Peripheral cardiac sympathetic hyperactivity in cardiovascular disease: role of neuropeptides

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Abstract

High levels of sympathetic drive in several cardiovascular diseases including postmyocardial infarction, chronic congestive heart failure and hypertension are reinforced through dysregulation of afferent input and central integration of autonomic balance. However, recent evidence suggests that a significant component of sympathetic hyperactivity may also reside peripherally at the level of the postganglionic neuron. This has been studied in depth using the spontaneously hypertensive rat, an animal model of genetic essential hypertension, where larger neuronal calcium transients, increased release and impaired reuptake of norepinephrine in neurons of the stellate ganglia lead to a significant tachycardia even before hypertension has developed. The release of additional sympathetic cotransmitters during high levels of sympathetic drive can also have deleterious consequences for peripheral cardiac parasympathetic neurotransmission even in the presence of β-adrenergic blockade. Stimulation of the cardiac vagus reduces heart rate, lowers myocardial oxygen demand, improves coronary blood flow, and independently raises ventricular fibrillation threshold. Recent data demonstrates a direct action of the sympathetic cotransmitters neuropeptide Y (NPY) and galanin on the ability of the vagus to release acetylcholine and control heart rate. Moreover, there is as a strong correlation between plasma NPY levels and coronary microvascular function in patients with ST-elevation myocardial infarction being treated with primary percutaneous coronary intervention. Antagonists of the NPY receptors Y₁ and Y₂ may be therapeutically beneficial both acutely during myocardial infarction and also during chronic heart failure and hypertension. Such medications would be expected to act synergistically with β-blockers and implantable vagus nerve stimulators to improve patient outcome.

Keywords: autonomic nervous system, cardiac, hypertension, myocardial infarction, neuropeptide Y
Importance of Autonomic Balance in Cardiovascular Disease

High cardiac sympathetic drive promotes myocyte calcium influx, increases the inotropic state of the heart, and increases myocardial oxygen demand. This can exacerbate the harmful effects of preexisting cardiac ischemia and precipitate life-threatening ventricular arrhythmias (63, 79). This is particularly prevalent when there is an abnormal structural phenotype to support reentrant pathways, such as an ischemic or dilated cardiomyopathy, hypertrophic cardiomyopathy, or arrhythmogenic right ventricular cardiomyopathy (121). High sympathetic drive to the heart can also precipitate arrhythmia when there is an abnormal electrophysiological substrate, with inherited chanelopathies such as the long QT or Brugada's syndrome. Excessive adrenergic activity is unsurprisingly a negative prognostic indicator postmyocardial infarction (48, 53) and during congestive cardiac failure (19, 77). Moreover it has also been implicated in both the etiology and progression of hypertension (35).

Increased sympathetic activity to the heart is correlated with hypertensive left ventricular remodeling and hypertrophy (94), an independent predictor of morbidity and mortality (58).

Under normal conditions the cardiac vagus may act as Nature's β-blocker preventing intracellular calcium overload and slowing heart rate, but it achieves this on a rapid time scale compared with the action of sympathetic stimulation. It can also directly raise the threshold for induction of ventricular fibrillation (72, 73). Conditions associated with high vagal tone [e.g., exercise training (23) and gene transfer of neuronal nitric oxide (NO) synthase (nNOS) (25, 71)] protect against mortality (20), while impaired vagal function has been demonstrated in both congestive cardiac failure (53) and hypertensive patients (56). However, the cardiac vagus is notoriously difficult to target pharmaco logically and, as a consequence, therapy has been directed at the sympathoadrenal axis and renin-angiotensin pathways, although a new drug that reduces heart rate directly by blocking the hyperpolarized-activated current (ivabradine) reduces cardiovascular death or hospital admissions with heart failure, as demonstrated by the SHIFT study (108). Randomized controlled trials have also demonstrated that β-blockers and angiotensin-converting enzyme (ACE) inhibitors are highly beneficial in the context of myocardial infarction, congestive heart failure, and hypertension [e.g., ISIS1 (33a), CIBIS II (17a), CONSENSUS (20a), SAVE (83)], although a significant mortality nevertheless remains.

