Interaction of prostaglandins with the renin-angiotensin system

Harald M. Stauss

Department of Exercise Science, The University of Iowa, Iowa City, Iowa 52242

IN ADDITION TO ITS PARAMOUNT ROLE IN THE REGULATION OF fluid and electrolyte homeostasis, the renin-angiotensin system (RAS) is also involved in renal development (1, 17). In adulthood, renal perfusion pressure, sodium chloride concentration at the site of the macula densa, and β-adrenergic receptor stimulation control release of renin. The mechanisms involved in prenatal renin synthesis and secretion, however, are less well understood. An article in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology by Mertz and colleagues (14) provides important new data regarding the interaction of prostaglandins and the RAS during fetal development in lambs.

Renal effects of prostaglandins were described more than 20 years ago (3, 7, 16). However, the mechanisms by which prostaglandins modulate renal function are still not completely understood. Recently, Cheng et al. (4) reported that the potentiating effects of prostaglandins on angiotensin-converting enzyme inhibitor-induced renin synthesis and release are mediated by the inducible cyclooxygenase isoform (COX-2), rather than the constitutively expressed cyclooxygenase (COX-1). This conclusion is based on experiments in adult mice with genetic deletion of the COX-1 gene. Captopril treatment increased plasma renin activity, renal renin mRNA expression, and renal renin concentration equally in wild-type and homozygous COX-1-deficient mice. The selective COX-2 inhibitor SC-58236 abolished these effects of the angiotensin-converting enzyme inhibitor. However, in a different study, stimulation of renocortical renin expression by the ANG II AT1 receptor antagonist candesartan could not be blocked by the COX-2 inhibitor celecoxib (12). Inasmuch as COX-2 mRNA and renin mRNA levels were similarly increased after AT1 receptor blockade, the authors concluded that ANG II is not required to stimulate COX-2 expression and that COX-2 activity is not required to stimulate renin expression. However, renocortical expression of renin and COX-2 appears to be highly coordinated. This is further substantiated by studies demonstrating that various stimuli for renin expression, such as ANG I-converting enzyme inhibition (18), ANG II AT1 receptor blockade (12, 18), salt restriction (8), and renal artery clipping (9), are all associated with increased COX-2 expression. Thus, in addition to a role of prostaglandins for the stimulation of renin synthesis and release (3, 7, 16), there is also a role of renin for stimulation of prostaglandin synthesis via induction of COX-2. In addition to COX-2-derived prostaglandins, COX-1-derived prostaglandins also seem to be important for the modulation of renin synthesis and release in response to other stimuli. The increase in plasma renin activity and renocortical renin mRNA levels in response to a low-salt diet could be blunted with a COX-1 selective antagonist but not with the COX-2 selective inhibitor rofecoxib (11). Thus, depending on the physiological stimulus, both COX-1- and COX-2-derived prostaglandins seem to modulate renin synthesis and release.

In the current study by Mertz et al. (14), the importance of COX-2-derived prostaglandins for fetal renin secretion and mRNA expression in response to β-adrenergic receptor stimulation was investigated. Chronic implantations of arterial and venous catheters in fetal lambs made it possible to apply β-adrenergic receptor agonists and specific COX-2 inhibitors intravenously and to collect blood for determination of plasma renin concentration. The increase in plasma renin concentration after β-adrenergic receptor stimulation was blunted by pretreatment with the COX-2 inhibitor NS-398. The authors further investigated possible mechanisms by which COX-2-derived prostaglandins may facilitate β-adrenergic receptor-induced renin secretion. The β-adrenergic receptors mediate their intracellular effects via the second messenger cAMP, which is synthesized by the enzyme adenylate cyclase and inactivated via hydrolysis by phosphodiesterases. Renin-containing renal cortical cells isolated from fetal lambs increased their renin mRNA expression in response to β-adrenergic receptor stimulation with isoproterenol, activation of adenylate cyclase with forskolin, and in response to inhibition of phosphodiesterases with isobutyl methylxanthine. Only the response to forskolin was preserved in cells isolated from fetal lambs pretreated with the COX-2 inhibitor. In addition to providing evidence to support an essential role for COX-2-derived prostaglandins in the β-adrenergic stimulation of the juxtaplomerular cells, these data suggest a broader role for COX-2-derived prostaglandins in the local regulation of the RAS. A tonic level of cAMP may be present within these cells that is dependent on COX-2-derived prostaglandins. Furthermore, COX-2-derived prostaglandins may be a significant component of any stimulus of the RAS that is mediated by a mechanism involving cAMP formation. Indeed, the interaction of prostaglandins with the cAMP second messenger system appears to be a more
general principle. In renal sensory nerves, prostaglandin $E_2$ causes release of substance P. This effect of prostaglandin $E_2$ is abolished by inhibitors of adenylyl cyclase or protein kinase A (13). Other examples are the inhibitory effect of prostacyclin (PGI$_2$) on platelet aggregation (10) and on activation of coagulation factor X (5). Both effects of PGI$_2$ are mediated by a prostacyclin-receptor antagonist icatibant in conscious lambs. Nature 266: 64–66, 1977.


REFERENCES


