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CHAPTER 34

A role for the endogenous cannabinoid system in the peripheral control of pain initiation

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Introduction

Although most pain signals arise from the stimulation of nociceptors located in peripheral tissues, the earliest stages of pain modulation are generally thought to occur within the central nervous system (CNS). This view has been challenged, however, by multiple evidence indicating that functionally active antinociceptive mechanisms are also present outside the CNS. For example, it is now recognized that endogenous opioid peptides released upon activation of immune cells during inflammation inhibit pain transmission through the interaction with opioid receptors on peripheral sensory nerve endings (see, for example: Stein et al., 1990; Inoue et al., 1998; Kolesnikov and Pasternak, 1999; Machelska et al., 1999; see also Ingram, 2000, this volume). This concept has both theoretical and clinical relevance, as it implies that peripherally applied opioid drugs may provide significant pain control without producing the undesirable effects that inevitably follow the recruitment of brain opioid receptors (Stein, 1991).

A role in the control of pain initiation has also been proposed for cannabinoid receptors, the molecular target of the *Cannabis* constituent Δ^9-tetrahydrocannabinol (Δ^9-THC), and for their attending system of endogenous ligands. The aim of this review is to outline the experimental evidence supporting such a role. To place this evidence into perspective, we will first describe the pathways of formation and inactivation of the endogenous cannabinoids (endocannabinoids) and the pharmacological properties of the receptors they activate. We will then focus on the implication of the endocannabinoid system in the central processing of pain signaling. Finally, we will turn our attention to the antinociceptive functions served by these compounds in peripheral organs and tissues and delineate several unresolved issues that still await experimentation.

Endocannabinoid formation and inactivation

The endocannabinoids, which include anandamide (arachidonylethanolamide) and 2-arachidonylglycerol (2-AG), are a class of lipid compounds found in the brain and other tissues (Devane et al., 1992; Di Marzo et al., 1994; Mechoulam et al., 1995; Sugiura et al., 1995; Stella et al., 1997) (Fig. 1). In contrast to classical neurotransmitters and neuropeptides, anandamide and 2-AG are produced upon demand by receptor-stimulated cleavage of lipid precursors, and are released from neurons and other cells immediately after their production. In the case of anandamide, the membrane precursor is represented by

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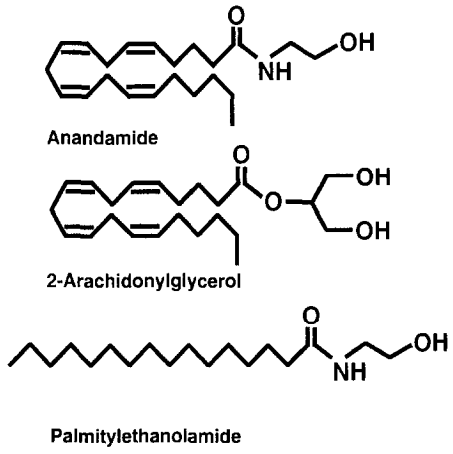

Fig. 1. Chemical structures of anandamide, 2-arachidonylglycerol and palmitylethanolamide.

an *N*-acylated species of phosphatidylethanolamine (PE), *N*-arachidonyl PE (Fig. 2). Activation of cell surface receptors triggers a chain of biochemical events that culminates in the enzymatic cleavage of *N*-arachidonyl PE by an unknown phospholipase D and in the extracellular release of anandamide (Di Marzo et al., 1994; Cadas et al., 1996; Sugiura et al., 1996; Giuffrida et al., 1999). An illustration of this receptor-dependent process has been provided by in vivo microdialysis studies, which suggest that anandamide may be released in the brain striatum upon activation of D_2-type dopamine receptors and that such release may be involved in counterbalancing the stimulatory effects of dopamine on motor activity (Giuffrida et al., 1999; Beltramo et al., 2000).

The most likely route of 2-AG biosynthesis involves the same enzymatic cascade responsible for the generation of second messengers, inositol trisphosphate and 1,2 diacylglycerol (DAG) (Fig. 3). Phospholipase C acting on phosphatidylinositol bisphosphate produces DAG, which is converted to 2-AG by a DAG-lipase activity (Stella et al., 1997). Additional pathways of 2-AG formation may implicate the hydrolysis of lysophospholipids or triacylglycerols (for a review, see Piomelli et al., 1998) (Fig. 3). Regardless of the mechanism involved, 2-AG biosynthesis may be triggered by neural activity or by occupation of membrane receptors. For example, in the rat hippocampus, 2-AG levels are strongly increased by stimulation of the Schaffer

