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Letters to the Editor

Reply to Karadeniz et al.—Could Branched-Chain Amino Acids Be a New Landmark in Metabolic Syndrome and Cardiac Arrhythmias?

To the Editor:

I thank Dr Karadeniz et al. for their insightful comments. We recently reported that elevated branched chain amino acid (BCAA) levels have proarrhythmic effects by dysregulating cardiac repolarisation and cardiomyocyte calcium homeostasis in a mammalian target of rapamycin (mTOR) pathway–dependent manner.[1] We furthermore showed that incubation of human induced pluripotent stem cell–derived cardiomyocytes with high levels of BCAAs induced action potential prolongation, intracellular calcium dysregulation, and arrhythmic events, indicating a direct effect on cardiomyocyte electrophysiology.[1] However, this does not preclude the possibility that BCAAs also exert proarrhythmic effects through other mechanisms. As mentioned by Karadeniz et al., a potential modulatory effect of BCAAs on platelet activity may be of relevance, but this requires further investigation.

Karadeniz et al. furthermore refer to the intriguing possibility that melatonin exerts antiarrhythmic activity through a modulatory effect on BCAAs. Indeed, a recent study showed that melatonin attenuated the angiotensin II–induced increase in atrial BCAA content by enhancing BCAA catabolism.[2] This was accompanied by a decrease in atrial diameter, fibrosis, mTOR activation, mitochondrial oxidative damage, and inducibility of atrial fibrillation.[2] Activation of the PKG-CREB-KLF15 axis was found to be critical in mediating these beneficial effects of melatonin.[2] The transcription factor Krüppel-like factor 15 (KLF15) has previously been identified as a key upstream regulator of BCAA metabolic enzymes, and down-regulation of myocardial KLF15 during heart failure has been linked to BCAA catabolic dysfunction in the setting of this disorder (as discussed by Yu et al.[2]). Interestingly, KLF15 has also been shown to regulate circadian transcription of ion channels and consequently cardiac repolarisation and arrhythmia susceptibility,[3] underscoring the need for further studies into the modulatory role of KLF15 and BCAAs (and their interplay) on cardiac arrhythmogenesis.

In addition to the observed attenuation of angiotensin II–induced atrial fibrillation, other preclinical studies have also demonstrated beneficial effects of melatonin on ventricular arrhythmias, particularly during myocardial ischemia/reperfusion.[4] Through its antioxidant, antiinflammatory, and immunomodulatory properties, melatonin protects against myocardial cell death, cardiac hypertrophy, and fibrosis,[4] and consequently may prevent arrhythmias in an indirect manner. Whether melatonin can also affect arrhythmogenesis through more direct effects on cardiac electrophysiology, via KLF15 and/or other mechanisms, remains to be explored. While these findings identify melatonin supplementation as a potential antiarrhythmic therapy, it remains to be seen whether it can actually be used as a therapeutic intervention, given its limited bioavailability after oral administration.[4] Nevertheless, further mechanistic studies may reveal additional approaches by which these observations may be used to develop novel antiarrhythmic strategies.

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Disclosures

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