Low Nitric Oxide and High C-Reactive Protein in Depression: Not a Paradox!

To the Editor: Cepeda et al[1] reported lower levels of (fractional exhaled) nitric oxide (NO) and higher levels of C-reactive protein (CRP) in 1,325 major depressive disorder (MDD) patients in comparison with 12,951 nondepressed subjects. The authors of this remarkable study considered their finding "paradoxical" because both CRP and NO are markers of chronic low-grade inflammation associated with MDD. However, their very important finding might be expected according to the interferon-γ (IFNG)-inducible kynurenines/pteridines inflammation cascade hypothesis.[2] Inflammatory factors such as IFNG, a key proinflammatory cytokine, activate indoleamine-2,3-dioxygenase 1, a first and rate-limiting enzyme of tryptophan-kynurenine metabolism, catalyzing formation of kynurenine from tryptophan. Concurrently, IFNG activates guanosine triphosphate (GTP) cyclohydrolase 1 (GTPCH), a first and rate-limiting enzyme of pteridine metabolism, catalyzing formation of 7,8-dihydroneopterin (BH_2) from GTP (Figure 1).

In humans, IFNG-induced stimulation of GTPCH does not result in correspondent up-regulation of pyruvoyl tetrahydropterin synthase (PTPS), catalyzing BH_2 conversion into tetrahydrobiopterin (BH_4). Hence, PTPS becomes the rate-limiting enzyme with consequent accumulation of BH_2 and its stable metabolite, neopterin.[3] Therefore, the enhanced production of neopterin occurs at the expense of BH_4 formation.[4] Downstream kynurenine metabolites are able to activate NOS, thus increasing demand for BH_4.[5,6] Up-regulation of nitric oxide synthase (NOS) activity (induced by kynurenine downstream metabolites) and decreased formation of the NOS mandatory cofactor, BH_4, result in uncoupling of NOS and shifting of arginine metabolism from formation of NO to production of reactive oxygen species (eg, superoxide anion and hydrogen peroxide).[7,8]

Although systemic inflammation is, by and large, associated with elevated production of both CRP and neopterin, it should be considered that neopterin and kynurenine are produced by monocyte-derived macrophages, dendritic cells, and astrocytes, while CRP is produced by liver.[9] Up-regulation of neopterin formation is, therefore, more specific than CRP as a marker of inflammation (eg, IFNG)-induced activation of tryptophan-kynurenine metabolism. Increased formation of kynurenines from tryptophan at the expense of serotonin biosynthesis[10] is one of the major factors contributing to mechanisms of depression in predisposed individuals.[11]

Dr Cepeda was shown this letter and declined to reply.

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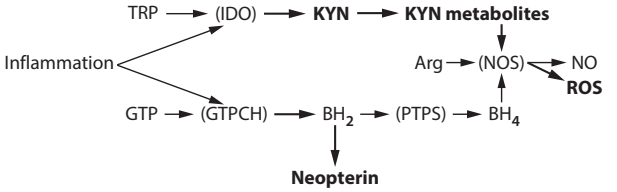
Figure 1. Inflammation-Induced Down-Regulation of Nitric Oxide Formation



Abbreviations: Arg = arginine, BH_2 = 7,8-dihydroneopterin, BH_4 = tetrahydrobiopterin, GTP = guanosine triphosphate, GTPCH = GTP cyclohydrolase 1, IDO = indoleamine-2,3-dioxygenase 1, KYN = kynurenine, NO = nitric oxide, NOS = nitric oxide synthase, PTPS = pyruvoyl tetrahydropterin synthase, ROS = superoxide anion and hydrogen peroxide, TRP = tryptophan.

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