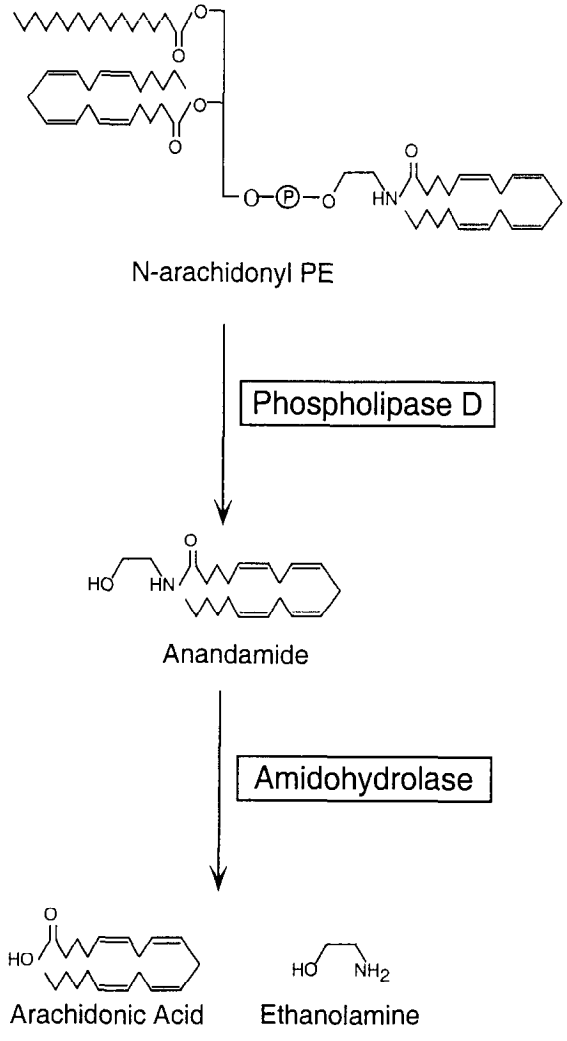

Fig. 2. Hypothetical model illustrating two primary pathways of anandamide formation and inactivation. Hydrolysis of *N*-arachidonyl phosphatidylethanolamine (*N*-arachidonyl PE) by an unknown phospholipase D produces anandamide, which is then released into the external milieu. After release, anandamide is taken up by cells via a selective carrier system (not shown in figure), and broken down by anandamide amidohydrolase to yield arachidonic acid and ethanolamine.

collaterals, an excitatory fiber tract that utilizes glutamate as a neurotransmitter and represents an essential component in the processing of information by the hippocampus (Stella et al., 1997).

After release, anandamide and 2-AG are thought to accumulate back into cells via a high-affinity transport system which, unlike amine and amino acid

