Sodium-retaining effect of insulin in diabetes

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Submitted 28 August 2012; accepted in final form 1 October 2012

Brands MW, Manhiani MM. Sodium-retaining effect of insulin in diabetes. Am J Physiol Regul Integr Comp Physiol 303: R1101–R1109, 2012. First published October 3, 2012; doi:10.1152/ajpregu.00390.2012.—Insulin has long been hypothesized to cause sodium retention, potentially of enough magnitude to contribute to hypertension in obesity, metabolic syndrome, and Type II diabetes. There is an abundance of supportive evidence from correlational analyses in humans, acute insulin infusion studies in humans and animals, and chronic insulin infusion studies in rats. However, the absence of hypertension in human insulinoma patients, and negative results for sodium-retaining or blood pressure effects of chronic insulin infusion in a whole series of dog studies, strongly refute the insulin hypothesis. We recently questioned whether the euglycemic, hyperinsulinemia model used for most insulin infusion studies, including the previous chronic dog studies, was the most appropriate model to test the renal actions of insulin in obesity, metabolic syndrome, and Type II diabetes. In those circumstances, hyperinsulinemia coexists with hyperglycemia. Therefore, we tested the sodium-retaining effect of insulin in chronically instrumented, alloxan-treated diabetic dogs. We used 24 h/day intravenous insulin infusion to regulate plasma insulin concentration. Induction of diabetes (~400 mg/dl) caused sustained natriuresis and diuresis. However, if we clamped insulin at baseline, control levels, i.e., prevented it from decreasing, then the sustained natriuresis and diuresis were completely reversed, despite the same level of hyperglycemia. We also found that 24 h/day intrarenal insulin infusion had the same effect in diabetic dogs but had no sodium-retaining action in normal dogs. This new evidence that insulin has a sodium-retaining effect during hyperglycemia may have implications for maintaining sodium balance in uncontrolled Type II diabetes.

diabetes; insulin; diuresis; natriuresis; sodium balance

RAISING THE QUESTION of whether insulin causes renal sodium retention, either in a scientific presentation or in the literature, immediately evokes one of two responses from the audience: 1) “I already know that insulin causes sodium retention”, or 2) “Insulin does not cause sodium retention.” Those maintaining the latter essentially have closed the book on the subject, and those holding to the former are interested in mechanisms but not the overarching question of whether insulin causes renal sodium retention. There is a wealth of literature to support both positions. However, nuances in many early studies raised issues that never were resolved. Inertia in the literature left many of those issues fading in the distance, all but erased from current thinking. We recently revisited the question about insulin and sodium retention, and our results were so striking that both positions on the subject warrant reconsideration. This review will chronologically present the literature supporting each position and show how our recent reports add new insight.

Insulin is a Sodium Retainer: Early Evidence

Atchley et al. reported in 1933 (4) that withdrawal of insulin therapy to diabetic subjects caused natriuresis and diuresis, which was reversed by resumption of insulin therapy. Miller and Bogdonoff demonstrated in 1954 (66) that acute insulin infusion significantly attenuated the osmotic natriuresis and diuresis caused by infusion of glucose or mannitol in normal human subjects. Saudek et al. in 1974 (81) reported findings similar to those of Atchley et al. (4) in diabetic subjects but did so under conditions of controlled sodium balance. These studies provided some of the earliest evidence that insulin could decrease urinary sodium excretion (UNaV). However, although the changes in UNaV were variably correlated to glucose excretion or blood glucose in those studies, the effect of systemic insulin administration on UNaV could not be dissociated from changes in blood glucose and filtered load of glucose, because blood glucose was not controlled.

DeFronzo et al. (29) addressed that by infusing insulin acutely into normal human subjects in whom blood glucose was held constant at normal levels, an approach that later came to be called the euglycemic, hyperinsulinemic clamp. They showed significant insulin-induced antinatriuresis independent
of changes in blood glucose and glomerular filtration rate (GFR) (29). A subsequent study by that group showed that acute, intrarenal insulin infusion in dogs significantly decreased UNaV (30). DeFronzo hypothesized in 1981 (28) that this sodium-retaining action of insulin caused, or at least contributed to, obesity hypertension via expansion of the extracellular fluid volume and increased cardiac output (28). Obesity already was known to be linked to hypertension (26, 86) and also to be associated with insulin resistance and hyperinsulinemia (8, 54, 84). Thus, in obesity, hyperinsulinemia was hypothesized to cause volume-loading hypertension (28).

