P373

Activation of cannabinoid system by central angiotensin AT_1 and muscarinic receptors results in gastric mucosal defence in the rat.

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Background: Paracrine transactivation of CB_1 receptor by angiotensin AT_1 (and M_1, M_3, M_5) receptors in Chinese hamster ovary cells was observed recently (Turu et al., J. Biol. Chem. 282, 7753, 2007; J. Biol. Chem. 284, 16914, 2009). Namely AT_1 (M_1, M_3, M_5) receptors are Gq-protein-coupled receptor and activation of Gq/11 protein-coupled receptors results in activation of phospholipase C, which generates inositol-trisphosphate and diacylglycerol (DAG) from phosphatidylinositol (4,5)-bisphosphate. From DAG 2-arachidonoyl-glycerol (2-AG), an endocannabinoid is generated by diacylglycerol lipases (DAGLs).

Aim: To clarify, if angiotensin II (Ang II) can induce gastric mucosal protection by activation of endocannabinoid system. Namely, anandamide and synthetic cannabinoids were found to induce gastric mucosal protective effect given centrally, which was mediated by cannabinoid CB1 receptors (Shujaa et al., J. Physiol. Pharmacol. 60 Suppl 7, 93-100).

Method: Gastric mucosal lesion was induced by acidified ethanol in male Wistar rats (140-170 g) and in CB1 +/+ and -/- mice after 24 h starvation. The mucosal lesions were examined 60 min after the ethanol challenge. The compounds were administered intracerebroventricularly (i.c.v). The mucosal level of calcitonin-gene related peptides (CGRP) in the rat was determined by radioimmune assay.

Results: 1. Gastric mucosal protection could be induced both by exogenously injected cannabinoids, anandamide (2.9-115 nmol i.c.v.) and 2-AG (3.3-26.4 nmol i.c.v.) and by the inhibitors of their metabolizing enzymes, URB 597 (1.5-29.5 nmol i.c.v.) and JZL 184 (0.3-1.3 nmol i.c.v.). 2. Mucosal CGRP content decreased from 1.34 fmol/mg to 0.25 fmol/mg values 60 min after oral administration of ethanol and anandamide (58 nmol i.c.v.) and 2-AG (26.4 nmol i.c.v.) given 10 min before ethanol administration restored the ethanol-induced decrease of mucosal level of CGRP. 3. Ang II inhibited the ethanol-induced gastric mucosal lesions in a dose-dependent manner (0.012-0.19 nmol/rat i.c.v.); the effect was antagonized by both the AT_1 receptor antagonist candesartan (16 nmol) and the inverse agonist of CB_1 receptor, AM 251 (1.8 nmol). 4. Tetrahydrolipstatin (THL) (0.2 nmol i.c.v.), inhibitor of DAG lipase, enzyme is responsible for the formation of 2-AG, inhibited the gastroprotective effect of Ang II (0.19 nmol). 5. Ang II (0.19 nmol) exerted gastroprotective effect also in wild type mice, however, it was ineffective in CB1 receptor KO mice. 6. Pilocarpine (35 nmol i.c.v.) also induced gastroprotective effect and both atropine and AM 251 reversed the protective action.

Conclusion: Activation of central angiotensin AT_1 or muscarinic receptors elicits gastroprotective action by stimulation of cannabinoid CB_1 receptors. Angiotensin AT_1 receptor-induced gastroprotective action is mediated via a DAGL-dependent mechanism.

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