

LETTERS

An endocannabinoid mechanism for stress-induced analgesia

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Acute stress suppresses pain by activating brain pathways that engage opioid or non-opioid mechanisms. Here we show that an opioid-independent form of this phenomenon, termed stress-induced analgesia¹, is mediated by the release of endogenous marijuana-like (cannabinoid) compounds in the brain. Blockade of cannabinoid CB₁ receptors in the periaqueductal grey matter of the midbrain prevents non-opioid stress-induced analgesia. In this region, stress elicits the rapid formation of two endogenous cannabinoids, the lipids 2-arachidonylglycerol² (2-AG) and anandamide³. A newly developed inhibitor of the 2-AG-deactivating enzyme, monoacylglycerol lipase^{4,5}, selectively increases 2-AG concentrations and, when injected into the periaqueductal grey matter, enhances stress-induced analgesia in a CB₁-dependent manner. Inhibitors of the anandamide-deactivating enzyme fatty-acid amide hydrolase⁶, which selectively elevate anandamide concentrations, exert similar effects. Our results indicate that the coordinated release of 2-AG and anandamide in the periaqueductal grey matter might mediate opioid-independent stress-induced analgesia. These studies also identify monoacylglycerol lipase as a previously unrecognized therapeutic target.

Stress activates neural systems that inhibit pain sensation. This adaptive response, referred to as stress-induced analgesia (SIA), depends on the recruitment of brain pathways that project from the amygdala to the midbrain periaqueductal grey matter (PAG) and descend to the brainstem rostro-mesencephalic medulla and dorsal horn of the spinal cord⁷. Endogenous opioid peptides have key functions in this process^{8,9}, but other as yet unidentified neurotransmitters are also known to be involved⁷. We proposed that endocannabinoids might be implicated in stress analgesia for two reasons. First, agonists of CB₁ receptors—the predominant cannabinoid receptor subtype present in the brain¹⁰—exert profound antinociceptive effects¹¹ and suppress activity in nociceptive neurons^{12–14}. Second, CB₁ antagonists increase the activity of nociceptive rostro-mesencephalic medulla neurons¹⁵ and enhance sensitivity to noxious stimuli¹⁶, indicating that an intrinsic endocannabinoid tone might regulate descending antinociceptive pathways¹⁷.

To study non-opioid SIA we delivered brief, continuous electric foot shock to rats and quantified their sensitivity to pain after stress by using the tail-flick test. As demonstrated previously^{18,19}, this stimulation protocol caused a profound antinociceptive effect that was not affected by intraperitoneal (i.p.) injection of the opiate antagonist naloxone (14 mg kg⁻¹) (Fig. 1a). However, the response was almost abolished by administration of the CB₁ antagonist SR141716A (5 mg kg⁻¹ i.p.) (Fig. 1a) or its analogue AM251 (5 mg kg⁻¹ i.p.) (Supplementary Fig. 1), but not by the CB₂

antagonist SR144528 (5 mg kg⁻¹ i.p.) (Fig. 1a). The effects of CB₁ antagonists cannot be attributed to changes in basal nociceptive threshold because, in the absence of the stressor, the drugs failed to alter tail-flick latencies (Supplementary Figs 1 and 2).

If CB₁ activation is required for the expression of non-opioid SIA, the latter should be lower in animals rendered tolerant to the

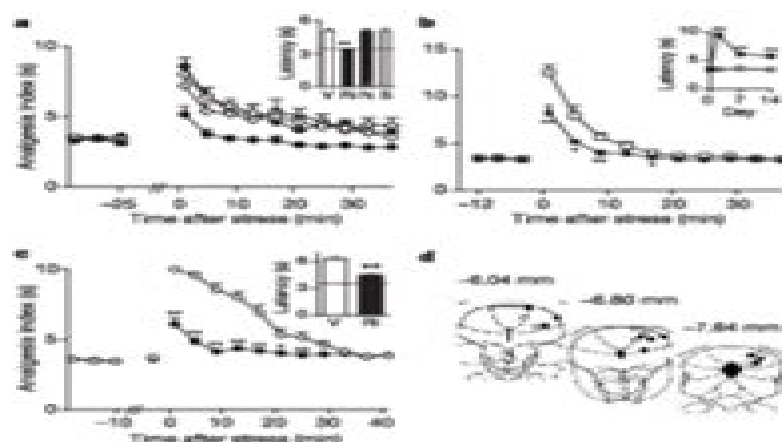


Figure 1 | CB₁ receptors mediate non-opioid stress-induced analgesia. **a**, CB₁ antagonists rimonabant (R; filled circles) block stress antinociception. Opiate antagonist naloxone (N; open diamonds) and CB₂ antagonist SR144528 (S; filled diamonds) have no effect. Open circles, vehicle (V). Inset: drug effects ($F_{(3,12)} = 5.99$, $P < 0.005$). The dotted line indicates the nociceptive threshold. Analgesia index was measured as the tail-flick latency. **b**, Stress antinociception is attenuated in WIN55212-2-tolerant rats (filled squares) compared with controls (open squares) ($F_{(1,12)} = 16.74$, $P < 0.0007$). Inset: non-stress cannabinoid antinociception is attenuated in WIN55212-2-tolerant rats ($F_{(1,12)} = 35.11$, $P < 0.00002$). **c**, Rimonabant in dorsolateral PAG suppresses stress antinociception ($F_{(1,12)} = 20.01$, $P < 0.0002$). Inset: drug effects ($F_{(1,12)} = 25.63$, $P < 0.00002$). **d**, PAG injection sites. Error bars, where visible, indicate s.e.m.; $n = 4–11$ per group. Asterisks, $P < 0.05$; two asterisks, $P < 0.01$ (analysis of variance, Fisher's PLSD test).

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