Renal dopamine and angiotensin II receptor signaling in age-related hypertension

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Chugh G, Pokkunuri I, Asghar M. Renal dopamine and angiotensin II receptor signaling in age-related hypertension. Am J Physiol Renal Physiol 304: F1–F7, 2013. First published October 24, 2012; doi:10.1152/ajprenal.00441.2012.—Kidneys play a vital role in long-term regulation of blood pressure. This is achieved by actions of many renal and nonrenal factors acting on the kidney that help maintain the body’s water and electrolyte balance and thus control blood pressure. Several endogenously formed or circulating hormones/peptides, by acting within the kidney, regulate fluid and water homeostasis and blood pressure. Dopamine and angiotensin II are the two key renal factors that, via acting on their receptors and counterregulating each other’s function, maintain water and sodium balance. In this review, we provide recent advances in the signaling cascades of these renal receptors, especially at the level of their cross talk, and discuss their roles in blood pressure regulation in the aging process.

aging; kidney; natriuresis; antinatriuresis; G protein-coupled receptors; blood pressure

THE KIDNEY, VASCULATURE, AND the central nervous system regulate sodium homeostasis and peripheral resistance and thus participate in the control of blood pressure. Several hormonal, neural, and humoral factors are involved in achieving this important task. Broadly speaking, these factors are classified as natriuretic and antinatriuretic factors. Natriuretic factors promote sodium excretion and vasodilatation whereas antinatriuretic factors cause sodium retention and vasoconstriction. These factors work in balance and, often by counterregulating each other’s function, keep the blood pressure within normal range. Of the many natriuretic and antinatriuretic factors, dopamine, as a natriuretic factor, and angiotensin II, as an antinatriuretic factor, are two important kidney factors responsible for the maintenance of sodium and water homeostasis as well as blood pressure.

Hypertension is a clinical factor typically associated with the aging process. It is a major risk factor for stroke, myocardial infarction, and heart and kidney failure (47). The aging process is inevitable and brings along with it a myriad of structural and functional changes in many organs, including the kidney (24, 75, 103). Kidney or renal aging, compared with that of other organs, is considered to have a greater impact on human physiology as it is one of the organs that ages fastest (69, 75). Therefore, we have focused on renal factors, more specifically on renal dopamine and angiotensin II, owing to their vital role in sodium and water metabolism and blood pressure regulation. Do renal dopamine and angiotensin II and their receptors’ signaling change during aging, impacting sodium and water homeostasis and blood pressure?

Herein, we provide the current state of knowledge on renal dopamine and angiotensin receptor signaling in the context of age-related hypertension. Furthermore, we also provide evidence, mostly based on our recent reports, that dopamine and angiotensin II are two important blood pressure-regulating renal factors; aberrant receptor signaling of both, and not just of one, contributes to age-related hypertension.

The Renal Dopaminergic System

Dopamine synthesis. The kidney synthesizes its own dopamine. l-3,4-Dihydroxyphenylalanine (l-DOPA), an immediate precursor of dopamine, is synthesized from tyrosine by the enzyme tyrosine hydroxylase. Neural cells but not renal proximal tubule (RPT) cells express tyrosine hydroxylase. Therefore, RPT cells cannot produce l-DOPA, but it is transported to RPT cells from the tubular filtrate. RPT cells, however, express aromatic acid decarboxylase (AADC), which converts l-DOPA into dopamine. Unlike neural cells, RPT cells do not express dopamine hydroxylase, hence synthesized dopamine is not converted to norepinephrine (9, 37, 100). However, the cellular content of dopamine in RPT cells is determined by its metabolizing enzymes, monoamine oxidase (MAO) and catechol-o-methyl transferase (COMT) (37, 94, 96). Another enzyme, renalase, recently has been implicated in the metabolism of catecholamines, including dopamine. Renalase is highly expressed in proximal tubules and is secreted in the urine. Unlike MAO and COMT, renalase seems to regulate luminal/urinary dopamine levels, impacting sodium excretion (33). Dopamine produced in RPT cells enters the peritubular space and the tubular lumen, promotes sodium excretion via acting on its receptors, and maintains normal blood pressure. Mice lacking kidney AADC, a dopamine-synthesizing enzyme, develop salt-sensitive hypertension (102). During basal or a low-sodium state, the levels of dopamine are not high enough (in the

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picomolar range) and cannot stimulate dopamine receptors. However, during the sodium-repleted state, higher levels of dopamine (in the nanomolar to low micromolar range) can be achieved in RPT cells, which can activate dopamine receptors (9, 37, 100).

