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THE CHEMOKINE CX3CL1/FRACTALKINE INTERFERES WITH THE ANTINOCICEPTIVE EFFECT INDUCED BY OPIOID AGONISTS IN THE PERIAQUEDUCTAL GREY OF RATS

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Abstract

We have reported that there is heterologous interaction between the mu, delta or kappa opioid receptors and the receptors for the chemokines CCL5/RANTES or CXCL12/SDF-1 in the regulation of antinociception in rats. CX3CL1/fractalkine, a chemokine that exclusively binds to CX3CR1, has been found to affect morphine analgesia and tolerance in the spinal cord. The purpose of the present study was to see if the interaction between the chemokine CX3CL1/fractalkine receptor and mu, delta or kappa opioid receptors occurs in the periaqueductal grey (PAG) of adult male S-D rats. The cold-water tail-flick (CWT) test was used to measure antinociception. The results showed that intra-PAG injection of 100 ng CX3CL1/fractalkine 30 min before administration of 400 ng DAMGO, 100 ng DPDPE or 20 μg dynorphin significantly reduced the antinociception induced by each of these peptides. These results demonstrate that activation of the CX3CL1 receptor diminishes the effect of mu, delta and kappa opioid agonists on their receptors in the PAG of rats.

Keywords

Chemokine; CX3CL1/fractalkine; Opioid Agonists; Antinociception; periaqueductal grey; Rats

1. Introduction

CX3CL1/fractalkine is a structurally unique chemokine reported to be constitutively expressed by neurons (Murphy et al., 2000). Chemokines, a family of cytokines that are chemoattractants for leukocytes, have similar structures and signal via G-protein-coupled receptors (GPCR) on the leukocytes. They have 4 subclasses of families: C family, CC family, CXC family and CX3C family (Murphy et al., 2000). Most chemokines (e.g., CCL5/RANTES), can bind to more than one chemokine receptor, but a few, like CXCL12/SDF-1 and CX3CL1/fractalkine, are specific to one receptor. CX3CL1/fractalkine's only receptor, CX3CR1, is expressed predominantly by microglia and astrocytes (Boddeke et al., 1999; Lindia et al., 2005; Milligan et al., 2004), but has also been reported in hippocampal neurons (Meucci et al., 1998; Meucci

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et al., 2000). Opioid receptors are also members of the GPCR family. There are three major types of opioid receptors - mu, delta and kappa. Opioid receptors play important roles in many physiological functions, including modulation of pain perception and body temperature regulation (Adler and Geller 1993).

An interaction between opioids (mu and delta) and either the chemokine CCL5/RANTES or the chemokine CXCL12/SDF-1 alpha has been reported in vitro in chemotaxis and in vivo in the regulation of antinociception in rats (Grimm et al., 1998; Homan et al., 2002; Rogers et al., 2000; Rogers and Peterson 2003; Steele et al., 2002; Szabo and Rogers 2001; Szabo et al., 2001; Szabo et al., 2002; Zhang et al., 2004). The PAG is known to be the most important region of the brain involved in pain modulation (Basbaum and Fields, 1984). These chemokines and their receptors have been reported to be involved in blockade of the analgesic effects of opioids within the PAG (Szabo et al., 2002; Adler et al., 2006). On the basis of the studies showing their interference with opioid receptor function, the present experiments were designed to investigate the possibility of the interaction between the chemokine CX3CL1/fractalkine and mu, delta or kappa opioid agonists in antinociception in rats.

2. Results

2.1. The antinociceptive effect induced by PAG injection of CX3CL1/fractalkine

Rats were divided into 5 groups as follows: aCSF (vehicle), 1, 25, 50 and 100 ng CX3CL1/fractalkine. A PAG injection of CX3CL1/fractalkine or aCSF was given at time 0 as shown in Figure 1. CX3CL1/fractalkine, in the dose range tested, has no antinociceptive or hyperalgesic activity in the CWT test. A dose-dependence study for the chemokines CCL5/RANTES and CXCL12/SDF-1alpha on the analgesia induced by the mu opioid receptor agonist DAMGO (Szabo et al., 2002) showed that 100 ng CCL5/RANTES or CXCL12/SDF-1alpha totally blocked the DAMGO-induced analgesia. Thus, a dose of 100 ng CX3CL1/fractalkine was chosen for the subsequent experiments.

