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Developmental Age Influences the Effect of Epidural Dexmedetomidine on Inflammatory Hyperalgesia in Rat Pups

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Background: **Epidural α_2-adrenergic agonists produce analgesic effects in children and adults, but efficacy and safety have not been established in neonates and infants. The aim of this study was to determine the effect of epidural dexmedetomidine on sensory processing, reversal of inflammatory hyperalgesia, and sedation during early development in rats.**

Methods: **In rat pups aged 3, 10, and 21 postnatal days, mechanical withdrawal thresholds of the hind limbs were measured at baseline and after unilateral inflammation due to carrageenan. The effect of epidural dexmedetomidine on withdrawal thresholds was measured for 90 min after injection, and dose–response curves were constructed for each age group. The duration of the righting reflex was measured to assess sedation. The effects of epidural and systemic administration of dexmedetomidine were compared.**

Results: **At all ages, carrageenan-induced hyperalgesia was reversed by doses of epidural dexmedetomidine that did not affect the threshold of the contralateral paw or prolong the righting reflex. Higher doses of epidural dexmedetomidine affected baseline nociception in the contralateral paw and produced sedation but had no effect when given systemically. Reversal of hyperalgesia and sedation were produced by lower doses of epidural dexmedetomidine in the youngest pups.**

Conclusions: **Spinally mediated selective reversal of inflammatory hyperalgesia by epidural dexmedetomidine can be achieved at all ages; relatively lower doses are effective in early life, but the therapeutic window is narrow. These data have implications for the use and dosing of epidural α_2 agonists in neonates and infants.**

EPIDURAL analgesia is frequently used in neonates, infants, and children for the management of acute postoperative pain.[1–3] Increasingly, nonopioid spinally acting analgesics are being added to local anesthetics and opioids with the aim of improving the quality or prolonging the duration of analgesia or to reduce side effects because lower doses are required with combination therapy.[4,5] In rats, it has recently been shown that significant age-related changes occur in response to epidurally administered opioids[6] and local anesthetics,[7] which is consistent with the developmental regulation of receptors and channels in the central nervous system during early life.[8]

Clonidine is an α_2-adrenergic agonist that produces spinally mediated analgesia in both laboratory[9] and clinical studies.[10] In pediatric practice, 1–2 μg/kg clonidine has been shown to prolong analgesia when added to caudal epidural local anesthetic injections,[5,11] and 0.08–0.12 $\mu g \cdot kg^{-1} \cdot h^{-1}$ clonidine produces a dose-related analgesic effect when added to lumbar epidural infusions.[12] However, clinical trials have recruited children older than 6–12 months, and there are no controlled data for epidurally administered clonidine in neonates and infants younger than 6 months. Recently, case reports of side effects after administration of caudal clonidine to neonates[13–15] raise the possibility that the response to epidural α_2 agonists is developmentally regulated.

Dexmedetomidine has greater selectivity for the α_2 receptor and is more potent than clonidine.[16] In adult animals, dexmedetomidine has antinociceptive and antihyperalgesic effects after systemic and spinal administration.[17] In isolated neonatal rat spinal cord, dexmedetomidine inhibits ventral root responses to stimulation of the dorsal root,[18,19] suggesting an effect on spinal nociceptive transmission, but the *in vivo* efficacy of spinally administered dexmedetomidine has not been compared at different developmental ages.

The aim of the current study was to examine the effect of postnatal age on the response to epidural dexmedetomidine in rats. We wished to determine whether (1) dose related analgesia could be demonstrated at all ages (2) a direct spinal analgesic action was evident at all ages, (3) reversal of inflammatory hyperalgesia could be achieved without nonspecific sensory effects, and (4) age is a significant factor in analgesic efficacy.

Materials and Methods

All experiments were performed with approval of the Royal North Shore Hospital and University of Technology Sydney Animal Care and Ethics Committee, New South Wales, Australia, in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes, 1990, or under personal and project licenses in accordance with the United Kingdom Animal

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(Scientific Procedures) Act 1986. Litters of male and female Sprague-Dawley rat pups on the 3rd (P3), 10th (P10), and 21st postnatal days (P21) were obtained from Gore Hill Laboratories (Sydney, Australia) or the Biologic Services Unit, University College London (London, United Kingdom). Animals were randomly assigned to treatment groups.

