Effects of Rostafuroxin in the bodily sodium handling and systolic blood pressure of undernourished rats

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Introduction. The lack of proper nutrition characterizes undernutrition in terms of quantity and quality or the inability to absorb food to meet the necessary demands of a healthy body. Undernutrition promotes pathological structural and functional changes in organs and tissues. These changes often result from upregulation of the local renin-angiotensin system. It has been shown that this upregulation can contribute to the increased release of cardiotonic steroids and activation of signaling pathways linked to $(Na^+ + K^+)$ATPase, culminating with the establishment of arterial hypertension.

Objectives. To investigate the effect of Rostafuroxin (Rosta; antagonist of cardiotonic steroids) in the changes caused by chronic undernutrition after weaning in $(Na^+ + K^+)$ATPase activity from proximal renal tubules, Na^+ intake, urinary flux (V_{ur}), urinary Na^+ excretion in 24 h ($U_{Na}V$), Na^+ plasma concentration ($[Na^+]_{pls}$), systolic blood pressure (SBP) and heart rate (HR).

Methods. Experimental design approved by the Ethics Committee on the Use of Animals in Research/UFRJ (protocol 012/19). Male Wistar rats aged 28 days were distributed in the groups CTR (commercial chow), RBD (the multideficient "regional basic diet"/RBD, which mimics the dietary habits of populations from vast regions of developing countries), CTR+Rosta (1 mg/kg of body mass from

60 days of age), RBD+Rosta (1 mg/kg body mass). $(Na^+ + K^+)$ATPase was evaluated by measuring P_i release from ATP. SBP and HR were measured by plethysmography. Statistics: Student's *t*-test to compare CTR *vs*. CTR+Rosta and RBD *vs*. RBD+Rosta.

Results. Rostafuroxin decreased body mass regardless of nutritional status. It restored SBP in RBD rats (from 145 to 130 mmHg) with no effect in the CTR group (130 mmHg), without changes in HR (both groups). It decreased $(Na^+ + K^+)$ATPase activity of the proximal tubules by 30% in CTR and RBD rats. It caused a marked increase in positive Na^+ balance (Na^+ intake minus $U_{Na}V$) (240% and 200%, respectively), without modifications in $[Na^+]_{pls}$ in both groups. It decreased V_{ur} by 20% in CTR and increased it by 40% in RBD rats.

Conclusion. Inhibition of $(Na^+ + K^+)$ATPase (the critical enzyme in body Na^+ homeostasis) by Rostafuroxin and the effects in Na^+ balance and $[Na^+]_{pls}$ depending on nutritional status, associated with decreased SBP in hypertensive RBD rats, suggested that the drug acts by mobilizing Na^+ to osmotically silent microenvironments. This view is reinforced by observing that the drug inhibits the $(Na^+ + K^+)$ATPase of proximal tubules in both groups. In the case of undernourished and hypertensive rats, this transfer – without $[Na^+]_{pls}$ modifications – would be sufficient for the normalization of SBP. The increase in V_{ur} suggests a selective effect on the urine concentration mechanism at the medullary level, depending on the nutritional status. The results, taken together, open a new vision for Rostafuroxin as a therapeutic agent for arterial hypertension associated with undernutrition.

Keywords: Undernutrition, Hypertension, Cardiotonic steroids, Rostafuroxin, Bodily sodium handling, Na/K-ATPase

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