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# Buprenorphine blocks diffuse noxious inhibitory controls in the rat

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**Abstract**

A C-fibre reflex elicited by electrical stimulation within the territory of the sural nerve was recorded from the ipsilateral biceps femoris muscle in anaesthetised rats. Such reflex responses can be inhibited by applying noxious conditioning stimuli to heterotopic areas of the body. These inhibitory processes have been termed diffuse noxious inhibitory controls. The responses were recorded before, during and after the immersion of the tail in a thermoregulated waterbath (at 50°C) for 1 min. The C-fibre reflex responses were depressed by a maximum of 71 ± 3% at 45 s after the start of such conditioning stimuli. A dose of 3 μg/kg buprenorphine completely blocked the inhibition and post-stimulus effects triggered by the heterotopic noxious stimuli. In the 0.3–3 μg/kg range, buprenorphine increased, in a dose-dependent manner, the magnitude of the inhibition. These doses did not produce any changes in the C-fibre reflex itself. The results are discussed in terms of the mechanisms underlying the analgesic properties of buprenorphine.

*Keywords:* C-fiber reflex; Buprenorphine; Nociception; Diffuse noxious inhibitory control; Descending inhibitory control; Spinal cord; Morphine

## 1. Introduction

Buprenorphine is a partial agonist of opioid receptors, with a high lipid solubility and high receptor affinity but a low intrinsic activity (Dum and Herz, 1981; Boas and Villiger, 1985). Because of these pharmacological properties, its clinical applications have been restricted to the control of postoperative pain (Harcus et al., 1980; Ellis et al., 1982).

It is well established that in animals and humans, opioid analgesia results from actions occurring at both spinal and supraspinal sites. The spinal action involves a potent depression of the transmission of nociceptive signals from the first relays in the central nervous system, i.e., the dorsal horn neurons of the spinal cord (see Duggan and North, 1984; Yaksh and Noueihed, 1985). In the rat, the C-fibre reflex is a useful tool for pharmacological studies of spinal nociceptive transmission (Strimbu-Gozariu et al., 1993; Guirimand et al., 1994). We reported recently that buprenorphine, whether applied via an intravenous, intrathecal or intracerebroventricular route, facilitated the C-fibre reflex and did not block spinal transmission of nociceptive signals (Guirimand et al., 1995a, b). The lack of a direct or indirect depressive spinal effect suggested that understanding the mechanism of action of buprenorphine required other hypotheses implicating supraspinal sites of action (Guirimand et al., 1995a, b). In fact, a second, indirect and complementary, antinociceptive action of opioids can result from their effects at some brain sites where they can modulate descending inhibitory controls which in turn modulate signals of pain. A number of studies, using intracerebral microinjection techniques, have focused on the involvement of particular supraspinal areas in morphine analgesia, e.g. the periaqueductal gray and nucleus raphe magnus (for a review, see Yaksh and Malmberg, 1994). However, although some electrophysiological studies in rats and cats support the proposal that morphine increases descending inhibitory controls (Bennett and Mayer, 1979; Jurna and Zetler, 1985; Gebhart et al., 1984; Du et al., 1984), other results lead to the opposite conclusion, namely that morphine decreases descending inhibitory controls

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(Sinclair, 1986; Bouhassira et al., 1988; Le Bars et al., 1980; Llewelyn et al., 1987; Dickenson and Le Bars, 1987a, b). Electrophysiological studies both in experimental animals (Le Bars et al., 1981) and in man (Le Bars et al., 1992) support the hypothesis that low systemic doses of morphine exhibit antinociceptive properties by blocking those descending inhibitory controls which are triggered by noxious stimuli and termed diffuse noxious inhibitory controls (see Discussion). In man, a 0.05 mg/kg intravenous dose of morphine did not induce any change in the $R_{III}$ reflex, indicating a lack of direct depressive effect; however such a dose completely blocked the inhibitory effects of heterotopic noxious thermal stimuli, thus suggesting a supraspinal site of action (Le Bars et al., 1992). The analgesic effects of low doses of morphine probably involve such mechanisms. By analogy with morphine, it has been proposed that buprenorphine produces analgesia by modulating descending inhibitory systems originating from the brainstem and acting on spinal nociceptive neurons.

