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113.SICKLE CELL DISEASE, SICKLE CELL TRAIT AND OTHER HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIAS: BASIC AND TRANSLATIONAL

Mildronate Ameliorates Kidney Function and Reduces Inflammation in SCD Mice

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INTRODUCTION:Sickle cell disease (SCD) is a genetic hemoglobin disorder characterized by hemolytic anemia, vaso-occlusive crisis and inflammation that affects organs such as the kidney, liver, brain, spleen, and heart. SCD is driven by a mutation in the β-globin gene that causes sickling of red blood cells (RBCs). More than 50% of SCD patients are affected by chronic kidney diseases (CKD) and other comorbidities. Vasculopathy is caused by hemolysis-related endothelial dysfunction and inflammation, which collectively contribute to the development of renal disease. Mildronate (also known as Meldonium) is an anti-ischemic and cardio protecting medication approved in Eastern Europe. Mildronate facilitates a switch from fatty acid oxidation to less oxygen-intensive glycolysis that allows less oxygen consumption by peripheral tissues and higher oxygenation of heart. We hypothesized that mildronate administration would reduce tissue hypoxia and decrease inflammation in SCD mice.
METHODS: The study was approved by the Institutional Animal Care and Use Committee at Howard University (IACUC). We employed the Townes SCD mouse model, which mimics SCD complications. SCD and control mice were injected with mildronate (400 mg/kg in saline) intraperitoneally or saline as vehicle control over the course of ten days. Blood and plasma were collected and used for hematological parameters analysis. Cytokines were measured by Bio-plex suspension array in plasma and real-time RT-PCR or ELISA in organs. Protein expression of HO-1, HIF-1α, NFκB and NRF2 was measured by Western blot. The effect of Mildronateon systemic and renal oxidative stress was measured by malondialdehyde (MDA) using ELISA (Abcam).
RESULTS: We observed significant reduction in the cytokine's levels of IFN-γ, IL-1, and TNF-α in plasma of SCD mice after mildronate injection. We also observed reduction in IL-6, IL-10 and IL-17 levels but differences were not statistically significant. There were no significant changes in hematological parameters (Hematocrit, MCV, MCH, CMCH, Erythrocytes, Hemoglobin) after mildronate injection. Also, we did not observe changes in MDA levels in plasma or kidney in SCD mice compared to control mice, both non-injected and mildronate injected. We further evaluated HO-1 and NRF2 protein expression by western blot and observed no significant differences between SCD mice with or without mildronate injection. In H&E staining, cortex glomerular area and medullar congestion area were significantly reduced after mildronate injection. We also observed reduction of proteinuria in SCD mice injected with mildronate.
DISCUSSION: Our examination of the effect of mildronate showed decreases inflammation in the mildronate injected SCD mice evidenced by reduced levels of IFN-γ, IL-1, IL-17, IL-6, IL-10, and TNF-α in circulation. There was a slight decrease in the expression levels of Nrf2 and HO-1 after mildronate injection. HO-1 is crucial for the catabolism of hemoglobin and protects against tissue damage in hemolysis. The HO-1 promoter has binding sites for several transcription factors, including phosphorylated Nrf2. Previous studies from our lab showed increased HIF-1α expression in PBMCs obtained from SCD patients. Here we did not detect significant changes in NFκB-p65 or HIF-1α expression levels. While we expected mildronate to decrease the oxidative stress, we did not observe significant reduction in MDA levels in treated mice compared to control mice.
CONCLUSION: Mildronate improved kidney function in SCD mice by reducing circulatory and renal inflammation. In future, we plan to assess in more details the mildronate's impact on kidney function and inflammation.
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Disclosures No relevant conflicts of interest to declare.

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