Editorial Comment

Relation Between Renin Release and Blood Pressure Response to Nonsteroidal Anti-inflammatory Drugs in Hypertension

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This issue of Hypertension features an article by Imanishi and colleagues entitled “Aspirin Lowers Blood Pressure in Patients With Renovascular Hypertension.” In their study, Imanishi and coworkers compared the effects of intravenously administered aspirin on arterial blood pressure, plasma renin activity in the renal veins and aorta, and plasma levels of prostaglandin E2 in the renal veins and aorta of six patients with unilateral renovascular hypertension and six patients with essential hypertension. Renovascular hypertension was defined by digital subtraction angiography and a renal vein plasma renin activity ratio (stenotic side/normal side) greater than 1.5.

In patients with renovascular hypertension, the level of prostaglandin E2 in the renal vein draining the stenotic kidney was elevated compared with the prostaglandin E2 level in the renal vein draining the nonischemic kidney. In contrast, prostaglandin E2 levels were similar in the left and right renal veins in patients with essential hypertension. Intravenous administration of aspirin lowered prostaglandin E2 levels at all sites in both groups of patients, lowered aortic levels of plasma renin activity in both groups of patients, and reduced the renal vein plasma renin activity ratio in renovascular hypertensive patients to less than 1.5. Interestingly, in patients with renovascular hypertension, aspirin reduced arterial blood pressure by 10 mm Hg. In contrast, aspirin significantly increased blood pressure by 4 mm Hg in patients with essential hypertension.

This editorial has three goals: 1) to underscore the significance of the work by Imanishi and colleagues to clinical medicine and to basic science; 2) to integrate the present study into a conceptual framework by highlighting certain aspects of the biology of prostaglandins. It is hoped that this framework will provide a basis for understanding the effects of nonsteroidal anti-inflammatory drugs on arterial blood pressure; and 3) to point out the relation of the study by Imanishi et al to earlier observations in both animals and humans.

It is widely appreciated that inhibition of prostaglandin biosynthesis with nonsteroidal anti-inflammatory drugs causes disparate effects on arterial blood pressure in hypertensive patients. Surprisingly, despite years of clinical experience with nonsteroidal anti-inflammatory drugs, no precise model has emerged that predicts how nonsteroidal anti-inflammatory drugs will affect the arterial blood pressure of a given hypertensive patient. Most likely, variability in the blood pressure response to nonsteroidal anti-inflammatory drugs has discouraged rather than encouraged investigators from determining whether the etiology of the hypertension contributes to the observed variability. In view of this absence of information, the article by Imanishi et al is particularly significant in that it represents the first head-to-head comparison of the effects of a nonsteroidal anti-inflammatory drug on arterial blood pressure in a group of well-defined renovascular hypertensive patients versus a group of essential hypertensive patients.

The study by Imanishi and coworkers is also significant from another perspective. In the early and mid 1970s, several independent research groups published studies linking prostaglandins to the regulation of renin release. In 1979, Oates and coworkers proposed that physiological activation of renin release involves two intercellular mediators. These authors suggested that stimulation of renin release via a change in either intrarenal vascular pressure or NaCl delivery to the macula densa is mediated by prostaglandins, which act on juxtaglomerular prostaglandin receptors. However, renin release in response to stimulation of renal sympathetic nerves is mediated by norepinephrine, which acts on juxtaglomerular β-adrenergic receptors. These “prostaglandin” and “adrenergic” pathways to renin release were envisioned by Oates and

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*In this editorial, the term “prostaglandin” is meant to denote any eicosanoid derived from prostaglandin endoperoxides even though some of these eicosanoids do not possess the prostanoic acid structure.
coworkers as distinct and parallel. This hypothesis has received both a healthy dose of responsible criticism, as well as a substantial degree of experimental support (infra vide). The study by Imanishi et al provides the first clear corroboration of the "prostaglandin" hypothesis in humans.

