteral ligation gave rise to acute hydronephrosis and ischemic-type destruction of the renal papilla (obstructive papillary necrosis). This led me to the view that cells in the renal papilla performed the antihypertensive function. These observations were followed by attempts to autotransplant renal tissue, unable to form urine, into various parts of the body to determine whether accelerated renoprival hypertension could be prevented. Transplants were introduced into various areas, including a peritoneal pouch, the lesser sac, and splenic and portal veins. Each time the tissue was too lumpy and necrosed. I decided to inject the tissue into the pleural space hoping that lung movement would spread out the tissue and possibly cause a take. At autopsy, we found a tract of renal tissue (tubules) in the lung itself; I had overshot the pleura. I thought, “the lung is the place to go.” We fragmented kidney and injected this intravenously hoping for a lung lodgement and growth. Rather, the dogs gasped, became cyanotic, had a convulsion, and died. (In time, it became apparent that we were injecting thromboplastic tissue and causing diffuse pulmonary thromboses.) About this time one of our coworkers, Frances Jones (a chemist), suggested we place pieces of tissue in the cup of a small Waring blender and activate it for a few seconds (settling on 5 seconds). This gave rise to fine particles (less than 1 mm in size). These could be washed, suspended, and injected intravenously. Renomedullary particles administered intravenously caused no problems for the dog and prevented accelerated renoprival hypertension. We found small nodules in the lungs containing clumps of “clear cells” by light microscopy. By using the Jones technique, it was possible to develop nodules of fragmented renal tissue elsewhere such as in the peritoneum, skeletal muscle, or subcutaneous tissue. Altogether, it required over 1 year to master the technique of auto-transplantation. Transplanted renal medulla prevented renoprival hypertension, whereas cortex and other tissues did not.

In time, renomedullary transplants were shown to lower the blood pressure of benign hypertensive rats, prevent malignant hypertension of rabbits, and prevent an extremely salt-loaded renoprival hypertension of the rabbit, whereas renocortical tissue was ineffective. In the renoprival model, the same level of fluid overload occurred in the protected (renomedullary) and the nonprotected (renocortical) animals. These experiments indicated that the renomedullary system of blood pressure control was effective against both volume-dependent (renoprival, one-kidney, one clip) and angiotensin-dependent (malignant) hypertensive states.

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About this time, Byron Leach and Larry Byers joined our group. We had great difficulty deriving antihypertensive activity from extracts of renal papilla (obtained from Pel-Freeze in Rogers, Arkansas). I decided to take a page from the prostaglandin book and homogenize fresh rabbit renal papilla and incubate this homogenate for about 30 minutes at 37°C before freeze-drying it and extracting the powder for total lipids. The incubation step was based on the possibility of enzymatic synthesis of the antihypertensive lipid, much as an acetone-dried powder of seminal vesicle plus arachidonic acid was used at that time to generate prostaglandins. We then added a reduction step to the lipids, first with lithium aluminum hydride and later with Vitride. This step was based on earlier work with Ed Daniels and Jack Hinman in consultation with Bill Lands suggesting that the antihypertensive lipid might be a glyceryl ether. The lipid derived by the reduction step caused a near immediate drop of the blood pressure, shock, and death. By lowering the dose, it was possible to identify an acute type vasodilator, a polar lipid we called the antihypertensive polar renomedullary lipid (APRL).4 APRL was identified as a group of alkyl glyceryl ethers of phosphatidylcholine with a short ester in the second position of the glycerol. The identity occurred in collaboration with Dom Deserio and Fred Snyder's group. APRL turned out to be identical to platelet activating factor (PAF-acether of Benveniste and AGEPC of Hanahan). It was not our sought after antihypertensive lipid.5 Work with this lipid, however, consumed considerable time.

ANRL was renamed medullipin I6 for the following reasons: ANRL as extracted from fresh renal papilla (a procedure developed by Larry Byers without the Vitride reduction step) gave rise to a characteristic vasodepressor effect. Given as a bolus intravenously to a hypertensive rat, there was a lag period of 1–2 minutes between the injection and the beginning of decline in blood pressure.7 This lag period was significantly shortened by injection of the lipid into the portal vein, which led us to the liver.

Several experiments secured the hepatic contribution to the renomedullary system.8 We turned to the effect of unclipping the Goldblatt hypertensive rat, a procedure used very successfully by Bjorn Folkow and John Swales and their associates. We had demonstrated earlier that unclipping lowered the blood pressure of one-kidney, one clip hypertensive rats to normal despite major salt-volume loads4 that could not be dispelled from the body (as following ureterocaval anastomosis). We had reason to believe that angiotensin II constrained this function.4 For this reason, we tested the effect of captopril, the converting enzyme inhibitor, on unclipping; it potentiated this effect in a big way. Destruction of the renal papilla with 2-bromoethylamine hydrobromide blocked the drop of blood pressure after unclipping whether captopril was given or not. (This confirmed an experiment by John Swales' group.) A reno-portal...
venous shunt potentiated the effect of unclipping, and removal of the liver from the circulation prevented the effect of unclipping on blood pressure. Potentiators of the cytochrome P-450-dependent enzyme systems (phenobarbital, ciprofibrate) accelerated the action of unclipping, whereas inhibitors of cytochrome P-450 (SKF 525A, ketoconazole, ETYA) blocked the action of unclipping. This work was done in consultation with Jorge Capdevila. We began thinking we were dealing with a product of the third pathway of arachidonic acid metabolism, the cytochrome P-450 pathway.

We proposed medullipin I as the hormone secreted by the renomedullary interstitial cells, carried to the liver by the blood, and converted there to its active form, medullipin II. This conversion appeared dependent on the cytochrome P-450 enzyme systems of the liver. Medullipin II is a vasodilator that suppresses sympathetic tone, causes diuresis-natriuresis, and has an effect on the central nervous system.

The coup de grace on the liver came when the liver was removed from the circulation of the hypertensive Goldblatt rat followed by unclipping. The blood pressure remained elevated. To the circulation of this animal, a normal rat liver was attached. The blood pressure receded to normal quickly and remained so for a prolonged period. (These various manipulations resulted from the surgical adroitness of Bennie Brooks). We suggested the liverless, unclipped, hypertensive rat accumulated medullipin I, which was converted to medullipin II in large amounts when the normal liver was connected to the circulation. Medullipin I may be a product of either arachidonic or adrenic acid. It likely has two OH groups in close proximity as it is inhibited when coupled with n-butyl boronic acid. The hypothesis considers medullipin II to result from modification of one or more double bonds of medullipin I.

The medullipin system is a powerful down-regulator of blood pressure. It represents a biologic "mirror image" of the renin-angiotensin system, which upregulates blood pressure. Theoretically, this homeostatic mechanism would be expected but was not demonstrated until the medullipins were discovered and elucidated. When available, the medullipins should be powerful prophylactic and therapeutic agents toward hypertension.

References


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