Dietary sodium intake modulates renal excretory responses to intrarenal angiotensin (1–7) administration in anesthetized rats

Julie O’Neill, Alan Corbett, and Edward J. Johns

Department of Physiology, University College Cork, Cork, Republic of Ireland

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The intrarenal actions of ANG (1–7) and its interaction with ANG II on renal hemodynamics and tubular fluid reabsorption have not been fully elucidated. Previous in vitro studies have demonstrated that exposure of isolated rat renal arteries (31) and rabbit afferent arterioles (23) to ANG (1–7) caused an increase in their diameter and that was taken as evidence for a local vasodilator action. However, the vasodilation was only demonstrated in vessels that had been preconstricted with either ANG II (31) or norepinephrine (23), suggesting that this action of ANG (1–7) was reactive as opposed to being active. Conversely, several in vivo studies have shown that intrarenal infusion of ANG (1–7) failed to produce any changes in renal blood flow, and thereby renal vascular resistance, in sodium replete rats (11), in the isolated rat kidney (6, 13), and following ANG II infusion into freely moving rats (31) even though glomerular filtration rate (GFR) was increased modestly (13).

The influence of ANG (1–7) on sodium and water transport in the kidney is uncertain. In the isolated and perfused rat proximal straight tubules (10) and the rat Loop of Henle (30), low doses of ANG (1–7) stimulated while higher doses inhibited sodium and water reabsorption. However, low doses of ANG (1–7) were found to inhibit and high doses to stimulate fluid transport in cultured renal epithelial cells (3) and in isolated rat proximal convoluted tubules (11). Despite these conflicting reports some in vivo studies have demonstrated that the intrarenal infusion of ANG (1–7) increased sodium and water excretion in dogs (12) and rats (5, 6, 11).

Recently, it has emerged that the status of sodium and water balance and the level of endogenous RAS activity may alter the actions of ANG (1–7). For example, it has been reported that ANG (1–7) has an antidiuretic effect in water-loaded rats (25). The influence of ANG (1–7) on sodium and water reabsorption in the kidney is dependent on the prevailing levels of angiotensin II and its receptor expression.

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The exact way in which angiotensin (1–7) exerts its effects may be dependent on the prevailing levels of angiotensin II and its receptor expression.

angiotensin (1–7); dietary sodium; renal hemodynamics; sodium excretion

THE RENIN ANGIOTENSIN SYSTEM (RAS) is a powerful endogenous hormonal cascade that plays a central role in the regulation of blood pressure, sodium balance, and body fluid homeostasis. Classically, this cascade culminates in the formation of the potent vasoconstrictor, antinatriuretic and antidiuretic peptide angiotensin II (ANG II) (7, 20). ANG II is produced from angiotensin I (ANG I) primarily via angiotensin-converting enzyme (ACE) but also via the tissue enzyme chymase. The latter has been shown to contribute to the production of ANG II in the diabetic mouse kidney (21). More recently, another RAS peptide called angiotensin (1–7) [ANG (1–7)] has been described as the endogenous counter regulator of ANG II (16) via activation of its “mas” receptor (24). ANG (1–7) is formed directly from ANG II by the ACE isof orm ACE 2 (27, 32) but can also be synthesized directly from ANG I via tissue-specific peptidases such as nephrilysin in the kidney (2).

MATERIALS AND METHODS

Male Wistar rats (250–350 g) were obtained from Harlan, (Bicester, UK) and maintained under a 12 h-12 h light-dark regime at 20 ±
3°C in the Biological Services Unit, University College Cork. Experimental procedures were performed under the European Community Directive 86/609/EC and were approved by the local Animal Experimentation Ethical Committee at University College Cork.

