Review

Volume reflex in diabetes

Kaushik P. Patel *

Department of Physiology and Biophysics, University of Nebraska Medical Center, 600 South 42nd Street, Box 984575, Omaha, NE 68198-4575, USA

Received 19 September 1996; accepted 9 December 1996

Keywords: Diabetes; Volume reflex; Renal hemodynamics; Autonomic nervous system

1. Introduction

Diabetes mellitus is characterized by altered fluid balance, blood volume and exchangeable sodium. In metabolically stable diabetes there is an increased exchangeable sodium content (10–15%). This occurs in diabetic subjects that are normotensive or hypertensive and those with or without complications [15,20,48,73]. Many of the studies on exchangeable sodium and studies in diabetics of short duration without complications suggest that sodium retention occurs early in the disease and may be relatively common [15,20,48,73]. It has been suggested that the diabetics that develop nephropathy are those who are unable to compensate for this sodium retention. With the kidney disease deteriorating with time the final outcome is often the development of hypertension. These facts, taken together, indicate that the regulation of fluid balance, particularly sodium handling, early during diabetes is of great importance in the overall long-term cardiovascular complications of the diabetic state. O’Hare and colleagues have reported a diminished natriuretic response to volume expansion-induced by water immersion in diabetic patients [46–50]. This altered sodium excretion in the diabetic could not be attributed to hemodynamic or hormonal changes (release of ANF, renin, and aldosterone during water immersion) [46,47,50]. These investigators [46–50] were unable to identify specific mechanisms for the altered sodium excretion in these patients. To determine whether a defect in neural component of the volume reflex is responsible for some of these abnormalities in the diabetic state, we have conducted a series of experiments to examine the various components of the volume reflex Fig. 1 in the streptozotocin (STZ)-induced diabetic rats [63] at the early phase of diabetes, 2–4 weeks after STZ injection [56,77].

Divided broadly the various components of the volume reflex are: (1) the afferent limb (including receptors, electromechanical coupling factors and afferent fibers), (2) the central neural processing of afferent input, and (3) the efferent limb (renal sympathetic nerve activity and the release and/or action of humoral factors). This review outlines the experiments performed to examine the volume reflex and further determine the mechanisms involved in the altered volume reflex in diabetes. This paper also outlines the major gaps in our knowledge, particularly with regard to the neural component of the volume reflex during diabetes.

2. Evidence for altered volume reflex in the early stage of diabetes

Fig. 1 outlines the major components of the volume reflex. The volume receptor reflex has an afferent limb (mostly via the vagus), central connections with the primary synapse in the nucleus tractus solitarii (NTS), and the efferent limb which consists of the renal sympathetic nerves and the humoral system [e.g., atrial natriuretic factor (ANF) and vasopressin (AVP)] [36,41,69]. Volume receptors respond to atrial and ventricular filling and are very sensitive to changes in heart chamber filling pressure in various species including primates [28,29,41,69]. Stimulation of these volume receptors by acute volume expansion produces a reflex increase in sodium excretion and urine flow in various species including primates [26,29,41,61]. Diabetes is accompanied by a variety of autonomic reflex abnormalities that impact on cardiovascular function [13,19,43,64,66]. Diabetic patients display an abnormal
Fig. 1. Schematic diagram of the volume reflex. An increase in blood volume causes a decrease in renal nerve activity, vasopressin (ADH) and angiotensin II (Ang II) and an increase in levels of atrial natriuretic factor (ANF), which in turn increases urine flow and sodium excretion. For a similar increase in volume there is a reduced renal sympatho-inhibition and subsequent urine flow and sodium excretion in diabetic rats compared to control rats.

R-R interval variation [43], and abnormal circulatory reflexes (altered Valsalva maneuver) [19,64]. Chang and Lund [13] have demonstrated an altered heart rate response to changes in arterial pressure in STZ-induced diabetic rats. These studies taken together suggest an altered overall autonomic function and/or reflex in the diabetic state [13,19,43,64,66]. It may well be that an altered volume reflex in the diabetic rat reflects autonomic reflex dysfunction.