Sites of Autonomic Dysfunction in Cardiovascular Disease

There is a wealth of data supporting the notion that the autonomic dysfunction associated with cardiovascular disease can arise at many distinct anatomical sites. For example, the success of renal sympathetic nerve denervation in reducing muscle sympathetic nerve activity, plasma catecholamines, and arterial blood pressure in patients with drug refractory hypertension supports the notion that renal afferents contribute, at least in part, to the generation and maintenance of the hypertension in these patients (32, 96). Evidence from preclinical animal models and human subjects also supports carotid body supersensitivity as a mechanism by which central sympathetic drive is promoted in heart failure and hypertension (81). There has therefore been a resurgence in interest in carotid body denervation as a therapeutic strategy in these conditions (81), as well as implantable carotid sinus stimulators to activate the high pressure arterial baroreflex and reduce sympathetic drive and increase vagal tone in hypertension (46).

Afferent signaling can also arise from the heart itself. Whereas the vagi relay sensory information to the nodose ganglion, mechanical and chemical information regarding the myocardium is relayed via neurons of the upper thoracic and lower cervical dorsal root ganglia and also within sensory neurons of the intrinsic cardiac plexi. This opens the possibility of afferent modulation of efferent signaling not just at the level of the brain stem but also at the levels of the intrinsic cardiac plexi (3), although this has not been directly demonstrated. Spinal sympathosympathetic reflexes may maintain sympathetic drive in response to both myocardial ischemia (66) and hypertension (65).

Centrally, afferent inputs converge on the nucleus tractus solitarius (NTS) in the medulla (26). This information is then relayed to the caudal ventrolateral medulla (CVLM), which provides a GABAergic inhibition of the rostral VLM. The NTS also relays via inhibitory GABAergic interneurons communicating with preganglionic vagal neurons of the nucleus ambiguous and dorsal motor nuclei of the vagus. Whereas these nuclei are key integrating sites and may influence efferent sympathetic outflow in both hypertension and heart failure (e.g., see Refs. 92, 33, 172), we have found that a significant component of the sympathetic hyperactivity observed in the genetic model of essential hypertension, the spontaneously hypertensive rat (SHR), originates at the level of the efferent...
postganglionic neuron (38, 59–61, 101, 103).

Invited Review: Peripheral cardiac sympathetic hyperactivity in cardio...

Peripheral Sympathetic Hyperactivity Precedes the Development of Hypertension in the Spontaneously Hypertensive Rat

The distribution of blood pressure in the human population is continuous and negatively skewed without a clear bimodal pattern to help define a subset of hypertensive patients. There is evidence linking impairment of the kidney, vasculature, and the autonomic nervous system in many patients with higher blood pressure who we define as being hypertensive. In addition clinically severe hypertension also results in renal and vascular end-organ damage thereby exacerbating the condition. Increased sympathetic activity and reduced vagal tone are now well established as major contributing factors to the pathophysiology of human hypertension (2, 24, 34, 36, 95, 99) and that observed in the SHR (17, 38, 57, 59, 61). Hypertension is associated with increased muscle sympathetic nerve activity (2, 36), increased levels of plasma norepinephrine (NE) (31, 95), and increased renal NE spillover (30, 95). Evidence for sympathetic hyperactivity has also been inferred from spectral analysis of heart rate variability in borderline and hypertensive patients where a linear correlation with blood pressure has been demonstrated (64). Increased muscle sympathetic nerve activity in response to mental stress has also been documented within normotensive offspring from families with a history of hypertension (78). This suggests that sympathetic activation may be an early marker of hypertension in those who are genetically predisposed to the disease.

In a recent series of papers we studied the SHR at 16 wk of age, when hypertension is well established and the animal is tachycardic compared with its Wistar-Kyoto (WKY) control (40), and also at 4 wk of age when it is phenotypically normotensive with no evidence of left ventricular hypertrophy (59). There are multiple methods of measuring blood pressure in rats at 4 wk of age including tail-cuff, radiotelemetry, and implanted devices with most previous studies investigating the 4-wk-old SHR consistently finding them to be normotensive (49, 50, 109). It is also worth noting that the SHR is often used as a model of attention deficit hyperactivity disorders, which may complicate these measurements. We therefore have also measured blood pressure at rest under general anesthesia with a large sample number (SHR, n = 18; WKY, n = 20) to confirm these findings (103).

Dysregulation of intracellular calcium handling in SHR cardiac sympathetic neurons.

