Kidney International, Vol. 6 (1974), p. 291–306

Effects of adrenergic nervous system and catecholamines on systemic and renal hemodynamics, sodium and water excretion and renin secretion

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The influences of the adrenergic nervous system on various organ systems in the body are protean. No attempt will be made in this review to survey these many effects; but rather the focus will be on the specific influences that adrenergic tone and catecholamines exert on systemic and renal hemodynamics, the excretion of sodium and water excretion and the secretion of renin. Where possible, emphasis will be placed on the integration of these functions into a teleologically oriented system of control of systemic hemodynamics and of body fluid volume and composition, including the implications for the pathogenesis of disease states.

Effect of adrenergic nervous system and catecholamines on systemic and renal hemodynamics. The endogenous catecholamines, norepinephrine and epinephrine, each exert a combination of alpha- and beta-adrenergic effects and the use of specific receptor blocking agents has allowed pharmacological separation of these two properties. When appropriate, therefore, the separate effects of alpha- and beta-adrenergic stimulation will be discussed.

The primary cardiovascular effect of beta-adrenergic stimulation relates to its inotropic and chronotropic action on the heart [1]. The increase in cardiac output associated with the beta-adrenergic agonist, isoproterenol, therefore is due to a rise in both heart rate and stroke volume. An increase in 3′5′-adenosine monophosphate (cyclic AMP) appears to be the intracellular hormonal mediator (secondary messenger) of the increase in stroke volume produced by isoproterenol [2]. Beta-adrenergic stimulation has also been demonstrated to exert a vasodilatory effect on the peripheral vasculature [1]. This decrease in total peripheral resistance may be a determining factor, in addition to the direct cardiac effect, in the increase in cardiac output during i.v. administration of isoproterenol. On the other hand, if the rise in cardiac output during infusion of isoproterenol increases arterial blood pressure, then the fall in peripheral vascular resistance may be mediated both by the direct peripheral vascular effect of the agonist and the baroreceptor-mediated reflex vasodilatation. Thus, several interrelated influences occur as a result of systemic beta-adrenergic stimulation and the summation of these influences may result in different effects on mean arterial blood pressure. In some instances isoproterenol administration may increase mean arterial pressure as a result of the predominant effect of the drug to increase cardiac output. In other circumstances the peripheral vasodilatation associated with i.v. administration of isoproterenol may predominate and cause a diminution in mean arterial pressure. In still other situations, the relative effect of beta-adrenergic stimulation to increase cardiac output and decrease peripheral vascular resistance may be such that arterial pressure is unchanged. The extent to which either of these effects of beta-adrenergic stimulation on systemic arterial pressure predominate appears to be related, at least in part, to the amount of the stimulating agent administered. Because of these extrarenal effects of beta-adrenergic stimulation on cardiac output and peripheral vascular resistance, it is difficult to isolate the intrarenal effects of beta-adrenergic stimulation during the i.v. administration of these agonists. For example, although i.v. administered isoproterenol decreases total peripheral resistance, renal vascular resistance may be unchanged or even increased if the net effect of the drug is to lower arterial pressure [3]. In this circumstance, the baroreceptor-mediated increase in renal sympathetic tone may obscure any

direct intrarenal effect that isoproterenol may have to decrease renal vascular resistance. Since none of the known adrenergic agents exerts selective effects on the kidney, neither the systemic administration of the agents nor the systemic blockade of their action permits delineation of any direct effects on the kidney. Moreover, due to the prolonged action of most beta- and alpha-adrenergic blocking agents, systemic effects are observed even when these blocking agents are administered into a renal artery. A selective intrarenal adrenergic blockade, therefore, has been difficult to obtain; thus, the intrarenal infusion of beta- and alpha-adrenergic agonists has been the primary mode of delineating the intrarenal effects of adrenergic stimulation.

In contrast to the effects of beta-adrenergic stimulation, the primary cardiovascular effect of alpha-adrenergic stimulation is vasoconstriction of the peripheral arterioles and venules [1]. This increase in peripheral vascular resistance results in an increase in arterial pressure which also may be secondarily modified by reflex changes in arterial baroreceptor tone. As with beta-adrenergic agonists, the intrarenal effect of alpha-adrenergic stimulation is best defined by direct infusion of the agonist into the renal artery. Norepinephrine possesses both alpha- and beta-adrenergic stimulating properties; therefore, the intrarenal alpha-adrenergic effect of the substance is best observed in the presence of beta-adrenergic blockade. Since the kidney has been demonstrated to be an effective site of inactivation of catecholamines, including isoproterenol [4] and norepinephrine [5], intrarenal effects of these agents can be produced in the absence of either systemic effects or effects in the contralateral kidney.

Evidence has been obtained that the kidney possesses both alpha- and beta-adrenergic receptors. The intrarenal infusion of the beta-adrenergic agonist, isoproterenol, has been demonstrated to produce vasodilatation of the kidney [6]. In quantitative terms this effect of isoproterenol appears to be less potent than other renal vasodilators such as acetylcholine [7, 8], bradykinin [7, 8] and prostaglandin E_1 [9]. In the presence of the beta-adrenergic blocker, propranolol, large doses of isoproterenol can be associated with renal vasoconstriction, an alpha-adrenergic effect [6]. Whether either the intrarenal beta- or alpha-adrenergic effect of isoproterenol is of physiological importance remains to be determined. In this regard, the intrarenal infusion of the beta-blocking agent, propranolol, has not been found to produce any detectable unilateral alterations in renal hemodynamics in anesthetized dogs which are known to have an increase in renal sympathetic tone [11]. The interpretation of these results must be tempered, however, by the knowledge of the relatively long $t_{\frac{1}{2}}$ value of this agent so that its accumulation may lead to extrarenal hemodynamic alterations which could obscure any intrarenal effects of beta blockade.

In contrast to beta-adrenergic stimulation, changes in alpha-adrenergic tone definitely appear to exert major physiological effects on renal hemodynamics. Norepinephrine, the adrenergic neurohumoral transmitter, is primarily an alpha-adrenergic agonist; therefore, increases in renal sympathetic tone produce vasoconstriction of the renal vasculature. It appears that several renal vascular sites for alpha-adrenergic stimulation exist including the afferent and efferent arterioles as well as the venules. With marked adrenergic stimulation, an increase in renal vascular resistance no doubt occurs as a result of vasoconstriction at all of these locations and the result is a decrease in both glomerular filtration rate and renal blood flow. Intrarenally administered norepinephrine and renal nerve stimulation, however, may exert a preferential vasoconstrictor effect on the efferent arteriole so that the fall in glomerular filtration rate is less than the decrease in renal blood flow; thus, filtration fraction increases. With modest doses of norepinephrine, either infused i.v. or into the renal artery, mild constriction of the afferent arteriole may be counterbalanced by sufficient constriction of the efferent arteriole so that glomerular filtration rate is maintained constant although renal blood flow decreases [12]. The counterpart of this effect may occur during beta-adrenergic stimulation with isoproterenol in which preferential vasodilatation of the efferent arteriole leads to a rise in renal blood flow as glomerular filtration rate remains constant [6].

