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Abstracts

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Combinatorial treatment with antihypertensive drugs prevents HELLP syndrome exacerbated by endothelial dysfunction in pregnant hypertensive mice

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HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelets) syndrome is a severe variation of preeclampsia, a common pregnancy disorder including hypertension, proteinuria, and intrauterine growth retardation (IUGR) in late pregnancy, and life threatening to mother and neonate. Current hypotheses propose that preeclampsia and HELLP syndrome is due to the abnormal dynamic state of vasoactive factors. These have gained wide acceptance, but scientific evidence remains less well-established. As the model of preeclampsia, we previously generated a transgenic mouse model that developed pregnancy-associated hypertension (PAH) by mating females expressing human angiotensinogen with males expressing human renin. PAH mice exhibit severe hypertension by the overproduction of angiotensin II, a potent vasopressor, on late pregnancy, which is accompanied by the maternal and fetal disorders including proteinuria, intrauterine growth retardation, and neonatal death. Here, we found the diagnostic features of HELLP syndrome in PAH mice, and revealed the impaired vasodilation with endothelial dysfunction. Although these maternal and fetal abnormalities are partially ameliorated by hydralazine, an antihypertensive authorized drug for preeclampsia and HELLP syndrome, angiotensin II type 1 receptor blocker (ARB) substantially prevents the development of these defects including the neonatal death. We also showed that a simultaneous lower-dose drug treatment of ARB and calcium channel blocker dramatically ameliorated the maternal and neonatal abnormalities in PAH mice. Our findings highlight the combined effect of antihypertensive drugs as a therapeutic target in HELLP syndrome.

KEYWORDS:

HELLP syndrome, preeclampsia, renin-angiotensin system, genetically engineered mouse model, vascular endothelial dysfunction

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Rho-kinase activation contributes to hypertension in rat model

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Our aim was to characterize spontaneously hypertensive stroke prone (SHRSP), and normotensive wistar kyoto (WKY) rat strains, to find possible differences in their blood pressure and cardiac system.

In our experiments, we detected the diameter changes of cannulated muscle arterioles, and the contractile force of the femoral artery. We measured the body, the heartweight, and the blood pressure. The body weight of the SHRSP rats (257 ± 2 g) was smaller than the WKY rats (361 ± 10 g, $p < 0.01$). The heart/body ratio (0.0047), the systolic (210 ± 12 Hgmm) and diastolic (161 ± 8 Hgmm) blood pressure of the SHRSP was significantly higher than in WKY rats (0.0027, 147 ± 9 Hgmm, 115 ± 7 Hgmm). The myogenic tone of the muscle arterioles was similar in the two groups. After pretreatment with Rho-kinase inhibitor fasudil (10 μ M) the myogenic tone decreased more in the SHRSP group ($82.5 \pm 6.2\%$) than in the WKY group ($34.4 \pm 9.8\%$). In the case of the femoral artery, treatment with 10-60mM KCL resulted in higher contractile force in SHRSP (8.96 ± 1.44 mN) than in WKY (6.39 ± 1.09 mN). Pretreatment with fasudil resulted in the normalisation of the higher contractile force in the SHRSP group (decreased to 4.08 ± 1.49 mN), but had no effect on the contractile force of the WKY group (6.79 ± 1.65 mN). By using serotonin we detected similar reaction (contraction for SHRSP: 14.33 ± 1.44 mN, which decreased to 9.25 ± 1.51 mN in the presence of fasudil, contraction for WKY: 8.17 ± 1.81 mN, which was 8.95 ± 1.84 mN after using fasudil).

According to our results, the Rho-kinase system probably plays an important role in the pathogenesis of high blood pressure. Better understanding of the pathogenesis may lead to a more effective drug development.

KEYWORDS:

Hypertension, Rho-kinase, SHRSP