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Different roles of α_2-adrenoceptors of the medulla versus the spinal cord in modulation of mustard oil-induced central hyperalgesia in rats

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Abstract

We attempted to determine the roles of spinal versus medullary α_2-adrenoceptors in modulation of central hyperalgesia in rats. Central hyperalgesia was produced by applying mustard oil (50%) to the skin of the ankle of one hindpaw. The threshold for eliciting a hindlimb flexion reflex was determined by applying a series of calibrated monofilaments to the glabrous skin of the hindpaw contralaterally (= control) or ipsilaterally to the mustard oil-treated ankle (= outside the area of primary hyperalgesia). Medetomidine (an α_2-adrenoceptor agonist; 1 μg), atipamezole (an α_2-adrenoceptor antagonist; 2.5 μg) or saline was microinjected into the lateral reticular nucleus of the medulla, the nucleus raphe magnus, or intrathecally to the lumbar spinal cord 12 min before the mustard oil treatment. Following saline injections, mustard oil produced a significant decrease of the hindlimb withdrawal threshold in the mustard oil-treated limb but not in the contralateral limb. Atipamezole in the lateral reticular nucleus produced a complete reversal of the hyperalgesia but no effect on the threshold of the intact limb. However, atipamezole in the raphe magnus nucleus or in the lumbar spinal cord did not produce a significant attenuation of the hyperalgesia. Medetomidine in the spinal cord, but not in the lateral reticular nucleus, reversed the hyperalgesia. At this dose range (up to 3 μg), medetomidine in the spinal cord of nonhyperalgesic control rats did not produce any significant change in the withdrawal response of hindlimbs or in the tail-flick latency. The results indicate that neurogenic inflammation induces significant plastic changes in the function of α_2-adrenergic pain regulatory mechanisms. In rats with mustard oil-induced central hyperalgesia, an α_2-adrenoceptor antagonist produces an antihyperalgesic effect due to an action on the caudal ventrolateral medulla, whereas an α_2-adrenoceptor agonist produces an enhanced antinociceptive effect due to a direct action on the spinal cord.

Keywords: Central hyperalgesia; Atipamezole; Medetomidine; α_2-Adrenoceptor; Neurogenic pain; Lateral reticular nucleus of the medulla; Spinal cord

1. Introduction

Previous studies have indicated that, in nonhyperalgesic rats, the spinal dorsal horn has a key role in the antinociceptive action induced by various α_2-adrenoceptor agonists (Danzebrink and Gebhart, 1990; Pertovaara, 1993; Yaksh, 1985). Concerning the possible role of supraspinal structures in α_2-adrenoceptor-mediated antinociception, the medullary lateral reticular nucleus is a site which has a significant role in the descending control of nociceptive signals (Gebhart and Ossipov, 1986; Mansikka and Pertovaara, 1995b; Ossipov and Gebhart, 1986). The lateral reticular nucleus is richly innervated by neurons with α_2-adrenoceptors (Bousquet et al., 1981; Cahusac and Hill, 1983; Scheinin et al., 1994), and the antinociception induced by stimulation of the lateral reticular nucleus can be reversed by α_2-adrenoceptor antagonists at the spinal cord level (Janss and Gebhart, 1987; Liu and Zhao, 1992). The nucleus raphe magnus in the rostroventromedial medulla is also considered an important source of descending control of spinal nociceptive neurons (Basbaum and Fields, 1984; Proudfit, 1988). There is evidence that, at least in a strain of Sprague-Dawley rats,

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the α_2-adrenoceptors of the raphe magnus nucleus may induce antinociceptive effects on a spinally initiated nocifensive reflex (Haws et al., 1990; Sagen and Proudfit, 1985). However, possibly due to genetic differences in the noradrenergic innervation between various rat strains (Clark and Proudfit, 1992), this seems not to be the case in our Hannover-Wistar rats (Hämäläinen and Pertovaara, 1993).