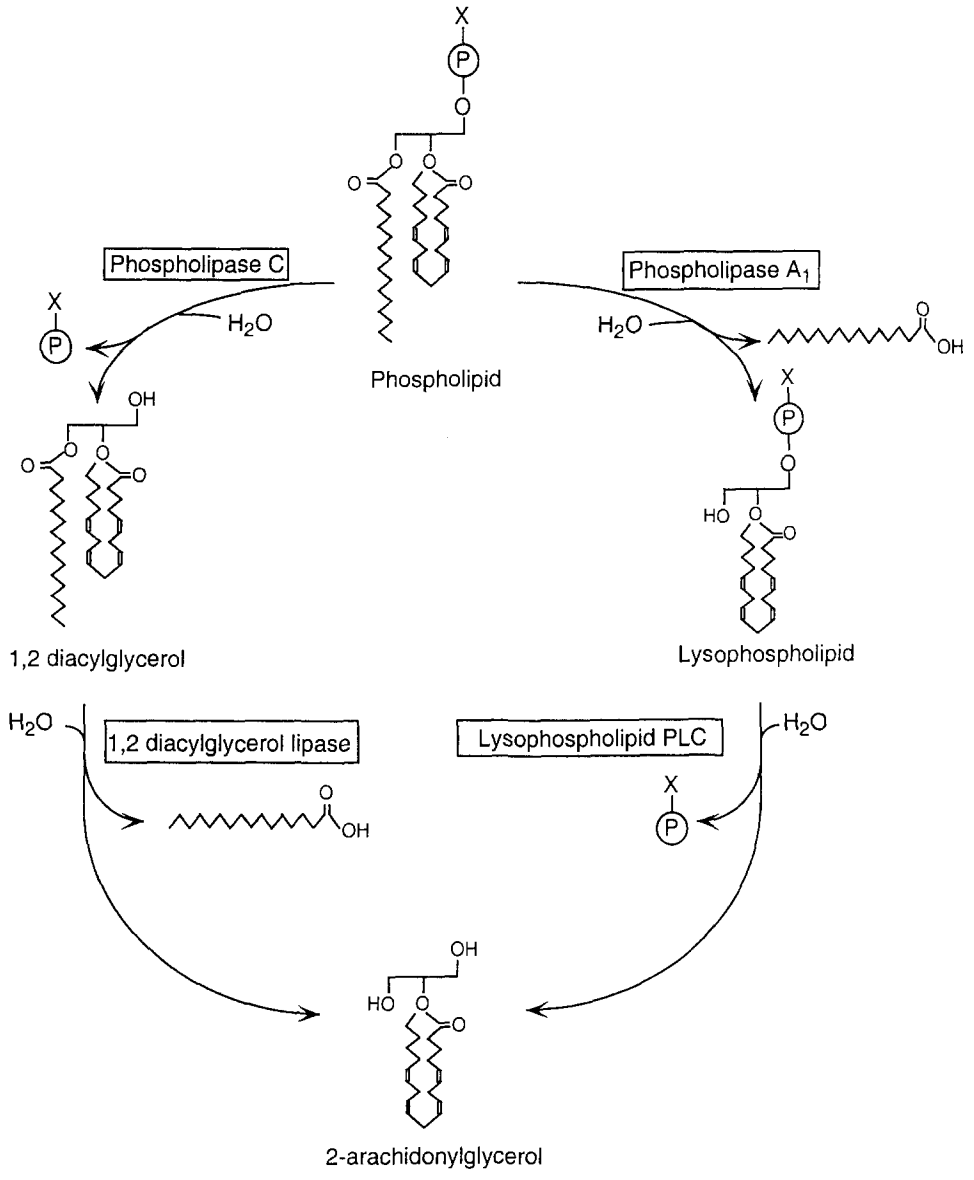

Fig. 3. Hypothetical model illustrating the pathways of 2-AG formation. (Left) Phospholipase C (PLC) acts on phospholipids generating 1,2 diacylglycerol. This diglyceride is cleaved in turn by an unknown 1,2 diacylglycerol-lipase, producing 2-arachidonylglycerol. (Right) Alternatively, a phospholipase A_1 activity may form a lysophospholipid, which is further hydrolyzed by a lysophospholipid PLC to yield 2-arachidonylglycerol.

transporters, is both energy- and Na^+-independent (Di Marzo et al., 1994; Beltramo et al., 1997; Hillard et al., 1997). Although this carrier system remains uncharacterized at the molecular level, its selectivity for anandamide and 2-AG over many other fatty acid ethanolamides and esters is reasonably well documented (Piomelli et al., 1999). Once inside cells, both anandamide and 2-AG are substrates for enzymes which catalyze their hydrolytic breakdown. The enzyme responsible for anandamide hydrolysis, referred to as anandamide amidohydrolase or fatty acid amide hydrolase (Desarnaud et al., 1995; Hillard et al., 1995; Ueda et al., 1995), has been purified and cloned (Cravatt et al., 1996; Giang and Cravatt,

1997). This enzyme is a membrane-bound amidase with relatively low substrate selectivity, which corresponds with the *N*-acylethanolamine amidohydrolase activity identified, before the discovery of anandamide, by Schmid and coworkers (Schmid et al., 1985). 2-AG may also serve as a substrate for anandamide amidohydrolase in vitro (Di Marzo et al., 1998; Goparaju et al., 1998, 1999). There is evidence, however, that a different enzyme, possibly a monoacylglycerol lipase, mediates 2-AG hydrolysis in intact cells (Beltramo and Piomelli, 2000).

In conclusion, the available data suggest that anandamide and 2-AG are released upon demand from neurons and other cells through distinct receptor-dependent mechanisms. This property, along with the short life spans of anandamide and 2-AG, suggest that these endocannabinoid lipids may act near their site of synthesis to modulate the effects of primary neurotransmitters and hormones.

Cannabinoid receptors

Two cannabinoid receptor subtypes, termed CB1 and CB2, have been cloned, and shown to belong to the superfamily of G protein-coupled membrane receptors (Devane et al., 1988; Matsuda et al., 1990; Munro et al., 1993). Although CB1 and CB2 receptors share only about 44% sequence identity, they have sufficient similarity to recognize with comparable affinities a variety of structurally distinct agonists, such as the compounds CP55940 (a bicyclic cannabinoid) and WIN55212-2 (an aminoalkylindole) (see, for a review: Howlett, 1995; Matsuda, 1997). It has been possible, however, to develop excellent subtype-selective antagonists/inverse agonists — such as the compounds SR141716A for the CB1 receptor (Rinaldi-Carmona et al., 1994) and SR144528 for the CB2 receptor (Rinaldi-Carmona et al., 1998) — while subtype-preferring agonists are just now beginning to emerge (Hanus et al., 1999).

CB1 and CB2 receptors differ quite dramatically not only in their molecular architecture, but also in their tissue and cell distribution. The CB1 receptor is predominantly found in brain neurons, where it is highly represented in areas involved in the processing of movement, cognition and pain (Herkenham et al., 1990, 1991a; Matsuda et al., 1993). In addition to the CNS, CB1 receptors are also present in many peripheral cells, including dorsal root ganglion neurons (see below) and inflammatory cells (Munro et al., 1993; Galiegue et al., 1995). By contrast, CB2 receptors are apparently absent from the normal brain, but they are abundantly expressed in immune cells such as B-lymphocytes, natural killer cells and monocytes (Galiegue et al., 1995).