The effect of alpha-adrenergic stimulation to constrict renal venules is another component of the increase in renal vascular resistance and, in the presence of drug-induced renal vasodilatation, may be primarily responsible for the observed increase in deep renal venous pressure with a norepinephrine infusion [13]. In addition to these renal vasoconstrictor effects of alpha-adrenergic stimulation, there have been reports that alpha-adrenergic stimulation may not produce homogeneous vasoconstriction throughout all of the nephrons. Using the ^{85}krypton washout method, Pomeranz, Birtch and Barger [14] suggested that renal nerve stimulation induced either by bilateral carotid ligation or splanchnic nerve stimulation decreased outer cortical and increased medullary blood flow. In contrast to these results, estimation of renal blood distribution by investigators using radioactive microspheres has failed to demonstrate any effect of renal nerve stimulation [15] or norepinephrine infusion [16] to redistribute renal cortical blood flow. However, several investigators using either the inert gas or radio-

active microsphere method have found a decrease in outer cortical blood flow during hemorrhage [15–18]. Norepinephrine has been suggested to be important in this effect of hemorrhage on cortical blood flow but attempts to reverse this redistribution with alpha-adrenergic blockade have produced conflicting results [15, 17, 18]. The results of recent studies using the radioactive microsphere technique suggest that the fall in arterial pressure during hemorrhage may be responsible for the associated decrease in outer cortical blood flow. In these studies, the lowering of renal perfusion pressure [15], but not the infusion of norepinephrine or angiotensin [16], was shown to mimic the effect of hemorrhage to decrease fractional blood flow to the outer cortical nephrons.

Adrenergic stimulation also has been suggested to cause a redistribution of blood flow away from the renal cortex in humans with heart failure and experimental models of sodium retention [19]. These results were obtained using the inert gas technique to estimate the distribution of renal blood flow. The administration of alpha-adrenergic blockers into the renal artery also has been found to reverse the increase in renal vascular resistance which occurs in patients [20] and experimental animals [21] with heart failure. There is also other evidence suggesting that increased renal adrenergic tone occurs in patients with cardiac failure. As with renal nerve stimulation and norepinephrine infusion, an increase in filtration fraction is a consistent occurrence in patients with severe heart failure [22]. Moreover, high concentrations of endogenous catecholamines have been measured in patients with heart failure [23]. The renal vasoconstriction which occurs during heart failure may be mediated both by an increase in renal sympathetic efferent tone, as well as elevated concentrations of endogenous catecholamines. Renal vasoconstriction observed in patients with advanced liver disease [24] also may be mediated, at least in part, by an increase in renal adrenergic tone and elevated concentrations of endogenous catecholamines. Of course, an additional importance of other circulating vasoconstrictor agents, such as angiotensin II, also may be involved in the renal vasoconstriction associated with cardiac or hepatic failure.

The baseline level of renal vascular tone also may be an important determinant of renal responses to various stimuli. For example, in the presence of a high control level of renal vascular resistance, alpha-adrenergic stimulation may be less effective but any vasodilating response may be accentuated. For example, patients with hepatorenal syndrome actually increase their glomerular filtration rate and renal blood flow in response to pressor doses of the alpha-adrenergic agonist, metaraminol [24]. In contrast, in normal subjects the same dose of metaraminol exerts profound renal vasoconstriction so that glomerular filtration rate and renal blood flow decrease. On the other hand, the renal vasodilatation which accompanies volume expansion is much more pronounced in patients with essential hypertension and increased renal vascular resistance than in normal subjects [25]. The exaggerated response of arterial pressure and renal hemodynamics to volume expansion in patients with autonomic insufficiency may be related primarily to an ineffective arterial baroreceptor mechanism [26]. Finally, alpha-adrenergic stimulation with norepinephrine may interfere with renal autoregulation but the exact mechanism has not been defined [27].

Effects of adrenergic nervous system and catecholamines on sodium reabsorption and excretion. Alterations in adrenergic neural tone may influence sodium reabsorption and excretion by several pathways. Changes in sympathetic neural tone might alter extrarenal mechanisms which in turn mediate changes in renal sodium excretion. Effects of adrenergic stimulation on renal hemodynamics may also affect renal sodium excretion. Finally, a direct effect of alpha- or beta-adrenergic stimulation on active sodium transport mechanisms by the renal epithelial cell may alter renal sodium excretion. There are several investigations which bear on the role of these potential pathways whereby adrenergic pathways affect renal sodium excretion.

Spinal cord section [28, 29] and cardiac denervation [30, 31] both have been used to incriminate extrarenal adrenergic mechanisms in the regulation of sodium excretion. The interruption of sympathetic afferent and efferent pathways by cervical spinal section has been demonstrated to impair the natriuretic response to volume expansion with both isotonic saline [28] and artificial whole blood [29]. The demonstration that cardiac denervation is associated with a similar blunting of the natriuretic response to volume expansion [30, 31] led to the suggestion that an intracardiac volume receptor is involved in the regulation of sodium excretion. This hypothesis was supported by the observation that spinal cord section at the cervical, but not at the sixth thoracic, level was associated with an impaired natriuretic response to volume expansion [28]. On the basis of these results [29–31], the thoracic sympathetic afferent pathways were thought to transmit signals arising from alterations in extracellular fluid volume to the central nervous system. However, since cord section and cardiac denervation interrupt both sympathetic afferent and efferent pathways, further studies were necessary to document this hypothesis. The hypothesis was found not to be tenable when selective interruption of thoracic sympathetic afferent

pathways by posterior rhizotomy did not impair the natriuretic response to expansion of the extracellular fluid volume [28]. Since interruption of vagal pathways also was found not to influence the natriuresis associated with volume expansion [28, 31], the interruption of sympathetic efferent pathways seemed the primary mediator of the impairment in sodium excretion following cervical spinal cord section [28, 29] or cardiac denervation [30, 31]. Support for this conclusion is provided by the observation that selective interruption of adrenergic or sympathetic efferent pathways by pharmacologic depletion of catecholamines is associated with a similar impairment in sodium excretion as cord section or cardiac denervation [32]. During volume expansion the primary hemodynamic consequence of interruption of adrenergic pathways is a diminution in total peripheral resistance and arterial pressure which occurs in the absence of any effect on the cardiac output [28, 32]. In this situation the diminution in renal perfusion pressure, which occurs in the absence of detectable changes in glomerular filtration rate, may mediate the increased tubular reabsorption of sodium [8, 32].

In the absence of alterations in systemic arterial pressure, the intrarenal effect of diminished adrenergic tone may predominate and be associated with an increase, rather than a decrease, in sodium excretion. For example, when tested in the supine position, individuals with idiopathic [26] or pharmacologically induced [33] autonomic insufficiency have been found to excrete a saline load more rapidly than normal subjects. An earlier escape from the sodium-retaining effect of mineralocorticoid hormones has also been demonstrated to occur in the presence of adrenergic impairment secondary to guanethedine administration [34]. Taken together, these results suggest that renal adrenergic impairment may enhance sodium excretion unless the fall in total peripheral resistance and arterial pressure associated with extrarenal adrenergic impairment obscures this intrarenal effect. When the extrarenal effect of adrenergic impairment predominates, renal sodium retention occurs. Such is generally the situation with the use of sympatholytic agents, for the treatment of hypertension and the concomitant administration of diuretics is necessary to avoid excessive sodium retention.

