

The cognitive impairment induced by prolylhydroxylase inhibitors in mice

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Background: In general, hypoxia can suppress neural activities and cause cognitive impairment. Hypoxia inducible factor-1 α (HIF-1 α) is known as a transcription factor expected to play pivotal roles in the response to hypoxia in various tissues. HIF-1 α is hydroxylated by prolylhydroxylase (PHD) in an oxygen-dependent manner, and then it is degraded in ubiquitin system. Preceding studies have revealed that PHD inhibitors increase HIF-1 α and induce hypoxia-like responses. In this study, we investigated the effects of PHD inhibitors on cognitive performance in mice.

Methods: Male 5-weeks-old ddY mice were subjected to novel object recognition test for evaluation of long-term memory performance. Dimethyloxallylglycine (DMOG) and roxadustat, PHD inhibitors, are subcutaneously injected.

Results: Single administration of DMOG or roxadustat 30 min before the learning phase of novel object recognition test significantly lowered discrimination index. The suppressive effect on memory performance of 5 consecutive daily administration of DMOG was similar to that of a single administration.

Conclusion: The present results suggest the possibility that an increase of HIF-1 α causes cognitive impairment. Since PHD inhibitors are candidates for the treatment of anemia, attention should be paid to the side effects on cognitive performance.