In an earlier study, we found that systemic administration of an α_2-adrenoceptor agonist, medetomidine, at low doses (< 30 μg/kg) produced a reversal of the central hyperalgesia induced by mustard oil (Mansikka and Pertovaara, 1995a). These doses of medetomidine had no effect on nocifensive responses of an intact limb. In nonhyperalgesic rats, considerably higher medetomidine doses (> 50 μg/kg) were needed to produce antinociceptive effects in the hot-plate and tail-flick tests (Pertovaara and Hämäläinen, 1994). Also, we found that systemic administration of an α_2-adrenoceptor antagonist, atipamezole, paradoxically produced a reversal of the central hyperalgesia at an intermediate dose (100 μg/kg), but had no effects on the hyperalgesia at a high (1000 μg/kg) or a low dose (10 μg/kg; Mansikka and Pertovaara, 1995a). Due to systemic administration of drugs, this earlier study did not allow any conclusions to be drawn concerning the possible sites of action of the enhanced antinociceptive potency of medetomidine or that of the paradoxical antinociceptive effect of atipamezole in hyperalgesic rats.

In the present study we attempted to localize the site of the enhanced antinociceptive potency of medetomidine and the site of the paradoxical antinociceptive effect of atipamezole in rats with mustard oil-induced hyperalgesia. We studied the roles of spinal versus medullary α_2-adrenoceptors in modulation of the mustard oil-induced central hyperalgesia by determining hindlimb withdrawal thresholds in response to mechanical stimulation of the paw following microinjections of medetomidine, atipamezole or saline (control) in the spinal cord, the medullary lateral reticular nucleus or the raphe magnus nucleus.

2. Materials and methods

The experiments were performed with adult male Hannover-Wistar rats (The Finnish National Laboratory Animal Center; weight range: 250–400 g). The experiments were approved by the Institutional Ethics Committee of the University of Helsinki.

2.1. Behavioral testing

To produce central hyperalgesia, mustard oil 50% in ethanol, Merck, Darmstadt, F.R.G.) was applied for 2 min on a piece of filter paper (2 cm^2) to the skin of the ankle of the rat. Mustard oil selectively activates the small diameter nociceptive fibers (Reeh et al., 1986), leading to primary hyperalgesia at the site of the treatment and to secondary hyperalgesia adjacent to the treated skin area. Since in this study we focused on central hyperalgesia, the test stimuli were applied to the area of secondary hyperalgesia, which is generally considered to be produced by central mechanisms. During testing the rat was standing or walking on a metal grid and the paw of the hindlimb ipsilateral or contralateral (= control site) to the mustard oil treatment was stimulated with a series of calibrated monofilaments (Stoelting, WoodDale, IL). The hairs used in this experiment produced forces ranging from 0.445 to 84.96 g. The stimulus site in the ipsilateral hindpaw was at least 2 cm distal from the border of the site to which mustard oil was applied. At each time point monofilaments were applied to the foot pad with increasing force until the rat withdrew its hindlimb. The lowest force producing a withdrawal response was considered the threshold. The left and right hindpaws were consecutively tested, and at each time point the threshold for each hindpaw is based on two separate measurements. In a control experiment, the tail-flick response was determined by using a commercially available instrument (Socrel DS-20, Ugo Basile, Italy) that focuses a radiant heat beam on the tail and automatically records the latency to tail removal. The average of three consecutive readings was recorded. To avoid tissue damage, the three consecutive measurements at each time point were made at 1 min intervals and the beam was applied to three different spots on the tail. The same three stimulus application sites were used in predrug and postdrug conditions. The cutoff latency in the tail-flick test was 12 s. During tail-flick measurements, the rats were immobilized in a plexiglass chamber. All the rats were habituated to the testing environment before behavioral testing by allowing them to spend 1–2 h in the laboratory during the day preceding the testing.

2.2. Surgical preparation of rats

When the effects of i.t. applied drugs were to be studied, the rats were implanted with a chronic polyethylene catheter as described by Yaksh and Rudy (1976). In brief, the animals were anesthetized by pentobarbitone (55 mg/kg). Then, they were positioned in a stereotaxic apparatus and a fine polyethylene-10 catheter (previously stretched to double its length when immersed in water at 75°C; final length 8.0 cm) was inserted into the subarachnoid space via the atlantooccipital membrane. The catheter extended to the rostral end of the lumbar enlargement. On the third postoperative day, the position of the tip of the catheter

was checked by injecting 10 μl of 4% lidocaine (Astra, Södertälje, Sweden) followed by a flush of 10 μl of 0.9% saline into the catheter. Only animals that developed reversible bilateral hindlimb paralysis within 5 min were accepted for further studies. Any animals that showed signs of neurological deficit after catheter implantation were excluded from the study.