Flexion Withdrawal Thresholds and Righting Reflex Duration

The mechanical threshold for hind-limb withdrawal was determined using calibrated nylon monofilaments (von Frey hairs) that exert logarithmically increasing stimulus strength, expressed linearly on a scale of 1–20 as the von Frey hair number. The range of hairs used in this study applied forces from 1.1 g (von Frey hair 9) to 22 g (von Frey hair 15). Pups were lightly restrained on a flat bench surface, and each von Frey hair was applied to the dorsal surface of the hind paw five times at 1-s intervals, and the number of evoked flexion withdrawals was recorded. The maximum force applied was that which evoked five withdrawal responses. The mechanical withdrawal threshold of both hind paws was determined at the following time points: baseline (time = t −180 min); immediately before epidural injection (time = t0); and then 15, 30, 45, 60, and 90 min after epidural injection.

The duration of the righting reflex was measured to assess sedation. Each animal was placed on its back on a flat bench surface, and the time taken for the animal to turn and place all four paws on the bench was measured. The average of two measurements was taken at each time point. A maximum cutoff time of 20 s was allowed.

Hind-paw Inflammation

Inflammation was induced by injection of a 2% solution of lambda carrageenan (Sigma, St. Louis, MO) into the left hind paw. Rat pups were briefly anesthetized with 2–4% halothane in oxygen, and injections were made into the midpoint of the plantar surface of the hind paw using a 30-gauge sterile needle and a calibrated syringe. The volumes of injectate were 5, 10, and 20 μl at P3, P10, and P21, respectively, to provide a dose approximating 10 mg/kg at all ages.[7]

Epidural Injection Technique

Three hours after hind-paw injection, animals were briefly anesthetized with halothane and oxygen. Using a 30-gauge needle and calibrated 100-μl glass Hamilton syringe, epidural injections were made between the lower lumbar vertebrae using a loss-of-resistance technique.[6,7] Solutions of saline and varying concentrations of epidural dexmedetomidine (0.5–10 μg/ml; Abbott Australasia Pty Ltd, Kurnell, Australia) were prepared and coded. The same investigator, who was blinded to the epidural solution, performed all epidural injections and sensory testing. By using the same volume (2 μl/g) of different concentrations of drug, equivalent doses per gram body weight could be given without compromising blinding. All solutions contained 1% Evans Blue as a marker. After an overdose of intraperitoneal pentobarbitone (100 mg/kg) at the end of each experiment, a laminectomy was performed, and the spinal cord was dissected. Data were only included from animals in which epidural placement could be confirmed by midline extradural spread of solution across low thoracic and lumbar segments, and dural puncture was excluded by lack of cerebrospinal fluid and spinal cord staining.

Dose and Age Groups

The maximum tolerated epidural concentration of dexmedetomidine was determined for each age group in pilot experiments. After 20 μg/kg (*i.e.*, 2 μl/g of 10 μg/ml) at P3 and 40 μg/kg (*i.e.*, 2 μl/g of 20 μg/ml) at P10 and P21, animals were markedly sedated, the withdrawal reflex could not be elicited, and the respiratory rate was visibly reduced. Data were therefore obtained from saline controls, four doses of dexmedetomidine in P3 pups (1, 2, 4, and 10 μg/kg), and five doses in P10 and P21 pups (1, 2, 4, 10, and 20 μg/kg). The sample size was six to eight for each treatment group.

The effect of systemic administration of dexmedetomidine was assessed by intraperitoneal injection of 10 μg/kg dexmedetomidine at P3 and 20 μg/kg at P10 and P21 (n = 4 in each group) 3 h after hind-paw carrageenan. The hind-paw injection technique and the testing protocol were as outlined above.

Statistical Analysis

For each test condition, the number of withdrawal responses was plotted against von Frey hair number. Because each increase in von Frey hair number corresponds to a $\log_{10}$ increase in applied force, a sigmoidal stimulus–response curve with variable slope was constructed using nonlinear regression (GraphPad Prism versions 3 and 4; GraphPad, San Diego, CA). The midpoint of the curve (50% maximum force) was determined and designated the threshold.[20,21] Changes in threshold were analyzed in von Frey hair number units as previously described.[7] Treatment groups were compared with one-way analysis of variance and Tukey *post hoc* comparison, two-way analysis of variance with time and treatment as variables, or two-tailed Student *t* test as appropriate (GraphPad Prism versions 3 and 4). $P < 0.05$ was designated as statistically significant.