Renal denervation has been known for some time to be associated with a natriuresis in the anesthetized dog [35]. Although this natriuretic effect of renal denervation may be partially related to the concomitant increase in glomerular filtration rate [36], prevention of this increase in filtration rate by injection of microspheres has failed to abolish this "denervation natriuresis" [37], thus suggesting some direct or indirect effect of renal neural tone on tubular sodium reabsorption.

There is considerable evidence that an increase in renal adrenergic tone may be partially responsible for the increased retention of sodium associated with low-output cardiac failure in humans and experimental animals. The intrarenal injection of alpha-adrenergic blocking agents has been demonstrated not only to decrease renal vascular resistance but to increase urinary sodium excretion in humans [20] and experimental animals [21] with low-output heart failure. Alpha-adrenergic blockade also abolishes the effect of acute constriction of the thoracic inferior vena cava to increase tubular sodium reabsorption, specifically the component of this enhanced sodium reabsorption which occurs independent of changes in renal arterial and renal venous pressures [38]. While this antinatriuretic effect of vena caval constriction seems to be partially due to changes in circulating catecholamines [38], the effect of hemorrhage to increase tubular sodium reabsorption has been demonstrated to be mediated primarily by increased renal adrenergic tone [39]. When the renal nerves of a hemorrhaged animal were left intact but the blood perfusing the same animal's kidneys was derived from another animal, an antinatriuresis in the hemorrhaged animal occurred in the absence of a detectable change in filtration rate [39]. This finding seems to focus on the importance of renal nerves and to exclude the need for changes in circulating concentrations of catecholamines, angiotensin or other vasoactive substances in the antinatriuretic effect of hemorrhage. While the authors suggested that this effect of renal nerve stimulation during hemorrhage might enhance sodium reabsorption by a direct effect on the active transport of sodium by the renal tubule cell, it is important to note that the antinatriuresis was associated with a consistent decrease in renal blood flow and increase in filtration fraction. In fact, in virtually all *in vivo* experiments demonstrating an effect of alterations in adrenergic tone on sodium excretion, the results do not differentiate between a direct effect on active sodium transport and an indirect effect mediated by some alteration in intrarenal hemodynamics.

As already alluded to, the intrarenal hemodynamic consequences of alpha-adrenergic stimulation which could be involved in the resultant decrease in sodium excretion include a diminution of glomerular filtration rate or renal cortical blood flow, or both, and an increase in filtration fraction. A decrease in glomerular filtration rate due to adrenergic stimulation, even in the presence of glomerulotubular balance, would certainly be expected to somewhat decrease urinary sodium excretion. There is considerable clearance [8, 13, 40, 41]

and micropuncture [42–44] evidence that a decrease in postglomerular hydrostatic pressure and an increase in postglomerular oncotic pressure, as might occur with the increased renal vascular resistance and filtration fraction during alpha-adrenergic stimulation, might lead to increased proximal tubular sodium reabsorption. It should, however, be mentioned that some recent micropuncture investigations [45, 46] have failed to demonstrate a substantial effect of these peritubular Starling forces on tubular sodium reabsorption. The mechanism whereby a redistribution of renal blood flow away from outer cortical to juxtamedullary nephrons might increase the tubular reabsorption of sodium also remains to be explained [19]. It has been proposed that since juxtamedullary nephrons possess longer loops of Henle than outer cortical nephrons, more avid sodium reabsorption may occur in the juxtamedullary nephrons. Results of recent experiments, however, have cast doubt on whether such redistribution in renal blood flow occurs during alpha-adrenergic stimulation [15, 18]. Moreover, such a redistribution in renal blood flow has been dissociated from changes in renal sodium excretion [15, 45]. Specifically, this alteration in renal blood flow distribution has been observed during sodium restriction in man using radioxenon washout measurements, but restoration to a normal blood flow pattern did not occur with the administration of large doses of alpha-adrenergic blocking agents into the renal artery [47]. Similarly, using the technique of radioactive microspheres to estimate cortical blood flow distribution, the decreased fractional blood flow to outer cortical nephrons which occurs during hemorrhage is not reversed by alpha-adrenergic blockade [15]. Other studies using the same microsphere method have been unable to correlate distribution of renal cortical blood flow with changes in sodium excretion but have found a correlation between sodium excretion and total renal vascular resistance [48].

There is another potential extrarenal effect of alpha-adrenergic stimulation on sodium excretion. Alpha-adrenergic stimulation is known to cause vasoconstriction of venules and veins [1]. This venoconstriction could impede the return of lymph flow into the thoracic veins and there is some experimental evidence that such an impedance to lymphatic flow may initiate renal sodium retention. Specifically, the resultant sodium retention and ascites formation associated with chronic constriction of the thoracic inferior vena cava may be attenuated by shunting the thoracic duct across the vena caval constriction into a thoracic vein [49]. It is thus possible that the increased adrenergic neural tone and catecholamine concentrations which are present in patients with cardiac failure [20, 23] may contribute to edema formation by causing venoconstriction and impeding lymphatic flow.

As with alpha-adrenergic stimulation, any effect of beta-adrenergic stimulation to decrease tubular sodium reabsorption [50] could be related either to alterations in intrarenal hemodynamics or to a direct effect on the active transport of sodium. Injection of large doses of isoproterenol into the renal artery has been shown to cause renal vasodilatation [6]; however, redistribution of cortical blood flow has not been found to occur during beta-adrenergic stimulation with isoproterenol [51].

In addition to the aforementioned extrarenal and intrarenal hemodynamic effects of adrenergic stimulation on the renal excretion of sodium, there is some evidence that beta- and alpha-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 [52], and frog skin [53], thus suggesting an increase in active sodium transport. A direct effect of alpha- and beta-adrenergic stimulation to alter net sodium transport in the proximal tubule has also been suggested on the basis of results obtained in the dog during water diuresis [50, 54]. Since norepinephrine and isoproterenol have been reported to decrease and increase renal cortical tissue cyclic AMP, respectively, in the dog [55] and rat [56], 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, dibutyryl cyclic AMP has been shown to increase urine flow in the dog during water diuresis in a manner similar to intrarenally administered isoproterenol [57]. However, although the dibutyryl cyclic AMP was infused into one renal artery, a bilateral renal effect was observed; thus, an extrarenal mechanism mediating this effect of the nucleotide could not be excluded.

Infusion of cyclic guanosine 3′5′-monophosphate (cyclic GMP) has also been reported in a preliminary communication to produce a similar decrease in urine flow as norepinephrine [58]. Since guanyl cyclase and cyclic GMP are known to be present in the kidney [59–61], it has been proposed that enhanced sodium reabsorption in the proximal tubule during alpha-adrenergic stimulation may be mediated by increased intracellular concentrations of cyclic GMP [54, 58]. 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. A similar effect of these nucleotides on renal gluconeogenesis and ammonia formation has also been proposed [62, 63]. While such a hypothesis remains attractive, it should be noted that two recent groups of investigators using micropuncture techniques in the

dog have failed to detect any effect of either alpha- or beta-adrenergic stimulation on proximal tubular sodium reabsorption [64, 65]. A small effect of adrenergic stimulation on tubular sodium reabsorption, which is not detectable by micropuncture techniques, however, cannot be excluded. Such a modest effect, if present, could be of considerable physiological significance over a period of hours or days.

