Hydroxyurea Induces Fetal Hemoglobin Expression by Activating the cAMP Signaling Pathway by Dual Signaling Mechanisms—New Hypothesis Accounts for Roles of Non-erythroid Cells in Fetal Hemoglobin Induction

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Abstract

Here we show that HU induces HbF expression by activating the cAMP pathway through two independent mechanisms. Although HU increased both cAMP and cGMP levels in CD34+ derived erythroblasts, only the cAMP pathway was found to be activated. However, HU-induced HbF expression was affected by the activities of both adenylate cyclase (AC) and soluble guanylate cyclase (sGC). HU decreased the expression of cGMP-inhibitable phosphodiesterase (PDE) 3B in a sGC-dependent manner, resulting in activation of the cAMP pathway. Second, HU induced the expression of cyclooxygenase-1 (COX-1) and increased the production of prostaglandin E2 (PGE2), which resulted in activation of the cAMP signaling pathway through AC. HU therapy elevated plasma PGE2 levels in sickle cell patients. These results demonstrate that HU induces HbF expression by activating the cAMP pathway via dual signaling mechanisms.

Results

1. Preparation of primary erythroblasts

2. Vasodilator-stimulated phosphoprotein (VASP), a maker of the cAMP and cGMP signaling pathways, is expressed in primary erythroblasts.

3. Signal transduction of cyclic nucleotide-dependent pathways in erythroid cells treated with HU

4. HU downregulates PDE3B expression in a sGC-dependent manner

5. Hydroxyurea activates AC through activation of COX-1 and Prostaglandin E2 (PGE2) production

Conclusions

1) HU induces HbF expression by activating both cAMP and cGMP signaling pathways. 2) HU downregulates PDE3B expression and upregulates COX-1 expression in a time-dependent manner. Our findings demonstrate that HU-induced PDE3B downregulation is an important role of PGE2 in HU-induced HbF expression. 3) It is likely that non-erythroid cells such as leukocytes and monocytes produce a large amount of PGE2. Previous clinical studies suggest that bone marrow reserve plays a role in regulating the response of HbF to HU. The involvement of PGE2 in HU-induced HbF expression may account for the important role of non-erythroid cells in inducing HbF expression.