ENDOVANILLOIDS CONTROL THE ACTIVITY OF DESCENDING PAIN MODULATORY SYSTEM

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In the ventrolateral periaqueductal grey (PAG), activation of glutamatergic output neurons projecting monosynaptically to "OFF" neurons in the rostral ventromedial medulla (RVM) causes anti-nociceptive responses, and is under the control of cannabinoid CB_1 and vanilloid TRPV1 receptors. We studied in rats the effect of elevation of PAG endocannabinoid levels produced by intra-PAG injections of the inhibitor of fatty acid amide hydrolase, URB-597, on: 1) nociception in the "plantar test"; 2) PAG levels of the endocannabinoids, anandamide and 2-arachidonoylglycerol (2-AG); and 3) firing activity of RVM neurons. Depending on the dose and time from administration, URB-597 (0.25-1.25 μg) either suppressed or increased thermal nociception via TRPV1 or CB_1 receptors, respectively. The TRPV1 or cannabinoid receptor agonists, capsaicin (6 nmol) and WIN55,212-2 (4 nmol), also suppressed or enhanced nociception, respectively. URB-597 dose-dependently enhanced PAG anandamide and/or 2-AG levels, with likely subsequent activation of TRPV1 or CB_1 receptors, respectively. The TRPV1-mediated antinociception and CB_1-mediated nociception caused by URB-597 correlated with enhanced or reduced activity of RVM "OFF" neurons, suggesting that they occur via stimulation or inhibition of glutamatergic PAG output neurons, respectively. Indeed, several of these neurons are known to co-express TRPV1 and CB_1 receptors. Finally, at the highest doses tested, URB-597 (2 μg) and, as previously reported, WIN55,212-2 (40 nmol) also caused CB_1-mediated analgesia, correlating with stimulation (disinhibition) of RVM "OFF" neurons. Thus, endocannabinoids affect the descending pathways of pain control by acting at either CB_1 or TRPV1 receptors under physiological conditions.