The present study was designed to test this hypothesis using systemic injections of buprenorphine and noxious thermal conditioning stimuli.

## 2. Materials and methods

### 2.1. Animal preparation

The general procedure was very similar to those described previously (Strimbu-Gozariu et al., 1993; Guirimand et al., 1994). In brief, experiments were carried out on Sprague-Dawley rats, weighing 350–400 g. During surgery (tracheotomy and cannulation of a jugular vein), the animals were deeply anaesthetised with 2.5% halothane in a nitrous oxide/oxygen mixture (2/3:1/3). After surgery, the concentration of halothane was lowered to 1.2% in 100% oxygen. Throughout the experiments, the animals were artificially ventilated (50 counts/min) and the heart rate was monitored continuously. The levels of $O_2$, end-tidal $CO_2$ (3.2–3.5%) and halothane (1.2%) were monitored continuously using a capnometer (Capnomac II, Datex Instruments, Helsinki, Finland). The measurements of $CO_2$ and halothane were performed by infra-red absorbtion and that of $O_2$ by a fast paramagnetic analyzer. These parameters were displayed digitally and were linked to an alarm. Body temperature was maintained at $37 \pm 0.5$°C by means of a homeothermic blanket system.

### 2.2. Electrophysiological recordings

The methods employed have been described previously (Strimbu-Gozariu et al., 1993; Guirimand et al., 1994, 1995a; Falinower et al., 1994). Electrophysiological recordings of C-fibre reflex activity elicited by electrical stimulation within the receptive field of the ipsilateral sural nerve were made from the biceps femoris muscle. For this purpose, a pair of non-insulated platinum-iridium needle electrodes was inserted subcutaneously in the medial part of the fourth and the lateral part of the fifth toe. Electromyographic (EMG) responses were recorded with another pair of non-insulated platinum-iridium needles that were inserted through the skin into the biceps femoris muscle.

The electrical stimuli were single square-wave shocks of 2 ms duration and were delivered once every 6 s from a constant current stimulator. The stimulus intensities and the EMG responses were fed to an oscilloscope for continuous monitoring and to a computerised system which digitized and recorded the EMG from 50 ms before until 450 ms after the start of the stimulus. The digitized EMG recordings were full-wave rectified and the C-fibre-evoked responses were integrated within a time-window starting 150 ms and finishing 450 ms after the start of the stimulus. The individual reflex responses were plotted either against time to allow the study of their temporal evolution or against stimulus intensity to build recruitment curves. The integrals were expressed in millivolts × milliseconds (mV × ms) and the current intensities in milliamperes (mA).

### 2.3. Control period characteristics and conditioning procedure

All experiments started with a control period during which the characteristics of the reflex were determined. Then, 20–30 min after the end of surgery and decrease in the level of anaesthesia (i.e. when the expired halothane was reduced to 1.2%), the application of 15 mA stimuli to the sural nerve receptive field resulted in stable supramaximal reflex responses which showed minimal fluctuations. This preliminary finding was regarded as a prerequisite for starting the conditioning procedure. In order to determine the threshold of the C-fibre reflex, a control recruitment curve was built by increasing the stimulus intensity. Reflex responses increased monotonically and reached a plateau at high intensities. The threshold of the C-fibre-evoked response was defined as being the intersection of the polymodal regression curve and the abscissa (see Guirimand et al., 1994). Thereafter, constant-current stimuli (1.5 × threshold) were applied. The stability of EMG responses was then checked for a period of 10 min.

As reported previously, various noxious (thermal or mechanical) heterotopic conditioning stimuli produced clear-cut depressions of C-fibre reflex activity (Falinower et al., 1994). Thermal conditioning stimuli were delivered using a thermoregulated (50°C) and agitated waterbath into which the tail was immersed up

to 2/3 of its length. This temperature was chosen following pilot studies and based on previous reports (Falinower et al., 1994) which concluded that inhibition was related to the temperature of the bath in the 47–52°C range. These conditioning procedures were applied for 1 min with an interval of at least 10 min between successive tests. Such an interval was chosen to allow the study of post-stimulus effects and to avoid any phenomenon of sensitization of skin receptors (Beitel and Dubner, 1976; Lamotte et al., 1982) which could introduce bias into the results. Two conditioning tests were performed during the control period.

