Chapter 9

Intrarenal Renin-Angiotensin System

The actions of angiotensin II in the kidney are often described in terms of the intrarenal RAS; a recent symposium carried the title "Physiological Role of the Intrarenal Renin-Angiotensin System" (NAVAR 1986). Obviously, the intention of using this term is to suggest that the intrarenal effects of angiotensin II are not, or not exclusively, mediated by systemically generated angiotensin II reaching the kidney via the circulation but rather by intrarenally formed angiotensin II. However, beyond the general agreement that local angiotensin II formation in the kidney occurs, there is considerable uncertainty and disagreement on the understanding of an intrarenal RAS. Therefore, we will first discuss briefly the characteristics of locally functioning RASs in general, consider the potential for the intrarenal formation of angiotensin II, then proceed to describe the intrarenal actions of exogenous and endogenous angiotensin II, and finally return to the consideration of whether an intrarenal RAS exists.

9.1 Local Renin-Angiotensin Systems

Basically, the concept of an intrarenal RAS has two major sources, one relating to the kidney itself, the other seeking parallelisms to local RASs in other organs. With regard to the kidney, the unique anatomical and functional arrangement of the JGA and adjacent structures has intrigued many investigators to speculate that renin secretion from epithelioid cells of the afferent arteriole serves the dual purpose of supplying the systemic circulation with renin and of providing the renal interstitium with the key enzyme for the extravascular generation of angiotensin II, which then controls renal functions in a "short-circuit" fashion and without systemic dilution. These intrarenal functions, thought to depend on or to be modulated by interstitially generated angiotensin II, include TGF and other vasoconstrictor effects of angiotensin II necessary to maintain GFR, as well as tubular effects. This concept was strengthened by the demonstration of renin, angiotensin I, and angiotensin II in renal hilar lymph, which drains the renal cortical interstitium, and by the recent discovery of angiotensin II in granulated cells of a few species (CELIO and INAGAMI 1981; TAUGNER and HACKENTHAL 1981). These aspects will be discussed in more detail below.

A second major line of argumentation in favor of an intrarenal RAS is indirect, that is, the extrapolation from a local RAS in other organs. For several decades, the RAS has been described as a systemic, hormonal system, in which the effector peptide angiotensin II is generated within the circulation and reaches various target organs, such as the adrenal cortex, brain, vascular smooth muscle, liver or intestine via the bloodstream, interacts with specific receptors, and induces changes collectively aimed at maintaining blood pressure and salt and water homeostasis. More recently, the local occurrence of the components of the RAS within several organs has been described. These organs seem to be capable of generating angiotensin II without requiring all, or sometimes even any, of the components of the systemic circulating RAS.

The best studied local RAS so far is that of the brain. Facilitated by the very limited diffusion or uptake of macromolecules from the blood into the interstitium of the brain, the easy experimental access to cerebrospinal fluid, as well as the advent of new immunocytochemical and molecular biological techniques, it has now been established that the brain not only contains all the components necessary to produce angiotensin II, but also that angiotensin II is indeed produced locally and influences certain functions of the brain independently of the systemic RAS (see reviews by GANONG 1984; GANTEN et al. 1984; REID 1984; GANTEN et al. 1987).

The RAS of the brain not only operates largely independently of the systemic RAS, it also appears...
to operate differently from the latter. In contrast to the intravasal or extracellular generation of angiotensin II in the systemic RAS, angiotensin II in the brain has the characteristics of a neuromodulator, i.e., it is synthesized intraneuronally, transported by axonal transport, and released upon neuronal stimulation to modulate the functions of other neurons. In accordance with the presumed intracellular generation of angiotensin II, renin does not seem to be secreted from neuronal tissue, and does not enter the cerebrospinal fluid. The intracellular precursor for angiotensin II has not yet been identified. Although the cerebrospinal fluid contains angiotensinogen, and angiotensinogen gene expression has been demonstrated in several areas of the brain (Healy and PRINTZ 1984; Campbell and HA-BENER 1986; OhKUBO et al. 1986; DZAU et al. 1987), neither uptake into nor intracellular synthesis of angiotensinogen in angiotensin II-producing neurons has been demonstrated. Altogether, the brain RAS appears to differ profoundly from the systemic RAS, even though many facets of this system are still unknown.

Many other local RASs have been postulated to exist, mainly because the local occurrence and/or synthesis of renin has been demonstrated by immunocytochemistry or by the isolation of renin mRNA. However, in none of these organs has the local synthesis of all components of the RAS been unequivocally demonstrated.

One of the reasons for this unclear situation is the fact that the separation of locally formed renin and/or angiotensinogen from plasma-derived components of the RAS is difficult to accomplish, if not impossible. For example, an arterial wall RAS has been postulated to be responsible for maintaining vascular tone independent of short-term changes of plasma renin activity (SwALES et al. 1983; Oliver and SCIACCA 1984; DZAU 1986, 1987). There is indeed evidence for the synthesis of renin in vascular smooth muscle and endothelial cells leading to the local production of angiotensin II (RE et al. 1981; DahlHEIM et al. 1983; Lilly et al. 1985). However, the major, if not exclusive, source of interstitial angiotensinogen in the vascular wall seems to be the circulation, and also a major part of interstitial renin is of systemic origin (LOUDON et al. 1983). Furthermore, in contrast to the situation in the brain, angiotensin II appears to be generated mainly extracellularly, although intracellular synthesis and secretion may contribute to total interstitial angioten-

9.2 Intrarenal Formation of Angiotensin II

With regard to the existence and functions of an intrarenal RAS, several sources and/or topographical pathways for the generation and the access of angiotensin II to vascular and tubular sites can be envisioned. (a) Angiotensin II is generated in the systemic circulation, carried into the kidney, and reaches its targets directly from the vascular lumen or via the peritubular capillaries. This includes angiotensin II that has been generated from angiotensin I within the renal circulation by plasma-converting enzyme or by converting enzyme of endothelial cells. Alternatively, angiotensin II may be formed extravascularly from systemic angiotensin I that has left the circulation via the peritubular capillaries and/or at other sites. (b) Angiotensin II is thought to be generated in the interstitium of the kidney by...