Investigating The Role Of The Putative Cannabinoid Receptor GPR55 in Vascular Control in mice

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Since the discovery that the classical cannabinoid receptors (CB_1/CB_2) do not account for all actions of cannabinoids, investigations began to identify the nature of the receptor(s) involved. Amongst others, the orphan G-protein coupled receptor GPR55 has been suggested as a putative cannabinoid receptor but its physiological role remains unknown. It was reported that knockout (KO) of GPR55 leads to increased arterial blood pressure without changes in heart rate in mice (Greasley et al. 2008). In the vasculature, GPR55 has been proposed to mediate the relaxation to some cannabinoids including the endocannabinoid anandamide (AEA) but direct evidence of that is lacking (John et al. 2007). Therefore, this study aimed to investigate the vascular responses to L-α-lysophosphatidylinositol (LPI), an endogenous lipid and potent agonist of GPR55, and AEA in GPR55 KO mice and age-matched, wild-type (WT, C57BL/6J) mice (18-28 weeks). The mice were killed by cervical dislocation, and body and heart weights were recorded. Mesenteric arteries were isolated and mounted on a wire myograph for isometric tension recording. Cumulative doses of LPI or AEA (1μM, 3μM 10μM, 30μM) were added to vessels which had been precontracted to 3μM methoxamine and 600nM U46619. Data are presented as % relaxation of precontracted tone ($n \geq 3$) and analysed by two-way or one way analysis of variance, where appropriate. In WT males, LPI induced small relaxations at 1μM (13.9±4.6%) and 3μM (16.9±4.5%) but contractions at higher concentrations (10μM: 15.5±4.7%, 30μM: 4.8±6.5%). Somewhat smaller responses were obtained in KO males (1μM: 9.3±3.4%, 3μM:14.2±3.6%, 10μM:11.8±5.1%, 30μM:-1.6±7.4%; not significant). In female WT mice, LPI induced concentration-dependent relaxation (maximal relaxation at 30μM: 30.6%±8.8). This relaxation was reverted to contraction in KO females (at 30μM: -26.2±15.1% $P<0.01$), suggesting gender differences in LPI/GPR55-mediated relaxations. Interestingly we also found that, in WT males, AEA caused concentration-dependent relaxation (maximal relaxation at 30μM: 52.7±7.6%) which was significantly diminished ($P<0.05$) in KO males (at 30μM: 28.7±4.3%). This is consistent with a role for GPR55 in AEA responses, at least in males. Significant differences were also found in body weight between the KO (33.7±0.9g) and WT (30.4±0.8g) males ($P<0.05$). Female WT and KO mice had a mean body weight of 27.4±1.1g and 23.6±0.6g respectively but the difference was not significant. Heart weights (recorded as % of body weight) were similar in WT and KO for both males and females (male, KO: 0.67±0.03% WT: 0.67±0.05%; female, KO: 0.62±0.02% WT: 0.63±0.02%). In conclusion, the data indicate, for the first time, that GPR55 activation could lead to vasorelaxation. The contribution of GPR55 to vascular control might vary according to the gender and endogenous agonists.

Greasley PJ et al. (2008) International Cannabinoid Research Society symposium, P89

John DG et al. (2007) Br J Pharmacol 152(5):825–831