Studies on cultured sympathetic neurons from the stellate ganglion and superior cervical ganglion from the SHR at 6 wk of age have demonstrated that the depolarization-induced rise in intracellular free Ca$^{2+}$, measured using fura-2-acetoxymethyl ester, is significantly larger and the decay of the Ca$^{2+}$ transient also faster in the SHR compared with age-matched WKY controls (59) (see Fig. 1A). The in vitro analysis of calcium handling by cultured stellate ganglion cells is used as a surrogate for the behavior of terminal varicosities in vivo. Endoplasmic reticulum (ER) Ca$^{2+}$ content and caffeine-induced Ca$^{2+}$ release were significantly higher in the SHR, with lower protein levels of phospholamban and increased ryanodine receptor mRNA (59). A lower mitochondrial membrane potential was also observed, resulting in impaired mitochondrial Ca$^{2+}$ uptake and release (59). Depletion of ER Ca$^{2+}$ stores with caffeine and thapsigargin (to prevent SERCA Ca$^{2+}$ reuptake), did not alter the differences of evoked Ca$^{2+}$ transient and decay time observed, whereas removing mitochondrial buffering did (59). Interestingly this calcium handling phenotype is also seen in stellate and superior cervical neurons of the SHR before the development of hypertension (in both neonates and at 4 wk of age) (59). A rise in intracellular Ca$^{2+}$ in response to cellular depolarization also stimulates the exocytotic vesicular release of NE in sympathetic neurons (16, 90). Cardiac NE release from the atria can be measured using a $[^3]$H-labeling technique (40). Significantly higher $[^3]$HNE release is observed in the SHR compared with age-matched WKY at 16 wk of age (40), but this can also be demonstrated at 4 wk of age (102) (see Fig. 1B).

Fig. 1.
The peripheral cardiac sympathetic phenotype of the spontaneously hypertensive rat (SHR). A: calcium transients (measured using Fura 2-AM) within cultured neurons from the stellate ganglia in response to cellular depolarization (100 mmol/l KCl) are larger ...

Impairment of NE reuptake transporter in SHR cardiac sympathetic neurons.
In addition to the neuronal calcium signal, the synaptic NE concentration is also regulated by the kinetics of NE degradation and removal from the cleft. The majority of released NE (>90%) is taken up into the sympathetic nerve terminal by the NE reuptake transporter (NET), with less than 5% being metabolized within the extracellular space (93). The increased concentration of cardiac NE release observed within the prehypertensive SHR might also be due to impairment of the NET. Previous studies into the role of NET in hypertension have produced inconclusive or conflicting results. In human hypertension the putative role of NET has been reported to be either reduced (31, 91, 95) or unaltered (47). This apparent disparity is likely to be due to the indirect methods used to measure NET, including traditional radiotracer overflow measurements (68), and the diverse range of tissues studied (15, 68). A novel fluorescent assay has been recently developed to temporally monitor NET dynamics within intact tissue and isolated sympathetic nerve preparations (80, 101). The technique uses a fluorescent NET substrate in a masking dye solution. When the substrate is transported intracellularly by NET and separates from the masking dye, the rate of increase of intracellular fluorescence then directly reflects the activity of NET (Fig. 1C). Using this assay, we have recently demonstrated impaired NET activity in cultured sympathetic neurons from the cardiac stellate in both the depolarized and resting state. This could be observed both in hypertensive and prehypertensive SHRs compared with age-matched WKY (101). No difference in NET activity was observed within sympathetic neurons isolated from the superior cervical ganglia, which predominantly innervates the head and neck region (8), nor sympathetic neurons isolated from renal sympathetic ganglia (101). Interestingly, the difference in [3H]NE release from isolated atria between prehypertensive SHRs and WKYs could be normalized using the NET inhibitor desipramine (102).

NE release can also be autoinhibited by presynaptic α2-adrenoreceptors (α2-AR) as part of a negative feedback mechanism. In the adult SHR, expression of α2A-AR mRNA assessed by RT-PCR is increased in the stellate ganglion, and inhibition of these receptors with yohimbine produces a greater increase in cardiac [3H]NE release in the adult WKY compared with the SHR (123). However, at 4 wk of age cardiac [3H]NE release remains significantly greater than the WKY (102) suggesting that autoinhibition does not contribute to increased sympathetic neurotransmission before the onset of hypertension.