Evidence that insulin acted directly to stimulate renal tubular sodium chloride reabsorption (30, 34, 52) grew in support of a renal sodium-retaining effect. There also was evidence that insulin could activate the sympathetic nervous system (3, 59, 70, 78), which suggested an indirect effect on blood pressure through neural control of the kidneys and systemic vasculature. Thus the early evidence supporting a sodium-retaining effect of insulin was wide-ranging: 1) the acute effect of insulin on urine sodium and volume excretion in animals and human subjects; 2) the acute effects of insulin on the renal tubules and the sympathetic nervous system; and 3) the correlation between obesity, hyperinsulinemia, and hypertension in human subjects. The last item of course links the sodium-retaining action mechanistically to hypertension.

**Insulin is a Sodium Retainer: Chronic Insulin Infusion Studies in Rats**

Reaven’s group showed that feeding rats a high-fructose diet caused insulin resistance, hyperinsulinemia, and hypertension (46, 75). Working in Hall’s laboratory, we tested whether the blood pressure association was due to hyperinsulinemia per se. Using 24 h/day methods for intravenous infusion and blood pressure measurement in chronically instrumented rats, we reported that a 5-day intravenous insulin infusion, with glucose coadministered intravenously to prevent hypoglycemia, significantly increased mean arterial pressure (MAP, Fig. 1) (18). We followed that with a series of studies probing mechanisms (16, 17, 19, 49, 51) and other laboratories have shown a similar effect of chronic insulin administration to raise blood pressure in rats (65, 85, 90). We measured daily urinary sodium excretion in all our studies and reported transient decreases in sodium excretion on the first day of insulin infusion (18, 19, 50). We measured increased GFR during the antinatriuresis on day 1, indicating an effect of the insulin infusion to stimulate tubular sodium reabsorption (50). Ecelbarger’s laboratory has reported that chronic insulin infusion in rats activates the epithelial sodium channel (ENaC) and the thiazide-sensitive Na-Cl cotransporter (85). The restoration and maintenance of sodium balance for up to 7 days of insulin-induced hypertension in our studies (16–19, 49, 51) confirmed that a sodium-retaining shift in kidney function had occurred (36, 43). Therefore, there is strong evidence from chronic insulin infusion studies in rats that support a sustained sodium-retaining and hypertensive effect of insulin.

**Conclusion 1: Insulin is a Sodium Retainer**

Evidence has continued to grow supporting renal tubular effects of insulin in humans and animals (10, 24, 31, 85, 87). There also has been continued support for an effect of insulin to stimulate the sympathetic nervous system (6, 67, 68, 96). Obesity is firmly established as a cause of hypertension, although additional mechanisms besides hyperinsulinemia have been proposed as mechanisms (35, 42, 56, 63). Therefore, it is not surprising that a sodium-retaining action of insulin has continued to be advanced as a contributing factor for sodium retention and hypertension in obesity or metabolic syndrome (53, 77, 80).

**Insulin is Not a Sodium Retainer**

Based on the evidence building in support of sodium-retaining, and potentially hypertensive, actions of insulin, Hall et al. began a series of chronic euglycemic, hyperinsulinemia studies in dogs that ran roughly in parallel with the chronic rat studies in his lab discussed above. Insulin was infused intravenously 24 h/day, with coadministration of intravenous glucose to maintain normal blood glucose. This caused approximately a four- to sixfold increase in plasma insulin in those studies. However, insulin infusion for 7–28 days failed to cause hypertension in normal dogs (20, 38), dogs with chronic norepinephrine infusion (38), or dogs with reduced kidney mass, high-salt intake, plus chronic angiotensin II infusion (41). In fact, there was significant systemic vasodilation (20), and MAP tended to decrease in all studies. The sodium retention that occurred was due to the decrease in MAP and withdrawal of pressure natriuresis. The systemic vasodilation suggested dogs were more insulin sensitive than rats, which...
showed a systemic vasoconstrictor response to chronic insulin infusion (19). Therefore, the insulin infusion was repeated in obese, insulin-resistant dogs (40). Again, there was a tendency for MAP to decrease just as in the previous dog studies (40). To isolate renal actions from potentially confounding systemic vasodilation, Hall et al. (39) infused insulin into the renal artery in dogs for 7 days, at a dose that showed modest spillover and one that did not. Neither dose caused hypertension or sustained sodium retention (39).

