42) The Effect of the Long-Term Administration of ONO 3144 upon Cerebral Vessels and Experimental Cerebral Ischemia

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ONO 3144 (2-aminomethyl-4-tert-butyl-6-propionylphenol), a new type of antiinflammatory drug with a property of a free radical scavenger and a thromboxane A₂ synthetase inhibitor, was administered for 21 weeks. Its effects upon the endothelium of cerebral vessels and the acute cerebral ischemia were studied.

Materials and Methods

The male stroke prone spontaneously hypertensive rats (SHRSP) aged 8 weeks were randomly divided to two groups. One group started the administration of ONO 3144 (20mg/kg/day) orally.

The other group was left not administered. After 21 weeks, the endothelial cells of the middle cerebral arteries and cerebral arterioles of both groups were observed by scanning electron microscopy (SEM). Plasma thromboxane B₂ and 6-keto-prostaglandin F_{1α} levels were examined.

Experimental cerebral ischemia was induced by bilateral common carotid ligation. After three hour ischemia, cerebral energy metabolites (ATP, lactate), cerebral water content as an measure of brain edema were examined. Cerebral vessels were examined by SEM after 3 hour of ischemia.

Results

There was no significant difference in the blood pressure, body weight, the survival rate, and the plasma TXB₂ and 6-keto-PGF_{1α} between the two groups.

From the observation of SEM, in the control group, the endothelial cells of middle cerebral arteries were found to show the increase in the number of microvilli and the disruptions of the endothelial linings. Arterioles were found to show the protrusions of endothelial cells and fissures along the marginal folds.

In the ONO 3144 group, they were found to show the flat surface of endothelial cells, and the fissures were not observed.

Cerebral water content after 3 hour ischemia was significantly low in the administered group compared to the control group.

ATP was higher and lactate was lower in the administered group than in the control group. In the SEM observation, ballooning and craters in MCA were observed in both groups after 3 hour ischemia.

Conclusions and Discussions

Long term administration of ONO 3144 were considered to relieve the damage of the endothelial cells of cerebral vessels, and also to ameliorate the brain edema and the energy failure in the acute cerebral ischemia. These results indicate that cerebral vascular lesions in SHRSP develop not only by hypertension but also by free radicals generated from the peroxidation of unsaturated fatty acids.