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# Role of Adrenal GRK2 in Heart Failure

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*S u m m a r y. Heart failure (HF) is characterized by sympathetic hyperactivity and enhanced circulating catecholamines (CA's). CA`s stimulating cardiac function are norepinephrine released from cardiac sympathetic nerves and circulating CA`s secreted from the adrenal gland. Adrenal $\alpha_2$-adrenoceptors ($\alpha_2$ARs), which are regulated by G-protein coupled receptor kinase-2 (GRK2), exert autocrine feedback inhibition on CA secretion. We sought to investigate whether adrenal GRK2 activity is abnormal in HF, leading to enhanced CA secretion. For this purpose, we used the rat model of chronic HF due to myocardial infarction. In this model, adrenal GRK2 mRNA and protein were found up-regulated, and this correlated with severe desensitization of adrenal $\alpha_2$ARs. Thus, in HF, adrenal GRK2 up-regulation increases CA secretion, thus contributing to the sympathetic overstimulation of the failing heart.*

## INTRODUCTION

HF represents one of the most significant health problems worldwide. One of its hallmark symptoms is elevated Sympathetic Nervous System (SNS) activity and outflow, reflected by enhanced levels of circulating CA`s in HF subjects, which accompanies and aggravates the disease (1). CA secretion from the adrenal gland, along with norepinephrine release from the Central Nervous System, is a major component of SNS outflow and activity (2). Various G-protein coupled receptors (GPCRs) have been shown to regulate it, some enhancing it (e.g. αARs), while some others inhibit it, most importantly the $\alpha_2$ARs (3). Regulation of these receptors in the adrenal medulla and, specifically in the chromaffin cells, remains largely elusive. On the other hand, since SNS activity is elevated in HF, adrenal CA secretion is expected to be enhanced and therefore the inhibitory $\alpha_2$ARs might be down-regulated in HF adrenals. GRK2 plays a prominent role in GPCR regulation (4). For this purpose, we investigated potential alterations in GRK2 expression and activity, in conjunction with levels of CA secretion and $\alpha_2$AR function in adrenal medullae from a rat model of chronic HF due to myocardial cryo-infarction (5).

## METHODS

We performed real-time PCR on total RNA, and Western blotting in protein, isolated from adrenal glands extracted from rats having chronic HF 10 weeks post-surgical myocardial infarction (HF rats) and from age-matched, healthy, sham-operated rats (sham rats). CA secretion was measured by ELISA in chromaffin cell culture supernatants.

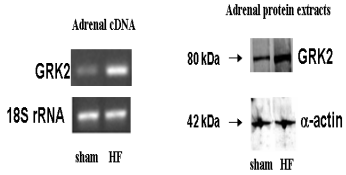


*Figure 1: Real-time PCR (left) and Western blotting (right) for adrenal GRK2 in sham and HF rats. Representative PCR gel and Western blot are shown (18S rRNA and α-actin are also shown as normalization controls)*

## RESULTS

GRK2 was found significantly elevated both at the mRNA and protein levels in HF rat adrenal glands, compared to age-matched sham rat adrenals (Figure 1).

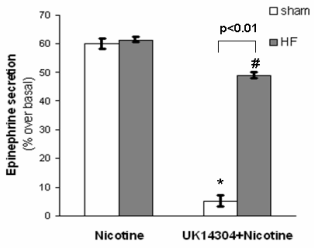


*Figure 2: In vitro epinephrine secretion from chromaffin cells isolated from adrenals of sham and HF rats, in response to 20 μM nicotine, following pre-treatment with vehicle (Nicotine) or with 10 μM UK14304 (UK14304+Nicotine). *p<0.01, compared to sham-Nicotine, #p<0.05, compared to HF-Nicotine, data from two independent experiments performed with triplicate samples, in cells derived from 4 rats (8 adrenals)/group each. The same assay for norepinephrine secretion produced similar results (data not shown)*

This was accompanied by severe desensitization of the $\alpha_2$AR-mediated inhibition of nicotine-induced CA secretion from chromaffin cells isolated from HF rat adrenals, whereas, in sham rat adrenal-derived chromaffin cells, the $\alpha_2$AR-agonist UK14304 inhibited CA secretion normally, as expected (Figure 2).

## DISCUSSION

Adrenal GRK2 is up-regulated in HF, which leads to chronic elevation of adrenal CA secretion by desensitizing the $\alpha_2$AR-mediated inhibition of this physiological response. Therefore, adrenal GRK2 might be a novel therapeutic target in chronic HF.

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