When evaluating the therapeutic potential for CB1 and CB2 receptor agonists, an important factor to consider is that these drugs cause a rapid receptor desensitization (Bouaboula et al., 1999; Jin et al., 1999). As shown for other G protein-coupled receptors, this process may be mediated by the G protein-coupled receptor kinase/β-arrestin pathway, and may be responsible for the loss of pharmacological activity that is associated with the prolonged administration of cannabinoid agonists in vitro and in vivo (Sim et al., 1996).

Central modulation of pain signaling

The reduction in pain behaviors observed after systemic administration of cannabinoid drugs is partly mediated by the activation of CB1 receptors located in the brain and spinal cord. Brain sites that participate in cannabinoid analgesia have been identified by local microinjections of CB1 receptor agonists, and include the amygdala, thalamus, superior colliculus, periaqueductal gray, and rostral ventromedial medulla (Lichtman and Martin, 1996; Martin et al., 1996; Tsou et al., 1996; Meng et al., 1998). In addition to the brain, CB1 receptors are also found in the dorsal horn and lamina X of the spinal cord (Herkenham et al., 1991b; Tsou et al., 1998), where they may be located on nerve terminals of afferent sensory neurons, on intrinsic spinal neurons and/or on terminals of supraspinal neurons (Hohmann et al., 1999a). The presence of cannabinoid receptors in pain-processing areas of the CNS and the ability of cannabinoid antagonists to produce hyperalgesia (see, for example, Richardson et al., 1998) have led to the suggestion that endocannabinoids may participate in the intrinsic regulation of pain signaling. Further support for this hypothesis has been provided by two findings. First, mutant $CB1^{-/-}$ mice are hypoalgesic in the hot plate and formalin tests, a phenotype that may be interpreted as an overcompensation triggered by the inactivation of an intrinsic

pain-controlling system (Zimmer et al., 1999). Second, electrical stimulation in the periaqueductal gray causes a 40% increase in local anandamide outflow, as indicated by in vivo microdialysis studies (Walker et al., 1999). If confirmed, these findings would indicate that spontaneous or stimulated release of anandamide contributes to neuronal excitability in pain-controlling circuits within the CNS (Meng et al., 1998), and that drugs that prevent anandamide inactivation may be useful as analgesics. However, the results obtained thus far show that at least one such compound, the anandamide transport inhibitor AM404, does not change nociceptive threshold in the hot plate test at doses that elicit significant inhibitory effects on motor activity (Beltramo et al., 2000). Therefore, additional data are required to clarify the analgesic potential of this new class of pharmacological agents.

Peripheral modulation of pain signaling

In addition to the CNS, CB1 receptors are also expressed in peripheral sensory neurons of the dorsal root ganglia (DRG). A small percentage of these CB1-expressing cells also contain the pronociceptive neuropeptides, substance P and α-calcitonin gene-related peptide (CGRP) (Hohmann and Herkenham, 1999b). Although quantitatively limited, the presence of CB1 receptors on CGRP-containing neurons is likely to be functionally significant, since CB1 agonists strongly decrease capsaicin-evoked CGRP release from dorsal horn tissue in vitro (Richardson et al., 1998). Immunohistochemical experiments indicate that CB1 receptors are present on central terminals of primary sensory afferents as well as on their peripheral counterparts. These experiments show in fact that CB1 receptors synthesized in the cell bodies of DRG neurons are transported by axonal flow to sensory terminals in peripheral tissues (Hohmann and Herkenham, 1999a).

In further support of this notion, administration of CB1 receptor agonists in the skin alleviates the behavioral responses evoked by the chemical irritant, formalin (Calignano et al., 1998). Injections of dilute formalin into the rodent hind paw elicits a pain behavior consisting of two phases of licking and flexing of the injected limb. The first phase, which involves the acute activation of sensory fibers, starts immediately after formalin injection and lasts for approximately 10 min. This phase is followed by a quiescent period lasting for 10–15 min, and then by a second, more sustained phase of pain behavior accompanied by central sensitization and inflammation (Dubuisson and Dennis, 1977). In mice, anandamide blocks the early phase of pain behavior when it is injected into the paw together with formalin, whereas both phases are prevented by synthetic cannabinoid agonists, such as WIN55212-2 and HU-210 (Fig. 4a and data not shown). These analgesic effects are prevented by the CB1 receptor antagonist SR141716A, but not by either the CB2 receptor antagonist SR144528 or the opioid receptor antagonist naloxone (Fig. 4a and data not shown). The rapid biological inactivation undergone by anandamide in tissues (see above) provides a likely explanation for why there is no effect of this compound during the late phase of the formalin response. This interpretation is supported by the fact that methanandamide, an inactivation-resistant anandamide analog, inhibits pain behavior during the entire duration of the test (Fig. 4a). Additional support for the peripheral antinociceptive actions of anandamide is provided by the ability of this compound to alleviate visceral pain in the turpentine model of urinary bladder inflammation. Systemically administered anandamide inhibits the viscero-visceral hyper-reflexia elicited by the injection of turpentine into the bladder. Unfortunately, the effects of cannabinoid receptor antagonists were not tested in these studies (Jaggar et al., 1998b).

