0031-6997/80/3103-0169$02.00/0
PHARMACOLOGICAL REVIEWS

Vol. 31, No. 3
Printed in U.S.A.

Catecholamines and Sodium Transport in the Kidney

JIN K. KIM, STUART L. LINAS, AND ROBERT W. SCHRIER

Department of Medicine, University of Colorado Health Sciences Center, Denver, Colorado

I. Introduction

AN INFLUENCE of the adrenergic nervous system on renal sodium reabsorption and excretion has been suggested and disputed for decades. Ever since Claude Bernard observed an increased urine flow after section of the splanchnic nerve in the anesthetized animal (19), there have been numerous studies that have attempted to elucidate the role of the adrenergic nervous system in renal sodium excretion. The nature of this controversy has been summarized in several reviews (33, 37, 54, 109, 111). In understanding the nature of the influence of any factor on renal sodium excretion, it is important to separate the specific effects of the factor on renal tubular sodium reabsorption and the indirect effects mediated by changes in systemic and renal hemodynamics. In this manuscript, we will review the evidence that has been used to support the hypothesis that the adrenergic nervous system directly influences renal tubular sodium transport.

II. Adrenergic Innervation of the Normal Mammalian Kidney

A. Morphological Evidence

The presence of adrenergic nerve endings in the kidney has been suggested repeatedly (9, 44, 46,72, 73, 82, 83, 87, 90, 94, 95, 113, 131) since Bradford demonstrated the direct innervation of renal blood vessels (23). In early studies utilizing light microscopy, adrenergic innervation of renal tubules was not clearly confirmed because of the nonspecific nature of the staining techniques for connective tissues. Even after development of electron microscopy and fluorescence histochemical techniques for catecholamines by Falck et al.(42), the significance of adrenergic innervation of the kidney was not completely clarified. However, the visualization of nerve terminals in direct contact with basement membranes of proximal and distal tubules of the monkey (91), rat (10), and dog (36) kidney leaves little doubt that the mammalian nephron is innervated by the adrenergic nervous system. Muller and Barajas (91) have shown that bundles of terminal varicose axons travel between the blood vessels and the tubules of the renal cortex of the monkey. Nerve endings in these bundles were shown to contact the basement membranes of both proximal and distal tubules as well as smooth muscle cells of the arterioles. In another electron microscopic study of serial sections of the rat juxtaglomerular apparatus, the distribution of "axon segments" was studied quantitatively for contact with the cells of the vascular and tubular system. Nerve endings were found on the cells of the afferent arteriole, efferent arteriole, and renal tubules (10). In addition, synapses of a single axon were reported to exist in both arteriolar and tubular cells. A similar adrenergic innervation in the basement membrane of proximal tubules was reported in an electron microscopic and histochemical fluorescence study of the dog kidney (36).

B. Pharmacological and Biochemical Evidence

Evidence for the presence of renal catecholaminergic receptors including alpha-adrenergic receptors, beta-adrenergic receptors, and dopaminergic receptors has been reported in many studies (13, 29, 30, 43, 75, 81, 84, 97, 100, 135). The presence of these receptors has been

confirmed by the use of specific receptor agonists and antagonists. For example, infusion of *l*-isoprenaline into the renal artery decreased renal vascular resistance and enhanced urine flow. These effects were diminished by beta-adrenergic blockade with propranolol (43). Isoproterenol seemed to stimulate both alpha and beta receptors. In high doses, isoproterenol resulted in renal vasoconstriction, an alpha-effect that was abolished or reversed by phentolamine, an alpha receptor antagonist. Low doses of isoproterenol resulted in a renal vasodilatory response that could not be potentiated by the alpha-adrenergic antagonist, phenoxybenzamine. Propranolol was again found to diminish or abolish the vasodilatation observed after isoproterenol (75).

Dopamine also causes renal vasodilatation. The vasodilatation after dopamine seems to be mediated by a different receptor than the receptor that mediates vasodilatation secondary to beta-adrenergic stimulation with isoproterenol. Dopamine-induced renal vasodilatation cannot be prevented by the beta-adrenergic blocking agent, propranolol. On the other hand, haloperidol, a dopaminergic antagonist, diminished dopamine-induced renal vasodilatation but did not affect the vasodilatation induced by isoproterenol or bradykinin (135). This study suggested that dopamine acts on a specific receptor in the renal vascular bed. A recent study with a new dopamine receptor agonist, SK&F 38393 (2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine), showed that renal blood flow was selectively increased by this dopamine agonist and was only inhibited by the selective peripheral dopamine receptor antagonist, bulbocapnine. These results, therefore, also supported the presence of dopaminergic receptors in renal tissue (98). The specific anatomic location of these dopaminergic receptors has not yet been identified. For example, one study has shown that dopamine causes vasoconstriction rather than vasodilatation of the isolated perfused intralobar renal artery (120). It is possible, therefore, that the major renal vasodilatation of dopamine is on the smaller resistance vessels of the kidney.

There are only a few studies of the distribution of catecholamines and enzymes of catecholamine synthesis in the renal tissue (4, 60). The content of epinephrine, norepinephrine, and dopamine has been measured in various tissues of different species. The catecholamine content of renal tissue has been found to be lower than that in the brain or heart, but the amount was comparable to other organs (4, 60). Recent interest in studying the physiological consequences of the adrenergic nervous system and renal function will, no doubt, stimulate more anatomical and pharmacological investigations.

III. Physiological Investigations of the Effect of the Adrenergic Nervous System and Catecholamines on Sodium Reabsorption and Excretion

Alterations in adrenergic neural activity may influence sodium reabsorption by one of several mechanisms. Changes in adrenergic neural tone might alter systemic hemodynamics, which may, in turn, secondarily influence renal function and sodium excretion. In addition, changes in renal adrenergic neural tone may alter renal sodium excretion either indirectly through changes in renal hemodynamics or directly by influencing renal epithelial cell sodium transport. Whereas many earlier studies failed to consider all of these possibilities when attempting to elucidate the role of the adrenergic nervous system on sodium excretion, results of recent studies suggest that all of these mechanisms may be important in adrenergically mediated control of sodium excretion.

A. Renal Nerve Stimulation and Renal Denervation Studies

Although renal denervation has been known for some time to be associated with a natriuresis and diuresis in the anesthetized animal (62), the mechanism of this effect has only recently been elucidated. Studies by DiBona (36) have identified a level of direct electrical renal nerve stimulation that decreased renal sodium excretion in the absence of detectable changes in glomerular filtration rate and renal blood flow or in the distribution of renal blood flow. This effect could be blocked by either phenoxybenzamine (137) or guanethidine (114). These results suggested that alpha-adrenergic stimulation directly increases sodium reabsorption. In clearance and micropuncture studies in the rat (17) during renal nerve stimulation, an increase in sodium reabsorption occurred in the proximal convoluted tubule in the absence of changes in glomerular filtration rate or renal plasma flow (17).

When renal denervation was produced in anesthetized rats by application of phenol to the renal artery, urinary sodium excretion increased approximately five- to six-fold in the absence of changes in glomerular filtration rate or renal blood flow (15). The increase in renal sodium excretion was accompanied by a decrease in fractional and absolute fluid reabsorption in the proximal tubule. These results suggest that the diuresis and natriuresis associated with renal denervation are mediated by a direct effect of adrenergic neural tone to diminish proximal tubular sodium and water reabsorption. A similar decrease in proximal tubule fluid and sodium reabsorption after unilateral renal denervation in the volume-expanded rat provided further support to the concept that renal nerves directly affect proximal nephron function (16). There is also some evidence that renal denervation alters sodium reabsorption beyond the proximal tubule. In a micropuncture study in dogs (126), unilateral splanchnectomy was associated with a decrease in both proximal and distal tubule sodium reabsorption. In contrast, however, Bello-Reuss et al. (15) demonstrated an increase in distal tubule sodium reabsorption after renal denervation.

Although renal nerve stimulation and renal denervation studies support the concept that adrenergic neural tone alters sodium reabsorption by a direct effect on the renal epithelial cell, an indirect process involving the

renin-angiotensin system or renal prostaglandins has only recently been examined. It is known that renal nerve stimulation increases the renal release of renin (125) and prostaglandins (39, 45), and thus could be involved in the effects on tubular sodium and water reabsorption. However, studies by DiBona and colleagues (38, 136) utilizing the angiotensin antagonist, saralasin, and the cyclooxygenase inhibitor, indomethacin, have convincingly demonstrated that neither enhanced angiotensin nor prostaglandin activity are necessary to demonstrate the antinatriuretic effect of renal nerve stimulation. These studies are discussed in more detail later.

