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LETTER TO THE EDITOR

Ca^{2+}/cAMP ratio: An inflammatory index for diabetes, hypertension, and COVID-19

Leandro Bergantin

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Abstract

Ca^{2+}/cAMP ratio could serve as an inflammatory index for diseases like hypertension, diabetes, and coronavirus disease 2019.

Key Words: Ca^{2+}/cAMP ratio; COVID-19; Inflammatory index; Diabetes

Core Tip: Ca^{2+}/cAMP ratio could serve as an inflammatory index for diseases like hypertension, diabetes, and coronavirus disease 2019.

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TO THE EDITOR

There is a clear relationship between Ca^{2+} signaling, *e.g.*, increased Ca^{2+} signals, and inflammatory responses[1,2]. Considering the cumulative data from the scientific literature, including data of high evidence such as meta-analysis and systematic reviews, we can now link Ca^{2+} dyshomeostasis as an upstream factor for hypertension, diabetes, and other inflammatory processes[1,2]. In fact, severe inflammatory outcomes are described to be linked to a critical coronavirus disease 2019 (COVID-19) result[1,3]. Intriguingly, some reports have also observed an increased severity of COVID-19 in patients with diabetes[1,3]. To assess this issue, a meta-analysis[3] was performed by conducting a literature review of Scopus, PubMed, Science Direct, and

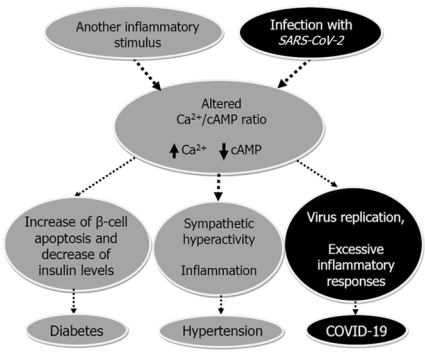

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Figure 1 Altered Ca2+/cAMP ratio resulting from an inflammatory stimulus and infection with SARS-CoV-2. Altered Ca2+/cAMP ratio stimulates uncontrolled inflammation, leading to virus replication, increase of β-cell apoptosis and decrease of insulin levels, and sympathetic hyperactivity. Up/down arrows: Increase/decrease; COVID-19: Coronavirus disease 2019.

Web of Science. Observational studies, case-reports, and case-series reports that analyzed diabetes in COVID-19 patients were included in this meta-analysis[3]. The authors concluded that diabetes is a risk factor and plays a role in the disease severity and in the mortality of individuals with COVID-19. In fact, a bidirectional relationship between COVID-19 and diabetes has been established[4]. Recent data have shown that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can produce a direct damage to the pancreas that could worsen hyperglycemia, and even cause the onset of diabetes in previously non-diabetic subjects[4]. Like diabetes, hypertension has also been recognized as a prevalent cardiovascular comorbidity in patients with COVID-19[5]. It is well established that hypertension increases the severity of SARS-CoV-2–infected patients[5]. In addition, obesity is a well-known risk factor for metabolic syndrome (MetS), hypertension, and diabetes. Recent reports revealed that it is also a vital risk factor for COVID-19, as demonstrated by a recent phenome-wide analysis of COVID-19[6].

Moreover, a link between infection with viruses and Ca^{2+} dyshomeostasis is well-discussed, *e.g.*, altering host cellular processes in the benefit of the viruses[7-10]. Thus, Ca^{2+} dyshomeostasis induced by viruses may trigger an alteration of the host cellular system that benefits virus survival and could serve as a link for an increased severity of COVID-19 in patients with diabetes[1,3].

An interesting longitudinal study also evaluated the relationship between serum Ca^{2+} levels and the incidence of MetS, diabetes, and hypertension[11]. This study[11] was performed through cross-sectional and longitudinal analyses (period 2010–2016). Logistic regression was used for cross-sectional analysis of the association between serum Ca^{2+} levels or albumin-corrected calcium (ACCA) and the prevalence of MetS, diabetes, or hypertension. Receiver operating characteristic curve analysis was applied for calculating an optimal cut-off value of serum Ca^{2+} levels and ACCA[11]. Cox proportional regression analysis for the development of MetS, diabetes, and hypertension according to different cut-off values of serum Ca^{2+} levels and ACCA was performed. At baseline, there were 27364 participants in this study[11]. The authors[11] concluded that higher serum Ca^{2+} levels were associated with an increased risk of MetS, diabetes, and hypertension. A hypothesis which could link hypertension and higher serum Ca^{2+} levels postulates that the influx of Ca^{2+} into the smooth muscle of the arteries could lead to muscle contracture, then increasing vascular resistance and, therefore, could result in the development of hypertension[11]. Our previous reports[1,2,12-15] also discussed this issue. In fact, we postulated that dysregulation of Ca^{2+} signaling is linked to a sympathetic hyperactivity, then leading to hypertension[1,12,16]. In addition, a hypothesis which could link diabetes and higher serum Ca^{2+} levels postulates that serum Ca^{2+} is associated with insulin resistance in adipocytes and skeletal muscle[17,18]. Our previous reports are in accordance with this hypothesis[1,12,15]. In fact, whereas a physiological increase in the cytoplasmic concentration of Ca^{2+} is a significant trigger for releasing insulin, an abnormal elevation of Ca^{2+} could stimulate β-cell apoptosis, then decreasing insulin levels, contributing to diabetes[1,15].

Furthermore, reports of our group undoubtedly established that a rise of the concentration of cAMP can stimulate a Ca^{2+} release from the endoplasmic reticulum, entitled as Ca^{2+}/cAMP signaling interaction[1,2,12-15]. In fact, a rise of the concentration of Ca^{2+} can markedly cause a decrease of the concentration of cAMP because of the negative feedback (Ca^{2+}/cAMP signaling interaction). Thus, a disruption of this interaction can be linked with disorders, *e.g.*, hypertension, diabetes, and COVID-19[1,2,15]. Although the interaction between these disorders may be linked with continued increases of the concentration of Ca^{2+}, whether these increases could disturb Ca^{2+}/cAMP signaling interaction needs more studies, *e.g.*, in animal models and clinical trials. Indeed, previous studies corroborate this concept. For instance, in patients with diabetes, plasma concentrations of cAMP were significantly lower than those of normal subjects[19]. In addition, cAMP contents of platelets were measured and observed to be lower in hypertensive than in normotensive subjects[20]. Figure 1 summarizes previous discussion.

In conclusion, Ca^{2+}/cAMP ratio could serve as an inflammatory index for diseases like hypertension, diabetes, and COVID-19[21,22].

FOOTNOTES

Author contributions: Bergantin LB is the sole author.

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