Bartter's Syndrome: A Disorder of Vascular Reactivity

Arthur C. Corcoran Memorial Lecture

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BARTTER'S syndrome, the syndrome of juxtaglomerular hyperplasia, hypokalemic alkalosis, hyperreninemia, and aldosteronism with normal blood pressure (BP), was initially described as an endocrine disorder. More recently, it has been described as a disorder of renal physiology. In this paper, we consider it a disorder of vascular reactivity and attempt to integrate endocrine and renal factors with those that control vascular reactivity.

From the earliest studies of so-called "Bartter's Syndrome," it was apparent that there were abnormalities in the vascular reactivity to pressor agents. In the first patient, for example, the BP was persistently normal even with expansion of extracellular fluid or intravascular volume. Not only was the plasma angiotensin II concentration some eight times normal in this patient, but plasma aldosterone was persistently very high as well. It was also apparent from these studies that: 1) the loss of potassium that produces hypokalemia, the cardinal sign of the syndrome, was by the renal route; and 2) this renal loss of potassium was partially dependent on sodium-retaining steroids including aldosterone, since it could be almost completely blocked with aldactone.

As has been amply demonstrated by studies from a number of laboratories, potassium depletion increases renin secretion while decreasing aldosterone secretion. Thus, untreated patients with the syndrome characteristically demonstrate a markedly elevated plasma renin activity (PRA) together with a moderately elevated plasma aldosterone. The pressor resistance to angiotensin was demonstrated with infusion of angiotensin (fig. 1). Whereas these studies showed a remarkable resistance to infused AII, they did not delineate the extent of the resistance.

Our first working hypothesis for the complex sequence of events that could bring together these findings (fig. 2) was based on a "proximate" resistance of blood vessels to the pressor action of AII, with a concomitant absence of resistance of adrenal cortical zona glomerulosa cells to AII. The concept that the elevation of plasma angiotensin resulted ultimately from the pressor resistance was supported by studies by Klaus and associates in Germany, by Kono and associates, and by Sasaki and associates in Japan, all of whom showed that a competitive antagonist to the action of AII, saralasin, promptly lowered the BP in untreated patients with the syndrome.

It was also apparent from the earlier studies that these patients also showed pressor resistance to the action of infused norepinephrine, although quantitatively this resistance was not so great as the dose required in normal subjects as was the resistance to AII. Silverberg and associates later found elevated plasma norepinephrine in five patients with the syndrome, whereas Gullner and associates found normal plasma values but elevated values for the 24-hour urinary excretion of norepinephrine. It is likely that the urinary values, by integration over 24 hours, give a more reliable index of the state of norepinephrine secretion in the untreated patients.

In an important study of the disorder(s) of vascular reactivity in the syndrome, Richards and associates tested directly the arterial responsiveness to intravenous infusion of AII and of norepinephrine in a patient with Bartter's syndrome (fig. 3). By plethysmography, they measured blood flow in the forearm so that peripheral arterial resistance could be calculated. They thus confirmed in their patient the arterial resistance to AII and to norepinephrine.

As the growing importance of prostaglandins became apparent, numerous studies of their physiological role in health and disease shed new light on the syndrome. It was early apparent that some of these prostaglandins and related agents (e.g., prostaglandin E, prostacyclin) are potent vasodilators,
whereas others (e.g., prostaglandin F₂₀, thromboxane A₂) are potent vasoconstrictors.

It was further shown that PGE₄ and prostacyclin can stimulate the release of renin from kidney slices studied in vitro, from renal arterial infusion as measured by renal vein concentrations in normal dogs, and in "non-filtering" kidneys in which tubular flow is minimal or absent. In 1976 it was reported that renal medullary interstitial cells, which produce prostaglandins in large quantities, may by hyperplastic in the syndrome, and that urinary and plasma PGA may be elevated. It was found by gas chromatography mass spectroscopy