Effects of the adrenergic nervous system and catecholamines on renal water excretion. There is considerable evidence in both man and experimental animals that alterations in adrenergic neural tone may influence the osmotic movement of water in the mammalian nephron. The i.v. infusion of norepinephrine has been known for some time to be associated with a solute-free water diuresis in both man [66–68] and animals [69, 70]. This diuresis has been demonstrated to occur in the absence of changes in two of the main determinants of renal water excretion, namely glomerular filtration rate and solute excretion [66–68]. Other results also indicate that this effect of norepinephrine on water excretion is related to its alpha-adrenergic stimulating properties since the diuresis is abolished by alpha- but not beta-adrenergic blockade [69]. In contrast, beta-adrenergic stimulation with i.v. administered isoproterenol has been shown to be associated with a consistent antidiuresis [3, 71–73] which also may occur independent of alterations in the rate of glomerular filtration or solute excretion [3]. This antidiuretic effect with i.v. administered isoproterenol is abolished by beta- but not alpha-adrenergic blockade [70]. On the basis of these results, it is evident that alpha- and beta-adrenergic stimulation exert consistent and competing effects on renal water excretion.

There are several investigations which bear on the mechanism(s) whereby adrenergic stimulation alters renal water excretion. Alpha- and beta-adrenergic stimulation may decrease [54] and increase [51] distal tubular fluid delivery, respectively; therefore, these effects would, if anything, modify both the diuretic effect of norepinephrine and the antidiuretic effect of isoproterenol rather than account for them. Since the i.v. infusion of norepinephrine is associated with an increase in systemic arterial pressure, the possibility existed that the resultant water-diuresis was mediated by the increase in renal perfusion pressure. A so-called "druck-diuresis" or pressure diuresis had been previously described in association with an increase in renal arterial pressure to a perfused kidney [74, 75]. Although the level of renal arterial pressure was greater in these previous studies [74, 75] than the renal arterial pressure which occurred during the i.v. infusion of norepinephrine [12, 66–69], a water diuresis was observed in both circumstances. Thus, the increase in renal arterial pressure during the norepinephrine infusion in earlier studies could have contributed to the water diuresis. The results of more recent investigations, however, have demonstrated that this water diuresis occurs in spite of maintenance of a constant renal perfusion pressure [12].

Isoproterenol administered i.v. may quantitatively diminish total peripheral resistance to a greater degree than it enhances cardiac output; thus, a diminution in systemic arterial pressure frequently occurs [3, 71–73]. The antidiuretic effect of beta-adrenergic stimulation therefore could be partially attributed to changes in renal arterial pressure. However, as with i.v. administration of norepinephrine, the antidiuretic effect of beta-adrenergic stimulation has been dissociated from alterations in renal arterial pressure [3]. These effects of systemic alpha- and beta-adrenergic stimulation on renal water excretion have also been demonstrated not to be dependent on renal sympathetic innervation [3, 12]. Thus, taken together, these results suggest that an adrenergic influence on renal water excretion appears to occur independent of changes in renal hemodynamics, renal innervation and renal perfusion pressure. A direct effect of adrenergic stimulation on the water-permeability of the renal tubule epithelium or on the release of vasopressin therefore was implicated.

There is some *in vitro* evidence which suggests that alpha-adrenergic stimulation with norepinephrine antagonizes the effect of vasopressin on water transport [52, 76]. It has been suggested that this antagonism by norepinephrine of the action of vasopressin on osmotic water movement in the toad bladder may be mediated by interference with the effect of vasopressin to increase cyclic AMP [52]. Recent *in vitro* results using dissected medullary collecting ducts support this hypothesis, since addition of norepinephrine abolished the effect of vasopressin to enhance cyclic AMP generation [56]. In contrast, the *in vitro* results examining the effect of isoproterenol on water transport and cyclic AMP, however, have not been consistent [52, 76]. While the *in vitro* addition of isoproterenol to dog kidney tissue has been found to increase medullary cyclic AMP [55], this finding was not confirmed in the rat kidney [56]. Recent studies from our laboratory, however, have demonstrated that the i.v. infusion of isoproterenol is associated with an increased renal medullary tissue concentration of cyclic AMP in water-diuresis intact rats but not in rats suffering from pituitary diabetes insipidus [77].

Beta-adrenergic stimulation with isoproterenol has been found, however, to directly activate adenylate cyclase and increase cyclic AMP in several nonrenal tissues of the body [78, 79]. If vasopressin and isoproterenol increase osmotic water movement in the mam-

malian nephron via the same cyclic AMP-mediated mechanism, then beta-adrenergic blockade with propranolol might be expected to abolish both antidiuretic responses. In this regard, propranolol administration has been found to abolish the antidiuretic effect of isoproterenol but not the antidiuretic effect of vasopressin [70]. In view of these findings, the proposal has been presented that an intermediate receptor in the renal tubule cell might be involved in the antidiuretic effect of beta-adrenergic stimulation [70].

In many *in vivo* studies which have suggested a direct intrarenal effect of the adrenergic nervous system on water transport, a role of endogenous vasopressin release unfortunately has not been excluded [66–73]. Moreover, the use of the bioassay for vasopressin has failed to allow definitive conclusions, since i.v. administered isoproterenol has been reported to increase endogenous vasopressin in man [80] but not in dogs [70]. A small antidiuretic effect of i.v. administered isoproterenol has been demonstrated to occur in rats suffering from hereditary diabetes insipidus [81]. However, although arterial pressure and renal hemodynamics were not measured in these studies [81], the dose/body weight ratio was such as to expect rather profound changes in these hemodynamic indexes [3]. If present, intrarenal hemodynamic alterations, such as a decrease in renal arterial pressure or glomerular filtration, or both [82, 83], could entirely account for the small increase in urinary osmolality (120 to 180 mOsm) which occurred with beta-adrenergic stimulation in these rats with pituitary diabetes insipidus [81].

There is some recent experimental evidence which fails to support a direct *in vivo* effect of either alpha- or beta-adrenergic stimulation on the permeability of the distal nephron to osmotic water movement [3, 12]. In these experiments norepinephrine [12] or isoproterenol [3] was infused directly into the renal artery in a dose estimated to deliver an amount of the drug to the renal circulation which was equal to or greater than that reaching the kidney during the i.v. infusion of the agents. Although both the water diuresis with norepinephrine and the antidiuresis with isoproterenol consistently occurred during i.v. infusion of these hormones, these effects on water excretion could not be duplicated by the intrarenal infusion of the substances [3, 12]. Since the doses of norepinephrine and isoproterenol which were infused into the renal artery were associated with either minimal or no detectable changes in renal hemodynamics or solute excretion [3,12], it was unlikely that any effect of the adrenergic agents on tubular water transport was obscured by such alterations. These results thus suggested that the effect of both alpha- and beta-adrenergic stimulation on water excretion may be primarily mediated by extrarenal mechanisms. Since the time of onset and nature of the effect of both systemic alpha- and beta-adrenergic stimulation on renal water excretion mimicked the action of vasopressin, the role of alterations in endogenous vasopressin release in these responses has been investigated.

