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Butyrate in the treatment of sickle cell disease and beta-thalassemia

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Abstract

The search for, and discovery of, a physiologic model in which the developmentally regulated switch from fetal to adult globin gene expression could be prevented has resulted in the development of a new class of therapeutic agents, consisting of simple fatty acids, such as butyric acid, for the treatment of the beta-hemoglobinopathies. Butyrate and related drugs stimulate fetal (gamma-) globin gene expression in erythroid cells cultured from patients, and in chicken, ovine, and primate animal models. The butyrates are perhaps the first class of drugs designed to transcriptionally activate specific genes--in this particular case, to reactivate the developmentally silenced fetal globin genes. Phase I-II clinical trials resulting from this basic research have been initiated on a small scale during the past 3 years. Analysis of two butyrate-derived therapeutic agents, one delivered intravenously and one orally, has shown initial efficacy in stimulating fetal hemoglobin expression in 50% to 85% of patients. Correction of the anemia from the beta-hemoglobinopathy has followed induction of fetal globin, and has been adequate to eliminate the need for erythrocyte transfusions in some patients with beta-thalassemia. These compounds have been relatively safe and without generalized cytotoxicity in patients, but drug tolerance develops in some patients after prolonged therapy. Third-generation, small two- to five-carbon butyrate derivatives are in development. The molecular basis for butyrate action is being defined. Binding of putative regulatory proteins to a specific region of the gamma-globin promoter is altered in vivo in patients receiving butyrate therapy. Further analysis of the mode of action may contribute to development of other therapeutic agents designed to regulate gene transcription.

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