Results

Effect of Postnatal Age and Carrageenan Inflammation on Mechanical Withdrawal Thresholds

The baseline mechanical withdrawal threshold increased with postnatal age, consistent with previous

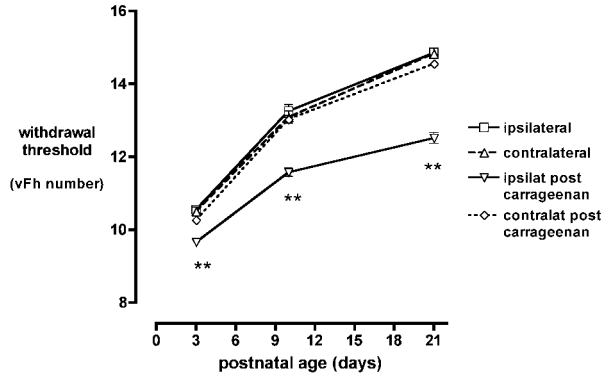

Fig. 1. Mechanical withdrawal threshold and response to inflammation at different developmental ages. The mechanical withdrawal threshold (von Frey hair number [vFH]) of the ipsilateral and contralateral paw is represented at baseline and 3 h after hind-paw injection of carrageenan (ipsilateral post carrageenan; contralateral post carrageenan). The withdrawal threshold increases with increasing postnatal age. At each age, the threshold of the ipsilateral injected paw after carrageenan was significantly lower than in all other groups. *Data points* = mean ± SEM. ** $P < 0.01$, one-way analysis of variance with Tukey *post hoc* comparison; n = 32–40 in all groups.

reports.[6,7,22] Within each age group, the thresholds of the ipsilateral and contralateral paw at baseline were not significantly different (fig. 1). Three hours after injection of carrageenan, the threshold of the injected hind paw in all age groups was significantly reduced in comparison to baseline values, consistent with the development of inflammatory hyperalgesia. In addition, the threshold of the inflamed paw was significantly lower than the threshold of the contralateral paw ($P < 0.01$), and the latter did not differ from its baseline value (fig. 1).

Effect of Epidural Dexmedetomidine on Carrageenan-induced Hyperalgesia

Figure 2 shows the change in threshold produced by inflammation and subsequent epidural injections in P21 (figs. 2A and B), P10 (figs. 2C and D), and P3 pups (figs. 2E and F). For each treatment group, changes from baseline threshold in von Frey hair number were plotted against time for the left inflamed hind paw (figs. 2A, C, and E) and the contralateral paw (figs. 2B, D, and F). A dose–response relation for epidural dexmedetomidine was demonstrated in all age groups. The effect of epidural dexmedetomidine was maximal 15–30 min after epidural injection, and the effect on inflammatory hyperalgesia was analyzed at these time points. Changes in threshold after different doses of epidural dexmedetomidine are represented as a proportion of the change produced by inflammation. Fifteen (fig. 3A) and 30 min (fig. 3B) after epidural injection, inflammatory hyperalgesia was reversed by 1 μg/kg dexmedetomidine in P3 pups, whereas 4 μg/kg dexmedetomidine was required in P10 and P21 pups. At these doses, the effect seen in P3 pups was significantly greater than that in P21 pups ($P < 0.05$).

Effect of Epidural Dexmedetomidine on Baseline Sensory Processing

At all ages, the dose of epidural dexmedetomidine that reversed inflammatory hyperalgesia did not affect the threshold of the contralateral paw (fig. 2). Fifteen minutes after epidural injection, the threshold of the contralateral paw was significantly increased above baseline by 10 μg/kg dexmedetomidine in P3 pups and by 20 μg/kg in P10 and P21 pups ($P < 0.05$, two-way analysis of variance). The threshold of the contralateral paw did not differ significantly from baseline after lower doses of epidural dexmedetomidine.

Effect of Systemic Dexmedetomidine on Carrageenan-induced Hyperalgesia

The maximum epidural dexmedetomidine dose (10 μg/kg at P3 or 20 μg/kg at P10 and P21) had no effect when given systemically. The mechanical withdrawal threshold was significantly higher 15 and 30 min after epidural administration when compared with the same dose by the intraperitoneal route ($P < 0.05$; fig. 4). At these doses, intraperitoneal dexmedetomidine had no effect on the hyperalgesia produced by carrageenan, because threshold values remained low and did not differ significantly from the control epidural saline group. The duration of the righting reflex was also not significantly increased after these doses of intraperitoneal dexmedetomidine in any age group (data not shown).