When drugs were to be microinjected into the brainstem, the rats were implanted with a chronic guide cannula made of stainless steel in the following way. The anesthetized rats were placed in a stereotaxic apparatus according to the atlas of Paxinos and Watson (1986). The desired injection sites were in the medullary lateral reticular nucleus (anterior −4.68 mm, lateral +1.80 mm, and dorsal −0.40 mm; reference: the ear bar) or in the raphe magnus nucleus (anterior −1.80 mm, lateral 0.00 mm, and dorsal −0.50 mm). The skull was exposed and a hole drilled for placement of a guide cannula (26 gauge). The tip of the guide cannula was positioned 2.00 mm dorsal to the desired injection site. The cannula was fixed into the skull by using a dental screw and dental cement. A dummy cannula was placed into the guide cannula between the test sessions. Before behavioral testing, the rats were allowed to recover from surgery for 3–7 days.

2.3. Drug administration

The drugs administered intrathecally (i.t.) in the lumbar spinal cord were delivered in a total volume of 10 μl, followed by 10 μl of saline to flush the catheter. The drug solution was separated from the saline solution by an air bubble to prevent mixing. When drugs were administered in the brainstem, the drug was microinjected through a 33-gauge stainless steel injection cannula inserted through and protruding 2 mm beyond the tip of the guide cannula. The microinjection was made by using a 10 μl Hamilton syringe which was connected to the injection cannula by a length of polyethylene tubing. The volume of injection was 0.5 μl. The efficacy of the injection was monitored by watching the movement of a small air bubble through the tubing. The injection lasted 30 s and the injection cannula was left in place for an additional 30 s to minimize flow of the drug solution back up the injector track. During injection the rat was held by one of the experimenters. The histologically verified injection sites were plotted on standardized sections derived from the stereotaxic atlas of Paxinos and Watson (1986).

Medetomidine (Virtanen et al., 1988) and atipamezole (Scheinin et al., 1988) were generously provided by Dr. R. Virtanen, Farmos Group, Orion, Turku, Finland. Medetomidine is a racemic mixture of dextro- and levoisomers of medetomidine. The effect of 2 mg of medetomidine equals 1 mg of dextroisomer of medetomidine (MacDonald et al., 1991). Medetomidine (1.0 μg) and atipamezole (2.5 μg) were dissolved in physiological saline to obtain the desired volume (0.5 μl with intramedullary injections or 10 μl with i.t. injections). Physiological saline was used in control injections.

2.4. The course of the study

There were seven experimental groups with neurogenic inflammation and one control group without neurogenic inflammation. In four groups with neurogenic inflammation, the drugs were administered into the medulla 12 min prior to mustard oil: (i) saline control into the lateral reticular nucleus of the medulla, (ii) medetomidine (1 μg) into the lateral reticular nucleus, (iii) atipamezole (2.5 μg) into the lateral reticular nucleus, (iv) atipamezole (2.5 μg) into the raphe magnus nucleus. In three groups with neurogenic inflammation, the drugs were administered i.t. 12 min prior to mustard oil: (v) saline control i.t., (vi) medetomidine (1 μg) i.t., (vii) atipamezole (2.5 μg) i.t. In all the above groups, the first control threshold determination was performed immediately prior to drug administration. Thereafter, the withdrawal threshold was determined at 5 min intervals at seven time points following mustard oil treatment. In one control group