In recent studies, acutely hypophysectomized dogs undergoing a water diuresis during glucocorticoid hormone replacement were used to investigate the role of vasopressin release in mediating the effect of adrenergic stimulation on renal water excretion. In the absence of water loading, these hypophysectomized animals have been found to excrete urine with a mean osmolality less than 100 mOsm and to respond to the administration of exogenous vasopressin [12]. In contrast to results in the intact animal, beta-adrenergic stimulation with i.v. administered isoproterenol in these hypophysectomized dogs was not associated with an antidiuresis although the systemic and renal hemodynamic responses were similar [3]. Moreover, in acutely hypophysectomized animals receiving a continuous infusion of either a large or small dose of exogenous vasopressin, i.v. administered norepinephrine was found not to be associated with a water diuresis [12]. These results in intact and hypophysectomized animals, during systemic alpha- and beta-adrenergic stimulation are shown in Figs. 1 through 3. Taken together, these findings provide substantial evidence that the primary effect of both alpha- and beta-adrenergic stimulation on renal water excretion is mediated by alterations in endogenous vasopressin release. The previous results in man [68] and dog [69] which demonstrated a diuretic effect of i.v. administered norepinephrine during an infusion of submaximal doses of vasopressin are best explained by failure of complete suppression of endogenous vasopressin or the effect of the concomitant increase in renal perfusion pressure to produce a "druckdiuresis" or both. Recent results in patients with diabetes insipidus indicate that the primary cause may have been failure of suppression of endogenous vasopressin [84]. Intravenous infusion of norepinephrine into patients suffering from pituitary diabetes insipidus, and receiving the same dose of vasopressin as used in the previous study [68], was not associated with a water diuresis. Moreover, the i.v. infusion of isoproterenol into the same patients with diabetes insipidus failed to produce an antidiuresis.

There are several pathways whereby alpha- and beta-adrenergic stimulation may result in the altered rate of release of endogenous vasopressin. Although the effect of adrenergic stimulation on renal water excretion has been dissociated from changes in renal perfusion pressure, consistent alterations in systemic

hemodynamics occur both during alpha and beta-adrenergic stimulation [3, 12]. The increase in mean arterial pressure during the i.v. administration of norpinephrine or the decrease in mean arterial pressure during the i.v. administration of isoproterenol, therefore, could be involved in the alterations in vasopressin release. Such an effect could be due to a direct effect of changes in cerebral arterial pressure or changes in cervical parasympathetic afferent tone on vasopressin release [85]. Since beta-adrenergic stimulation with i.v. administered isoproterenol increases renin release [86], the resultant antidiuretic effect also could be mediated by an effect of antiotensin II to increase vasopressin release. Such a mechanism is possible, since some investigators have suggested that angiotensin II stimulates vasopressin release [87]. Other workers have failed, however, to confirm this observation using similar bioassay techniques [88], and moderate hemorrhage also has been shown to stimulate renin but not vasopressin release [89]. In recent studies in dogs undergoing a water diuresis, neither i.v. nor intracarotid infusion of antiotensin II was found to alter renal water excretion [90]. Taken together, these results thus suggest that increased antiotensin II concentrations during beta-adrenergic stimulation are not involved in the resultant antidiuresis. Since i.v. administered norepinephrine stimulates renin release [91–93] and, yet, is associated with a water diuresis, angiotensin II appears to be unimportant in this effect of alpha-adrenergic stimulation to suppress vasopressin release.

In an effort to demonstrate a direct effect of catecholamines on vasopressin release, both isoproterenol [94] and norepinephrine [95] have been infused into the carotid artery of dogs at doses estimated to deliver an amount of the drug comparable or greater than that reaching the cerebral circulation during the i.v. infusion of these adrenergic agents. The intracarotid infusion of neither alpha- nor beta-adrenergic agonists

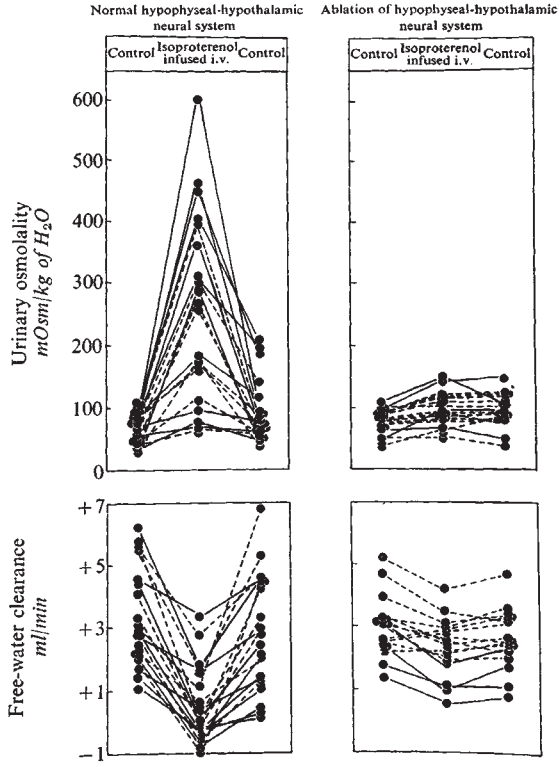

Fig. 1. *Effect of i.v. administration of isoproterenol on urinary osmolality and free water clearance in the intact dog* (left) *vs. the dog with ablation of the hypothalamo-neurohypophysial system* (right). The *broken lines* indicate the results in the denervated kidneys, and the *solid lines* indicate the results in the innervated kidneys. Each *point* is the mean of three to five periods (reproduced with permission of publisher, Ref. 3).

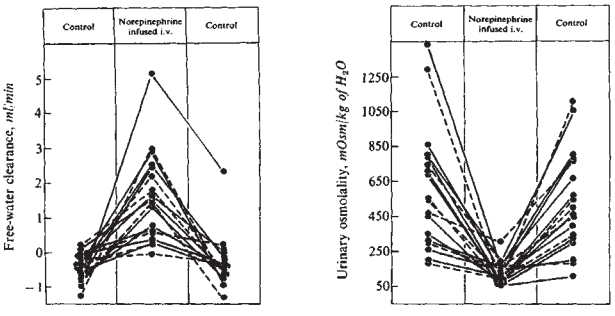

Fig. 2. *Effect of i.v. adminstration of norepinephrine on free water clearance* (left) *and urinary osmolality* (right) *in the hydropenic dog.* Each *point* represents the mean of three to five collection periods. *Solid lines* denote results in innervated kidneys and *dotted lines* in denervated kidneys (reproduced with permission of publisher, Ref. 12).