To determine whether the extent to which the volume reflex is altered in diabetes, the renal excretory responses to acute volume expansion (VE) were measured in rats 2 and 4 weeks after STZ injection [56,77]. Urine flow and sodium excretion from innervated kidneys, but not from denervated kidneys, were significantly lower in diabetic rats than those in control rats during acute VE. Correcting the diabetic condition with insulin (third group) rectified the blood glucose levels and the blunted responses to VE from intact kidneys (Figs. 2 and 3). The glomerular filtration rate (GFR) measurements indicated that hemodynamic changes did not account for the blunted responses in the diabetic rats [77]. These results confirmed that hemodynamic changes per se were not responsible for the altered volume reflex in the diabetic rats at this stage. Furthermore, these studies demonstrated that the volume reflex is blunted at 2 and 4 weeks after STZ injection with an abnormality of the neural mechanism. Therefore, at this phase in the diabetic disease the neural component of the volume reflex is blunted.

The change in volume reflex is unique at this stage of diabetes since baroreflex-mediated inhibition of renal sympatheic nerve activity is not altered [59]. Furthermore, the angiotensin II (AII) system does not alter volume reflex in diabetic rats at 2 weeks after STZ injection [58]. However, vasopressin fails to potentiate the baroreflex in diabetic rats as it does in the euglycemic normal rats [59]. In terms of other reflexes, ventilatory responses to hypercapnic and hypoxic challenges were significantly less in diabetic rats than those in control rats and diabetic rats treated with insulin by 3–4 weeks after induction of diabetes [32]. Whether the reduced ventilatory responses at this stage have a common central site abnormality, such as altered neuronal activity in NTS (primary site for various visceral reflexes) [32]...
afferents) [38], producing the altered volume reflex, remains to be examined.

2.1. Reduced renal responses to acute saline load in obese Zucker rats (Type II model of diabetes)

We have demonstrated an altered volume reflex in the Type I diabetes. This led us to examine whether a similar abnormality exists in Type II diabetes. Thus, we determined whether the reflex response to a saline load is altered in another model of diabetes, the obese Zucker rat—Type II model of diabetes [74]. The obese Zucker rat is a genetic model of obesity and insulin-resistant diabetes which has been reported to have high blood pressure. We examined the reflex renal responses to acute volume expansion in both anesthetized obese and lean Zucker rats. Initial blood pressure was significantly elevated in the obese Zucker rats compared to the lean controls. Urine flow and sodium excretion from innervated and denervated kidneys were measured before and after acute volume expansion with normal saline. Volume expansion resulted in significantly less urine flow and sodium excretion in the obese than in the lean Zucker rats, regardless of innervation. However, if one compares the data from innervated lean Zucker rats with those from the denervated kidneys in obese Zucker rats, improvement is found in excretory function due to removal of renal nerves. First, these results demonstrate that the volume reflex is altered in the obese Zucker rat model of diabetes [74]. Secondly, the neural component of the reflex does not appear to be totally responsible for the altered renal excretory function in this model of diabetes.

This initial work revealed that: (1) the volume reflex is blunted in STZ-induced diabetic rats studied 2 and 4 weeks after STZ injection [56,77] and (2) restoring the glucose levels to normal by chronic insulin treatment normalized the blunted volume reflex [56,77]. In obese Zucker rats with insulin-resistant diabetes the volume reflex is blunted as well [74]. These data suggest that diabetic rats display an abnormality somewhere within the reflex arc, linking the stimulus of volume expansion to the effector mechanisms producing diuresis and natriuresis. There are several possible ‘intermediate steps’ that could be altered in diabetic rats. Generally the volume reflex can be broken down into: (1) an afferent limb of the volume receptor reflex, (2) central sites of integration for volume receptor reflex and (3) an efferent limb of the volume receptor reflex. Problems associated with each of these components of the volume reflex arc in diabetes will be summarized below.

