Arvanil, anandamide and N-arachidonoyl-dopamine (NADA) inhibit emesis through cannabinoid CB$_1$ and vanilloid TRPV1 receptors in the ferret


Cannabinoid (CB) and transient receptor potential vanilloid-1 (TRPV1) receptor agonists are anti-emetic (Andrews et al., 2000; Hall et al., 2005). Anandamide (AEA) and N-arachidonoyl-dopamine (NADA) are endogenous agonists at both CB$_1$ and TRPV1 receptors. Arvanil is a synthetic “hybrid” agonist of these receptors (Melck et al., 1999). URB597 is a specific inhibitor of fatty acid amide hydrolase, capable of elevating brainstem AEA levels. Previously, the anti-emetic effects of cannabinoids were proposed to be through the activation of cannabinoid CB$_1$ or CB$_2$ receptors expressed in nucleus of the solitary tract (NTS), dorsal motor nucleus of the vagus (DMNX) and area postrema (AP) (Van Sickle et al., 2003; 2005). With the purpose of assessing whether: i) AEA, NADA and arvanil inhibit emesis and related behaviours in a way mediated by both CB$_1$ and TRPV1 receptors, and ii) CB$_1$ and TRPV1 receptors are expressed at similar sites in the brainstem nuclei controlling emesis, pharmacological and immunohistochemical studies were performed in six adult male ferrets (Mustela putoris furo, 900-1500g) and three mice (Swiss, 60-70g). Antagonists (TRPV1: iodoresiniferatoxin, IRTX, 0.1 or 0.2 mg kg$^{-1}$; CB$_1$: AM251, 5 mg kg$^{-1}$; CB$_2$: AM630, 5 mg kg$^{-1}$) were administered 15 min prior to other agents (vehicle: 2% DMSO, 1% Tween 80 in PBS; arvanil, 1 & 2 mg kg$^{-1}$; NADA, 1 & 2 mg kg$^{-1}$; AEA, 1 mg kg$^{-1}$; URB597 5 mg kg$^{-1}$) (all i.p.) and 15 min later the emetic agent, morphine 6 glucuronide (0.05 mg kg$^{-1}$, s.c., M6G) was administered. The ferrets were observed for 1 hour to count the number of emetic episodes (n). Quantitative pharmacological data were compared using ANOVA followed by a Bonferroni post hoc test and showed significant (P<0.01) reduction of emesis episodes in response to M6G (n=7±0.2) for each administered compound (example: n=2.2±0.6 Arv2/M6G vs n=7.0±0.2 M6G); these effects were attenuated by both AM251 (n=4.8±0.4 vs n=2.2±0.6 Arv2/M6G), which was pro-emetic per se (n=9.0±0.5 vs n=7.0±0.2 M6G), and the TRPV1 antagonists IRTX (n=5.2±0.5 vs n=2.2±0.6 Arv2/M6G) and AMG9810, which were without pro-emetic effects per se. For immunohistochemical studies, ferret and mouse brainstem floating sections were processed for TRPV1-CB$_1$-ir. TRPV1-CB$_1$-ir was largely restricted to the NTS and extensively co-localized with CB$_1$-ir in the mouse. Our findings suggest that CB$_1$ and TRPV1 receptors in the brainstem play a major role in the control of emesis by agonists of these two receptors. While there appears to be an endogenous “tone” of CB$_1$ receptors inhibiting emesis, this does not seem to be the case for TRPV1 receptors, indicating that endocannabinoids/endovanilloids endogenously released following M6G administration inhibit emesis preferentially via CB$_1$ receptors. However, pharmacologically elevated AEA levels inhibit emesis via both CB$_1$ and TRPV1.

**References**

Andrews et al., 2000 *Br J Pharmacol*, 130, 1247-1254
Hall et al., 2005 *Lancet Oncol*, 6, 35-42;
Melck et al., 1999 *Biochem Biophys Res Commun*, 262, 275-84;