SOCIETÀ ITALIANA
DI GERONTOLOGIA
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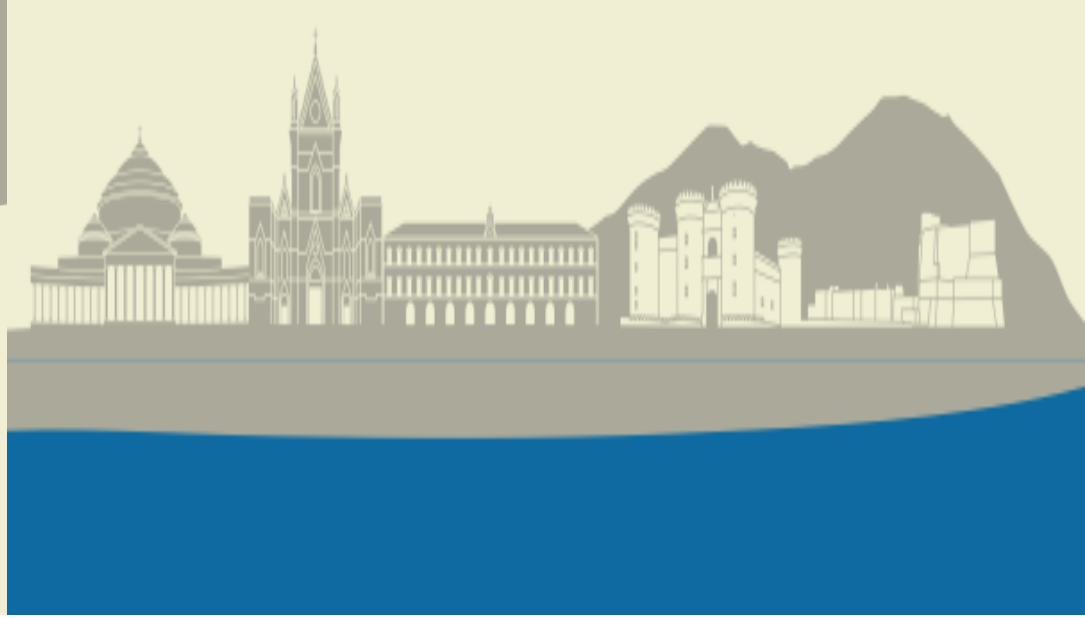
60° CONGRESSO NAZIONALE

NAPOLI 25-28 Novembre 2015



Midollare del surrene e disfunzione autonomica

Giuseppe Rengo, MD, PhD

Department of Translational Medical Sciences
University of Naples “Federico II”

Salvatore Maugeri Foundation
Scientific Institute of Telese Terme – IRCCS –

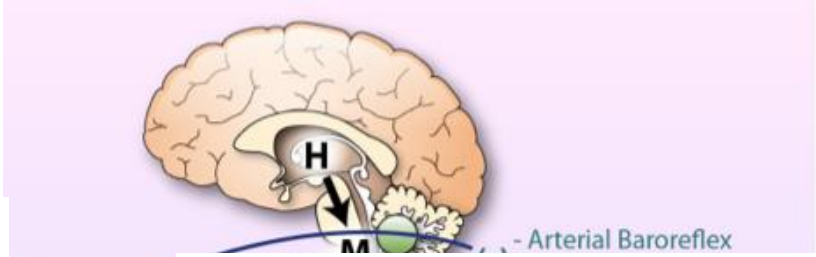
Sympathetic Nervous System

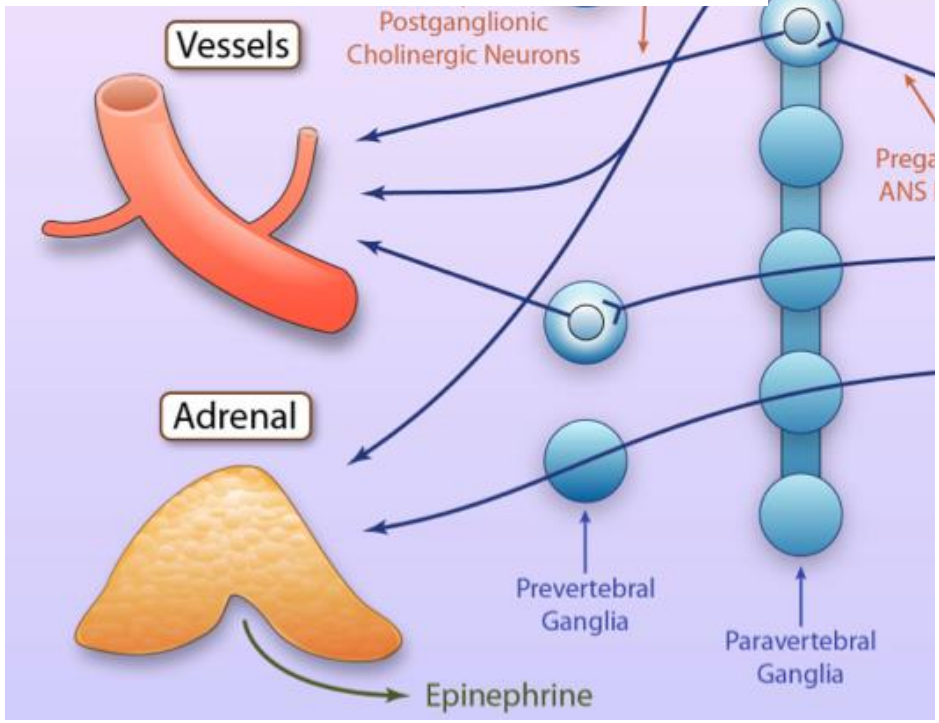
The NEW ENGLAND JOURNAL of MEDICINE

Decreased Catecholamine Sensitivity and β-Adrenergic-Receptor Density in Failing Human Hearts

Michael R. Bristow, M.D., Ph.D., Robert Ginsburg, M.D., Wayne Minobe, B.S., Roger S. Cubicciotti, M.S., W. Scott Sageman, M.S., Keith Lurie, M.D., Margaret E. Billingham, M.D., Donald C. Harrison, M.D., and Edward B. Stinson, M.D.

N Engl J Med 1982; 307:205-211 | July 22, 1982





ELSEVIER

Cardiovascular Research 31 (1996) 152–156

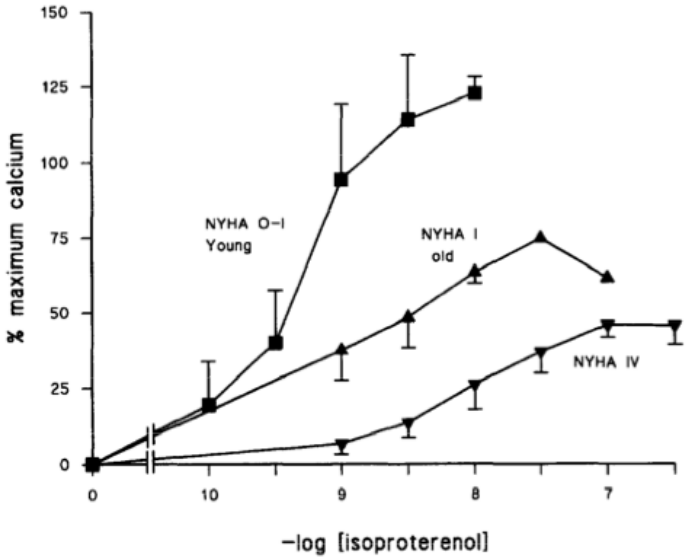
Cardiovascular Research

β-Adrenoceptor function changes with age of subject in myocytes from non-failing human ventricle

C.H. Davies, N. Ferrara, S.E. Harding *

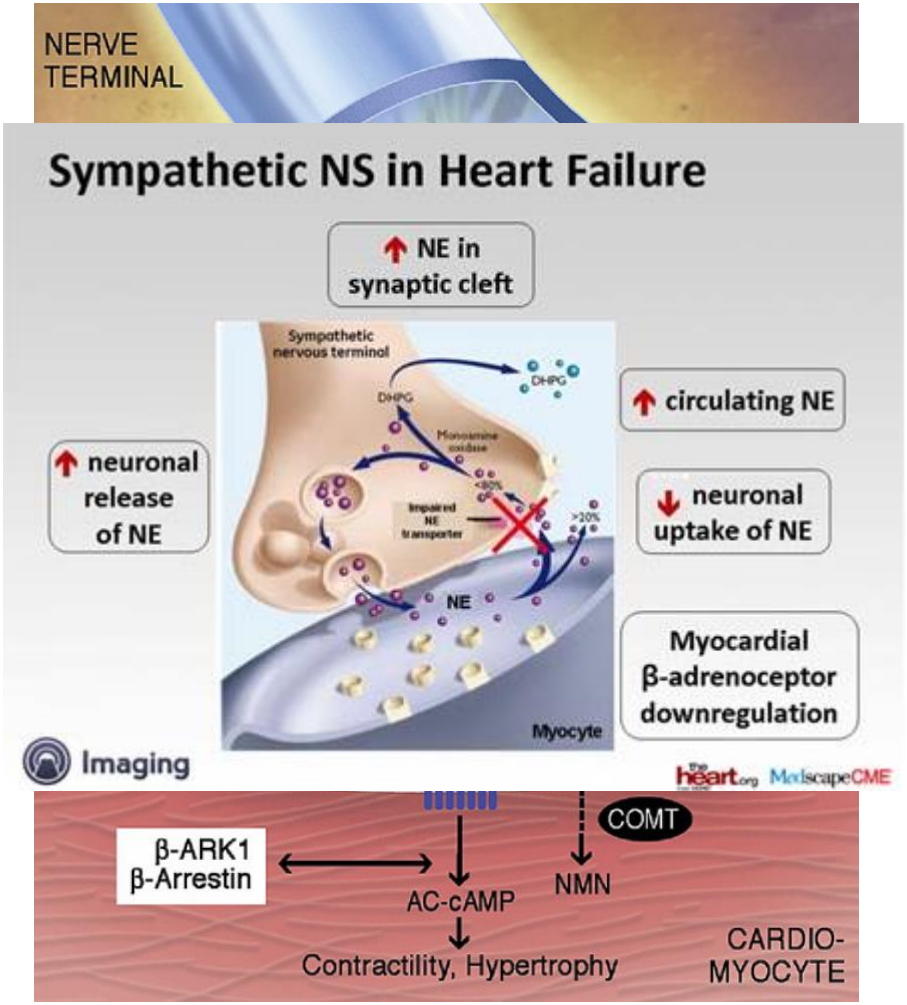
Department of Cardiac Medicine, National Heart and Lung Institute, Dovehouse St., London SW3 6LY, UK