**Conclusion 2: Insulin is not a Sodium Retainer**

There was no evidence from chronic dog studies suggesting that insulin caused sodium retention or hypertension. The intrarenal infusion study argued very strongly that the stimulation of sodium chloride transport reported in acute insulin infusion studies were acute phenomena and not sustained chronically. In addition, the lack of hypertension in human insulinoma patients (32, 73, 92) suggested insulin was not a sodium-retaining or hypertensive factor in humans. That relationship also showed that the chronic response to hyperinsulinemia in humans was represented more closely by the response to chronic insulin infusion in dogs than rats. From these data, it is surprising that insulin continues to be discussed as a contributing factor for sodium retention and hypertension in obesity or metabolic syndrome in humans (53, 77, 80). Many laboratories, in fact, are pursuing exciting new mechanisms besides insulin to explain hypertension in metabolic syndrome and obesity (21, 42, 56, 74).

**Nuances from Previous Insulin Infusion Studies**

A subtle observation in our chronic rat studies, that we did not focus on at the time, is that blood glucose increased (16, 18, 19, 49–51). Glucose was coinfused 24 h/day to prevent the insulin infusion from causing hypoglycemia, but blood glucose increased consistently, and often it was statistically significant. DeFronzo’s laboratory (55) followed up on this by repeating the insulin infusion experiment in rats; however, they varied the glucose infusion rate so that they infused the exact amount of glucose needed to prevent hypoglycemia rather than infusing a fixed glucose dose as we had done (16–19, 49, 51). The total glucose infused was significantly less than in our studies, and they measured no sodium retention or hypertension (55). This suggested that the glucose infusion dose we used exceeded what was necessary to prevent insulin-induced hypoglycemia. Therefore, the hyperinsulinemia measured was a combination of the insulin we infused plus insulin that was secreted by the rat in response to the intravenous glucose load. We addressed that by chronically infusing the glucose dose by itself in rats for 7 days but without insulin infusion (14). We measured hyperinsulinemia, transient sodium retention, and hypertension similar to the responses in our insulin infusion studies, and blood glucose also increased similarly (14). Therefore, whether we infused insulin plus glucose (16, 18, 19, 49–51), or glucose alone (14), the result was hyperinsulinemia, hyperglycemia, and hypertension. However, when DeFronzo et al. (55) titrated the glucose dose so as to achieve true euglycemic hyperinsulinemia, no hypertension was measured. These findings suggested to us that hyperglycemia was required for hyperinsulinemia to cause sodium retention and hypertension in rats.

What about the chronic dog experiments? In the chronic insulin infusion studies in dogs, plasma glucose levels decreased despite the coinfusion of glucose (20, 38, 40, 41). Therefore, we conducted a similar experiment in normal dogs by infusing the glucose dose we used previously but without the coinfusion of insulin (15). The dogs became hyperinsulinemic, but they also became hyperglycemic. That was different from what occurred in all the previous intravenous insulin infusion studies in dogs but similar to the responses in rats. Moreover, there was significant sodium retention without the decrease in MAP that occurred in the previous dog studies. When a COX-2 inhibitor was used to target vasodilatory prostaglandins, there was a significant increase in MAP (15). These blood pressure and sodium-retaining responses were more consistent with the rat data.

There still are significant differences in the rat and dog responses, independent of whether insulin plus glucose or glucose alone was infused. The dogs have sustained systemic and renal vasodilation during the infusion period (13, 20), whereas rats have sustained systemic and renal vasoconstriction (14, 19, 27, 50, 51). The opposite systemic vascular responses likely are due to greater skeletal muscle insulin sensitivity in dogs versus rats, because the vasodilation was attenuated significantly in obese, insulin-resistant dogs (40). The mechanism for the opposite renal vascular response is not known but may be related to the significant role of nitric oxide inhibition in the response in rats (27). The mechanisms for sodium excretion effects also may be opposite. The only previous “positive” insulin data in dogs regarding sodium excretion were correlations in glucose-infused dogs (13, 15), but the decreased sodium excretion occurred with renal vaso dilation and increased GFR. That indicates tubular reabsorption was the mechanism. In rats, on the other hand, we have limited evidence for renal vasodilation and increased tubular reabsorption on the first day of insulin infusion (50). However, the sustained sodium-retaining shift in pressure natriuresis was due to renal vasoconstriction (14, 19, 27, 50, 51). Despite these differences, the blood pressure and sodium-retaining responses in rats and dogs during hyperinsulinemia were linked to hyperglycemia.

