ENTERIC GLIA ACTIVATION BY HIV-1TAT-INDUCED DIARRHEA DRIVES A GLIAL INFLAMMATORY REACTION TO THE CENTRAL NERVOUS SYSTEM ASSOCIATED WITH A SIGNIFICANT COGNITIVE DECLINE

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Introduction: Acquired immunodeficiency syndrome (AIDS)-associated gastrointestinal and cognitive dysfunctions are enteric and neurological complications related to HIV infection that significantly increase the AIDS morbidity and mortality. A potential effector of these clinical manifestations is the viral HIV-1Trans activating factor protein (Tat), a crucial viral protein involved in the replication of the HIV-1virus. In the gut, HIV-1Tat induces to mucosal damage responsible for resulting secretory diarrhea. Afterward, HIV-1Tat may reach the nerve part of the gut, the enteric nervous system (ENS), affecting its functions and amplifying the intestinal dysfunction. Since in the central nervous system (CNS) the glial cells are directly involved in mediating neurotoxic effects induced by HIV-1Tat, the possible role played by enteric glial cells (EGCs) to trigger and spread an HIV-1Tat-induced neuroinflammatory response throughout the "gut-brain" axis was investigated.

Materials and methods: In eight-weeks-old Wistar male rats, HIV-1Tat peptide (100 ng/ml) was injected into the lumen of the animal colon at day 1. In a subset of animals, HIV 1-Tat was administered immediately after lidocaine topic application in a single dose (0.03% w/v). In another group of animals, a single dose of bisacodyl (20 mg/Kg) was administrated orally by gavage. Animals were euthanatized at different time points (7, 12, 14and 21days) depending upon the scheduled experimental plan, and colon, thoracic and cervical spinal cord and brain were isolated to perform immunofluorescence, in situ hybridization and biochemical/molecular analyses.

Results: A marked increase of EGCs sustained neuro-inflammatory response was evoked at day 7following HIV-1Tat enema, with consequent NF-kB, iNOS, TLR-4, GFAP, and S100B protein expression increase in submucosal plexus homogenates. In parallel, a significant S100B/iNOS co-expression rise was observed in submucosal plexus. HIV-1Tat-induced diarrhea was inhibited by lidocaine and this was accompanied to a marked EGC neuroinflammatory response inhibition. As signs of "ascending" gliosis from gut to the brain, 12, 14and 21days following the acute phase of HIV-1Tat-induced diarrhea, late onset of the same neuropathological features was observed in rats, respectively in the thoracic, cervical spinal cord and frontal cortex in comparison with the vehicle group. As a consequence of this, a significant deterioration of cognitive performance was detected, in HIV-1Tat diarrhea group versus vehicle. Further experiments demonstrated that gut-brain axis induction by HIV-1Tat enema, was under connexin-43/S100B control and suppression of ENS activity by lidocaine administration has significantly attenuated it.

Discussion: The valence of the experimental data obtained confirm the hypothesis that in certain circumstances the gut may be the "entrance door" by which neurotoxic agents may migrate to the brain to finally cause CNS damage and cognitive decline. Moreover, we can identify in EGCs a possible new therapeutic target to improve the clinical symptoms of diarrhea and cognitive performances in AIDS patients. This project aim was also to expand the knowledge related to the etiology of clinical complications that play a major role in the quality of life of patients with AIDS.

Conclusion: Our study demonstrates that a single colonic application of HIV-1Tat induces acute diarrhea that is at least partially modulated by the activation of glial cells in the submucosal plexus. This local response is able to trigger and activate glial cells in the spinal cord and brain cortex through the expression of Cx43, that results in an inflammatory reaction in the brain and that is associated with a significant cognitive decline in treated rats. These observations point out the role of glial cells as putative effectors in HIV-1Tat-associated gastrointestinal and neurological manifestations and key regulators of gut-brain signaling.