### 2.4. Pharmacological procedure and processing of data

The effects of intravenous buprenorphine hydrochloride (Schering-Plough) on diffuse noxious inhibitory controls were determined for four doses of the drug (0.3, 1, 2 and 3 μg/kg) and compared to those of saline, using the analysis of variance. Drugs were injected over a period of 30 s. The two conditioning procedures were repeated 30 min after the administration of the drug. For each sequence, the mean control response was calculated over the 3 min preceding the conditioning period and each reflex response of the sequence was expressed as a percentage of this mean. Calculating the areas under the time-course curves between the start of the conditioning test and a 3 min post-stimulus period provided an overview of the inhibitory processes and allowed a comparison of the effects of saline and various doses of buprenorphine. In order to analyse these effects in more detail, the percentage inhibition due to diffuse noxious inhibitory controls in each individual sequence, was calculated with reference to the unconditioned C-fibre reflex responses in that particular sequence. Inhibitions were calculated during the first 30 s of immersion of the tail. For each animal, the percentage decrease in diffuse noxious inhibitory controls was calculated as:

$$100 \times \left(1 - \frac{\text{mean inhibition after injection}}{\text{mean control inhibition}}\right)$$

A mean dose-response curve was built on a semilogarithmic plot to illustrate the effect of buprenorphine on diffuse noxious inhibitory controls. Least squares linear regression was used for curve fitting and analysis of variance was performed to test the linearity of the dose-response curve. Results were considered significant at $P < 0.05$. The data are expressed as means ± S.E.M. Each dose was studied in five to seven rats, each of which was used only once.

## 3. Results

### 3.1. General findings

The experimental procedure consisted of sequences during which the C-fibre reflex elicited by stimulation

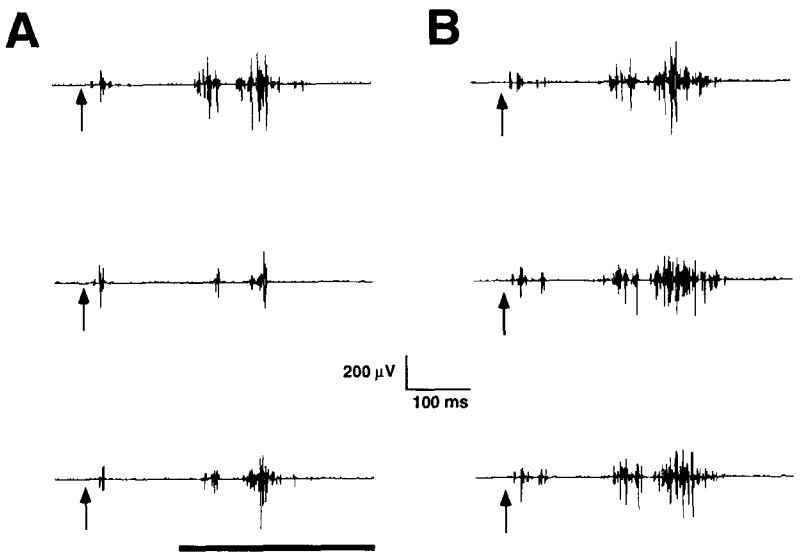


Fig. 1. Individual examples of reflex responses to C-fibre activation: EMG recordings from the biceps femoris. The responses were elicited by electrical stimulation (2 ms duration; 1.5 × threshold intensity) of the sural nerve territory at the time indicated by an arrow. The responses were analysed within a 150–450 ms post-stimulus time-window (horizontal bar). The upper traces were recorded before the conditioning procedure. The intermediate traces were recorded during the conditioning procedure, i.e. immersion of the tail for 1 min in a 50°C waterbath. The lower traces were recorded during the 3 min after the conditioning procedure (post-stimulus effects). (A) Recordings during the control period. The C-fibre reflex responses were depressed during and after the application of the heterotopic noxious thermal stimuli. (B) 30 min following 3 μg/kg intravenous buprenorphine, no change occurred in the control response (upper traces) but the depression of C-fibre reflex triggered by heterotopic noxious stimuli was completely blocked (middle traces). Post-stimulus effects were also completely blocked (lower traces).