**Surgical protocol.** Rats were fasted overnight but did have access to water. Anesthesia was induced intraperitoneally with 1 ml of chloralose-urethane (16.5 and 250 mg/ml, respectively) and maintained using intravenous bolus doses of 0.05 ml every 30 min. A tracheostomy was carried out to ensure a patent airway. Cannulas were inserted in to the right femoral vein to facilitate the infusion (B. Braun Melsungen, Germany) of sustaining saline (3 ml/h of NaCl 9 g/l) and subsequently saline containing FITC inulin (3 ml/h of FITC Inulin, 2 g/l, Sigma-Aldrich) and the right femoral artery to permit the measurement of blood pressure (MAP), heart rate (HR), and the collection of blood samples. A flank incision was used to expose the left kidney, and its ureter was cannulated to facilitate urine collection. A small cannula (0.61 mm outer diameter) was inserted 4.0–4.5 mm into the rostral pole of the kidney to lie approximately at the corticomedullary border to facilitate the intrarenal (IR) infusion of saline (NaCl 9 g/l) or ANG (1–7) at 1 ml/h. This technique was initially shown to result in an accumulation of compound primarily in the medulla with smaller concentrations accumulating in the cortex (19). In preliminary studies, removing and sectioning the kidney at the end of the experiment verified the location of the cannula at the corticomedullary border. In these studies, Evans blue was also infused, and the pattern of dye distribution was mainly in the medulla but also in the cortex. The successful use of the technique has been reported elsewhere (1). A 1.5-h postsurgical stabilization period was given before the commencement of the experiment.

**Experimental groups.** For the purpose of this study rats were divided into three dietary groups: the first group received a normal sodium diet (0.3% Na+, Harlan-Teklad, Bicester, Oxon, UK); the second group was placed on a high-sodium diet (3% Na+ Lillico, Surrey, UK); and the third group was placed on a low-sodium diet (0.03% Na+, Lillico). The animals were maintained on these diets for 2 wk before experimentation. Each dietary group was subsequently divided into two subgroups (n = 5–8): the first subgroup received a low-dose intrarenal infusion of ANG (1–7) (15 ng/min); and the second group received a higher dose of intrarenal ANG (1–7) (50 ng/min). Importantly, the diets only differed in terms of their NaCl content while the concentrations of all other food groups such as vitamins, minerals, proteins, fats, and carbohydrates were similar across all three diets.

**Control groups.** All animals received a normal sodium diet (0.3% Na+, Harlan-Teklad) and were divided into two groups. The first group (n = 5) was the saline time control group and the second group (n = 6) received an intravenous infusion of the higher dose of ANG (1–7) (50 ng/min).

**Experimental protocol.** A sequence of four 20-min clearance periods were taken, two clearances before and two during the infusion of intrarenal saline (time control), intrarenal ANG (1–7), or intravenous ANG (1–7). A period of 45 min was given before initiating the third and fourth clearances in both control and experimental groups as preliminary studies had indicated that this time frame ensured that the ANG (1–7) was exerting its maximal effect. The average values of clearances one and two and the averages values for clearances three and four were presented in the figures. Urine flow was determined gravimetrically. Blood samples (0.4 ml) were taken before and after collection of each pair of clearances and were subsequently centrifuged at 14,000 rpm for 1 min. Plasma (75 μl) was removed for analysis, and heparinized (0.2 ml heparin in 50 ml saline) saline of equal volume was added to the remaining red cells and immediately returned to the animal. A blood pressure transducer (Spectromed, Oxnard, CA) and an amplifier (Grayden Electronics, Birmingham, UK) operated in conjunction with a computer (Power Macintosh 8600/250, Apple) and appropriate software (Lab View 4, National Instruments, Austin, TX) to monitor and record MAP and HR. After the completion of the experiment the animal was euthanized using an anesthetic overdose.

**Measurement of plasma renin and ANG (1–7).** After exposure to a 2-wk normal (0.3% Na+), high- (3% Na+), or low-sodium diet (0.03% Na+), animals were anesthetized, blood samples were taken, and blood plasma was yielded using the methods described previously in this paper. Animals were subsequently killed using anesthetic overdose. The plasma renin concentration of normal (n = 6), high-sodium (n = 6), and low-sodium (n = 6)-fed rats was measured using a rat renin ELISA kit (CSB-E08702e) that was purchased from Cusabio Biotech (Hubei Province 430223, P. R. China). The plasma angiotensin (1–7) levels in normal (n = 5), high-sodium (n = 5), and low-sodium (n = 5)-fed rats were measured using a rat angiotensin (1–7) ELISA kit that was purchased from MyBioSource (San Diego, CA).

