CCL5-glutamate crosstalk in mouse central nervous system

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The study was aimed at extending the knowledge of the role of Regulated upon Activation Normal T cells Expressed and Secreted (RANTES, CCL5) as modulator of glutamate transmission in mammalian central nervous system (CNS) and focussed on the CCL5-induced modification to the release of glutamate [quantified as release of preloaded [^{3}H]D-aspartate ([^{3}H]D-ASP)] from synaptosomes and gliosomes isolated from mouse cortex and spinal cord. CCL5 (0.01-1 nM) facilitated the spontaneous and the 15 mM K^+-evoked release of [^{3}H]D-ASP from cortical and spinal cord synaptosomes, respectively, but inhibited the 12 mM K^+-evoked release of [^{3}H]D-ASP in mouse cortex. CCL5-induced effects were prevented by CCR1 and CCR5 antagonists as well as by anti CCR1 and CCR5 receptor antibodies raised against the NH_2-terminal of receptor proteins, but only CCL5-mediated inhibition of cortical [^{3}H]D-ASP exocytosis was sensitive to CCR3 receptor antagonist/antibody. Facilitation of release relied on PLC-sensitive events, involving IP_3 production and mobilization of Ca^{2+} ions from thapsigargin-sensitive stores, while inhibition was negatively coupled to adenylyl cyclase/cAMP pathway. CCR1, CCR3 and CCR5 receptor proteins were present in synaptosomal membranes from mouse cortex and spinal cord as well as in gliosomal membranes although CCL5-induced changes to glutamate release could not be observed at this level. Our results confirm the role of CCL5 as central modulator of glutamate transmission and validate the use of mouse as an appropriate model to study its effects in CNS. CCL5-mediated control of glutamate transmission occurs in a area-specific manner and involves different receptor repertoires.