Chronic Stress Augments the Cardiogenic Sympathetic Afferent Reflex in Sprague-Dawley Rats

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ABSTRACT

Chronic psychological stress increases sympathetic nerve activity and is a well-known risk factor for hypertension and cardiovascular diseases. Myocardial ischemia leads to the release of bradykinin, which stimulates cardiac afferents, causing sympathetic excitation and chest pain. This response, called the cardiogenic sympathetic afferent reflex (CSAR), is characterized by a sympathetically mediated rise in blood pressure to maintain cardiac perfusion. This reflex increases cardiac workload and can worsen ischemic injury. Disorders such as Post Traumatic Stress Disorder (PTSD), Generalized Anxiety Disorder (GAD) and Major Depressive Disorder (MDD) are associated with cardiovascular dysfunction. This study investigates the augmentative effects of chronic stress on the CSAR.

***Methods*:** Sixteen Sprague-Dawley rats were used. The experimental group (n=8 total rats: 4 males and 4 females) was conditioned with two-hour bouts of foot shock twice daily for fifteen consecutive days. Control rats (n=8 total rats: 4 males and 4 females) were not administered foot shock. After conditioning, we anesthetized the rats and measured heart rate (HR), blood pressure (BP), and renal sympathetic nerve activity (RSNA) during baseline and the reflex response to epicardial bradykinin (10 µg/ml).

***Results*:** Rats administered shock stress exhibited a significantly ($p < 0.05$) elevated baseline BP (112±4.4mmHg), and RSNA (0.0052±0.009µV) compared with controls (BP: 87±3.0mmHg, & RSNA: 0.024±0.004µV). Epicardial bradykinin in the experimental group elicited a significant ($p < 0.05$) increase in BP (147±3.9mmHg) and RSNA (0.103±0.014µV), compared with controls (BP: 131±4.9mmHg, & RSNA: 0.071±0.009µV). Neither the baseline heart rate nor the reflex tachycardia was significantly different in controls compared with those administered shock.

***Conclusions*:** Chronic stress increases basal cardiovascular sympathetic activity and augments the CSAR. These results advance our understanding of the link between chronic stress and the potential to augment ischemic injury. Further studies are aimed at determining the central sympathetic mechanisms that link stress with augmenting this neurogenic reflex.

METHODS

Animals: Sprague Dawley (n=16, 8 female & 8 male) or Borderline Hypertensive Rats (n=9; all males) underwent 15 days of foot shock stimulus (2-hour sessions/ twice daily) or control (no shock).

In-vivo Electrophysiology: Recordings were performed in terminally anesthetized (α-chloralose, 100 mg/kg, IV) & mechanically ventilated rats to assess the neurophysiological effect of chronic stress on sympathetic cardiovascular activity and the reflex response to stimulation of epicardial nociceptors.

Arterial blood pressure was recorded from the left carotid artery. Heart rate was measured by systolic triggering of the arterial pressure. Sympathetic nerve activity was recorded from the left renal nerve. A thoracotomy exposed the heart for epicardial bradykinin application using a cotton applicator.

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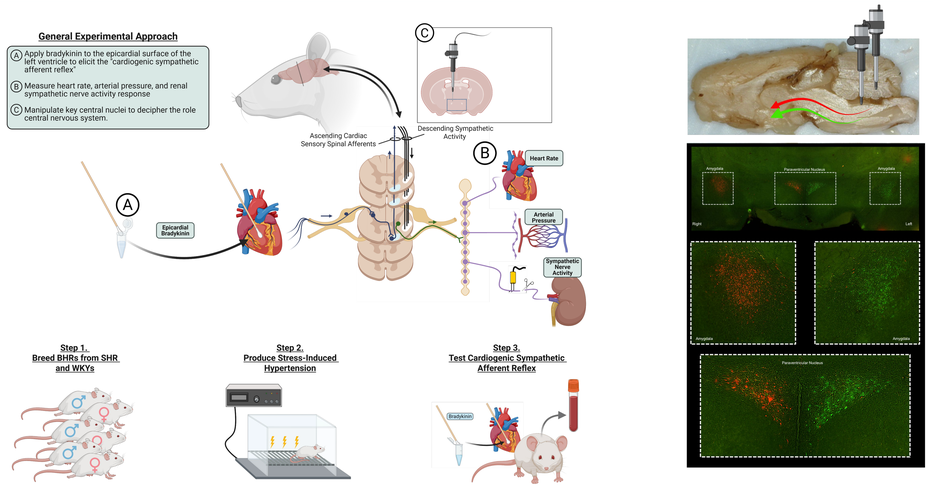

