Valproic acid prevents retinal angiogenesis via a proteasome-dependent mechanism in neonatal mice

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Pathological retinal angiogenesis contributes to the development and progression of vision-threatening eye diseases, such as retinopathy of prematurity and diabetic retinopathy. Valproic acid, a widely used antiepileptic drug, exerts anti-angiogenic effects by inhibiting histone deacetylase (HDAC). We previously reported that valproic acid and vorinostat, a HDAC inhibitor, suppress pathologic retinal angiogenesis in mice with oxygen-induced retinopathy. In this study, using neonatal mouse retina, we examined the mechanisms of anti-angiogenic effects of valproic acid and vorinostat. Mice were subcutaneously injected with valproic acid, vorinostat, or vehicle once a day from postnatal day (P) 0 to P3. At P4, the delayed retinal angiogenesis was observed in mice treated with valproic acid or vorinostat. The expression level of vascular endothelial growth factor (VEGF) was reduced 2 or 6 hours after a single injection of valproic acid or vorinostat in P4 mice. Both drugs suppressed the VEGF-mediated activation of mammalian target of rapamycin pathway in proliferating endothelial cells. The proteasome inhibitor MG132 prevented valproic acid- and vorinostat-induced reduction in the VEGF expression level.These results suggest that valproic acid suppresses retinal angiogenesis by decreasing retinal VEGF levels by a proteasome-dependent mechanism.