SUPRASPINAL CONTRIBUTION TO HYPERALGESIA AND ALLODYNIA BY PERIPHERAL NEUROPATHY: MULTIPLE MECHANISMS OF GLUTAMATE AND ENDOCANNABINOIDS/ENDOVANILLOIDS

SABATINO MAIONE

Dipartimento di Medicina Sperimentale, Facoltà di Medicina e Chirurgia, Seconda Università degli Studi di Napoli, via Copstantinopoli, 16 80138 Napoli

The endogenous antinociceptive systems are made up of a complex neural networks belonging to several limbic and non limbic structures [i.e. prefrontal/cingulate cortex, insular cortex (IC), amygdala, dorsal raphe (DR), periaqueductal gray (PAG) matter, rostral ventromedial medulla (RVM)]. There is growing evidence that chronic pain (.e. neuropathic pain) may generate supraspinal morphological, biomolecular and functional changes. In rodents with spared nerve injury (SNI), or chronic constrictive injury (CCI) of sciatic nerve, apoptotic-like phenomena may occur in the IC, DR, PAG and RVM. The first part of this presentation will focus on the increased expression of the bax (40±2%), bid (16±2%), caspase-1 (84±3%), caspase-8 (53±6%), caspase-9 (25±6%), caspase-12 (58±2%), TNF (32±2%) genes in the CNS. Also, peripheral neuropathies result in significantly elevated anandamide and 2-arachidonoylglycerol levels in the DR, PAG and RVM. Furthermore, as well as thermal and mechanical hyperalgesia, SNI or CCI also change RVM activity of pro-nociceptive ON e antinociceptive OFF cells, in a way that is consistent with a decrease in the functioning of the antinociceptive systems. Consistent with biomolecular and functional data, morphological analysis confirms a marked increase in TUNEL-positive and caspase-positive profiles. The second part of this presentation will focus on cell protective and anti-allodynic effects of metabotropic glutamate (mGlu) or vanilloid/cannabinoid receptor ligands. The selective mGlu5 receptor antagonist MPEP (but not the mGlu1 antagonist JNJ16259685), may prevent the development of thermal hyperalgesia and may transiently reduce mechanical hyperalgesia. Despite the MPEP treatment, which normalizes *bax/bcl-2* and *bcl-xL/bcl-xS* ratios at all times post-nerve injury, mechanical hyperalgesia reappears few days later. Similarly, MPEP is cytoprotective after 3, but not 7 days. The analgesic potential of the cannabinoid agonists has been shown recently in healthy rats, in rats and mice treated with formalin and in rats with CCI. *N*-arachidonoyl-serotonin (AA-5-HT) is a non-competitive inhibitor of fatty acid amide hydrolase (FAAH), the enzyme responsible of the hydrolysis of the endocannabinoid anandamide, and a non-competitive antagonist at rat and human transient receptor potential vanilloid-1 (TRPV1) receptors. AA-5-HT prevented the development of thermal hyperalgesia and allodynia and normalised the mRNA levels of the bax, bid, caspase-1, caspase-8, caspase-9, and caspase-12 and also reduced apoptotic and active caspase-positive profiles in the brain areas analysed. In conclusion, there is growing evidence that chronic pain may induce morphological, biomolecular and functional changes with apoptotic phenomena within supraspinal structures like the insula, DR and PAG-RVM pathway. Moreover, some selective ligands at mGlu receptor, as well as inhibitors of endocannabinoid metabolism, could be novel strategies for neuropathic pain management.

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