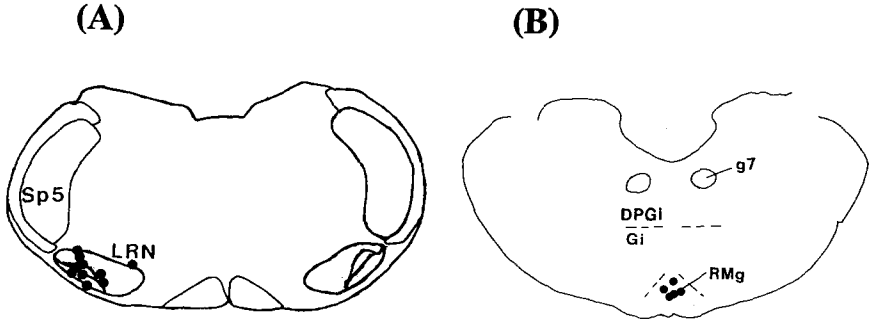

Fig. 1. The centers of the histologically verified injection sites (dots) in the caudal (A) and rostral (B) medulla. LRN = lateral reticular nucleus, RMg = raphe magnus, Sp5 = spinal trigeminal nucleus, DPGi = dorsal paragigantocellular nucleus, Gi = gigantocellular nucleus. g7 = genu of facial nerve. The section A is 4.68 mm and the section B 1.80 mm posterior to the interaural line.

without neurogenic inflammation, medetomidine was applied i.t. at two doses (1 and 3 μg), and the withdrawal threshold was determined 15 min following drug administration. Additionally, the latency of the heat-induced tail-flick response was determined in the untreated control animals prior and 12 min following drug administration. The drug doses used were selected on the basis of our preceding study in which these same drugs were administered systemically (Mansikka and Pertovaara, 1995a); the drug doses used were below the doses producing systemic effects. Each animal was used only in one test condition of the present experiments.

Statistical evaluation was done with one- and two-way analysis of variance (ANOVA) and *t*-test. $P < 0.05$ was considered to represent a significant difference. Since the drug effects and mustard oil-induced changes were expected to be maximal 5–20 min after the administration of mustard oil (Mansikka and Pertovaara, 1995a), the average withdrawal threshold during this period was calculated for each hindlimb of each animal. These average threshold values were then used in comparisons between the mustard oil-treated versus untreated limbs within the group (*t*-test) and between the different groups (2-way-ANOVA).

3. Results

3.1. Administration of drugs into the medullary nuclei

Fig. 1 indicates the centers of the histologically verified injection sites in the caudal (A) and rostral (B)

