JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 7, NO. 11, 2022

EDITORIAL COMMENT

Sponging Away Cardiac Injury

A Natural Compound Shows Cardioprotective Promise*

Gizem Kayki-Mutlu, PhD,[a,b] Kimberly M. Ferrero, MS,[a,c] Walter J. Koch, PhD[a]

Heart failure (HF), commonly associated with ischemia-based causes, is a major health problem worldwide. Despite the available therapies that provide symptomatic benefit, prognosis and life quality of patients with HF still remains poor. This makes the need for effective therapeutic strategies especially addressing underlying mechanisms urgent. Pathophysiology of HF is complex, but mitochondrial abnormalities have recently emerged as a significant target because the failing heart is "energy-deprived" and mitochondrial abnormalities are a primary reason for energy supply-demand imbalance. Whereas current therapies target reducing high-energy demand, novel potential interventions are focusing on increasing ATP supply.[1] Moreover, because the mitochondria is a major location of reactive oxygen species formation and apoptosis, which play critical roles in the pathogenesis of various diseases including HF, therapies reversing mitochondrial dysfunction is a yet unmet need. The current study is interesting because it focuses on this unique organelle.

In this issue of *JACC*: *Basic to Translational Science*, Kim et al[2] evaluated a novel natural compound, Neopetroside A (NPS A), that is isolated from the marine sponge *Neopetrosia sp*. The authors have previously shown that NPS A improved mitochondrial function with no toxic effects.[3] With regard to this beneficial effect of NPS A on mitochondria, the authors aimed to investigate the clinical potential of NPS A in the treatment of cardiac diseases in the present study. Following the demonstration of NPS A as nontoxic in vivo and in vitro, the authors showed that NPS A augments glycolysis, oxidative phosphorylation, and ATP production in vitro. However, this mitochondrial function enhancer effect was not observed in isolated mitochondria, which was interpreted as occurring via changes in intracellular pathways. Importantly, NPS A treatment was demonstrated to ameliorate ischemia/reperfusion injury both ex vivo and in vivo. First, Langendorff-perfused hearts receiving NPS A following ischemia exhibited improved heart function, smaller infarct size, and lower reactive oxygen species. Then, the authors investigated whether NPS A prevents myocardial infarction in vivo. Upon myocardial infarction surgery, mice received NPS A intraperitoneally every 2 days for 4 weeks. Survival rate was higher in the group of mice treated with NPS A, along with a reduction in infarct size and decreased fibrotic markers COL1A1 and a-SMA in the same group.

The authors then screened energy metabolism pathways affected by NPS A treatment using in vitro kinase activity assays. They found that glycogen synthase kinase-3 (GSK-3) subtype GSK-3β activity was reduced upon NPS A treatment. Molecular docking simulations showed direct binding of NPS A with GSK-3β. Interestingly, this binding did not lead to GSK-3β phosphorylation different from that of traditional GSK-3β inhibitors. NPS A inhibits GSK-3β via direct binding and had effects on downstream targets.

GSK-3β is known as a complex kinase and is known to play several roles in the heart through several signaling pathways. It has been implicated in various diseases such as bipolar disorder, Alzheimer's

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

From the [a]Center for Translational Medicine, Temple University School of Medicine, Philadelphia, Pennsylvania, USA; [b]Faculty of Pharmacy, Department of Pharmacology, Ankara University, Tandogan, Ankara, Turkey; and the [c]Department of Cardiovascular Sciences, Temple University School of Medicine, Philadelphia, Pennsylvania, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2022.06.019

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 7, NO. 11, 2022
NOVEMBER 2022:1117–1119

disease, inflammation, cancer, diabetes, and HF. GSK-3β has also been shown to play regulatory effects on mitochondrial biogenesis, permeability, motility, and apoptosis. Considering these data within mitochondria, it seems logical that targeting GSK-3β is considered as a potential therapeutic option in various diseases including ischemic heart disease. Administration of the GSK-3β inhibitor, Lithium, in the treatment of bipolar disorder long-term is evidence that inhibiting GSK-3β can be effective and well tolerated. However, its large number of kinase substrates and many affected signaling pathways still raise concern about its effectiveness as a new treatment option. As more work is done to understand the role of GSK-3β, the future goal of development of novel GSK-3β inhibitors[4] is to determine which specific cells or signaling pathways to target.

