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Effects of Radolmidine, A Novel α_2-Adrenergic Agonist Compared with Dexmedetomidine in Different Pain Models in the Rat

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Background: **Intrathecally administered α_2-adrenoceptor agonists produce effective antinociception, but sedation is an important adverse effect. Radolmidine is a novel α_2-adrenoceptor agonist with a different pharmacokinetic profile compared with the well-researched dexmedetomidine. This study determined the antinociceptive and sedative effects of radolmidine in different models of acute and chronic pain. Dexmedetomidine and saline served as controls.**

Methods: **Male Sprague-Dawley rats were studied in acute pain (tail flick), carrageenan inflammation, and the spinal nerve ligation model of neuropathic pain. Mechanical allodynia was assessed with von Frey filaments, cold allodynia with the acetone test, and thermal hyperalgesia with the paw flick test. Locomotor activity–vigilance was assessed in a dark field. Dexmedetomidine and radolmidine were administered intrathecally in doses of 0.25 μg, 2.5 μg, 5 μg, and 10 μg.**

Results: **In the tail flick test, radolmidine showed a dose-dependent antinociceptive effect, being equipotent compared with dexmedetomidine. In carrageenan inflammation, intrathecal doses of 2.5 μg or 5 μg of dexmedetomidine/radolmidine produced significant antinociception compared with saline ($P < 0.01$). The two drugs were equianalgesic. In the neuropathic pain model, an intrathecal dose of 5 μg dexmedetomidine–radolmidine had a significant antiallodynic effect compared with saline ($P < 0.01$). The two drugs were equipotent. Intrathecal administration of both dexmedetomidine and radolmidine dose dependently decreased spontaneous locomotor activity–vigilance, but this effect was significantly smaller after intrathecal administration of radolmidine than after intrathecal dexmedetomidine.**

Conclusions: **Radolmidine and dexmedetomidine had equipotent antinociceptive effects in all tests studied. However, radolmidine caused significantly less sedation than dexmedetomidine, probably because of a different pharmacokinetic profile. (Key words: Inflammation; neuropathy; spinal.)**

INTRATHECAL administration of α_2-adrenoceptor agonists produces antinociception in laboratory animals[1,2] and analgesia in humans.[3] Dexmedetomidine, a selective and specific α_2-adrenoceptor agonist has been shown to produce antinociception at the spinal cord level in behavioral tests[4] and also in single cell recordings from the spinal cord during noxious electrical stimulation of the receptive fields.[5] Intrathecally administered dexmedetomidine has also reversed nerve ligation–induced allodynia.[6] Intracerebroventricular and intrathecally administered α_2-adrenoceptor agonists have produced dose-dependent sedation.[7] Sedation has been a common problem with the currently available α_2-adrenoceptor agonists after both systemic and spinal administration.

As a lipophilic agent, dexmedetomidine is rapidly absorbed into blood circulation and causes systemic effects even after intrathecal administration. The novel α_2-adrenoceptor agonist radolmidine (2,3-dihydro-3-(1H-Imidazol-4-ylmethyl)-1H-indan-5-ol-hydrochloride), like dexmedetomidine, is a full agonist at all α_2-adrenergic receptors.[8] However, it has a different pharmacokinetic profile with less activity to cross the blood–brain barrier and with less rapid distribution within the central nervous system.[8,9] The present series of studies was designed to characterize radolmidine in comparison with dexmedetomidine in various pain models representing both acute and chronic nociception. In addition, the effects of

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intrathecal injection of radolmidine and dexmedetomidine on locomotion–vigilance were assessed in this study.

Materials and Methods

Animals

Male Sprague-Dawley rats (Bkl:SD; B&K Universal Ab, Sollentuna, Sweden) weighing 150–175 g in the beginning of the experiment were used. Laboratory chow (R36; Lactamin Specialföretaget, Stockholm, Sweden) and water were available *ad libitum*. Rats were housed in groups of five in plastic cages in artificial lighting with a fixed 12-h light–dark cycle. Guidelines for animal research by local authorities and the International Association for the Study of Pain[10] were adhered to, and the study protocol was approved by the institutional animal investigation committee.

Drugs

Dexmedetomidine was used as a control compound to study the effects of the new α_2-adrenergic agonist radolmidine. Atipamezole, the selective α_2-adrenoceptor antagonist, was used to reverse the effects. Atipamezole, dexmedetomidine, and radolmidine were provided by Dr. Raimo Virtanen, Orion Corporation, Turku, Finland. Saline served as an inactive control.