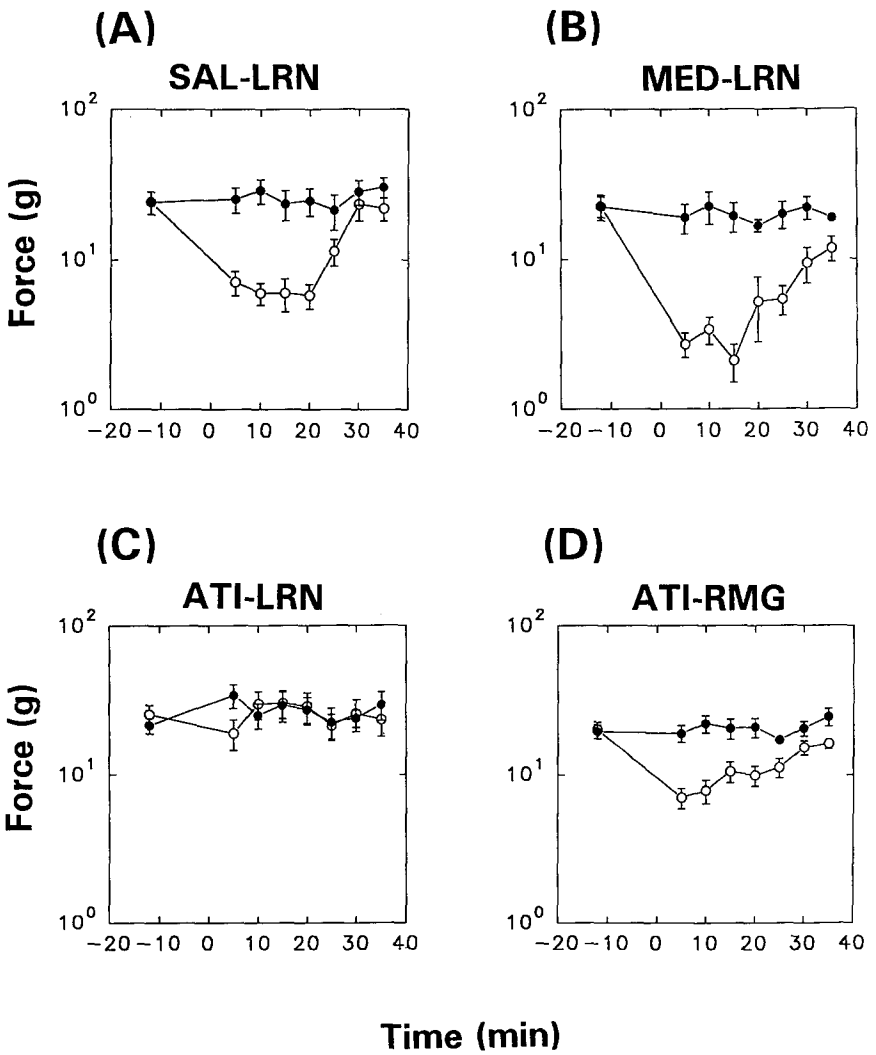

Fig. 2. Effect of intramedullary drug administration on the mustard oil-induced decrease in the threshold of a hindlimb withdrawal response to mechanical stimulation. (A) Saline in the medullary lateral reticular nucleus (LRN). (B) Medetomidine (1 μg) in the lateral reticular nucleus. (C) Atipamezole (2.5 μg) in the lateral reticular nucleus. (D) Atipamezole (2.5 μg) in the raphe magnus nucleus (RMG). In all cases, mustard oil was applied at time point 0, and the intramedullary drug administration was performed 12 min prior to mustard oil. The first control measurement was taken immediately before drug administration. The open symbols indicate the threshold in the mustard oil-treated hindlimb, and the filled symbols indicate the threshold in the contralateral untreated hindlimb. The error bars represent ±S.E.M. ($n = 4$–7 in each group).

medulla. In general, drug administration into the medulla had a highly significant effect on the hindlimb withdrawal threshold ($F(3,30) = 8.57$, $P = 0.0003$, 2-way-ANOVA). Also, the two hindlimbs (ipsi- versus contralateral to mustard oil) showed a highly significant difference in the effect of treatment ($F(1,30) = 25.24$, $P < 0.0001$, 2-way-ANOVA). There was no significant interaction between the drug treatment effect and the side of the hindlimb ($F(3,30) = 2.43$, ns, 2-way-ANOVA). Following saline administration in the medullary lateral reticular nucleus, the withdrawal threshold in response to mechanical stimulation was significantly lower in the mustard oil-treated hindlimb than in the contralateral limb ($P < 0.005$, t-test; Fig. 2A). Also following medetomidine (1 μg) in the medullary lateral reticular nucleus, the withdrawal threshold in the mustard oil-treated hindlimb was significantly lower than in the contralateral limb ($P = 0.005$, t-test, Fig. 2B). However, following atipamezole (2.5 μg) in the medullary lateral reticular nucleus, mustard oil produced no decrease of the withdrawal threshold (Fig. 2C). In contrast, following atipamezole (2.5 μg) in the raphe magnus nucleus, mustard oil did produce a significant decrease in the withdrawal threshold ($P < 0.005$, t-test). Although mustard oil seemed to induce a stronger hyperalgesia following medetomidine than saline in the lateral reticular nucleus, this difference was not of statistical significance (Fig. 2A versus 2B, t-test). The magnitude of the mustard oil-induced hyperalgesia was not significantly different following saline in the lateral reticular nucleus versus atipamezole in the raphe magnus nucleus (Fig. 2A versus 2D, t-test). In all groups, the withdrawal threshold of the untreated limb remained at the