2.2. The effect of intra-PAG injection of CX3CL1/fractalkine (100 ng) on the antinociceptive effect induced by DAMGO

Rats were divided into 3 groups: aCSF + DAMGO, CX3CL1/fractalkine + saline, and CX3CL1/fractalkine + DAMGO. They were given a PAG injection of CX3CL1/fractalkine (100 ng) or vehicle a half-hour before PAG injection of saline or DAMGO. In figure 2, pretreatment with CX3CL1/fractalkine (100 ng) 30 min before DAMGO administration is shown to significantly reduce the antinociceptive effect induced by the mu opioid agonist DAMGO at a dose that has no effect by itself.

2.3. The effect of CX3CL1/fractalkine (100 ng, PAG) on the antinociceptive effect induced by DPDPE

In this experiment, the design was similar to that in the previous one, except for substitution of the DAMGO by DPDPE. The results, shown in figure 3, demonstrated that CX3CL1/fractalkine (100 ng), 30 min before 100 ng DPDPE administration, significantly reduced the antinociceptive effect induced by the delta opioid agonist DPDPE.

2.4. The effect of CX3CL1/fractalkine (100 ng, PAG) on the antinociceptive effect induced by dynorphin (1–17)

In this experiment, the design was similar to those with DAMGO or DPDPE, except for use of the kappa opioid agonist dynorphin. The data show that CX3CL1/fractalkine (100 ng), 30 min before the administration of 20 μg dynorphin, significantly reduced the antinociceptive effect induced by dynorphin (shown in figure 4).

3. Discussion

CX3CR1 is functionally unique among chemokine receptors in mediating direct cell-to-cell adhesion (Haskell et al., 1999; Imai et al., 1997). CX3CL1/fractalkine has been detected on neurons (Johnston et al., 2004) and has been found throughout rat brain (Milligan et al., 2004; Verge et al., 2004). This chemokine has been reported to be involved in atherogenesis and plaque destabilization in humans (Damas et al., 2005). It also appears to modulate the effects of intrathecal morphine, because coadministration of morphine with an intrathecal neutralizing antibody against the CX3CL1/fractalkine receptor potentiated acute morphine analgesia and attenuated the development of tolerance, hyperalgesia, and allodynia (Johnston et al., 2004).

DAMGO and DPDPE are synthetic opioid peptides that are selective for mu and delta opioid receptors, respectively (Handa et al., 1981; Mosberg et al., 1983). Dynorphin acts selectively on the kappa opioid receptor (Goldstein et al., 1979). All three opioid agonists produce significant antinociception in the CWT test (Chen et al., 1995; Xin et al., 1997). As shown in the above experiments, pretreatment with CX3CL1/fractalkine can significantly block the antinociceptive effect of the mu opioid receptor agonist DAMGO when both agents are administered into the PAG, the area of the brain most involved with analgesic responses. The kappa opioid receptor agonist dynorphin (1–17) and delta opioid receptor agonist DPDPE also show an antagonistic interaction with CX3CL1/fractalkine. Although CX3CL1/fractalkine has been reported to induce spinal nociceptive facilitation in the von Frey and Hargreaves tests (Milligan et al., 2005; Milligan et al., 2004), the results shown in figure 1 demonstrate that PAG injection of CX3CL1/fractalkine, at doses from 1 ng to 100 ng, is ineffective on its own and does not result in either antinociception or hyperalgesia in the CWT test. As compared to the total blockade by CCL5/RANTES and CXCL12/SDF-1 alpha of DAMGO antinociception (Szabo, et al., 2002), the same dose (100 ng, PAG) of CX3CL1/fractalkine in the present experiment only partially blocked the DAMGO antinociceptive effect. Intracerebroventricular administration of the opioid antagonist naloxone (1–10 μg) or the mu-selective antagonist CTAP (1 μg) antagonized morphine in a competitive fashion (Adams, et al., 1994). Because there is no evidence that chemokines can bind to opioid receptors, a naloxone-like antagonism is not a likely mechanism. The lack of a hyperalgesic effect of fractalkine makes a physiological antagonism also highly unlikely. For these reasons, in addition to our in vitro findings (Szabo et al., 2002), we suggest that a heterologous desensitization between chemokine and opioid receptors is the most plausible explanation.