A considerable amount of evidence links prostaglandins to the control of renin release. First, in the absence of activation of intrarenal β-adrenergic receptors, inhibition of prostaglandin biosynthesis with nonsteroidal anti-inflammatory drugs attenuates the renin release response to a reduction in renal perfusion pressure or a decrease in NaCl delivery to the macula densa. On the other hand, the renin release response to stimulation of intrarenal β-adrenergic receptors in the absence of changes in perfusion pressure or NaCl delivery to the macula densa is not reduced by nonsteroidal anti-inflammatory drugs. When all three mechanisms of renin release are activated simultaneously, nonsteroidal anti-inflammatory drugs usually, but not always, decrease renin release. Second, prostaglandin I₂, 6-keto-prostaglandin E₁ (an active metabolite of prostaglandin I₂), and prostaglandin E₂ are potent renin secretagogues both in vitro and in vivo. Third, the metabolite precursor of prostaglandins, arachidonic acid, also stimulates renin release both in vitro and in vivo. Fourth, the renin release response to arachidonic acid is blocked by nonsteroidal anti-inflammatory drugs. Fifth, the renal cortex synthesizes prostaglandins I₂, 6-keto-prostaglandin E₁, and prostaglandin E₂. Finally, in dogs a reduction in renal perfusion pressure causes a net increase in the renal secretion rate of 6-keto-prostaglandin F₁α, an inactive metabolite of prostaglandin I₂.

Taken together, the evidence indicates that prostaglandins, at least in part, mediate in renin release response to activation of the intrarenal baroreceptor and macula densa pathways. Which prostanoi is the major player in mediating renin release is unresolved; however, it is worth mentioning that prostaglandin I₂ and 6-keto-prostaglandin E₁ are more potent renin secretagogues than prostaglandin E₂, and selective blockade of prostacyclin synthase in vitro attenuates the renin release response to arachidonic acid while enhancing the biosynthesis of prostaglandin E₂. Thus, prostaglandin I₂ or its active metabolite may be somewhat more important than prostaglandin E₂ with respect to the control of renin release.

Inasmuch as activation of the renin-angiotensin system can cause hypertension, renal cortical prostaglandin production may be associated with an increase in arterial blood pressure. In support of this hypothesis, intrarenal infusions of prostaglandin E₂ for several days in dogs cause hypertension, and the increase in arterial blood pressure induced by intrarenal infusion of prostaglandin E₂ has an almost perfect linear correlation with the increase in plasma renin activity induced by prostaglandin E₂.

Stimulation of renin release, however, is not the only conceivable mechanism by which prostaglandins can increase blood pressure. One prostaglandin, thromboxane A₂, is a potent vasoconstrictor, reduces renal function (via constriction of the renal vasculature), and in some circumstances may facilitate the exocytosis of norepinephrine from noradrenergic nerve terminals. Interestingly, selective blockade of thromboxane A₂ biosynthesis attenuates the development of hypertension in spontaneously hypertensive, mineralocorticoid-salt hypertensive, and renoprival hypertensive rats, which suggests that thromboxane A₂ may participate in these types of high blood pressure. Finally, prostaglandins of the E series can increase blood pressure via a central nervous system mechanism when infused into the cerebral ventricles.

Although prostaglandins have the potential to increase arterial blood pressure by several mechanisms, they also can exert antihypertensive effects that could either outweigh or counterbalance their hypertensive actions. Prostaglandin E₂ and prostaglandin I₂ are potent vasodilators in most vascular beds and can attenuate vascular responses to a variety of vasoconstrictors, including norepinephrine and angiotensin II. Also, both of these prostaglandins, at least in vitro, inhibit the exocytosis of norepinephrine. With respect to vascular effects, prostaglandin I₂ is more efficacious than prostaglandin E₂, but the opposite is true with respect to prejunctional effects. Last, but by no means least, both prostaglandin E₂ and prostaglandin I₂ increase renal excretory function by increasing renal blood flow and by inhibiting the reabsorption of sodium at multiple sites along the nephron. The fact that most patients experience some degree of salt and water retention while taking nonsteroidal anti-inflammatory drugs demonstrates the physiological significance of endogenous renal prostaglandins in this regard.