2.2. Afferent limb of the volume receptor reflex

Peripheral neuropathy, particularly sensory, has been observed in diabetic patients; however, there is no clear evidence for such an abnormality in the afferent limb of the volume reflex. Diabetic patients have been reported to have reduced numbers of fibers in carotid sinus nerves [68]. Altered baroreflex sensitivity in STZ-induced diabetic rats has also been observed at a late stage of diabetes [13]. There is also evidence for decreased motor nerve conduction in the diabetic state [27]. It remains to be determined whether the blunted volume reflex (subserved primarily by vagal afferents) observed in diabetic rats is due to a defect in the afferent limb of the volume reflex. Recent studies in our laboratory have addressed the postulate that the altered volume reflex in diabetic rats reflects reduced distensibility of the right atrium and the veno-atrial junction, structures known to possess a large number of volume receptors [60].

The distensibility was assessed by measuring the stiffness constants (slope of the pressure–volume curve, ΔP/ΔV) of the right atrium and veno-atrial junction in 2-week streptozotocin (STZ)-induced diabetic rats and control rats. Similar pressure–volume curves were also determined in an additional group of diabetic rats under daily insulin treatment (2 U/rat/day) which normalized plasma glucose (91 ± 5 mg/dl). Fig. 4 illustrates that the stiffness constant (slope) of the right atrium and veno-atrial junction in diabetic rats was significantly greater than the mean slope of the control and insulin-treated diabetic rats. These data reveal that the diabetic rats have stiffer right atria and veno-atrial junctions, which may reduce stimulation of the volume receptors to volume load. Moreover, the increased stiffness in diabetic rats is prevented by chronic insulin treatment. These data have uncovered a decreased compliance in the veno-atrial junction of diabetic rats compared to control rats [60]. In heart failure, the decrease in diastolic compliance in the left atrium has been shown to limit the change in receptor discharge as left atrial pressure increases during filling [78]. Such a change in receptor discharge in diabetic rats remains to be determined. Although the possibility of altered vagal afferent sensitivity
in diabetes has not been assessed, the data available to date indicate that an altered afferent limb of the volume reflex may contribute to the overall blunted diuretic and natriuretic response to volume load observed in diabetic rats.

2.3. Central sites of integration for the volume receptor reflex

Anatomical, electrophysiological and histological evidence have clearly identified the nucleus of the tractus solitarius (NTS) as the primary site of termination for afferent vagal fibers [36]. In addition, the forebrain has been examined thoroughly for its involvement in various aspects of fluid balance, cardiovascular control and autonomic outflow [34,67]. Within the forebrain are structures that have been implicated in sympathetic outflow, AII-induced drinking, and increases in arterial pressure [34,67]. The paraventricular nucleus (PVN) and the supraoptic nucleus (SON) are known to produce AVP, an important humoral factor involved in fluid balance [34,67]. In addition to these effects, the PVN has also been implicated in the control of sympathetic outflow [67]. Swanson et al. [67] have suggested that the PVN may specifically affect the heart and the kidney since there are direct projections from the PVN to the intermediolateral cell column in the spinal cord at levels where cardiac and renal postganglionic sympathetic nerves originate. Thus, the PVN may be an ideal site to relay information regarding the volume receptor reflex, especially since neurons in this region respond to volume load. Diabetic patients, as well as rats, have been reported to have increased levels of circulating AVP [70,75]. In addition, osmotic regulation of AVP secretion is reset in diabetes, such that higher plasma AVP levels are evident at comparable levels of plasma sodium [75]. This resetting may be one explanation for the blunted volume reflex in diabetic rats.

Some investigators have demonstrated altered monoamine levels and metabolism in various large central areas of the brain during diabetes in rats [9,10]. However, these studies did not explore the possibility that specific central nuclei may exhibit altered noradrenergic activity within the hypothalamus or the brainstem. In recent studies, we assessed the effect of STZ-induced diabetes (2 weeks after STZ–early phase of diabetes) on neural activity in discrete regions of the brain by histochemical localization and photodensitometric quantification of the metabolic enzyme, hexokinase [38]. Diabetic rats exhibited significant increases in hexokinase activity in the magnocellular division of the PVN of the hypothalamus (12.1%), the medial subdivision of the NTS (15.5%), and the commissural subdivision of the NTS (10.9%) (Fig. 5). An increase, though just below the level of significance, was also observed in the supraoptic nucleus (SON) of the hypothalamus (11.5%). No changes in hexokinase activity were seen in the subfornical organ, medial preoptic area, paraventricular division of the PVN, locus coeruleus or dorsal motor nucleus of the vagus in diabetic rats. These results reinforce the idea that the brain is not exempt from the changes associated with diabetes and suggest that the altered activity in the PVN (and SON) and two divisions of the NTS is probably related to the changes in plasma vasopressin levels and blood volume regulation.

