JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 6, NO. 1, 2021

EDITORIAL COMMENT

Targeting the Brain to Protect the Heart*

Gary D. Lopaschuk, PhD

Heart failure that results from a myocardial infarction is a serious medical condition that is associated with a high mortality and poor heart function. Although it is well known how heart failure impacts central nervous system (CNS) function, it is less clear how altering CNS function can affect the progression of heart failure. Part of this confusion relates to the fact that some of the approaches used to treat heart failure may have both peripheral cardiovascular actions and direct CNS effects. An example of this is the adipocyte-derived peptide leptin, which not only exerts a direct effect on cardiac energy metabolism and inflammation, but also has prominent actions in the CNS. Although leptin can reduce the severity of cardiac dysfunction and remodeling that can occur following chronic ischemic heart failure (1), it is not known if this is due to central or peripheral effects of leptin.

In this issue of *JACC: Basic to Translational Science*, Gava et al. (2) addressed this issue by chronically applying intracerebroventricular (ICV) leptin into the lateral ventricle of the brain of rats subjected to myocardial infarction (MI). This centrally applied leptin markedly attenuated the cardiac dysfunction that normally occurs following MI. ICV injection of melanotan II (MTII) provided a similar degree of protection as leptin. However, ICV injection of leptin or MTII did not confer any cardiac protection if rats subjected to MI were lacking the melanocortin 4 receptor (MC4R). This study provides compelling data to suggest that activation of the CNS leptin-melanocortin system can protect the heart from adverse remodeling after MI (**Figure 1**).

The important issue arises as to how these CNS effects of leptin result in cardioprotection. The beneficial effects of CNS-administered leptin on cardiac function post-MI were associated with increases in cardiac mitochondrial glucose and fatty acid oxidative metabolism in the nonischemic area of the heart. The failing heart is energy starved, and impaired glucose oxidation in the heart post-MI is an important contributor to contractile dysfunction (3). As a result, increasing myocardial glucose oxidation and improving energy production may be partially responsible for the cardioprotective effects of CNS-administered leptin. Unfortunately, no insights were provided in the Gava et al. (2) study as to how CNS leptin or MTII mediate these cardiac metabolic effects. Sympathetic stimulation increases glucose oxidation in the heart (4). However, no evidence is provided as to whether the CNS effects of leptin or MTII are stimulating the sympathetic nervous system, or any other neural signaling pathway. Regardless, many studies have suggested that stimulating the sympathetic nervous system is not desirable in the post-MI heart. Stimulating the parasympathetic system (PNS) may have potential benefits in protecting the post-MI hearts, although it is not clear from this study whether the CNS actions of leptin are modifying the PNS. In addition, it has not been previously determined if modifying the PNS can increase glucose and fatty acid oxidation in the heart.

As expected, CNS-administered leptin and MTII resulted in significant decreases in body weight of the rats throughout the 4-week treatment period (see Figure 1C in Gava et al. [2]). This raises the issue as to whether the cardiovascular benefits of leptin could be secondary to weight loss. Indeed, decreasing body weight can improve heart function in failing hearts, which is associated with an increase in myocardial glucose oxidation (5). To rule out the effects of leptin-induced effects on weight loss, Gava et al. (2) treated

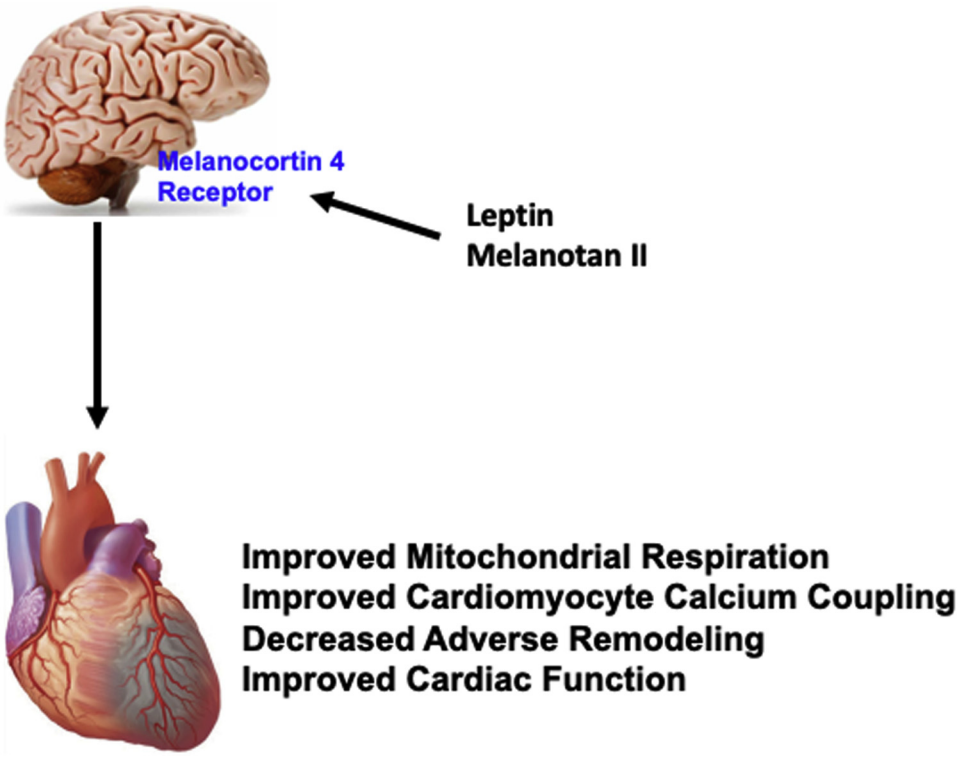
*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

From the Cardiovascular Research Centre, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada.

