# CCL5-mediated control of glutamatergic transmission in EAE mouse central nervous system

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We investigated the Regulated upon Activation Normal T cells Expressed and Secreted (RANTES, CCL5)-glutamate interaction in the cortex and in the spinal cord of mice suffering Experimental Autoimmune Encephalomyelitis (EAE) at different stages of disease. In naive mice, CCL5 presynaptically inhibited glutamate exocytosis from cortical synaptosomes, while in spinal cord synaptosomes it potentiated glutamate exocytosis. An early increase of CCL5 levels was observed in the plasma and in the cortical homogenates of EAE mice before the symptomatic phase of disease, at 13 days post immunization (d.p.i.), and persisted at the peak of disease (21 and 30 d.p.i.). Concomitantly, the 12 mM KCl-evoked [$^3$H]D-aspartate ([$^3$H]D-ASP) exocytosis and the forskolin-induced [$^3$H]D-ASP release from cortical nerve terminals were reduced. Unexpectedly, CCL5-mediated inhibition turned to facilitation in EAE mice at 13 d.p.i., then becoming undetectable at 21 and 30 d.p.i.. A significant reduction of the 12 mM $K^+$-evoked cyclic adenosine monophosphate (cAMP) production, but not of inositol 1,4,5-trisphosphate ($IP_3$), was also detected. All these functional modifications did not match with the presence of inflammatory infiltrates and demyelinating processes in cortical slices of EAE mice. In spinal cord, CCL5 content in homogenates increased at 21 d.p.i.. Concomitantly, the 15 mM $K^+$-evoked [$^3$H]D-ASP exocytosis and the 15 mM $K^+$-evoked $IP_3$ and cAMP productions were augmented when compared to control. In EAE mice spinal cord at 13, 21 and 30 d.p.i. CCL5 facilitated [$^3$H]D-ASP exocytosis, as occured in naive mice. Inflammatory infiltrates, CCL5 immunopositivity and demyelinating processes were detected in spinal cord slices at all stages of disease. We conclude that CCL5-glutamate interaction undergo severe area-dependent modifications in EAE mice that occur at different stages of disease and could participate to the molecular events involved in multiple sclerosis ethiopathogenesis.