LETTER TO THE EDITOR

Antonio De Pascalis, MD, Giuseppe Cianciolo, MD, PhD

Do SGLT-2 Inhibitors Act Only Through a Functional Tubuloglomerular Feedback Induced by the Increased Outflow of Sodium?

To the Editor:

In the report by Neuwirt et al,[1] the authors observed that in a patient with renal glucosuria due to a genetic mutation in the sodium-glucose cotransporter 2 (SGLT-2) transporter, the sensitivity of tubuloglomerular feedback is maintained over time. Ultimately, the authors speculate that even in the presence of Na-K-2Cl channel inhibition by loop diuretics, sodium and chloride ions may still activate tubuloglomerular feedback pathways by entering macula densa.[1] This conclusion is clinically important; however, in our opinion, some physiologic observations should be made. A strong off-target effect of SGLT-2 inhibitors on the sodium-hydrogen exchangers (NHEs) on the cell surface and intracellular organelles may explain the wide-ranging effects of these agents. In addition, SGLT-2–mediated glucose uptake has been shown to stimulate NHE-3, which is responsible for a considerable amount of sodium reabsorption in the proximal tubule.[2] NHE-1 is not present within the human kidney, so sodium and chloride ions could not activate tubuloglomerular feedback pathways by entering macula densa; however, NHE-3 is located at the proximal tubule and NHE-4, at the thick ascending limb of the loop of Henle.[3]

However, these observations are independent of the coadministration of loop diuretics if we consider that SGLT-2 inhibitors, by inhibiting the Na-K-2Cl channel on the macula densa, act as loop diuretics.[4]

In our opinión, the physiologic effects of SGLT-2 inhibitors on sodium remain largely unknown and an improved understanding is needed to explain their beneficial effects on kidney and cardiovascular outcomes.[5]

ARTICLE INFORMATION

Authors' Affiliations: Nephrology and Dialysis Department, Ospedale Vito Fazzi, Lecce (ADP); and Department of Experimental Diagnostic and Specialty Medicine (DIMES), Nephrology Dialysis and Renal Transplant Unit, S. Orsola Hospital, University of Bologna, Bologna, Italy (GC).

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