JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 67, NO. 7, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.12.008

EDITORIAL COMMENT

When Sweet Turns Salty

Glucose-Induced Suppression of Atrial Natriuretic Peptide by MicroRNA-425*

Temo Barwari, MD, Philipp Skroblin, PhD, Manuel Mayr, MD, PhD

One of the most challenging aspects of obesity is its link to "metabolic syndrome," when abdominal obesity is accompanied by high fasting blood glucose, low levels of high-density lipoprotein cholesterol, high levels of triglycerides, and elevated blood pressure. With rising obesity rates, metabolic syndrome is likely to become more common in the years ahead (1). Although progress has been made in identifying this syndrome's individual components, their interplay across several organ systems is not well understood; that is, the near-linear relationship between body mass index and blood pressure. Obesity is often recognized as a predictor of treatment-resistant hypertension (2). One of the main endocrine pathways that has been implicated involves natriuretic peptides (3). Natriuretic peptides exert their antihypertensive effects predominantly by inducing natriuresis but have additional effects beyond blood pressure regulation. For example, an antihypertrophic effect, independent of blood pressure, was observed in the heart (4). Other reports demonstrate the ability of atrial natriuretic peptide (ANP) to promote lipolysis (5) and activate the brown fat thermogenic program (6). Notably, levels of natriuretic peptides are lower in obese subjects and patients with type 2 diabetes (7).

Genetic studies demonstrated that the single nucleotide polymorphism rs5068 (A/G) is most strongly associated with plasma ANP levels. Carriers of the minor G allele are less obese, have a lower risk of hypertension, and a decreased incidence of

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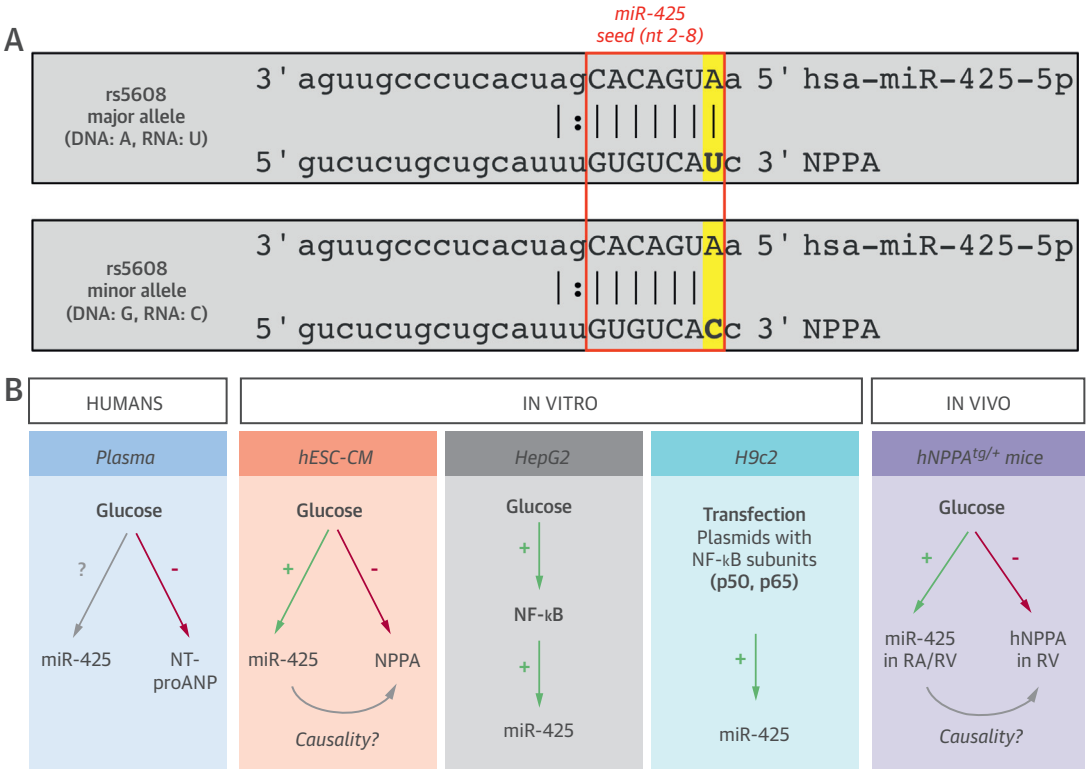
cardiovascular events (8). In this issue of the *Journal*, Arora et al. (9) expand upon their previous finding that the variant rs5068 (A/G) influences ANP production (10). *NPPA*, which encodes for ANP, is a target of micro ribonucleic acid (miRNA)-425 (miR-425). miR-425 is predicted to bind the sequence spanning rs5068 for the A, but not the G allele (**Figure 1**). Overexpression of miR-425 in human cardiomyocytes derived from induced pluripotent stem cells reduced *NPPA* messenger RNA and N-terminal (NT)-proANP protein levels (10).

