Heme Oxygenase Induction
A Possible Factor in Aluminum-Associated Anemia

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ABSTRACT

The effect of repeated parenteral administration of aluminum (Al) was investigated to determine if a relationship exists between the severity of anemia and increase in hepatic heme oxygenase activity. Female Swiss Webster mice were dosed for 11 d with 50 mg Al/kg, as Al lactate, and sodium lactate was given to control mice. On d 12, hematocrit, hemoglobin, blood smears, hepatic heme oxygenase activity, and cytochrome P450 levels were assessed. Significant decreases in hematocrit (39.1 ± 0.7 vs 43.1 ± 0.3% in controls) and hemoglobin (13.1 ± 0.4 vs 14.2 ± 0.2 g/dL in controls) were produced by Al administration. Blood smears from Al-treated mice consistently showed smaller, more irregular red cells. Cytochrome P450 content was significantly decreased (0.443 ± 0.043 vs 0.665 ± 0.055 nmol/mg) whereas hepatic heme oxygenase activity was significantly increased (2.75 ± 0.34 vs 1.66 ± 0.20 nmol/mg/h) in Al-treated animals. The production of mild anemia by parenteral aluminum correlated significantly with the increase in heme oxygenase activity, which, although only 66% greater than in control, preceded a significant loss of cytochrome P450. The increased heme oxygenase activity, with subsequent increased destruction of heme and/or heme proteins is discussed as a possible mechanism for the microcytic, hypochromic anemia associated with Al overload.

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INTRODUCTION

A normochromic, normocytic anemia is commonly present in dialysis patients (1). Administration of human erythropoietin is able to resolve this anemia unless it is complicated by iron, vitamin B₁₂, or folate deficiency (2). In addition a microcytic, hypochromic anemia, which is resistant to iron supplementation, is found in many patients undergoing dialysis for kidney failure, and is associated with Al overload (3–5). Not only do uremic patients fail to excrete Al normally, but Al accumulation poses a particular problem for those on dialysis or total parenteral nutrition, since natural barriers to absorption in the gastrointestinal tract are bypassed (6). Experimentally, the development of microcytic, hypochromic anemia in rats has been reproduced by intraperitoneal administration of Al in normal and uremic rats (7,8).

Several mechanisms have been considered in an effort to understand Al-associated anemia (9). The hypochromic, microcytic nature of the anemia indicates an abnormality in hemoglobin synthesis. Aluminum has been shown to decrease hemoglobin synthesis and cell growth in erythroleukemia cells (10). Several steps in the heme biosynthetic pathway have been considered potential sites of Al interference, including p-aminolevulinic acid dehydratase (ALAD), uroporphyrinogen decarboxylase, and ferrochelatase (9). Although Al-induced anemia is not associated with an iron deficiency, interference with Fe uptake and release has also been considered as a cause of the anemia. Aluminum binding to transferrin has been shown to interfere with the uptake of iron by transferrin, possibly by down-regulating transferrin-receptor expression or interfering with the intracellular release of iron from transferrin (11). Other factors that have been considered to play a role in Al-induced anemia are low erythropoietin production, blood loss caused by transfusion, hyperphosphatemia, and the presence of other toxicants (1,9). To date none of those mechanisms proposed appear to have effects of sufficient magnitude to account for the development of anemia.

Heme oxygenase is the rate-limiting enzyme of heme degradation and a specific isozyme is induced by many metals (12) and agents causing oxidative stress (13). An increase in heme oxygenase would be expected to result in a loss of heme proteins such as cytochrome P₄₅₀ and hemoglobin. The same agents that induce heme oxygenase are also likely to induce another metal-binding stress protein, metallothionein (12). We previously reported that AlCl₃ increased the amount of hepatic metallothionein when given intraperitoneally to rats, and decreased the amount of hepatic cytochrome P₄₅₀ and P₄₅₀-dependent metabolism (14). The objective of this work was to determine if anemia is produced by subchronic Al administration and whether it is related to an increased loss hemoproteins following increased hepatic heme oxygenase activity.