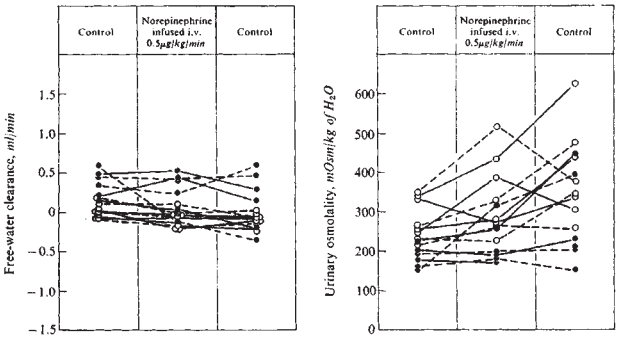

Fig. 3. *Absence of effect of i.v. administration of norepinephrine on free water clearance* (left) *and urinary osmolality* (right) *in hypophysectomized dogs receiving 20 to 40 μU/kg/min of vasopressin.* Each *point* is the mean of three to five collections. *Solid lines* denote results in innervated kidneys and *dotted lines* in denervated kidneys. The *open circles* represent experiments in which 40 μU/kg/min of vasopressin was infused and the *closed circles* represent experiments in which 20 μU/kg/min of vasopressin was infused (reproduced with permission of publisher, Ref. 12).

has been found to alter renal water excretion [94, 95]. Also, no evidence for a direct effect of changes in cerebral arterial pressure on vasopressin release was obtained in experiments in which the carotid arteries of animals with denervated baroreceptors were pump-perfused at different levels of arterial pressure [95]. Since alterations in arterial baroreceptor tone may influence vasopressin release [85], the effect of i.v. administration of norepinephrine on renal water excretion was compared in sham-operated animals vs. animals with denervated arterial baroreceptors. Alpha-adrenergic stimulation with i.v. administered norepinephrine was associated with a water diuresis only in the sham-operated animals (Fig. 4) [95]. Similarly, i.v. administration of isoproterenol was associated with a consistent antidiuresis in sham-operated animals but not in the animals with denervated arterial baroreceptors (Fig. 5) [94].

These results thus suggest that the effect of both alpha- and beta-adrenergic stimulation on vasopressin release involves alterations in arterial baroreceptor tone. It also is possible that this same pathway may be involved in other circumstances in which renal water excretion is altered by nonosmotic influences. In this regard, the antidiuretic effect of nicotine recently has been demonstrated to be dependent on intact cervical parasympathetic pathways [96]. Whether alterations in renal water excretion during changes in volume or

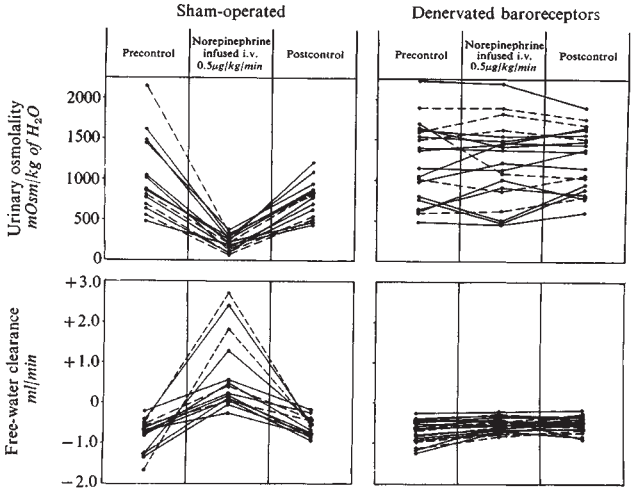

Fig. 4. *Effect of i.v. administration of norepinephrine on urinary osmolality* (above) *and free water clearance* (below) *in animals with cervical sham operation* (left) *and denervation of baroreceptors* (right). Denervation of baroreceptors abolished the diuretic effect of i.v. administered norepinephrine. Each *point* represents the mean value of three to five urine collections for a single kidney. The *broken lines* represent results from denervated kidneys and the *solid lines* represent results from innervated kidneys (reproduced with permission of publisher [95]).

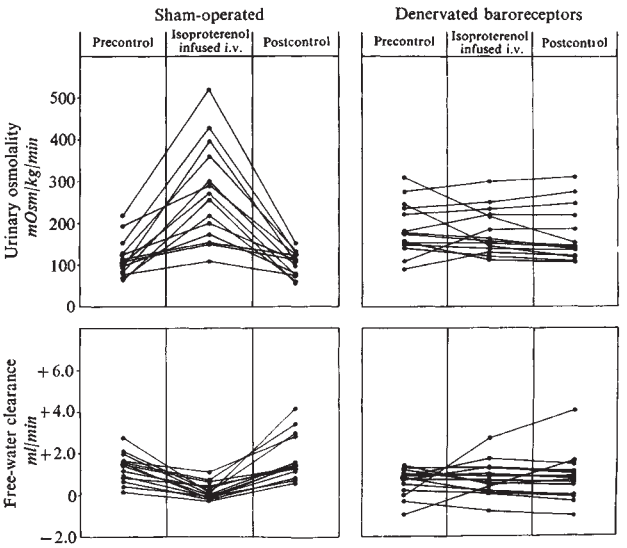

Fig. 5. *Effect of i.v. administration of isoproterenol on urinary osmolality* (above) *and free-water clearance* (below) *in animals with cervical sham-operation* (left) *and denervation of baroreceptors* (right). Each *point* represents the mean value of three to five urine collections from a single kidney (reproduced with permission of publisher [94]).

emotional status, endocrine dysfunction, cardiac or hepatic failure and administration of various drugs such as barbituates and opiates involve this baroreceptor-mediated pathway of vasopressin release remains to be determined.

Effect of adrenergic nervous system on renin secretion. There is considerable evidence that increased activity of the adrenergic nervous system provides a potent stimulus to increase renin secretion. Several maneuvers are known to stimulate both sympathetic neural pathways and renin release including hemorrhage [97–100], carotid occlusion [98], direct stimulation of renal nerves [91, 101, 102], infusion of catecholamines or ganglionic stimulating agents [91, 98], hypoglycemia [103, 104] and stimulation of the midbrain [105–107]. It has been proposed that either circulating catecholamines from the adrenal medulla or norepinephrine liberated at renal adrenergic nerve terminals, or a combination thereof, may mediate these responses. Evidence in support of a role of circulating catecholamines from the adrenal medulla is derived from experiments in which adrenal, but not renal, denervation abolished the effect of hypoglycemia to increase plasma renin activity [104]. It is not known, however, whether release of norepinephrine from nonadrenal extrarenal adrenergic nerve endings can substantially alter circulating levels of norepinephrine so as to mediate effects on renin secretion. A local effect of norepinephrine release at renal sympathetic nerves is

suggested by the finding that increased plasma renin activity associated with midbrain stimulation can be attenuated or abolished by renal denervation [107].