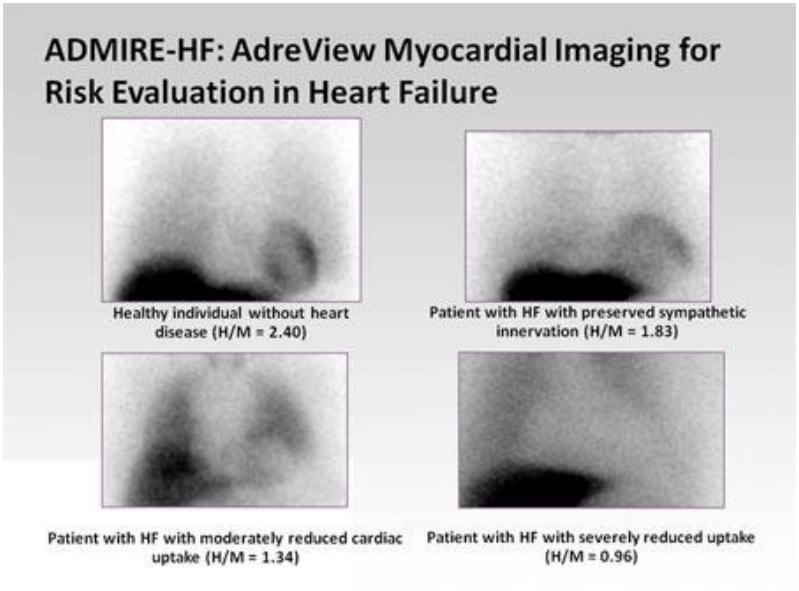
Received 27 January 1995; accepted 27 February 1995



Lymperopoulos A, Rengo G,

Adrenergic Excess, hNET1 Down-Regulation, and Compromised *mIBG Uptake in Heart Failure*



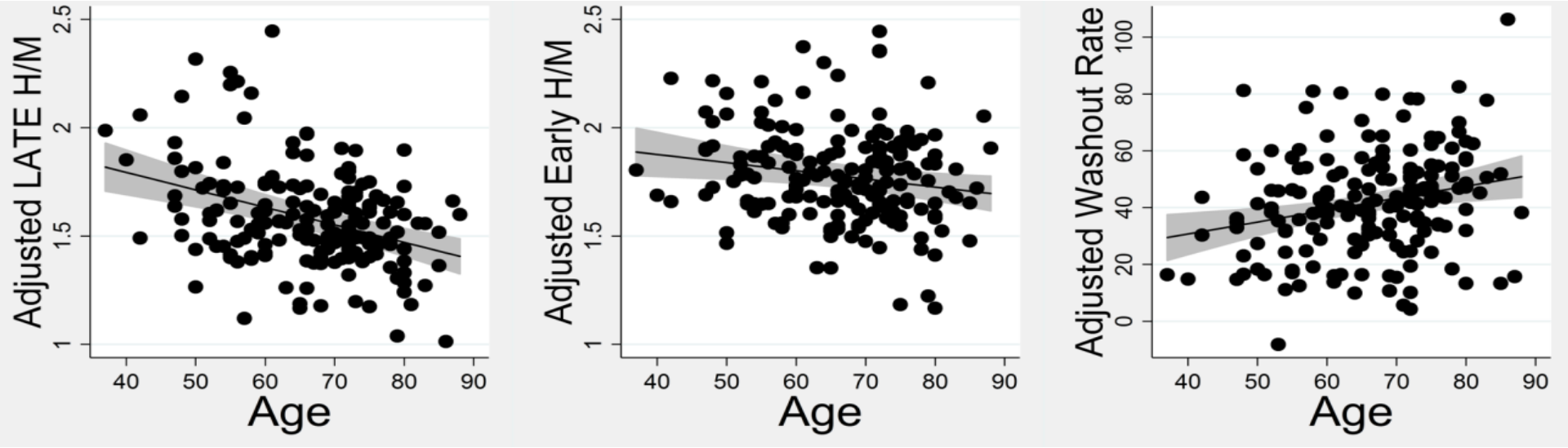


$$\text{H/M Ratio} = \frac{H}{M}$$

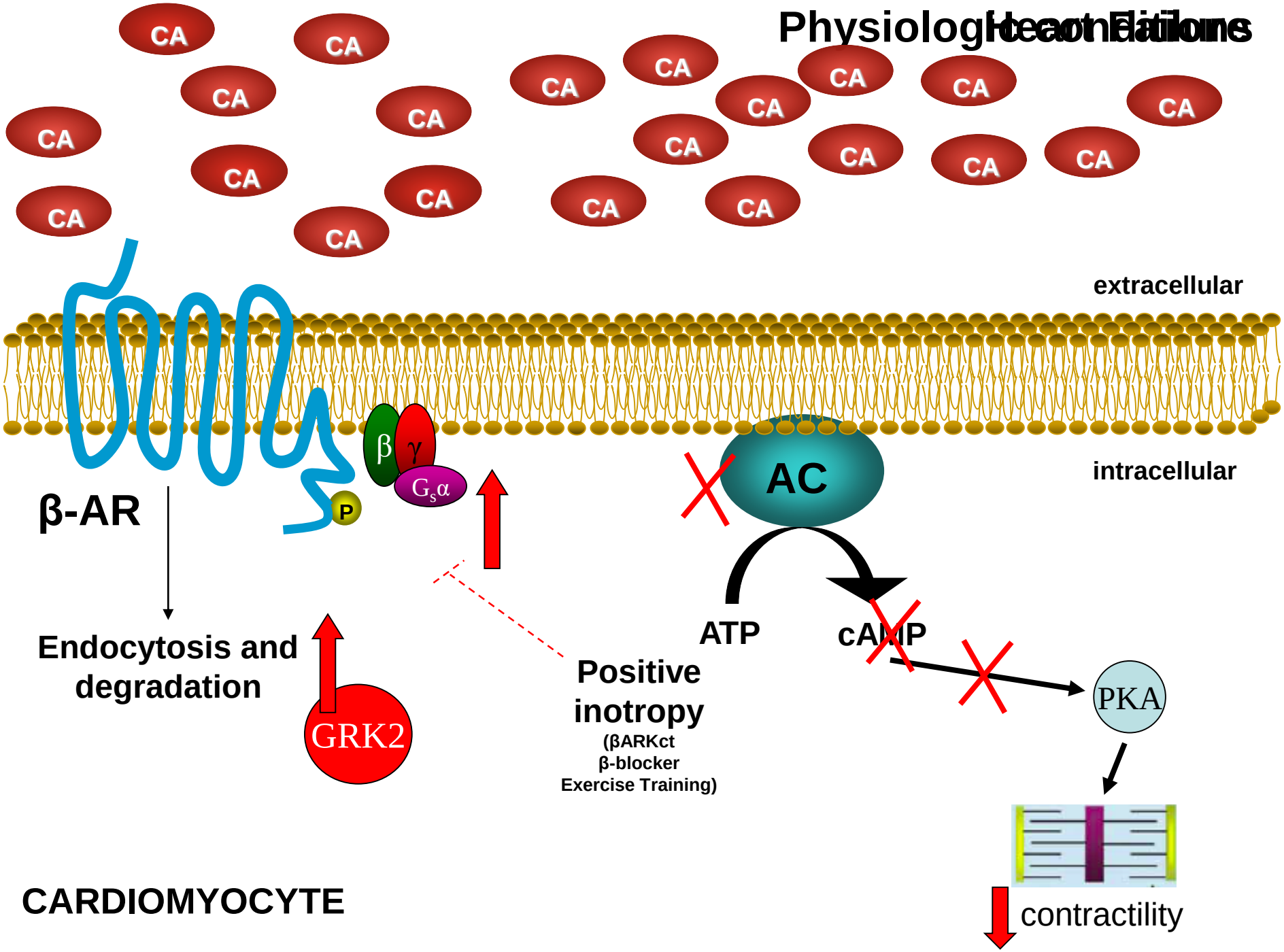
$$\text{Washout Rate} = \frac{\text{Early Image (H – M)} - \text{Delayed Image (H – M)}}{\text{Early Image (H – M)}} \times 100\ (\%)$$

Haider N et al. J A C C Cardiovascular Imaging 2010

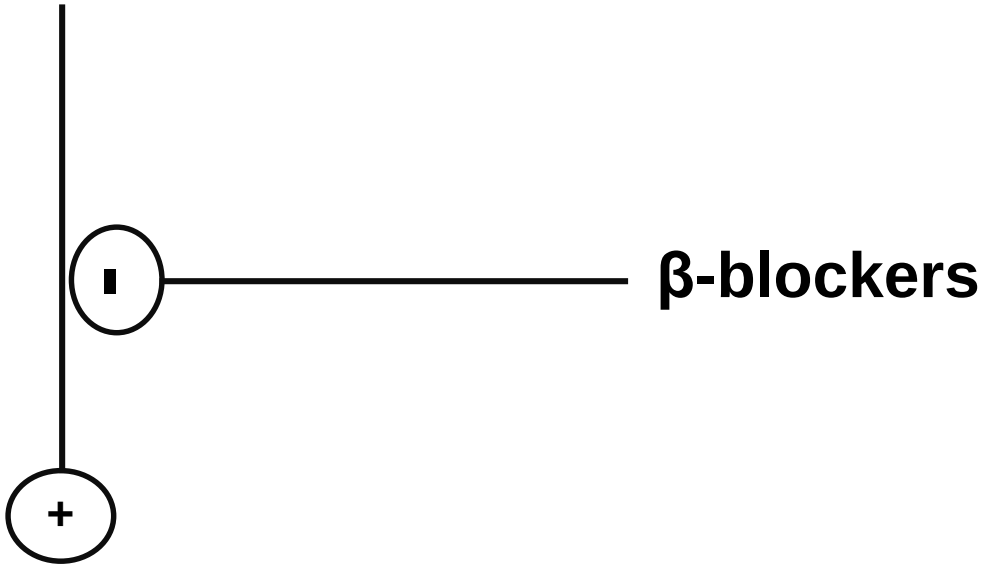
Impact of aging on cardiac sympathetic innervation measured by ^{123}I-mIBG imaging in patients with heart failure