Do tissue factors, especially dopamine, change during renal aging? A recent review by Choudhuri and Levi (24) describes the state of different tissue factors, such as angiotensin II, advanced glycation end products, oxidative stress, and klotho, during renal aging. However, limited information is available regarding cellular dopamine levels during renal aging. In Fischer 344 (F344) and Wistar rat aging models, an age-related increase in renal tissue levels of dopamine was reported (4, 89). This was linked to increased synthesis, and not to decreased metabolic degradation, of tissue dopamine. Activity of renal tissue AADC, the enzyme responsible for dopamine synthesis from L-DOPA, is reported to be elevated without any difference in the activities of MAO and COMT, enzymes responsible for cellular dopamine degradation, in the aging rats (89). An inverse correlation between serum reninase and age is reported to exist in the patients undergoing hemodialysis (99). The reason for higher renal dopamine production and reduced degradation during aging is not known, but quite likely is the outcome of a feedback mechanism to protect the declining function of the aging kidney (24).

Dopamine receptors. Dopamine exerts its biological effects via receptors belonging to the superfamily of seven transmembrane receptor proteins known as G protein–coupled receptors (GPCRs). Based on the molecular structure and receptor pharmacology, dopamine receptors are divided into two subtypes, D1-like and D2-like receptors. D1-like receptors have been cloned in mammals and are further classified into D1 and D5, D1A and D1B in rodents, respectively (9, 37, 100). These are linked to Gαo, the stimulatory G protein, which is known to stimulate adenylyl cyclase activity and inhibit sodium transporters such as Na-K-ATPase, Na/H and CI/HCO3 exchanger, and Na-HCO3 cotransporter (37, 100). In addition to coupling to Gαo protein, D1 receptors also couple to Gαq protein, stimulate phospholipase C (PLC), produce inositol phosphates and diacylglycerol, and regulate downstream targets such as protein kinase C (PKC) and sodium transporters (16, 36, 54, 65). Regulation of sodium transporters is implicated in blood pressure control (52, 93). Besides direct action on sodium transporters, renal hemodynamic effects of dopamine, mediated via D1-like receptors, also contribute to maintaining sodium homeostasis and blood pressure. When administered exogenously, dopamine or D1-like receptor agonists increase sodium excretion by increasing renal blood flow and glomerular filtration rate, and by reducing renal vascular resistance (11). At higher doses, sodium clearance is further increased; however, this change is accompanied by increased mean arterial pressure and reduced renal blood flow, suggesting a pressure-natriuresis effect. The latter effect may involve a non D1-like receptor component since high doses of dopamine also activate α- and β-adrenergic receptors (73). The lower endogenous levels of dopamine are not capable of modulating the pressure-natriuresis response; however, it can exert its natriuretic effect independently of changes in renal blood flow (11).

Whereas D2-like receptors are subdivided into D2, D3, and D4 receptors, linked to inhibitory G proteins Gαi/Gαo, which inhibit adenylyl cyclase (3, 55, 58, 59) and stimulate sodium transporter (Na-K-ATPase) (71, 97), D2-like receptors also regulate ion channels (62, 68). Selective activation of D2-like receptors by bromocriptine, a D2-like receptor agonist, increases Na-K-ATPase activity (53); however, D2-like receptors, when activated in concert with D1-like receptors, inhibit Na-K-ATPase and synergistically increase sodium excretion (15, 17, 80, 95). Besides, selective activation of prejunctional D2-like receptors located on postganglionic sympathetic nerve terminals by bromocriptine cause vasodilation by inhibiting norepinephrine release (73). D2-like receptors (D4 receptor) may also facilitate diuresis and natriuresis by antagonizing the hydrosmotic effect of vasopressin and inhibiting aldosterone secretion, respectively, in the cortical collecting duct (22, 70, 83).

