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LETTER TO THE EDITOR

Role of AMP-activated protein kinase in sepsis-induced cardiovascular dysfunction

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TO THE EDITOR: As founding members of a laboratory working on AMP-activated protein kinase (AMPK) for more than 20 yr, we have carried a lot of interest to the recent study regarding the effect of AMPK activation by 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) on age-dependent cardiac function during experimental sepsis performed by Inata et al. (4) and highlighted by an Editorial Focus (7). We would like to comment on the proposed hypothesis taking into account data we previously published on the same issue (2).

In agreement with Inata et al.'s paper, we also think that AMPK activation has to be considered as a new potential therapeutic approach in sepsis-induced cardiovascular impairment. However, we believe that the protection conferred by AMPK more likely relies on an endothelial action (as endothelial cells mainly express the α_1-AMPK isoform) rather than on cardiomyocytes (which mainly express the α_2-AMPK isoform). This conclusion is based on data that we already published in *Critical Care Medicine* in 2013 (2). Our arguments are supported by several observations.

First, we demonstrated that α_1-AMPK knockout (KO) mice did not tolerate sublethal doses of LPS (10 mg/kg, *Escherichia coli* O55B5). Indeed, a dramatic increase in mortality has been observed in young mice (2 mo of age), associated with an increased cardiac vascular permeability leading to a massive myocardial edema. We identified α_1-AMPK as a key contributor for the control of intercellular endothelial junctions. The latter is a crucial determinant of vascular leakage, which constitutes one of the main features of septic cardiomyopathy (2). More importantly, we showed no significant phenotypic differences between α_2-AMPK KO and wild-type mice submitted to sepsis concerning mortality, left ventricular function, myocardial edema, and endothelial barrier integrity, ruling out a major role of α_2-AMPK and cardiomyocytes in sepsis-induced dysfunction.

Second, we and others have shown that AICAR is unable to activate AMPK in adult cardiomyocytes (6), suggesting that the protective effects of AICAR do not result from a direct action on cardiomyocytes. Accordingly, AICAR treatment barely affects cardiac AMPK activity (as assessed by Thr^{172} phosphorylation) in the study of Inata and colleagues (4).

Third, sepsis in young mice mostly affects left ventricular end-diastolic volume, a parameter that crucially depends on blood volemia, and microvascular dysfunction (4). The resulting decreased cardiac preload could explain the reduced ejection fraction, independently of myocardial injury. This is reinforced by the clear disconnection between myocardial injury and left ventricular function observed by Inata et al. (4). Moreover, AICAR treatment in septic young mice led to a preservation of left ventricular end-diastolic volume. One may postulate that AICAR improves endothelial function and lowers vascular leakage, leading to enhanced blood volemia, tissue perfusion, and oxygen diffusion. This is in line with our previous observation that AICAR prevents LPS-induced left ventricular edema (2).

In conclusion, AMPK protects against sepsis-induced cardiovascular impairment. The pathophysiological mechanisms involved, as well as the potential protection that AMPK activation could offer, need to be deepened. Nevertheless, on the basis of several arguments from others and us, we postulate that those mechanisms primarily involve the preservation of vascular integrity. Given that AICAR application in vivo remains challenging, new clinically usable AMPK activators like antidiabetic drugs (1, 3, 5) should be considered as a perspective to unravel the involvement of AMPK in septic cardiomyopathy.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

M.A. and C.B. drafted manuscript; M.A., D.C.-Z., L.B., S.H., and C.B. edited and revised manuscript; M.A., D.C.-Z., L.B., S.H., and C.B. approved final version of manuscript.

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