Involvement of Arachidonate Metabolites on the Stroke Onset in Stroke-Prone Spontaneously Hypertensive Rats (SHRSP).

Koji Machii, Korekiyo Wakitani, Tadao Okegawa, and Akiyoshi Kawasaki.
Minase Research Institute, Ono Pharmaceutical Co., Ltd., Osaka-fu 618.

To determine the involvement of arachidonate metabolites on development of severe hypertension and stroke onset in SHRSP, effects of thromboxane A2 (TXA2) synthetase inhibitor (OKY-046 Na), TXA2 receptor antagonist (ONO-8809), prostacyclin (PGI2) analog (OP-2507) and cyclooxygenase inhibitor (indomethacin) were examined.

Male SHRSP were fed with 2% salt-loaded diet from 8 weeks of age. OKY-046 Na (10, 30 and 100mg/kg s.c., b.i.d.), ONO-8809 (10, 100 and 1000ug/kg p.o., b.i.d.), OP-2507 (10 and 100ug/kg s.c., b.i.d.) or indomethacin (2mg/kg s.c.) were administered in the respective groups. Development of stroke was evaluated by abnormal symptoms characterized by paw lifting response, hyperirritability or hemiplegia. Renal vascular changes were inferred from the amount of urinary protein excreted. When the level of urinary protein was over 300mg/dl, proteinuria was considered positive. At the end of the experiment, changes in serum biochemical findings were examined and histological studies of organs were performed.

Two percent salt loading progressively accelerated the development of hypertension. Blood pressure in the control at seventeen weeks of age showed 240mmHg and was significantly higher than that in the intact (normal diet). OKY-046 Na (30, 100mg/kg) delayed the development of hypertension whereas OP-2507, ONO-8809 and indomethacin did not. Eighty percent of control animals exhibited abnormal symptoms during the experimental period. Time course of typical abnormal symptoms was as follows: early phase (piloerection, paw lifting response, hyperirritability), intermediate phase (weight loss, hemiplegia, mydriasis) and late phase (depression, urinary incontinence, coma). Hyperphagia or deformity of the skull for brain edema were seen rarely. Treatment with OKY-046 Na, ONO-8809 or OP-2507 delayed the onset of stroke in a dose-dependent manner, and incidences of stroke with the respective groups were 37.5%, 41.6% and 50.0% (100% for control). Most of the animals with stroke indicated proteinuria. The pattern of the incidence of proteinuria was similar to stroke incidence. Rodent mortality was reduced by the treatment of OKY-046 Na, ONO-8809 and OP-2507. On the other hand, indomethacin showed no significant benefit. Treatment with OKY-046 Na increased values of albumin, reduced values of creatinine and blood urea nitrogen in serum and attenuated the increases in weights of brains, hearts and kidneys as compared to the control significantly. Histological studies of controls revealed vascular lesions such as fibrinoid necrosis of the wall, cellular thickening of the intima and media of the arterioles. Such vascular changes were conspicuous not only in the cerebrovasculature but also in kidneys and hearts. Advanced cerebrovascular lesions were accompanied by spongy changes, infarction, hemorrhage and thrombosis. OKY-046 Na, ONO-8809 and OP-2507 treatments attenuated these lesions in the organs.

These results indicate that pharmacological applications of TXA2/PGI2 are effective in reducing the development of pathological changes in SHRSP, suggesting correlated involvements of TXA2 and PGI2 in the pathophysiology of SHRSP.