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Anandamide and the question of its functional role for activation of capsaicin receptors

Three recent articles[1–3] discussed evidence for and against the physiological endogenous function of anandamide as a ligand for vanilloid VR1 capsaicin receptors on capsaicin-sensitive primary afferent neurones. The main points that appear to be agreed by the authors of these reports are as follows.

(1) Anandamide is an endogenous ligand that exhibits an agonist effect at both the G-protein-coupled metabotropic cannabinoid receptor and the ionotropic VR1 capsaicin receptor.
(2) On one hand, activation of cannabinoid receptors inhibits the function of capsaicin-sensitive peptide-containing primary afferent neurones, which leads to antinociception and a decrease in the release of peptide mediators both at their peripheral and central terminals. On the other hand, activation of the noxious-heat-responsive VR1 receptors on the same set of neurones elicits the opposite effects.
(3) Anandamide induces vasorelaxation in several isolated arterial preparations via release of calcitonin gene-related peptide (CGRP) following activation of VR1 receptors on sensory fibres and it is also an agonist at VR1 receptors of transfected cell lines.
(4) The amount of anandamide released from peripheral tissues might be sufficient for activation of at least one set of receptors on sensory nerves.
(5) It is possible that anandamide-like endogenous lipophilic ligands that possess more potent VR1 agonist effects than anandamide but are devoid of the opposing cannabinoid action exist.

The root of the dispute resides in the concentration ratios for the agonist effect at cannabinoid receptors and VR1 receptors of the capsaicin-sensitive, mainly nociceptive, primary afferent neurones. Hargreaves's group[4,5] have shown that anandamide, injected under the skin of the rat paw or into the intrathecal space, elicited an antihyperalgesic effect in response to noxious heat stimuli and inhibited the release of CGRP from superfused rat skin with at least a 300 times lower threshold concentration than that of the nanomolar range reported for either vasorelaxation[2,6] or activation of the human VR1 receptors in transfected cell lines[3,7]. These data[4,5] were not questioned by Zygmunt *et al.*[2] or Smart and Jerman[3]. However, Zygmunt and co-workers regarded these observations as 'exceptions' and argued that EC_{50} values of anandamide at cannabinoid CB_1 or CB_2 receptors for inhibition of mediator release in response to stimulation of autonomic efferent fibres in isolated organs (e.g. mouse vas deferens, rat atria, guinea-pig ileum and mouse urinary bladder) were similar to those obtained for anandamide-induced CGRP release and vasorelaxation through activation of VR1 capsaicin receptors. The fact that the fall in blood pressure following intravenous injection of anandamide was absent in CB_1 knockout mice and in rats after administration of a CB_1 receptor antagonist suggests that anandamide is not a functionally relevant endogenous ligand at VR1 receptors that is suitable for overcoming or bypassing the powerful inhibitory action on sensory nerve endings[1]. Furthermore, recent evidence (J. Szolcsányi *et al.*, unpublished) demonstrated that systemic release of CGRP or somatostatin following intravenous injection of the VR1 agonist resiniferatoxin was inhibited by anandamide in a similar fashion to that of the *in vitro* release of sensory neuropeptides from the rat trachea. Release of sensory neuropeptides induced by anandamide, which is indicative of VR1 activation, was also observed but only at higher concentrations than that required for inhibition of peptide release (J. Szolcsányi *et al.*, unpublished).

I agree with Zygmunt *et al.*[2] that beyond an overall response such as nociception or changes in blood pressure, local sensory-efferent CGRP release from some capsaicin-sensitive afferents that are not supplied by cannabinoid receptors should also be taken into account. In fact, the generalized concept that capsaicin-sensitive afferents in various smooth muscle preparations and around the vessels serve a dual sensory-efferent function was proposed by myself[8] and the first evidence in isolated tissues was obtained in our laboratories[9] where it is still a focus of interest[10]. Thus, to define anandamide as an endogenous ligand for VR1 capsaicin receptors requires evidence to demonstrate that anandamide, released under physiological or pathophysiological

conditions, elicits one of the described sensory-efferent responses[9,10] of capsaicin-sensitive afferents.

Regarding the interesting point of an interaction between VR1 agonists and the anandamide membrane transport system, further evidence is needed to determine whether VR1 agonists bind to both the VR1 protein and its lipid interface[1] or a unique transporter system exists[1–3]. On this basis, the fact that cannabinoid and VR1 capsaicin receptors 'used to be considered two completely separate receptor systems'[3] might require unification. In any case, the term vanilloid receptor was recently defined by their inventors as a 'misnomer'[11]. The name 'cannabinoid' refers to the plant source and 'vanilloid' unusually refers to the chemical structure of the respective exogenous lead molecules. In this sense, the proposed endogenous ligand is not a vanilloid, but mimics the action of capsaicin at the cloned receptor (cf. muscarinic or nicotinic acetylcholine receptors[1]). Furthermore, the exceptionally high potency of resiniferatoxin at this receptor is not a result of its homovanillic moiety[12] and Julius' group, who cloned the receptor and coined the acronym VR1, still denotes this receptor as the capsaicin receptor[13]. Alternative use of designations[1,3,6,7,11,13] results in misinterpretation and confusion. Therefore, a proposal of the IUPHAR Nomenclature Committee for a common terminology would be helpful in this fascinating, fast-growing research field.

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