NITRIC OXIDE IS AN ANTIPYRETIC MOLECULE IN THE VENTROMEDIAL PREOPTIC REGION OF THE RAT BRAIN

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We tested the hypothesis that nitric oxide (NO) acts in the ventromedial preoptic (VMPO) region modulating fever. To this end, body core temperature (Tc) of awake, freely moving rats was monitored by biotelemetry before and after pharmacological modulation of the NO pathway. The animals were equipped with a guide cannula for intra-VMPO microinjections, which was implanted under tribromoethanol (250 mg/kg, ip) anesthesia. Nitrite/Nitrate and cGMP levels in the AV3V region (obtained from decapitated rats), where the VMPO is located, were also determined. Intra-VMPO microinjection of the nonselective NOS inhibitor L-NMMA (12.5 µg) did not affect basal Tc, but it anticipated the onset of LPS fever, indicating that NO plays an antipyretic role in the VMPO. In agreement, intra-VMPO microinjection of the NO donnor sodium nitroprusside (5 µg) reduced Tc. The antipyretic effect of NO is likely to be mediated by activation of soluble guanylate cyclase and consequent rise in cGMP levels since: 1. NO is known to activate soluble guanylate cyclase; 2. intra-VMPO microinjection of the cGMP analogue 8-Br-cGMP reduced Tc similarly to the NO donnor; and 3. the changes in AV3V levels of Nitrite/Nitrate and cGMP were similar in the course of fever. Surprisingly, we observed that Nitrite/Nitrate and cGMP levels decreased in the AV3V after, but not before, the onset of LPS fever, showing that the activity of the NO-cGMP pathway is reduced in the AV3V after i.p. LPS, a mechanism which could contribute to the genesis and maintenance of fever. Therefore, we suggest that the latency for the onset of fever is determined not only by the time that peripherally generated pyrogens signal the brain, as usually thought, but also seems to be under the control of antipyretic pathways. It was also observed that the efficacy of 8-Br-cGMP to reduce Tc in the VMPO is increased after LPS. This response could explain why intra-VMPO L-NMMA anticipated the onset of fever, even though the activity of the NO pathway before the onset of fever was similar to that of euthermic animals. In summary, these data support an antipyretic role of the NO-cGMP pathway in the VMPO, inhibition of which seems to contribute for the genesis of fever.

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