Further support for the importance of neurogenic control of sodium reabsorption has been derived from studies in which renal sympathetic nerve traffic was increased or decreased by indirect means. When renal nerves were stimulated indirectly by isolated carotid sinus perfusion, there was a significant decrease in urinary sodium excretion observed in the absence of changes in glomerular filtration rate or in renal blood flow (138). This effect could be completely prevented by pretreatment with either phenoxybenzamine or guanethidine. Conversely, when renal sympathetic nerve traffic was decreased by maneuvers such as left atrial distention or stellate ganglion stimulation, there was an increase in sodium excretion. The increase in sodium excretion was associated with a 40% decrease in renal sympathetic nerve activity (44), while glomerular filtration rate and renal blood flow remained constant (102). These studies indicate that physiological reflex alterations of renal sympathetic nerves may directly alter renal tubular sodium reabsorption.

There are a considerable number of studies that demonstrate that chronic renal denervation may also exert a direct action on renal tubular transport of sodium. Bencsath et al. (18) showed that unilateral denervation for one to three weeks resulted in a marked ipsilateral increase in sodium and water excretion without changes in either glomerular filtration rate or renal cortical blood flow. Although single nephron glomerular filtration rate was unchanged in the chronically denervated kidney, both late proximal and distal fractional sodium reabsorption were significantly decreased. In addition, there was a decrease in absolute proximal tubular reabsorption of sodium and water in these denervated kidneys. Moreover, the natriuretic response to volume expansion was increased in kidneys denervated for one to three weeks (33, 124, 127). These results, therefore, are similar to the changes in tubular sodium reabsorption observed in acutely denervated kidneys.

The role of the adrenergic nervous system has also been evaluated in many pathophysiological states. For example, an increase in renal sympathetic activity has been suggested to contribute to the sodium retention of congestive heart failure in man and acute thoracic inferior vena cava (TIVC) constriction in animals (5, 47, 72, 112, 116). Gill et al. (47) demonstrated that systemic pentolinium, a ganglionic blocker, augmented sodium excretion in dogs with TIVC constriction. Azer et al. (5) also demonstrated that renal denervation partially restored the natriuretic response to saline loading in dogs with TIVC constriction. While Schrier et al. (112) did not alter the antinatriuretic effect of acute TIVC constriction with renal denervation, pharmacological sympathetic blockade did abolish the antinatriuresis. Finally, Slick et al. (115) have attempted to evaluate the role of renal denervation and local, rather than systemic, adrenergic blockade in reversing the antinatriuretic effect of acute TIVC constriction. Unilateral renal denervation, phenoxybenzamine, or guanethidine administration resulted in an ipsilateral natriuresis and fall in proximal nephron fractional reabsorption. The ipsilateral natriuresis could not be explained by alterations in systemic or renal hemodynamics or by a redistribution of renal blood flow. Thus, the antinatriuresis of TIVC constriction seemed to be mediated by a direct effect of the renal sympathetic nerves on tubular sodium transport.

Since many of the aforementioned studies were performed on anesthetized, acutely stressed animals, it is possible that some of the findings attributed to the adrenergic nervous system may not be present in the unstressed, conscious state. In a study by Sadowski et al. (108), utilizing conscious and anesthetized hydrated dogs, denervated kidneys excreted more sodium and water than innervated kidneys under basal conditions. The results, however, differed after a saline load. While the denervated kidneys continued to excrete more sodium and water in the anesthetized dog, the innervated kidneys excreted more sodium and water in the conscious dog. The authors suggested that the greater sodium excretion of the innervated kidneys after acute saline loading in the conscious dogs was due to inhibition of sodium-retaining action of renal efferent nerve activity by acute extracellular volume expansion, an effect that could not be observed in denervated kidneys. These authors warned, therefore, that renal denervation studies under anesthesia should be interpreted cautiously.

In summary, in the anesthetized animal, renal sympathetic nerve activity appears to decrease renal sodium excretion, while a decrease in sympathetic nerve activity increases urinary sodium excretion. These effects are most likely mediated by a direct effect on the renal tubular epithelial cell rather than by an indirect effect on renal hemodynamics. The proximal tubule is the most prominent segment of the nephron where these effects are observed.

B. Alpha-Adrenergic Stimulation and Blockade

Although renal nerve stimulation has been demonstrated to decrease renal sodium excretion, the receptor by which this effect is mediated is not entirely clear. Much of the confusion has been caused by the varied protocols utilized to elucidate this mechanism. For example, adrenergic agonists or antagonists have been infused alone or in various combinations (e.g., alpha-adrenergic agonist plus beta-adrenergic antagonist, beta-

adrenergic agonist plus alpha-adrenergic antagonist) systemically or into the renal artery of innervated or denervated kidneys. Since the systemic effects of any of these agents may obscure a direct intrarenal effect, it is important to consider the experimental design of the numerous studies that have been reported before making conclusions about renal adrenergic receptors.

In intact dogs, low-dose infusion of norepinephrine into the renal artery decreases sodium excretion in the absence of detectable changes in glomerular filtration rate or total renal blood flow (96). In the water-diuresing hypophysectomized dog, the arterial infusion of norepinephrine into kidneys receiving beta-adrenergic blocking agents resulted in a decrease in urine volume and free water excretion (50). Assuming that urine flow is a reliable index of proximal sodium reabsorption during a water diuresis and thus relative water impermeability of the distal nephron, the results of this study support the concept that renal alpha-adrenergic stimulation enhances renal sodium reabsorpion in the proximal nephron.

In contrast to the results obtained from studies with alpha-adrenergic agonists, the results obtained from studies with the alpha-adrenergic antagonist, phenoxybenzamine, have been inconsistent. For example, Chou et al. (32) have shown that the i.v. infusion of phenoxybenzamine into normal dogs results in a marked increase in urinary sodium excretion. On the other hand, i.v. phenoxybenzamine did not alter sodium excretion in either sodium-depleted dogs or in animals with chronic TIVC constriction (32). Thus, these authors concluded that alpha-adrenergic activity may enhance renal sodium reabsorption in normal animals but not in animals with TIVC constriction or with sodium depletion. These results in chronic TIVC-constricted dogs are different from earlier studies (65, 115), which demonstrated that phenoxybenzamine prevented the antinatriuretic response to acute TIVC constriction. The most likely explanation for these differences is that the earlier studies utilized acute rather than chronic TIVC constriction.

Several micropuncture studies have examined an effect of beta- and alpha-adrenergic blockade on sodium reabsorption in the proximal tubule (22, 122). Blendis et al. (22) reported that there was no difference in single nephron glomerular filtration rate or in proximal sodium or water reabsorption following intrarenal beta-adrenergic blockade alone or intrarenal beta-adrenergic blockade plus alpha-adrenergic stimulation. Strandhoy et al. (122) have also shown that phenoxybenzamine infusion into the renal artery increased urinary sodium excretion without producing changes in glomerular filtration rate, renal blood flow, filtration fraction, or in proximal sodium reabsorption as assessed by micropuncture techniques. The results of these last two studies suggest that the antinatriuretic effect of alpha-adrenergic stimulation is mediated by an increase in sodium reabsorption at sites beyond the proximal tubule.

Perhaps the most convincing evidence that alpha-adrenergic stimulation causes an increase in tubular sodium reabsorption comes from the previously discussed studies of DiBona and his colleagues. Both low level renal nerve stimulation (137) and baroreceptor reflex renal nerve stimulation (138) led to a decrease in urinary sodium excretion in the absence of changes in glomerular filtraton rate and renal blood flow. When phenoxybenzamine or guanethidine was infused into the renal artery of the ipsilateral kidneys, the usual antinatriuretic effect of nerve stimulation was demonstrated only in the contralateral but not the ipsilateral kidneys. These studies, therefore, demonstrate that renal alpha-adrenergic stimulation results in an increase in renal sodium reabsorption that can be prevented with alpha-adrenergic antagonists.

