Renal \( \alpha_2 \)-Adrenergic Receptors and Hypertension

In 1964 \( \alpha_2 \)-adrenergic receptors were first described pharmacologically using the in vitro melanocyte granule dispersion technique in \textit{Rana pippens}. The goal of these studies was to assess the intrinsic activity on \( \alpha_2 \)-adrenergic receptors of methyldopa’s neurotransmitter metabolites and other catecholamines. Publication of this description was delayed for 13 years, until the evidence for a receptor agonist mechanism of centrally acting antihypertensive drugs became apparent. These observations provided the basis for a functional classification of \( \alpha_2 \)-adrenergic and \( \alpha_3 \)-adrenergic receptors that was analogous to Ahlquist’s original classification of \( \alpha \)-adrenergic and \( \beta \)-adrenergic receptors.

The existence of adrenergic receptors in organs and tissues usually has been demonstrated by a physiological or biochemical response. However, renal \( \alpha_2 \)-adrenergic receptors were first demonstrated by using radioligand binding techniques. Even with the demonstration of increased renal \( \alpha_2 \)-adrenergic receptor density in genetically hypertensive rats several years later, there was essentially no characterization of either physiological or biochemical effects of renal \( \alpha_2 \)-adrenergic receptor activation.

The lack of clearly defined physiological effects of renal \( \alpha_2 \)-adrenergic receptor activation has limited investigation on the pathophysiological role of altered \( \alpha_2 \)-adrenergic receptor regulation in genetic rat hypertension. Some investigators, including DiBona and Sawin, whose article is published in this issue of \textit{Hypertension}, have taken the approach of infusing \( \alpha_2 \)-adrenergic receptor selective blocking agent into the kidney of genetically hypertensive rats. Because they did not see any effects of \( \alpha_2 \)-adrenergic receptor blockade on vascular resistance or sodium retention, they concluded that altered \( \alpha_2 \)-adrenergic receptor regulation could not contribute to the pathogenesis of genetic hypertension. These observations are of considerable interest and have been made by investigators who have already made important contributions to our understanding of renal adrenergic receptor control mechanisms. Nevertheless, given the complexity of these mechanisms, these findings warrant careful consideration.

Several years ago we started on the same approach as that of DiBona and Sawin by infusing yohimbine into the renal artery during activation of renal sympathetic nerves in the anesthetized dog. Our results were also negative, so we elected to develop and characterize biochemical and physiological test systems that would allow qualitative and partially quantitative expression of \( \alpha_2 \)-adrenergic receptor effects in the kidney.

\( \alpha_2 \)-Adrenergic receptors mediate, in many tissues, inhibition of adenylate cyclase and thus reduce cyclic adenosine 3',5'-monophosphate (cAMP) formation and effects induced by this nucleotide. A number of hormones can selectively activate adenylate cyclase in different segments of the nephron. These hormones include parathyroid hormone, thyrocalcitonin, histamine, vasopressin, isoproterenol, and prostaglandins. \( \alpha_2 \)-Adrenergic receptor activation can inhibit cAMP accumulation induced by these agents in most, but not all, of the microdissected tubule fragments of the rat. For example, when given in the presence of prazosin and propranolol to block \( \alpha_2 \)-adrenergic and \( \beta \)-adrenergic receptors, respectively, epinephrine inhibits cAMP accumulation induced in the glomerulus by parathyroid hormone but not that due to prostaglandin stimulation. Thus, there appears to be hormone-specific compartmentalization of cAMP regulation-inhibition in various segments of the nephron. Additionally, epinephrine did not reverse cAMP accumulation induced by any hormone in the thick ascending limb. At the biochemical level, therefore, the effects of \( \alpha_2 \)-adrenergic receptor activation are both hormone-selective and anatomical site-specific.
Vasopressin is a particularly potent stimulant to cAMP accumulation in the collecting duct, and this effect is inhibited,\textsuperscript{10} along with salt and water conductance, by epinephrine through \( \alpha_2 \)-adrenergic receptors. Interestingly, this vasopressin effect is markedly increased specifically in the cortical (but not medullary) collecting tubule of the deoxycorticosterone acetate (DOCA)-sodium\textsuperscript{14} rat. This increased response is specific for vasopressin and, by leading to excess sodium retention, may be a contributing factor to hypertension in this mineralocorticoid model.\textsuperscript{15, 16} Studies are currently underway to determine if there are analogous alterations in cAMP generation in genetically hypertensive rats.