Experimental Procedures

Intrathecal Cannulation. For the insertion of the intrathecal cannula, rats were anesthetized with a subcutaneous injection of midazolam 5.0 mg/kg (Dormicum; Roche, Basle, Switzerland) and 1.0 ml/kg of the mixture of fentanyl 0.2 mg/ml and fluanisone 10 mg/ml (Hypnorm; Janssen Pharmaceutica, Beerse, Belgium). A thin polyethylene cannula (PE-10; Meadox Surgimed A/S, Stenløse, Denmark) was inserted through the cisterna magna into the lumbar subarachnoid space, 8 cm from the insertion, and fixed with a suture to the paravertebral muscles.[11] After cannulation the animals were housed individually in standard Plexiglass cages. To verify the proper placement of the cannula, 10 μl of 5% hyperbaric lidocaine (Lidocain Pond, Medipolar, Oulu, Finland) was injected. Only rats that developed reversible symmetrical paralysis of both hind limbs and the tail after the injection of lidocaine were used in the experiments.

Inflammatory Pain: Carrageenan-induced Hind Paw Inflammation. The rats were anesthetized with halothane, and λ-carrageenan (Sigma, St. Louis, MO) 0.2 mg in 0.1 ml of saline was injected into the palm of the left hind paw 2 h before the behavioral measurements were begun.

Neuropathic Pain Model: Ligation of Spinal Nerves 5–6. The model of neuropathic pain introduced by Kim and Chung[12] in 1992, the spinal nerve ligation model, was used. In brief, the animals were anesthetized with 1% halothane (Trothane, ISC Chemicals, Bristol, United Kingdom) in N_2O and O_2 (70%:30%). The left L5 and L6 spinal nerves were exposed by removing a small piece of the paravertebral muscle and a part of the left spinous process of the L5 lumbar vertebra. The L5 and L6 spinal nerves were then carefully isolated and tightly ligated with 6-0 silk. After checking hemostasis, the muscle and the adjacent fascia were closed with sutures, and the skin was closed with metal clips.

Tests for Allodynia, Hyperalgesia, and Thermal Nociception. The rats were always habituated to handling, and the testing equipment (30 min of handling per day for 3 days) before the experiments. Thermal nociception (noxious heat) was tested with the tail flick apparatus (Ugo Basile, Comerio, Italy) with a cutoff time of 8 s to prevent tissue damage. The animals were restrained in transparent Plexiglass tubes during the tail flick tests. Tail flick results are expressed as percentage of the maximum possible effect (MPE%) calculated with the following formula:

MPE% = (postdrug latency − predrug latency)/(cutoff latency − predrug latency) × 100%.

The tail flick test was also used to determine whether the selective α_2-adrenergic antagonist atipamezole (100 μg administered intrathecally) could reverse the antinociceptive effect of radolmidine (3 μg administered intrathecally). Atipamezole was administered either 15 min before or after radolmidine.

Heat hyperalgesia was tested with the paw flick test apparatus (Ugo Basile). The stimulus intensity was set at 40 (arbitrary units on a scale of 0–90). The cutoff time was 16 s to prevent tissue damage. The measurements were performed on both hind paws three times at each time point. The stimulus was begun only when the tested paw was set on the glass floor of the device.[13,14]

Threshold for mechanical allodynia was measured with a series of von Frey filaments (Semmes-Weinstein monofilaments, Stoelting, IL).[15,16] The rats were standing on a metal mesh covered with a plastic dome. The plantar surface of the paw was touched with different von Frey filaments with a bending force from 0.217 to 12.5 grams (g) until the threshold force that induced paw withdrawal in more than half of the stimuli was

found. The testing was begun by seeking the allodynic areas of the ventral surface of the paw with the von Frey filament of 12.5 g. If the rat responded to the stimulation with a paw withdrawal, the next lighter filament was used until the threshold was found. To avoid excessive stimulation, the probing was started in the following testing sessions with the weakest filament that had elicited withdrawal responses in the previous session. If the strongest filament did not give a response, 12.5 g was recorded as the threshold. Higher forces should not be used with this method, because the paw would be lifted up by the testing stimulus even in a normal animal.[17]

Cold allodynia was measured as the foot withdrawal response after application of acetone to the plantar surface of the paw.[18] The rats were standing on a metal mesh. A drop of acetone was gently applied to the heel of the rat with a syringe connected to a thin polyethylene tube. A brisk foot withdrawal response after the spread of acetone over the plantar surface of the paw was considered as a sign of cold allodynia. The testing was started with the paw contralateral to the nerve injury and repeated five times for both paws with an interval of approximately 2 min between each test.

