Serotonin and Dopamine in Essential Hypertension

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Serotonin is a biogenic amine that can be generated from its amino acid substrate, 5-hydroxytryptophan (5-HTP), by the enzyme L-aromatic amino acid decarboxylase (LAAD). L-aromatic amino acid decarboxylase has particularly high activity in the kidney, and is the same enzyme that converts L-3,4-dihydroxyphenylalanine (L-dopa) to dopamine. We have shown that infusion of 5-HTP directly into the isolated, non-blood-perfused rat kidney is associated with increases in perfusion pressure and serotonin formation, and have found that both of these effects were blocked by the inhibition of LAAD with carbidopa.[1] However, carbidopa did not block the constrictor response to intrarenally injected serotonin. We also found that 5-HTP was readily converted to serotonin by rat kidneys *in vivo*, in that the intravenous infusion of 5-HTP markedly increased the urinary excretion of serotonin without any change in plasma levels of serotonin.[2] Carbidopa markedly reduced the effect of 5-HTP on urinary serotonin excretion and reversed the attendant alterations in renal hemodynamics and salt and water excretion. These findings, together with our intrarenal infusion studies, are consistent with the intrarenal formation of serotonin by LAAD.

In this issue of the *American Journal of Hypertension*, Hirose and coworkers[3] report on the plasma and urinary levels of serotonin and dopamine in hypertensive patients with and without microalbuminuria. They found that urinary serotonin excretion and the ratio of serotonin to dopamine in the urine were significantly higher in patients with essential hypertension and microalbuminuria than in patients with essential hypertension but without microalbuminuria. However, the plasma levels of biogenic amines and the urinary excretion of dopamine, whose intrarenal synthesis is also catalyzed by LAAD, did not differ in the groups of patients with essential hypertension accompanied or unaccompanied by microalbuminuria. These findings provide new clinical evidence in support of serotonin as a mediator of hypertensive renal injury. The increase in urinary excretion of serotonin without concomitant increases in plasma serotonin levels would be consistent with production of serotonin by the kidney. However, further research will be needed to define the mechanism responsible for the altered production of serotonin in hypertension with microalbuminuria, and to determine whether this reflects altered synthesis or degradation of serotonin, or perhaps a platelet effect within the kidney.

An important consideration relevant to the study of Hirose and coworkers and beyond the levels of biogenic amines is the abundance, distribution, and responsiveness of renal receptors for serotonin and dopamine. Dopamine is a renal vasodilator and produces natriuresis. In studies done with spontaneously hypertensive rats (SHR), we examined whether the renal formation of dopamine was diminished. We found that SHR produce as much or more dopamine as normotensive Wistar Kyoto rats. Subsequent studies by Jose and coworkers[4] demonstrated that SHR have a defect in the coupling of the dopamine receptor to the G-protein/effector enzyme complex. Thus, although dopamine levels were not reduced in SHR, these rats had a diminished ability to respond to dopamine. It is now known that there are at least five subtypes of dopamine receptor (D_1 to D_5), and it has been reported that the knockout of each of these receptor subtypes in mice is linked to an increase in blood pressure (BP).[5] Likewise, serotonin (5-HT) has multiple subtypes of receptor ($5\text{-}HT_1$ to $5\text{-}HT_7$),[6] and in future studies it will be important to learn whether the location, abundance, and responsiveness of these receptor subtypes is altered in hypertensive states with and without pathology, and the way in which selective serotonin receptor antagonists and agonists effect changes in BP and in target organ damage.

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