Although it is likely that the neurogenic effect of alpha-adrenergic stimulation is mediated by a direct effect on the tubule, an indirect effect has not been fully excluded. Since changes in either peritubular hydrostatic or oncotic pressure may cause changes in sodium reabsorption (24, 25, 40, 41, 77), it would be necessary to demonstrate that none of these factors are altered after either renal nerve stimulation or the intrarenal infusion of norepinephrine. Such a micropuncture study has not yet been reported. Renal alpha-adrenergic stimulation also could indirectly increase tubular sodium reabsorption by altering the distribution of renal blood flow. A decrease in cortical renal blood flow has been demonstrated in acute TIVC-constricted dogs (64, 65) and in some studies utilizing either direct or indirect renal nerve stimulation (101, 114). On the other hand, low-dose norepinephrine infusion does not alter the distribution of renal blood flow (28, 105, 110), and yet sodium excretion diminished with this maneuver (28). Finally, Slick et al. (114) have demonstrated that renal nerve stimulation can alter renal sodium excretion in the absence of changes in renal blood flow distribution. In their series of studies, the left renal nerve was stimulated first at high and then at lower levels of intensity. High intensity stimulation caused a decrease in sodium excretion that was associated with a redistribution of renal blood flow away from the outer cortex. Alpha-adrenergic blockade prevented the antinatriuresis and the redistribution of renal blood flow. However, low level renal nerve stimulation also caused a decrease in urinary sodium excretion in the absence of changes in glomerular filtration rate, total, or distribution of renal blood flow. This effect could also be reversed by alpha-adrenergic blockade (114, 137). Thus, it seems reasonable to conclude that both low-level renal nerve stimulation and low-dose norepinephrine infusion can alter tubular sodium reabsorption in the absence of changes of either total, or distribution of, renal blood flow.

Aside from the aforementioned physical peritubular factors, it is possible that the antinatriuretic effects of renal nerve stimulation are hormonally mediated. For example, low-level direct renal nerve stimulation has

been shown to result in an increase in renin secretion rate and thus, most likely, plasma angiotensin levels (61, 128). Zambraski and DiBona (136) have shown that the antinatriuretic effect of low-level renal nerve stimulation in dogs is the same before and after intrarenal blockade of angiotensin II with the competitive inhibitor, saralasin. Thus, the antinatriuretic effect of low-level renal nerve stimulation is not dependent on the generation of angiotensin II. Similarly, the antinatriuretic effect of renal nerve stimulation could be mediated by the suppression of hormones that have been postulated to enhance renal sodium excretion. For example, prostaglandins have been suggested to decrease tubular sodium reabsorption in man and experimental animals (3, 63, 123). However, renal nerve stimulation (39) and norepinephrine infusion (45) have been shown to increase, not decrease, renal prostaglandins. Moreover, the antinatriuretic effect of renal nerve stimulation is not altered by inhibition of prostaglandin synthesis. These results, therefore, indicate that the antinatriuretic effect of renal nerve stimulation is independent of changes in renal prostaglandins (38). Bradykinins also have been shown to increase sodium excretion (21, 118, 121), but no studies are available that assess the role of these compounds in the antinatriuresis resulting from renal nerve stimulation.

In summary, there is convincing evidence to suggest that the antinatriuretic effect of renal nerve stimulation is mediated by alpha-adrenergic receptors in the kidney. Although the evidence suggests that this effect is direct and is independent of glomerular filtration rate, total, and distribution of, renal blood flow, angiotensin II, and prostaglandins, there are virtually no experiments that examine whether changes in peritubular capillary Starling forces are involved.

C. Beta-Adrenergic Stimulation and Blockade

As in studies evaluating the relationship between the alpha-adrenergic nervous system and renal sodium excretion, any effect of beta-adrenergic stimulation could be related either to extrarenal reflex pathways that secondarily affect the kidney or to a direct effect of beta-adrenergic stimulation on the kidney. Systemic injection of isoproterenol has been reported to be associated with either no change (106) or a decrease in sodium excretion (55, 56, 71, 96). Moreover, studies employing the systemic administration of the beta-adrenergic blocking agent, propranolol, have yielded conflicting results. Several studies have reported an increase in urinary sodium excretion after the i.v. administration of propranolol (30, 71). On the other hand, at least two groups have demonstrated that the acute i.v. administration of propranolol leads to marked decreases in urinary sodium excretion (26, 93). In a study by Nies et al. (93), i.v. propranolol resulted in significant decreases in cardiac output (25%) and renal blood flow (25%), while both systemic (28%) and renal vascular resistances (37%) increased. Glomerular filtration rate remained unchanged, while urinary sodium excretion decreased by 36%. In this study, all of the renal effects of propranolol could be explained by the changes in systemic hemodynamics, since intrarenal propranolol infusion resulted in little change in sodium excretion. Although it is not readily apparent as to the reason for the discrepancies between all of these studies, the most likely source of confusion may result from differences in experimental protocols.

The infusion of large doses of isoproterenol into the renal artery causes renal vasodilatation (43, 96) and a natriuresis (96). The natriuresis of beta-adrenergic stimulation, therefore, could be a direct effect on tubular reabsorption or an effect secondary to the renal vasodilatation. Gill and Casper (48) have evaluated the effect of intrarenal beta-adrenergic stimulation with isoproterenol in cortisone-replaced, hypophysectomized dogs undergoing a water diuresis. With intrarenal isoproterenol, ispilateral glomerular filtration rate remained unchanged while both urine volume and free water clearance increased significantly. Since sodium excretion remained unchanged, the authors concluded that beta-adrenergic stimulation decreased proximal tubular sodium reabsorption while distal nephron sodium reabsorption was increased. In several other studies, however, the intrarenal infusion of low doses of isoproterenol that caused no changes in systemic or renal hemodynamics caused no changes in either urinary sodium excretion (106, 119) or in proximal nephron sodium reabsorption (116, 119). Moreover, infusions of propranolol into the renal artery have been shown by some (103) but not others (93) to alter urinary sodium excretion. It has, therefore, been difficult to confirm that beta-adrenergic stimulation or blockade has a specific effect on tubular sodium transport. Any change in sodium excretion after the systemic or renal administration of beta-adrenergic agonists may be mediated primarily by the resultant changes in systemic or renal hemodynamics.

Another system that has been utilized to assess the role of catecholamines on renal sodium excretion has been the isolated, perfused kidney. This system allows for the evaluation of the direct effect of various agents on renal function, since the kidney is denervated and perfused outside of the body with artificial medium devoid of renin substrate (thus no angiotensin I is produced) or any other known vasopressor substances. The concentration of catecholamines or inhibitors can be altered and, most importantly, renal perfusion pressure or renal flow can be controlled. In a recent study by Besarab et al. (20), both norepinephrine and epinephrine were shown to have a direct action on the isolated kidney. When perfusion pressure was held constant, sodium excretion decreased sharply after the addition of either of these agents. Of interest was the fact that this effect was abolished by the beta-adrenergic blocker, propranolol. In these studies, alpha-adrenergic blockade failed to reverse the antinatriuretic effect of norepinephrine. Beta-adrenergic stimulation with isoproterenol in the isolated per-

fused kidney also led to a decrease in urinary sodium excretion. Thus, the results of this study indicate a direct role of beta-adrenergic stimulation to increase tubular sodium reabsorption, at least in the isolated perfused kidney. Moreover, in contrast to studies in intact animals, this study in the isolated perfused kidney suggests that beta-adrenergic, rather than alpha-adrenergic, stimulation results in enhanced tubular sodium reabsorption. At present, it is impossible to reconcile the difference between these various results other than the obvious differences in methodologies.

In addition to the aforementioned studies in intact animals, there is in vitro evidence that alpha- and beta-adrenergic stimulation may directly alter active sodium transport. In this regard, norepinephrine has been demonstrated to increase the short circuit current in the toad bladder (58) and frog skin (11), which suggests an increase in active sodium transport. Moreover, a direct effect of alpha- and beta-adrenergic stimulation to alter sodium transport has been proposed on the basis of studies that have demonstrated that norepinephrine and isoproterenol decrease and increase renal cortical tissue cyclic 3′,5′-adenosine monophosphate (cyclic AMP) respectively (12, 68). The results of these studies will be discussed in section IV A and section IV B.