There are several mechanisms whereby adrenergic stimulation might cause an increase in renal secretion of renin. The renal vasoconstriction association with alpha-adrenergic stimulation could increase renin release by either diminishing the rate of sodium delivery to [108], or transport at [109], the macula densa. Such an effect could be caused by either a diminished filtration rate of sodium, an increase in sodium reabsorption in the proximal tubule, or a combination thereof. Adrenergic stimulation could also increase renin secretion by diminishing the pressure at an intrarenal vascular receptor site which influences renin release [110, 111]. Although systemic arterial pressure may increase during renal nerve stimulation [101, 102], carotid occlusion [98] and midbrain stimulation [105–107]; it may remain unchanged during moderate hemorrhage [98] and hypoglycemia [103, 104] or decrease during severe hemorrhage [97]; yet, in all these situations the concomitant renal nerve stimulation and renal vasoconstriction could diminish pressure at some intrarenal pressure-sensitive receptor and stimulate renin release from the juxtaglomerular cells.

In addition to the importance of these so-called macula densa [108, 109] and baroreceptor mechanisms [110, 111], some investigators have suggested that renal nerve stimulation may increase renin release by a direct effect on the juxtaglomerular cells [101, 102, 112, 113]. This possibility has been considered tenable since juxtaglomerular cells of the afferent arteriole are richly innervated by postganglionic neural fibers [114, 115]. Moreover, it has been reported that stimulation of renal nerves increases the release of renin in both the normal [112] and nonfiltering kidney [113] in which vascular reactivity has been diminished by a renal arterial infusion of papaverine. Since the responsiveness of any intrarenal vascular receptor governing renin release may be abolished by the papaverine infusion and any effect of sodium delivery to, or transport at, the macula densa is presumably precluded by use of the nonfiltering kidney, these results have been interpreted in support of a direct effect of adrenergic pathways on renin release. Other support for a direct action on the juxtaglomerular cells is the observation that catecholamines may increase production or release of renin from renal cortical slices *in vitro* [116]. A redistribution of blood flow away from the outer portion of the renal cortex, which contains the highest renal concentration of renin, is another potential mechanism whereby renal nerve stimulation might cause an increased release of renin. As discussed earlier, although results using radioxenon washout curves suggested that adrenergic stimulation might produce such a redistribution of cortical blood flow [14, 17], more recent studies using the radioactive microsphere method failed to demonstrate such an effect on cortical blood flow distribution during either norepinephrine infusion [16] or renal nerve stimulation [15].

There is some evidence that beta-adrenergic stimulation may provide a more important pathway for control of renin release than alpha-adrenergic stimulation. Several of the maneuvers known to stimulate renin release including hypoglycemia [104], renal nerve stimulation [101, 102] and midbrain stimulation [107] have been found to be attenuated or abolished by the administration of the beta-adrenergic blocking agent, propranolol, but are either enhanced or unaffected by alpha-adrenergic blockade. In contrast to these results, however, are the findings of Winer, Chokshi and Walkenhorst [117], which demonstrated that both propranolol and the alpha-adrenergic antagonist phentolamine blocked the effects of norepinephrine to increase renin secretion. The beta-adrenergic blocker propranolol also abolished the effect of cyclic AMP to stimulate renin secretion [117]. These authors therefore suggested that phentolamine and propranolol suppress renin secretion at a site distal to cyclic AMP production, rather than by blockade of plasma membrane alpha- or beta-adrenergic receptors or inhibition of adenyl cyclase. Winer et al [117] also have reported that both the D- and L-isomers of propranolol block the effect of norepinephrine to increase renin release, even though only the L-isomer possesses beta-adrenergic blocking properties. Since lidocaine, a local anesthetic, did not prevent the isoproterenol-induced rise in renin secretion, the authors concluded that the anesthetic properties of propranolol did not account for the capacity of these agents to block the effect of isoproterenol to stimulate renin secretion [117]. Renal denervation also has failed to abolish the effect of i.v. administered isoproterenol to increase renin secretion [86].

As yet there is no adequate explanation for the reported different effects of alpha-adrenergic blocking agents on the effect of various adrenergic stimuli to increase renin secretion. It is known, however, that alpha-adrenergic blockade alone is a potent stimulator of renin secretion [101]. In this regard, most investigators who have failed to attenuate the increases in plasma renin activity during various adrenergic stimuli by alpha-adrenergic blockade, have used large doses of blockers. These larger doses of alpha-adrenergic blocking agents are associated with a decrease in systemic arterial pressure, and this hypo-

tensive effect may account for the rise in renin secretion observed during their administration. Thus, the independent effect of the alpha-adrenergic blockers to stimulate renin secretion may have obscured any effect that these alpha-adrenergic blockers may have had to inhibit renin release caused by the primary stimulus. Studies are therefore needed to examine whether smaller doses of alpha-adrenergic blocking agents, which do not independently stimulate renin secretion but produce effective alpha-adrenergic blockade, exist.

Not only are the results of studies using alpha- and beta-adrenergic blockers difficult to synthesize into firm conclusions, but the results of investigations using alpha- and beta-adrenergic stimulators also do not conclusively favor the predominance of either an alpha- or beta-adrenergic receptor in the regulation of renin secretion. Both relatively specific beta-adrenergic agonists, such as isoproterenol [3, 118, 119], and alpha-adrenergic agonists, such as metaraminol and methoxamine [120, 121], have been shown to stimulate renin release. Some authors have found that with similar doses of epinephrine and norepinephrine, epinephrine provides the more potent stimulation of renin release, thus favoring the predominance of a beta-adrenergic receptor [97]. Recent studies by Johnson, Davis and Whitty [113], however, have shown that the effect of epinephrine, but not norepinephrine, to stimulate renin release in the nonfiltering kidney is blocked by papaverine. This finding would suggest that any direct effect of these catecholamines on the juxtaglomerular cells may involve alpha-adrenergic receptors. The finding that cyclic AMP [117] and theophylline (a phosphodiesterase inhibitor, which increases tissue concentrations of cyclic AMP) [122, 123], increase renin secretion has been used to support a predominant role of beta-receptors in the control of renin release. The basis for this argument is that beta-, but not alpha-, adrenergic stimulation increases renal cortical tissue concentrations of cyclic AMP [55, 56]. It must be emphasized, however, that conflicting results as to the effect of cyclic AMP on renin secretion have been reported [117, 124].

The exact location of an alpha- or beta-adrenergic receptor for regulation of renin release also has been a matter of some debate. Evidence has been presented for the existence of an intrarenal beta-receptor which affects renin secretion [101, 102]. The histologic findings previously mentioned [114, 115] which demonstrated many adrenergic nerve endings among the juxtaglomerular cells provide the anatomical setting for an intrarenal receptor site whereby adrenergic stimulation influences renin release. In support of this hypothesis is the finding that norepinephrine, epinephrine and cyclic AMP have been reported to stimulate renin release *in vitro* [116]. Other investigators, however, have not been able to demonstrate similar *in vitro* effects of catecholamines in renin release [125, 126]. Moreover, *in vitro* results may not be readily transferable to *in vivo* conditions.

