27O-ISMS08 Treatment of Ischemic Stroke by Combination Therapy with Liposomal Neuroprotectants and Tissue Plasminogen Activator

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Ischemic stroke is one of the leading cause of death and severe disability worldwide. Tissue plasminogen activator (t-PA) is the only globally approved therapeutic agent for ischemic stroke treatment, while its use has been quite limited due to the narrow therapeutic time window (TTW) and the risk of cerebral hemorrhage. Also, cerebral ischemia/reperfusion (I/R) injury is often induced after the restoration of blood flow diminished by ischemia, resulting in poor prognosis of the patients. Therefore, development of a new therapeutic agent which can extend the TTW of t-PA and ameliorate cerebral I/R injury has been desired. It has been reported that, after the onset of ischemic stroke, permeability increase in the blood-brain barrier (BBB) is induced around the ischemic region both in experimental animals and human patients. By focusing on this phenomenon, we have demonstrated that 100-nm liposomes can pass through the disintegrated BBB and accumulate in the ischemic region under ischemic state and after reperfusion [1)]. Moreover, our previous studies have shown that delivery of neuroprotectants by use of liposomal drug delivery system (DDS) is useful for the treatment of cerebral I/R injury in ischemic stroke model rats. In addition, our recent study reported that combination treatment with liposomal drugs and t-PA is effective to suppress deleterious actions of t-PA involved in cerebral hemorrhage and to prolong its narrow TTW in a rat model prepared by photochemically induced thrombosis [2)]. Based on these findings, it is suggested that liposomal DDS should be useful for the treatment of ischemic stroke. In this presentation, we will discuss about our findings on the combination therapy with liposomal neuroprotectants and thrombolysis using t-PA.

1) Fukuta T., *et al*. *Eur. J. Pharm. Biopharm.*, 7, 1-7 (2015), 2) Fukuta T., *et al*. *FASEB J.*, 31: 1879-1890 (2017).