D. Dopaminergic Stimulation

Dopamine is a natural occurring catecholamine that is an intermediate in the biosynthesis of epinephrine and norepinephrine. Although the physiological role of dopamine in the central nervous system has been extensively studied, the action of dopamine on the renal excretion of sodium has not been clarified. A natriuretic effect of i.v. dopamine has been consistently reported in man and experimental animals (1, 6, 34, 53, 81, 84, 99). Moreover, administration of carbidopa, an agent that inhibits the peripheral conversion of dopa to dopamine, results in a marked decrease in both urinary dopamine and sodium excretion (7). Although i.v. dopamine administration may cause changes in systemic and renal hemodynamics, it is possible to administer dopamine in a dose range that increases renal blood flow without altering systemic hemodynamics (52, 84). When dopamine is administered i.v. in a dose range that causes no alterations in systemic pressure, there is an increase in renal blood flow and an increase in urinary sodium excretion (27, 86). Moreover, when dopamine was infused into the renal artery, there were ipsilateral changes in renal blood flow and in urinary sodium excretion (86). Finally, SK&F 38393, a new dopamine receptor agonist, causes an increase in renal blood flow and a marked natriuresis in the absence of changes in systemic hemodynamics (98). Although bulbocapnine, a selective dopamine receptor antagonist, has been shown to block the renal vasodilatory effect of SK&F 38393, the effect on urinary sodium excretion of bulbocapnine has not been reported (98).

The mechanism of the natriuretic effect of dopamine is not understood. Although it has been postulated that the natriuretic effect can occur independently of changes in systemic or renal hemodynamics (35, 57, 86), a direct effect on tubule sodium transport in the absence of renal hemodynamic changes has not been reported. It has been suggested that the natriuretic effect of dopamine is mediated by an enhanced intracellular generation of cyclic AMP (67); however, further studies are necessary to examine this possibility.

In summary, it is clear that dopamine causes an increase in renal blood flow and in urinary sodium excretion that is independent of changes in systemic hemodynamics. It has been shown that the effect on renal blood flow is mediated by dopaminergic receptors but it has not been proved that there is any direct effect of dopamine on renal epithelial sodium transport.

IV. Studies on Sodium Transport and Cyclic Nucleotides

A. Effect of Catecholamines on Sodium Transport in Epithelial Tissues

The possibility that catecholamines might directly influence renal tubular sodium reabsorption has been supported by results from studies evaluating short circuit current or sodium transport across the isolated frog skin epithelium. In this regard, Watlington (132) demonstrated that alpha-adrenergic stimulation in the presence of beta-adrenergic blockade decreased predominantly sodium influx. In contrast, beta-adrenergic stimulation produced an increase in both sodium influx and outflux with no change in net flux. These results, therefore, suggest opposing effects of alpha- and beta-adrenergic stimulation on sodium influx, although possibly on different pathways for sodium transport. When frog skin epithelial layers were separated from the dermis (which has been shown to have secretory mucous and venom glands that make it difficult to evaluate unidirectional fluxes of ions), low doses of norepinephrine increased active sodium influx (104). This effect of norepinephrine was blocked by propranolol. Higher doses of norepinephrine necessitated the presence of phentolamine to demonstrate an increase in active sodium influx. These results were interpreted as demonstrating the presence of both alpha- and beta-adrenergic receptors in frog skin (104, 132). Moreover, these receptors appear to be involved in active sodium transport in this system (104). Whereas most studies have supported the findings that sympathomimetic-induced changes in short circuit current and active sodium influx in frog skin are mediated by beta-adrenergic receptors (2, 104, 129, 130, 132), other studies have questioned the validity of such an interpretation (79). Finally, it has been shown that the increase in active sodium transport induced by antidiuretic hormone cannot be prevented by either alpha- or beta-adrenergic blockade, thereby implying separate sodium transport mechanisms for catecholamines and antidiuretic hormone (2).

There have been very few studies evaluating the effect of catecholamines on sodium transport in the isolated toad bladder since the report by Leaf et al. (70) that epinephrine had no effect on short circuit current. Other studies by Handler et al. (58) also suggested that the response of the toad bladder to isoproterenol was variable. However, a more recent study has demonstrated that both norepinephrine and epinephrine, but not isoproterenol, increase short circuit current in the toad bladder (134). The increase in short circuit current caused by norepinephrine was almost completely abolished by alpha-adrenergic blockade but was not influenced by beta-adrenergic blockade. Thus, in the toad bladder, current evidence suggests that the direct effect of alpha-adrenergic stimulation is to cause an increase in active sodium influx.

There is also evidence to support the observation that there are separate dopaminergic receptors in frog skin. In a recent study, dopamine was found to increase short circuit current in frog skin pretreated with both alpha- and beta-adrenergic blockers. Haloperidol, a specific dopaminergic antagonist, was found to antagonize the increase in short circuit current induced by dopamine (133).

In summary, there is convincing evidence for a direct effect of catecholamines on epithelial cell sodium transport. However, the specific receptors that mediate this response may vary depending on the various epithelial tissues.

B. Effect of Catecholamines on Renal Tissue Cyclic Nucleotides

It is well established that catecholamines, like other humoral substances, affect cellular function by interacting with specific receptors, which then trigger cellular events leading to a physiological response. There is a voluminous literature describing catecholamine receptors and their relationship to cyclic nucleotides and it is recognized that beta-receptors are an integral part of the adenylate cyclase system. This concept is based on the observation that most of the physiological effects associated with beta-adrenergic receptors are associated with an enhanced intracellular level of cyclic AMP. Robison et al. (107) suggested that an effect of alpha-adrenergic receptors may be associated with a decrease in intracellular level of cyclic AMP.

The characteristics of adrenergic receptors and their association with cyclic nucleotides have been reviewed recently (74, 107, 117) and only the relationship between catecholamines and the kidney will be reviewed in this section. Stimulation of cyclic AMP by catecholamines has been reported in renal tissues and in isolated tubules from many species. Isoproterenol or norepinephrine stimulates adenylate cyclase in rat (14, 69, 78), dog (12), and human (66) renal cortex. This effect is prevented by pretreatment with the beta-adrenergic receptor antagonist, propranolol, an agent that has no direct effect of its own (66, 69). Isoproterenol and norepinephrine have also been reported to stimulate adenylate cyclase from the rat (68), human (92), and dog (12) renal medulla. In addition, isoproterenol has been shown to increase the cyclic AMP level from the rat medulla in situ (80).

Recently, techniques have been developed that allow the microdissection of individual nephron segments. From this microdissection technique, isolated tubular segments can be identified and the effects of various hormones on both biochemical and physiological parameters can be assessed. Early studies using a nonspecific preparation of tubules rather than a specific preparation of isolated nephron segments demonstrated that epinephrine stimulated adenylate cyclase activity, an effect that was blocked by propranolol but not by phentolamine (85). Recent studies of isolated tubular segments have further defined the specific sites of hormone action (85, 88, 89). Chabardes et al. (31) have shown that isoproterenol does not affect adenylate cyclase activity in proximal convoluted and straight tubules, in thin and thick ascending limbs of Henle, or in the early portion of the distal convoluted tubule of rabbit kidneys. However, isoproterenol did stimulate adenylate cyclase activity in the late portion of the distal convoluted tubule and in the cortical but not medullary collecting tubules. Isoproterenol stimulated adenylate cyclase activity in these nephron segments in a dose-dependent manner and this effect was blocked by propranolol but not phentolamine. These studies have strongly suggested the presence of beta-adrenergic receptors in the late distal and cortical collecting tubules.

Recently, Imai (59) has demonstrated that isoproterenol increases the transtubular voltage across the isolated connecting tubule, a segment of the nephron that is located between the distal tubule and cortical collecting tubule of the rabbit. The increase in transtubular voltage invoked by isoproterenol was 100-fold greater in the connecting tubule than in the cortical collecting tubule. This physiological response to isoproterenol correlates very well with the biochemical findings of Morel et al. (88, 89).

In summary, it is still not entirely clear as to the specific segmental sites of hormone receptors that mediate a direct effect of circulating catecholamines on cyclic AMP formation in the nephon. With the development of the microdissection techniques, it will be possible in the next several years to correlate the specific segmental biochemical and physiological responses to circulating catecholamines.