Heterologous desensitization occurs when a GPCR, activated by an agonist, initiates a signaling process leading to the inactivation (desensitization) of an unrelated GPCR. Both the opioids and chemokines mediate their effects on leukocytes through the activation of GPCR. Oligomerization of mu, kappa and delta opioid receptors with the chemokine receptor CCR5 on the cell membrane of human or monkey lymphocytes has been reported and suggests that opioid receptors interact with CCR5 in cells coexpressing both receptors (Suzuki et al., 2002). The kappa opioid receptor has been shown to regulate thymocyte C-C Chemokine receptor 2 expression (Zhang and Rogers 2000) and a kappa agonist inhibits monocyte chemoattractant protein-1 (CCL2) production by human astrocytes (Sheng et al., 2003) and SDF-1alpha receptor CXCR4 expression on CD4+ lymphocytes (Lokensgard et al., 2002). In addition, unpublished data from our collaborators indicate the co-localization of both opioid and chemokine receptors in several brain areas, including PAG (L. Kirby, personal communication). Thus, there is some evidence that heterologous desensitization may occur between mu, kappa or delta opioid receptors and CX3CL1/fractalkine receptors in the brain of rats.

Another possible explanation as to why fractalkine blocks the antinociception induced by opioid agonists might be that fractalkine binds to microglial cells (Verge et al., 2004), which then cause the release of proinflammatory cytokines (interleukin 1, IL-1) (Johnston et al., 2004; Milligan et al., 2005). It is possible that this may contribute to the results of the present study, as fractalkine-induced release of proinflammatory cytokines occurs very rapidly, in accord with the speed of effects observed here. In some reports (Johnston et al., 2004; Watkins et al., 2006; Shavit et al., 2005), IL-1 decreased the antinociceptive effects of morphine in the mice hot-plate tail-flick test and the rat thermal tail flick test. However, IL-1 has no antinociceptive effect alone nor did it affect morphine antinociception in the rat hot-plate test or in the cold-water (−3°C) tail-flick test (Adams et al., 1993).

Our laboratories were the first to report an apparent in vivo inactivation of mu and delta opioid receptors by chemoattractant factors CCR5 and CXCR4 (Chen et al., 2007; Szabo et al., 2002). Similarly, the present studies demonstrated the interaction between the mu, delta or kappa opioid agonists and CX3CL1/fractalkine in vivo. These findings suggest that the analgesic activity of the opioids in the brain can be overcome in situations in which there are elevated levels of chemokines and thus open up new avenues of research for pain management.

4. Experimental Procedures

4.1. Animals

Male Sprague-Dawley rats (Zivic-Miller), weighing 175–200 g, were housed in groups of 3–4 for at least 1 week in an animal room maintained at 22±1°C and approximately 50±5% relative humidity. Lighting was on a 12/12 h light/dark cycle (lights on at 7:00 and off at 19:00). All tests were performed during the light part of the rats' light-dark cycle in the present experiments. Rats were allowed free access to food and water. All animal use procedures were conducted in strict accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and were approved by the Institutional Animal Care and Use Committee.

4.2. Surgery procedures

Rats were anesthetized with a mixture of ketamine hydrochloride (100–150 mg/kg) and acepromazine maleate (0.2 mg/kg). A sterilized stainless steel C313G cannula guide (22 gauge, Plastic One) was implanted into the lateral PAG and fixed with dental cement. The stereotaxic coordinates for PAG were as follows: bite bar 3.3 mm below 0, 7.8 mm posterior to bregma, 0.5 mm from midline and 5 mm ventral to the dura mater (Paxinos and Watson, 1998). A C313DC cannula dummy (Plastic One) of the identical length was inserted into the guide tube to prevent its occlusion. The animals were housed individually after surgery. Experiments began 1 week postoperatively. Each rat was used only once. At the end of the experiment, cannula placements were verified using microinjection of 1% bromobenzene blue according to the standard procedures in our laboratory (Xin et al., 1997).