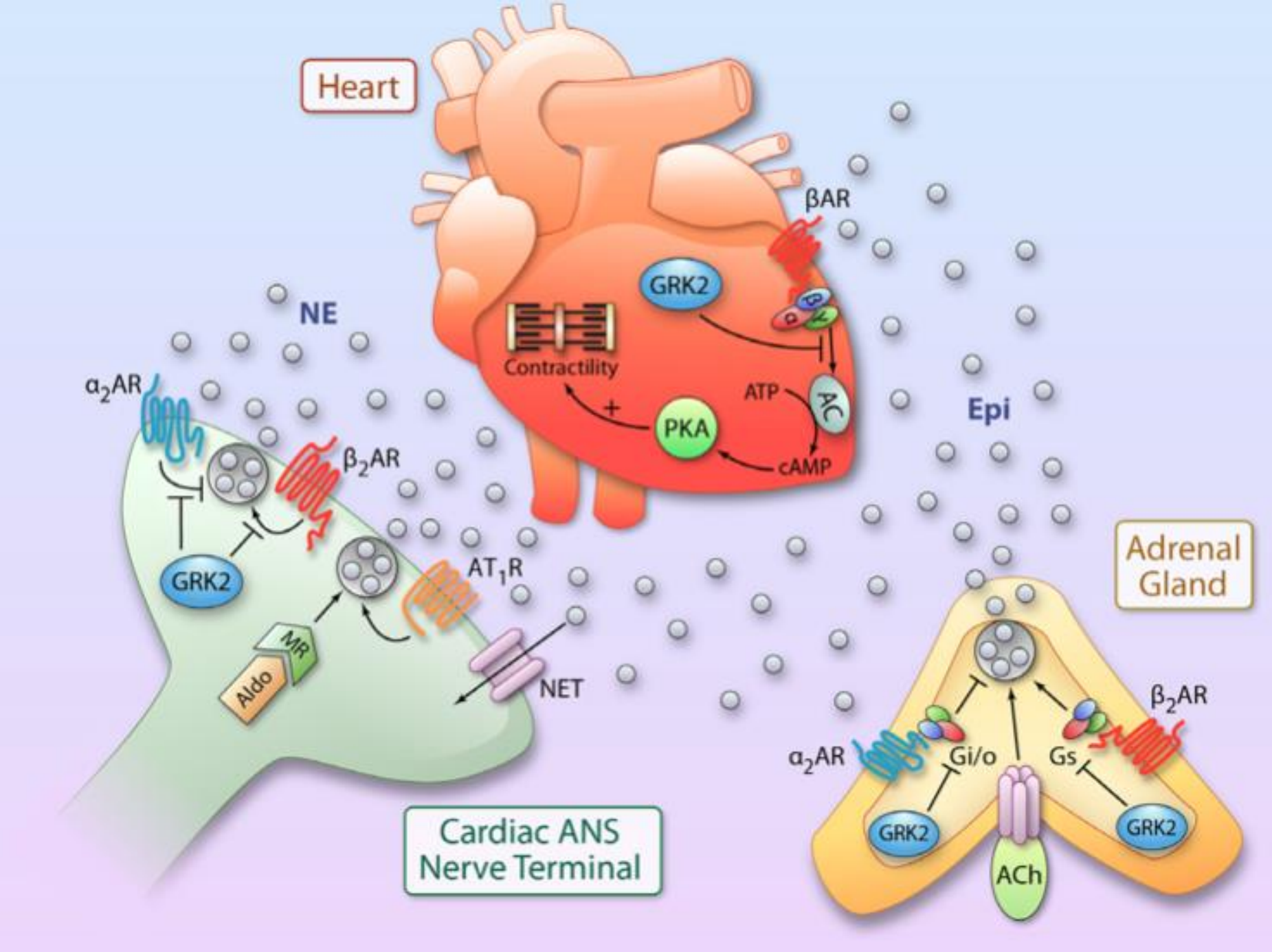
Rengo G et al. J Gerontol A Biol Sci Med Sci submitted 2015


Physiologic Reactions
CA
extracellular
intracellular
β-AR
P
β
γ
$G_s\alpha$
AC
ATP
cAMP
PKA
Endocytosis and degradation
GRK2
Positive inotropy
(βARKct
β-blocker
Exercise Training)
contractility
CARDIOMYOCYTE

SNS Hyperactivity



Myocardial oxigen consumption *(J Mol Cell Cardiol 1985);*
Cardiac interstitial fibrosis *(Eur J Pharmacol 2004);*
Myocyte apoptosis *(Cardiovasc Res 2004);*
Adverse remodeling *(Am J Physiol Heart Circ Physiol 2007);*
Reduction of the inotropic reserve *(NEJM 1982);*
Myocardial ROS production *(J Cell Mol Med 2007);*
Risk of arrythmias *(NEJM 1991);*
Renin-angiotensin-aldosterone system *(Am J Physiol 1992);*
Renal and peripheral vascular resistance *(JACC 2009);*



Lymperopoulos A, Rengo G, Koch WJ. Circ Res 2013.

Am J Physiol Heart Circ Physiol 283: H1838–H1845, 2002.
First published July 26, 2002; 10.1152/ajpheart.01063.2001.

Abnormal cardiac function associated with sympathetic nervous system hyperactivity in mice

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DANIEL BERNSTEIN,[4] AND BRIAN KOBILKA[2,5]
[1]*Department of Pathology, Veterans Administration Medical Center, Palo Alto 94305; and* [2]*Departments of Medicine and Molecular and Cellular Physiology,* [3]*Department of Anesthesia,* [4]*Division of Cardiology, Department of Pediatrics, and* [5]*Howard Hughes Medical Institute, Stanford University, Stanford, California 94305*

Received 4 December 2001; accepted in final form 12 July 2002

Brum, Patricia C., Jon Kosek, Andrew Patterson, Daniel Bernstein, and Brian Kobilka. Abnormal cardiac function associated with sympathetic nervous system hyperactivity in mice. *Am J Physiol Heart Circ Physiol* 283: H1838–H1845, 2002. First published July 26, 2002; 10.1152/ajpheart.01063.2001.—α_{2A}-Adrenergic receptors (ARs) in the midbrain regulate sympathetic nervous system activity, and both α_{2A}-ARs and α_{2C}-ARs regulate catecholamine release from sympathetic nerve terminals in cardiac tissue. Disruption of both α_{2A}- and α_{2C}-ARs in mice leads to chronically elevated sympathetic tone and decreased cardiac function by 4 mo of age. These knockout mice have increased mortality, reduced exercise capacity, decreased peak oxygen uptake, and decreased cardiac contractility relative to wild-type controls. Moreover, we observed significant abnormalities in the ultrastructure of cardiac myocytes from α_{2A}/α_{2C}-AR knockout mice by electron microscopy. Our results demonstrate that chronic elevation of sympathetic tone can lead to abnormal cardiac function in the absence of prior myocardial injury or genetically induced alterations in myocardial structural or functional proteins. These mice provide a physiologically relevant animal model for investigating the role of the sympathetic nervous system in the development and progression of heart failure.

α_2-adrenergic receptor; knockout mice; heart failure

and a progressive deterioration in cardiac function (4, 5, 9, 34). However, direct experimental evidence that the sympathetic nervous system plays a predominant role in the development of heart failure is lacking, and there are no suitable murine models of heart failure based on elevated sympathetic nervous system activity without concomitant alterations of myocardial structural or functional proteins. Most murine models of heart failure are based on the disruption of genes for cardiac specific proteins (2) or the use of cardiac-specific promoters to overexpress proteins that disrupt myocyte function (10, 12, 13, 15, 21, 33, 42). Whereas these models have been used to test novel approaches for the treatment of heart failure (17, 20, 25, 37, 38, 41, 43), they may not accurately reflect the pathogenesis of this disorder in humans. Here we report a model of heart failure based on the disruption of genes that regulate sympathetic nervous system activity.

There are three α_2-adrenergic receptor (α_2-AR) subtypes: α_{2A}, α_{2B}, and α_{2C}. α_2-ARs regulate the sympathetic nervous system in several ways. α_{2A}-ARs in the brain stem regulate sympathetic tone (1, 29), and both α_{2A}-AR and α_{2C}-AR act as presynaptic autoreceptors regulating catecholamine release in the murine atria (18). We have previously reported that disruption of

The α_{2A}-AR is the main presynaptic inhibitory autoreceptor in the CNS, lowering sympathetic outflow/BP in response to α_2-AR agonist drugs and, along with the α_{2C}-AR, inhibits NE release in mouse atria (*Hein et al., 1999, Nature 402:181–184*). α_2-ARs are responsible for the autocrine feedback inhibition of CA release from the adrenal gland (*Brede et al., 2003, Mol. Endocrinol. 17:1640-1646*).