of the sural nerve was recorded before, during and after the application of a noxious thermal conditioning stimulus (50°C) to the tail. Such sequences were performed before and 30 min following the administration of saline or buprenorphine. Buprenorphine blocked the inhibition elicited by the heterotopic noxious stimulus in a dose-dependent manner.

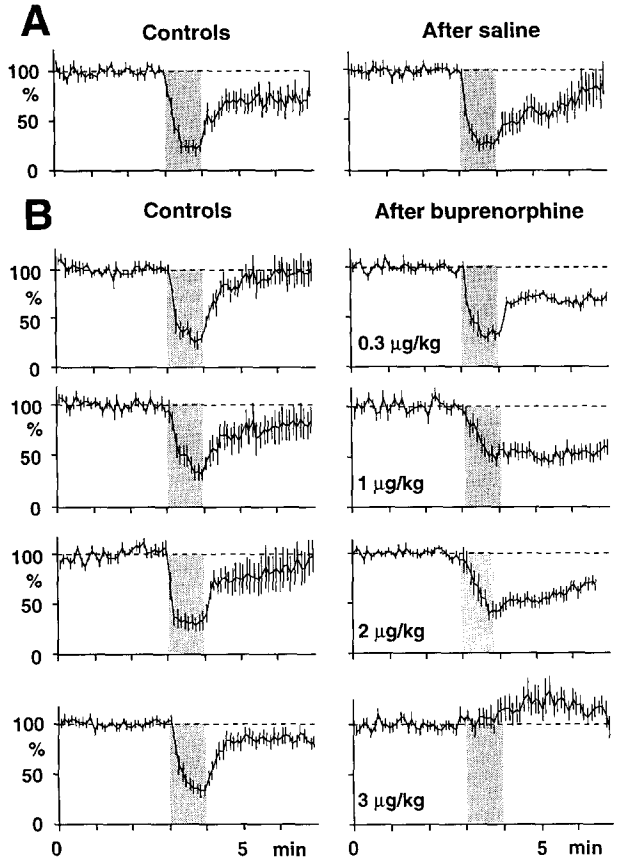


Fig. 2. Overall results showing the time courses of the effects of saline or buprenorphine on diffuse noxious inhibitory controls. Ordinate: C-fibre-evoked EMG responses, elicited by a constant stimulus intensity (1.5 × threshold for the C-fibre reflex in the control situation) and expressed as percentages of the mean control values calculated during the 3 min period preceding the conditioning procedure. Saline (A) or buprenorphine (B) was injected following a control period of at least 10 min. For clarity of presentation, only the 3 min before and after the conditioning procedure are represented. The shaded areas represent the 1 min period of the conditioning procedure. For each dose, the mean result from five to seven rats was considered while for each animal, the mean result from two conditioning tests separated by an interval of more than 10 min was considered. Saline (A) and 0.3 µg/kg buprenorphine did not modify the depression of the C-fibre reflex seen during and after the application of the heterotopic noxious stimuli. Buprenorphine (1 and 2 µg/kg) reduced the inhibitions elicited by heterotopic stimuli and delayed them by comparison with the controls. Buprenorphine (3 µg/kg) completely blocked the depression of the C-fibre reflex induced by the application of a heterotopic noxious stimulus. This dose also completely blocked post-stimulus effects.