\( \alpha_2 \)-Adrenergic receptor activation is effective in reducing the augmented cAMP accumulation induced by vasopressin in the cortical collecting tubule of both DOCA-Na and control rats (personal observations, 1986). Thus, there is no obvious alteration of the \( \alpha_2 \)-adrenergic receptor in this model, in terms of either receptor density\textsuperscript{9} or receptor-mediated alterations in cAMP response.

Philosophically, the issue here is that absence of evidence is not evidence of absence. The facts are that 1) \( \alpha_2 \)-adrenergic receptors are the numerically dominant adrenergic receptor in the kidney, 2) their density is increased in the kidneys of genetically hypertensive rats, and 3) their density is augmented further with high salt diets even before the salt increases blood pressure. This increased density occurs in Dahl salt-sensitive and in spontaneously hypertensive rats (SHR). It even occurs in Wistar-Kyoto rats, which become hypertensive with high salt diets, but not in Dahl salt-resistant rats, which fail to become hypertensive with high salt diets.

In light of this evidence and given the predominant role of dietary sodium and genetics in human essential hypertension, it may be premature and unwise to discard the notion of a pathogenetic role for renal \( \alpha_2 \)-adrenergic receptors in genetic hypertension. For example, in contrast to the results of DiBona and Sawin,\textsuperscript{8} de Leeuw et al.\textsuperscript{17} recently observed a marked increase in renal blood flow and renin release with the infusion of yohimbine into the renal artery of conscious patients with essential hypertension. In these preliminary studies, yohimbine was much more effective than prazosin, suggesting a predominant role for the \( \alpha_2 \)-adrenergic receptor in the control of renal vascular resistance in patients with essential hypertension.

The isolated rat kidney perfused with an appropriate oncotic substance and amino acids and efficiently oxygenated by use of a pediatric dialysis coil has provided a valuable model for physiological study of renal \( \alpha_2 \)-adrenergic receptor effects in a controlled environment.\textsuperscript{18, 19} \( \alpha_2 \)-Adrenergic receptor activation in this model reverses the natriuresis, polyuria, and increased urinary cAMP excretion resulting from arachidonic acid or furosemide infusion.\textsuperscript{19, 20} Blockade of adenylate cyclase (activated as already described) using an adenosine p'-site agonist produces effects identical to \( \alpha_2 \)-adrenergic receptor activation. The presence of either furosemide or arachidonic acid (or similar activator of the function-specific adenylate cyclase) is essential to demonstrate these effects of \( \alpha_2 \)-adrenergic receptor or p'-site activation. Thus, in the absence of adenylate cyclase activation, epinephrine has no sodium-retaining effects in this model system, which includes \( \alpha_2 \)-adrenergic and \( \beta \)-adrenergic receptor blockade.

Vasopressin, like furosemide and arachidonic acid, produces adenylate cyclase activation. Unlike the latter agents, however, vasopressin promotes salt and water retention. Moreover, \( \alpha_2 \)-adrenergic receptor activation reverses this effect of vasopressin, resulting in increased salt and water excretion.\textsuperscript{21} Thus, the effects of \( \alpha_2 \)-adrenergic receptor activation appear to be determined qualitatively and quantitatively by the particular renal hormonal mechanism that is predominating at any given time. Is it really surprising, then, that DiBona and Sawin\textsuperscript{8} failed to demonstrate remarkable changes in salt and water excretion with \( \alpha_2 \)-adrenergic receptor blockers infused into the renal artery of anesthetized animals? Or could the failure to alter salt and water excretion merely be due to a canceling out of only one inhibitory hormonal pathway? Alternatively, are these negative findings the result of anesthesia-induced artifacts masking the effect of \( \alpha_2 \)-adrenergic receptor blocking agents? Or is there a modest tonal role of increased renal \( \alpha_2 \)-adrenergic receptors that affects only a small percentage of total sodium excretion?

