Dysregulation of plasma amino acid levels in HIV-infection and cancer and its relevance for the immune system

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Summary. T cells have a weak membrane transport activity for cystine but strong transport activity for cysteine. Even moderate variations of the cysteine concentration affect T cell functions in spite of the high concentration of cystine in cultures with physiological amino acid concentrations. The IL-2 dependent DNA synthesis and the activation of cytotoxic T cells are positively regulated by cysteine, while the activity of the transcription factor NFκB and the production of IL-2 are stimulated by active oxygen species and inhibited by cysteine or GSH. Macrophages, in contrast to T cells, take up more cystine than they need and release the excess after intracellular reduction as cysteine into the extracellular space. This “cysteine pumping activity” of macrophages raises intracellular GSH levels and DNA synthesis of T cells in the vicinity. The difference between the cystine transport activities of T cells and macrophages, therefore, enables T cells to switch between prooxidant and antioxidant states. The “cysteine pump” favors selectively the antigen-specific T cells that are about to be stimulated by antigen-presenting macrophages. The capacity of macrophages to take up cystine and to release cysteine is inhibited, however, by elevated extracellular glutamate concentrations. Elevated plasma glutamate levels have been found in several pathological conditions including cancer and HIV-infection. In HIV-infected patients, the hyperglutamataemia is aggravated by hypocystinaemia and hypocysteinaemia. Our studies, therefore, suggest that the cysteine supply is impaired in several pathological conditions with immunodeficiencies including AIDS. N-acetyl-cysteine (NAC) is a safe and well established drug that may be considered for the treatment of patients with HIV-infection.

Keywords: Amino acids – HIV-induced cysteine deficiency – HIV-induced glutathione deficiency – Cysteine, role in AIDS – Glutamate, role in cancer and AIDS – N-Acetyl-cysteine as a treatment of HIV-infection
Introduction

HIV-infected patients at all stages of the disease were found to have, on the average, markedly elevated plasma glutamate and decreased plasma cystine and cysteine concentrations (Dröge et al., 1988b; Eck et al., 1989b) and decreased intracellular glutathione (GSH) levels (Eck et al., 1989b). Decreased GSH levels have been found subsequently also by other laboratories (Buhl et al., 1989; Roederer et al., 1991). Elevated glutamate levels are expected to aggravate the cysteine deficiency in HIV-infected persons, since glutamate inhibits competitively the membrane transport of cystine (Watanabe and Bannai, 1987; Bannai, 1986; Makowske and Christensen, 1982; Takada and Bannai, 1984; Hishinuma et al., 1986). Even a moderate increase of extracellular glutamate levels was found to cause a substantial decrease of intracellular cysteine levels (Gmünder et al., 1991b; Eck and Dröge, 1989a) and to inhibit lymphocyte functions (Dröge et al., 1988b; Dröge et al., 1988a) in cultures with otherwise approximately physiological amino acid concentrations.

The conclusion that the dysregulation of plasma amino acid levels is indeed the consequence of retroviral infection was supported also by the observation that plasma glutamate levels increase and cysteine levels start to decrease within 1 week after inoculation of SIVmac into rhesus macaques (Eck et al., 1991). In this review we describe the available evidence showing that cysteine has both positive and negative regulatory effects on the immune system and that macrophages play a key role in regulating the supply of cysteine to the responding T cells.

The limiting baseline supply of cysteine in T cells

The weak membrane transport activity for cystine in T cells is the key element of a mechanism that ensures a limited baseline supply of cysteine to T cells and that allows T cells to switch between prooxidant states and antioxidant states. The major cysteine derivative in the blood plasma is the disulfide cystine (120–160 μM 1/2 cystine), while the concentration of reduced cysteine (10–20 μM) is extremely low in comparison with other amino acids. Studies with a large series of human and murine T cell clones and T cell tumors and ex vivo derived lymphocyte preparations showed, however, that T cells and T cell tumors have generally a strong transport activity for cysteine and only a weak transport activity for the amino acids cystine and glutamate (Gmünder et al., 1991a) which share the same transport system (Watanabe and Bannai 1987; Bannai, 1986; Makowske and Christensen, 1982; Takada and Bannai, 1984; Hishinuma et al., 1986). These observations confirmed and extended earlier studies with unfractionated murine spleen cell populations (Ishii et al., 1987).

Evidence that the cysteine supply is indeed a limiting factor that determines the magnitude of T cell functions is based mainly on laboratory experiments in vitro. It has been known for almost two decades that both T cell and B cell responses can be strongly augmented in vitro by high concentrations of cystine, cysteine or other sulfhydryl compounds such as 2-mercaptoethanol (2-ME). However, culture systems with approximately physiological amino acid concentrations have been studied only recently (Eck et al., 1989b; Gmünder et al., 1990a).