RESULTS

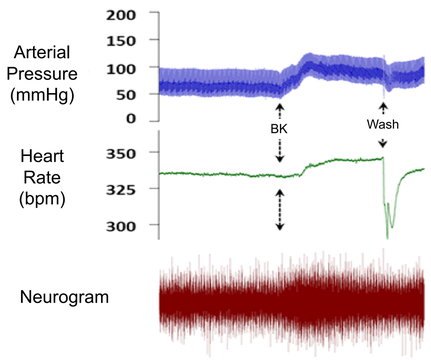

Figure 1 . Original tracings showing arterial pressure, heart rate, and RSNA responses to epicardial bradykinin (BK, 10 µg/mL).

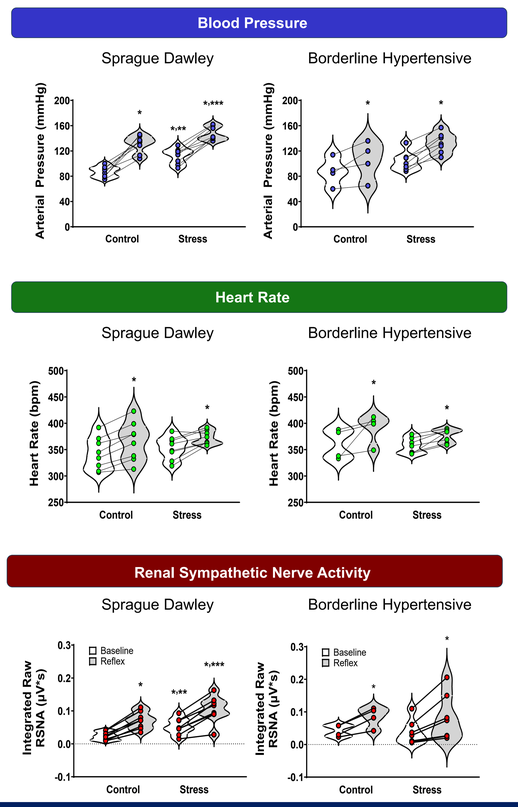

Figure 2. Group data showing arterial pressure (A), heart rate (B), and RSNA (C) during baseline and the reflex response to epicardial bradykinin in Sprague Dawley (left), control (n=8) and stress-treated rats (n=8), and Borderline Hypertensive Rats (right) control (n=4) and stress-treated rats (n=7). A two-way ANOVA was used to identify a main effect of stress treatment or bradykinin application and interaction, followed by Fisher's LSD pos-hoc analysis. * = significant increase from respective baseline, ** = significantly greater than control baseline, *** = significantly greater than control reflex ($P < 0.05$)

SUMMARY

Chronic stress significantly increased baseline arterial pressure and sympathetic activity in during baseline and augmented the reflex response to bradykinin compared with controls ($P < 0.05$) in the Sprague Dawley but not the Borderline Hypertensive rats.

Our findings suggest that chronic stress not only elicits a neurogenic hypertension but also augments the cardiogenic sympathetic afferent in Sprague-Dawley rats. When subjected to the application of epicardial bradykinin, the experimental group showed a pronounced reflexive elevation in both blood pressure and RSNA, indicating that stress not only primes the cardiovascular system for heightened sympathetic responses but also exacerbates the CSAR, a reflex that helps maintain cardiac perfusion during ischemia. These results implicate chronic stress as a likely contributor to a cycle of increased sympathetic activity, potentially worsening ischemic injury in conditions such as myocardial infarction or stress-induced hypertension.

The differential response to bradykinin between experimental and control rats demonstrates an amplifying effect that chronic stress has on the cardiovascular system, further implicating chronic stress as a catalyst for more severe cardiovascular events, particularly in populations suffering from Post-Traumatic Stress Disorder or Generalized Anxiety Disorder.

CONCLUSIONS

- Both the Sprague Dawley and Borderline Hypertensive Rats displayed a significant blood pressure, heart rate and sympathetic nerve activity response to epicardial bradykinin.
- Chronic foot shock stress significantly increased baseline blood pressure and sympathetic activity and augmented the bradykinin-induced reflex response in arterial pressure and sympathetic nerve activity in the Sprague Dawley but not the Borderline Hypertensive rats.

NEXT STEPS

1. Using a variety of optogentic approaches we will determine the central pathways and neural plasticity that occurs in the Sprague Dawley rat that occurs after stress.
2. Chronic inhibition of forebrain neurons to abolish the development of the stress-induced sympathoexcitation and hypertension.

NEXT STEPS

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