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Evidence that BDNF regulates heart rate by a mechanism involving increased brainstem parasympathetic neuron excitability

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Abstract

Autonomic control of heart rate is mediated by cardioinhibitory parasympathetic cholinergic neurons located in the brainstem and stimulatory sympathetic noradrenergic neurons. During embryonic development the survival and cholinergic phenotype of brainstem autonomic neurons is promoted by brain-derived neurotrophic factor (BDNF). We now provide evidence that BDNF regulates heart rate by a mechanism involving increased brainstem cardioinhibitory parasympathetic activity. Mice with a BDNF haploinsufficiency exhibit elevated resting heart rate, and infusion of BDNF intracerebroventricularly reduces heart rate in both wild-type and BDNF+/− mice. The atropine-induced elevation of heart rate is diminished in BDNF+/− mice and is restored by BDNF infusion, whereas the atenolol-induced decrease in heart rate is unaffected by BDNF levels, suggesting that BDNF signaling enhances parasympathetic tone which is diminished with BDNF haploinsufficiency. Whole-cell recordings from pre-motor cholinergic cardioinhibitory vagal neurons in the nucleus ambiguus indicate that BDNF haploinsufficiency reduces cardioinhibitory vagal neuron activity by increased inhibitory GABAergic and diminished excitatory glutamatergic neurotransmission to these neurons. Our findings reveal a previously unknown role for BDNF in the control of heart rate by a mechanism involving increased activation of brainstem cholinergic parasympathetic neurons.

Keywords: BDNF, GABA, glutamate, nucleus ambiguus, parasympathetic, vagus nerve.

enhance synaptic plasticity and protect neurons against injury and disease (see Mattson 2012 for review).

While its involvement in neuroplasticity in the hippocampus and cerebral cortex is established, it is not known whether BDNF influences the function of autonomic neurons in the brainstem that regulate heart rate. Two lines of evidence suggested to us the possibility that BDNF plays a role in heart rate regulation. First, exercise and intermittent fasting that increase BDNF expression in many brain regions (Lee \textit{et al.} 2002; Wu \textit{et al.} 2011) can also reduce resting heart rate by increasing parasympathetic activity (\textit{Wan et al.} 2003; Buchheit \textit{et al.} 2010). Second, BDNF induces the expression of choline acetyltransferase and increases acetylcholine synthesis and release in developing autonomic neurons in culture (\textit{Yang et al.} 2002; Zhou \textit{et al.} 2004). Pre-ganglionic cholinergic cardioinhibitory vagal neurons (CVNs) in the nucleus ambiguus (NA) of the brainstem send their axons through the vagus nerve to the heart, where they release acetylcholine onto cardiac ganglia cells and thereby reduce heart rate (Mendelowitz 1999; Wang \textit{et al.} 2001a). The NA CVNs receive excitatory glutamatergic input and inhibitory GABAergic input (\textit{Wang et al.} 2001b, 2009; Corbett \textit{et al.} 2003; Jameson \textit{et al.} 2008; Frank \textit{et al.} 2009). Brainstem vagal pre-ganglionic neurons, including those in the NA, express the high-affinity BDNF receptor trkB (Zaidi \textit{et al.} 2005; Liu and Wong-Riley 2013).

Here, we measured heart rates of wild-type and BDNF+/- mice in their home cages using telemetry probes, under control conditions and during intracerebroventricular administration of BDNF. BDNF protein levels are reduced by 30–70% throughout the brain of BDNF+/- mice including the brainstem (Duan \textit{et al.} 2003; Abidin \textit{et al.} 2006; Saylor \textit{et al.} 2006). Together with patch-clamp recordings of excitatory post-synaptic currents (EPSCs) and inhibitory post-synaptic currents (IPSCs) in NA CVNs in brainstem slices from wild-type and BDNF+/- mice, our data suggest that BDNF enhances the activity of parasympathetic NA CVNs and thereby reduces heart rate.