In the present study, Arora et al. (9) explored miR-425 as a link between glycemia and ANP expression, thereby providing a potential explanation for lower NT-proANP plasma levels after food consumption (11). The authors demonstrated that: 1) a carbohydrate challenge lowered plasma ANP, but not brain natriuretic peptide; 2) high glucose increased miR-425 and decreased *NPPA* expression in human cardiomyocytes derived from embryonic stem cells; 3) a glucose stimulus enhanced the transcription downstream of the miR-425 promoter in HepG2 cells, a human liver carcinoma cell line; and 4) miR-425 expression was nuclear factor kappa B (NF-κB)-dependent in H9c2 cells, a rat

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the King's British Heart Foundation Centre, King's College London, London, United Kingdom. The research was funded/supported by the National Institute of Health Research (NIHR) Biomedical Research Centre based at Guy's and St. Thomas' NHS Foundation Trust and King's College London in partnership with King's College Hospital, Diabetes UK and Heart Research UK. King's College London has filed patents on miRNA biomarkers. Dr. Barwari has been awarded an interdisciplinary PhD studentship of the British Heart Foundation (BHF). Dr. Mayr is a Senior Fellow of the BHF and member of a network on "MicroRNA-based Therapeutic Strategies in Vascular Disease" funded by the Fondation Leducq. Dr. Mayr has received research funding from AstraZeneca. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

FIGURE 1 Association of miR-425 With ANP



(A) In the base pairing between microribonucleic acid 425 (miR-425) and the 3′ untranslated region (3′ UTR) of human *NPPA*, the **red box** indicates the seed sequence (position 2 to 8). **Yellow** = variants of rs5068. **(B)** The in vitro and in vivo effects as observed in the study by Arora et al. (9). DNA = deoxyribonucleic acid; hESC-CM = human embryonic stem cell–derived cardiomyocyte; NF = nuclear factor; NT-proANP = N-terminal pro-atrial natriuretic peptide; RA = right atrium; RNA = ribonucleic acid; RV = right ventricle.

cardiomyoblast cell line (Figure 1). Importantly, the human, but not the rodent, *NPPA* gene was a target of miR-425. By using transgenic mice carrying the human *NPPA* gene ($NPPA^{tg/+}$ mice), the authors provided in vivo evidence for an inverse association of miR-425 and human *NPPA* expression in the right ventricle after glucose administration.

Key questions remain unanswered: Can inhibition of endogenous miR-425 attenuate the glucose-induced decrease in *NPPA* transcription or are miR-425-independent mechanisms responsible for regulating *NPPA* levels upon glucose stimulation? The latter could have been addressed by determining whether the endogenous mouse *NPPA* levels were unchanged after the glucose gavage. Moreover, miRNA targets can change depending on the cell context. Does inhibition of endogenous miR-425 result in a similar rise of ANP secretion in all cardiomyocyte-like cells? It remains unclear whether miR-425 is associated with cardiometabolic phenotypes in mice as observed by targeting other miRNAs (12). No data were included on metabolic parameters, blood pressure, and cardiac function of $NPPA^{tg/+}$ mice.

A direct effect of endogenous miR-425 on ANP expression levels should have been confirmed in vitro and in vivo, to rule out a possible contribution by other miRNAs. For example, miR-103 and -107 are expressed in the heart (13), and are predicted to target the human *NPPA* gene. Expression levels of miR-103 and 107 are increased in livers of obese mice and regulate insulin sensitivity (14). A 20% to 30% increase of miR-425 expression was observed in the right atria and the right ventricles after $NPPA^{tg/+}$ mice were gavaged with 2 g/kg glucose (9). The authors inferred that the concurring decrease of human *NPPA* expression in the right ventricle was the result of