**Neither Conclusion has been Supported Adequately**

Returning to the debate about whether insulin is, or is not, a sodium retainer, the only direct, experimental data that show a chronic sodium-retaining and/or hypertensive effect of insulin are from chronic rat studies. The chronic dog data (20, 38–41) and human insulinoma patient data (32, 73, 92) actually refute the insulin hypothesis, and that includes the convincing evidence from Hall’s study showing no effect of chronic intrarenal insulin infusion (39). Therefore, we believe there has not been sufficient cause-and-effect evidence to support a conclusion that insulin causes chronic sodium retention or hypertension in humans. However, we also believe there has not been sufficient evidence to support a conclusion that insulin does not cause sodium retention or hypertension. That is because we believe that, before our recent reports (61, 62), the appropriate experiments had not been performed. This is where the nuances regarding hyperglycemia in the early hyperinsulinemia experiments come into play.
Previous insulin infusion studies were designed to isolate insulin as a controlled independent variable. In most systemic infusion studies, and in all the chronic insulin studies in collaboration with Hall et al. in rats and dogs, this involved coadministration of glucose to maintain normal blood glucose levels. Although this was the appropriate approach to test the question about effects of insulin, we wondered whether it was appropriate in the context of the human subjects in which the insulin-hypertension question was most relevant. Hypertensive subjects with obesity and metabolic syndrome are hyperglycemic and hyperinsulinemic (8, 35, 56, 63, 88). Therefore, we questioned whether euglycemic, hyperinsulinemia was the appropriate model. The chronic dog studies (20, 38–41) and human insulinoma data (32, 73, 92) were the primary argument against insulin sodium retention or hypertension, but was that relevant to human obesity and metabolic syndrome? As discussed above, our analysis of previous chronic insulin and glucose infusion studies in rats and dogs suggested an interdependence between hyperglycemia and insulin-induced sodium retention. Therefore, we recently hypothesized that hyperglycemia was required for insulin to cause a sustained sodium-retaining effect (61, 62).

**Diabetic Natriuresis is Because of Decreased Insulin**

The negative results from insulin infusion studies in dogs (20, 38–41) and the greater translational relevance of the dog model necessitated using chronically instrumented dogs to test this hypothesis. However, the significant systemic vasodilation in dogs during hyperinsulinemia, with or without hyperglycemia (15, 20, 40), meant that we could not simply infuse insulin and/or glucose chronically to test it. We needed a unique approach that ideally tested the sodium-handling role of endogenous insulin. DeFronzo in 1981 (28) asked whether the natriuresis in poorly controlled diabetes could be due in part to lack of insulin. We used that question to devise an approach to test our hypothesis. According to DeFronzo’s question, if insulin is a sodium-retaining hormone, then the increase in urinary sodium and volume excretion in Type I diabetes should be caused at least partially by the loss of insulin. Thus glycosuria and resultant osmotic diuresis would not be the sole cause of diabetic natriuresis as commonly held (7, 37, 91). In support of this, Blantz et al. reported evidence that osmotic diuresis was not the cause of hyperglycemia-induced volume loss (9). Therefore, we probed for an insulin-glucose interactive effect on urinary sodium excretion by testing the role of lack of insulin in causing diabetic natriuresis and diuresis (61).

We administered alloxan to decrease endogenous insulin production in chronically instrumented dogs (61). As soon as hyperglycemia was documented, we brought them into normal glycemic control using a 24 h/day intravenous insulin replacement infusion. The control period was alloxan-treated dogs that were normoglycemic because of insulin replacement. Figure 2 shows this period and also shows that the diabetic period was initiated by decreasing the insulin infusion dose. This achieved hyperglycemia in the range of 400 mg/dl, which was maintained for 6 days. This was the Type I diabetes group. Figure 3 shows how we tested the role of insulin. In this group, the alloxan treatment and control periods were the same. However, for the 6-day diabetic period we held the 24 h/day insulin infusion constant at the control-period replacement dose. Diabetes at the same ~400 mg/dl level was achieved by infusing glucose intravenously 24 h/day. Because the dogs were alloxan treated,
the glucose infusion did not increase plasma insulin, and because of our steady insulin infusion they did not have the decrease in insulin that occurred in the Type I diabetes group. Thus both alloxan-treated groups had the same level of diabetes for the 6-day period, but the second group did not have a decrease in circulating insulin. It was maintained at baseline levels. Figure 4 shows that this completely prevented the sustained natriuresis. The effect on the diuretic response was similar. The natriuresis and diuresis on the first day of hyperglycemia likely were due to glycosuria and osmotic diuresis, but it is clear that there was no sustained urinary salt and water loss if circulating insulin did not decrease from normal. The key aspect of insulin’s antinatriuretic effect we discovered here is rather subtle: The antinatriuresis was not caused by hyperinsulinemia. This effect was not due to insulin infusion as typically envisioned, i.e., we did not increase plasma insulin concentration with our insulin infusion. Rather, this was normal plasma insulin levels suddenly coexisting with hyperglycemia. Therefore, hyperglycemia seemed to “turn on” a sustained sodium-retaining action of insulin, which was powerful enough to completely reverse the osmotic diuresis and natriuresis. This strongly supported our hypothesis that hyperglycemia was required for insulin to exert a sustained sodium-retaining effect.

