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Development of Evaluation Method for Brain Reactive Oxygen Species by Antihypertensive Treatment in Salt-Sensitive Hypertension: Effect of Angiotensin Receptor Blocker or Combination Therapy Using in vivo ESR Method

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Summary

We demonstrated that oxidative stress is involved in the neural mechanisms of hypertension. Recent studies suggest that angiotensin type 1 (AT1) receptor stimulation increases reactive oxygen species (ROS) generation. It is difficult, however, to evaluate oxidative stress in the brain *in vivo*. The aim of this study was to apply the *in vivo* electron spin resonance (ESR)/spin probe technique to measure ROS generation in the brains of stroke-prone spontaneously hypertensive rats (SHRSP) and to examine the effects of anti-hypertensive treatment with the AT1 receptor blocker olmesartan (Olm) on the ROS generation. Two groups of 12-week-old SHRSP were treated with either Olm (10 mg/kg/day) or hydralazine (Hyd, 20 mg/kg/day)/hydrochlorothiazide (HCT, 4.5 mg/kg/day) for 30 days (n = 5 for each). Systolic blood pressure decreased after each treatment (151 ± 8 mm Hg [Olm] and 156 ± 13 mm Hg [Hyd/HCT], NS), although heart rate and urinary norepinephrine excretion increased only in Hyd/HCT-treated rats. A blood-brain barrier-permeable nitroxyl radical, methylcarbonyl-PROXYL (MC-P), was used as the spin probe for the low frequency ESR system. The ESR signal intensities of accumulated MC-P in the brain were measured sequentially and plotted as a function of time for the signal decay. The ESR signal decay rates in the SHRSP brains were significantly increased compared with those in age-matched normotensive Wistar-Kyoto rats (0.121 ± 0.010 /min vs. 0.098 ± 0.011 /min, $P < 0.01$, n = 6 for each). Dimethylthiourea, a potent hydroxyl radical scavenger, or apocynin, an NAD(P)H oxidase inhibitor, attenuated the increased ESR signal decay rate in the SHRSP brains. Olm attenuated the increased signal decay rate (0.120 ± 0.008 /min and 0.102 ± 0.004 /min, $P < 0.01$, before and after treatment), but Hyd/HCT did not. These results suggest that the AT1 blocker Olm has a beyond blood pressure-lowering anti-oxidative effect in the brains of SHRSP as measured using an *in vivo* ESR method.