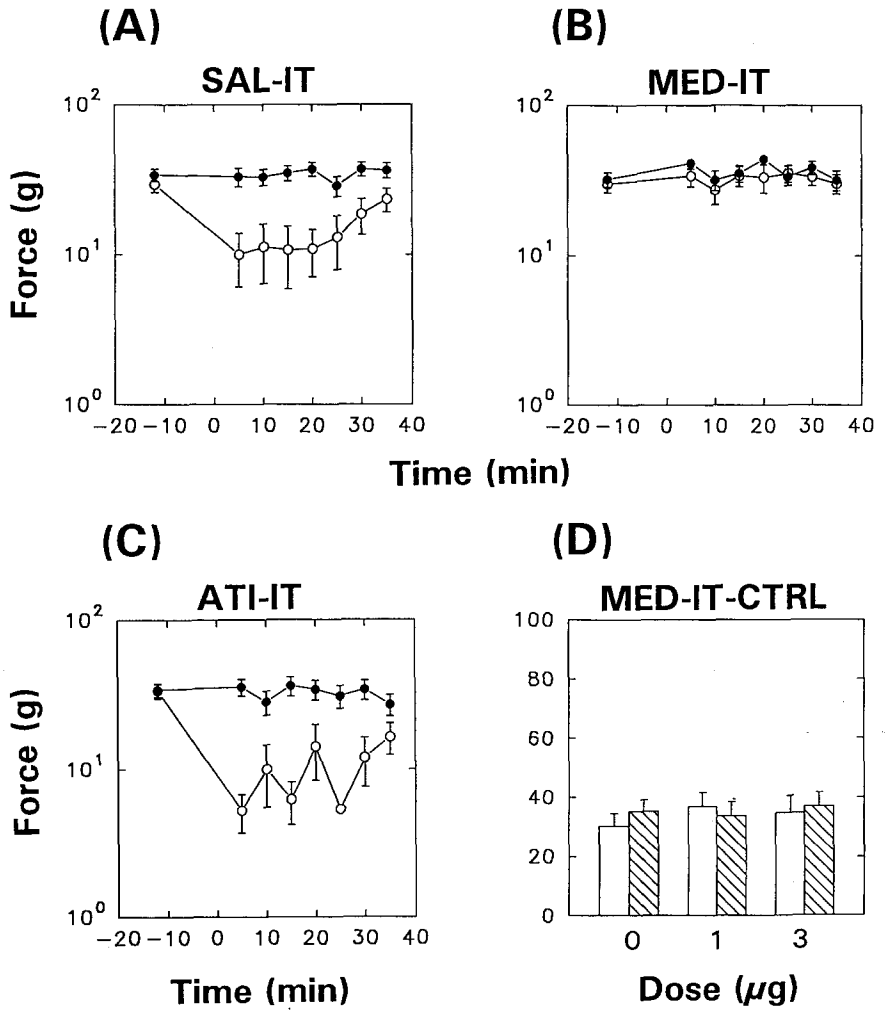

Fig. 3. Fig. 3. Effect of intrathecal drug administration on the threshold of a mechanically induced hindlimb withdrawal response following mustard oil treatment (A-C) or in untreated control animals (D). (A) Saline i.t. (B) Medetomidine (1 μg) i.t. (C) Atipamezole (2.5 μg) i.t. (D) Medetomidine (1–3 μg) i.t. without mustard oil-induced inflammation. In D, the thresholds were measured 15 min following drug administration, and the withdrawal threshold (g) is in linear scale. The open bars represent the threshold of the right hindfoot and the striped bars those of the left hindfoot, measured 15 min following drug administration. For other explanations, see the leg. for Fig. 2. In A-C, $n = 4$–6, in D $n = 8$.

same level following mustard oil and drug administration as before the administration.

3.2. Administration of drugs i.t. at the lumbar level

I.t. drug treatments had a significant effect on the hindlimb withdrawal threshold ($F(2,26) = 4.01$, $P = 0.0303$, 2-way-ANOVA). The hindlimbs showed a significant side-dependent difference in the effect of treatments ($F(1,26) = 18.78$, $P = 0.0002$, 2-way-ANOVA). There was no interaction between the drug effect and the side of the hindlimb ($F(2,26) = 1.87$, ns, 2-way-ANOVA). Following i.t. saline administration, the withdrawal threshold of the mustard oil-treated hindlimb was significantly lower than that of the contralateral hindlimb ($P = 0.03$, t-test; Fig. 3A). Following i.t. administration of medetomidine (1 μg), mustard oil produced no decrease of the hindlimb threshold (Fig. 3B). Following i.t. administration of atipamezole (2.5 μg), however, the withdrawal threshold of the mustard oil-treated hindlimb was significantly lower than in the contralateral limb ($P < 0.01$, t-test; Fig. 3C). Following i.t. administered saline, medetomidine (1 μg) or atipamezole (2.5 μg), mustard oil produced no changes in the withdrawal threshold of the contralateral hindlimb.