In another approach to examining central mechanisms involved in influencing diuretic and natriuretic effects, we examined the impact of diabetes (2 weeks after STZ) on diuretic and natriuretic responses produced by central (i.c.v.) administration of clonidine [76]. This study revealed that the i.c.v. administration of clonidine evokes (1)
a blunted diuresis in diabetic rats, possibly due to reduced inhibition of antidiuretic hormone release and/or action, and (2) a blunted natriuresis in diabetic rats that may be related to decreased renal sympatho-inhibition. Taken together, these results lead us to suggest that there may be a defect in central neural processing contributing to the blunted volume reflex previously observed in diabetic rats. We believe that further examination of these central sites and the noradrenergic mechanisms within these sites will shed more light on the role of the central nervous system in the blunted volume reflex observed in diabetic rats.

2.4. Efferent limb of the volume receptor reflex

Overall the efferent mechanisms for the reflex diuretic and natriuretic responses to volume expansion have both neural [16,35,41], and humoral [37,41] components (Fig. 1). It has been well established that the neural component of the diuretic and natriuretic response is decreased renal sympathetic nerve activity (RSNA) [16,35]. Since RSNA produces retention of salt and water, decreased RSNA can contribute to diuresis and natriuresis [16,41]. Several humoral factors contribute to the efferent limb of the volume reflex. Renin release is inhibited via reflex decline in RSNA which occurs in response to atrial stretch [41]. The resulting decrease in angiotensin II levels allows increased salt and water excretion. In addition, stimulation of right atrial receptors by stretching the veno-atrial junction decreases firing of neurosecretory cells in the SON and the PVN, areas known to be the source of vasopressin [37]. Hence, plasma levels of vasopressin are depressed in response to acute volume expansion, thus contributing to the diuresis [41]. Finally, atrial stretch accompanying volume expansion is a direct stimulus for atrial natriuretic factor release [40]. Increased levels of ANF would cause a natriuresis and diuresis.

2.4.1. Neural component

Our initial results show an attenuated decrease in sodium excretion from the innervated kidneys of diabetic rats (2 weeks after STZ) compared to innervated kidneys of control rats (Fig. 3); however, the sodium excretion from the denervated kidneys of diabetic rats was similar to that from innervated kidneys of control rats [56]. Furthermore, in 4-week diabetic rats, urine flow and sodium excretion from the innervated kidneys, but not the denervated kidneys, were significantly lower than those in control rats [77]. These results suggest that part of the blunted natriuresis to volume expansion in diabetic rats is due to the tonic impact of renal nerves. The decreased response in innervated kidneys of diabetic rats may be due to (1) decreased central inhibition of RSNA or (2) a hyperactive response at the neuro-effector junction (effector site). The recording of RSNA would distinguish between the effects at the neuro-effector site versus alterations in RSNA. The renal excretory data provided indirect evidence that increased RSNA may be responsible for the altered volume reflex in the STZ-induced diabetic rats. To ascertain whether or not altered control of RSNA was responsible for the increased salt and water retention during acute volume expansion, we measured RSNA responses to VE in three groups of rats (control, diabetic and diabetic + insulin). The results (Fig. 6) reveal that diabetic rats display a blunted renal sympatho-inhibition in response to graded VE with isotonic saline (10% of body weight over 40 min), compared to control and chronically insulin-treated diabetic rats [58]. The contralateral innervated kidney of these diabetic rats exhibited blunted natriuretic and diuretic responses to VE, relative to control and insulin-treated diabetic rats. These results clearly suggest that the lack of renal sympatho-inhibition in diabetic rats is responsible for the blunted volume reflex in diabetic rats. Moreover, the blunted renal sympatho-inhibition was not corrected by acute normalization of blood glucose in rats with diabetes [58], suggesting that this phenomenon is a primary abnormality accompanying diabetes.

