Are contractile responses of guinea pig isolated ileum to 2-phenylethylamine through a trace amine receptor?

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The trace amine 2-phenylethylamine (2-PEA) is widely regarded as an indirectly acting sympathomimetic amine (Burn & Rand 1958). However, it also has high affinity for trace amine binding sites in the brain (Hauger et al 1982) and in guinea pig lung causes contraction of smooth muscle possibly through activation of phenylethlaminergic receptors (Hawthorn et al 1985). Recently, the latter reports were confirmed by the discovery and cloning of G-protein coupled trace amine receptors (Borowsky et al 2001). There is paucity of data on pharmacological responses of the gastrointestinal (GI) tract to trace amines, particularly 2-PEA, and the mechanism of action. Hence, we tested the hypothesis that 2-PEA-mediated responses of GI tract in the guinea pig ileum are via trace amine receptors.

The small intestine was removed from male Dunkin Hartley guinea pigs (300 – 1000g), the 10 cm nearest to the ileocaecal junction discarded. After washing out the luminal contents, 2 cm lengths were mounted in Krebs bicarbonate solution at 37°C (gassed with 5% CO₂ in 95% O₂, pH 7.4), (Broadley et al 1985). A resting tension of 0.5g was applied and ilea were allowed to equilibrate for 1 h before cumulative-concentration response curves (CCRCs) to acetyl-β-methylcholine (MCh) followed by 2-PEA were generated in the absence and presence of antagonists: alosetron (1 µM, 5HT₃), atropine (1 µM, muscarinic cholinceptors), phentolamine (1 µM, alpha adrenoceptors), propranolol (1 µM, β adrenoceptors), ritanserin (1 µM, 5HT₂). Prism (GraphPad Software, CA, USA) was used to calculate -logEC₅₀ (pEC₅₀, concentration of half-maximal response) and Eₘₐₓ values for each CCRC. Results are expressed as means ± SEM.

MCh (1µM) produced an 80% of maximum contractile response. The response to this concentration was used to standardize the CCRCs to 2-PEA, which produced a concentration-dependent contractile response (maximum: 3 × 10⁻³M), and this was followed by a relaxation. The pEC₅₀ value was 3.06±0.1, and the Eₘₐₓ was 54±6% (n=20). In the presence of antagonists there were no significant differences in potency (pEC₅₀): atropine (pre: 3.27±0.14 vs post: 3.5±0.06, n=4), phentolamine (pre: 3.6±0.07 vs post: 3.6±0.04, n=4), propranolol (pre: 3.6±0.07 vs post: 3.6±0.04, n=4), alosetron (pre: 3.8±1.5 vs post: 3.3±0.2, n=4), and ritanserin (pre: 3.5±0.1 vs post: 3.3±0.2, n=4), or the maximum responses (Eₘₐₓ) between pre and post inhibitor effects.

To conclude, the results demonstrate that non-adrenergic, non-cholinergic, and non-serotonergic receptors may be involved in 2-PEA-mediated effects in the guinea pig ileum, and suggest the possibility of trace amine receptors mediating contractile and inhibitory activity. We propose a role for trace amines in GI tract homeostasis.

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