**Insulin + Glucose Antinatriuretic Action is Because of Direct Renal Effect of Insulin**

Because this first study of ours (61) involved systemic manipulation of insulin and glucose, we needed to infuse insulin chronically into the renal artery to determine whether insulin was acting directly in the kidney. We again used two groups of alloxan-treated dogs, but both were typical Type I diabetes, i.e., we induced the 6-day diabetic period in both groups by decreasing the insulin replacement infusion (62). The renal effect of insulin on sodium excretion was tested by infusing insulin into the renal artery of one group 24 h/day during the 6-day diabetic period. The dose of 0.3 mU·kg⁻¹·min⁻¹ was the lower of the two intrarenal doses used by Hall et al. in normal dogs (39). This insulin dose did not spillover in our study (62) or in Hall’s study (39), as determined by the lack of significant changes in circulating insulin or glucose levels. Figure 5 shows that diabetic natriuresis was reversed completely by the intrarenal insulin infusion. Figure 6 shows the similarly striking reversal of diuresis. The complete normalization of urine volume and urinary sodium excretion occurred despite sustained hyperglycemia in the 400 mg/dl range, which was not different between groups.

Because this intrarenal insulin dose was shown previously not to have a sustained sodium-retaining effect in normal dogs (39), our results strongly suggested that the presence of hyperglycemia is what “triggered,” or enabled, the antinatriuretic effect of insulin in diabetic dogs (62). To further test this, we repeated the intrarenal insulin infusion for 6 days in normal dogs (62), essentially repeating the earlier study of Hall et al. (39). In a separate group we infused glucose intrarenally at 17 mg/min (24 g/day) for 6 days, which was calculated to increase renal artery glucose by approximately 14 mg/dl. Neither infusion significantly affected urinary sodium excretion (62). However, when the two infusions were combined, there was significant, sustained antinatriuresis (Figure 7) (62).
How do Insulin and Glucose Interact to Cause Antinatriuresis?

Hyperglycemia in dogs with uncontrolled Type I diabetes caused the expected natriuresis and diuresis over 6 days (61, 62). Preventing the decrease in insulin completely reversed that response due to a renal mechanism that required the presence of hyperglycemia (61, 62). The renal mechanism was through tubular sodium reabsorption, because the intrarenal insulin infusion in diabetic dogs prevented the natriuresis, diuresis, and increased sodium clearance in the face of increased GFR and decreased renal vascular resistance (62). What we do not know is where in the renal tubule insulin and glucose are interacting to exert the antinatriuretic effect.

There is evidence that insulin can stimulate sodium chloride reabsorption in the proximal tubule (33, 98) and loop of Henle (52), as well as the distal nephron (29, 31, 85, 87), but now we need to consider this in the context of the requirement for hyperglycemia. This immediately brings the sodium-glucose cotransporter (SGLT) to mind as a potential proximal tubular mechanism. The increases in GFR, fractional lithium reabsorption, and plasma renin activity we reported (61, 62) are consistent with increased proximal tubule sodium transport and withdrawal of the tubuloglomerular feedback signal at the macula densa (93, 97). The marked attenuation of urinary glucose excretion we measured (61, 62) provides further support and also suggests a role for SGLT. We have no experimental evidence that the well-known effect of glucose to stimulate SGLT in diabetes (64, 94) is amplified in the presence of insulin, but serum and glucocorticoid-inducible kinase 1 (SGK1) has been shown to regulate proximal tubular glucose transport (1) and to be stimulated by glucose (1, 45, 79) and insulin (45, 57). Therefore, an effect of insulin to amplify glucose-driven sodium-glucose cotransport via SGK1 is an interesting potential explanation for the antinatriuretic effect of insulin we reported in diabetes (61, 62).