Since RSNA produces retention of sodium and water, decreased RSNA can contribute to diuresis and natriuresis during VE [37,41]. The excretory influences of the renal nerves are mediated primarily by alpha-1 receptors. There are no studies to date reporting the density of noradrenergic receptors in the kidneys of diabetic rats. However, an enhanced noradrenergic alpha-1 receptor activity has been reported in the hearts of alloxan-induced diabetic lambs [18]. Such an increased alpha-1 activity in the kidney of diabetic rats may contribute to the increased retention of sodium by the kidney [17,41] via the renal nerves. The alpha-1 receptors exert their effect by their action on
vascular alpha-1 adrenoceptor (generally alpha-1A subtype) and/or other alpha-1B adrenoceptor actions on the renal tubules. Thus, if we could find a way to block renal tubular alpha-1B but not vascular alpha-1A adrenoceptors, we may get a beneficial natriuresis and diuresis without vascular changes. One third of the proximal tubular and nearly all of the medullary thick ascending limb of Henle alpha-1 receptors are chloroethcyclonidine (CEC)-sensitive (i.e., the alpha-1B subtype) [21]. It is thus possible to block a large component of the tubular innervation without altering vascular alpha-1A receptors. In preliminary studies, we have found that CEC administration mimics the beneficial impact of renal denervation on excretory responses to acute VE in diabetic rats [55]. CEC did not alter blood pressure or heart rate and the increased sodium excretion was observed without a parallel change in renal hemodynamic parameters (such as blood pressure or GFR). These observations indicate a tubular effect of alpha-1B blockade on sodium excretion and implicate inappropriate alpha-1B-dependent activation as one factor contributing to the blunted natriuretic response to VE in diabetes. These results have very exciting possibilities for the therapeutic use of CEC in the altered fluid balance regulation accompanying diabetes, as well as in edematous states characterized by increase in RSNA such as heart failure, cirrhosis of the liver and nephrotic syndrome etc.

Despite the accumulating evidence that the neural effector limb of the volume reflex is blunted in diabetes, several key questions remain unanswered: Is the RSNA abnormally elevated before and during acute volume expansion in diabetic rats? Is diabetes accompanied by an altered relationship between RSNA and the subsequent release of norepinephrine (affected by various factors such as turnover of NE, presynaptic excitation or inhibition, etc.)? Is the renal excretory response to sympathetic nerve stimulation augmented in diabetic rats? Is renal noradrenergic receptor density increased in diabetes? Answers to all these questions will identify some of the specific mechanisms by which the renal sympathetic nerves are involved in sodium retention in response to acute volume expansion in diabetes.

2.4.2. Humoral component

Several humoral maladaptations have been reported to accompany diabetes [53,70,75]. In light of the direct impact of atrial stretch on release of atrial natriuretic factor (ANF), the report of elevated basal ANF levels in diabetic rats [53] gains potential relevance to the response to VE. Moreover, VE does not increase ANF levels in diabetic rats to the same extent that it does in non-diabetic control rats [31]. To determine whether or not renal responses to ANF are altered in the diabetic state, the diuretic and natriuretic responses to ANF were assessed in the innervated and denervated kidneys of anesthetized control and diabetic rats [57,77]. Blood glucose levels were significantly elevated in the diabetic rats compared with control rats. Compared with control rats, diabetic rats exhibited significantly blunted diuretic and natriuretic responses to ANF (Fig. 7), and this effect was independent of renal innervation status [77]. Moreover, diabetic rats receiving chronic insulin treatment exhibited normal urine flow and sodium excretion responses to ANF [57,77]. The GFR measurements indicated that hemodynamic changes did not account for the blunted responses in the diabetic rats. These results confirm that hemodynamic changes per se are not responsible for the altered volume reflex in diabetic rats at this stage, and indicate that renal excretory re-
sponses to ANF are blunted in diabetes regardless of the presence of renal nerves.

