DISEASE-MODIFYING EFFECTS OF CANDESARTAN MAY BE LIMITED TO INTERFERENCE WITH THE EARLY STAGES OF 6-OHDA-INDUCED NIGROSTRIATAL DAMAGE

S. Sarre, B. Mertens, M. Varçin, P. Vanderheyden, Y. Michotte, Research Group Experimental Neuropharmacology
Vrije Universiteit Brussel, Brussels, Belgium

Introduction: All components of the central renin-angiotensin system (RAS), including AT1 and AT2 receptors are present in the striatum. Angiotensin II (Ang II) contributes to oxidative stress via AT1-mediated activation of NADPH oxidase. Candesartan, an AT1 receptor antagonist, has been shown to be neuroprotective in several models of Parkinson's disease.

Aim: The disease-modifying effect of candesartan was tested in the striatal 6-hydroxydopamine (6-OHDA) rat model. Also, the role of the AT1 receptor in the generation of oxidative stress was evaluated in vivo.

Methods: Treatment with 3 mg/kg (sc.) candesartan started 7 days before lesioning was compared to one where administration was started 24 hours after lesioning and was continued for 11 days. Outcome measures were TH-positive cell counts in the substantia nigra and dopamine content in the striatum. AT1-mediated production of hydroxyl radicals was determined via in vivo microdialysis salicylate trapping in the striatum.

Results: While pretreatment with candesartan was protective, treatment started 24 hours after lesioning was without effect. The Ang II-induced production of hydroxyl radicals in the striatum in vivo was blocked by candesartan perfusion. Furthermore, this Ang II-induced ROS production was NADPH oxidase and protein kinase C dependent as it was blocked in the presence of apocynin and chelerythrine.

Conclusion: The neuroprotective effects of candesartan seem to be limited to an interference with the early events of 6-OHDA-induced cell death since no protection was observed when treatment was initiated after lesioning. We provide evidence that candesartan may influence the amount of ROS produced after 6-OHDA infusion.