Temperature. The temperature of both the neuropathic (left) and nonneuropathic (right) paws was measured to determine if the neuropathy changes the baseline temperature of the paw and if the studied drugs have different effects on the temperature of the affected and nonaffected paws. The temperatures were measured using a Tempett infrared thermometer (Senselab, Stockholm, Sweden) before the drugs were given and at 30 and 60 min from the intrathecal injection of saline, dexmedetomidine (0.5, 2.5, 5.0 μg), and radolmidine (0.5, 2.5, 5.0 μg).

Spontaneous Locomotor Activity. Spontaneous locomotor activity was assessed in a dark field[19] with an automatic measurement system (Kungsbacka Mät- & Reglerteknik AB, Kungsbacka, Sweden). The rats were placed in a sound isolated box (70 $\times$ 70 $\times$ 35 cm) that had two series of photocells located 2 cm and 12 cm above the floor, and the cover of the box was closed to isolate it from ambient light and noises. The lower series of photocells detected movement of the animal as crossing of the photocell lines and the upper photocells registered rearing. Six 5-min measurement periods were used to cover a 30-min assessment time. Decrease in spontaneous locomotor activity could reflect, for example, motor dysfunction or sedation. For the dose–response curve, mean percentage of inhibition at 0–15 min after the drug administration was calculated as the mean of:

$$\{\text{mean}\ [(\text{AUCsal}_{0\text{-}15} - (\text{AUCdrug}_{0\text{-}15})]/\text{mean}\ (\text{AUCsal}_{0\text{-}15})\} \times 100\%$$

where $\text{AUCdrug}_{0\text{-}15}$ is the area under the curve from 0 to 15 min after the drug administration, and ($\text{AUCsal}_{0\text{-}15}$) is the area under the curve from 0 to 15 min after the injection in the saline control group.

Statistical Analysis

Continuous normally distributed variables, such as the paw temperature, were analyzed using analysis of variance or analysis of variance for repeated measures, as appropriate. Variables that did not fulfill these criteria, *e.g.*, the mean percent of inhibition in the activity test, were analyzed using the Mann–Whitney U test.

Results

Acute Nociception

In the tail flick test, intrathecal administration of radolmidine and dexmedetomidine produced clear dose-related antinociception with a maximum effect at 30 min (fig. 1). The two drugs were equipotent. The maximum antinociceptive effect represented by a nearly 100% MPE was achieved with 10 μg radolmidine. The antinociceptive effect was significantly different from the saline group from 15 to 60 min in both groups ($P < 0.001$).

The antinociceptive effect of 3 μg intrathecal radolmidine was significantly reduced when atipamezole was given either before or after radolmidine. The MPE% of the tail flick latency after 3 μg intrathecal radolmidine was reduced from 72% to 12% at 15 min after pretreatment with 100 μg of atipamezole compared with saline ($P = 0.002$). When atipamezole was given 15 min after the administration of 3 μg intrathecal radolmidine, the MPE% of the tail flick latency decreased from 80% to 16%, whereas it increased from 70% to 87% after saline ($P < 0.001$).

Inflammatory Pain

Carrageenan inflammation produced both mechanical allodynia and heat hyperalgesia (figs. 2A and 2B). The mean predrug thresholds for the von Frey filaments were approximately 4 g compared with > 12.5 g in the normal rat. Dexmedetomidine and radolmidine decreased mechanical allodynia as measured with von Frey filaments in the inflamed paw in a dose-dependent fashion (fig. 2C). The thermal hyperalgesia in the paw flick test