\section*{Materials and methods}

\subsection*{Animals and telemetry}
Male heterozygous BDNF\textsuperscript{tm1Jae/J} mutant (BDNF+/-) and congenic wild-type (WT) mice were purchased from Jackson Laboratories (Bar Harbor, ME, USA). Mice were maintained under a 12 h light/12 h dark cycle with food and water available \textit{ad libitum}. All procedures were approved by National Institute on Aging Animal Care and Use Committee and complied with NIH guidelines. Telemetry transmitters TA10ETA-F20 (Data Sciences International, St. Paul, MN, USA) were surgically implanted, as described previously (\textit{Wan et al.} 2003) into wild-type and BDNF+/- mice (n = 6 for each genotype). Two biopotential leads were routed subcutaneously laterally to midpoint in the chest to monitor heart rate under various experimental conditions. After transmitter implantation, mice were allowed to recover for 1 month before initiating experiments.

\subsection*{Intracerebroventricular cannulation and i.c.v. infusion}
Each mouse was implanted with a chronic guide cannula (Plastics One Inc., Roanoke, VA, USA). The tip of the cannula was located in the lateral ventricle (AP = –0.25 mm, L 1.0 mm, depth 2.5 mm). An injector (Plastics One Inc. VA) was adapted for intracerebroventricular (i.c.v.) infusion using a microdialysis pump (CMA Microdialysis, North Chelmsford, MA, USA) to provide a constant infusion rate (0.5 \mu L/min).

\subsection*{Drug treatments and BDNF infusion}
Recombinant human BDNF (ProSpec, Tany TechnoGene Ltd., Ness-Ziona, Israel) was dissolved in sterile phosphate-buffered saline (PBS) at the concentration of 3.0 \mu g/\mu L. Atropine methyl nitrate was used as parasympathetic blocker (2 mg/kg, i.p.; MP Biomedical LLC, OH, USA). Atenolol was used as sympathetic blocker (MP Biomedical LLC, Santa Ana, CA, USA; 2 mg/kg, i.p.). Hexamethonium bromide was used as a ganglionic blocker (30 mg/kg, i.p., Sigma, MO, USA). Preliminary test injections with PBS (i.p.) indicated that heart rate returned to baseline levels within 30 min after injection. Therefore, change in heart rate was assessed as the difference between the averaged heart rate recorded for 30 min prior to injection and the averaged heart rate recorded between 30 min and 3 h after injection. PBS lacking or containing BDNF was infused (i.c.v.) at a constant rate of 0.5 \mu L/min for 6 min. After infusion, the injector remained in the guide cannula for additional 2 min before it was removed. During the infusion, the mouse was under light sedation provided by inhalation of 2% isoflurane, which allowed the mouse to recover quickly for telemetric recording in its home cage.

\subsection*{Brainstem slice preparation and patch-clamp electrophysiological recordings}
Mice in a separate group were anesthetized via hypothermia and cooled to \(-4^\circ\text{C}\). Once heart rate significantly slowed and no pain reflex was elicited, a right thoracotomy was performed to expose the heart, and the retrograde tracer rhodamine (XRITC; 2\% solution, Sigma, MO, USA) was injected into the aortic arch. Brain tissue was collected and placed in 4\% formaldehyde solution. Brainstem slices that included the nucleus ambiguus were obtained and submerged in a recording chamber that allowed optical illumination and infrared-sensitive video detection cameras to gain enhanced spatial resolution. Patch pipettes were filled with a solution at pH 7.3 consisting of either KCl (150 mM), CaCl\textsubscript{2} (2 mM), Na\textsubscript{2}HCO\textsubscript{3} (26 mM), glucose (5 mM) and HEPES (10 mM). Slices (400 \mu m) that included the nucleus ambiguus were obtained and submerged in a recording chamber that allowed perfusion above and below the slice with 22\°C artificial CSF with the following composition: NaCl (140 mM), KCl (5 mM), CaCl\textsubscript{2} (2 mM), glucose (5 mM), and HEPES (10 mM). Slices (400 \mu m) that included the nucleus ambiguus were obtained and submerged in a recording chamber that allowed perfusion above and below the slice with 22\°C artificial CSF with the following composition: NaCl (12 (5 mM), KCl (3 mM), CaCl\textsubscript{2} (2 mM), Na\textsubscript{2}HCO\textsubscript{3} (26 mM), glucose (5 mM), HEPES (5 mM) in equilibrium with 95\% O\textsubscript{2}, 5\% CO\textsubscript{2}. The osmolality of all solutions was 285–290 mOsm, and the pH was maintained between 7.35 and 7.4. CVNs were identified by the presence of the fluorescent tracer and differential interference contrast optics along with infrared illumination and infrared-sensitive video detection cameras to gain enhanced spatial resolution. Patch pipettes were filled with a solution at pH 7.3 consisting of either KCl (150 mM), MgCl\textsubscript{2} (4 mM), EGTA (10 mM), Na\textsubscript{2}ATP (2 mM), HEPES (10 mM) or K-glutamic acid (150 mM), HEPES (10 mM), EGTA (10 mM), MgCl\textsubscript{2} (1 mM), CaCl\textsubscript{2} (1 mM) to isolate inhibitory or excitatory currents, respectively. Identified CVNs were voltage clamped at a holding potential of \(-80\text{ mV}\). To isolate only one neurotransmission for study,
receptors for the other two major neurotransmitters were blocked. Gabazine (Sigma-Aldrich, St. Louis, MO, USA; 25 μM) was used to block GABAergic inhibitory neurotransmission,strychnine (1 μM) was used to block glycinegic inhibitory neurotransmission, and d(-)-2-amino-5-phosphopentanoic acid (AP5; 50 μM) and 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX; 50 μM) were used to block glutamatergic excitatory neurotransmission. Threshold for IPSCs and EPSCs was 5X RMS noise. Average frequency of EPSCs and IPSCs was obtained from 2 min of stable recording. The scientist performing the electrophysiological experiments was not informed of the genotype of the animal until after the results were analyzed.