Several results indicate that the analgesic actions of anandamide on the formalin response are mediated by peripheral CB1 receptors. First, local (intraplantar) anandamide administration is not accompanied by the classic signs of central cannabimimetic activity, such as catalepsy or immobility. Second, anandamide is approximately 100-fold more potent when applied locally than systemically (Fig. 4b). Third, when radioactively labeled anandamide is injected into the paw, most of the radioactivity (94%) is confined to the injected limb. Thus, the ability of anandamide to inhibit formalin-evoked nociception may be accounted for by an interaction of this compound with local CB1 receptors, possibly present on the peripheral endings of sensory neurons (Hohmann and Herkenham, 1999b; Hohmann et al., 1999b). This conclusion agrees well with the

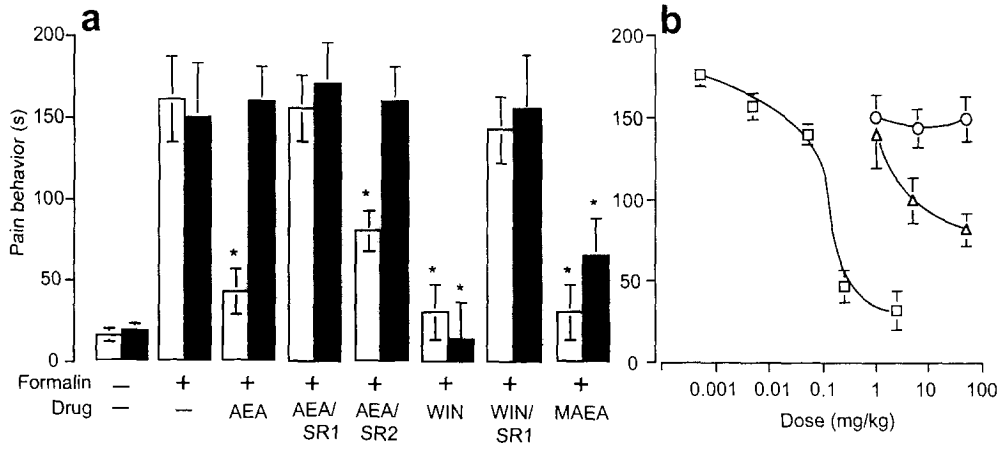

Fig. 4. Inhibition of formalin-evoked nociception in mice by anandamide and other CB1 agonists. (a) Effects of anandamide (*AEA*, 50 μg intraplantar, i.pl.), WIN-55212-2 (*WIN*, 500 μg i.pl.) and methanandamide (*MAEA*, 50 μg i.pl.), in the absence or presence of the CB1 antagonist SR141716A (*SR1*, 0.1 mg per kg intravenous, i.v.) or the CB2 antagonist SR144528 (*SR2*, 0.1 mg per kg i.v.). (b) Dose-dependent effects of anandamide following i.pl. (squares), i.v. (triangles) or intraperitoneal (i.p., circles) administrations. *, $P < 0.01$ ($n = 12$–18 for each condition). Open bars, early phase, closed bars, late phase of the formalin response. Modified from Calignano et al. (1998), with permission.

finding that locally applied cannabinoid receptor agonists reduce capsaicin-induced thermal nociception in rhesus monkeys (Ko and Woods, 1999) and inhibit CGRP release from superfused rat skin in vitro (Richardson et al., 1998).

An intriguing question raised by these studies is whether anandamide (and/or other endocannabinoids), generated spontaneously or as a result of tissue injury, participates in the intrinsic control of pain initiation. The presence of relatively high levels of anandamide in unstimulated skin suggests that this may be possible. Gas chromatography/mass spectrometry (GC/MS) analyses indicate indeed that rat skin contains about 50 pmol of anandamide per g of tissue, a concentration 5 to 15 times greater than that measured in plasma (Calignano et al., 1998; Giuffrida and Piomelli, 1998; Giuffrida et al., 2000).

Another line of evidence supporting a role for the endocannabinoids in the processing of peripheral pain information is derived from experiments using the CB1 receptor antagonist/inverse agonist SR141716A. Administration of SR141716A potentiates formalin-evoked pain in mice (Fig. 5). This hyperalgesic effect is particularly pronounced after local injection of the drug, and is observed during both the early and the late phases of the test (Fig. 5) (Calignano et al., 1998). However, SR141716A does not produce hyperalgesia in rats (A.S. Rice, pers. commun.), indicating that the extent to which the endocannabinoid system participates in peripheral analgesia may depend on experimental conditions and/or species differences.

Palmitylethanolamide as a peripheral analgesic

As we have seen above, anandamide may be generated from the enzymatic cleavage of the phospholipid precursor *N*-arachidonyl PE (Fig. 2). *N*-arachidonyl PE belongs to a family of *N*-acylated PE species varying in the fatty acyl group linked to the primary amino group of PE. These *N*-acyl PE species give rise to fatty acid ethanolamides, such as palmitylethanolamide (PEA) and oleylethanolamide, the physiological roles of which are still unclear (see, for a review, Piomelli et al., 1998). PEA (Fig. 1) was originally isolated in 1963 by S. Udenfriend and coworkers (Bachur et al., 1965) and its anti-inflammatory properties are fairly well-characterized. However, its mechanism of action is still unclear (Aloe et al., 1993; Facci et al., 1995; Mazzari et al., 1996).