It has been suggested that since either propranolol administration or renal denervation abolishes the effect of midbrain stimulation to increase plasma renin activity, the effect must involve an intrarenal beta-receptor [107]. Such an interpretation, however, can be accepted only with some reservation. Although renal hemodynamics were not measured in these experiments [107], it is known from other studies that midbrain stimulation is associated with a marked diminution in glomerular filtration rate [127]. Such an effect of midbrain stimulation on renin secretion could be mediated, therefore, by either a baroreceptor or macula densa mechanisms in the absence of any direct effect on the juxtaglomerular cells. In this regard, the effect of renal denervation to abolish the effect of midbrain stimulation to increase plasma renin activity could be related to the attenuation of these renal hemodynamic alterations [107]. Moreover, the extrarenal hemodynamic effects of midbrain stimulation were markedly altered by systemic beta-adrenergic blockade with propranolol. Specifically, the rise in arterial pressure with midbrain stimulation was much less after administration of propranolol. These results with midbrain stimulation [107], therefore, do not establish the presence of an intrarenal beta-adrenergic receptor which regulates renin secretion.

The studies which more directly investigate the presence of an intrarenal adrenergic receptor involve either renal nerve stimulation [101, 102, 113] or infusion of catecholamines into the renal artery [91–93]. Since the doses of norepinephrine which stimulate renin secretion may also produce renal vasoconstriction, a direct effect of this catecholamine on the juxtaglomerular cells to release renin is difficult to assess. The infusion of the beta-adrenergic agonist isoproterenol into the renal artery has been shown to stimulate renin secretion in the absence of renal vasoconstriction, but in some of these studies the doses of isoproterenol used may have produced extrarenal alterations [118, 119]. A comparison of the effect of isoproterenol on renin secretion in the infused and contralateral kidneys was also not examined in these studies in an effort to document an intrarenal effect.

The study by Ayers, Harris and Lefer [118] has provided some evidence for the presence of an intrarenal beta-adrenergic receptor which regulates renin secretion. In this study the intrarenal infusion of iso-

proterenol into the constricted renal artery of animals with renal vascular hypertension produced a more pronounced effect on renin secretion than an i.v. infusion of the same dose of the drug. The renal arterial infusion, however, was begun one hour after the i.v. infusion, and no control studies were performed to examine whether a continuous i.v. infusion of isoproterenol for the same duration of time would have produced similar results. A recent study in dogs also has compared the effect of the same dose of isoproterenol infused i.v. and into a renal artery on renin secretion [86]. Because of the capacity of the kidney to inactivate isoproterenol [4], the intrarenal infusion was not associated with extrarenal hemodynamic alterations [86]. Only the i.v. infusion of isoproterenol was found to exert a significant effect on plasma renin activity and renin secretion (Fig. 6). These results therefore suggested that an extrarenal mechanism was responsible for the effect of isoproterenol to increase renin secretion. The dose of isoproterenol used in these dog studies was sufficient to produce a 50% increase in cardiac output when infused i.v. and, yet, did not affect renin secretion when infused into the renal artery [86]. If present, therefore, any intrarenal beta-receptor influencing renin release must be considerably less sensitive than the extrarenal cardiovascular beta-receptors.

In intact animals the effect of larger intrarenal doses of isoproterenol to stimulate renin release is difficult to evaluate with respect to an intrarenal beta-receptor, since these large doses of isoproterenol may produce extrarenal hemodynamic alterations [118, 119]. However, in a recent study in the isolated perfused rat kidney, large doses (per g of kidney wt) of isoproterenol were found to stimulate renin secretion [128]. Whether this effect is of pharmacologic or physiologic significance, however, remains to be determined.

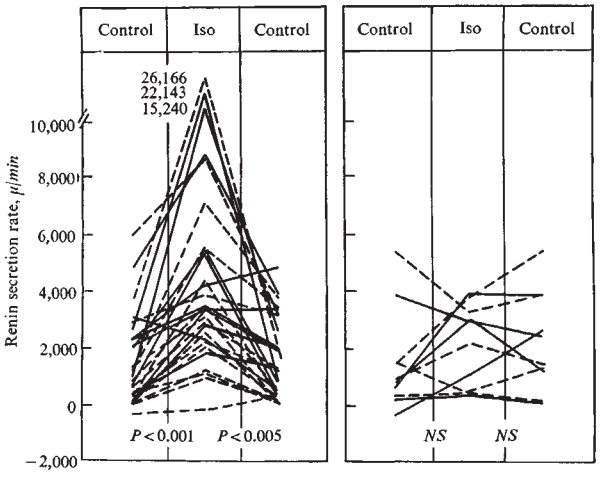

Fig. 6. *Effect of i.v. administered but not intrarenal isoproterenol (Iso) to increase renin secretion rates.* Results in denervated and innervated kidneys are shown by *broken* and *solid lines*, respectively (reproduced from data published in [86]).

As previously mentioned, the effect of renal nerve stimulation to increase plasma renin activity has been reported to be abolished by propranolol administration [101, 102]. Since renal hemodynamics were not measured in these studies [101, 102] and propranolol administration could alter the renal hemodynamic response to renal nerve stimulation, further studies are necessary to differentiate between a direct effect of renal nerve stimulation on the juxtaglomerular cells and an effect on renin release mediated by either a baroreceptor or macula densa mechanism. The studies of Johnson et al [113] have demonstrated that renal nerve stimulation increases renin secretion in the nonfiltering kidney receiving a papaverine infusion. While these results suggest a direct effect of renal nerve stimulation on the release of renin by the juxtaglomerular cells, they do not differentiate between an alpha- or beta-adrenergic receptor. As previously discussed, the finding that papaverine administration abolished the effect of epinephrine but not norepinephrine to increase renin secretion in the nonfiltering kidney suggested an importance of an intrarenal alpha-receptor [113].

In summary, there seems little doubt that adrenergic stimulation provides a potent stimulus to renin secretion by both extrarenal and intrarenal mechanisms. This effect on renin secretion may be mediated by several pathways including a direct effect on the juxtaglomerular cells, a change in pressure at an intrarenal vascular receptor or a change in sodium delivery to, or transport at, the macula densa. Whether there is a predominant role of alpha- or beta-adrenergic receptors, or whether this pharmacologic approach used to define the mechanism is even appropriate, awaits further investigations. A primary or secondary role of adrenergic stimulation in the increased renin secretion observed in clinical circumstances including salt restriction and hypovolemia; adrenal insufficiency; congestive failure; hepatic cirrhosis; nephrotic syndrome; anesthesia; and high renin, accelerated hypertension seems likely and must be investigated further.

Acknowledgments

Some of the studies reported in this review were supported by Public Health Service grants HL 15467 and 15629 from the National Institutes of Health, and a grant from the Hoechst Pharmaceutical Company. Ms. Linda Benson and Ms. Diana LaRocco provided

secretarial assistance in the preparation of the manuscript. The advice collaboration and work of the following individuals was instrumental in the performance of many of the studies described in this review: Drs. Laurence Earley, Tomas Berl, Ian Reid, Michael Humphreys, Robert Ufferman, Keith McDonald, David Lauler, Robert Anderson, John Boykin and Pravit Cadnapaphornchai; Ms. Judith Harbottle; Mr. Lowell Gilbert; Ms. Abby McCool; and Mr. Gary Aisenbrey.

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