The increased sympathetic neurotransmission in the SHR also appears to be functionally significant in terms of changes in heart rate. In isolated atrial preparations with the right stellate ganglion still intact, the tachycardic response to direct stimulation of the stellate is significantly greater in the 16-wk SHR compared with WKY control at a range of stimulation frequencies (40), and this is also observed at 4 wk of age at higher stimulation frequencies despite the heart rate response to exogenous NE being no different from the WKY (102) (Fig. 1D). Interestingly a small, but significant, resting tachycardia can also be measured in vivo in the SHR under general anesthesia at this developmental stage and others have confirmed this using radio telemetry data (50). Despite this the intrinsic rate of the isolated hearts is no different between 4-wk-old SHRs and WKYs reinforcing the idea that dysregulation of the sympathetic nervous system may be one of the early hallmarks of the hypertensive phenotype (13).

**Indirect Consequences of Sympathetic Hyperactivity: Sympathovagal Cross Talk**

The idea that nerve cells may release more than one neurotransmitter with distinct postsynaptic targets and actions was postulated by Burnstock in 1976 (12). This went against the traditional view based on Dale's principle that nerves of the same class only utilize one neurotransmitter (107). To date cotransmitters have been identified within most major nerve populations both centrally and peripherally. However, the role of different cotransmitters varies greatly between different species, disease, and developmental state (13). The release of cotransmitters is highly dependent on the level of neuronal activity and they are usually slowly diffusing molecules. Cotransmitters and their metabolites often have a longer biological half-life than the main neurotransmitter, although there are notable exceptions such as ATP (9).

Cross talk between different neuronal populations by cotransmitters has been extensively studied within the central nervous system and identified as an important modulator of neural activity (10, 14, 54, 70, 119). However, increasing evidence is emerging that cross talk between neural populations in the heart is also important in autonomic control.

The phenomenon that high levels of cardiac sympathetic stimulation is coupled to a subsequent long-lasting inhibition of cardiac vagal function in vivo was first observed by Potter as early as 1982 (84, 87). Interestingly,
this phenomenon is only observed in vitro with direct stimulation of the sympathetic and vagus nerves rather than replacing neuronal stimulation with exogenous application of one or both of the respective neurotransmitters (39) (Fig. 2C). This suggests that the phenomenon is dependent on interneuronal signaling rather than convergence at the level of myocyte second messenger pathways. High sympathetic drive and reduced vagal tone is the characteristic phenotype associated with congestive heart failure and myocardial infarction. La Rovere in 1998 commented “... in ischemic patients a reduction in vagal activity, which is almost always accompanied by a concomitant increase in sympathetic activity, is sufficient to facilitate cardiac death by several mechanisms” (53). This may occur at least in part due to the release of sympathetic cotransmitters acting locally on cardiac cholinergic nerves to reduce acetylcholine release, in a process known as “sympathovagal cross talk” (43).

Fig. 2. Cardiac sympathovagal cross talk. Evidence for the release of the neuromodulators neuropeptide-Y (NPY) and galanin (GAL) from cardiac sympathetic nerves and their action on cardiac vagal function. A: after a period of prolonged (2 min), high-frequency ...

Sympathetic nerves throughout the autonomic nervous system contain cotransmitters such as ATP, neuropeptide Y (NPY), and galanin in addition to NE (62) (39, 52, 115). NE itself is not thought to regulate cardiac vagal acetylcholine release within humans or guinea pigs (67, 98), although there is evidence of a short-lived inhibition on acetylcholine release due to NE within rat atria via α-adrenoceptors (118). ATP also appears to be unable to alter acetylcholine release in the human or guinea pig heart (67, 98).

Levels of sympathetic stimulation identical to those that impair vagal function have also been shown to release NPY into the perfusate of isolated atria in vitro (39) (Fig. 2A) as well as into coronary sinus blood in vivo (116). The release of galanin can also be detected in vitro but at lower levels than that observed for NPY (39). Evidence for galanin release as a cotransmitter under conditions of high sympathetic stimulation has also been reported within the liver and the gut (7, 51) Antagonists of the Y2 receptor and GALR1 can reverse the inhibition of vagal bradycardia inhibition postsympathetic stimulation in vitro (39) and in vivo (104) as can genetic knockout of these receptors in vivo (88, 105, 106). Immunohistochemical labeling has localized the NPY Y2 receptor (41) as well as the galanin GALR1 receptor (39) to vagal neurons in the right atria and around the sinoatrial node providing the anatomical basis for the sympathovagal cross-talk model.