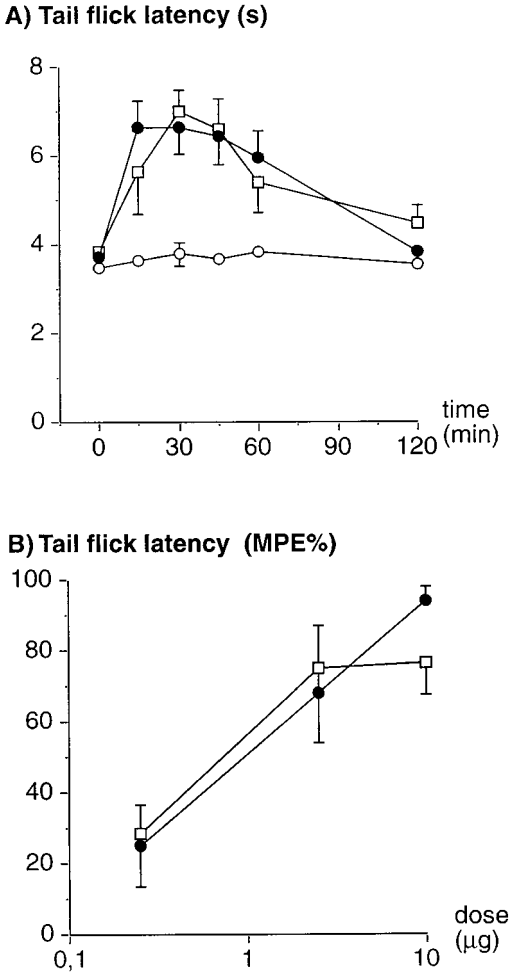

Fig. 1. The effects of radolmidine and dexmedetomidine in the tail flick test. (*A*) Mean (SEM) of the tail flick latency after intrathecal administration of radolmidine 2.5 μg (filled circles), dexmedetomidine 2.5 μg (open squares), or saline 10 μl administered intrathecally (open circles). (*B*) Dose–response curves for radolmidine (filled circles) and dexmedetomidine (open squares) plotting mean MPE% (SEM) of the tail flick latency 30 min after intrathecal administration of the drug.

was also reduced with both drugs (fig. 2D). The peak antiallodynic effect in the mechanical test was observed at 30–45 min (fig. 2A), whereas the maximum increases in the paw flick latencies were detected at 15 min (fig. 2B). The dose–response curves showed that the two drugs had very similar antiallodynic and antihyperalgesic effects in the carrageenan model (figs. 2C and 2D).

Neuropathic Pain

The animals that responded to a von Frey filament force < 12.5 g and with at least one positive response in the acetone test were considered to have neuropathic symptoms and were eligible to enter the study. Thus, 70% of the rats could be included. The low thresholds for mechanical stimulation and significant cold allodynia produced by the neuropathy can be seen in the predrug values in figures 3A and 3B. A normal rat would not respond to acetone stimuli. Heat hyperalgesia was not evident as the paw flick latencies in the ipsilateral and contralateral paws were comparable (data not shown).

Both dexmedetomidine and radolmidine in intrathecal doses of 0.5, 2.5, and 5.0 μg had a significant dose-dependent antiallodynic effect at 30 min when tested with von Frey filaments ($P < 0.01$; figs. 3A and 3C). In the acetone test, dexmedetomidine and radolmidine had a significant dose-dependent antiallodynic effect compared with saline ($P < 0.01$; figs. 3B and 3D). Cold allodynia was virtually abolished by 30 min. In the paw flick test, dexmedetomidine and radolmidine in an intrathecal dose of 5.0 μg increased the paw flick latency in both paws (data not sown). The maximum effect was reached 30 min after intrathecal administration. The two drugs were equipotent. The neuropathy model that was used did not alter the temperature of the affected paw as compared with the contralateral paw (results not shown). The temperatures in either of the paws were not significantly affected by any of the doses of the drugs tested (results not shown).

Spontaneous Locomotor Activity

In the locomotor activity measurements, intrathecal administration of both dexmedetomidine and radolmidine dose dependently decreased spontaneous locomotor activity (fig. 4). However, this effect was significantly smaller after intrathecal administration of radolmidine than after intrathecal dexmedetomidine (fig. 4; $P < 0.001$ for 2.5 μg, $P = 0.012$ for 5 μg, and $P = 0.03$ for 10 μg, when the percent of inhibition at 0–15 min after the drug administration produced by radolmidine was compared with that of dexmedetomidine).

