Editorial

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Since it has been demonstrated that the constellation of behavioral changes that are displayed by individuals who are afflicted with infectious or inflammatory diseases is due to the brain action of proinflammatory cytokines, many studies have addressed the question of the molecular mechanisms that regulate these effects [1]. Proinflammatory cytokines induce the expression of a vast number of genes in their cell targets, including the inducible forms of cyclooxygenase and of NO synthase. In line with the therapeutic efficacy of nonsteroidal anti-inflammatory drugs on fever and associated symptoms, many effects of cytokines on their cell targets, including sickness behavior, have been found to be mediated by the production of prostaglandins, at least at the periphery [2]. However, the role of prostaglandins in the brain is not yet clear even if there is much evidence for the induction of COX-2 in endothelial cells of brain capillaries in response to peripherally produced cytokines [3]. Since proinflammatory cytokines also induce the expression of the inducible form of NO synthase, it was logical to look for a possible role of peripheral and central NO in cytokine-induced sickness behavior. This gaseous molecule is well known to play an important regulatory modulatory role in a variety of inflammatory conditions. NO synthase actually exists in three isoforms: a constitutively expressed neuronal NO synthase (NOS1 or nNOS), a constitutively expressed endothelial NOS (NOS3 or eNOS), and an inducible isoform (NOS2 or iNOS) that is responsible for a high output of NO during inflammation.

Neuroanatomical studies show that in rats injected with the cytokine inducer lipopolysaccharide (LPS), the propagation of IL-1 β from a circumventricular organ,

such as the area postrema, to a neural structure embedded in the brain parenchyma such as the nucleus tractus solitarius, is accompanied by the expression of iNOS at the interface between the area postrema and the nucleus tractus solitarius [4]. These findings have been interpreted to suggest that NO might allow the passage of the blood-brain barrier by cytokines, with the freely diffusing NO being responsible for the synthesis of cytokines on the brain side of the blood-brain barrier. However, the data that have been obtained in in vitro experiments do not support this interpretation since they show that exogenous or endogenous NO attenuates the expression of proinflammatory cytokines [5, 6]. The results of in vivo studies are in accordance with the in vitro data since they show that in contrast to the initial expectations of pharmacologists, the inhibition of NO synthase exacerbates endotoxemia and potentiates cytokine-induced sickness behavior. In the very first attempt to assess the role of endogenous NO in the behavioral effects of IL-1 β , Bluthé et al. [7] at the University of Bordeaux 2 used the supposedly selective inhibitor of neuronal NOS, N^G-nitro-L-arginine methyl ester (L-NAME). This treatment administered at the same time as IL-1 β potentiated sickness behavior. The effects of L-NAME were inhibited by L-arginine but not by D-arginine. In the same manner, Rivier [8] at the Salk Institute demonstrated that L-NAME augments the ACTH response to blood-borne cytokines. At that time, it was already apparent that, like any other so-called specific inhibitor, L-NAME was much less selective than previously thought since it actually inhibited all three isoforms of NO synthase.

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In an attempt to reexamine the role of NO in cytokine-induced sickness behavior, Connor et al. [9] decided to use another nonselective inhibitor, N^G-nitro-*L*-arginine (L-NA) and to measure plasma levels of cytokines as well as sickness behavior in rats treated with the cytokine inducer LPS. They basically replicated the findings of Bluthé et al. in mice, by showing that L-NA increased the severity of LPS-induced sickness behavior, but they added to this the observation that L-NA also increased the plasma levels of TNF α , without significantly altering the levels of IL-1 β and IL-6. These last findings are important since they confirm that NO is likely to be involved in a feedback downregulatory loop controlling the synthesis of TNF α by monocytes and macrophages. They went one step further to show that inhibition of the synthesis of

TNF α by pentoxifylline abrogated the exacerbating effects of L-NA on LPS-induced sickness behavior. They also clarified the role of the different isoforms of NOS in these effects, by trying to mimic the effects of L-NA with a specific neuronal NOS inhibitor, 7-nitroindazole, and a specific inhibitor of the inducible NO synthase, aminoguanidine. Since none of these inhibitors had any effect, they concluded that the endothelial isoform of NOS that mediates the constitutive synthesis of NO is responsible for the tonic inhibitory control of TNF α production. These findings agree with the results of neuroanatomical studies showing that NO produced by the constitutive endothelial form of NO synthase inhibits TNF α -induced NF- κ B activity and COX-2 transcription in the endothelium of cerebral capillaries [10].

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