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Meeting abstract

Interactions of the G protein-coupled receptor-associated sorting proteins (GASP) 1 and 2 with the novel cannabinoid receptor GPR55

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GPR55 was recently found to be a novel cannabinoid receptor and a member of the G protein-coupled receptor (GPCR) subfamily A. GPR55 is activated by different cannabinoid ligands as well as by the lipid ligand lysophosphatidylinositol (LPI). Generally, the activity of GPCRs is coordinated by receptor signaling, receptor desensitization and receptor resensitization. The latter two mechanisms are typically associated with the sorting of the GPCRs between degradation or recycling pathways and are highly regulated. Several sorting proteins have recently been identified, for example the G protein-coupled receptor-associated sorting protein-1 (GASP-1). GASP-1 was originally found to target delta opioid receptors (DORs) to lysosomes and hence a degradative pathway. This study shows that GPR55 can internalize after ligand activation and is subsequently targeted to intracellular vesicles of the lysosomal compartments. This result and the close similarity of GPR55 to the cannabinoid receptor CB_1 – which is targeted to lysosomes via the GASP-1 protein – suggested that GASP may be involved in targeting GPR55 to lysosomes. In fact, here we show that the C-terminus of GPR55 binds GASP-1, cGASP-1 (the C-terminal part of GASP-1) and GASP-2 (the closest homologue to GASP-1) *in vitro*. Both GASP-1 and cGASP-1 show a high affinity to the C-terminus of GPR55 *in vitro*, with a ~2-fold higher affinity for GASP-1 when compared to the DOR. Interestingly, the GASP-2 isoform has the highest affinity for GPR55 with ~85% when compared to GASP-1 and cGASP-1 (~80%). This study provides first evidence that the novel cannabinoid receptor GPR55 is targeted to lysosomes after prolonged agonist stimulation and this mechanism is likely regulated by members of the newly discovered G protein-coupled receptor-associated sorting proteins, i.e GASP-1 and GASP-2.