### *3.2. Characteristics of the reflex, and effects of the heterotopic noxious conditioning stimulus in the control period*

As described previously (Strimbu-Gozariu et al., 1993; Guirimand et al., 1994, 1995a; Falinower et al., 1994), electrical stimulation within the receptive field of the sural nerve elicited a two-component response in the ipsilateral biceps femoris muscle. The first component had a short latency (10–100 ms) and a low threshold. The second had a longer latency (150–450 ms) and a higher threshold (10.4 ± 0.5 mA). This latter threshold was higher than that reported in a previous study (6.8 ± 0.2 mA; Guirimand et al., 1994) in which a lower concentration of halothane was used (0.9% as opposed to 1.2% in the present study). The first component of the reflex response is probably due to activation of myelinated cutaneous afferent fibres; it has been demonstrated that the second is elicited by activation of unmyelinated afferent fibres and thus it has been termed the C-fibre reflex (Falinower et al., 1994). The present work focused on the analysis of this C-fibre reflex elicited by a stimulus intensity of 1.5 × threshold.

Fig. 1 shows individual examples of electromyographic responses elicited by a 1.5 × threshold stimulus intensity. These reflexes exhibit the classical electrophysiological features of a polysynaptic reflex. As illustrated in Fig. 1A, the C-fibre reflex responses were strongly depressed during (middle trace) and after (lower trace) the application of the noxious thermal (50°C) conditioning stimuli to the tail. The overall time courses of the inhibitory effects elicited by the heterotopic noxious stimulus are shown in Fig. 2A. In the control periods, there were no statistical differences between the various experimental groups. Pooling all data from the control periods allowed the characteristics of these inhibitions to be determined carefully: the depressive effects appeared rapidly, within less than 6 s of the start of the conditioning stimulus; the maximal effect (71 ± 3%) occurred 45 s following the start. This depressive effect outlasted the conditioning period by several min: for example, 3 min after removal of the tail from the hot water, there remained an inhibition of 15 ± 4%.

### *3.3. Characteristics of responses following intravenous buprenorphine*

#### *3.3.1. Effects of buprenorphine on the C-fibre reflex responses*

As shown in the individual example (Fig. 1A,B, upper traces), no change in the reflex response was seen when 3 µg/kg buprenorphine was injected. In order to analyse the effects of buprenorphine, the reflex responses recorded 30 min after the injection of saline or buprenorphine over a 3 min period preceding

the conditioning test, were expressed as percentages of the corresponding control period (the 3 min preceding the first conditioning test). The analysis of variance was used to compare the effects of buprenorphine with those of saline. Buprenorphine in the 0.3–3 μg/kg range never induced a significant change in the unconditioned C-fibre reflex responses, at least not at the low stimulus intensity (1.5 × threshold) used in this study ($F(4,49) = 1.01$; $P = 0.41$).

*3.3.2. Effects of buprenorphine on diffuse noxious inhibitory controls*

As shown by in the individual example (Fig. 1B, middle trace), the inhibition of the C-fibre reflex elicited by immersion of the tail in 50°C water, was completely blocked following the injection of 3 μg/kg buprenorphine. Overall, buprenorphine blocked the depressive effect induced by the conditioning heterotopic noxious stimuli in a dose-dependent manner. Following 0.3 μg/kg buprenorphine, no changes were noticed (Fig. 2B). Intermediate doses (1 and 2 μg/kg) reduced the inhibitions (Fig. 2C,D) while 3 μg/kg buprenorphine completely blocked all inhibitions (Fig. 2E). When the areas under the time-course curves starting at the beginning of the conditioning stimulus and lasting 4 min were analysed, only the highest dose of buprenorphine (3 μg/kg) achieved a statistically significant effect in comparison with the controls ($P < 0.0001$). More detailed analysis showed that following 1 and 2 μg/kg buprenorphine, the depressive effect appeared later than it did during the control periods. This phenomenon is shown in Fig. 3 in which the first 30 s after the onset of the conditioning stimulus are considered: the percentage decrease in the inhibitions elicited by the heterotopic noxious stimuli increased with the dose. This percentage was linearly related to the logarithm of the dose in the 0.3–3 μg/kg range. Over a longer period, the decrease in diffuse noxious inhibitory controls was less significant, suggesting that the phenomenon was slowed but not abolished.