**Statistical analysis**

Repeated measures ANOVA and one- or two-way ANOVA were applied to the telemetric recorded parameters and other results for which the appropriate tests were applicable. For post hoc analysis the Student–Newman–Keuls test or Student’s t-test was performed to determine whether differences between two groups or treatments were statistically significant. p values less than or equal to 0.05 were considered statistically significant.

**Results**

**Heart rate is elevated in BDNF+/- mice and is reduced by ventricular BDNF infusion**

Four weeks after implantation of transmitters, heart rate was recorded continuously during a 24 h period in WT and BDNF+/- mice in their home cages. The heart rate of BDNF+/- mice was significantly greater than WT mice during both the dark and light periods (Fig. 1a).

WT mice that received an i.c.v. bolus infusion of BDNF (3.0 μg) exhibited a significantly lower heart rate compared with those that received i.c.v. PBS (Fig. 1b). The lowering of heart rate in response to i.c.v. BDNF was evident within 2 h of infusion, persisted for 8–10 h, and then returned to the basal level. BDNF+/- mice given an i.c.v. bolus of BDNF exhibited a heart rate significantly lower than those treated with i.c.v. PBS (Fig. 1c). The heart rate lowering effect of i.c.v. BDNF was evident within 30 min of infusion and persisted for 10 h. A repeated ANOVA test for the first 10 h after infusion revealed that there were significant effects of time (p < 0.05) and treatment (PBS vs. BDNF, p < 0.05) such that BDNF infusion resulted in a significant lowering of heart rate compared with PBS (Fig. 1b, c). There was also a significant effect of genotype on the BDNF effect on heart rate with the reduction in heart rate being greater in the BDNF+/- mice (WT vs. BDNF+/- mice, p < 0.05) (Fig. 1b, c).

**BDNF enhances parasympathetic regulation of heart rate, without affecting sympathetic tone or intrinsic heart rate**

To elucidate the mechanism whereby BDNF lowers heart rate, we measured heart rate in WT and BDNF+/- mice during treatment with drugs that block cholinergic/parasympathetic (atropine) and β-adrenergic/sympathetic (atenolol) autonomic inputs to the heart. Within 30 min of atropine administration, the heart rate of WT mice was increased by approximately 200 bpm and then slowly decreased during the next 2.5 h (Fig. 2a). The magnitude of the increase in heart rate in response to atropine was significantly less in BDNF+/- mice compared with WT mice, suggesting a lower level of parasympathetic activity in the BDNF+/- mice (Fig. 2). Treatment of mice with atenolol resulted in a decrease in the heart rates of all mice; the heart rates were reduced by more than 100 bpm at 1 and 2 h of atenolol injection (Fig. 2). The heart rate responses to atenolol were identical in WT and BDNF+/- mice, suggesting that BDNF does not affect sympathetic activation of the heart. Finally, to determine whether BDNF might affect intrinsic heart rate, we measured heart rates of WT and BDNF+/- mice that were treated with hexamethonium, a ganglionic blocker (Tucker and Domino 1988). Heart rate was elevated in response to hexamethonium in all mice, with no statistically significant differences between WT and BDNF+/- mice (Fig. 2).

