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MEETING ABSTRACT Open Access

The trafficking of GPR55 is regulated by the G protein-coupled receptor-associated sorting protein 1

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Background

The G protein-coupled receptor 55 (GPR55) has recently been suggested to be responsible for those cannabinoid responses that could not be attributed to either the cannabinoid 1 (CB_1) or cannabinoid 2 (CB_2) receptor. Several potent GPR55 agonists were identified, such as lysophosphatidylinositol (LPI) and synthetic cannabinoids: One of these is rimonabant (SR141716A), which until that date was known to be an inverse agonist/antagonist on the CB_1 receptor. Rimonabant has further attracted attention since it was marketed to induce weight loss and reduce smoking. However, due to severe side effects after prolonged use, such as the development of anxiety and depression, rimonabant was taken off the market. Generally, the activity of GPCRs is coordinated by receptor signaling, receptor desensitization and receptor resensitization. One regulatory mechanism to guarantee appropriate GPCR expression levels in physiological conditions is that of downregulating GPCRs via the G protein-coupled receptor-associated sorting protein 1 (GASP-1), thus leading to an attenuation of cellular signaling events. GASP-1 was originally found to target δ opioid receptors to lysosomes and, hence, to be a degradative pathway. It was shown that GASP-1 is a key determinant in the development of analgesic tolerance to cannabinoids via its role in facilitating downregulation of the CB_1 receptor.

Methods

All experiments were performed using Human Embryonic Kidney (HEK293) cells and HEK293 cells stably expressing FLAG-tagged GPR55. Knock-down of endogenous GASP-1 levels were induced by infection with Lenti-shGASP-1 (shGASP-1) or Lenti-shScrambled (shScr) virus. The post-endocytic trafficking of GPR55 and its regulation by GASP-1 was elucidated by means of immunocytochemistry and biotinylation degradation experiments.

Results

By a variety of approaches, we demonstrated that GPR55 directly interacts with GASP-1 and is targeted to the degradative pathway via GASP-1 in a recombinant HEK293 cell model. For instance, knockdown of endogenous GASP-1 in HEK293 cells using shRNA silencing changes the trafficking properties of GPR55.

Conclusions

This work provides tangible evidence that GPR55 is degraded after prolonged agonist stimulation and this mechanism is regulated by the G protein-coupled receptor-associated sorting protein 1.

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