In mice, PEA is as potent as anandamide at inhibiting formalin-evoked pain behavior (Fig. 6a) (Calignano et al., 1998). This effect cannot be accounted for by attenuation of inflammatory hyperalgesia, as it is not associated with a reduction of formalin-evoked edema. In six mice, the average

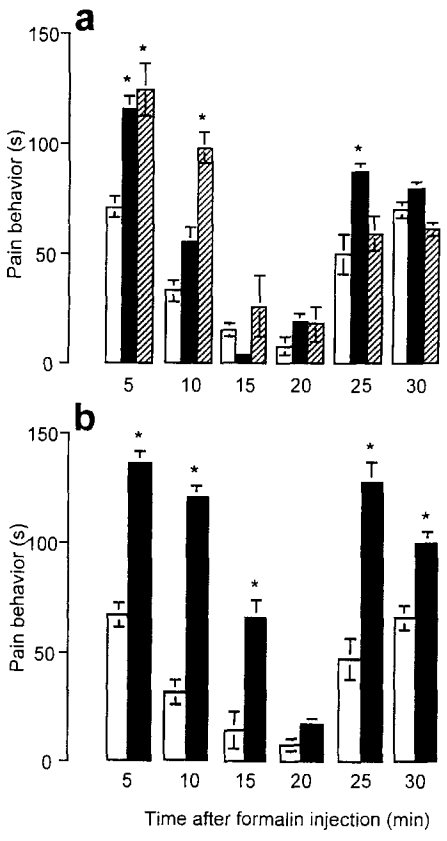

Fig. 5. Hyperalgesic effects of CB1 and CB2 antagonists on formalin-evoked nociception. (a) Effects of systemic administration of the CB1 antagonist SR141716A (filled bars) and the CB2 antagonist SR144528 (hatched bars). The responses to formalin alone are illustrated by the empty bars. The antagonists were administered by i.v. injection at the dose of 0.1 mg per kg. (b) Hyperalgesic effects of local administration of SR141716A (filled bars). 10 μg of SR141716A were administered by i.pl. injection. *, $P < 0.01$ ($n = 6$). Modified from Calignano et al. (1998), with permission.

paw volumes are 0.18 ± 0.003 ml under control conditions, 0.37 ± 0.006 ml 30 min after injection of formalin, and 0.35 ± 0.006 ml after injection of formalin plus PEA (50 μg). PEA-induced analgesia is reversed by pretreatment with the CB2 receptor antagonist SR144528 (Fig. 6a), whereas the CB1 receptor antagonist SR141716A and the opioid receptor antagonist naloxone are ineffective (Fig. 6a and data not shown). Like anandamide, PEA is more potent when injected locally (by intraplantar injection) than when administered systemically (Fig. 6b). Together, these findings suggest that the antinociceptive activity of PEA may be mediated by CB2-like cannabinoid receptors in skin. Importantly, PEA has similar antinociceptive actions when administered in rats, where systemic applications of this compound alleviate both formalin-evoked pain behaviors and turpentine-evoked bladder hyper-reflexia (Jaggar et al., 1998a).

Despite the fact that the actions of PEA are prevented by the CB2-selective receptor antagonist SR144528, it is important to emphasize that PEA does not interact with the cloned CB2 receptor expressed in immune cells (Showalter et al., 1996). Thus, the structural relationship between the CB2-like receptor activated by PEA and other cannabinoid receptor subtypes, if any, remains at present unresolved. The cellular localization of the putative PEA receptor is also unknown. There is evidence that CB2 receptors may be present on peripheral neurons (Pertwee, 1999). However, PEA does not prevent nociceptive responses that require sensory neuron activation. For example, PEA does not inhibit capsaicin-induced pain and does not affect the behavioral response to acute thermal stimuli in the hot plate test (A. Calignano, G. La Rana and D. Piomelli, unpubl. results). This absence of effect suggests that the putative PEA receptor may not be localized on neurons, but rather on non-neuronal cells that participate in triggering the pain response elicited by chemical tissue damage.

Is PEA produced in the skin and does it act locally to regulate pain initiation? As is the case with anandamide, GC/MS analyses reveal the presence of relatively high concentrations of PEA in unstimulated skin (692 ± 119 pmol per g of tissue, $n = 8$). In addition, systemic administration of the CB2 receptor antagonist SR144528 causes a selective enhancement of the early phase, but not the late phase, of the formalin response (Fig. 7). The selectivity of this effect is unlikely to result from a rapid elimination of SR144528 following the early phase, because the drug reverses PEA-evoked analgesia during both early and late-phase pain behavior (Fig. 6). Thus, a plausible interpretation of these results is that locally generated PEA may participate in reducing the early stages of nociception following chemical skin damage.