For comparison, the effect of low medetomidine doses (1 and 3 μg) administered i.t. was determined in nonhyperalgesic control rats. In nonhyperalgesic control rats, these doses of medetomidine administered i.t. were not high enough to produce significant effects on the mechanically induced withdrawal response (Fig. 3D; 2-way-ANOVA, ns) or on the latency of the heat-induced tail-flick response (1-way-ANOVA, ns, $n = 6$, data not shown).

4. Discussion

In the current study, atipamezole, an α_2-adrenoceptor antagonist, microinjected into the lateral reticular nucleus of the medulla reversed the central hyperalgesia induced by mustard oil, without having any effect on nocifensive withdrawal thresholds of an intact limb. However, atipamezole microinjected into the raphe magnus nucleus or into the lumbar spinal cord did not produce a significant attenuation of the mustard oil-induced hyperalgesia. Also, the mustard oil-induced hyperalgesia was reversed following microinjection of medetomidine, an α_2-adrenoceptor agonist, into the lumbar spinal cord at a dose which was considerably below the minimum dose needed to produce attenuation of nociceptive signals from an intact skin. In the medullary lateral reticular nucleus, medetomidine at the dose used had no significant effects on spinal hyperalgesia. The present results indicate that the antihyperalgesic effect induced by medetomidine at a low dose that is subantinociceptive in nonhyperalgesic animals is due to a direct action on the spinal cord. Furthermore, the present results indicate that the antihyperalgesic effect of atipamezole can be explained by an action on the medullary lateral reticular nucleus or a structure immediately adjacent to it. However, we cannot exclude the possibility that an action of atipamezole on some other brainstem structure, not studied in the present study, might contribute to the antihyperalgesic effect induced by systemically administered atipamezole.

4.1. α_2-Adrenoceptor agonist-induced effects

Numerous behavioral and neurophysiological studies in nonhyperalgesic animals have indicated that α_2-adrenoceptor agonists have antinociceptive properties and that the spinal dorsal horn has an important role in their antinociceptive action (cf. refs. Pertovaara, 1993). In line with the results of the present control experiment, also previous studies indicate that when administered i.t., medetomidine or dexmedetomidine has to be administered at a dose higher than 1 μg to produce a significant antinociceptive effect in nonhyperalgesic animals (Fisher et al., 1991; Hämäläinen and Pertovaara, 1993; Kalso et al., 1991). However, in hyperalgesic animals this low dose of medetomidine was enough to produce a complete reversal of the hyperalgesia. This result adds to the accumulating evidence indicating that α_2-adrenoceptor agonists have an enhanced antinociceptive potency in various pathophysiological models of pain (Hylden et al., 1991; Idänpään-Heikkilä et al., 1994; Kayser et al., 1992; Stanfa and Dickenson, 1994; Xu et al., 1992). Our earlier (Mansikka and Pertovaara, 1995a) and present results support this evidence and indicate that the enhanced antinociceptive potency of α_2-adrenoceptor agonists also applies to mechanical hyperalgesia of central origin induced by neurogenic inflammation. In line with the present results, previous studies performed with other models of hyperalgesia have suggested that the enhanced antinociceptive potency of α_2-adrenoceptor agonists might be, at least partly, due to a direct action on the spinal cord, as indicated by the strong behavioral analgesia following i.t. drug administration (Hylden et al., 1991; Idänpään-Heikkilä et al., 1995; Stanfa and Dickenson, 1994; Xu et al., 1992).

In our previous studies with nonhyperalgesic Hannover-Wistar rats, medetomidine applied into various brainstem structures (Hämäläinen and Pertovaara, 1993, 1995; Pertovaara et al., 1994), including the medullary lateral reticular nucleus (Mansikka and Pertovaara, 1995b), produced no significant effects on

nociceptive responses if the dose was low enough to act only locally in or near the injection site (≤ 3 μg). Following high medetomidine doses in the brainstem (> 6 μg), spinal reflex and sensory neuronal responses induced by noxious stimulation were attenuated. Since medetomidine in the brainstem produced this attenuation of nociceptive spinal responses also following spinalization, the effect of supraspinally administered medetomidine in nonhyperalgesic animals could be explained by spread of the drug (e.g. via circulation) to act directly on α_2-adrenoceptors of the spinal dorsal horn (see refs. above). If anything, the activation of supraspinal α_2-adrenoceptors by medetomidine facilitated nociception at the spinal cord level. This was shown by the enhanced antinociceptive potency of supraspinally administered medetomidine on spinal sensory neuronal and reflex responses following spinalization (Hämäläinen and Pertovaara, 1993, 1995; Pertovaara et al., 1994). In the present experiment, the dose of medetomidine administered in the medullary lateral reticular nucleus was not high enough to produce a direct spinal antinociceptive effect, which explains the lack of effect on withdrawal thresholds following medetomidine administration in the medulla.