4.3. Nociceptive test

The latency to flick the tail in cold water was used as the antinociceptive index, according to a standard procedure in our laboratory (Pizziketti et al., 1985). A 1:1 mix of ethylene glycol:water was maintained at −3°C with a circulating water bath (Model 9500, Fisher Scientific; Pittsburgh, PA). Rats were held over the bath with their tails submerged approximately half-way into the solution. All animals were tested at 60, 15 and 0 min before drug injection. For each animal, the first reading was discarded and the mean of the second and third readings was taken as the baseline value. Rats whose baseline values fell within a range of 10 to 20 s were used in the experiments. About 5% of them were discarded. Latencies to tail flick after injection were expressed as percentage change from baseline. The percentage

of maximal possible antinociception (MPA%) for each animal at each time was calculated using the formula: %MPA = [(test latency − baseline latency)/(60 − baseline latency)] × 100. A cutoff limit of 60 s was set to avoid damage to the tail.

4.4. Drugs

The mu opioid receptor agonist (D-Ala2,N-Me-Phe4,Gly5-ol)enkephalin (DAMGO) (Handa et al., 1981), delta opioid receptor agonist [D-Pen2, D-Pen5]-enkephalin (DPDPE) (H-Tyr-D-Pen-Gly-Phe-D-Pen-OH) (Mosberg et al., 1983) and kappa opioid receptor agonist dynorphin A (1–17) (H-Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln-OH) (Goldstein et al., 1979) were made by Multiple Peptide Systems, San Diego, CA. These drugs were dissolved in the 0.9% saline.

CX3CL1/fractalkine, a DNA sequence encoding the mature 76-amino-acid variant (amino acid residues 25 – 100) of the chemokine domain of the mature rat CX3CL1 protein sequence (Harrison et al., 1998), was obtained from R&D System, Minneapolis, MN. CX3CL1/fractalkine was dissolved in artificial cerebrospinal fluid (aCSF, CMA Microdialysis AB, MA).

4.5. Injections

One week after surgery, either chemokine and aCSF or opioid agonists and saline were injected into the PAG in a volume of 1.0 μl over a 30-second period. With aseptic procedures, the C313I internal cannula (28 gauge, Plastics One) was connected to a 10 μl Hamilton syringe by polyethylene tubing. CX3CL1/fractalkine was administered 30 min before 400 ng DAMGO, 100 ng DPDPE or 20 μg dynorphin.

4.6. Statistical analysis

The data are expressed as the mean and standard error. Statistical analysis of difference between groups was assessed with an analysis of variance (ANOVA) followed by Tukey's test. $P \leq 0.05$ was taken as the significant level of difference.

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Abbreviations

PAG

periaqueductal grey

CWT

Cold water tail-flick test

aCSF

artificial cerebrospinal fluid

MPA%

the percentage of maximal possible antinociception

DAMGO

(D-Ala2,N-Me-Phe4,Gly5-ol)enkephalin

DPDPE

(H-Tyr-D-Pen-Gly-Phe-D-Pen-OH)enkephalin

Dynorphin A (1-17)