**Analytical techniques.** The sodium concentration of both plasma and urine was determined by flame photometry (model 410C, Ciba, Corning, Halsted, Essex, UK). GFR was calculated as the clearance of FITC inulin, and FITC inulin concentration of the urine and plasma samples was determined using a fluorometric multilabel counter plate reader (VICTOR 2, Wallac). Plasma renin and ANG (1–7) levels were determined by the measurement of absorbance (OD 450 nm) on a microtiter plate reader (VICTOR 2, Wallac).

**Statistical analysis.** Data quoted as means ± SE were analyzed using a two-tailed Wilcoxon signed rank test (Prism, Graph Pad Software). A mean value of the first and second clearances was compared with the mean value of the third and fourth clearances. A one-way ANOVA with Bonferroni posttest (Prism, Graph Pad Software) was performed to compare the differences between groups when data were normally distributed. A Kruskal Wallis with Dunnes multiple comparison test was used to compare the difference between groups when data had a nonnormal distribution. Significance was taken when P < 0.05.

**RESULTS**

**Mean arterial blood pressure.** Baseline MAP was similar in all groups (Fig. 1, A and B) and did not change following infusion of intrarenal saline, the low dose of intrarenal ANG (1–7), or the intravenous ANG (1–7), and it was not significantly different in rats receiving a normal, low-, or a high-sodium diet.

**Glomerular filtration rate.** Baseline GFR was similar in all groups (Fig. 2, A and B). Administration of both the low and high doses of intrarenal ANG (1–7) had little consistent effect on GFR in the rats on a normal sodium intake (Fig. 2A). The low dose and the high dose of intrarenal ANG (1–7) significantly increased GFR in rats receiving a low-sodium diet by 45% and 37%, respectively (both P < 0.05). In the rats receiving a high-sodium diet, the low dose of intrarenal ANG (1–7) increased GFR by 15% relative to baseline (P < 0.05), whereas it did not change following the high dose of intrarenal ANG (1–7). In the control animals, GFR remained relatively unchanged by either the intrarenal saline or by the intravenous ANG (1–7) infusion (Fig. 2B).

**Urine volume (UV).** Baseline values for UV were similar in all groups (Fig. 3, A and B). The low and high doses of intrarenal ANG (1–7) significantly (P < 0.05) increased UV relative to baseline values in the normal sodium-fed rats by 100% and 117%, respectively. However, in the low-sodium-fed rats the low dose and high dose of intrarenal ANG (1–7) caused approximately 190% and 200% increases in urine flow, respectively (both P < 0.05). The magnitude of the increases in urine flow in response to both doses of intrarenal ANG (1–7)
was markedly greater in low-sodium-fed rats compared with the normal sodium diet group. By contrast, in high-sodium-fed rats the low and high doses of intrarenal ANG (1–7) increased UV only by 24% and 69%, respectively (both P < 0.05). The increase in UV in response to both doses of intrarenal ANG (1–7) in the rats given the high-sodium diet was clearly blunted compared with those obtained in the animals on a normal and low-sodium (both P < 0.05) intake. In the control animals, UV remained unaltered by either intrarenal saline or intravenous ANG (1–7) infusion (Fig. 3B).

**Fractional sodium excretion.** Fractional sodium excretion (FENa) baseline values were similar in the normal and the high-sodium diet groups but were markedly less in both the control and low-sodium groups (Fig. 5, A and B). The low dose and high doses of intrarenal ANG (1–7) significantly increased FENa in the normal sodium diet rats by 100% and 192%, respectively (both P < 0.05). The magnitude of the increase in FENa in normal sodium-fed rats in response to the high dose of intrarenal ANG (1–7) was significantly greater than that of the low dose. Intrarenal ANG (1–7) at the low and high dose increased FENa by some 300% in rats receiving the low-sodium diet (both P < 0.05). The magnitude of the increases in

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**Mean Arterial Pressure (MAP)**

![MAP Diagram](image)

**GFR (ml/min/Kg) vs. Sodium Diet**

![GFR Diagram](image)