Dopamine receptors and blood pressure. The role of dopamine receptors in blood pressure regulation comes from studies encompassing genetically modified mouse and rat hypertensive models [spontaneously hypertensive rats (SHRs), Dahl salt-sensitive (Dahl-SS), and DOCA salt-sensitive rats] as well as hypertensive patients (9, 37, 100). Deleting genes for D1-like (D1-D5) and D2-like (D2, D3, D4) receptors in mice produces a hypertensive phenotype, advocating their role in blood pressure regulation (2, 10, 98). Readers are directed to a recent review elegantly compiled by Zeng and Jose (100) for greater detail of the role of each receptor subtype in blood pressure regulation. Below, we summarize the current knowledge regarding the D1-like receptor, as this is perhaps the only dopamine receptor studied in the aging kidney in the context of blood pressure (6, 7, 25, 26, 35).

The renal D1-like receptors, once activated by endogenous ligand dopamine, inhibits sodium transporters (Na/H exchanger, Na-K-ATPase, Na-HCO3 cotransporter), increase sodium excretion, and maintain electrolyte balance and normal blood pressure. Between D1 and D5 receptors, D1 is considered to play a major role in the natriuretic process (56). Impaired ability of D1 receptors to inhibit sodium transporters and produce natriuresis, mainly due to D1 receptor-G protein uncoupling in RPTs, is linked to pathogenesis of hypertension in SHRs, Dahl-SS rats, and essential hypertensive patients (38, 57). On the contrary, D5 receptor coupling to G protein is not impaired in SHRs, Dahl-SS rats, and in hypertensive patients (37). There seems to be receptor and nephron segment specificity and organ selectivity with regard to D1 receptor uncoupling in hypertension, which precedes the onset of and cosegregates with hypertension (57).

D1 receptor-G protein uncoupling in hypertension is mainly mediated by a kinase, G protein–coupled receptor kinase-4 (GRK4), which via phosphorylation uncouples the receptor from the G protein effector complex (34, 38, 57). Another subtype of GRK, GRK2, also causes D1 receptor-G protein uncoupling; however, it does not seem to play a major role in hypertension (9, 86). GRK4 variants, such as R65L, A142V, and A486V, with higher constitutive activity are reported in the kidneys of hypertensive patients (38). Increased renal GRK4 expression in SHRs and salt-sensitive hypertensive C57BL/6J mice (from Jackson Laboratories) are also reported (34, 57). Reducing renal GRK4 protein using GRK4 antisense oligodeoxynucleotides decreased serine-phosphorylated D1 receptors, increased sodium excretion, and reduced blood pressure in SHRs (79). Further evidence for GRK4 in blood pressure regulation, via D1R, comes from depleting the GRK4 gene in

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C57BL/6J mice, which decreases basal blood pressure and prevents salt sensitivity in these animals (34).

Renal D1 receptor and aging. Renal D1 receptor signaling has been studied widely in our laboratory in the normotensive F344 rat aging model (6, 7, 13, 35, 40, 60). Lately, greater interest has been shown in another model, Fischer 344 X Brown Norway F1 hybrids (FBNs), a preferred rat aging model recommended by the National Institute on Aging. FBNs show similar age-related changes in heart and muscle as in humans (77, 91). We became interested in this model as these rats demonstrate an age-related hypertensive phenotype determined both under anesthesia (26) as well as in the conscious state as determined by radiotelemetry (Chugh G, Williams J, and Ashgar M, unpublished observations).

F344 rats do not develop age-related hypertension (25, 43) as well as salt sensitivity during aging (unpublished observations). Conversely, FBNs show high blood pressure (26) and salt sensitivity during aging (unpublished observations). High blood pressure in aged FBNs and salt sensitivity in other animal models are linked to oxidative stress-induced dysfunction of renal D1 receptors (25, 37, 100). This phenomenon might be attributed to the kidney p67phox subunit of NADPH oxidase, a superoxide radical-generating enzyme. Disrupting p67phox in Dahl-SS rats by zinc-finger nuclease technology abrogates salt-sensitive hypertension and reduces kidney oxidative stress (39). The gp91phox subunit of NADPH oxidase does not seem to contribute to age-related hypertension and salt sensitivity. Despite the age-associated increase in gp91phox expression in both F344 and FBN rats, only aged FBN rats are salt sensitive (unpublished observations) and develop age-related hypertension (5, 25, 26). Moreover, gp91phox does not seem to participate in the production of oxidative stress in the kidney and salt-sensitive hypertension in Dahl-SS rats (39). Whether p67phox levels are altered in the kidneys of FBNs and contribute to the development of hypertension and salt sensitivity with aging in these rats remains to be determined.

