NITRIC OXIDE OVERPRODUCTION IN HEAT STROKE

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Background-Heat stroke is a major killer worldwide. The reaction of the nitricergic system to ischemic/hypoxia is always associated with an increase in nitric oxide (NO•) production leading to increased nitrosative stress. The detailed mechanisms of the role of NO in heatstroke pathophysiology have not been studied. Since cytokine profile has a bearing on the balance of inflammatory and repair mechanisms, the regulation of constitutive NOS (eNOS), inducible nitric oxide synthase (iNOS) and arginase were investigated at various times after heatstroke. The current work investigates the role of NO and other associated inflammatory pathways in heatstroke, its regulation by the administration of L-arginine (LR), the endogenous substrate for NO production, at the correct therapeutic window, in a murine model. Procedure-We subjected the mice to acute heat stress by exposing them to whole body hyperthermia (WBH) treatment and used it as a model to study heat stroke and the host inflammatory responses were monitored. LR at different times was administered to see the alteration of the host inflammatory pathways leading to rescue of mice from lethality induced by heat stroke. Results-Present studies demonstrated for the first time that LR administration 2 h after the LD50 dose of WBH protected all the mice from death. The levels of iNOS in the liver, nitrite and inflammatory cytokines like interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) in the serum, increased in WBH treated mice. The activation of iNOS leads to accumulation of nitrite, upregulation of p53, activation of caspases and DNA fragmentation. The levels of above markers of heat stress significantly decreased and the levels of Th2 cytokines and arginase significantly increased in LR treated mice. LR administration increased the levels of Th2 cytokines and arginase. The activity of eNOS was not changed by the administration of LR. Conclusions-The results demonstrate for the first time that the modulation of heat stress by LR administration is associated with a shift in the LR metabolism towards arginase with a concomitant decrease in the expression of iNOS, without compromising the constitutive NOS expression. The results also indicated that the up regulation of Th2 cytokines and arginase as well as the down regulation of iNOS, by the administration of LR is central to the rescue of the mice from heatstroke-induced death. The results indicated that the metabolic pathways of LR decide its beneficial or deleterious effect in modifying heatstroke-induced death.