GS01-4 **Effects of valproic acid on diabetic retinopathy − From basic research to clinical practice −**

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Pathological retinal angiogenesis causes visual impairment and blindness of ischemic retinal diseases such as diabetic retinopathy (DR). Valproic acid (VPA), a widely used antiepileptic drug, exerts anti-angiogenic effects by inhibiting histone deacetylase (HDAC). We investigated the effects of VPA on 1) pathological retinal angiogenesis in mice, and 2) the onset of DR in patients with diabetes mellitus (DM).

1) Pathological retinal angiogenesis (neovascular tufts) was induced in neonatal mice exposed to 80% oxygen for 3 days, followed by room air. Phosphorylated ribosomal protein S6 (pS6), which indicates high proliferative activity, was detected in the neovascular tufts. VPA and the HDAC inhibitor vorinostat significantly prevented pathological retinal angiogenesis. VPA also decreased the immunoreactivity of pS6 in the neovascular tufts. 2) Since VPA suppressed pathological retinal angiogenesis in mice, we hypothesized that the onset of DR is suppressed in DM patients who are taking VPA. To test the hypothesis, we carried out a survey of medical records. We found that the incidence of DR was 9.3%, which was lower than that reported for DM patients without VPA treatment. In addition, the total prescription days/doses, and average daily prescriptions of VPA in the DR (−) group were significantly higher than those in the DR (+) group. These results suggest VPA may suppress the onset of DR by preventing pathological retinal angiogenesis.