Furthermore, there is dissimilarity in some of the signaling components of the D1 receptor between these two aging models. In F344 rats, the age-related decline in D1 receptor mRNA in RPTs corresponds to a decline in the proteins and the numbers of the receptor (6, 13, 40, 60). However, in FBN rats, the age-related decline in D1-like receptor, D1A and D1B, mRNA (Fig. 1, B and C) corresponds to a decline in receptor numbers but not in receptor proteins (25). The reason for this is not known. There is an age-related increase in PKC activity in RPTs of F344 rats, which is not seen in FBNs (8, 25). Another notable dissimilarity between these models is at the level of GRKs. The levels of GRK2 but not GRK4 protein increase with aging in RPTs of F344 rats (25, 35). An opposite scenario is present in the RPTs of FBNs, where GRK4 but not GRK2 protein increases with aging (25). These changes, especially at the levels of GRK4, given its role in hypertension and salt sensitivity as noted above, might be contributing factors for age-related hypertension and salt sensitivity in FBNs (unpublished observations).

The Renin-Angiotensin System

The renin-angiotensin system (RAS) is an important regulator of blood pressure and fluid balance. It maintains fluid balance by regulating sodium and water handling in the kidney. RAS is a multienzyme system.

The renin enzyme, mainly from the kidney, converts angiotensinogen, the major substrate, into the inactive peptide angiotensin I (ANG I). Another enzyme, angiotensin-converting enzyme, metabolizes ANG I into the physiologically active peptide ANG II (27). Renin, by itself, is formed from prorenin, presumably by kidney proteases (27, 31). Prorenin and renin can bind receptors present in the kidney and initiate profibrotic and inflammatory pathways independent of ANG II generation (27). Overactivation of RAS leads to the development of hypertension and target organ damage. Inhibiting the synthesis or activity of ANG II by pharmacological agents improves cardiovascular outcomes, which highlights the importance of the RAS in clinical medicine (1, 18, 64, 76).

In addition to systemic RAS, there is local tissue RAS, including in kidney tissue, which perhaps plays a greater role in blood pressure (21, 72). A recent study indicates the presence of even nuclear RAS, contributing to cardiovascular functioning (46). Plasma as well as aortic and heart tissue RAS activity increases with aging (12, 45, 92). There are mixed reports regarding kidney tissue RAS activity during aging. An earlier study demonstrated a decline in kidney tissue RAS activity with aging in rats (24); however, later studies have

Fig. 1. The levels of mRNA of the AT1A receptor increase whereas those of D1A and D1B receptors decrease with aging in renal proximal tubules (RPTs) of Fischer 344 X Brown Norway F1 hybrid rats (FBNs). There were a 5-fold increase in AT1A (A) and an ~50% decrease in D1A (B) and D1B (C) receptor mRNA levels in the RPTs of 21-month aged compared with 3-month old FBNs. mRNAs from RPTs were isolated, reverse transcribed to cDNA, and used in TaqMan real-time PCR. PCR reagents and primer-probe for AT1A (A), D1A (B), and D1B (C) receptors as well as the internal control, 18S ribosome (18S rRNA), were purchased from Applied Biosystems. The data for AT1A (A), D1A (B), and D1B (C) receptors were normalized to 18S rRNA and presented as bar diagrams. **Significantly different from 3-month old adult FBNs (P < 0.01) by t-test; n = 3 rats.
showed an age-related increase in renal RAS activity in these animals (75, 84).

Angiotensin receptors. AngII responsiveness at the cellular level is mediated by angiotensin receptors, pharmacologically divided into two classes: type 1 (AT1) and type 2 (AT2) (82, 85). Gene-targeting studies suggest that most of the ANG II responsiveness is transduced through AT1 receptors (29). Two subtypes of the AT1 receptor are present in the rat and mouse, designated as AT1A and AT1B (19). AT1A receptors predominate in most organs and are considered the closest murine homolog to the single human AT1 receptor. Studies using the kidney cross-transplantation approach in wild-type and AT1A-deficient mice provide strong evidence for a role of kidney AT1A/AT1 receptors in sodium retention and blood pressure elevation in hypertension (27). The primary function of AT2 receptors is to counteract AT1 receptor function (20).