4.2. α_2-Adrenoceptor antagonist-induced effects

An antinoceptive effect induced by high doses of some other α_2-adrenoceptor antagonists, yohimbine and idazoxan, has been described earlier (Dennis et al., 1980; Hayes et al., 1986; Kanui et al., 1993; Kayser et al., 1992; Paalzow and Paalzow, 1983). In our earlier study, we described a selective antihyperalgesic effect of systemically administered atipamezole, an α_2-adrenoceptor antagonist, in a model of central hyperalgesia induced by mustard oil (Mansikka and Pertovaara, 1995a). This antihyperalgesic effect produced by systemically administered atipamezole was obtained only at an intermediate dose (100 μg/kg) and only in hyperalgesic limbs. The present results indicate that the reversal of central hyperalgesia induced by systemically administered atipamezole can be explained due to its direct action on the medullary lateral reticular nucleus, since administration of atipamezole in the raphe magnus nucleus or in the lumbar spinal cord did not attenuate hyperalgesia induced by mustard oil. In contrast, in nonhyperalgesic animals, administration of atipamezole in the medullary lateral reticular nucleus was without an effect on nocifensive thresholds (Mansikka and Pertovaara, 1995b), suggesting that inflammation-induced changes need to occur before atipamezole produces an antinociceptive effect by its action on the caudal ventolateral medulla.

The reversal of hyperalgesia produced by administering atipamezole in the medullary lateral reticular nucleus suggests that spinopetal inhibition is under tonic inhibitory control by endogenous α_2-adrenoceptor agonists acting on the caudal ventrolateral medulla. In other words, inflammation induces a facilitatory spino-medullary-spinal loop that involves α_2-adrenoceptors in the caudal ventrolateral medulla. Interestingly, anatomical studies have demonstrated a spino-medullary-spinal loop that involves the caudal ventrolateral medulla (Tavares and Lima, 1994). The antihyperalgesic effect of an α_2-adrenoceptor antagonist in the medulla contrasts with the concomitant enhanced antinociceptive potency of an α_2-adrenoceptor agonist in the spinal cord of mustard oil-treated animals.

I.t. administered atipamezole did not have any significant effects on the withdrawal thresholds of hyperalgesic or nonhyperalgesic limbs. This is in line with the results of a recent electrophysiological study reporting that atipamezole i.t. did not alter the spinal neuronal responses in animals with carrageenan-induced inflammation (Stanfa and Dickenson, 1994). These results with i.t. atipamezole suggest that inflammation induced no tonic spinopetal inhibitory control involving spinal α_2-adrenoceptors. However, this conclusion is complicated by the finding that i.t. idazoxan, another α_2-adrenoceptor antagonist, did produce a significant facilitation of C-fiber-evoked responses in the rat spinal dorsal horn following inflammation (Stanfa and Dickenson, 1994). On the other hand, in another study i.t. idazoxan did not influence the hindpaw withdrawal latencies to noxious heat in inflamed or noninflamed paws (Hylden et al., 1991). This result with idazoxan is consistent with the present finding with i.t. atipamezole.

4.3. Implications

α_2-Adrenoceptor agonists may provide a clinically important alternative for treating pain and hyperalgesia induced by inflammation, since these compounds seem to attenuate inflammatory pain at very low doses, without having effects on normal nociception and with minor, if any, side-effects. The most effective way of administering α_2-adrenoceptor agonists is direct application in the spinal cord, because spinal α_2-adrenoceptors have a key role in mediating the antinociceptive effects as, supraspinally, these compounds may even counteract spinal antinociceptive effects and as most of the side-effects are due to supraspinal actions.

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