We have recently shown that both exogenous NPY and galanin can reduce the heart rate response to vagus nerve stimulation in vitro, while being unable to alter the bradycardic response to the stable analogue to acetylcholine, carbacholylcholine (39, 41). At the same concentration range both NPY and galanin can also reduce [3H]acetylcholine release (Fig. 28). Intravenous administration of NPY and galanin are also able reduce the magnitude of the vagal bradycardia in vivo, but these experiments may be complicated by potential changes in haemodynamics and circulating factors (86, 106, 114). In our atrial preparation with intact right vagus nerve, inhibitors of protein kinase C completely abolish the action of both NPY and galanin, while protein kinase A inhibitors have no effects. Conversely, a protein kinase C activator can mimic the effects of these cotransmitters and reduce [3H]acetylcholine release (39). The exact mechanisms linking GALR1 and Y2 receptor binding, protein kinase C signaling, and the release of acetylcholine have not yet been elucidated.

Galanin is a 29/30 amino acid neuropeptide, first isolated from the porcine gut (111), while NPY is a 36-amino acid peptide that was first isolated from the porcine brain (110). NPY within the heart is the most abundant neuropeptide and was first identified in intramural sympathetic nerves in close association with myocytes and coronary blood vessels (1). In addition to its action as a neuromodulator of parasympathetic control of heart rate, significant evidence points toward a role for NPY in controlling vascular function during the development and maintenance of hypertension (69, 117). NPY has also been implicated in the development and progression of left ventricular hypertrophy (LVH), as the peptide is a hypertrophic factor (69) with increased plasma levels of the
neuropeptide during hypertension correlating to the severity of LVH (28, 44).

**Indirect Consequences of Sympathetic Hyperactivity: Sympathovascular Cross Talk**

Independent of changes in heart rate, the cardiac vagus nerve can also increase myocardial perfusion (55, 89) and improve microcirculatory flow in patients with coronary artery disease (120). During conditions of high sympathetic drive such as during myocardial infarction, it is therefore conceivable that cotransmitter release could impair parasympathetic mediated vasodilation and exacerbate on-going ischemia. Several sympathetic neurotransmitters are also directly vasoactive. ATP released either as a cotransmitter from sympathetic nerves or from the vascular lumen in response to changes in blood flow or hypoxic stress can dilate or contract vessels (11). Within the vascular endothelium it is thought to predominantly act through the P₂Y₁ and P₂Y₂, G<sub>i</sub>/11-coupled receptors, although the half-life of ATP is short and sympathetic released ATP is not thought to have a significant effect on the coronary microcirculation (29). While the breakdown product of ATP, adenosine, is a predominantly vasodilating metabolite, its half life is also short and the main action of sympathetic stimulation remains coronary vasoconstriction. NPY has a far longer half-life and intracoronary infusion causes microvascular constriction in humans and can precipitate angina and ischemic electrocardiographic changes (18). NPY can also constrict isolated human coronary arteries in vitro (112). This may be in part by inhibition of acetylcholine release through a Y<sub>2</sub> receptor mechanism but could also occur via a direct action on vascular smooth muscle to cause vasoconstriction or by potentiatting the actions of other vasoconstrictors such as NE, angiotensin II, serotonin, endothelin-1, and prostaglandins (27) via a Y<sub>1</sub> receptor mechanism. Of note, the vasoconstrictive action of NPY as well as its potentiating effect on other vasoconstrictors is lost in the Y1 receptor knockout mouse (82). The evidence for NPY being as a potent vasoconstrictor released during sympathetic stimulation is reviewed in detail elsewhere (69).

NPY gene polymorphisms are linked to an increased risk of early-onset atherosclerosis (100), and NPY can influence angiogenesis and ventricular remodelling, effects linked to the Y<sub>2</sub> and Y<sub>5</sub> receptors (85, 124). Animal studies suggest that cardiac NPY is released from sympathetic nerves during experimentally induced myocardial infarction (37) and several studies published over 20 years ago demonstrate that plasma NPY levels are elevated following acute coronary syndromes and during left ventricular failure in humans where they correlate positively with the severity of heart failure and 1-yr mortality (44, 113).

