An examination whether KCC2, a K^+-Cl^- co-transporter, is efficient as a target to attenuate the neuronal dysfunction that is associated with radiation therapy for brain tumor by using oxytocin.

Kento Igarashi[1,2], Kazuo Tomita[1,2], Koh-Ichi Tanaka[1,2], Yoshikazu Kuwahara[1,3], Nobuyoshi Nishiyama[3], Akihiro Kurimasa[3], Tomoaki Sato[1]

[1]Lab. of applied pharmacology, Grad. Sch. Med. and Dent. Sci., Kagoshima Univ., [2]Dept. Pharm., Pharm., Hyogo Univ. of Health Sciences, [3]Dept. Rad. Biol. and Med., Med., Tohoku Medical and Pharmaceutical Univ.

Background and objective: Radiation therapy is applied to overcome brain tumors. To mitigate adverse effects including cognitive dysfunction, smaller dose of irradiation has been considered advantageous. However, it is not fully understood how the cells that survived after irradiation is damaged. Previously, it was reported that the decrease of KCC2, a K^+-Cl^- co-transporter, and consequent imbalance of responses to gamma-aminobutyric acid (GABA) are predisposition to neuronal disorders after stress (Tsukahara et al., 2015; Furukawa et al., 2017). To elucidate the association of KCC2 with the neuronal dysfunction after irradiation, we performed following experiments.

Methods and Results: We performed immunofluorescence staining and found that peri-membrane KCC2 signals of the primary-cultured neuronal cells declined at 24 h after X-ray (1.5 Gy) irradiation. We further investigated GABA-induced cell death by using trypan blue exclusion test. We found that the death fraction of X-ray-irradiated cells were increased compared with non-irradiated cells. We then performed immunofluorescence staining and found that KCC2 signals were increased in the cells that were administered with oxytocin. In addition, we irradiated γ-ray (1.5 Gy) to the head region of 4-week-old mice. In the novel object recognition tests, the mice that were irradiated with γ-ray showed lower discrimination score at 1 week after irradiation compared with non-irradiated mice. On the other hand, the mice that were irradiated with γ-ray and concomitantly administered with oxytocin showed an increase in discrimination score.

Discussion: It was suggested that KCC2 expression is declined in irradiated cell. Lower KCC2 expression may lead to higher intracellular chloride concentration, which may be a cause of hyperexcitability or neurotoxicity after GABA administration to the X-ray-irradiated cells. It was also suggested that oxytocin is a possible candidate to attenuate the neuronal dysfunction after radiation therapy for brain tumor.