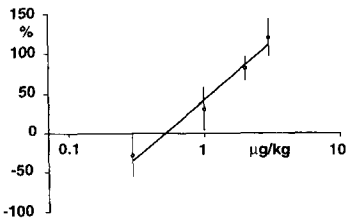


Fig. 3. Dose-response relationship for the effects of buprenorphine on diffuse noxious inhibitory controls. The dose-response curve was built by plotting on a semi-logarithmic scale the percentage reductions in diffuse noxious inhibitory controls, calculated during the first 30 s after the start of the conditioning stimulus (ordinate) with respect to the dose (abscissa). The relationship was linear in the 0.3–3 μg/kg range ($F(1,19) = 27.7$; $P < 0.01$).

## 4. Discussion

The results of the present study confirmed that the C-fibre reflex can be strongly inhibited by a heterotopic noxious thermal stimulus. Low doses of intravenous buprenorphine, which did not modify the characteristics of the C-fibre reflex itself, blocked in a dose-dependent fashion these inhibitory effects triggered by heterotopic noxious conditioning stimuli.

*4.1. Effects of a noxious conditioning stimulus on the C-fibre reflex response*

It was reported recently that, in normal anaesthetised rats, electrical stimulation within the territory of the sural nerve elicited a C-fibre reflex which was inhibited by noxious conditioning stimuli (Falinower et al., 1994). When the conditioning stimulus was immersion of the hind paw or tail in a thermoregulated waterbath, these inhibitions were temperature-dependent. As discussed elsewhere (Falinower et al., 1994), such inhibitory processes are very reminiscent of diffuse noxious inhibitory controls, which modulate the activities of dorsal horn convergent neurons (for a review, see Le Bars et al., 1986, 1995). The principal feature of diffuse noxious inhibitory controls is that they can be triggered by conditioning stimuli applied to any part of the body distant from the excitatory receptive field of the neuron under study, provided that the stimuli are clearly noxious. With strong stimuli, the inhibitory effects are powerful and are followed by long-lasting after-effects which can persist for several min. We chose immersion of the tail in a 50°C thermoregulated waterbath as the conditioning stimulus in the present study, although preliminary studies had indicated that immersion of the contralateral hind paw elicited stronger inhibition. In the latter case, the inhibitions resulted from synergy between two inhibitory processes: 1 – diffuse noxious inhibitory controls, which involves supraspinal structures; 2 – propriospinal mechanisms which were revealed by the presence of such effects in spinal animals. In contrast, immersion of the tail triggers inhibitions which disappear completely in spinal rats (Falinower et al., 1994). Since our purpose was to test buprenorphine on supraspinally mediated inhibitory mechanisms, we chose immersion of the tail as the conditioning stimulus. The immersion of the tail in a 50°C waterbath induced powerful inhibitory effects followed by long-lasting post-stimulus effects that could persist for several min.

In order to limit pharmacological interactions as much as possible, we deliberately used halothane as single anaesthetic agent. Pilot studies indicated that 1.2% end-tidal halothane was a good choice for studying diffuse noxious inhibitory controls under our experimental conditions. Lower concentrations (i.e. < 1.1%)

resulted in tonic electromyographic discharges when such a strong noxious conditioning stimulus was applied. During the same period, other muscles (e.g. thoracic) also exhibited such electromyographic discharges, suggesting that there may have been a partial, weak awakening of the animal, albeit without movement. Morgan et al. (1994) reported recently that the application of a spatially remote noxious stimulus shortened the latency for a hindpaw withdrawal reflex movement. The low level of halothane (0.6–1.2%) used in that study could, at least partly, explain such a result. Pilot studies indicated that higher concentrations of halothane (i.e. > 1.4%) resulted in a depressive effect on the C-fibre reflex itself and a lack of inhibitions triggered by noxious conditioning stimuli. The latter effect was probably due to the blocking effects of halothane on both diffuse noxious inhibitory controls and the spinal transmission of nociceptive signals. Thus it appears that studies of diffuse noxious inhibitory controls acting on reflexes requires the use of a narrow range of halothane concentrations. Interestingly, the threshold of the C-fibre reflex studied with the present level of anaesthesia was higher than that for responses elicited at a lower concentration of halothane in $O_2$ (Guirimand et al., 1994) or in an $O_2/N_2O$ mixture (Falinower et al., 1994).