Since beta-adrenergic stimulation has been shown to increase tissue cyclic AMP formation, it has been proposed that the effect of adrenergic stimulation on proximal tubular sodium reabsorption may involve a cyclic AMP-mediated mechanism. In this regard the cyclic AMP analogue, dibutyryl cyclic AMP, has been shown to increase sodium excretion in a manner similar to that of intrarenal isoproterenol infusion (49, 76). It has also been proposed in a preliminary communication (51) that

guanosine 3′,5′-monophosphate (cyclic GMP) produces a decrease in urine flow similar to that of norepinephrine. Thus, increased cyclic AMP and cyclic GMP have been proposed to mediate the effect of beta- and alpha-adrenergic stimulation on proximal tubular sodium reabsorption respectively. While such a hypothesis is attractive, it remains to be proved.

V. Conclusion

There is considerable evidence to support the hypothesis that the adrenergic nervous system alters renal sodium excretion independent of catecholamine-induced changes in systemic or renal hemodynamics. Morphological studies have clearly confirmed the presence of adrenergic innervation of renal vessels and of proximal and distal renal tubules. Both renal nerve stimulation and direct intrarenal administration of alpha- and beta-adrenergic agonists have been shown to alter sodium excretion in the absence of changes in renal hemodynamic and humoral factors that may alter sodium excretion. It seems likely, but not totally proved, that the effect of alpha- and beta-adrenergic stimulation directly influence renal tubular epithelial sodium transport. Such a conclusion is also supported by the finding that catecholamines can directly influence sodium transport in anuran membranes. The biochemical pathways and the specific nephron segments involved in this response have not been clearly elucidated. Dopamine receptors also appear to be present in the kidney and further studies are needed to define more clearly their direct role in sodium transport. Finally, it would appear that the development of microdissection techniques for the isolation of specific renal tubular segments will allow for direct examination of the biochemical and physiological responses of the kidney to the adrenergic nervous system.

REFERENCES

1. Alexander, R. W., Gill, J. R., Jr., and Yamabe, H.: Effects of dietary sodium and of acute saline infusion on the interrelationship between dopamine excretion and adrenergic activity in man. J. Clin. Invest. **54:** 194–200, 1974.
2. Ambalavanar, S., Foster, R. W., and Schneiden, H.: The adrenoceptors mediating catecholamine effects in frog isolated skin. J. Pharm. Pharmacol. **25:** 55–59, 1973.
3. Anderson, R. J., Berl, T., McDonald, K. M., and Schrier, R. W.: Prostaglandins: Effects on blood pressure, renal blood flow, sodium and water excretion. Kidney Int. **10:** 205–215, 1976.
4. Anton, A. H., and Sayre, D. F.: The distribution of dopamine and dopa in various animals and a method for their determination in diverse biological material. J. Pharmacol. Exp. Ther. **145:** 326–336, 1964.
5. Azer, M., Gannon, R., and Kaloyanides, G. J.: Effect of renal denervation on the antinatriuresis of caval constriction. Amer. J. Physiol. **223:** 611–616, 1972.
6. Ball, S. G., and Lee, M. R.: Increased urinary dopamine in salt loaded rats. Clin. Sci. Mol. Med. **52:** 20p–21p, 1977.
7. Ball, S. G., and Lee, M. R.: The effect of carbidopa administration on urinary sodium excreted in man. Is dopamine an intrarenal natriuretic hormone? Brit. J. Clin. Pharmacol. **4:** 115–119, 1977.
8. Ball, S. G., Lee, M. R., and Oates, N. S.: The effect of inorganic salts on renal tissue dopamine levels in the rat. Brit. J. Pharmacol. **63:** 343p, 1978.
9. Barajas, L.: The innervation of the juxtaglomerular apparatus. An electron microscopic study of the innervation of the glomerular arterioles. Lab. Invest. **13:** 916–929, 1964.
10. Barajas, L., and Muller, J.: The innervation of the juxtaglomerular apparatus and surrounding tubules: A quantitative analysis by serial section electron microscopy. J. Ultrastruct. Res. **43:** 107–132, 1973.
11. Bastide, F., and Jard, S.: Action of noradrenalin and oxytocin on the active transport of Na^+ and the permeability of frog skin to water. Role of cyclic AMP. Biochim. Biophys. Acta **150:** 113–123, 1968.
12. Beck, N. P., Reed, S. W., Murdaugh, M. V., and Davis, B. B.: Effects of catecholamines and their interaction with other hormones on cyclic 3′,5′-adenosine monophosphate of the kidney. J. Clin. Invest. **51:** 939–944, 1972.
13. Bell, C., and Lang, W. J.: Neural dopaminergic vasodilator control in the kidney. Nature, New Biol. (London) **246:** 27–29, 1973.
14. Bell, N. H.: Evidence for a separate adenylate cyclase system responsive to beta-adrenergic stimulation in the renal cortex of the rat. Acta Endocrinol. **77:** 604–611, 1974.
15. Bello-Reuss, E., Colindres, R. E., Pastoriza-Munoz, E., Mueller, R. A., and Gottschalk, C. W.: Effects of acute unilateral renal denervation in the rat. J. Clin. Invest. **56:** 208–217, 1975.
16. Bello-Reuss, E., Pastoriza-Munoz, E., and Colindres, R. E.: Acute unilateral renal denervation in rats with extracellular expansion. Amer. J. Physiol. **232:** F26–F32, 1977.
17. Bello-Reuss, E., Trevino, D. L., and Gottschalk, C. W.: Effect of renal sympathetic nerve stimulation on proximal water and sodium reabsorption. J. Clin. Invest. **57:** 1104–1107, 1976.
18. Bencsath, P., Asztalos, B., Szalay, L., and Takacs, L.: Renal handling of sodium after chronic renal sympathectomy in the anesthetized rat. Amer. J. Physiol. **236:** 513–518, 1979.
19. Bernard, C.: Leçons sur les Propriétés Physiologique des Liquides de l'Organisme, 172 pp., Baillière, Paris, 1859.
20. Besarab, A., Silva, P., Landsberg, L., and Epstein, F. H.: Effect of catecholamines on tubular function in the isolated perfused rat kidney. Amer. J. Physiol. **233:** F39–F45, 1977.
21. Blasingham, M. C., and Nasjletti, A.: Contribution of renal prostaglandins to the natriuretic action of bradykinin in the dog. Amer. J. Physiol. **237:** F182–F187, 1979.
22. Blendis, L. M., Audl, R. B., Alexander, E. A., and Levinsky, N. G.: Effect of renal beta- and alpha-adrenergic stimulation on proximal sodium reabsorption in dogs. Clin. Sci. (London) **43:** 569–576, 1972.
23. Bradford, J. R.: The innervation of the renal blood vessels. J. Physiol. (London) **10:** 358–407, 1889.
24. Brenner, B. M., Falchuk, K. M., Keimowitz, R. I., and Berliner, R. W.: The relationship between peritubular capillary protein concentration and fluid reabsorption by renal proximal tubule. J. Clin. Invest. **48:** 1519–1531, 1969.
25. Brenner, B. M., and Troy, J. L.: Postglomerular vascular protein concentration: Evidence for a causal role in governing fluid reabsorption and glomerulotubular balance by the renal proximal tubule. J. Clin. Invest. **50:** 336–349, 1971.
26. Cacciaguida, R. J., Pablo, N. C., Basillo, R. D., and Porush, J. G.: Antinatriuresis associated with propranolol administration in the dog. Nephron **11:** 58–64, 1973.
27. Cadnapaphornchai, P., Taher, S. M., and McDonald, K. D.: Mechanisms of dopamine induced diuresis in the dog. Amer. J. Physiol. **232:** F524–F528, 1977.
28. Cant, J. R., and Vander, A. J.: Sodium excretion and intrarenal distribution of blood flow with small doses of norepinephrine (abstract). Fed. Proc. **32:** 767, 1973.
29. Capponi, A. M., and Vallotton, M. B.: Renin release by rat kidney slices incubated in vitro. Role of sodium and of alpha- and beta-adrenergic receptors, and effect of vincristine. Circ. Res. **39:** 200–203, 1976.
30. Carrara, M. C., and Baines, A. D.: Propranolol induced acute natriuresis by beta blockade and dopaminergic stimulation. Can. J. Physiol. Pharmacol. **54:** 683–691, 1976.
31. Chabardes, D., Imbert-Teboul, M., Montegut, M., Clique, A., and Morel, F.: Catecholamine sensitive adenylate cyclase activity in different segments of the rabbit nephron. Pflügers Arch. Eur. J. Physiol. **361:** 9–15, 1975.
32. Chou, S. Y., Liebman, P. H., Ferder, L. F., Levin, D. L., Cacciaguida, R. J., and Porush, J. G.: Effects of alpha-adrenergic blockade on sodium excretion in normal and chronic salt retaining dogs. Can. J. Physiol. Pharmacol. **54:** 209–218, 1976.
33. Colindres, R. E., and Gottschalk, C. W.: Neural control of renal tubular sodium reabsorption in the rat. Fed. Proc. **37:** 1218–1221, 1978.
34. Cuche, J. L., Kuchel, O., Barbeau, A., Boucher, R., and Genest, J.: Relationship between the adrenergic nervous system and renin during adaptation to upright posture: A possible role for 3,4-dihydroxyphenethylamine (dopamine). Clin. Sci. (London) **43:** 381–391, 1972.
35. Davis, B. B., Walter, M. J., and Murdaugh, H. V.: The mechanism of the increase in sodium excretion following dopamine infusion. Proc. Soc. Exp. Biol. Med. **129:** 210–213, 1968.
36. DiBona, G. F.: Neurogenic regulation of renal tubular sodium reabsorption. Amer. J. Physiol. **233:** F73–F81, 1977.
37. DiBona, G. F.: Neural control of renal tubular sodium reabsorption in the dog. Fed. Proc. **37:** 1214–1217, 1978.
38. DiBona, G. F., Zambraski, E. J., Aguilera, A. J., and Kaloyanides, G. J.: Neurogenic control of renal tubular sodium reabsorption in the dog. Circ. Res. **40:** suppl. I, I-127–I-130, 1977.
39. Dunham, E. W., and Zimmerman, B. G.: Release of prostaglandin-like material from dog kidney during nerve stimulation. Amer. J. Physiol. **219:**