Afferent arteriolar hypertrophy increases with the duration and severity of hypertension. It encroaches on the blood vessel lumen and decreases glomerular blood flow. This decreased glomerular blood flow relative to that of normotensive rats at any given perfusion pressure markedly enhances passive reabsorption of sodium in the proximal tubule. In fact, the sodium excretion in isolated perfused kidneys of Dahl salt-sensitive rats at normal perfusion pressures is so low that there is insufficient ureteral sodium to...
demonstrate sympathetic nerve-stimulated sodium retention. Are such rats with passive absorption of sodium at 2 to 4 months of age appropriate models for the type of study conducted by DiBona and Sawin? Is the absence of a natriuretic effect of α₂-adrenergic receptor blockers in these animals meaningful in excluding an α₂-adrenergic receptor contribution to sodium retention before the hypertrophy occurs? According to this reasoning, studies of α₂-adrenergic receptor blocking agents on renal salt and water retention may be more revealing if performed in the prehypertensive phase in very young rats.

The complexity of the prejunctional, postjunctional, and extrajunctional locations of α₁-adrenergic and α₂-adrenergic receptors also could explain the absence of renal functional effects of α₂-adrenergic receptor blockade in the study by DiBona and Sawin, even though α₂-adrenergic receptors may be maintaining a substantive sodium-retaining or vascular effect (or both). Normally, the α₁-adrenergic receptors are postjunctional and the α₂-adrenergic receptors are extrajunctional and prejunctional. Prejunctional α₁-adrenergic receptors function to inhibit norepinephrine release. In vascular tissues of SHR, α₂-adrenergic receptors are also postjunctional and mediate part of the vasoconstriction induced by norepinephrine release from sympathetic nerves. α₂-Adrenergic receptor blockade simultaneously enhances norepinephrine release, which induces vasoconstriction, and salt retention through α₂-adrenergic receptor activation. In the absence of postjunctional α₂-adrenergic receptors, yohimbine shifts the dose-response curve of nerve-stimulated vasoconstriction to the left. In the presence of postjunctional α₂-adrenergic receptors, as may have been present in the SHR studied by DiBona and Sawin, the two opposing effects may nullify each other and little shift in the dose response may occur, as noted in their results. Thus, absence of change in salt excretion or vasoconstriction (or both) with α₂-adrenergic receptor blockade could be interpreted as evidence supportive of postjunctional α₂-adrenergic receptors in renal tubules or renal blood vessels (or both) of SHR. Most importantly, a negative result is inconclusive evidence concerning pathogenetic roles of altered α₂-adrenergic receptor regulation in genetically hypertensive rats.

We have recently manipulated the number and functional location of renal α₂-adrenergic receptors. A prazosin-induced, 3-day blockade of α₁-adrenergic receptors caused renal α₂-adrenergic receptor density to increase to the same level as occurs in genetically hypertensive rats, and the α₂-adrenergic receptors moved into or were synthesized de novo at postjunctional sites that govern sympathetically mediated sodium retention at the renal tubular level. For the reasons described in the previous paragraph related to increased norepinephrine release during α₂-adrenergic receptor blockade, it was necessary to have α₁-adrenergic receptors blocked with prazosin as a reference point in sodium excretion before the administration of the α₂-adrenergic receptor blocker. Only with the use of this sequence of α₁-adrenergic receptor blocker administration were we able to demonstrate α₂-adrenergic receptors postjunctionally as mediators of sympathetically induced sodium retention in the chronically α₂-adrenergic receptor-blocked rat. The chances of success for DiBona and Sawin in demonstrating α₂-adrenergic receptor mediation of sodium retention in SHR may have been enhanced by a similar approach. Because of the similarities in α₂-adrenergic receptors in genetically hypertensive and in α₁-adrenergic receptor-blocked animals, we would not be surprised to see α₂-adrenergic receptor mediation of hypertensinogenic effects in genetically hypertensive rats.

Clearly, the observations of DiBona and Sawin reported in this issue of Hypertension have resulted from carefully designed and executed studies. Therefore, the thrust of this editorial is not to raise questions regarding the validity of their findings but merely to provide insights into the complexities involved in evaluating renal adrenergic receptor pathways. Such considerations suggest that, instead of closing the door on the issue of renal α₂-adrenergic receptors in hypertension, the findings of DiBona and Sawin provide an impetus for further studies.

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