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Roles of nutrients and hormones in erythropoiesis. Negative impact of Cationic Amphiphilic Drugs (CADs) such as tricyclic antidepressants on erythropoiesis

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The progressive differentiation of short-term hematopoietic stem cells in the bone marrow leads, among others things, to the formation of an erythroid lineage from which terminally differentiated hemoglobin-containing human erythrocytes (hRBCs) arise. This dynamic production process of erythrocytes, referred to as erythropoiesis (1), requires an adequate supply of folates, vitamin B12 (cobalamin) and ferrous iron (Fe2+). Deficiency in one or more of these substances results in nutrition-related anemia. Tricyclic antidepressants (TCAs) influence norepinephrine (NE) and serotonin (SER) transporters (2). Desipramine, a representative of TCAs, has two primary targets. On one hand, it preferentially interacts with the NE-transporter and increases NE synaptic transmission by inhibiting NE reuptake, thereby relieving depressive symptoms (3). On the other hand, desipramine has a direct inhibitory effect on lysosomal acid ceramidase and acid sphingomyelinase. Both acid ceramidase and acid sphingomyelinase are aberrantly over-expressed and highly active in patients with dysregulated sphingolipid metabolism. Under acidic conditions, e.g., in lysosomes, endosomes, or in the cytoplasm of glycolytically active cells, TCAs act as cationic amphiphilic drugs (CADs) (TCAs + H+ → CADs), their reactions resembling the formation of ammonium from ammonia and a proton ($NH_3 + H^+ \rightarrow NH_4^+$). The secondary amine and basic lipophilic drug desipramine follows the same principle: it acts as a proton (H+-ion) acceptor, depleting the free proton and thus increasing the intracellular pH. Elojeimy et al. (2006) showed that in cancer cell lines, desipramine, even at a relatively low dose of 5 μM, neutralizes lysosomal pH (4). By the same principle, desipramine and other CADs like imipramine, amitriptyline, chlorpromazine, and chloroquine would be able to neutralize the luminal acidification of endosomes in glycolytically active erythroid precursors. Consequently, H+-coupled Fe2+ transport into the cytosol of these cells, and thus the proper heme biosynthesis and heme-dependent erythropoiesis, might be severely affected (5).

Biography

Mehrdad Ghashghaeinia studied biology in Stuttgart (Germany) with the following specializations: Genetics, Immunology and Biochemistry. Currently he works as principal investigator at the Department of Vegetative und Clinical Physiology in Tübingen. His main interests includes: human erythrocytes (hRBCs), cancer, transcription factors (NFkB); redox & NO systems and signaling pathways, e.g. apoptosis. In addition, he has the following functions: Vice President of the Department, lecturer and study representative, seminars leader as well as examiner in physiology for prospective students of human and dental medicine.