S04-1 Vascular toxicity as a factor underlying the site-specific neuropathy caused by methylmercury

◯Takashi HIROOKA[1], Toshiyuki KAJI[2]

[1]Org. for Frontier Res., Hokuriku Univ., [2]Fac. of Pharm. Sci., Hokuriku Univ.

Methylmercury is a potent neurotoxin that causes severe neuropathy in the brain of exposed human and animals. In the adult brain, methylmercury-induced damage is observed in specific sites, such as granule cell layer in the cerebellum and the calcarine region of cerebrum. According to Eto's "Edema hypothesis", methylmercury induces cerebral edema in white matter leading to a disturbance of circulation near the deep sulci followed by a local damage of neurons in specific area of the brain. This hypothesis indicates that functional damage of brain microvessel cells is important for understanding the site specificity of damage in neurons of the brain exposed methylmercury. Since permeability of the blood vessels is an important mechanism of edema, we investigated the effects of methylmercury on the VEGF system that regulates the permeability using a culture system of human brain microvascular endothelial cells and pericytes. It was found that methylmercury acts on these two cell types in different manners. Specifically, in the endothelial cells, methylmercury caused a higher expression of both the functional receptor VEGFR2 and its decoy receptor VEGFR1; the expression of PlGF that is a member of the VEGF family, which is selectively bound to VEGFR1, was also increased. In contrast, methylmerury stimulated the expression of VEGF-A in pericytes. These results suggest that the autocrine/paracrine regulation of the VEGF system is a target of the toxicity of methylmercury in the brain microvessels. The increased activity of the VEGF system may be one of the molecular mechanisms of "Edema hypothesis".