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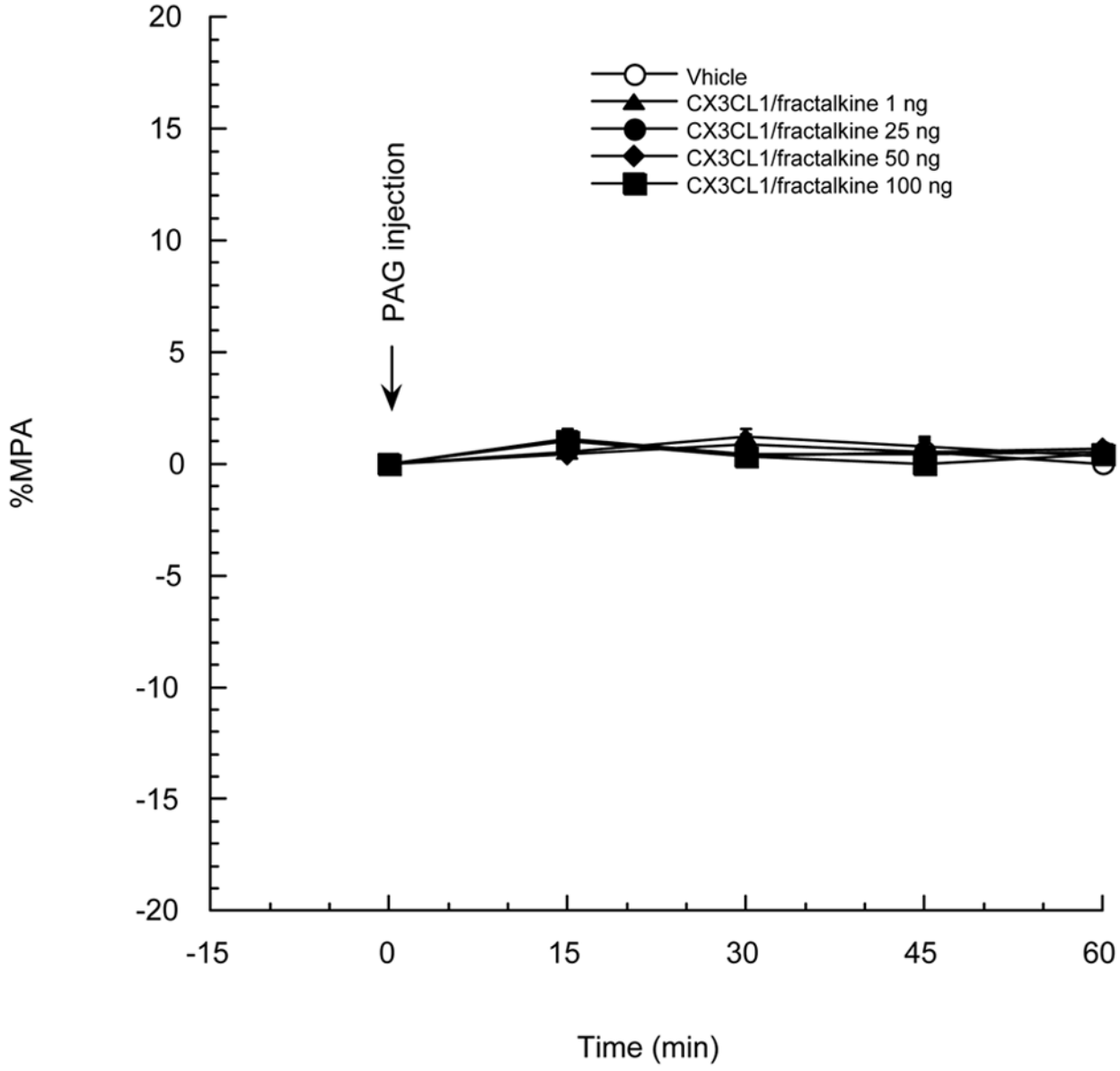

Figure 1.
Rats were divided into 5 groups and were given a PAG injection of CX3CL1/fractalkine 1, 25, 50, 100 ng or vehicle, respectively. P>0.05 between all two groups. N=5–6 per group. Each point represents the mean + SE.