Discussion

α_2 Adrenoceptors are found in the dorsal horn of the spinal cord and in multiple areas of the brain.[20] The antinociceptive effects of spinally and systemically administered α_2-adrenergic agonists have been verified with a number of agonists in different pain models in both animals[4,21,22] and humans.[3] The spinal site of action is crucial for the antinociceptive effect, as intrathecally administered α_2-adrenergic agonists produce antinoci-

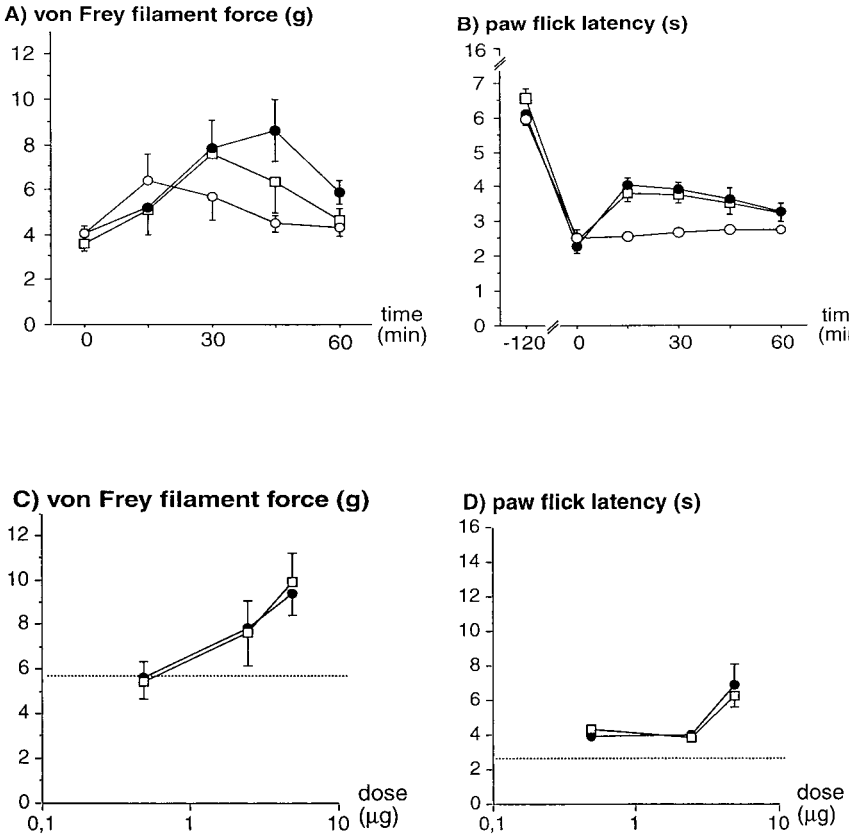

Fig. 2. The carrageenan model of inflammation caused significant mechanical allodynia (low thresholds for von Frey filament stimulation) (*A*) and a significant decrease from the precarrageenan levels of paw flick latencies in the ipsilateral paw (*B*), as indicated by the decrease in the baseline values after carrageenan injection (−120 min). Time course of the effects of intrathecal radolmidine 2.5 mg (filled circles) and intrathecal dexmedetomidine 2.5 mg (open squares) on the means (SEM) of the von Frey filaments (*A*) and the paw withdrawal latency (*B*) are shown (open circles indicate the results after saline 10 μl administered intrathecally). Dose–response curves for radolmidine (filled circles) and dexmedetomidine (open squares) are shown in the von Frey filament force that induced paw withdrawal (*C*) and paw withdrawal latency in the paw flick test in the ipsilateral paw (*D*) 30 min after intrathecal administration. The dotted lines indicate the baseline values 120 min after the carrageenan injection.

ception in much lower doses than what is needed for an effect after systemic administration.[4] In addition, transection of the spinal cord does not abolish the antinociceptive effect of systemically administered α_2-adrenergic agonists.[23] Recent studies further support the conclusion that the supraspinal sites do not play an important role in α_2-adrenoceptor–mediated antinociception,[9,23–25] although contradicting views have also been proposed.[26]

Like dexmedetomidine, radolmidine is a highly potent, specific and selective α_2-adrenergic agonist showing full agonist efficacy on all three α_2 adrenoceptors (α_{2A}, α_{2B}, α_{2C}).[8] Recently, Eisenach *et al.*[9] showed that intrathecal radolmidine produced antinociception to a mechanical stimulus in a sheep model of acute pain. The ED_{50} of radolmidine was approximately 30% less than that of dexmedetomidine in sheep. Previously, dexmedetomidine has been shown to be effective in acute nociception as evidenced by increases in hot plate and tail flick latencies.[4,22] In the present study, radolmidine and dexmedetomidine were equipotent in the tail flick test. A 50% MPE was achieved with approximately 1 μg radolmidine, and 10 μg produced a 100% effect. In addition, the duration of the effect was comparable after the two drugs. The antinociceptive effects of radolmidine were reversed by 80% with atipamezole 100 μg/kg, indicating that the antinociceptive effect was mediated by α_2 adrenoceptors.