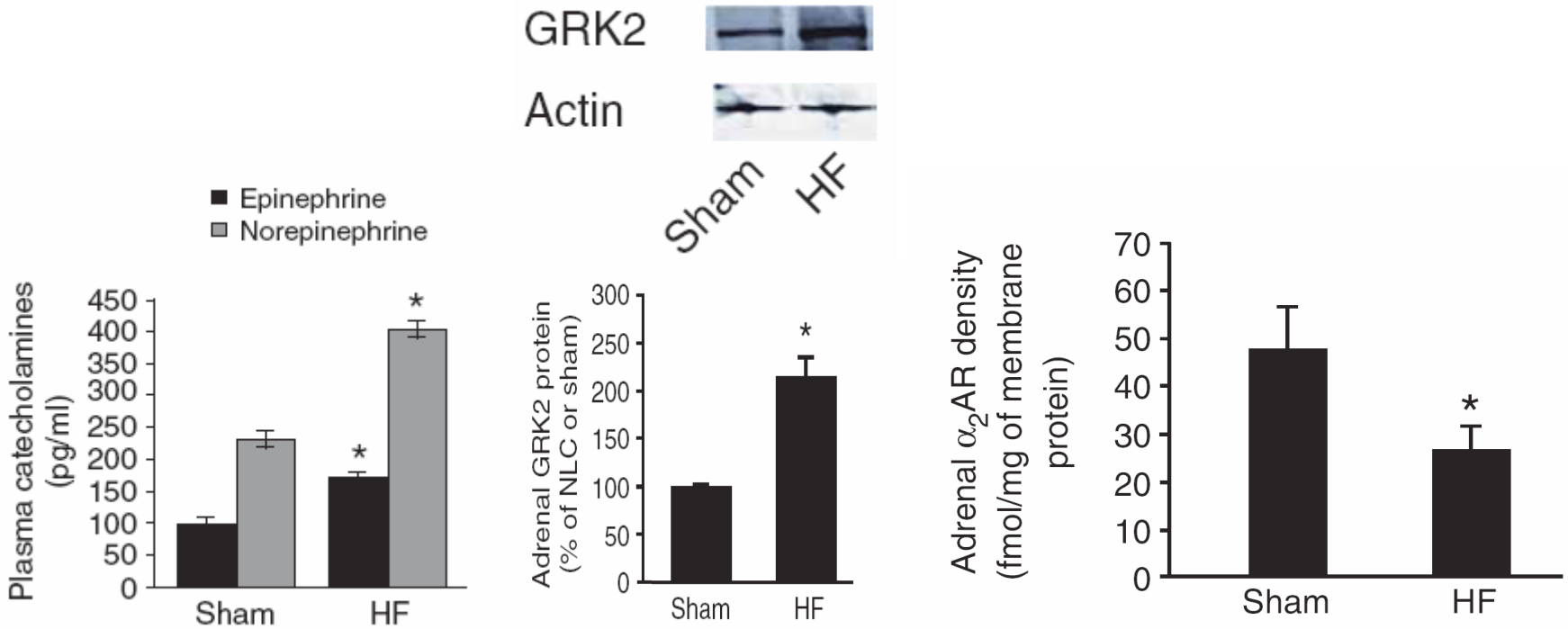
α_2ARs of cardiac sympathetic nerves and adrenal gland play an essential role in regulation of SNS activity/outflow in HF *(Brede et al., 2002, Circulation 106, 2491-2496, Brum et al., 2002, Am. J. Physiol. Heart Circ. Physiol. 283, H1838-H1845, Small et al., 2002, N. Engl. J. Med. 347, 1135-1142*).

ARTICLES

nature medicine

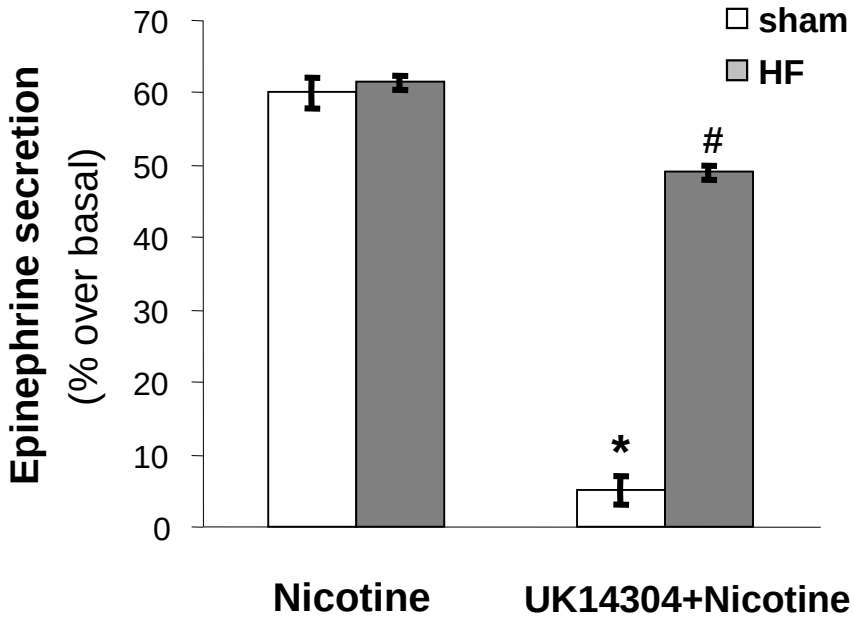
Adrenal GRK2 upregulation mediates sympathetic overdrive in heart failure

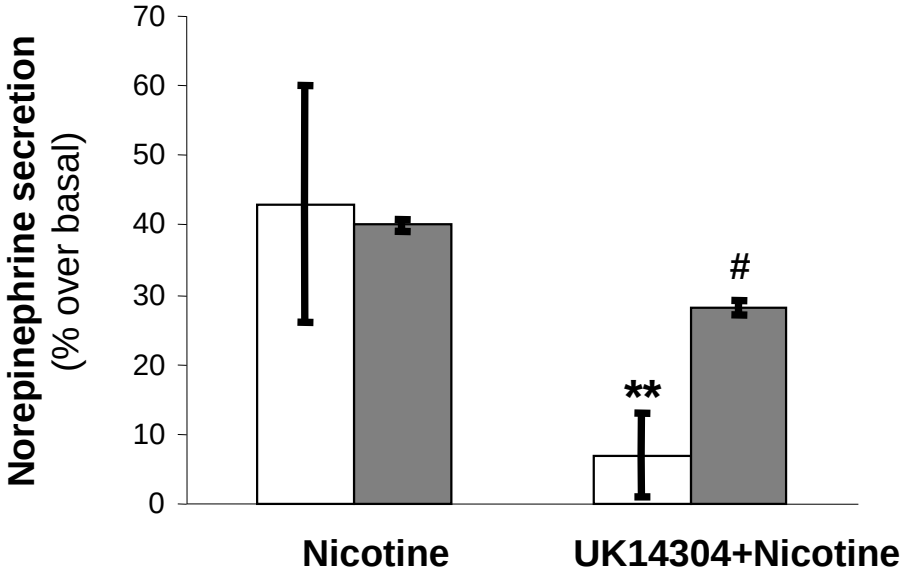
Anastasios Lymperopoulos[1,2], Giuseppe Rengo[1,2], Hajime Funakoshi[1], Andrea D Eckhart[1,3] & Walter J Koch[1,2]



Lymperopoulos A, Rengo G et al Nat. Med. 2007

Desensitization of α_2ARs in HF rat adrenal-derived chromaffin cells

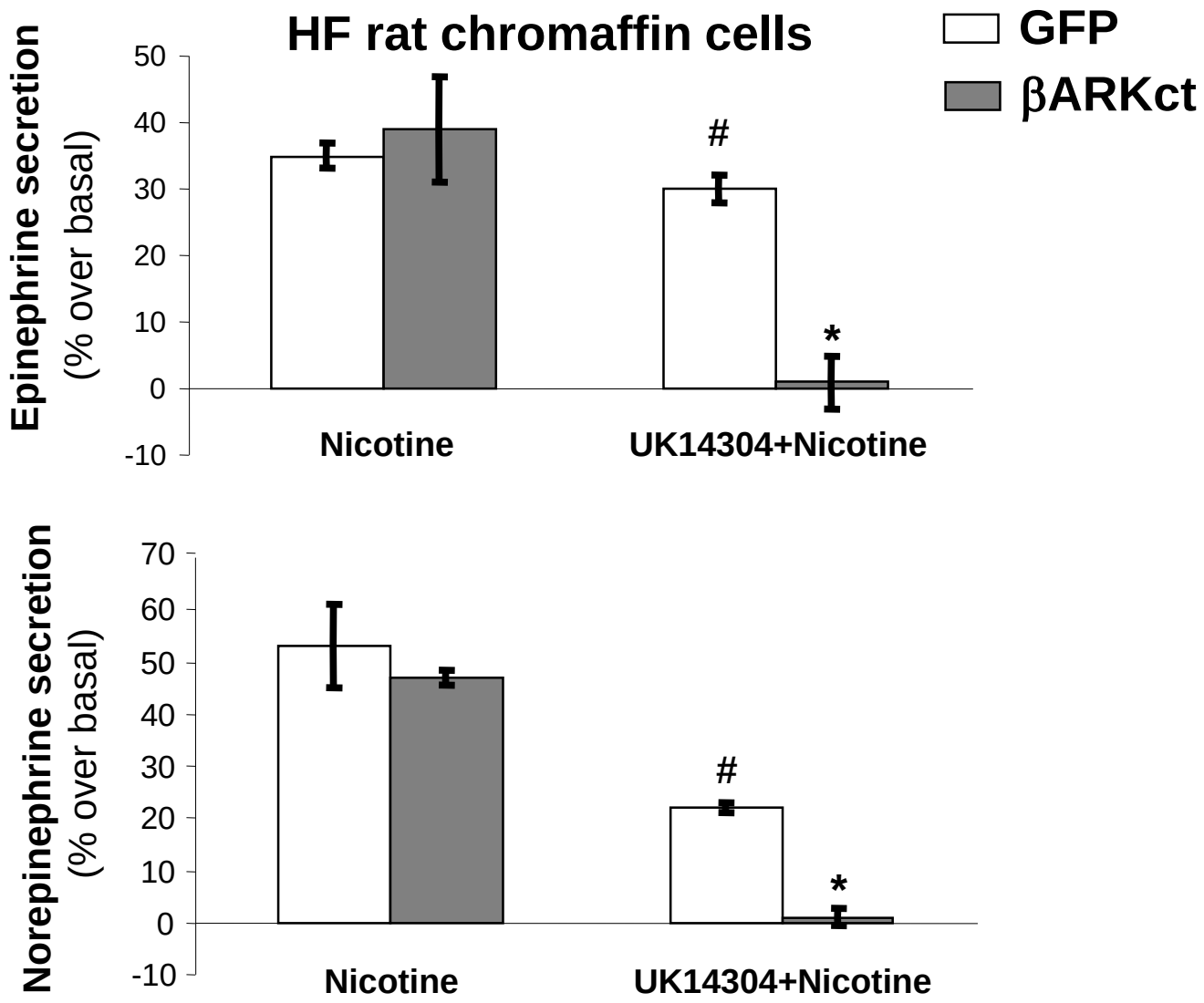




*, p<0.01 vs. Nicotine-sham, **, p<0.05, vs. Nicotine-sham, #, p<0.05 vs. Nicotine-HF, n=6