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**Absolute sodium excretion.** Baseline absolute sodium excretion (U\textsubscript{Na}V) levels were similar in the normal, high-sodium diet, and control groups (Fig. 4, A and B). Intrarenal ANG (1–7) significantly (P < 0.05) increased U\textsubscript{Na}V in normal sodium-fed rats in a dose-dependent way, by 129% and 200% (both P < 0.05), respectively. The magnitude of these increases were greater in low-sodium-fed rats compared with normal-sodium-fed rats. By contrast, in the rats fed a high-sodium diet, intrarenal ANG (1–7) caused significant increases in U\textsubscript{Na}V of 40% and 98% (both P < 0.05), which were responses that were markedly smaller than those obtained in the rats fed a normal and low-sodium (P < 0.05) diet. U\textsubscript{Na}V in the control animals was not altered by either intrarenal saline or intravenous ANG (1–7) infusion (Fig. 4B).
FENa was larger in the low-sodium-fed rats compared with that obtained in the rats on a normal sodium intake. In the high-sodium diet group, the low dose and high doses of intrarenal ANG (1–7) increased FENa by 5% and 75%, respectively. The magnitude of the responses in FENa to both a low dose and a high dose of intrarenal ANG (1–7) was blunted compared with those obtained in the normal and low-sodium \((P < 0.05)\)-fed rats. FENa in the control animals remained unchanged following either intrarenal saline infusion of intravenous ANG (1–7) (Fig. 5B).

**DISCUSSION**

The interaction between ANG II and ANG (1–7) in the regulation of renal hemodynamic and excretory function has not yet been resolved and no clear picture has emerged. The hypothesis tested in the present study was that the regulation of GFR and sodium and water excretion by the local intrarenal infusion of ANG (1–7) could be determined by the level of sodium intake and be associated with the degree of activation of the endogenous renin-angiotensin system. The approach taken was to manipulate the dietary sodium intake, which would either activate or suppress the renin angiotensin system and to determine how this influenced the renal hemodynamic and excretory responses to ANG (1–7).

This was achieved by infusing ANG (1–7) locally into the kidney. Local infusion was facilitated by inserting a cannula into

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**Fig. 3.** A: influence of ANG (1–7) on urine flow (UV) in rats fed either a normal, low-, or high-sodium diet. \(*P < 0.05\) and indicates that renal interstitial infusion of either a low or high dose of ANG (1–7) (filled bars) significantly increases UV relative to baseline (open bars). B: effect of intrarenal saline infusion (filled bars) and intravenous (IV) ANG (1–7) infusion (checkered bars) on UV in control animals.

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**Plasma renin concentration.** Plasma renin concentration was increased by 40% in low-sodium-fed rats. In high-sodium-fed rats, plasma renin concentration was decreased by 70% relative to that of normal sodium-fed rats and by some 136% \((P < 0.05)\) when compared with that of low-sodium-fed rats (Fig. 6A).

**Plasma ANG (1–7) concentration.** Plasma ANG (1–7) concentration was increased by 83% in low-sodium-fed rats. In high-sodium-fed rats, plasma ANG (1–7) concentration was reduced by 200% relative to that of normal sodium-fed rats and by

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**Fig. 4.** A: effect of ANG (1–7) on absolute sodium excretion \((U_{NaV})\) in rats fed either a normal, low-, or high-sodium diet. \(*P < 0.05\) and indicates that renal interstitial infusion of either a low or high dose of ANG (1–7) (filled bars) significantly increases \(U_{NaV}\) relative to baseline (open bars). B: effect of intrarenal saline infusion (filled bars) and intravenous (IV) ANG (1–7) infusion (checkered bars) on \(U_{NaV}\) in control animals.
the kidney at approximately the corticomedullary border. This technique has been found to deliver compounds into the renal interstitium with a distribution that is highest in the medulla but somewhat lower in the cortex (1, 19). The doses used in the present study were chosen on the basis of those utilized by others (5) and scaled in a way to ensure a maximal action within the kidney with minimal spill over into the systemic circulation. The decision was also taken not to measure renal blood flow because this would have risked partially or totally denervating the kidney, which could have confounded the interpretation of the local responses induced by ANG (1–7).