1279–1285, 1970.
40. Earley, L. E., and Friedler, R. M.: The effects of combined renal vasodilatation and pressor agents on renal hemodynamics and the tubular reabsorption of sodium. J. Clin. Invest. **45:** 542–551, 1966.
41. Falchuck, K. H., Brenner, B. M., Tadokoro, M., and Berliner, R. W.: Oncotic and hydrostatic pressures in peritubular capillaries and fluid reabsorption by proximal tubule. Amer. J. Physiol. **220:** 1427–1433, 1971.
42. Falck, B., Hillays, N. A., Thieme, G., and Torp, A.: Fluorescence of catecholamines and related compounds condensed with formaldehyde. J. Histochem. Cytochem. **10:** 348–354, 1962.
43. Fenyvesi, T., and Kallay, K.: The presence of beta-adrenergic receptors in the renal vascular bed. Acta Physiol. Acad. Sci. Hung. **38:** 159–166, 1970.
44. Fourman, J.: The adrenergic innervation of the efferent arterioles and the vasa recta in the mammalian kidney. Experientia (Basel) **26:** 293–294, 1970.
45. Fujimoto, S., and Lockett, M. F.: The intrarenal release of prostaglandin E by noradrenaline (Abstract). 4th Int. Congr. Pharmacol., Basel, p. 122, 1969.
46. Gosling, J. A., and Dixon, J. S.: The fine structure of the vasa recta and associated nerves in the rabbit kidney. Anat. Rec. **165:** 503–506, 1969.
47. Gill, J. R., Carr, A. A., Fleischmann, L. E., Casper, A. G. T., and Bartter, F. C.: Effects of pentolinium on sodium excretion in dogs with constriction of the vena cava. Amer. J. Physiol. **212:** 191–196, 1967.
48. Gill, J. R., Jr., and Casper, A. G. T.: Depression of proximal tubular sodium reabsorption in the dog in response to renal beta-adrenergic stimulation by isoproterenol. J. Clin. Invest. **50:** 112–118, 1971.
49. Gill, J. R., Jr., and Casper, A. G. T.: Renal effect of adenosine 3′,5′-cyclic monophosphate and dibutyryl adenosine 3′,5′-cyclic monophosphate. J. Clin. Invest. **50:** 1231–1240, 1971.
50. Gill, J. R., Jr., and Casper, A. G. T.: Effect of renal alpha-adrenergic stimulation on proximal tubular sodium reabsorption. Amer. J. Physiol. **223:** 1201–1205, 1972.
51. Gill, J. R., Jr., Tate, J., and Kelly, G.: Evidence that guanosine 3′,5′-cyclic monophosphate but not guanosine 5′-monophosphate increases sodium reabsorption by proximal tubule. Abstr. 5th Annu. Meet. Amer. Soc. Nephrol., p. 26, 1971.
52. Goldberg, L. I.: Cardiovascular and renal actions of dopamine: Potential clinical applications. Pharmacol. Rev. **24:** 1–30, 1972.
53. Goldberg, L. I., McDonald, R. H., and Zimmerman, A. M.: Sodium diuresis produced by dopamine in patients with congestive heart failure. N. Engl. J. Med. **269:** 1060–1064, 1963.
54. Gottschalk, C. W.: Renal nerves and sodium excretion. Annu. Rev. Physiol. **41:** 229–240, 1979.
55. Greven, J.: Evidence for redistribution of filtrate among nephrons after beta-adrenergic stimulation and blockade. Naunyn-Schmiedeberg's Arch. Pharmacol. **282:** 171–180, 1974.
56. Greven, J., and Heidenreich, O.: A micropuncture study of the effect of isoprenaline on renal tubular fluid and electrolyte transport in the rat. Naunyn-Schmiedeberg's Arch. Pharmacol. **287:** 117–128, 1975.
57. Greven, J., and Klein, H.: Effects of dopamine on whole kidney function and proximal transtubular volume fluxes in the rat. Naunyn-Schmiedeberg's Arch. Pharmacol. **296:** 289–292, 1977.
58. Handler, J. S., Bensinger, R., and Orloff, J.: Effect of adrenergic agents on toad bladder response to ADH, 3′,5′-cyclic AMP, and theophylline. Amer. J. Physiol. **215:** 1024–1031, 1968.
59. Imai, M.: The connecting tubules: A functional subdivision of the rabbit distal nephron perfused in vitro (Abstract). *In* Proceedings of the VII International Congress of Nephrology, Montreal, ed. by R. Barcello, M. Bergeron, S. Carriere, J. H. Dirks, K. Drummond, R. D. Guttmann, G. Lemieux, J. G. Mongeau, and J. F. Seeley, p. R-3, S. Karger, Basel, 1978.
60. Iversen, L.: Distribution of catecholamines and the storage of noradrenaline in sympathetic nerves. *In* The Uptake and Storage of Noradrenaline, ed. by L. Iversen, pp. 30–50, Cambridge University Press, London, 1967.
61. Johnson, M. D., and Malvin, R. L.: Stimulation of renal sodium reabsorption by angiotensin II. Amer. J. Physiol. **232:** F298–F306, 1977.
62. Kaplan, S. A., and Rapoport, S.: Urinary excretion of sodium and chloride after splanchnicotomy: Effect on the proximal tubule. Amer. J. Physiol. **164:** 175–181, 1951.
63. Kauker, M.: Prostaglandin E_2 effect from the luminal side on renal tubular ^{22}Na efflux: Tracer microinjection studies. Proc. Soc. Exp. Biol. Med. **154:** 274–277, 1977.
64. Kilcoyne, M. M., and Cannon, P. J.: Influence of thoracic caval occlusion on intrarenal blood flow distribution and sodium excretion. Amer. J. Physiol. **220:** 1220–1230, 1971.
65. Kilcoyne, M. M., and Cannon, P. J.: Neural and humoral influences on intrarenal blood flow distribution during thoracic caval occlusion. Amer. J. Physiol. **220:** 1231–1237, 1971.
66. Kim, J. K., Frohnert, P. P., Hui, Y. S. F., Barnes, L. D., Farrow, G. M., and Dousa, T. P.: Enzymes of 3′,5′-nucleotide metabolism in human renal cortex and renal adenocarcinoma. Kidney Int. **12:** 172–183, 1977.
67. Kuchel, O., and Hamet, H.: Dopamine, extracellular cyclic AMP and sodium excretion. Eur. J. Clin. Invest. **7:** 75–76, 1977.