![Diagram of the original schema proposed to explain the physiologic defect(s) in Bartter's syndrome. A block in the ability of angiotensin II to elevate blood pressure results in decreased inhibition of renin production, increased production of renin, angiotensin I, and angiotensin II, and increased aldosterone secretion. (Reprinted with permission from Am J Med 33: 811, 1962.)](image)

![Diagram of the effect of brachial arterial infusions of angiotensin II and norepinephrine on forearm blood flow measured by plethysmography before and during indomethacin. Dashed line depicts response (mean ± SEM) of nine normal subjects not receiving indomethacin. (Reprinted with permission from Circulation 58: 544, 1978.)](image)
that urinary PGE was elevated in all untreated patients studied. In 1976 it was shown that bradykinin, a potent vasodilator, is also present in very high concentrations in the plasma of untreated patients with the syndrome. It was also found that urinary kallikrein is abnormally high in untreated subjects with the syndrome.

Further, it was found that when an inhibitor of cyclooxygenase, such as indomethacin or ibuprofen, was given to patients with the syndrome there was a prompt reduction, not only in urinary PGE and 6-keto-PGF$_{1α}$, but also in PRA, aldosterone secretion, urinary aldosterone, and in urinary potassium. Serum potassium rose toward normal, but was not completely corrected. Plasma bradykinin and urinary kallikrein returned to normal. With these changes, there was prompt reduction to normal of the pressor dose of All and also of the pressor dose of norepinephrine. As shown in figure 4, Sasaki et al. also showed that, after the plasma All was lowered to normal with indomethacin (see below), the agonist action of the same dose of saralasin was readily apparent as a rise in BP.

In our own experience, considerable insight into the mechanisms behind the abnormalities of Bartter's syndrome was gained by the study of patients who produce in themselves a similar syndrome by persistent vomiting. As in the syndrome, these patients were found to have hypokalemic alkalosis, increased PRA, increased aldosterone secretion, resistance to the pressor action of angiotensin and of norepinephrine, and elevation of urinary prostaglandin E. With control of vomiting and replenishment of body potassium stores, the serum potassium returned to normal, and all these defects disappeared.

In studies of renal function in the syndrome, it has been reported that two abnormalities may be present in Bartter's syndrome; indeed, one of them appears to be a hallmark of the syndrome, having been found in all patients in whom it has been sought. The first defect, increased distal delivery of solute from the proximal tubules, is present in patients in whom overall renal function is impaired. Thus, the extent of this defect appears to be inversely related to the glomerular filtration rate. As it is not present in patients with the syndrome whose glomerular filtration rate is normal, it is clearly not an integral part of the syndrome.

The second defect, a decrease in fractional solute chloride reabsorption in the thick ascending limb of the loop of Henle produces a limitation in medullary hypertonicity. It can account for the limitation in minimal osmolality, seen in the patients as a higher value of urinary (NA + K) concentration under conditions of maximum hydration as compared to normals. Finally, it can account for potassium secretion on the assumption that the increased distal tubular flow rate resulting from the defect is an adequate stimulus to potassium secretion in the distal tubule and collecting duct as demonstrated by Khuri et al. and by Kunau et al.

The second assumption involves the increased secretion of PGE$_2$ (and probably PGI$_2$) with a decrease in potassium concentration bathing renal and vascular cells. It is assumed, as discussed above, that one or both of these prostaglandins stimulate the increased secretion of renin. Finally, it has been shown that both All and aldosterone can stimulate an increase of urinary kallikrein. It is assumed that renal kallikrein, acting on substrate available in renal blood and lymph and probably tubules, is responsible for the increased plasma concentration of bradykinin in the syndrome.

Ultimately, the abnormalities of vascular reactivity in the syndrome are thus seen as the resultant of prostacyclin and bradykinin, both tending to depress
BP and decrease vascular constriction, and of All and norepinephrine (and perhaps aldosterone), all tending to increase vascular constriction. According to this schema, the decrease of BP in patients with Bartter's syndrome that follows the administration of competitive inhibitors of All, such as saralasin, can be explained as a result of the excess of prostacyclin and bradykinin, now unopposed by the three agents normally tending to increase BP.

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