**Central BDNF infusion eliminates the difference in heart rate response to atropine in BDNF+/- mice compared with WT mice**

Because of the reduced heart rate response to atropine in BDNF+/- mice, without altered responses to atenolol or hexamethonium, we determined whether i.c.v. infusion of BDNF would restore the heart rate response to atropine. Atropine was injected (i.p.) 3 h after BDNF infusion (3.0 μg/3 μL, i.c.v.). The magnitude of the elevation of heart rate in response to atropine was not different in WT and BDNF+/- that had been administered i.c.v. BDNF (Fig. 3), in contrast to a significantly lower heart rate response to atropine in BDNF+/- mice not administered BDNF (Fig. 2a). These findings indicate that BDNF haploinsufficiency results in reduced parasympathetic control of heart rate and that this abnormality can be reversed by CNS BDNF administration.

**Evidence that BDNF increases excitatory activation of brainstem cardiac vagal neurons**

The results of measurements of heart rate in BDNF+/- mice, and mice administered i.c.v. BDNF suggested that BDNF enhances parasympathetic activity. To directly test this possibility we directly recorded glutamatergic EPSCs and GABAergic and glycinegic IPSCs in NA CVNs in brainstem slices from WT and BDNF+/- mice. The GABA IPSC frequency was significantly greater in NA CVNs in slices from BDNF+/- mice compared with WT mice (Fig. 4a). The glutamate EPSC frequency was significantly lower in NA CVNs from BDNF+/- mice compared with WT mice (Fig. 4b). There was no difference in glycinegic IPSC frequency between WT and BDNF+/- mice (WT, 1.1 ± 0.9 Hz; BDNF+/-, 1.0 ± 0.4 Hz; p = 0.9). Collectively, these electrophysiological data suggest that BDNF signaling sustains excitatory and blunts inhibitory neurotransmission to CVNs as BDNF haploinsufficiency reduces

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CVN activity by increased inhibitory GABAergic and diminished excitatory glutamatergic neurotransmission to these neurons.

Discussion

The present findings reveal a previously unknown role for BDNF in the regulation of heart rate by brainstem cardiac vagal neurons. Our measurements of heart rate in WT and BDNF+-/- mice, under basal conditions and after acute intraventricular infusion of BDNF, provide evidence that BDNF plays important roles in the autonomic regulation of heart rate. The elevated resting heart rate in BDNF-haploinsufficient mice suggests that BDNF signaling is necessary for normal resting CNS-mediated cardioinhibitory parasympathetic drive to the heart. Consistent with the latter possibility,
we found that infusion of BDNF into the brain reduced heart rate in both WT and BDNF+/− mice. Moreover, the elevation in heart rate in response to atropine administration was significantly attenuated in BDNF+/− mice, and this abnormality was reversed by central infusion of BDNF. Collectively, these findings suggest that BDNF normally acts to increase parasympathetic tone, thereby reducing resting heart rate. Heart rate response to atenolol and hexamethonium was not different in WT and BDNF+/− mice, indicating that BDNF does not affect sympathetic stimulation of heart rate or intrinsic beat frequency of the heart.

The differences in heart rate between wild-type and BDNF+/− mice could result from developmental effects and/or more acute effects of reduced BDNF signaling. However, the fact that central infusion of BDNF normalized heart rate in BDNF+/− mice, with no differences between WT and BDNF+/− mice.