What, then, is the overall effect of nonsteroidal anti-inflammatory drugs on arterial blood pressure in hypertensive patients? On the one hand, prostaglandins increase renin release, exert centralpressor effects, and thromboxane A₂ is a potent vasoconstrictor. On the other hand, prostaglandin E₂ and prostaglandin I₂ are vasodilators, attenuate vascular responsiveness, inhibit noradrenergic neurotransmission, and increase sodium excretion. Matters are further complicated by the fact that blockade of cyclooxygenase may increase the flux of arachidonic acid down the lipoxygenase or cytochrome P₄₅₀ pathways to produce non-prostaglandin eicosanoids, such as leukotrienes and epoxide derivatives of arachidonic acid, that affect the cardiovascular system. Additional complexities arise from the likelihood that different antihypertensive drugs may accentuate or attenuate the relative importance of various prostaglandins. Obviously, the answer to the posed question is that it depends on a number of factors, not the least of which would be the etiology of the hypertension. The challenge is
to sort out hypertensive individuals into categories that are predictive with respect to the overall effects of nonsteroidal anti-inflammatory drugs on arterial blood pressure.

The degree of activation of the renin-angiotensin system is a major determinant of the level of arterial blood pressure. Inasmuch as nonsteroidal anti-inflammatory drugs decrease renin release, it seems logical to hypothesize that nonsteroidal anti-inflammatory drugs may reduce blood pressure in patients with high renin hypertension. However, as a consequence of the fragile balance between the hypertensive and antihypertensive effects of endogenous prostaglandins, nonsteroidal anti-inflammatory drugs should exert variable and generally unpredictable effects on blood pressure in patients with normal renin or low renin hypertension. This hypothesis received anecdotal support in a study by Frolich and coworkers. In this study, administration of indomethacin did not alter the average blood pressure in a small group of patients; however, the effects of indomethacin on blood pressure were variable, with some patients experiencing an increase in blood pressure, others a decrease in blood pressure, and still others no discernable change. Interestingly, one patient with renovascular hypertension and an elevated plasma renin activity experienced a reduction in blood pressure and plasma renin activity during administration of indomethacin. These changes were readily reversible when the indomethacin was discontinued. Similarly, deJong et al noted an antihypertensive effect of indomethacin in two siblings with renin-dependent hypertension, hyperaldosteronism, and hypokalemia.

The hypothesis that nonsteroidal anti-inflammatory drugs can lower blood pressure in renin-dependent hypertension was tested in a controlled study by Jackson et al in rats with aortic ligation between the renal arteries. This model of hypertension is characterized by an extremely high level of plasma renin activity caused by severe ischemia of the left kidney. Interestingly, indomethacin lowered plasma renin activity and arterial blood pressure in rats with aortic ligation, and the decreases in these two parameters were correlated. This study established that, in hypertension characterized by inordinately high levels of renin, nonsteroidal anti-inflammatory drugs can lower blood pressure by reducing renin release.

Investigations into the effects of nonsteroidal anti-inflammatory drugs on arterial blood pressure in alternative animal models of experimental hypertension have yielded conflicting results. Nonsteroidal anti-inflammatory drugs have been reported to either attenuate or accentuate some forms of experimental renovascular hypertension. In most of these studies, the extent to which the hypertension was renin dependent was ill defined. The effects of nonsteroidal anti-inflammatory drugs on arterial blood pressure in spontaneously hypertensive rats, a normal renin type of experimental hypertension, is variable (i.e., some studies report no effect of nonsteroidal anti-inflammatory drugs and others show a worsening of hypertension in spontaneously hypertensive rats).

In the present study, in patients with essential hypertension, aspirin had a variable effect on blood pressure; some patients experienced essentially no change and others demonstrated a clinically significant increase in blood pressure. This contrasted with the consistent antihypertensive effect of aspirin in patients with renin-dependent, renovascular hypertension. Thus, the present study is consistent with previous anecdotal reports of nonsteroidal anti-inflammatory drugs lowering blood pressure in human renin-dependent hypertension and extrapolates findings in a previous animal study to humans. Also, the variable effect of aspirin on blood pressure in patients with essential hypertension is consistent with the results of many other studies that illustrate the delicate balance between hypertensive and antihypertensive actions of endogenous prostaglandins.

References


KEY WORDS: renin, prostaglandins, anti-inflammatory drugs, aspirin, indomethacin, renovascular hypertension, essential hypertension

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