Enteric glia regulates HIV-Tat-induced diarrhea and cognitive dysfunction through gut-brain axis connection

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Diarrhea is the most common enteric manifestation of human immunodeficiency virus (HIV) infection, representing one of the greatest cause of morbidity and mortality in patients with AIDS (Weber, 1999). Nevertheless, the late development of neurological complications related to HIV infection have an extremely negative impact on the therapeutic management of the AIDS patient, and they too, like the secretory diarrhea virus, significantly poorer quality of life of the patient (Biswal, 2014). Individuals who develop neuroAIDS also show a delayed progressive motor function and loss of dexterity and coordination. Therefore, the development of neuroAIDS can be fatal, representing a socio-therapeutic issue of extreme importance. This research project aims to study in an animal model, the possible link between diarrhea and onset of neuroAIDS as two pathological events. It will scan, also, the possible role played by 'axis gut-brain triggered by immunological stimulation at the level of enteric nervous system (ENS) operated by the HIV-1 Tat protein. Here we demonstrated that 7 days following HIV-1 Tat enema, a secretory diarrhea in rats was induced. A marked increase of enteric glia (EGC) sustained neuro-inflammatory response was evoked, with consequent NF-kB, iNOS, TLR-4 and S100B protein increased expression in cell homogenates. A significant increase of S100B/iNOS co-expression was observed by immunofluorescence analysis in submucosal plexi. HIV-1 Tat induced diarrhea was inhibited by lidocaine topic application in single dose and this was accompanied to a marked EGC neuroinflammatory response inhibition. At 12-14 and 21 days following acute phase of HIV-1 Tat induced diarrhea, a late onset of neuropathological features was observed in rats, characterized by increasing expression of GFAP, iNOS and S100B expression respectively in thoracic, cervical spinal cord and frontal cortex was observed in comparison with vehicle group, as signs of 'ascending' gliosis from gut to the brain. As consequence of this, a significant deterioration of cognitive performance was observed, in HIV-1 Tat diarrhea group versus vehicle. Further experiments demonstrated that gut brain axis induction by HIV-1 Tat enema, was under connexin-43/S100B control and suppression of ENS activity with lidocaine administration was capable to significantly attenuate it. The valence of the experimental data obtained allow, therefore, to identify a possible new pathway EGC-mediated at the base of an interconnection between neuropathological processes viral intestinal and central. Looking ahead, the data obtained from this research project will clarify whether and how the EGC may be a new therapeutic target intervention in the improvement of the clinical / symptoms of diarrhea and neuroAIDS. This project therefore aims to expand the field of knowledge (albeit currently in preclinical key) concerning 'etiology of clinical complications that play a major role in the quality of life of patients with AIDS.

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