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Dual molecular regulations of nitric oxide at the peripheral and central levels in experimental African sleeping sickness

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The two-stage trypanosomiasis exists in rats infected with *Trypanosoma brucei brucei*, the neurological phase appearing after 9 to 12 days of infection. NO was determined in rats before and after infection (15 and 21 days) using a specific voltammetric sensor in the central nervous system (CNS) and peripheral (blood) compartments. Opposite changes were observed in the two compartments: a decrease in the periphery, an increase in the CNS (13 days after infection). This duality was analyzed in both healthy and infected Wistar rats using a molecular approach of the metabolic pathways of L-arginine, as it is the substrate of NOS, arginase and protein synthesis. In the peripheral compartment of infected animals, the decrease in inducible iNOS activity is counterbalanced by the rise in arginase activity resulting in an overproduction of related aminoacids (arginine, proline, glutamine, glutamate). Contrarily in the CNS, iNOS activity increased while that of arginase did not vary (no variation in related aminoacid concentrations). Concomitantly, there was an increased activity of dimethylarginine dimethyl aminohydrolase (DDAH), a regulatory enzyme metabolizing asymmetric dimethylarginine (ADMA), an end product of proteolysis inhibiting iNOS activity. In conclusion, the duality of NO behavior in the CNS and periphery is backed by different molecular regulations. In the peripheral compartment of rats, mice and humans (a decrease in blood NO was also observed in patients), the reduced NO production reflects the strategy deployed by the trypanosome to impair the immune processes The increased brain NO certainly accounts for blood-brain barrier and CNS pathophysiological alterations.