Inhibition of neuronal nitric oxide synthase causes attenuation of cerebrovascular dysfunction in experimental heatstroke

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摘要

Abstract

The present study was performed to assess the prophylactic effect of 7-nitroindazole (7-NI), an inhibitor of neuronal nitric oxide synthase (nNOS), in an animal model of heatstroke. Anesthetized rats, immediately before the start of heat stress, were divided into two major groups and given the following: vehicle solution (1 mL per kg body weight) or 7-NI (5-20mg/mL per kg body weight) intraperitoneally. They were exposed to ambient temperature of 43 degrees C to induce heatstroke. Another group of rats were exposed to room temperature (24 degrees C) and used as normothermic controls. Their physiologic and biochemical parameters were continuously monitored. When the vehicle-pretreated rats underwent heat stress, their survival time values were found to be 21-25 min. Pretreatment with intraperitoneal doses of 7-NI significantly improved survival during heatstroke (55-164 min). As compared to those of normothermic controls, all vehicle-pretreated heatstroke animals displayed higher levels of core temperature, intracranial pressure, nitric oxide metabolite (NO(2)(-)), glutamate, glycerol, lactate/pyruvate ratio, neuronal damage score and nNOS expression in the hypothalamus, and tumor necrosis factor-alpha (TNF-alpha) in the serum. In contrast, all vehicle-pretreated heatstroke animals had lower levels of mean arterial pressure, cerebral perfusion pressure, cerebral blood flow, and brain PO(2). Administration of 7-NI before the start of heat exposure significantly reduced the hyperthermia, intracranial hypertension, nNOS-dependent NO(2)(-), glutamate, glycerol, lactate/pyruvate ratio, and neuronal damage score in the hypothalamus, as well as overproduction of TNF-alpha in the serum that occurred during heatstroke. The data show that reduction of nNOS-dependent NO(2)(-) with 7-NI causes attenuation of cerebrovascular dysfunction, hyperthermia, and TNF-alpha overproduction during heatstroke in the rat.