Lymperopoulos A, Rengo G et al Nat. Med. 2007

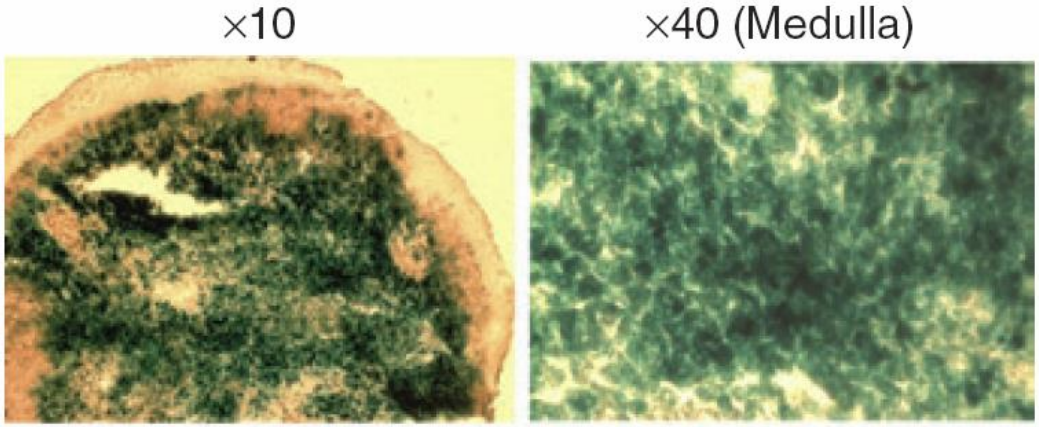
βARKct restores adrenal α_2AR-induced CA secretion inhibition in HF rats



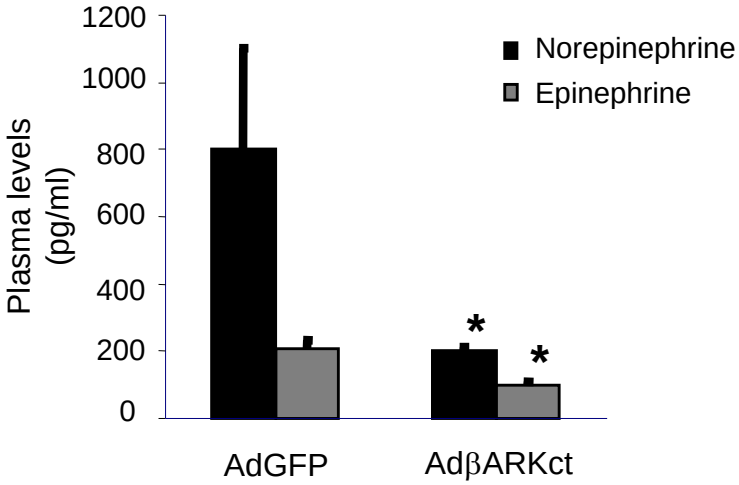
*, p<0.05 vs. UK14304+Nicotine-GFP, p<0.01 vs. Nicotine-βARKct, #, p<0.05 vs. Nicotine-GFP, n=9

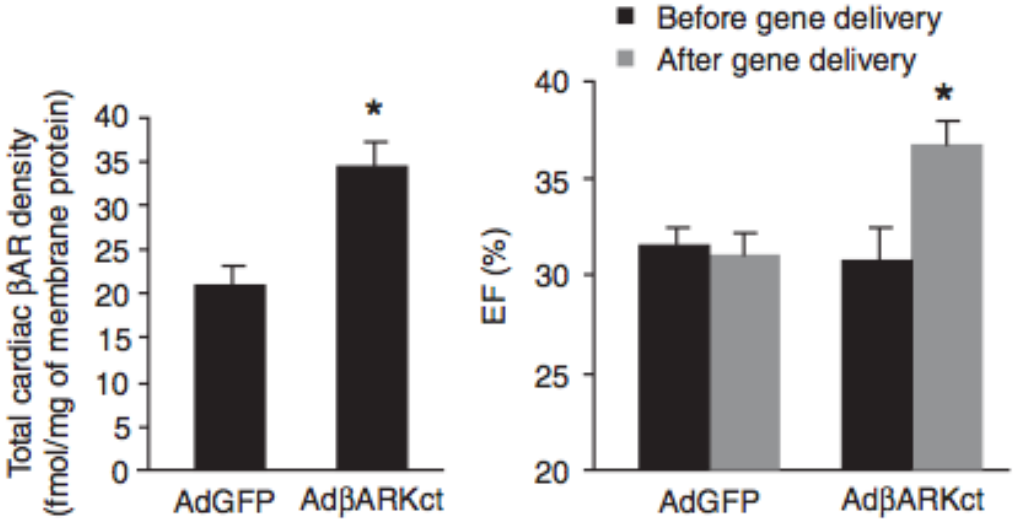
Lymperopoulos A, Rengo G et al Nat. Med. 2007

Adrenal GRK2 upregulation mediates sympathetic overdrive in heart failure



Lymperopoulos , Rengo et al. Mol Ther 2008



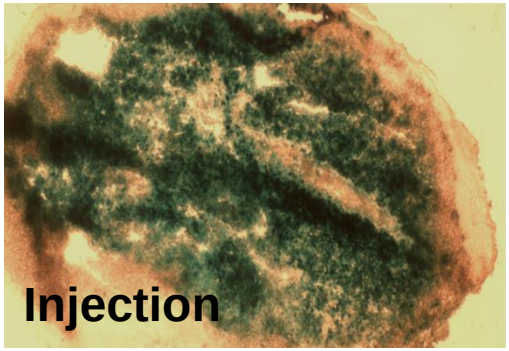


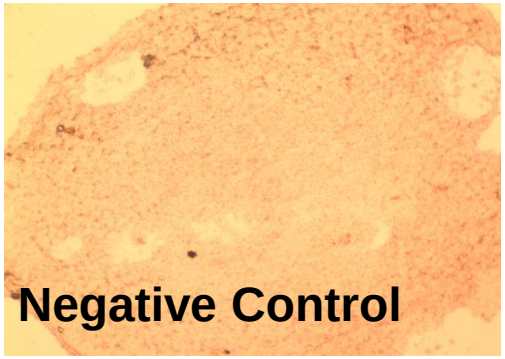
*, p<0.05 vs. AdGFP

Lymperopoulos A, Rengo G et al Nat. Med. 2007

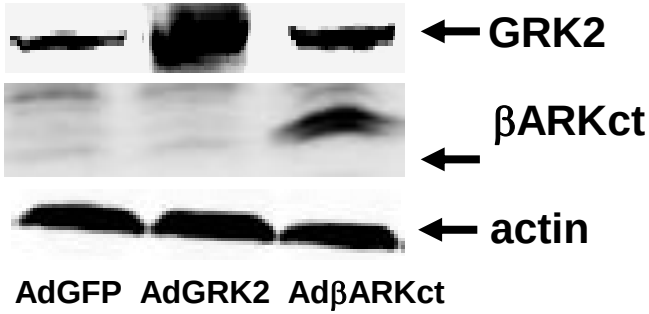
Manipulation of adrenal GRK2 levels modulates plasma CA level in vivo