Another interesting potential mechanism is stimulation of the epithelial sodium channel (ENaC). ENaC is rate limiting for mineralocorticoid receptor (MR)-mediated sodium reabsorption, and the MR is the main regulator of ENaC-dependent Na+ transport in the distal nephron (60, 69). In addition to aldosterone, insulin has a well-described effect to stimulate ENaC (5, 10, 11, 23, 76, 82, 85, 95). However, data from chronic insulin infusion studies in dogs (20, 38–41) and human insulinoma patients (32, 73, 92) suggest that stimulation of ENaC by hyperinsulinemia alone is not powerful enough or sustained sufficiently to cause chronic sodium retention in dogs or humans. Can hyperglycemia amplify that effect? This has not been studied yet, but insulin stimulates ENaC via SGK1 (10, 12, 95). Glucose also can increase renal tubular SGK1 (1, 45, 79), with evidence specifically for an effect in the distal nephron (44). This suggests that induction of hyperglycemia possibly could amplify stimulation of ENaC by insulin, making this mechanism another potential candidate to explain the sodium retaining effect of insulin.

Perspectives: Implications of Insulin+Glucose-Induced Antinatriuresis

DeFronzo hypothesized that lack of insulin may contribute to natriuresis and diuresis in diabetes (28). Our results supported that hypothesis but surprisingly showed more than a contribution. We found that the sustained natriuresis and diuresis in diabetes does not occur if insulin does not decrease, i.e., lack of insulin rather than hyperglycemia per se is the cause of sustained renal salt and water loss in uncontrolled diabetes (61). Our hypothesis that hyperglycemia is required for insulin to exert a sustained sodium-retaining effect is supported by that study and even more convincingly by the results from our intrarenal insulin infusion study (62). This could be the discovery of a novel physiological interaction between insulin and
glucose, and it potentially is a new mechanism to explain the sustained natriuresis and diuresis in Type I diabetes.

It also may have implications for our understanding of renal sodium handling and hypertension in Type II diabetes. One could ask: Given the effect of hyperglycemia to promote renal salt and water loss, what is the mechanism for maintaining salt and water balance in persons who develop sustained hyperglycemia during the progression of obesity, metabolic syndrome, and Type II diabetes? Compensatory systems such as the renin-angiotensin and sympathetic nervous systems undoubtedly play a role, but could insulin contribute? The progressive increase in circulating insulin that accompanies the worsening hyperglycemia could have an antinatriuretic action. Thus, in addition to working to control glucose homeostasis, the hyperinsulinemia in persons as they progress toward overt Type II diabetes could have an important physiological function to help prevent renal salt wasting. Preventing renal salt wasting in chronic hyperglycemic states could be a new physiological role for insulin that previously was unknown.

Preventing renal salt wasting is an important description of what our studies actually showed (61, 62). We did not measure increased sodium balance. The antinatriuretic effect of insulin+glucose reversed, or prevented, the sustained natriuresis and diuresis in the diabetic period. Blood pressure did not increase in either study. To extrapolate the sodium-retaining effect to hypertension in obesity and Type II diabetes likely would require other factors, functional or structural, that impair renal salt and water excretion during chronic hyperglycemia. Thus a physiological action of insulin+glucose may have an additive effect on aldosterone-stimulated ENaC activity. The conclusion that insulin does cause sodium retention is supported by these results in diabetic dogs show that insulin does have a chronic sodium-retaining effect during hyperglycemia. The new data in chronic diabetic dogs gives evidence of an antinatriuretic effect in a more translational animal model. Moreover, it shows that insulin+glucose needs to be targeted in future studies probing the renal mechanisms. It is possible that new physiological interactions for insulin have been revealed, and there is new potential that hyperinsulinemia could participate in the pathophysiology of renal function and blood pressure in obesity and Type II diabetes.

ACKNOWLEDGMENTS

The authors acknowledge the technical assistance of Tuere Sheppard.

GRANTS

This work was supported by the National Heart, Lung, and Blood Institute Grant HL-56259.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: M.W.B. conception and design of research; M.W.B. and M.M.M. performed experiments; M.W.B. and M.M.M. analyzed data; M.W.B. and M.M.M. approved final version of manuscript.

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