

7th Global Experts Meeting on

NEUROPHARMACOLOGY

July 31-August 02, 2017 | Milan, Italy

The molecular basis of the neurotrophic action of vitamin B₁₂ (Cobalamin)

Giuseppe Scalabrino
University of Milan, Italy

Our experimental and clinical studies have highlighted the non-coenzyme functions of cobalamin (Cbl, vitamin B₁₂). Cytokine and growth factor (GF) imbalance in the central nervous system (CNS) of Cbl-deficient (Cbl-D) rats is a key point in the pathogenesis of Cbl-D neuropathy. The increased molecules are tumour necrosis factor (TNF)- α , nerve GF and the soluble (s) CD40:sCD40Ligand dyad; the decreased molecules are epidermal GF (EGF) and interleukin-6. The *in vivo* administration of the lacking myelinotrophic molecules or agents antagonizing the excess myelintoxic agent is as effective as Cbl in repairing or preventing Cbl-deficiency-induced CNS myelin lesions. Cbl deficiency morphologically affects also glial cells, which normally synthesize and release various cytokines and GFs. Therefore, Cbl deficiency triggers the rearrangements of glia gene expression, eventually leading to a changed pattern of cytokine and GF production. Such an opposite imbalance in TNF- α and EGF similar to that observed in CNS of Cbl-D rats has been found in the sera of adult patients with pernicious anaemia (but not in patients with iron-deficient anaemia) and it was rectified by Cbl therapy. This imbalance has also been found in the cerebrospinal fluid (CSF) of adult patients with Cbl-D neuropathy. Given that TNF- α and EGF regulate the expression of normal prions (PrPcs) and PrPcs play a crucial role in myelin maintenance, we investigated whether CNS PrPc levels are indirectly regulated by Cbl. PrPc levels had increased by the time Cbl-D-induced myelin lesions appeared. This increase was mediated by excess TNF- α and prevented by EGF. Cbl deficiency greatly reduced CNS PrPc-mRNA levels, which were subsequently increased by Cbl and EGF. Similar increases in PrPc levels also occur in the serum and CSF of adult Cbl-D patients, and the serum increase has been corrected by Cbl therapy. Therefore, Cbl may regulate the PrPc levels in the serum and CSF in humans.

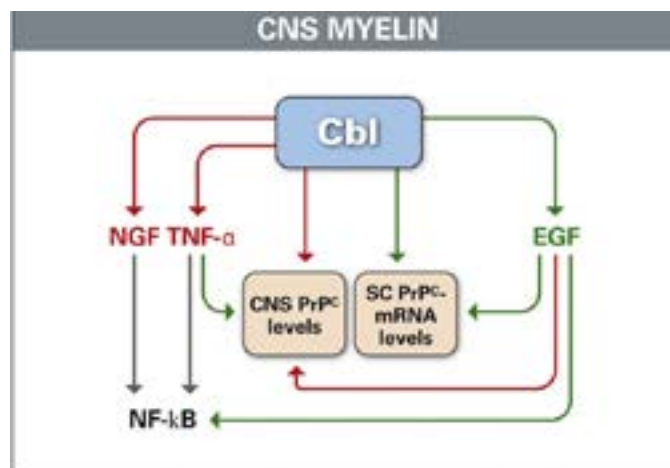


Figure 1: Cbl as a fulcrum between physiologically myelinotrophic (green) and potential myelinodamaging agents (red) in rat CNS. This is highlighted by the Cbl-mediated stimulation of EGF, the Cbl- and EGF-mediated stimulation of PrPc synthesis (green arrows), and the reduction of TNF- α and NGF levels (red arrows), eventually leading to a low NF- κ B level.

Biography

Giuseppe Scalabrino studied at the School of Medicine of the University of Milan and received his MD degree. He has held a number of academic positions in the Faculty of Medicine of the University of Milan. He was an Associate Professor of General Pathology between 1971 and 1985; full Professor of General Pathology from 1986 till 2014. He has been Invited Speaker in various conferences, mainly dealing with the role of polyamines in oncology and subsequently with the cobalamin (vitamin B₁₂) neurotrophism. Among his numerous honours, he has also received the International Award "Roentgen" from Italian Accademia dei Lincei in Rome for Oncological Research in 1983. He is the author of more than 100 scientific papers and reviewer of numerous international journals. His studies of cobalamin neurotrophism have been mentioned and reviewed in 12 American textbooks of Neurology, Biochemistry, Hematology and Vitaminology.

giuseppe.scalabrino@unimi.it