Effect of Epidural Dexmedetomidine on the Righting Reflex

The dose of epidural dexmedetomidine that reversed carrageenan-induced hyperalgesia did not produce significant sedation as assessed by prolongation of the righting reflex. The righting reflex becomes more coordinated and rapid with increasing postnatal age ($P < 0.01$). Within each age group, the baseline times to right (mean ± SEM) did not differ across treatment groups and were 4.36 ± 0.39, 1.91 ± 0.08, and 0.71 ± 0.02 s at P3, P10, and P21, respectively. Epidural dexmedetomidine increased the duration of the righting reflex at all ages in a time- and dose-dependent manner, because effects were more prolonged and occurred at lower doses in younger animals (fig. 5). In P21 rat pups, the lowest dose that significantly prolonged the duration of the righting reflex was 20 μg/kg epidural dexmedetomidine ($P < 0.01$), whereas in P3 pups, doses of 2, 4, and 10 μg/kg dexmedetomidine were sufficient to prolong the reflex ($P < 0.05$). In four of six animals in both the P10 20-μg/kg group and the P3 10-μg/kg group, epidural dexmedetomidine prolonged the righting reflex beyond the 20-s cutoff period. This degree of effect was not seen at any dose or time in P21 pups.

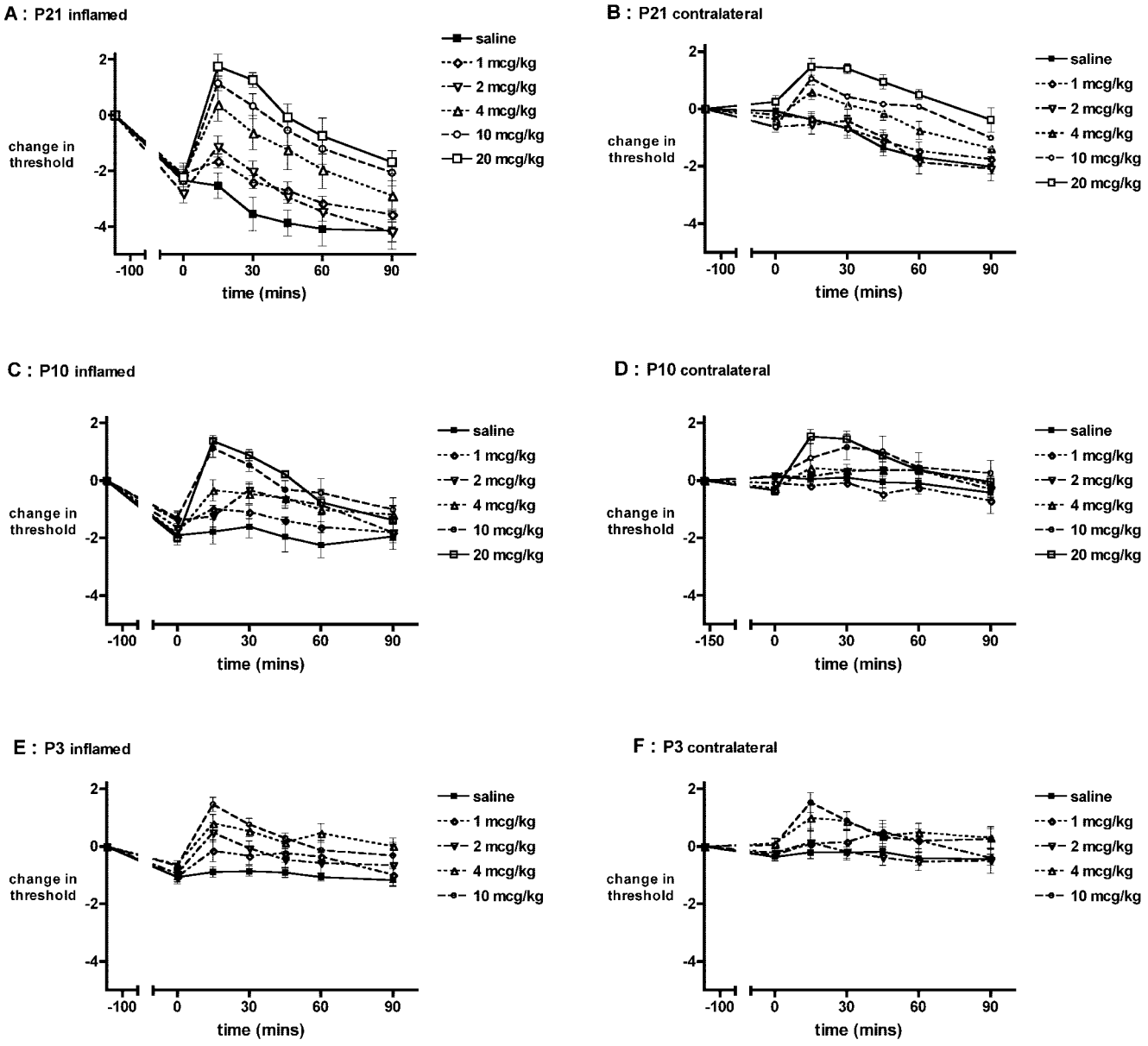

Fig. 2. Change in withdrawal threshold after inflammation and epidural dexmedetomidine at ages P21, P10, and P3 (n = 6–8 in all groups). Data are represented as the change in von Frey hair number (mean ± SEM) from the baseline value (−180 min) and for 90 min after epidural injection of saline or dexmedetomidine (1–20 