In a series of experiments, the authors also demonstrated that NPS A treatment increased the NAD^+/NADH ratio. This activated signaling pathway has been suggested as the underlying mechanism of NPS A-mediated mitochondrial function protective effect, which was proven because silencing this pathway abolished NPS A-mediated cardioprotection. NAD levels are known to be critical regulators of cardiac metabolism and play significant roles in ATP production. Derangement of the NAD pool is associated with cardiac remodeling and disrupted mitochondrial function. Indeed, increasing cellular NAD levels is suggested as a treatment option for HF. Moreover, the NAD^+/NADH ratio increasing effect of NPS A was demonstrated to mediate through the NAD(P)H quinone oxidoreductase 1/nuclear factor erythroid 2-related factor 2 (Nrf2/Nqo1) pathway in the present study. Targeting Nrf2 signaling in cardiac diseases is suggested to be beneficial because Nrf2 regulates antioxidant mechanisms and is known to be reduced in the failing heart.

These observations by Kim et al[2] not only suggest a new treatment option against ischemic heart disease, but also provide information for the development of novel therapy strategies targeting the aforementioned pathways. In addition, NAD^+/NADH regulation through GSK-3β inhibition and the activated Nrf2/Nqo1 pathway was demonstrated to be present in the brain,[5] but its demonstration in the heart is novel, contributes significant information on the role of mitochondria in the pathogenesis of HF, and would lead to future studies.

Despite the findings of the present study on the novel GSK-3β inhibitor, NPS A should be considered with caution because the authors did not assess whether this drug has an effect on the second GSK isoform, GSK-3α. Two isoforms, GSK-3α and GSK-3β, have opposing functions in the heart. GSK-3α is known to mediate cardioprotective effects. Thus, any potential GSK-3α inhibitory effect of NPS A will be worth investigating in further studies to be more clinically relevant.

Nevertheless, it is quite exciting to find potential therapeutic effects from a compound mined from a natural product such as a sponge. This shows the clear potential to learn from nature on how to explore chemical interactions between molecules of importance and demonstrates the relevance of such research. Such work as this study also shows the importance of not only descriptive work but also delving into mechanistic experiments to delineate causation to potential therapeutic effects to help us understand these natural products for further development and potential pharmaceutical advancement.

Overall, the current study by Kim et al[2] demonstrates that NPS A inhibits GSK-3β, which activates Nrf2/Nqo1 and increases the NAD^+/NADH ratio. This rise improves mitochondrial function and exerts a cardioprotective effect in cardiac ischemic injury models. Effectiveness of NPS A is promising, although additional studies are needed before clinical trials. Yet, the results of the current study are still encouraging because they advance our understanding for the underlying mechanisms related to mitochondria, which remain a promising therapeutic target against HF.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Walter J. Koch, Center for Translational Medicine, Temple University School of Medicine, Medical Education and Research Building (MERB), 3500 North Broad Street, 9th floor, Room 941, Philadelphia, Pennsylvania 19140, USA. E-mail: walter.koch@temple.edu.

REFERENCES

1. Sabbah HN. Targeting the mitochondria in heart failure: a translational perspective. *J Am Coll Cardiol Basic Trans Science*. 2020;5(1):88–106.

2. Kim HK, Kim M, Marquez JC, et al. Novel GSK-3β inhibitor neopetroside A protects against murine myocardial ischemia/reperfusion injury. *J Am Coll Cardiol Basic Trans Science*. 2022;7(11):1102–1116.

3. Shubina LK, Makarieva TN, Yashunsky DV, et al. Pyridine nucleosides neopetrosides A and B from a marine neopetrosia sp. sponge synthesis of neopetroside A and its beta-riboside analogue. *J Nat Prod*. 2015;78(6):1383-1389.

4. Beurel E, Grieco SF, Jope RS. Glycogen synthase kinase-3 (GSK3): regulation, actions, and diseases. *Pharmacol Ther*. 2015;148:114–131.

5. Martin SA, Souder DC, Miller KN, et al. GSK3β regulates brain energy metabolism. *Cell Rep*. 2018;23(7):1922–1931.

KEY WORDS glycogen synthase kinase-3 beta (GSK-3β), heart failure, mitochondria, neopetroside A (NPS A), nicotinamide adenine dinucleotide (NAD^+)