Contemporary treatment of ST-elevation myocardial infarction (STEMI) involves emergency primary percutaneous coronary intervention (PPCI) to reopen the occluded epicardial coronary artery (Fig. 3A). Microcirculatory “no-reflow” can be identified in nearly one-third of patients and correlates with persistent ST elevation, larger infarctions, and poor ejection fraction and prognosis (21, 22, 74). Distal atherothrombotic embolization from the ruptured plaque during PPCI may contribute to this phenomenon, but there is also an important functional vasoactive component that is poorly understood. Several possible candidates have been implicated including endothelin-1 (76), thromboxane A2 (75), and B-type naturitic peptide (45). Working with collaborators, we have recently explored the possibility that NPY may play a key role in this important clinical entity (22).

![Fig. 3.](image)

**Fig. 3.**

Sympathovascular cross talk during ST-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PPCI): a role of neuropeptide-Y (NPY)? A: schematic diagram of an epicardial coronary artery stent, inserted during ...

In 64 patients presenting throughout the 24-h cycle of clinical activity to a University hospital heart center being treated with PPCI for STEMI, plasma NPY levels sampled from peripheral blood were significantly elevated in the first 6 h from presentation before plateauing but remaining elevated compared with the normal range. Before, immediately after PPCI, and at several time points during the first 48 h of presentation, plasma NPY levels were significantly higher in those patients with no angiographic reflow (Fig. 3A) and strongly correlated with coronary flow reserve and the index of microcirculatory resistance measured using a coronary pressure wire and thermodilution techniques (Fig. 3B). Importantly, plasma NPY levels also correlated with the resolution of ST elevation (Fig. 3C) and the size of the infarct assessed by total troponin release (22). We did not directly measure...
cardiac NPY release via a coronary arterial/sinus concentration difference, because clinically this is difficult to obtain compared with a peripheral blood sample and can only be performed at the time of PCI limiting its utility. The strong correlations with plasma NPY levels we observe lead us to speculate that maintained microvascular vasoconstriction post-PPCI by NPY contributes to larger myocardial infarctions and that Y1 receptor antagonism may be beneficial at the time of revascularization in PPCI to improve angiographic reflow and prognosis.

Perspectives and Significance

High levels of sympathetic drive in several cardiovascular diseases including postmyocardial infarction, during chronic congestive heart failure, and hypertension are reinforced through dysregulation of afferent input and central integration of autonomic balance. However, recent evidence suggests that a significant component of sympathetic hyperactivity may also reside peripherally at the level of the postganglionic neuron. This has been studied in depth in the animal model of genetic essential hypertension, the spontaneously hypertensive rat, where larger neuronal calcium transients, increased release, and impaired reuptake of NE in neurons of the stellate ganglia lead to a significant tachycardia even before hypertension has developed. The release of additional sympathetic cotransmitters during high levels of sympathetic drive can also have deleterious consequences for peripheral cardiac parasympathetic neurotransmission even in the presence of β-blockers. Stimulation of the cardiac vagus reduces heart rate, lowers myocardial oxygen demand, improves coronary blood flow, and independently raises ventricular fibrillation threshold. Recent data demonstrates a direct action of the sympathetic cotransmitters NPY and galanin on the ability of the vagus to release acetylcholine and control heart rate, as well as a strong correlation between plasma NPY levels and coronary microvascular function in patients with ST-elevation myocardial infarction being treated with primary percutaneous coronary intervention. Targeting NPY receptors pharmacologically may therefore be a useful therapeutic strategy both acutely during myocardial infarction and also during chronic heart failure and hypertension. Such medications would be expected to act synergistically with β-blockers and new technologies targeting efferent parasympathetic outflow such as implantable vagus nerve stimulators (97) to improve patient outcome.

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

Author contributions: J.S. and N.H. performed experiments; J.S. and N.H. analyzed data; J.S. and N.H. interpreted results of experiments; J.S. and N.H. prepared figures; J.S. and N.H. drafted manuscript; J.S. and N.H. edited and revised manuscript; J.S. and N.H. approved final version of manuscript; N.H. conception and design of research.

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