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![Fig. 2](image2.png)

**Fig. 2** Brain-derived neurotrophic factor (BDNF) deficiency reduces parasympathetic regulation of heart rate, while not affecting sympathetic activity or intrinsic heart rate. After recording baseline heart rate, WT mice (n = 6) and BDNF+/− mice (n = 6) received intraperitoneal injections of 2 mg/kg atropine, 2 mg/kg atenolol, or 30 mg/kg hexamethonium bromide. Heart rate was then measured at the indicated time points. Values (mean and SEM) are expressed as change in heart rate relative to the baseline (pre-drug). *p < 0.01. Atropine significantly increased heart rate in all mice in a time-dependent manner (F(3) = 30.35, p < 0.01). BDNF+/− mice had significantly less elevation of heart rate compared with the response of WT mice (F(1,20) = 14.87, p < 0.01). Atenolol administration reduced heart rate in all mice in a time-dependent manner (F(3) = 8.08, p < 0.01) and there was no statistical difference in the response to atenolol between WT mice and BDNF+/− mice. The ganglionic blocker hexamethonium was used to examine the intrinsic heart rate. Hexamethonium increased heart rate in both WT and BDNF+/− mice (time, F(3) = 20.3, p < 0.01), with no differences between WT and BDNF+/− mice.

![Fig. 3](image3.png)

**Fig. 3** Central brain-derived neurotrophic factor (BDNF) infusion eliminates the difference in heart rate response to atropine in BDNF+/− mice compared with WT mice. BDNF was infused intracerebroventricularly at a dose of 3.0 μg in WT and BDNF+/− mice. Three hours later atropine was injected (2 mg/kg, i.p.) and heart rates were recorded at the indicated time points. Values are the mean and SEM (six WT mice and six BDNF+/− mice).

we found that infusion of BDNF into the brain reduced heart rate in both WT and BDNF+/− mice. Moreover, the elevation in heart rate in response to atropine administration was significantly attenuated in BDNF+/− mice, and this abnormality was reversed by central infusion of BDNF. Collectively, these findings suggest that BDNF normally acts to increase parasympathetic tone, thereby reducing resting heart rate. Heart rate response to atenolol and hexamethonium was not different in WT and BDNF+/− mice, indicating that BDNF does not affect sympathetic stimulation of heart rate or intrinsic beat frequency of the heart.

The differences in heart rate between wild-type and BDNF+/− mice could result from developmental effects and/or more acute effects of reduced BDNF signaling. However, the fact that central infusion of BDNF normalized heart rate in BDNF+/− mice within hours of administration indicates that there is indeed an effect at the time of the experiment. This does not rule out the possibility that BDNF haploinsufficiency alters the development of neural circuits that control heart rate, but does suggest that if this is the case, then enhancement of BDNF signaling can rapidly overcome any such developmental abnormality. In a previous study, BDNF was infused into the lateral ventricles of adult rats, and blood pressure and heart rate were measured 20 min later; blood pressure increased, whereas heart rate was unchanged (Wang et al. 2012). Focal injection of BDNF into the medial nucleus of the tractus solitarius resulted in a rapid (within seconds) increase in blood pressure and heart rate in rats (Clark et al. 2011). On the other hand, injection of
BDNF into the rostral ventrolateral medulla had no significant acute (seconds to minutes) effect on heart rate (Wang and Zhou 2002). All the previous studies examined possible acute effects of central BDNF administration on heart rate. Our data suggest that BDNF signaling has a slower acting (hours) negative chronotropic effect on heart rate that is sustained for several hours after a single bolus infusion. Although not investigated in this study, this time course is consistent with a mechanism involving a change in gene expression in response to BDNF receptor activation. It was previously reported that BDNF can induce the expression of choline acetyltransferase (Klein et al. 1999), which is one potential explanation of enhanced cholinergic parasympathetic modulation of heart rate by BDNF.

Our electrophysiological data indicate that BDNF enhances the activity state of brainstem parasympathetic cholinergic CVNs in the NA that are known to control heart rate. The frequency of glutamatergic EPSCs was decreased and the frequency of GABAergic IPSCs was increased in NA CVNs in brainstem slices from BDNF+/− mice. While the molecular mechanisms underlying the effects of endogenous BDNF on CVN activity are unknown, they are presumably mediated by the high-affinity BDNF receptor trkB and/or the p75 low-affinity neurotrophin receptor. Brainstem cholinergic neurons produce BDNF (Peiris et al. 2004) and express trkB (Tang et al. 2010). Second, cell culture studies have shown that BDNF stimulates the p75-mediated production and release of acetylcholine from autonomic neurons resulting in a slowing of spontaneous contraction of cardiac myocytes (Yang et al. 2002). It is also possible that BDNF acts on the neurons that provide glutamatergic or GABAergic input to the CVNs. Indeed, BDNF enhances glutamate release from pre-synaptic terminals of hippocampal and visual cortex neurons (Alder et al. 2005; Abidin et al. 2006), and BDNF also modifies