It was evident that in rats fed a normal sodium intake the infusion of ANG (1–7) was without effect on blood pressure or GFR and caused an obvious diuresis and dose-dependent natriuresis. Importantly, the increases in sodium and water excretion were due to the local intrarenal infusion of ANG (1–7) and were not time dependent as was shown by the intrarenal saline infusion control study. In addition the intravenous infusion of the higher dose of ANG (1–7) did not alter blood pressure nor did it have any effect upon sodium or water excretion.

The infusion of ANG (1–7) increased GFR in the rats subjected to the low-sodium diet, although the magnitude of GFR responses were similar for both the low and high doses of the peptide. Conversely, in the rats given the high-sodium diet, the ANG (1–7)-mediated increase in the GFR response was smaller at the low dose and completely blunted following the administration of the high dose. These observations would suggest that ANG (1–7) can have a vasodilator action at the resistance arterioles to cause a rise in filtration pressure and hence filtration rate. The mechanisms by which ANG (1–7) caused the rise in GFR are uncertain.
On the one hand, there is evidence for an afferent arteriolar action as Ren et al. (23) have previously demonstrated in 2002 that ANG (1–7) dilates isolated rabbit afferent arterioles in vitro. On the other hand, in the absence of changes in renal vascular resistance, the ANG (1–7)-induced rise in GFR may have resulted from an increase in glomerular filtration surface area due to mesangial cell relaxation (6, 13).

The local infusion of ANG (1–7) into the kidney caused a diuresis and a dose-related natriuresis in normal sodium-fed rats. It was important that the impact of any hemodynamic responses be minimized and to that end attention was focused on fractional sodium excretion. It was clear that FENA, which is an indirect indicator of tubular sodium reabsorption by the nephron, was increased by ANG (1–7). This observation would suggest that ANG (1–7) was having a direct inhibitory effect on sodium reabsorption at the level of the tubule that was similar to that reported previously in the rat and dog (6, 11, 13, 29).

The primary question addressed was whether the excretory responses to ANG (1–7) were in any way influenced by the prevailing levels of circulating or intrarenal levels of ANG II. The approach taken was to manipulate the dietary intake of sodium to either elevate or suppress the endogenous RAS. Plasma renin concentration was measured in this study to determine whether the low- and high-sodium diets fed did in fact enhance and suppress the endogenous RAS, respectively. Renin is the rate-limiting step in the production of ANG II through its conversion of angiotensinogen into angiotensin I (22) and therefore gives an indication of overall endogenous RAS activity. The current study has demonstrated that plasma renin concentration was augmented in low-sodium-fed rats and markedly reduced in high-sodium-fed rats, and these data concurred with findings from other groups (9, 14). Furthermore, previous studies have shown both circulating (8, 15) and intrarenal (9, 14) ANG II levels were also increased in low-sodium-fed rats and reduced in high-sodium-fed rats.

Plasma ANG (1–7) levels were also measured to put the exogenous intrarenal infusion of ANG (1–7) into a physiological context. The differences in plasma ANG (1–7) levels in following the low- and high-sodium diets were similar to the pattern of changes in plasma renin levels observed in the current study and to those of ANG II observed in previous studies (8, 15). The low-sodium diet tended to increase plasma ANG (1–7), whereas the high-sodium diet caused a marked reduction in plasma ANG (1–7). These findings concur with studies carried out in humans whereby the low-sodium diet caused a twofold increase in plasma ANG (1–7). ANG I, and ANG II levels relative to those observed in subjects administered the high-sodium diet (18).

In the present study, the rats fed a low-sodium diet had markedly reduced baseline sodium excretions, whereas in animals on the high-sodium diet it was no different compared with the rats on a normal diet. This latter observation was unexpected but was probably the result of the anesthesia and stress involved in the surgical preparation as we have reported previously (17) that in the conscious state sodium excretion is markedly elevated in rats fed a high-sodium diet.