We also examined the excretory responses to ANF in Type II diabetes in obese Zucker rats [74]. Obese Zucker rats were infused with ANF to determine if natriuretic and diuretic responses were altered in these rats [74]. The diuretic action of ANF was not significantly reduced in the obese Zucker rats. However, the natriuretic action of ANF was significantly attenuated in the obese rats. The results indicate that the reflex response to an acute saline load are attenuated in the obese Zucker rat and that this decreased response may be due to a reduction in the direct action of ANF in the kidney and to augmented renal sympatho-inhibition.

It has been suggested that diabetics who develop nephropathy are those who are unable to compensate for sodium retention and by developing systemic and intrarenal hypertension progress in a downward spiral of nephron loss [11]. Brenner and colleagues [4,11,12,33,45] have advanced the hypothesis that the hypertension developed during diabetes is due to glomerular hypertension and hyperfiltration observed during early stages of diabetes. Anderson and Brenner have also demonstrated that treating diabetic rats with enalapril, an angiotensin I converting enzyme inhibitor, reduces glomerular hypertension [3]. It has been suggested that the improvement in the increased glomerular ultrafiltration pressure in vivo in kidneys of diabetic rats by ACE-inhibitors results from reduced efferent arteriolar resistance secondary to reduced AII activity at this site. These facts taken together indicate that the renin–angiotensin system may in part mediate the regulation of fluid balance, particularly sodium handling, during early stages of diabetes. However, it is not known whether improvement of renal function by enalapril treatment in diabetic rats is mediated by alteration of renal nerve response to acute volume expansion. We reasoned that since angiotensin is known to increase sympathetic nerve activity and cause release of norepinephrine, elevated levels of angiotensin observed in diabetes would be expected to limit the renal sympatho-inhibition during acute VE in diabetic rats. We performed a study to determine the contribution of the previously reported elevated renin–angiotensin on the altered volume reflex in diabetic rats. We compared the diuresis and natriuresis and RSNA in response to acute VE in diabetic rats treated with enalapril (ACE inhibitor 10 mg/ml in their drinking water) and in those that received the saline vehicle. Enalapril treatment for the 2 weeks of diabetes does not alter the blunted diuretic and natriuretic and renal sympatho-inhibition responses to acute volume expansion [58]. These results demonstrate that regardless of ACE inhibitor there was no improvement in the neural component of the volume reflex in diabetic rats. These data indicate that the beneficial effects of enalapril [3] do not appear to be mediated by affecting the renal nerves and improving the volume reflex.

3. Intrarenal factors involved in renal excretory responses produced by acute volume expansion

During the early stages of diabetes, renal blood flow (RBF) and glomerular filtration rate (GFR) are higher in diabetic rats than in normal rats. In addition to the well-known glomerular damage, pre- and post-glomerular microvessels are also reported to be altered in diabetes [62]. Acute VE produces an increase in RHP concurrent with diuresis and natriuresis [24]. It has been suggested that an increase in papillary blood flow during VE leads to an increase in RHP, which ultimately promotes diuresis and natriuresis [22]. It is not known whether or not regulation of RHP is disrupted in diabetes. Our preliminary studies indicate that a blunted rise in RHP may contribute to the attenuated natriuretic response to acute VE in diabetic rats [54]. No information is available concerning RHP, its responsiveness to acute VE, or the translation of changes in RHP to changes in tubular sodium transport in diabetic animals.