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**Fig. 4** The activation of nucleus ambiguus cardiac vagal neurons is reduced in brain-derived neurotrophic factor (BDNF)-deficient mice. Spontaneous inhibitory GABAergic (a) and excitatory glutamatergic excitatory post-synaptic currents (EPSCs) (b) were isolated and recorded from labeled cardioinhibitory vagal neurons (CVNs) in the nucleus ambiguus (NA) using the whole-cell patch-clamp configuration. Representative traces from both wild-type (WT) and BDNF+/− mice are shown on the left, whereas average data are illustrated on the right (*p < 0.05). BDNF+/− mice possessed significantly lower frequencies of excitatory glutamate EPSCs than in WT mice, 1.9 ± 0.5 Hz (BDNF+/−) versus 4.6 ± 1 Hz (WT) (*p < 0.04). In contrast, BDNF+/− mice had significantly higher levels of inhibitory GABA inhibitory post-synaptic currents (IPSCs) events, 3.1 ± 0.7 Hz (BDNF+/−) versus 1.0 ± 0.3 Hz (WT) (*p < 0.03). Values are the mean and SEM. Inhibitory GABAergic events were recorded from nine neurons from nine WT mice (one neuron per mouse) and from 10 neurons from 10 BDNF+/− mice (one neuron per mouse). Glutamatergic EPSCs were recorded from eight neurons from WT mice, and eight neurons from BDNF+/− mice, in slices from seven WT and seven BDNF+/− mice.
activity at GABAergic synapses (Wardle and Poo 2003). We cannot rule out a contribution of an indirect effect of BDNF on heart rate by, for example, an initial effect of BDNF on blood pressure. However, the results of the brainstem slice electrophysiological data suggest that there is indeed an effect of BDNF levels on the excitability of brainstem cardiovagal inhibitory neurons that is entirely consistent with a more direct effect of BDNF on these neurons. When taken together with previous reports that BDNF can increase the expression of choline acetyltransferase and the vesicular acetylcholine transporter, and enhance acetylcholine release from cholinergic neurons (Knüsel et al. 1991; Takei et al. 1997; Klein et al. 1999), our findings suggest that BDNF enhances cholinergic regulation of heart rate.

BDNF is produced by neurons and released from them in a synaptic activity-dependent manner (Matsuda et al. 2009). Vigorous exercise and intermittent fasting stimulate BDNF production in many different brain regions including those involved in sensory–motor function and cognitive processing (Lee et al. 2002; Duan et al. 2004; Gomez-Pinilla 2008; Marais et al. 2009; Marlatt et al. 2012). Our findings suggest that BDNF acts in the brainstem to enhance parasympathetic activity and reduce resting heart rate. Because exercise and intermittent fasting also reduce resting heart rate by a mechanism involving enhanced vagal parasympathetic tone (Shi et al. 1995; Wan et al. 2003; Mager et al. 2006), it will be of considerable interest to determine whether BDNF mediates the effects exercise and intermittent fasting on autonomic regulation of heart rate. Finally, our findings suggest a potential role for altered BDNF signaling in disorders involving dysregulation of autonomic function. Consistent with such a possibility, it was recently reported that huntingtin mutant mice exhibit an elevated heart rate associated with a significant reduction in brainstem BDNF levels (Griffioen et al. 2012). In addition, subjects with a common polymorphism in the BDNF gene exhibit an anxiety phenotype and reduced heart rate variability associated with decreased parasympathetic activity (Yang et al. 2010). Moreover, administration of paroxetine, a serotonin-selective reuptake inhibitor that increases BDNF production in the brain (Duan et al. 2004), increases parasympathetic control of heart rate in humans suffering from panic disorder (Tucker et al. 1997).

Acknowledgments and conflict of interest disclosure

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All experiments were approved by National Institute on Aging Intramural Research, NIH, the IACUC committee at GWU, and Glenn Foundation for Medical Research and were conducted in compliance with the ARRIVE guidelines.

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