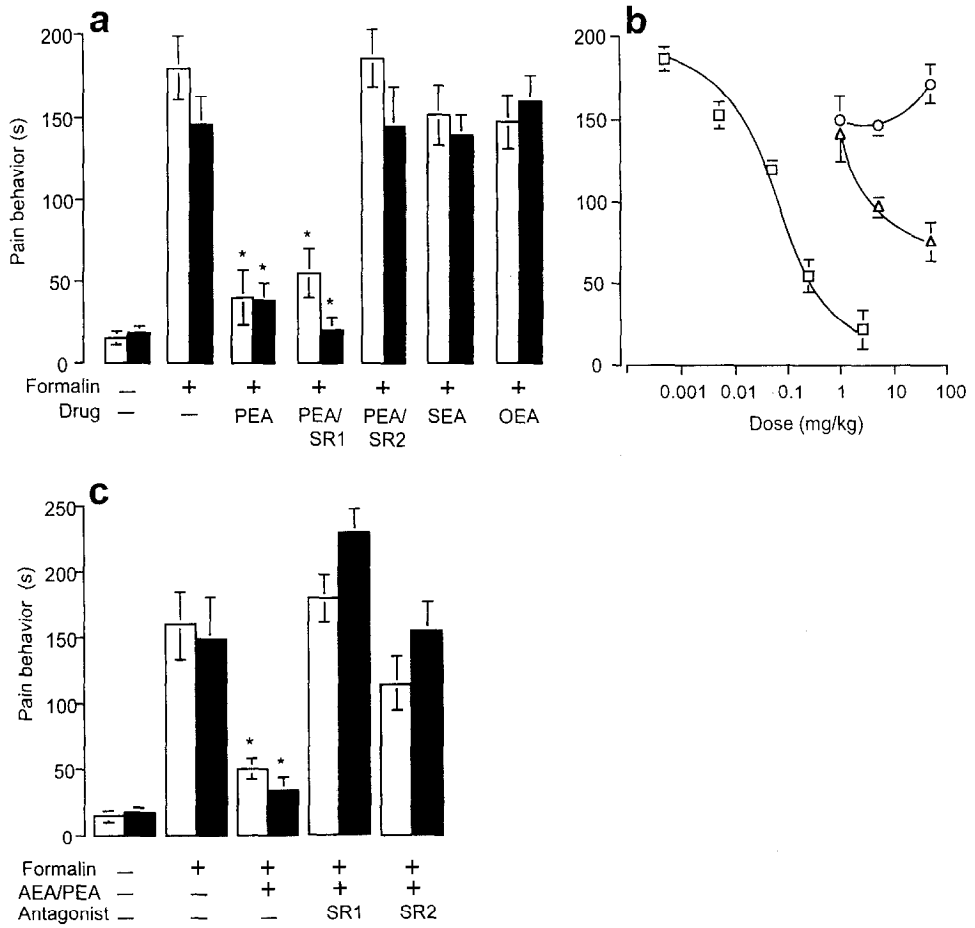

Fig. 6. Inhibition of formalin-evoked nociception in mice by PEA. (a) Effects of palmitylethanolamide (*PEA*, 50 μg i.pl.), stearylethanolamide (*SEA*, 50 μg i.pl.) and oleylethanolamide (*OEA*, 50 μg i.pl.), in the absence or presence of the CB1 antagonist SR141716A (*SR1*, 0.1 mg per kg i.v.) or the CB2 antagonist SR144528 (*SR2*, 0.1 mg per kg i.v.). (b) Dose-dependent effects of PEA following i.pl. (squares), i.v. (triangles) or i.p. (circles) administrations. *, $P < 0.01$ ($n = 12$–18). Open bars, early phase and closed bars, late phase of the formalin response. Modified from Calignano et al. (1998), with permission.

Synergistic inhibition of pain

When anandamide and PEA are administered together in equal doses, they inhibit the early phase of formalin-evoked pain behavior with a potency that is about 100-fold greater than either of the compounds separately (Fig. 7a). A comparable enhancement is observed during the late phase, when anandamide produces no effect when given alone (Fig. 7b). Pretreatment with either a CB1 or CB2 receptor antagonist completely prevents this response, suggesting that the cannabinoid receptors act in a truly synergistic manner (Fig. 7c).

This synergism between anandamide and PEA is reminiscent of those seen between other analgesic compounds (see, for example, Yaksh and Reddy, 1981), and appears to be restricted to peripheral tissues. Thus, direct injection of PEA into the third cerebral ventricle has no effect on the nociceptive threshold in the hot plate test, and does not enhance the inhibitory activity of anandamide when administered by the same route (Table 1). These findings suggest that peripheral CB1 receptors activated by anandamide and CB2-like receptors activated by PEA may cooperate in the control of pain initiation. However, the mechanism underlying this cooperation is at present unknown.