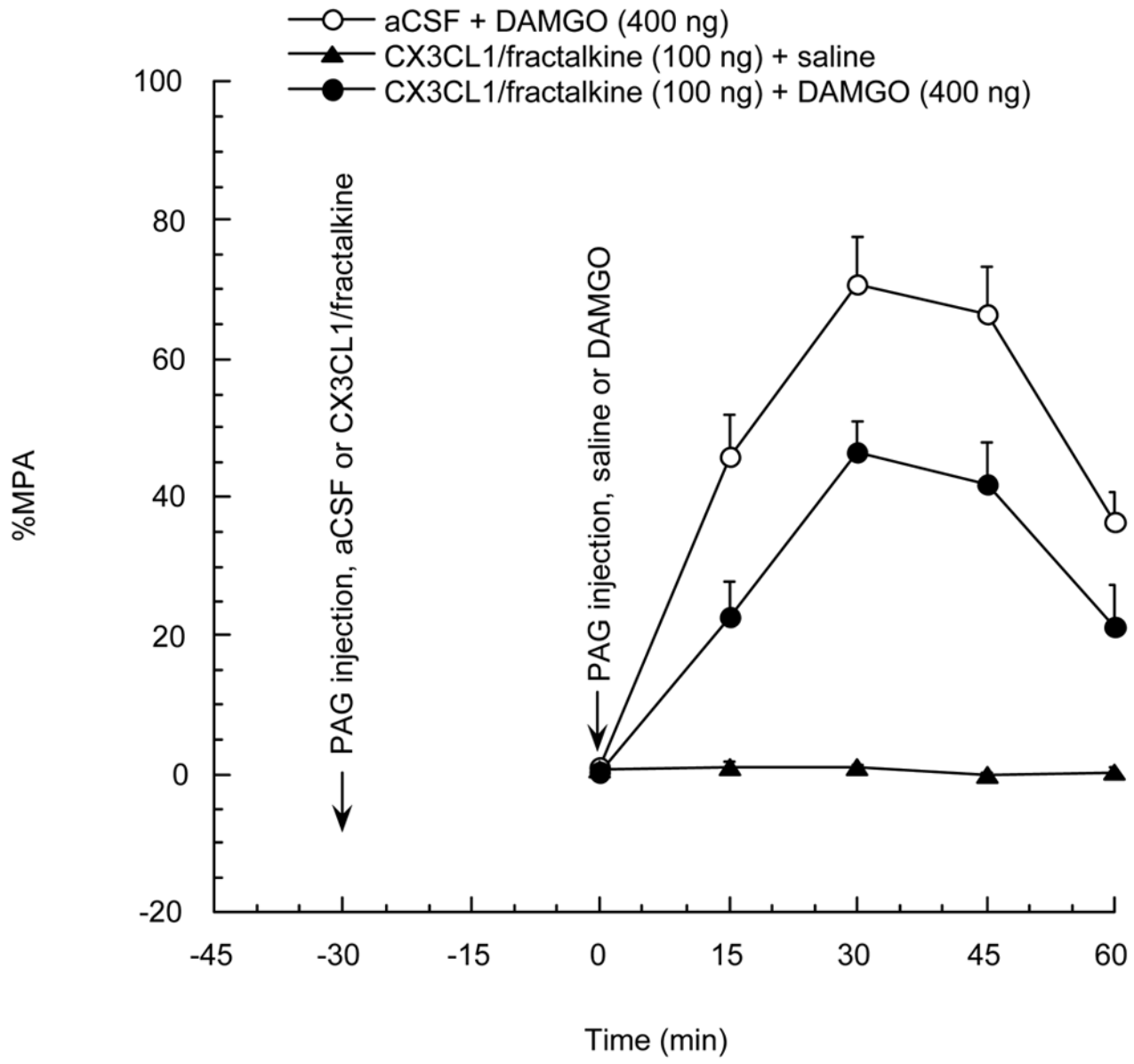

Figure 2.

Rats were divided into 3 groups and were given a PAG injection of CX3CL1/fractalkine 100 ng or vehicle 30 min before PAG injection of DAMGO 400 ng or saline, respectively. $P<0.05$ for aCSF + DAMGO group vs CX3CL1/fractalkine + DAMGO group. N=3–4 per group. Each point represents the mean + SE.