Carrageenan-induced inflammation causes edema of the paw and enhanced sensitivity of the paw toward both thermal and mechanical stimuli. Intrathecal administration of dexmedetomidine has been shown to increase paw pressure thresholds and tail flick latencies in both the control rats and those with unilateral carrageenan inflammation.[27] In the present study, both radolmidine and dexmedetomidine increased paw flick latencies and thresholds for von Frey filament forces in the inflamed paw. Radolmidine and dexmedetomidine were equianalgesic. Interestingly, lower doses of radolmidine were needed to reverse mechanical compared with thermal hyperalgesia. However, the antihyperalgesic doses of the α_2-adrenergic agonists were in the same range as those showing efficacy in the tail flick test, whereas opioids can reverse inflammation-induced thermal hyperalgesia in doses that are not effective against noxious heat.[13,15]

The ligation of the spinal nerve L5–L6 paravertebrally

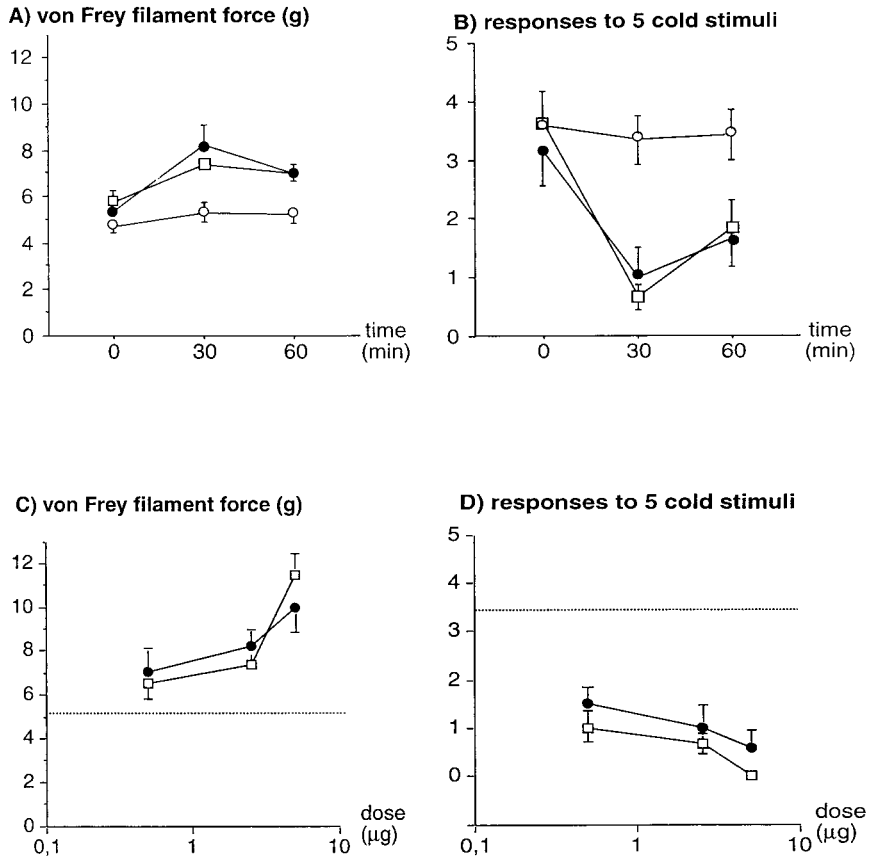

Fig. 3. The spinal nerve ligation of neuropathic pain model caused significant mechanical allodynia (low thresholds for von Frey filament stimulation) (*A*) and cold allodynia (responses to acetone) (*B*) in the ipsilateral paw. Time course of the effects of intrathecal radolmidine 2.5 μg (filled circles), intrathecal dexmedetomidine 2.5 μg (open squares), and intrathecal saline 10 μl (open circles) are shown. The mean (SEM) von Frey filament force that induced paw withdrawal (*A*) and the mean number of withdrawals to five consecutive acetone stimuli (*B*) are shown. The respective dose–response curves are shown (*C* and *D*).The dotted lines indicate the baseline values.