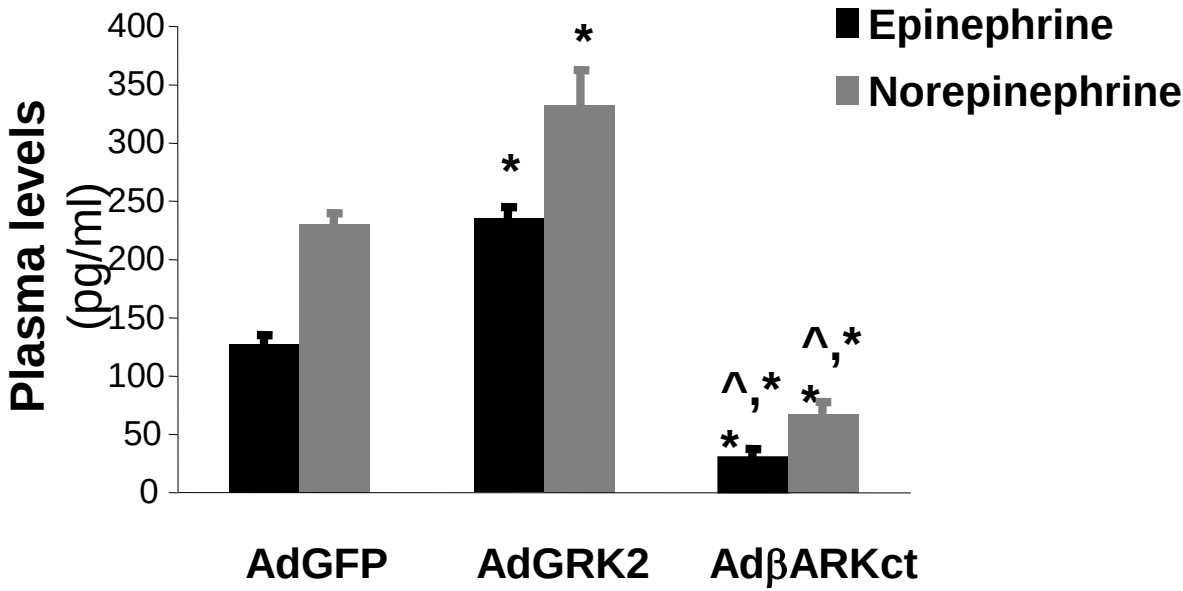
10X





Immunoblotting in rat adrenals

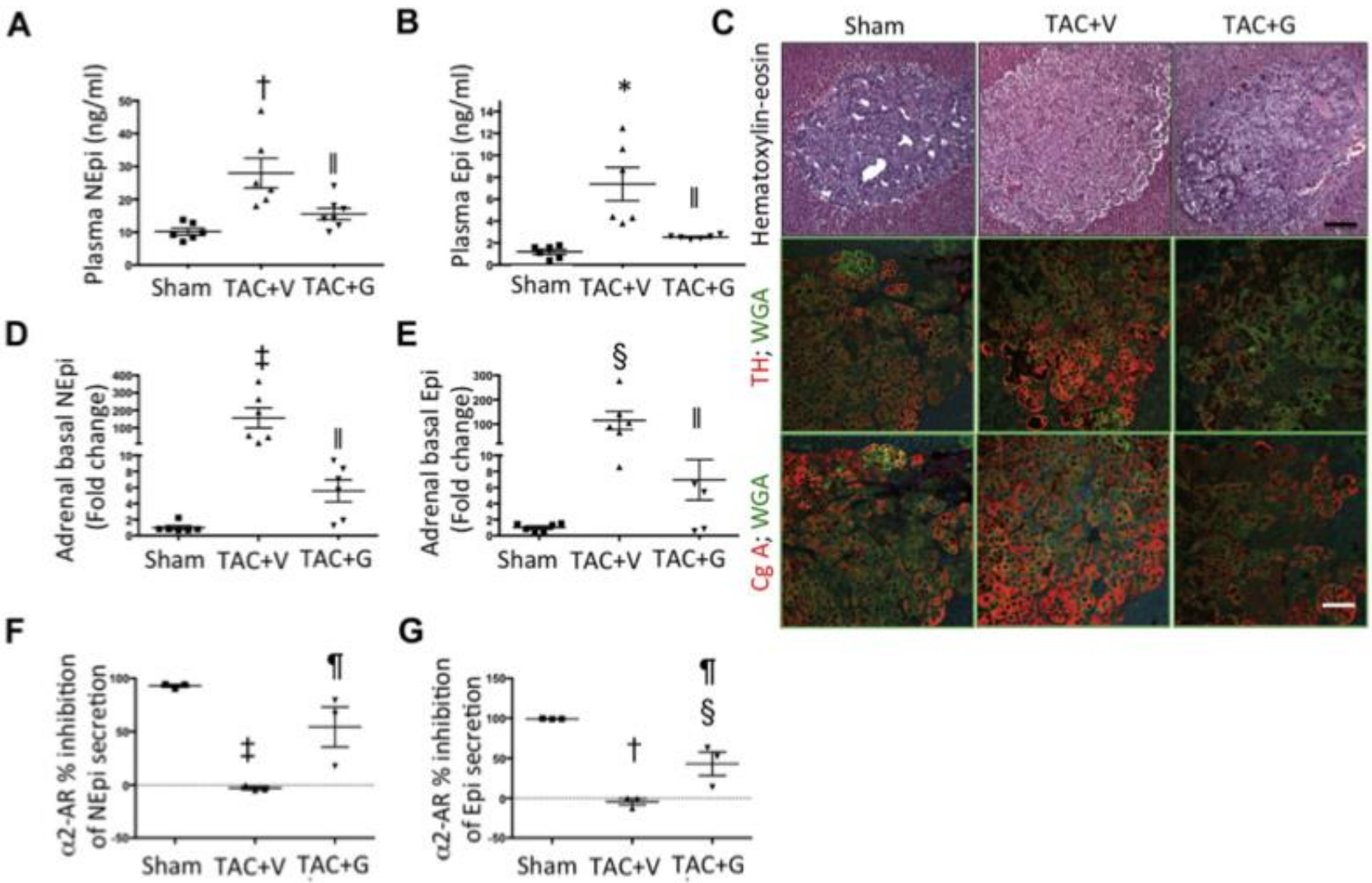




*, p<0.05, compared to AdGFP, ^, p<0.05, compared to AdGFP, **, p<0.05, compared to AdGRK2

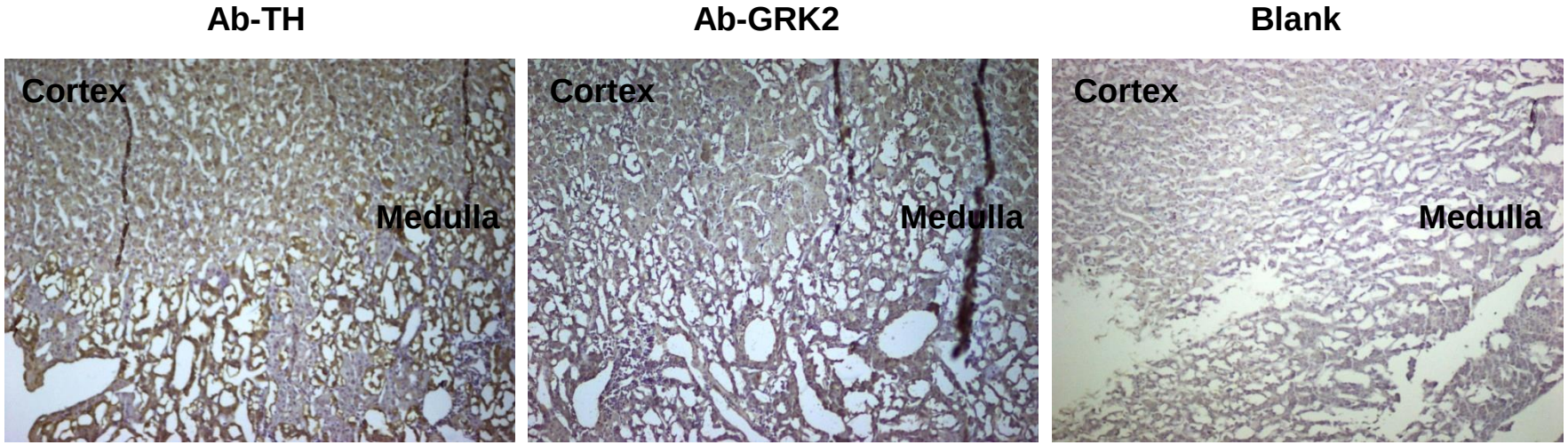
Lymperopoulos , Rengo et al. Mol Ther 2008

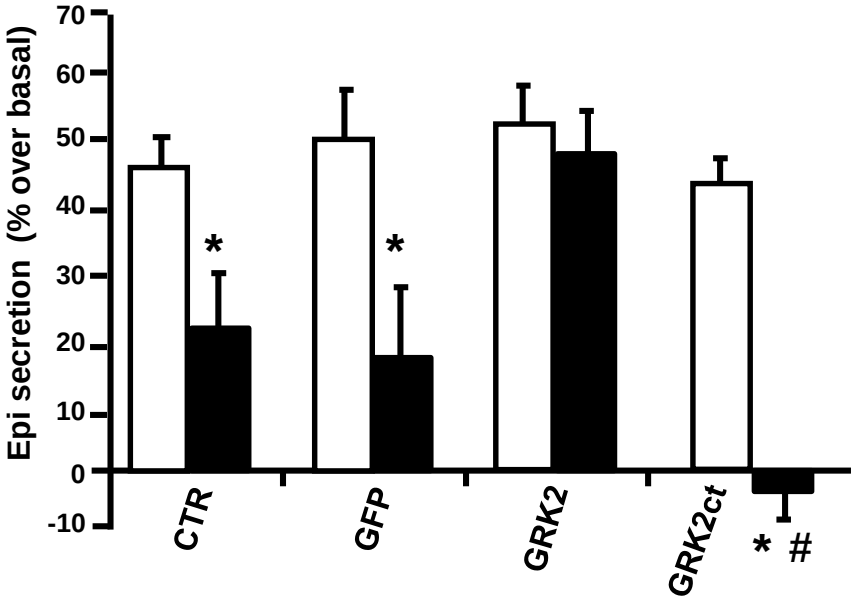
Gallein Reduced Plasma CAs and adrenal Hypertrophy, and restores α2-AR feedback inhibition of CA release

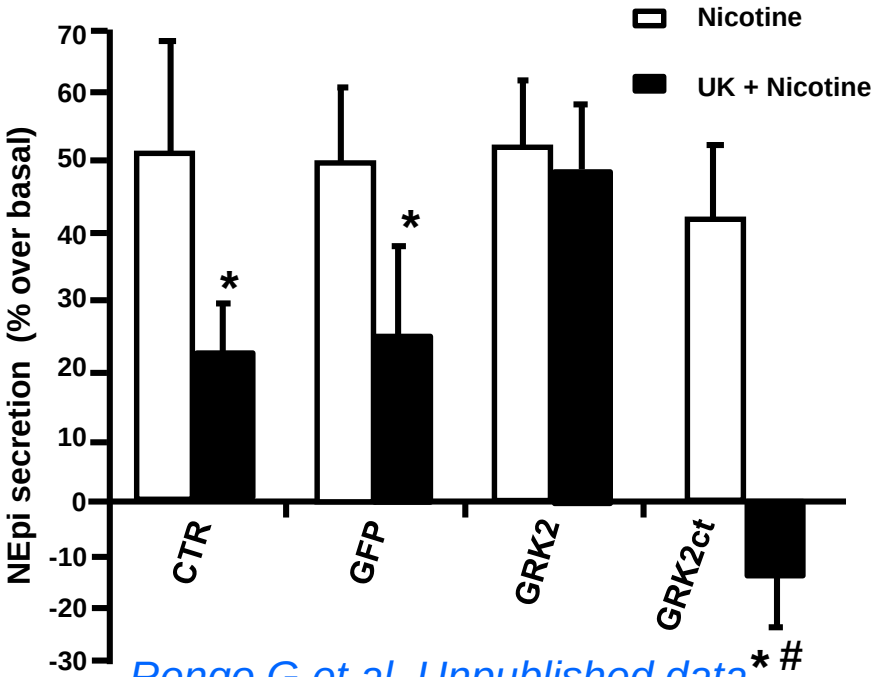


Kamal FA et al. JACC 2014.