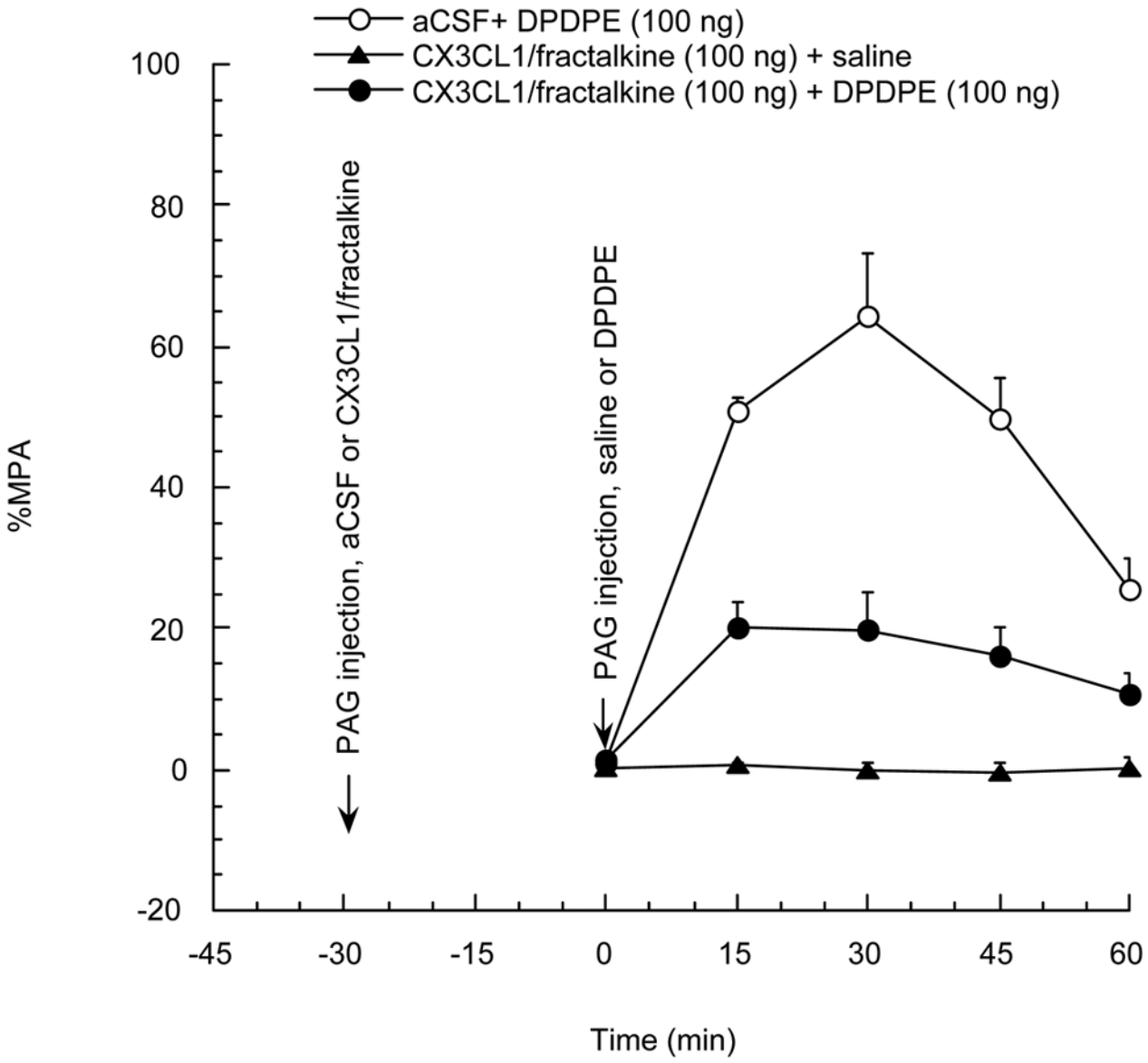

Figure 3.

Rats were divided into 3 groups and were given a PAG injection of CX3CL1/fractalkine 100 ng or vehicle 30 min before PAG injection of DPDPE 100 ng or saline, respectively. $P<0.05$ for aCSF + DPDPE group vs CX3CL1/fractalkine + DPDPE group. N=3–4 per group. Each point represents the mean + SE.

