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Ghrelin potentiates cardiac reactivity to stress by modulating sympathetic control and beta-adrenergic response

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ABSTRACT

Prior evidence indicates that ghrelin is involved in the integration of cardiovascular functions and behavioral responses. Ghrelin actions are mediated by the growth hormone secretagogue receptor subtype 1a (GHS-R1a), which is expressed in peripheral tissues and central areas involved in the control of cardiovascular responses to stress.

Aims: In the present study, we assessed the role of ghrelin – GHS-R1a axis in the cardiovascular reactivity to acute emotional stress in rats.

Main methods and key findings: Ghrelin potentiated the tachycardia evoked by restraint and air jet stresses, which was reverted by GHS-R1a blockade. Evaluation of the autonomic balance revealed that the sympathetic branch modulates the ghrelin-evoked positive chronotropy. In isolated hearts, the perfusion with ghrelin potentiated the contractile responses caused by stimulation of the beta-adrenergic receptor, without altering the amplitude of the responses evoked by acetylcholine. Experiments in isolated cardiomyocytes revealed that ghrelin amplified the increases in calcium transient changes evoked by isoproterenol.

Significance: Taken together, our results indicate that the Ghrelin-GHS-R1a axis potentiates the magnitude of stress-evoked tachycardia by modulating the autonomic nervous system and peripheral mechanisms, strongly relying on the activation of cardiac calcium transient and beta-adrenergic receptors.

1. Introduction

Ghrelin is a 28 amino acid peptide that stimulates the growth hormone (GH) release from the anterior pituitary [1]. Pioneer studies performed by Kojima and colleagues identified ghrelin as the endogenous ligand for the growth hormone secretagogue receptor subtype 1a (GHS-R1a) [2]. The attachment of a fatty acid side-chain to the serine residue at position 3, which is mediated by the ghrelin O-acyltransferase (GOAT) enzyme, is required to set ghrelin affinity for the GHS-R1a binding site [2].

Peripherally, ghrelin is produced in the stomach, placenta, lymphocytes, testicles, lungs, kidneys, pancreas and other tissues [3–7]. In the central nervous system, ghrelin mRNA was revealed in areas associated with the control of neuroendocrine and cardiovascular responses to potential danger or aversive stimuli, such as the dorsomedial hypothalamus, arcuate nucleus, paraventricular nucleus, hippocampus and amygdala [8–11]. Ghrelin actions in the brain are able to affect food intake and glucose metabolism [12]. In addition, prior studies indicate that ghrelin alters reproductive functions and is involved in sleep modulation, besides being responsible for an increase in stomach

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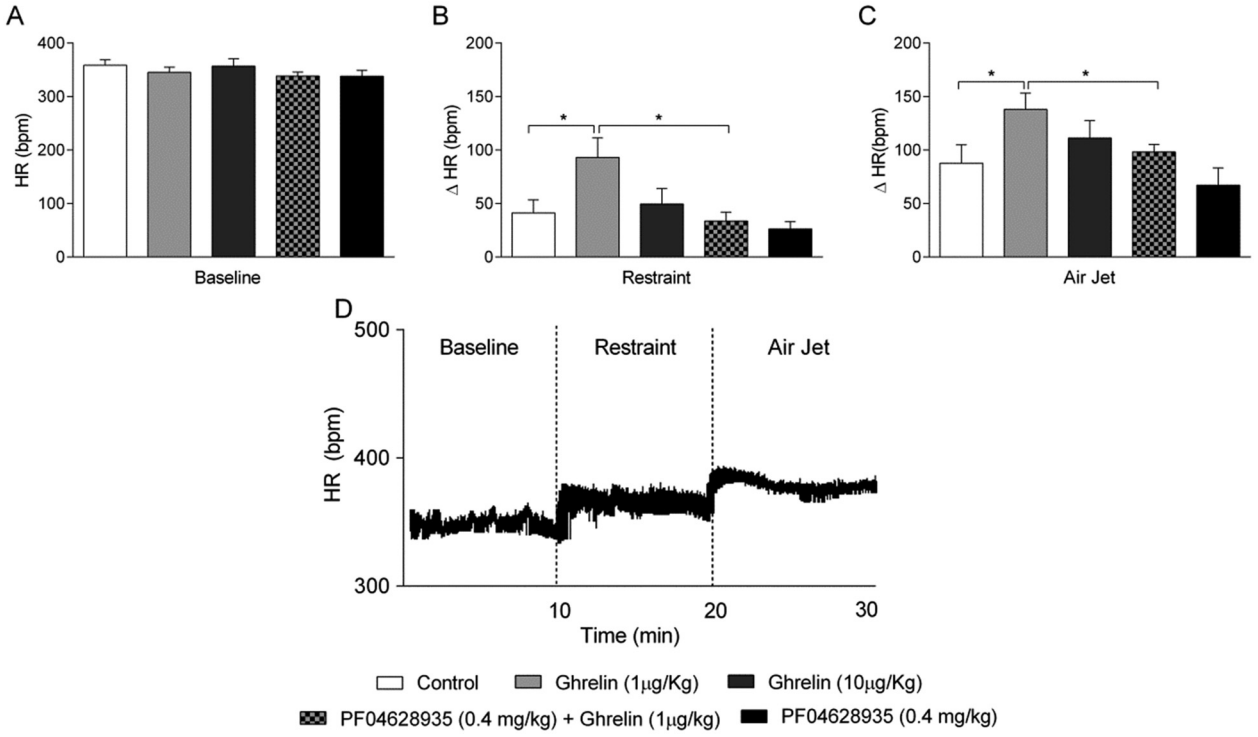