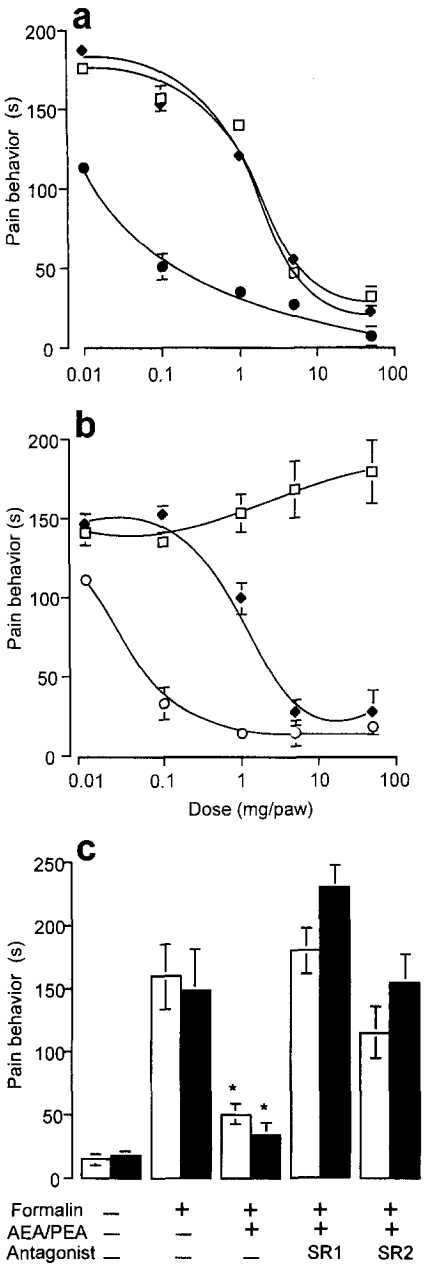

Fig. 7. Synergistic effects of anandamide and PEA on formalin-evoked pain behavior: (a) early phase; (b) late phase. Equal amounts of anandamide and PEA, indicated in the abscissa, were injected into the paw (c). The CB1 antagonist SR141716A (*SR1*) and the CB2 antagonist SR144528 (*SR2*) prevent the effects of anandamide plus PEA (0.1 μg each). Antagonists were given by i.v. injection (0.1 mg per kg); *, $P < 0.01$ ($n = 18$). Open bars, early phase, closed bars, late phase of the formalin response. Modified from Calignano et al. (1998), with permission.

TABLE 1

Effects of anandamide and PEA in the hot-plate test

Time (min.)	Vehicle	AEA hot-plate latencies (s)	PEA	AEA/PEA
5	24 ± 2	24 ± 4	22 ± 3	25 ± 2
10	24 ± 2	23 ± 3	23 ± 3	26 ± 4
15	22 ± 3	29 ± 3	21 ± 2	30 ± 3
20	25 ± 2	35 ± 2*	25 ± 4	37 ± 3*
30	25 ± 3	40 ± 3*	26 ± 5	39 ± 2*
40	25 ± 3	30 ± 3	22 ± 4	35 ± 5
60	26 ± 2	28 ± 3	24 ± 2	26 ± 3

Latencies to jump were measured after intracerebroventricular administration of vehicle (10% DMSO in saline, 5 μl), anandamide (AEA, 10 μg), PEA (10 μg) or anandamide plus PEA (10 μg each). Results are expressed as the mean ± s.e.m. of six experiments. Asterisks indicate $P < 0.01$ by ANOVA and subsequent Dunnett's test.

Conclusions and perspectives

Although cannabinoid analgesia has been generally associated with the activation of cannabinoid receptors in the CNS, the evidence reviewed here indicates that cannabinoid receptor agonists can exert potent antinociceptive effects by interacting with receptors located in peripheral tissues. Two distinct receptor subtypes have been implicated in this response: CB1 receptors that are activated by anandamide and blocked by the CB1 receptor antagonist SR141716A; and CB2-like receptors that are activated by PEA and blocked by the CB2 receptor antagonist SR144528. The presence of CB1 receptors on terminals of sensory neurons tallies well with these pharmacological findings, suggesting that CB1 agonists may produce peripheral antinociception by preventing the transmission of pain signals to the CNS. On the other hand, the molecular structure and cellular localization of the CB2-like receptor activated by PEA are still unknown. Yet, the potent antinociceptive effects of PEA suggest that this putative receptor may represent an important target for analgesic drugs and underscore the need for its molecular identification. Additional experimentation is also needed to characterize in greater detail the pharmacological activity of PEA in vitro and in vivo, including the potential effects of this compound on a wider variety of experimental models of acute and persistent pain.

Abbreviations

2-AG	2-arachidonyl glycerol
AEA	anandamide
CB1	cannabinoid receptor 1
CB2	cannabinoid receptor 2
CGRP	calcitonin gene-related peptide
CNS	central nervous system
DAG	1,2-diacylglycerol
DRG	dorsal root ganglia
OEA	oleylethanolamide
PE	phosphatidyl ethanolamine
PEA	palmitylethanolamide
SEA	sterarylethanolamide

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