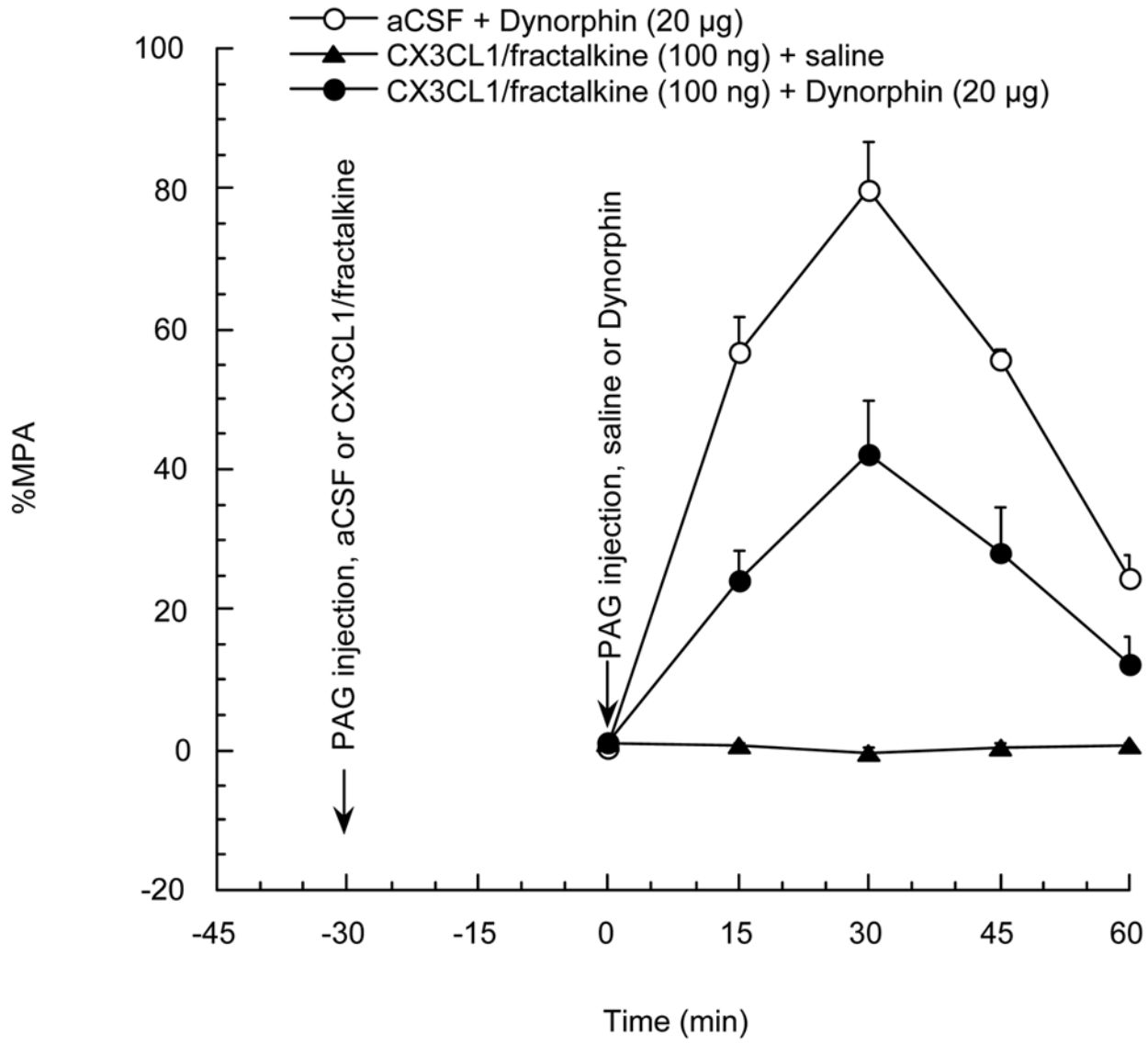

Figure 4.

Rats were divided into 3 groups and were given a PAG injection of CX3CL1/fractalkine 100 ng or vehicle 30 min before PAG injection of dynorphin 20 µg or saline, respectively. $P<0.05$ for aCSF + dynorphin group vs CX3CL1/fractalkine + dynorphin group. N=3–5 per group. Each point represents the mean + SE.