68. Kurokawa, K., and Massry, S. G.: Interaction between catecholamines and vasopressin on renal medullary cyclic AMP of rat. Amer. J. Physiol. **225:** 825–829, 1973.
69. Kurokawa, K., and Massry, S. G.: Evidence for two separate adenyl cyclase systems responding independently to parathyroid hormone and beta-adrenergic agents in the renal cortex of rat. Proc. Soc. Exp. Biol. Med. **143:** 123–126, 1973.
70. Leaf, A., Anderson, J., and Page, L. B.: Active sodium transport by the isolated toad bladder. J. Gen. Physiol. **41:** 657–668, 1958.
71. Lees, P.: The influence of beta-adrenoceptive receptor blocking agents on urinary function in the rat. Brit. J. Pharmacol. **34:** 429–444, 1968.
72. Leranth, C., Ungvary, G., and Donath, T.: The innervation of the juxtaglomerular apparatus. Acta Morphol. Acad. Sci. Hung. **17:** 131–141, 1969.
73. Ljungqvist, A., and Wagermark, J.: The adrenergic innervation of intrarenal glomerular and extraglomerular circulatory routes. Nephron **7:** 218–229, 1970.
74. Maguire, M. E., Ross, E. M., and Gilman, A. G.: Beta-adrenergic receptor: Ligand binding properties and the interaction with adenyl cyclase. *In* Advances in Cyclic Nucleotide Research, vol. 8, ed. by P. Greengard, and G. A. Robison, pp. 1–84, Raven Press, New York, 1977.
75. Mark, A. L., Eckstein, J. W., Abboud, F. M., and Wendling, M. G.: Renal vascular responses to isoproterenol. Amer. J. Physiol. **217:** 764–767, 1969.
76. Martinez-Maldonado, M., Eknoyan, G., and Suki, W. N.: Natriuretic effects of vasopressin and cyclic AMP: Possible site of action in the nephron. Amer. J. Physiol. **220:** 2013–2020, 1971.
77. Martino, J. A., and Earley, L. E.: Demonstration of a role of physical factors as determinants of the natriuretic response to volume expansion. J. Clin. Invest. **46:** 1963–1978, 1967.
78. Marx, S. J., Fedak, S. A., and Aurbach, G. D.: Preparation and characterization of a hormone-responsive renal plasma membrane fraction. J. Biol. Chem. **247:** 6913–6918, 1972.
79. McAfee, R. D., Thurman, E., Mendez-Cordova, R., and Locke, W.: Adrenergic blocking agents modify catecholamine stimulation of short circuit current in isolated frog skin. Proc. Soc. Exp. Biol. Med. **146:** 276–278, 1974.
80. McDonald, K. M., Kuruvila, K. C., Aisenbrey, G. A., and Schrier, R. W.: Effect of alpha- and beta-adrenergic stimulation on renal water excretion and medullary tissue cyclic AMP in intact and diabetes insipidus rats. Kidney Int. **12:** 96–103, 1977.
81. McDonald, R. M., Jr., Goldberg, L. I., McNay, J. L., and Tuttle, E. P., Jr.: Effect of dopamine in man: Augmentation of sodium excretion, glomerular filtration rate, and renal plasma flow. J. Clin. Invest. **43:** 1116–1124, 1964.
82. McKenna, O. C., and Angelakos, E. T.: Adrenergic innervation of the canine kidney. Circ. Res. **22:** 345–354, 1968.
83. McKenna, O. C., and Angelakos, E. T.: Development of adrenergic innervation in the puppy kidney. Anat. Rec. **167:** 115–119, 1970.
84. McNay, J. L., McDonald, R. H., Jr., and Goldberg, L. I.: Direct renal vasodilatation produced by dopamine in the dog. Circ. Res. **16:** 510–517, 1965.
85. Melson, G. L., Chase, L. R., and Aurbach, G. D.: Parathyroid hormone-sensitive adenyl cyclase in isolated renal tubules. Endocrinology **86:** 511–518, 1970.
86. Meyer, M. B., McNay, J. L., and Goldberg, L. I.: Effects of dopamine on renal function and hemodynamics in the dog. J. Pharmacol. Exp. Ther. **156:** 186–192, 1967.
87. Moffat, D. B.: The fine structure of the blood vessels of the renal medulla with particular reference to the control of the medullary circulation. J. Ultrastruct. Res. **19:** 532–545, 1967.
88. Morel, F., Chabardes, D., and Imbert-Teboul, M.: Functional segmentation of the rabbit distal tubule by microdetermination of hormone-dependent adenylate cyclase activity. Kidney Int. **9:** 264–277, 1976.
89. Morel, F., Chabardes, D., and Imbert-Teboul, M.: Heterogeneity of hormonal control in the distal nephron. *In* Proceedings of the VII International Congress of Nephrology, Montreal, ed. by R. Barcelo, M. Bergeron, S. Carriere, J. H. Dirks, K. Drummond, R. D. Guttmann, G. Lemieux, J.-G. Mongeau, and J. F. Seeley, pp. 209–216, S. Karger, Basel, 1978.
90. Mukacsi, I.: Distribution of the intrarenal monoaminergic nerves in the kidneys of the desert rat (Dipodomys merriami) and the white rat (Rattus norvegicus). Acta Anat. **73:** 56–68, 1969.
91. Muller, J., and Barajas, L.: Electron microscopic and histochemical evidence for a tubular innervation in the renal cortex of the monkey. J. Ultrastruct. Res. **41:** 533–549, 1972.
92. Mulvehill, J. B., Hui, Y. S. F., Barnes, L. D., Palumbo, P. J., and Dousa, T. P.: Glucagon-sensitive adenylate cyclase in human renal medulla. J. Clin. Endocrinol. Metab. **42:** 380–384, 1976.
93. Nies, A. S., McNeil, J. S., and Schrier, R. W.: Mechanism of increased sodium reabsorption during propranolol administration. Circulation **44:** 596–604, 1971.
94. Nilsson, O.: The adrenergic innervation of the kidney. Lab. Invest. **14:** 1392–1395, 1965.
95. Norvell, J. E.: A histochemical study of the adrenergic and cholinergic innervation of the mammalian kidney (Abstract). Anat. Rec. **163:** 236, 1969.
96. Pearson, J. E., and Williams, R. L.: Analysis of direct renal actions of