GRK2 regulates adrenal α2-AR-CA production axis in human chromaffin cells



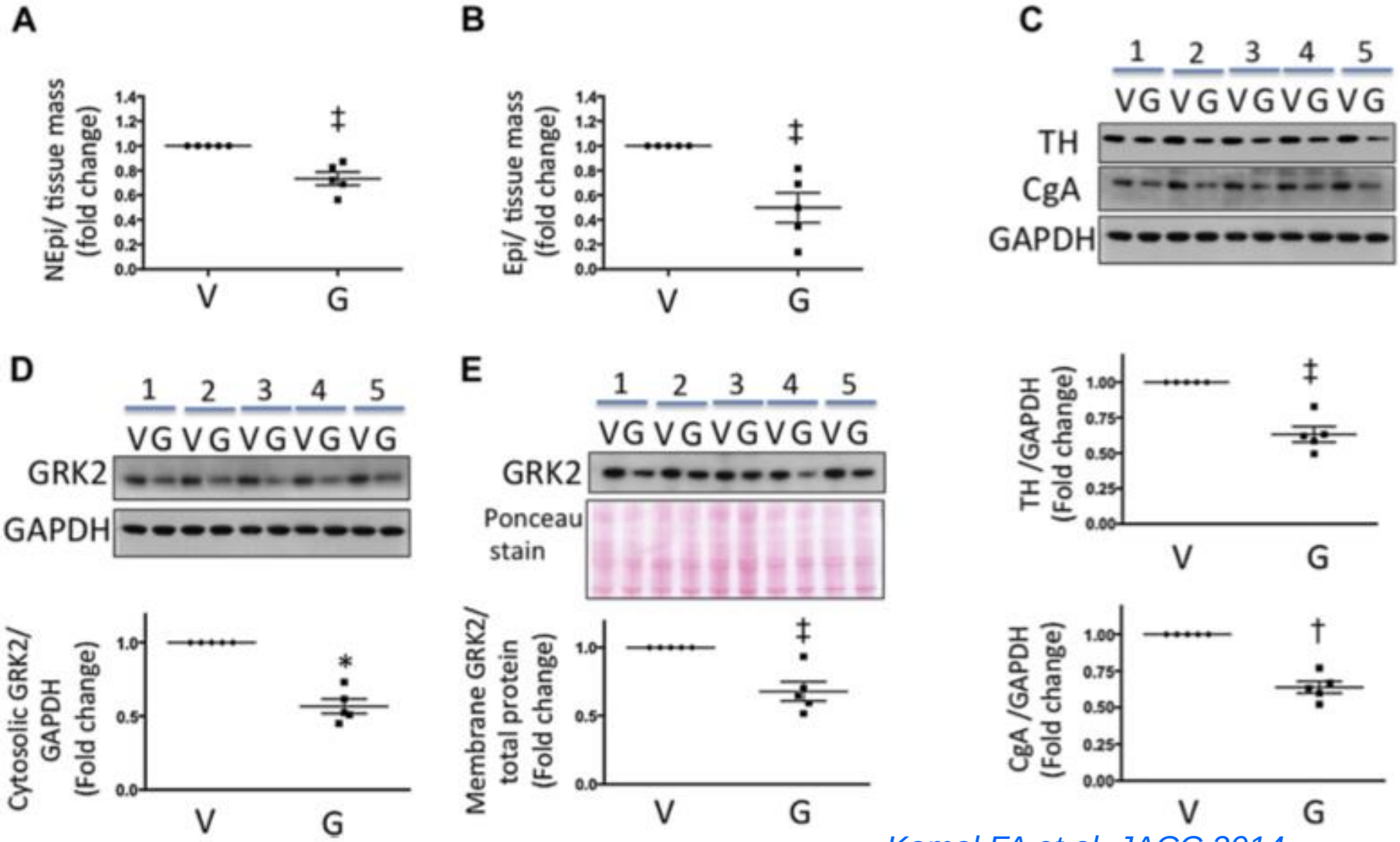




*, p<0.05, vs. Nicotine; #, p<0.05, vs. UK+Nicotine of other groups

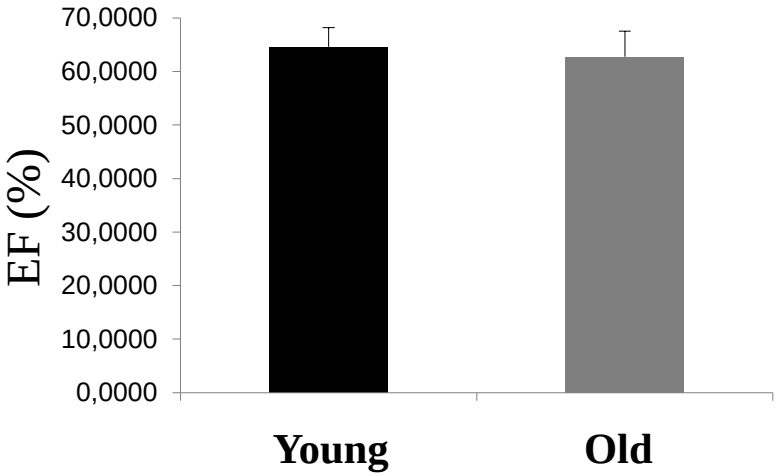
Rengo G et al. Unpublished data

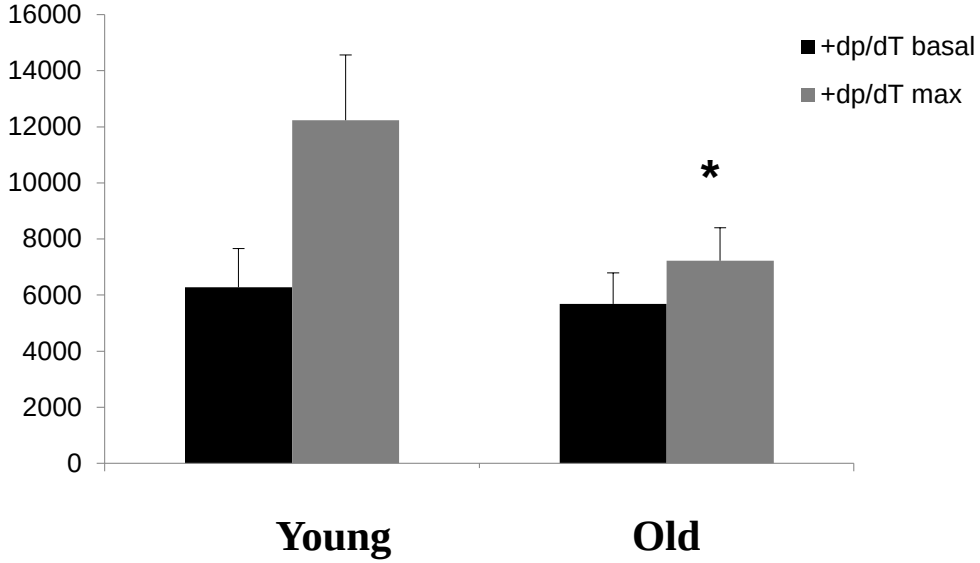
Gallein reduces CA secretion and normalizes α2-AR feedback inhibition in pheochromocytoma human adrenal medulla

