ABSTRACT

Oxidative stress on the regulation of renal amino acid transporters in hypertension and aging

The renal dopaminergic system opposes the anti-natriuretic activity of the renin-angiotensin-aldosterone system (RAAS) and inhibits reactive oxygen species (ROS) generation. In this study we hypothesized that oxidative stress could play a role in the regulation of the candidate amino acid transporters for L-DOPA uptake, in hypertension and aging. The activity and expression of ASCT2 transporter were found to be lower in immortalized renal proximal tubular epithelial (PTE) cells from spontaneous hypertensive rat (SHR) than in Wistar-Kyoto (WKY) PTE cells. In both cell lines, high- and low-affinity components were identified for the sodium-dependent [^{14}C]-L-alanine (an ASCT2 preferential substrate) uptake process. In SHR PTE cells, treatment with apocynin, a NADPH oxidase inhibitor, inhibited the low affinity component for the sodium-dependent [^{14}C]-L-alanine uptake. This effect was found to be reversible and exclusive to SHR PTE cells. In vivo studies showed that aging was associated with increases in renal H_2O_2 levels in WKY and SHR. The abundance of $p22^{phox}$ and Nox4 proteins were increased in the renal cortex of aged WKY and SHR, as well as the expression of the antioxidant enzymes SOD2, SOD3 and catalase. Aging was also accompanied by the upregulation of renal cortical ASCT2 in WKY and of LAT2/4F2hc and ASCT2 in SHR. Subsequently, it was shown that the renal aldosterone/mineralocorticoid receptor system was activated in aged WKY and SHR. However, although renal oxidative stress and plasma aldosterone levels were similar to that observed in age-matched SHR, blood pressure values were significantly lower in aged WKY. Moreover, in aged WKY long-term food restriction resulted in significant weight loss which paralleled decreases in renal oxidative stress and reductions in plasma aldosterone levels. In WKY and SHR the modulation of amino acid transporters may be an attempt to overcome activation of the RAAS and increases in renal ROS levels during the aging process. The data presented in this thesis may contribute to a better understanding of the regulation of renal amino acid transporters and the role of ROS in hypertension.