leads to reliable and prominent tactile allodynia.[12] Mechanical and cold allodynia were also clear in the present experiments. The paw flick latencies were almost identical in the ipsilateral and contralateral paws, indicating lack of thermal hyperalgesia in this model of neuropathic pain.[28] In previous studies in which heat hyperalgesia has been present, it has clearly been a less significant symptom than mechanical or cold allodynia. A decrease of approximately 20% in the paw flick latency of the ipsilateral as compared with the contralateral paw has been described,[29] whereas in mechanical allodynia there is a greater than 100-fold decrease in the force inducing paw withdrawal.[29] Normal rats do not show any cold allodynia.[30] The spinal nerve ligation model has an important feature in being one of the least opioid sensitive[31,32] of the many neuropathic pain models. Surgical sympathectomy has been shown to reduce this allodynic state.[29] The spinal nerve ligation model thus bears a close resemblance to the clinical neuropathic pain, which often is poorly opioid responsive, shows cold allodynia, and may also be maintained by the activity of the sympathetic nervous system.[33] Previous studies have already indicated that α_2-adrenergic agonists are effective in this opioid-insensitive pain model.[6,28,34,35] It has also been suggested that the endogenous α_2-adrenergic system may be important in controlling the neuropathic symptoms as atipamezole, the selective α_2-adrenergic agonist, has kindled allodynia in nerve-injured animals that do not initially display cold or tactile allodynia.[28,36] In agreement with this, both radolmidine and dexmedetomidine produced dose-related antiallodynic effects. The antiallodynic doses were lower than those needed for antinociceptive effects in the tail flick test. Cold allodynia was already significantly reduced with the lowest doses tested, 0.5 μg. Poree *et al.*[34] also showed that the analgesic potency of dexmedetomidine is enhanced after nerve injury. However, these investigators administered dexmedetomidine systemically and suggested that the effect could be peripheral.

This increased efficacy of α_2-adrenergic agonists against allodynia in the spinal nerve ligation model could be mediated *via* release of acetylcholine. Intrathecally administered clonidine increases concentrations of acetylcholine in microdialysates from spinal cord dorsal

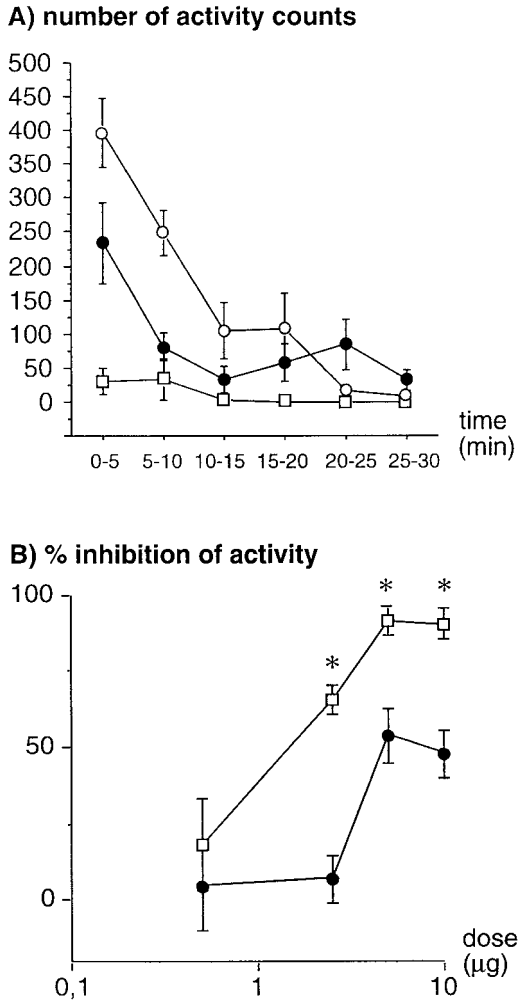

Fig. 4. The effects of radolmidine and dexmedetomidine on spontaneous locomotion. As an example of the decrease in locomotion, the mean (SEM) number of activity counts in the motility box after intrathecal administration of radolmidine 5 μg (filled circles), dexmedetomidine 5 μg (open squares), or saline 10 μl (open circles) is shown (*A*). The dose–response curves for radolmidine (filled circles) and dexmedetomidine (open squares) plotting mean percentage of inhibition of activity, as compared with the locomotor activity in the saline control group (SEM) 0–15 min after intrathecal administration of the drugs, are shown (*B*). The asterisks indicate statistically significant difference between the drugs.