The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution 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.2020.12.004

FIGURE 1 Direct Action of Leptin and Melanotan II on Melanocortin 4 Receptors in the Central Nervous System Protect the Heart From a Myocardial Infarction



The beneficial effects of leptin and melanotan II are associated with an increase in cardiac mitochondrial oxidative metabolism and respiration, as well as with improved cardiomyocyte calcium coupling, leading to improved cardiac contractile function.

a group of rats with a food-restricted diet and showed that no cardioprotection was observed post-MI. However, these experiments did not provide a comparator group that was fed a normal diet, and no measurements of body weight or cardiac mitochondrial oxidative metabolism were provided. As a result, it may be premature to rule out that the beneficial cardioprotective effects of centrally acting leptin or MTII could be secondary to the orexigenic effects of these compounds.

The relationship between leptin and MTII and their beneficial effects on mitochondrial oxidative metabolism are confusing. Although ICV administration of leptin and MTII had similar beneficial effects on cardiac function in the post-MI rat hearts (Figure 1 in Gava et al. [2]), leptin increased myocardial glucose oxidation rates, whereas MTII had no effects on glucose oxidation (Figure 3C in Gava et al. [2]). Curiously, MTII increased myocardial fatty acid oxidation rates, whereas leptin had no effect on fatty acid oxidation rates (Figure 3D in Gava et al. [2]). These differing effects of leptin and MTII on cardiac glucose and fatty acid oxidation are not clear and are not explained. An increase in phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) was seen in the hearts of the rats treated with both leptin and MTII (indicative of an increase in AMPK activity). Although increased AMPK activity can result in an increase in cardiac fatty acid oxidation (6), it is also associated with a decrease in glucose oxidation. As a result, although an increase in AMPK activity may explain the effects of MTII on cardiac fatty acid oxidation, it is unlikely to explain the effects of leptin on glucose oxidation.

The increase in myocardial glucose oxidation with ICV leptin and the increase in fatty acid oxidation with IICV MTII raises the question as to whether it is an overall increase in mitochondrial oxidative metabolism that is important in the post-MI heart, as opposed to a specific increase in either glucose or fatty acid oxidation. It also raises the question as to whether these increases in mitochondrial oxidative

metabolism may simply be reflective of a better functioning heart, as opposed to mediating the beneficial effects of leptin and MTII? Unfortunately, no cardiac function values were shown in the isolated perfused heart studies. This raises the issue as to whether centrally acting leptin and MTII improve cardiac function in these hearts, and whether any effects on mitochondrial oxidative metabolism are simply due to a better functioning heart.

In summary, the study of in Gava et al (2). provides compelling evidence that leptin acting in the CNS can have beneficial effects on the heart following MI. It also demonstrates that activating the CNS MCR4 can increase cardiac mitochondrial oxidative metabolism and respiration, improve mitochondrial efficiency, and improve cardiomyocyte calcium coupling, resulting in increased contractile function in the post-MI heart. It also suggests that targeting the CNS may be a potential therapeutic strategy to treat heart failure. However, to fully realize this possibility, I believe that future studies need to establish what pathway(s) and mechanisms link the activation of the CNS leptin-MCR4 pathway to its beneficial cardiac effects. It would also be helpful to better understand if the beneficial effects of centrally acting leptin can be unequivocally linked to its effects on cardiac mitochondrial function and cardiomyocyte calcium handling.

AUTHOR DISCLOSURES

Dr. Lopaschuk has reported that he has no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Gary D. Lopaschuk, Cardiovascular Research Centre, Faculty of Medicine and Dentistry, University of Alberta, 423 Heritage Medical Research Centre, Edmonton, Alberta T6G 2S2, Canada. E-mail: gary.lopaschuk@ualberta.ca.

REFERENCES

1. McGaffin KR, Sun C-K, Rager JJ, et al. Leptin signalling reduces the severity of cardiac dysfunction and remodelling after chronic ischaemic injury. Cardiovasc Res 2008;77:54–63.

2. Gava FN, da Silva AA, Dai X, et al. Restoration of cardiac function after myocardial infarction by long-term activation of the CNS leptin-melanocortin system. J Am Coll Cardiol Basic Trans Science 2021;6:55–70.

3. Masoud WG, Ussher JR, Wang W, et al. Failing mouse hearts utilize energy inefficiently and benefit from improved coupling of glycolysis and glucose oxidation. Cardiovasc Res 2014;10:30–8.

4. Collins-Nakai RL, Noseworthy D, Lopaschuk GD. Epinephrine increases ATP production in hearts by preferentially increasing glucose metabolism. Am J Physiol 1994;267:H1862–71.

5. Karwi QG, Zhang L, Altamimi TR, et al. Weight loss enhances cardiac energy metabolism and function in heart failure associated with obesity. Diabetes Obes Metab 2019;21:1944–55.

6. Kudo N, Barr AJ, Barr RL, Desai S, Lopaschuk GD. High rates of fatty acid oxidation during reperfusion of ischemic hearts are associated with a decrease in malonyl-CoA levels due to an increase in 5′-AMP-activated protein kinase inhibition of acetyl-CoA carboxylase. J Biol Chem 1995;270:17513–20.

KEY WORDS appetite, blood pressure, cardiac metabolism, heart failure, MC4R