Intrarenal NO production has also been suggested to play an important role in regulation of renal excretory response to extracellular VE [2]. The inner medulla appears to be a major site involved in regulating renal sodium excretion. It also appears to be a major site for NO synthesis within the kidney [1]. In the renal microvasculature, NOS is located in both afferent and efferent arterioles [5,6]. Furthermore, NOS activity (reflected by diaphorase labeling) appears to be greater in arterioles of juxtaglomerular than in the arterioles associated with midcortical or superficial glomeruli [5]. NO-dependent vasodilation of numerous vascular beds is impaired in animal models of insulin-dependent diabetes mellitus, whereas vasodilator responses to endothelium-independent agents are not affected [8,39,42]; however, the sparse data available concerning the influence of NO on renal macrovascular or microcirculation function in diabetes are conflicting in nature. In vivo functional studies at the whole kidney level indicate that both acetylcholine (ACh)-stimulated renal vasodilation and the increase in renal vascular resistance evoked by NO synthesis inhibition are attenuated in rats with STZ-induced diabetes [7,71]. Dai et al. [14] have described impaired responses to endothelium-dependent vasodilators in isolated renal interlobar arteries from STZ rats. In contrast, Gebremedhin et al. [25] reported that renal artery strips from alloxan-treated dogs exhibit enhanced sensitivity to ACh, with no alteration in the maximum relaxation induced by this agonist. To date, only two studies have examined the endothelium-dependent regulation of renal arteriolar function in diabetes. Isolated perfused hydronephrotic (non-filtering) kidneys from STZ-induced diabetic rats failed to display any defect in the afferent arteriolar vasodilator response to ACh [30]. However, Ohishi and Carmines [51] were able to document markedly suppressed juxtaglomerular afferent and efferent arteriolar vasoconstrictor responses to NOS inhibition in
kidneys from STZ rats, suggesting a reduced basal impact of endogenous NO on these microvascular segments. Thus, although changes in both the function [52] and endothelial morphology [72] of renal arterioles are evident as early as 2 weeks after the induction of diabetes, the effect of NO on renal arterioles in this disease state remains uncertain. Abnormalities in NO production or its second messenger response in diabetic kidneys could also contribute to blunted natriuretic responses to sodium loading and other stimuli. These possibilities remain to be examined. Changes in the function of other paracrine factors could also be important [44]. Abnormalities in dopamine turnover responses and production and/or function of eicosanoids have also been reported in diabetics [23,65]. Investigation of a role for these substances as well as vasoconstrictor autacoid substances such as thromboxanes and endothelin are potential subjects for future studies in this area.

4. Summary

After examining various components of the volume reflex in different models of diabetic rats, it is clear that the neural component of the volume reflex is altered in the early stage of diabetes. Nevertheless, the mechanisms involved in the neural component need to be examined further in diabetes. In terms of the humoral component of the effector limb of the volume reflex, the actions of ANF within the kidney appear to contribute to the altered volume reflex in diabetes. Results of our preliminary studies suggest that intrarenal factors may also contribute to these changes in renal excretory responses to acute VE in early diabetes. Finally, the present review has outlined the major abnormalities in the volume reflex in diabetes and the gaps in our knowledge of the various components of the volume reflex in diabetes.

Acknowledgements

This study was supported by NIH grant RO1-HL 48023.

References

34 Johnson AK. Role of periventricular tissue surrounding the an- 
32 Hein MS, Schlenker EH, Patel KP. Altered control of ventilation in 
29 Hainsworth R. Reflexes from the heart. Physiol Rev 1991;71:617– 
47 O'Hare JP, Anderson JV, Millar ND, et al. Hormonal response to 
49 O'Hare JP, Ferriss JB, Twomey BM, Gonggrijp H, O'Sullivan DJ. 
46 O'Hare JP, Anderson JV, Millar ND, Dalton N, Bloom SR, Corrall 
45 Neuringer JR, Brenner BM. Glomerular hypertension: Cause and 
43 Murray A, Ewing DJ, Campbell IW, Neilson JM, Clarke BF. RR 
42 Mayhan WG. Impairment of endothelium-dependent dilation of the 
39 Lash JM, Bohlen HG. Structural and functional origins of suppressed 
37 Swanson LW, Sawchenko PE. Hypothalamic integration: Organiza-
36 Kidd, C. Central neurons activated by cardiac receptors. In: 
34 Johnson AK. Role of pereventricular tissue surrounding the anter- 
30 Hayashi K, Epstein M, Loutzenhiser R, Forster H. Impaired myo- 
genic responsiveness of the afferent arteriole in streptozotocin-in- 
29 Hainsworth R. Reflexes from the heart. Physiol Rev 1991;71:617– 
13 Ohishi K, Okwueze ML, Var RC, Carmines PK. Juxteduodenal microvascular dysfunction during the hyperfiltration stage of dia-


