DISTRIBUTION, REGULATION AND PHYSIOPATHOLOGICAL ROLE OF BRAIN TRPV1 RECEPTORS

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Conclusive evidence exists for the presence of transient receptor potential vanilloid type 1 (TRPV1) channels in the brain. In particular, immunohistochemical studies from our laboratory, using TRPV1 knock-out mice to probe the specificity of the antibodies used, showed that TRPV1 receptors are expressed together with cannabinoid CB_1 receptors in the hippocampus, basal ganglia, thalamus, hypothalamus, cerebral peduncle, pontine nuclei, periaqueductal grey matter (PAG), cerebellar cortex and dentate cerebellar nucleus (Cristino et al., 2006). Two general patterns of neuronal TRPV1/CB_1 localization were observed: *i*) one in which the expression of the two receptors is overlapping in the cytoplasm and perinuclear compartments, as in hypothalamic neurons and in neurons of the cerebellar nuclei; *ii*) another, where the two receptors co-occur on somata and processes of the same cells (perisomatic and axonal labelling), as in neurons of basal ganglia and ventral PAG, in hippocampal CA2 pyramidal neurons and in Purkinje cells. TRPV1 receptors are also present on dendrites of hippocampal principal neurons of the Ammon's horn. TRPV1 expression has been shown to co-localize also with enzymes deputed to the inactivation of putative endogenous agonists of these receptors, the "endovanilloids" anandamide and *N*-arachidonoyldopamine, i.e.: fatty acid amide hydrolase (FAAH) and catechol-*O*-methyl-transferase (COMT), respectively. NADA and anandamide are endogenous agonists also of CB_1 receptors, whose activation can sensitise the activity of TRPV1 receptors expressed in the same cell (Hermann et al., 2003).
Electrophysiological evidence suggests that the same endovanilloid can exert TRPV1-mediated stimulation of glutamate release and CB_1-mediated inhibition of glutamatergic or GABAergic signalling (Marinelli et al., 2007). Opposing TRPV1- and CB_1-mediated effects on glutamate and GABA release, respectively, probably underlie endovanilloid-induced: *i*) supra-spinal analgesia in rats at the level of the PAG (Maione et al., 2006), *ii*) hippocampal long term potentiation and anxiety-like responses in mice (Marsch et al., 2007); and *iii*) anti-emetic effects at the level of the dorsal motor nucleus of the rat vagus (Derbenev et al., 2006). Interestingly, selective FAAH inhibition causes anti-emetic effects in ferrets in a way mediated by both TRPV1 and CB_1 receptors (Sharkey et al., in press). The potential role of TRPV1 receptors in synaptic plasticity and other brain functions, together with the possible therapeutic implications of the pharmacological manipulation of TRPV1 receptors in the brain, will be discussed.