Unlike dopamine, autocrine and paracrine actions of ANG II on sodium and water handling via AT1 receptors are exerted through both tubular and hemodynamic mechanisms (21). Kidney AT1 receptors play a dominant role in promoting sodium retention and blood pressure elevation in hypertension (28). The primary mechanism of sodium retention by AT1 receptors is via stimulation of renal tubular sodium transporters such as Na-K-ATPase, the Na/H exchanger, and epithelial sodium channel. Strong evidence for the renal AT1 receptor in hypertension, linking sodium transporters, comes from a study where mice underwent genetic manipulation to specifically express AT1 receptors in the kidney. These mice, when fed with a low-sodium diet, demonstrated attenuation of the hypertensive response to ANG II, implicating AT1 receptor-mediated salt reabsorption as a major factor in ANG II-dependent hypertension (30, 51). The direct hemodynamic effects of ANG II on renal vasculature include vasconstriction of both afferent and efferent arterioles, leading to a decrease in renal blood flow, glomerular filtration rate, and sodium excretion (50). RAS and specifically ANG II play a central role in maintaining the pressure-natriuresis relationship by regulating arterial pressure. ANG II reduces pressure-natriuresis by increasing sodium reabsorption through an increase in tubular uptake and/or a decrease in glomerular filtration rate (44).

The AT1 receptor and aging. It also appears that the renal AT1 receptor plays an important role in the hypertensive phenotype during aging. Renal AT1 receptor function, measured as a natriuretic response to the AT1 receptor blocker candesartan as well as the ANG II response on Na-K-ATPase in RPTs, was greater in hypertensive, aged FBNs compared with their normotensive adult counterparts (25, 26). This finding suggests that a hyperactive renal AT1 receptor contributes to hypertension in aging. This notion seems likely since renal AT1 receptor function in normotensive, aging F344 rats is not hyperactive and is very similar to that in their adult counterparts with normal blood pressure (25).

The reason for hyperactive renal AT1 receptor function in aging is most likely the result of age-associated oxidative stress, as antioxidant tempol supplementation to aged FBNs restores renal AT1 receptor function and reduces blood pressure in these rats (25, 26). This observation provides compelling evidence for a role of age-associated oxidative stress in renal AT1 receptor hyperactivation and hypertension in aging. What could be the likely mechanism for this? We found an increase in ANG II-mediated stimulation of AT1 receptor-G protein coupling as well as Na-K-ATPase in the RPTs of aged FBN rats, which was normalized with tempol treatment (22). We do not know the exact mechanism of this finding; however, we speculate that the age-associated increase in oxidative stress by modifying AT1 receptor protein conformation increases the affinity of the receptor for ANG II, thereby causing an increase in AT1 receptor-G protein coupling, as seen in aged FBN rats. Indirect evidence for this proposed mechanism comes from studies which demonstrate that sulfhydryl-containing antioxidants N-acetylcysteine and dithiothreitol cause rapid and concentration-dependent decreases in ANG II radioligand binding to the AT1 receptor and the AT1 receptor-mediated signaling response in cultured vascular smooth muscle cells (87, 88). Furthermore, in a similar study in HEK293 cells, antioxidant ascorbic acid decreases the binding affinity of the AT1 receptor for ANG II (63).

Another likely mechanism could be that oxidative stress directly, or indirectly via GRK4, increases the transcription of renal AT1 receptors, contributing to hyperactivation of the receptor. This notion is based on our own findings as well as findings from other laboratories (25, 37, 90). In RPTs, we have reported higher GRK4 levels, which decrease with tempol in aged FBNs (25), and observed an age-related increase in the levels of AT1 receptor mRNA in these rats (Fig. 1A). Interestingly, both GRK4 overexpression in mice and constitutively active GRK4A4 Val also increase expression as well as activity of the AT1 receptor (37, 90). In hypertensive patients, higher basal GRK4 activity due to functional polymorphism also increases AT1 receptor activity (48, 49). Taken together, these studies provide evidence for the role of age-associated oxidative stress, via GRK4, in overexpression and hyperactivation of the renal AT1 receptor in aging FBNs. However, the question regarding the source of oxidative stress in the kidney of aging FBNs persist. In this regard, NADPH oxidase and mitochondria need due attention. NADPH oxidase and mitochondrial dysfunction are two major sources of reactive oxygen species (ROS), contributing to the cellular burden of oxidative stress. While the gp91phox subunit of NADPH oxidase is overexpressed (25), however, mitochondrial dysfunction, a hallmark of the aging process, is yet to be determined in the aging kidneys in FBNs. The hyperactive AT1 receptor in aging kidneys of FBNs may also provide a continuous source of ROS generation via NADPH oxidase and mitochondria as activation of the AT1 receptor, with ANG II, is linked to ROS generation via these two sources (32).

