JCI The Journal of Clinical Investigation

In sickle disease, unlike wine, dry is not good.

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J Clin Invest. 1993;92(1):1-1. https://doi.org/10.1172/JCI116536.

Editorial

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Despite seemingly complete information concerning the amino acid substitution that leads to sickle disease and the underlying and associated molecular biologic changes, the pathophysiology of sickle disease remains elusive. Proceeding from a substitution of glutamic acid for valine (Glu → Val) at the 6th position of the β globin polypeptide, in the homozygous state there is a surprisingly heterogenous disorder characterized by hemolytic anemia, acute and chronic vaso-oclusive episodes, and organ damage presumably caused by the vaso-oclusion. This amino acid change allows the deoxysickle hemoglobin to polymerize and this biophysical change lies at the heart of the pathogenesis (1). The polymerization of sickle Hb is an exponential function of the concentration of HbS in affected red cells. Thus the higher the mean corpuscular hemoglobin concentration (MCHC) in sickle disease, the shorter will be the delay time to gelation. Given what we know clinically about the autoamplifying events in sickle disease it is consistent to find that the polymerization of HbS somehow leads to loss of ions and water resulting in dehydration, increased red cell density, and MCHC values of 45–50 and then more polymerization. The role of MCHC is so powerful in sickle disease that it has been proposed that prevention of dehydration could provide clinical benefit (2). If that goal is to be achieved an understanding of how sickle hemoglobin and sickling cause dehydration becomes a prerequisite. A complete review of ion and water movement in red blood cells (RBC) is beyond the scope of this editorial but there are several pathways that seem to account for much of the problem.

Upon deoxygenation induced sickling the RBC membrane ion barrier is broached (3). Passively, Na^+ rushes in and K^+ rushes out about equally, but the Na^+K^+ ATPase pump has a stoichiometry of $3Na^+$ out to $2K^+$ in which would tend to produce a net cation loss. Probably of greater importance is the fact that Ca^{+2} also enters the red cell driven by a 3–4 order of magnitude concentration gradient between plasma and RBC cytosol. Much of this Ca^{+2} is protein bound or trapped in vesicles, but some of it seems to be able to activate the "Gardos channel" named after the Hungarian hematologist who first discovered this Ca^{+2}-activated K^+ channel. Once activated by Ca^{+2} entering during deoxygenation-induced sickling, the channel can mediate loss of K^+ and water even after the RBC is reoxygenated and unsickled.

There are at least two other transport systems that could serve to deplete sickle RBC of ions and water even under fully oxygenated conditions. The K-Cl cotransport system (4), present normally in reticulocytes and very young RBC, mediates coordinate efflux of K^+ and Cl^-. It is volume and pH dependent so that intracellular swelling or hypotonicity or acid pH triggers its activation. Presumably it functions normally in RBC remodeling as the reticulocyte reduces its volume to become a mature discocyte. Partly because of the relative RBC youth in sickle disease and perhaps mediated by the binding to the membrane of the unusual hemoglobin in sickle disease or HbC syndromes the K-Cl co-transporter stays active contributing to K^+ and water loss. Additionally there is a deformation induced cation leak in sickle RBC that seems to be dependent on the presence of increased amounts of lipid hydroperoxides in the membrane (5). And while K^+ efflux and Na^+ influx are balanced in this deformation dependent leak the Na^+K^+ ATPase with its 3:2 stoichiometry would act to dehydrate the cell.

Recent studies have shown that, in vivo, the important pathways leading to sickle RBC dehydration are the K-Cl co-transporter and the Gardos channel (6). Brugnara and colleagues (2) needed to find an agent that could easily and safely be chronically administered and that would block either the K-Cl co-transporter or the Gardos channel. These practicalities lead to the observation that clotrimazole blocks the dehydration caused by activation of the Gardos channel. It now remains to be determined if treatment of sickle cell diseases with clotrimazole prevents RBC dehydration and if that change in turn produces a clinical benefit.

In this context it is potentially useful to consider the role of other recently tested agents for the treatment of sickle disease. Hydroxyurea increases the production of fetal hemoglobin which is known to interfere with the polymerization of sickle hemoglobin (7). It also and, perhaps independently (8), results in the formation of macrocytes accompanied by a decrease in RBC density and both of these effects would reduce the tendency to polymerization. The addition of erythropoietin to hydroxyurea seems to enhance the production of fetal hemoglobin, may further decrease the proportion of dense cells, and has a hydroxyurea sparing effect. Treatment with butyrate, on the other hand, only produces an impressive increase in HbF (9). As proposed by Brugnara and colleagues (2) it is interesting to contemplate a therapeutic approach wherein administration of a butyrate analogue (or hydroxyurea) to increase HbF production would be combined with an agent like clotrimazole to prevent cellular dehydration. Such a 1–2 punch could conceivably really block polymerization of sickle hemoglobin with an anticipated clinical benefit.

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J. Clin. Invest.

0021-9738/93/07/0001/01 $2.00
Volume 92, July 1993, 1