Kalliomäki et al. (1992) reported recently that the withdrawal reflexes of various hindlimb muscles were controlled differentially by descending pathways activated by distant noxious stimuli, suggesting that withdrawal reflexes of different hindlimb muscles are mediated by different spinal pathways. These authors reported that conditioning stimuli elicited inhibitory effects on withdrawal reflexes in extensor digitorum brevis, extensor digitorum longus, the anterior tibialis and posterior biceps muscles. In contrast, withdrawal reflexes in the interossei muscles were reported to be strongly potentiated. Earlier reports had described only depressive effects of remote conditioning stimuli on reflex responses: the reflex discharge in the common peroneal nerve following electrical stimulation of the sural nerve in the rat was inhibited by pinching the muzzle or tail (Schouenborg and Dickenson, 1985); the gastrocnemius medialis reflex evoked by sural nerve stimulation in the decerebrate rabbit was inhibited by electrical stimulation of the contralateral common peroneal or either the ipsi- or contralateral median nerves (Taylor et al., 1991); the digastric reflex evoked by tooth-pulp stimulation in the cat was found to be inhibited by toe pinch, percutaneous electrical stimulation of a limb or electrical stimulation of the saphenous nerve (Cadden, 1985; Clarke and Matthews, 1985). Our results confirmed that the withdrawal reflex in biceps femoris can be depressed by noxious conditioning stimuli. These inhibitions and diffuse noxious inhibitory controls acting on the convergent neurons of the dorsal horn suggest that at least some convergent neurons are likely to be intercalated in the withdrawal reflex pathways (Schouenborg and Dickenson, 1985; Schouenborg and Sjölund, 1983; Kalliomäki et al., 1992; Falinower et al., 1994). Concomitant recordings of dorsal horn neurons and reflex activities confirm parallels between their behaviours in various physiological and pharmacological situations, thus providing further evidence that dorsal horn convergent neurons are incorporated in the neuronal circuitry responsible for the reflexes.

### *4.2. Buprenorphine blocks diffuse noxious inhibitory controls*

We have reported here that doses of 0.3–3 $\mu$g/kg buprenorphine induced no change in the C-fibre reflex response evoked by a low stimulus intensity (1.5 × threshold). This intensity was chosen in the light of our previous finding that the C-fibre reflexes evoked by stimulus intensities higher than 2–4 × threshold were facilitated following 1 and 3 $\mu$g/kg intravenous buprenorphine (Guirimand et al., 1995a). Naloxone was not injected following buprenorphine because it had been found that this drug never reversed the effects of buprenorphine on the C-fibre reflex responses (Guirimand et al., 1995aGuirimand et al., 1995b). This lack of naloxone reversibility has already been described for other experimental (Dickenson et al., 1990; Cowan et al., 1977) and clinical situations (Knape, 1986; Thorn et al., 1988).

We reported previously that low doses of intrathecal or intracerebroventricular buprenorphine facilitated the C-fibre reflex, indicating that the antinociceptive properties of this drug cannot be related primarily to a direct or indirect spinal depressant effect (Guirimand et al., 1995b). Since intrathecal buprenorphine also enhanced the C-fibre-evoked responses of dorsal horn convergent neurons (Dickenson et al., 1990), it is clear that, at least at low doses, this drug does not have a spinal depressive effect. Note however that high intrathecal or intracerebroventricular doses were able to depress the C-fibre reflex elicited by low stimulus intensities, possibly because the spinal effect requires a large occupancy of spinal opioid receptors (Guirimand et al., 1995b). In any case, these experimental data cannot explain the analgesic properties of buprenorphine: in man, buprenorphine exhibited analgesic properties following intravenous doses in the 3–10 $\mu$g/kg range, which did not depress the C-fibre reflex in the rat, suggesting that mechanisms other than a direct spinal effect might induce analgesia (Guirimand et al., 1995b). By analogy with the proposed antinociceptive mechanism of low doses of morphine, this mechanism could be related, at least partly, to blockade of diffuse noxious inhibitory controls.