The first novel finding was that a reduction in dietary sodium intake resulted in a marked enhancement of the diuretic and natriuretic actions of ANG (1–7), which appeared to be at a tubular level as the responses in fractional sodium excretion were also enhanced. Interestingly, in these groups of low-sodium-diet rats, the maximal effect of ANG (1–7) on urine flow, absolute and fractional sodium excretions appear to have been achieved at the lowest dose as the magnitude of the response in these variables to the higher dose of peptide was no larger. These observations would support those of Burgelova and coworkers in 2005 (4) who reported in high renin rat models of hypertension and those subjected to a reduced sodium intake that blockade of ANG (1–7) action resulted in much greater antinatriuretic responses. Indeed, administration of a low-sodium diet similarly activates the endogenous RAS, which might explain in part, the enhanced diuretic and natriuretic responses to the ANG (1–7) under these conditions.

The second important observation of the present study was that feeding a high-sodium diet markedly blunted the excretory responses to ANG (1–7). These findings would provide further support for the view that there is an interaction between ANG (1–7) and ANG II in determining the overall impact on the excretory responses to the infused peptide. That is, if there is a reduction in ANG II generation, then the renal responses to ANG (1–7) are blunted, and conversely, if ANG II levels are elevated, then the actions of ANG (1–7) are enhanced. The current findings provide much more direct evidence for the view that ANG (1–7) counters the antidiuretic and antinatriuretic actions of ANG II (7, 20).

The exact mechanisms that underlie these interactions between ANG (1–7) and ANG II in determining the antidiuretic and antinatriuretic actions have not yet been elucidated. There is evidence that ANG (1–7) activation of its “mas” receptor in proximal tubular cells is dependent on the degree of stimulation of ANG II AT1 receptors (26). Thus, when ANG II levels are elevated, for example, by decreasing sodium intake, ANG (1–7) is able to cause a greater effect by blocking the antidiuretic and antinatriuretic actions of ANG II. Conversely, the actions of ANG (1–7) will be blunted when the endogenous renin-angiotensin system is suppressed by feeding the high-sodium diet. There does seem to be an interaction between the “mas” and AT1 receptor in determining the excretory responses to ANG (1–7), and therefore the level of AT1 receptor density will also impact on excretory responses obtained.

The current study has demonstrated that local administration of ANG (1–7) can cause small increases in GFR, which appears more prominent in low-sodium-fed rats. There were dose-related increases in FENA in response to the ANG (1–7), suggesting a direct tubular action within the kidney. The high-sodium diet blunted and the low-sodium diet enhanced the renal excretory responses to ANG (1–7), supporting the hypothesis that the level of activity of the endogenous RAS can determine the intrarenal actions of exogenous ANG (1–7). These findings are consistent with the view that ANG (1–7) has a counter regulatory action within the kidney in the presence of its biological opponent ANG II. Whether this blunting or enhancement results from a change in receptor density remains to be determined.

Perspectives and Significance

ANG (1–7) is primarily generated as a consequence of the second isoform of ACE (ACE2). It is potentially an important metabolite that may exert significant actions, either directly or indirectly, to increase sodium and water excretion by the kidney. The most striking thing about this study is that the
magnitudes of ANG (1–7)-induced increases in sodium and water excretion are directly proportional to plasma renin levels and thereby ANG II levels. The interesting thing is that plasma ANG (1–7) levels are also increased. It would seem that both ANG II and ANG (1–7) are increased healthy animals and both are balanced such that they are in constant state of dynamic equilibrium. Thus it would appear that production of endogeneous ANG 1–7 exceeds ANG II and hence a natriuresis and diuresis ensues. The question is why the magnitude of this natriuresis and diuresis is compromised in high-sodium fed animals and enhanced in low-sodium-fed animals? The answer may lie in changes in the tubular expression of ANG II AT 1 and AT 2 receptors and the ANG (1–7) “mas” receptor or indeed their respective signaling pathways. Either way, when ANG II levels are elevated, as may occur in pathophysiological states, the natriuretic and diuretic actions of exogenous ANG (1–7) are enhanced perhaps pointing to this metabolite as having a therapeutic application.

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

J.O., A.C., and E.J.J. conception and design of research; J.O., A.C., and E.J.J. performed experiments; J.O., A.C., and E.J.J. analyzed data; J.O., A.C., and E.J.J. drafted manuscript; J.O., A.C., and E.J.J. edited manuscript; J.O., A.C., and E.J.J. approved final version of manuscript.

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