alpha- and beta-adrenergic stimulation upon sodium excretion compared to acetylcholine. Brit. J. Pharmacol. **33:** 223–241, 1968.
97. PENDLETON, R. G., FINLAY, E., AND SHERMAN, S.: Effect of bulbocapnine as a peripheral dopamine receptor antagonist in the anesthetized cat. Naunyn-Schmiedeberg's Arch. Pharmacol. **289:** 171–178, 1975.
98. PENDLETON, R. G., SAMLER, L., KAISER, C., AND RIDLEY, P. T.: Studies on renal dopamine receptors with a new agonist. Eur. J. Pharmacol. **51:** 19–28, 1978.
99. PENDLETON, R. G., AND SHERMAN, S. S.: Studies concerning dopamine diuresis in the rat. Arch. Int. Pharmacodyn. Ther. **222:** 94–102, 1976.
100. PENDLETON, R. G., AND WOODWARD, P. W.: Studies on the action and interaction of dopamine and prostaglandin A_1 in the renal vasculature. Arch. Int. Pharmacodyn. Ther. **221:** 250–260, 1976.
101. POMERANZ, B. H., BIRTCH, A. G., AND BARGER, A. C.: Neural control of intrarenal blood flow. Amer. J. Physiol. **215:** 1067–1081, 1968.
102. PROSNITZ, E. H., AND DIBONA, G. F.: Effect of decreased renal sympathetic nerve activity on renal tubular sodium reabsorption. Amer. J. Physiol. **235:** F557–F563, 1978.
103. PROSNITZ, E. H., AND DIBONA, G. F.: Effects of propranolol on renal function (Abstract). Clin. Res. **28:** 64A, 1980.
104. RAJERISON, R. M., MONTEGUT, M., AND JARD, S.: The isolated frog skin epithelium: Presence of alpha- and beta-adrenergic receptors regulating active sodium transport and water permeability. Pflügers Arch. Eur. J. Pharmacol. **332:** 313–331, 1972.
105. RECTOR, J. B., STEIN, J. H., BAY, W. H., OSGOOD, R. W., AND FERRIS, T. E.: Effect of hemorrhage and vasopressor agents on distribution of renal blood flow. Amer. J. Physiol. **222:** 1125–1131, 1972.
106. REID, I. A., SCHRIER, R. W., AND EARLEY, L. E.: An effect of extrarenal beta-adrenergic stimulation on the release of renin. J. Clin. Invest. **51:** 1861–1869, 1972.
107. ROBISON, G. A., BUTCHER, R. W., AND SUTHERLAND, E. W.: Catecholamines. *In* Biochemical Actions of Hormones, ed. by G. Litwack, pp. 81–111, Academic Press, New York, 1972.
108. SADOWSKI, J., KURKUS, J., AND GELLERT, R.: Denervated and intact kidney responses to saline load in awake and anesthetized dogs. Amer. J. Physiol. **237:** F262–F267, 1979.
109. SCHRIER, R. W.: Effects of adrenergic nervous system and catecholamines on systemic and renal hemodynamics, sodium and water excretion and renin secretion. Kidney Int. **6:** 291–306, 1974.
110. SCHRIER, R. W., AND BERL, T.: Mechanism of effect of alpha-adrenergic stimulation with norepinephrine on renal water excretion. J. Clin. Invest. **52:** 502–511, 1973.
111. SCHRIER, R. W., AND DE WARDENER, H. E.: Tubular reabsorption of sodium ion: Influence of factors other than aldosterone and glomerular filtration rate. N. Engl. J. Med. **285:** 1292–1303, 1971.
112. SCHRIER, R. W., HUMPHREYS, M. H., AND UFFERMAN, R. C.: Role of cardiac output and the autonomic nervous system in the antinatriuretic response to acute constriction of the thoracic superior vena cava. Circ. Res. **29:** 490–498, 1971.
113. SIMPSON, J. O., AND DEVINE, C. E.: The fine structure of autonomic neurotransmitter contacts in arterioles of sheep renal cortex. J. Anat. **100:** 127–137, 1966.
114. SLICK, G. L., AGUILERA, A. J., ZAMBRASKI, E. J., DIBONA, G. F., AND KALOYANIDES, G. J.: Renal neuroadrenergic transmission. Amer. J. Physiol. **229:** 60–65, 1975.
115. SLICK, G. L., DIBONA, G. F., AND KALOYANIDES, G. J.: Renal sympathetic nerve activity in sodium retention of acute caval constriction. Amer. J. Physiol. **226:** 925–932, 1974.
116. SPARKS, H. V., KOPALD, H. H., CARRIERE, S., CHIMOSKEY, J. E., KINOSHITA, M., AND BARGER, A. C.: Intrarenal distribution of blood flow with chronic congestive heart failure. Amer. J. Physiol. **223:** 840–846, 1972.
117. STEER, M. L.: Adrenergic receptors. Clin. Endocrinol. Metab. **6:** 577–597, 1977.
118. STEIN, J. H., CONGBALAY, R. C., KARSH, D. L., OSGOOD, R. W., AND FERRIS, T. E.: The effect of bradykinin on tubular sodium reabsorption in the dog: Evidence for functional nephron heterogeneity. J. Clin. Invest. **51:** 1709–1721, 1972.
119. STEIN, J. H., OSGOOD, R. W., AND FERRIS, R. F.: The effect of beta-adrenergic stimulation on proximal tubular sodium reabsorption. Proc. Soc. Exp. Biol. Med. **141:** 901–905, 1972.
120. STRANDHOY, J. W., CRONELLY, R., LONG, J. P., AND WILLIAMSON, H. E.: Effects of vasoactive agents and diuretics on isolated superfused interlobar renal arteries. Proc. Soc. Exp. Biol. Med. **141:** 336–345, 1972.
121. STRANDHOY, J. W., OTT, C. E., SCHNEIDER, E. G., WILLIS, L. R., BECK, N. P., DAVIS, B. B., AND KNOX, F. G.: Effects of prostaglandins E_1 and E_2 on renal sodium reabsorption and Starling forces. Amer. J. Physiol. **226:** 1015–1021, 1974.
122. STRANDHOY, J. W., SCHNEIDER, E. G., WILLIS, L. R., AND KNOX, F. J.: Intrarenal effects of phenoxybenzamine on sodium reabsorption. J. Lab. Clin. Med. **83:** 263–270, 1974.
123. STROKES, J. B., AND KOKKO, J. P.: Inhibition of sodium transport by prostaglandin E_2 across the isolated, perfused rabbit collecting tubule. J. Clin. Invest. **59:** 1099–1104, 1977.
124. SZALAY, L., BENCSATH, P., AND TAKACS, L.: Renal sodium reabsorption and oxygen consumption after unilateral splanchnicotomy in the dog. Pflügers Arch. Eur. J. Pharmacol. **349:** 359–367, 1974.
125. TAHER, M. S., MCLAIN, L. G., MCDONALD, K. M., AND SCHRIER, R. W.: Effect of beta-adrenergic blockade on renin response to renal nerve stimulation. J. Clin. Invest. **57:** 459–465, 1976.
126. TAKACS, L., BENCSATH, P., AND DEMECZKY, L.: Renal sodium and water excretion after unilateral splanchnicotomy in the dog. Acta Physiol. Acad. Sci. Hung. **39:** 283–291, 1971.
127. TAKACS, L., BENCSATH, P., AND SZALAY, L.: Decreased proximal tubular transport capacity after renal sympathectomy. *In* Proceedings, VII International Congress of Nephrology, Montreal, ed. by R. Barcelo, M. Bergeron, S. Carriere, J. H. Dirks, K. Drummond, R. D. Guttmann, G. Lemieux, J.-G. Mongeau, and J. F. Seely, pp. 553–558, S. Karger, Basel, 1978.
128. THURAU, K.: Intrarenal action of angiotensin. *In* Angiotensin, ed. by I. H. Page and F. M. Bumpus, pp. 475–489, Springer-Verlag, Berlin, 1974.
129. TOMLINSON, R. W. S., AND WOOD, A. W.: Catecholamine-induced changes in ion transport in short-circuited frog skin and the effect of beta-blockade. J. Physiol. (London) **257:** 515–530, 1976.
130. TOMLINSON, R. W. S., AND WOOD, A. W.: Effect of amiloride on catecholamine-induced changes in ion transport in short-circuited frog skin. J. Memb. Biol. **40** (special issue): 135–150, 1978.
131. WAGERMARK, J., UNGERSTEDT, U., AND LJUNGQVIST, A.: Sympathetic innervation of the juxtaglomerular cells of the kidney. Circ. Res. **22:** 149–153, 1968.
132. WATLINGTON, C. O.: Effect of catecholamines and adrenergic blockade on sodium transport of isolated frog skin. Amer. J. Physiol. **214:** 1001–1007, 1968.
133. WIGLUX, Z., AND KOROLKIEWICZ, Z.: The influence of dopamine on active sodium transport across frog skin measured as short circuit current. Eur. J. Pharmacol. **53:** 127–134, 1979.
134. WOOD, A. W., AND TOMLINSON, R. W. S.: The effect of catecholamines on ion transport in the toad bladder. Biochim. Biophys. Acta **367:** 375–384, 1974.
135. YEH, B. K., MCKAY, J. L., AND GOLDBERG, L. I.: Attenuation of dopamine renal and mesenteric vasodilation by haloperidol: Evidence for a specific dopamine receptor. J. Pharmacol. Exp. Ther. **168:** 303–309, 1969.
136. ZAMBRASKI, E. J., AND DIBONA, G. F.: Angiotensin II in antinatriuresis of low-level renal nerve stimulation. Amer. J. Physiol. **231:** 1105–1110, 1976.
137. ZAMBRASKI, E. J., DIBONA, G. F., AND KALOYANIDES, G. J.: Specificity of neural effect on renal tubular sodium reabsorption. Proc. Soc. Exp. Biol. Med. **151:** 543–546, 1976.
138. ZAMBRASKI, E. J., DIBONA, G. F., AND KALOYANIDES, G. J.: Effect of sympathetic blocking agents on the antinatriuresis of reflex renal nerve stimulation. J. Pharmacol. Exp. Ther. **198:** 464–472, 1976.