We have suggested in some detail elsewhere that

diffuse noxious inhibitory controls may provide a physiological basis for a system for detecting nociceptive signals (Bouhassira et al., 1988; Le Bars et al., 1986, 1995). In brief, a fundamental property of convergent neurons is that they respond to both noxious and non-noxious stimuli. The emergence of a nociceptive signal from a 'background spinal noise' requires two conditions: excitation of nociceptive neurons and reduction in the activity of all other neurons which are not directly concerned with the nociceptive input. This last condition results from activation of diffuse noxious inhibitory controls which involve a spino-bulbo-spinal loop. The supraspinal structures involved in diffuse noxious inhibitory controls include the subnucleus reticularis dorsalis (Bouhassira et al., 1992b), a structure in the more caudal part of the brainstem which contains neurons that probably play a key role in the processing of specifically nociceptive information (Bing et al., 1990; Roy et al., 1992; Villanueva et al., 1988, 1989). Note that other more rostral structures are not involved in diffuse noxious inhibitory controls: the periaqueductal grey, cuneiform nucleus, parabrachial area, locus coeruleus/subcoeruleus, rostral ventromedial medulla including nucleus raphe magnus and the gigantocellular and paragigantocellular nuclei (Bouhassira et al., 1990, 1992a, 1993).

The effects of morphine on diffuse noxious inhibitory controls have been widely discussed: diffuse noxious inhibitory controls are blocked by morphine administered either in low systemic doses (Le Bars et al., 1981), intracerebrally within nucleus raphe dorsalis (Dickenson and Le Bars, 1987a, b) or intracerebroventricularly (Bouhassira et al., 1988). In all these studies, the dose of morphine which blocked diffuse noxious inhibitory controls was low, at least to the extent that it was less than the doses which depress the transmission of nociceptive signals at the spinal level. Thus morphine must have been exerting its effect at supraspinal sites. Abundant electrophysiological data support the hypothesis that the lifting of diffuse noxious inhibitory controls following systemic morphine is due, at least in part, to binding of the drug within the periaqueductal grey; mostly because: (i) microinjection of morphine directly within the periaqueductal grey produces a significant depression of diffuse noxious inhibitory controls (Dickenson and Le Bars, 1987b), (ii) the depressive effect of systemic morphine on diffuse noxious inhibitory controls is blocked in periaqueductal grey-lesioned animals (Bouhassira et al., 1992a). Our results suggest that buprenorphine could exhibit a similar supraspinal mechanism; indeed since a higher dose of buprenorphine is required (30–100 $\mu$g) for the intravenous or intrathecal routes in order to produce a direct spinal depressive effect (Guirimand et al., 1995a, b), the effect of a dose as low as 3 $\mu$g/kg of buprenorphine is also likely to be mediated via supraspinal sites.

In view of the decrease in diffuse noxious inhibitory controls induced by low doses of systemic buprenorphine, what could be the mechanism for buprenorphine analgesia? This topic has been discussed in detail elsewhere for morphine (for a review, see Le Bars et al., 1986, 1995) and only a brief summary will be given here. As mentioned previously, it has been proposed that one of the physiological roles of diffuse noxious inhibitory controls is to facilitate the extraction of nociceptive information by increasing the signal-to-noise ratio between the pool of neurons activated by a noxious stimulus and the remaining population of neurons. Buprenorphine, like morphine, at a systemic dose low enough not to depress the excitatory signals from the spinal relay, can restore the background noise by decreasing diffuse noxious inhibitory controls and thus reducing the contrast between nociceptive and non-nociceptive signals. In other words, the effects of buprenorphine or morphine could result in jamming of the detection system for nociceptive information.

In conclusion, blockade of diffuse noxious inhibitory controls may contribute to the analgesic properties of buprenorphine. The antinociceptive mechanism of buprenorphine does not result from spinal blockade of nociceptive pathways, as does that of high doses of morphine, but rather from jamming of the detection system for nociceptive information, as with low doses of morphine. One can speculate that the lower potency of buprenorphine to alleviate clinical pain results from such an absence of synergy between spinal and supraspinal mechanisms of action.

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