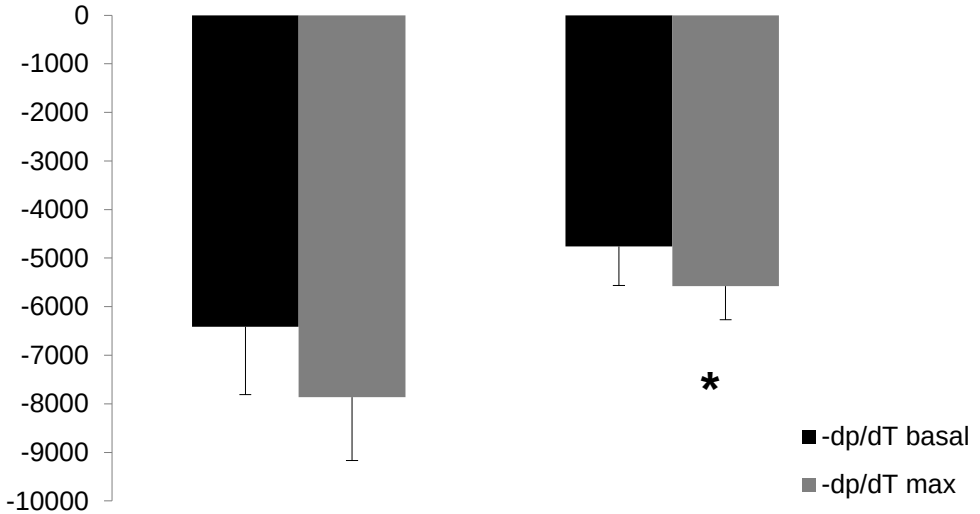


Kamal FA et al. JACC 2014

Effects of age on cardiac function and inotropic reserve



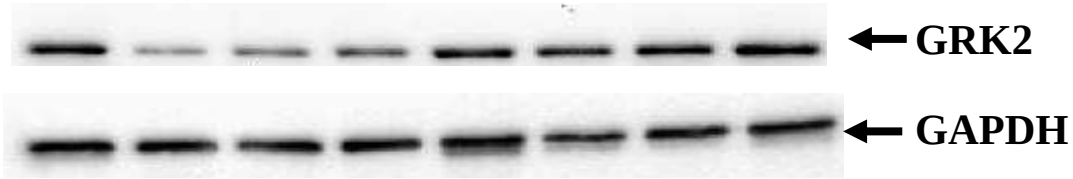


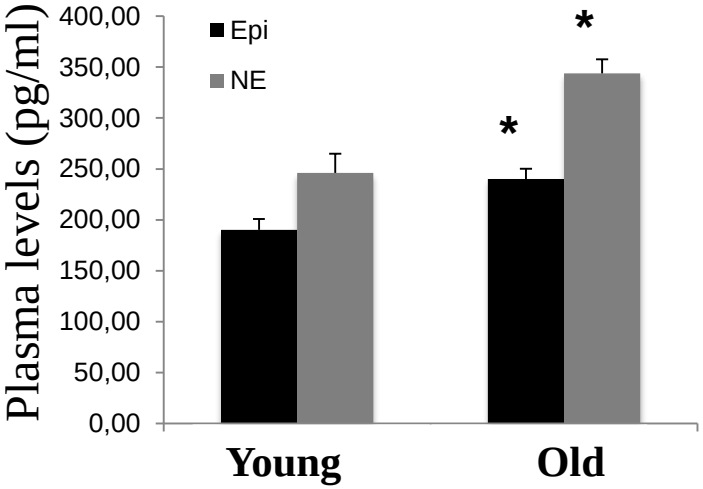


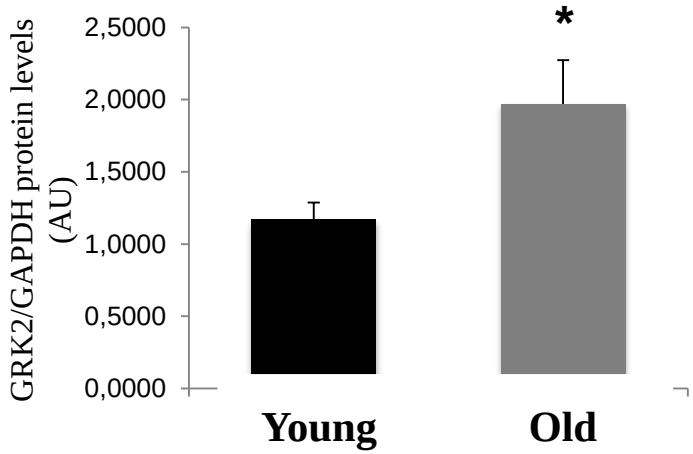
*, p<0.05, vs. Young

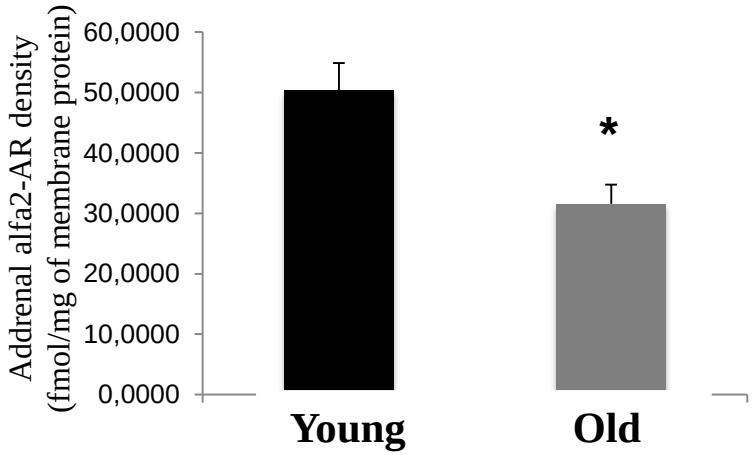
Rengo G et al. Unpublished data

Age-related alterations of adrenal GRK2-α2-adrenergic receptor-catecholamine production axis





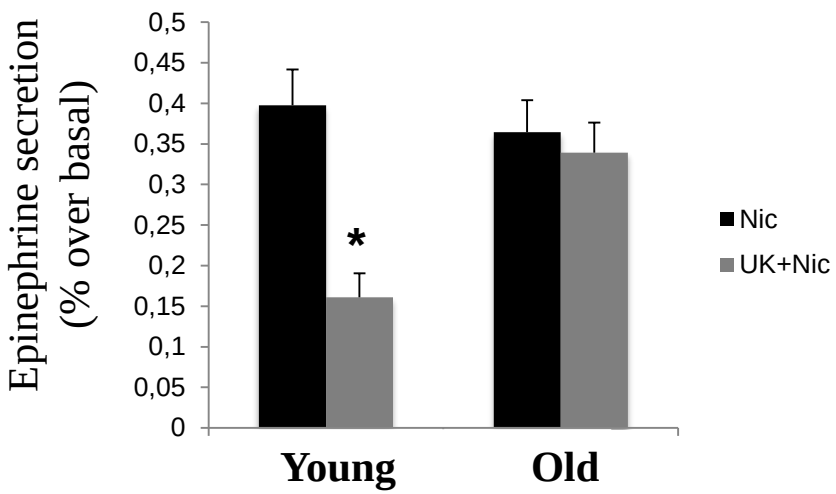


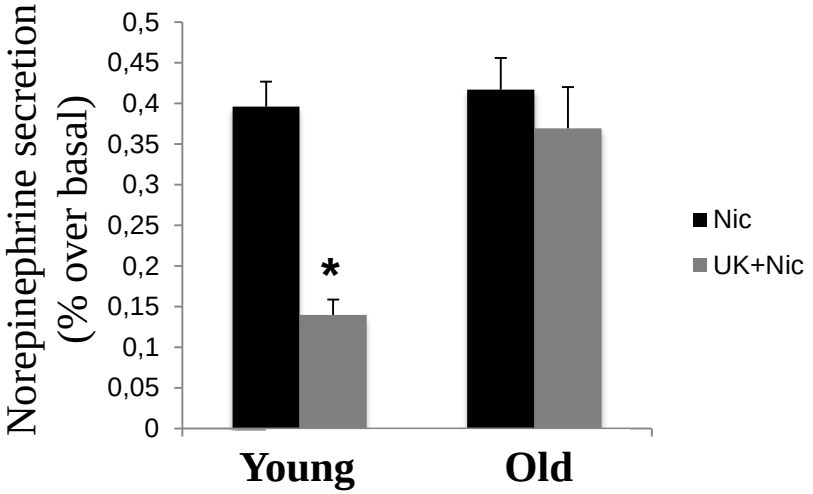


*, p<0.05, vs. Young

Rengo G et al. Unpublished data

α2-adrenergic receptor responsiveness in adrenal chromaffin cells extracted from young and old rats

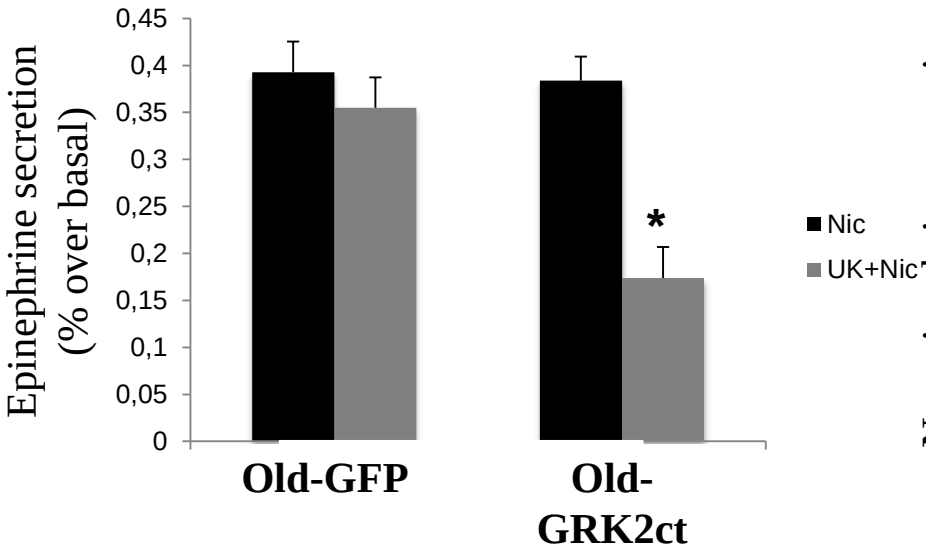


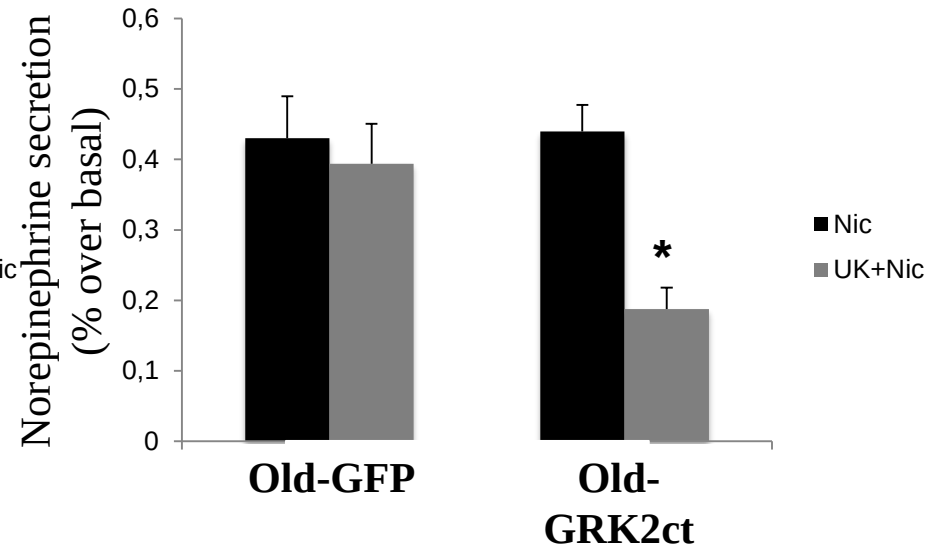


*, p<0.05, vs. Nicotine

Rengo G et al. Unpublished data

Effects of GRK2 inhibition on α2-adrenergic receptor responsiveness in adrenal chromaffin cells extracted from old rats





*, p<0.05, vs. Nicotine

Rengo G et al. Unpublished data

CONCLUSIONS

- SNS hyperactivity is a salient characteristic of chronic HF and of physiological ageing

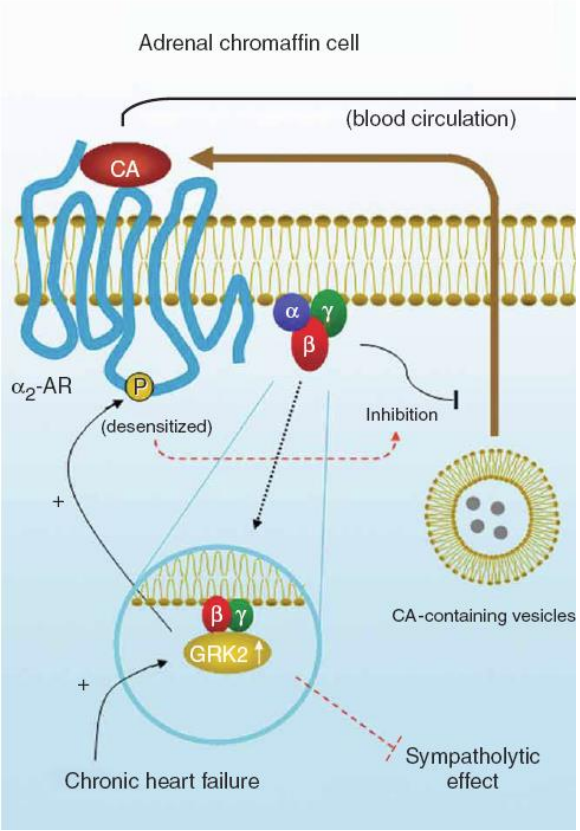
- Cardiac β-AR dysregulation is strictly related to SNS overdrive

- Adrenal medulla seems to play a relevant role in the determination of CA circulating levels

- GRK2-mediated α2-adrenergic receptor dysfunction is a crucial mechanism of SNS overdrive in HF

- GRK2 regulates CA realease also from human chromaffin cells

- GRK2 inhibition in chromaffin cells extracted from old rats resulted in enhanced α2-AR responsiveness and reduced CA release



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