horn.[37] Recently, Pan *et al.*[35] showed that the antiallodynic effect of clonidine was attenuated by anticholinergic agents. We previously reported that physostigmine reversed tactile allodynia in a dose-dependent way in rats but had no effect on the paw flick test, indicating a differential effect of acetylcholine in heat nociception and mechanical allodynia in the spinal nerve ligation model.[38]

Sedation is a major adverse effect caused by most of the present α_2-adrenergic agonists. Because of the potent sedative effect, dexmedetomidine has recently been approved by the Food and Drug Administration for use in the sedation of patients in the intensive care unit. The locus coerulaeus (LC) is likely to have an important contribution to the sedative effects induced by α_2-adrenergic agonists.[23] Activation of α_2 adrenoceptors in the LC hyperpolarizes cell bodies in the LC.[39] Suppression of LC neurons is known to be connected with a decrease in vigilance.[40] Sedation after spinal administration of α_2-adrenergic agonists is considered to reflect supraspinal redistribution of the spinally delivered agent.[41]

Sedation was assessed as reduction of spontaneous locomotor activity in a motility box where the animals could move freely. Hypolocomotion can be caused by decreased vigilance and sedation or motor impairment. High doses α_2-adrenergic agonists have been reported to produce hind limb motor weakness and sedation.[6] However, no motor impairment was detected in the present study. In addition, no motor impairment was detected after intrathecal dexmedetomidine (4.05 μg) in the rotarod test.[27] When the animals were put into the motility boxes, they initially showed much spontaneous locomotor activity when exploring the novel environment for approximately 15–20 min, and thereafter settled down.

After dexmedetomidine administration, the animals showed significantly less spontaneous locomotor activity compared with after radolmidine administration. This was observed at all doses tested. Even after intrathecal administration of dexmedetomidine, it has been difficult to find a therapeutic window dissociating the analgesic effect from the sedative one.[34] The present results suggest that radolmidine produces equipotent antinociception compared with dexmedetomidine, but it has a therapeutic window for antinociception without sedation. The different sedative effects of these two α_2-adrenergic agonists can most likely be explained by different pharmacokinetics and, consequently, different distribution in the central nervous system after intrathecal administration. This hypothesis is supported by previous research. Eisenach *et al.*[4,9] have shown that radolmidine differs from dexmedetomidine by lack of antinociception after large intravenous and epidural doses. The bioavailability of radolmidine after epidural administration was only 7% compared with 22% after epidural dexmedetomidine.[4] Because radolmidine does not cross the blood–brain barrier as readily as dexmedetomidine, it will not escape from the subarachnoid space to produce supraspinally mediated sedation. The hypothesis of different distribu-

tions is also supported by Xu *et al.*,[42] who showed that the sedative effects of dexmedetomidine were less dependent on the exact injection site in the brainstem compared with radolmidine that had to be injected exactly into the LC to produce sedation. Other differences between the molecules may also play a role, as 3 μg dexmedetomidine in the LC produces a highly significant suppression of locomotor activity, whereas radolmidine produced a significant suppression of locomotor activity only at the 10-μg dose.

Hemodynamic effects of intrathecal radolmidine were not assessed in the present study. Eisenach *et al.*[9] recently showed that in doses up to three times the antinociceptive ED_{50}, radolmidine did not decrease arterial blood pressure or heart rate in the sheep, and the hemodynamic effects of radolmidine were significantly less compared with those of clonidine. Direct comparisons of the hemodynamic effects of dexmedetomidine and radolmidine have not been published. The indirect evidence from studies in sheep[4,9] would indicate that the hemodynamic effects of radolmidine are less compared with those of dexmedetomidine.

In summary, radolmidine has an equipotent antinociceptive effect compared with dexmedetomidine, both against acute noxious heat, and inflammation-induced heat hyperalgesia and mechanical allodynia. Radolmidine and dexmedetomidine also show equipotent antiallodynic effects in the spinal nerve ligation model of neuropathic pain. Radolmidine produces both less hemodynamic and sedative effects than dexmedetomidine in laboratory animals. If these differences can be shown to be of clinical relevance, radolmidine may be a useful spinal analgesic in humans.

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