Fig. 1. Baseline values (panel A) and mean maximal changes in heart rate (HR) after i.v. injection of vehicle, ghrelin (1 or 10 μg/kg) or antagonist of GHS-R1a (PF04628935) in rats submitted to acute restraint (panel B) and air jet stresses (panel C). Top panels show baseline (A) and mean maximal changes in HR responses elicited by restraint (B) and air jet (C) stresses, respectively. Panel D shows a representative tracing. Results are presented as mean ± SEM. Comparisons between groups were performed with one-way analysis of variance followed by Newman-Keuls post hoc test. *$p < 0.05$.

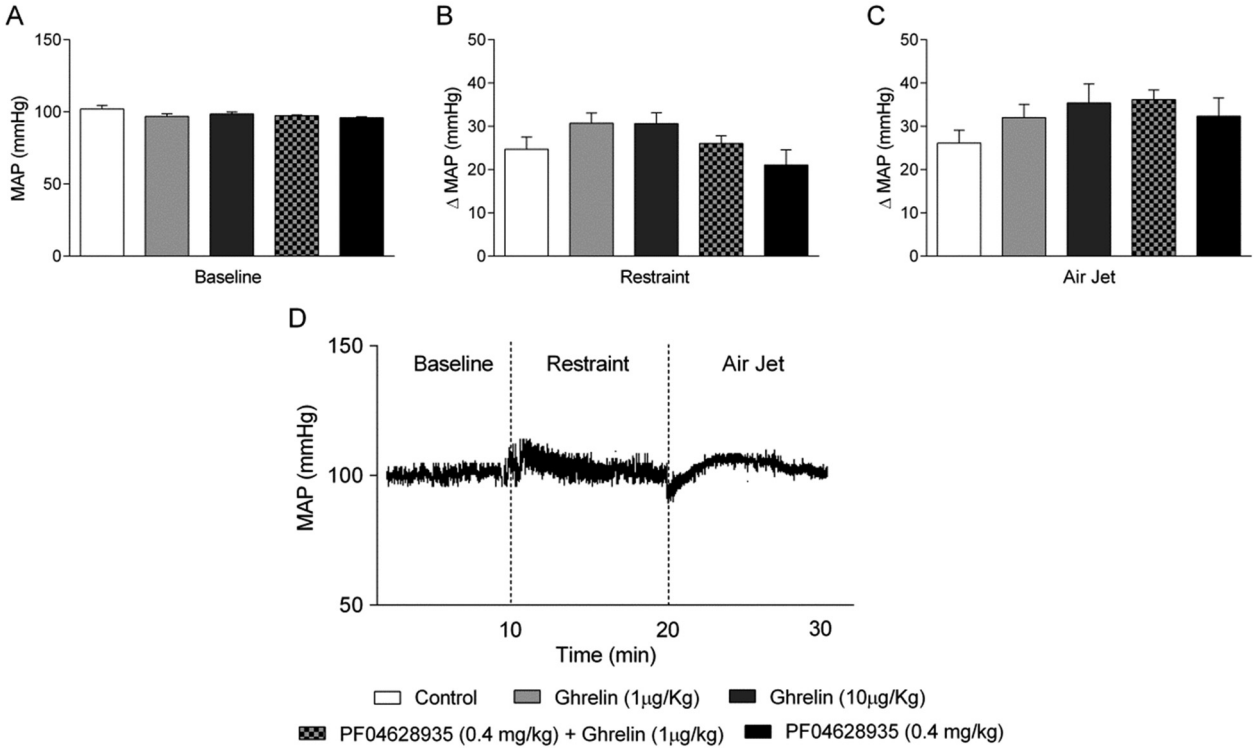

Fig. 2. Baseline values (panel A) and mean maximal changes in arterial pressure (AP) after i.v. injection of vehicle, ghrelin (1 or 10 μg/kg) or antagonist of GHS-R1a (PF04628935) in rats submitted to acute restraint (panel B) and air jet stresses (panel C). Top panels show baseline (A) and mean maximal changes in HR responses elicited by restraint (B) and air jet (C) stresses, respectively. Panel D shows a representative tracing. Results are presented as mean ± SEM. Comparisons between groups were performed with one-way analysis of variance followed by Newman-Keuls post hoc test. *$p < 0.05$.