Interaction between D1 and AT1 receptors. Dopamine receptors interact with many components of the RAS, including angiotensin receptors, to maintain sodium homeostasis and normal blood pressure. Both subtypes of dopamine receptors, D1-like and D2-like receptors, are reported to interact with angiotensin receptors (100). Since the D1-like receptor is the most studied dopamine receptor in aging kidneys, we limit our discussion to the interaction between D1-like and angiotensin receptors.

D1-like (D1 and D5) and angiotensin receptors, especially the AT1 receptor, interact at the protein-protein level as well as transcription and posttranslational levels (23, 42, 101). D1-like receptor activation mediates internalization of the AT1 receptor (23, 61), possibly via D5 receptor-induced c-src activation mechanisms (42). An enhanced natriuretic response to D1-like receptor activation is seen upon blockade of either ANG II
production or AT₁ receptors (22). Different mechanisms for this observation are reported, encompassing augmentation of membranous D1 receptor (66) as well as AT₂ receptor expression (41, 74, 78). A reciprocal gene expression profile between these receptors exists, where deletion of one increases the expression of the other (41). In mice, deletion of the D5 receptor gene increases AT₁ receptor expression and contributes to high blood pressure in these animals (67).

Only a handful of studies are available relating to interaction between these receptors in aging kidneys. Our own study demonstrates the existence of a reciprocal interaction between D1 and AT₁ receptors at the transcriptional level (Fig. 1) in the aging kidneys of FBNs. Lower D1 and higher AT₁ receptor mRNA levels were observed to be associated with hypertension in aging FBNs (26). Another study demonstrates that reducing D1 receptor function, by depleting kidney dopamine production in AADC−/− mice, increases AT₁ receptor but decreases AT₂ receptor expression and results in hypertension in the aging knockout mice (102). Whether the AT₂ receptor also participates in the interaction between D1 and AT₁ receptors, and decreases in the aging kidneys of FBNs, remains to be determined. However, the interaction between the two receptors seems likely as the intrarenal AT₁/AT₂ receptor ratio is reported to increase with aging in Sprague-Dawley rats (81). Interestingly, D1 and AT₁ receptors do not seem to interact in the aging kidneys of normotensive F344 rats (25). The age-related decline in D1 receptor function is not associated with higher AT₁ receptor function in the kidneys of aging F344 rats (13, 25).

Conclusion

It is clear from the above discussion that D1 and AT₁ receptors are two major kidney receptors involved in the maintenance of sodium and fluid volume as well as normal blood pressure not only during adulthood but also during aging. Aberrant functioning of both the renal receptors, decline in D1 and exaggeration of AT₁ receptors, may culminate in age-related hypertension. The p67phox and not the gp91phox subunit of NADPH oxidase as well as GRK4 seem to play a pivotal role in this process. These molecules may represent targets for next-generation drugs to treat hypertension in aging, especially “resistant hypertension,” which is a hallmark of the aging process. Currently available antihypertensive medications are not effective in treating resistant hypertension. Furthermore, the D1 receptor is reported to be antiaging whereas the AT₁ receptor is proaging (14, 102). Therefore, the clinical relevance of targeting the D1 receptor with agonists and the AT₁ receptor with antagonists as a combination therapy might be expected to reduce/prevent deteriorating changes associated with renal aging and promote better physiological outcomes in the elderly population.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are there as declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: G.C. and M.A. conception and design of research; G.C. performed experiments; G.C. analyzed data; G.C. and M.A. interpreted results of experiments; G.C. and M.A. drafted manuscript; G.C. and I.P. edited and revised manuscript; I.P. prepared figures; M.A. approved final version of manuscript.

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