μg/kg) in the ipsilateral (*A*, *C*, and *E*) and contralateral (*B*, *D*, and *F*) hind paw. At all ages, the threshold in the ipsilateral paw is reduced 3 h after hind-paw carrageenan (t = 0), and increasing doses of dexmedetomidine progressively reverse inflammatory hyperalgesia. High doses of epidural dexmedetomidine increase the threshold above baseline in both the ipsilateral and the contralateral paw.

Discussion

We have shown that epidural dexmedetomidine has a dose-dependent and developmentally regulated analgesic effect in rat pups. Selective reversal of hyperalgesia can be achieved at all ages, without affecting the threshold of the contralateral paw or causing significant prolongation of the righting reflex. The dose of epidural dexmedetomidine required to reverse hyperalgesia is lower in the youngest pups, which are also more sensitive to the sedative effects. The analgesic effect of epidural dexmedetomidine is spinally mediated, because systemic administration of the same dose has no effect.

α_2-Adrenergic receptors are functionally coupled to G proteins from early in development[23] and have an inhibitory influence on neuronal activity.[17] α_2-Adrenoreceptors within the spinal cord are present on the terminals of primary afferents, interneurons, and descending norepinephrine-containing fiber pathways from cell groups A5, A6 (locus ceruleus), and A7 (subceruleus) in the pons.[24,25] Three subtypes of the α_2 receptor (2A, 2B, and 2C) have been identified,[17] and studies in mice with a

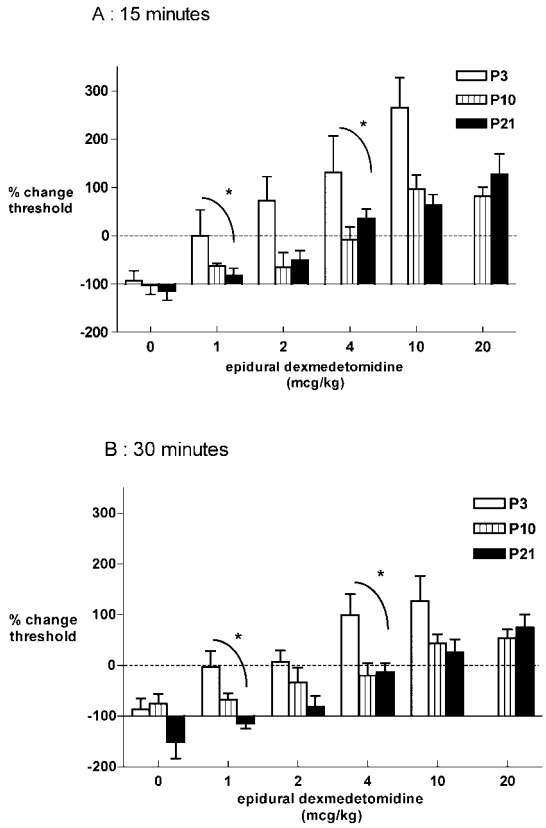

Fig. 3. Effect of epidural dexmedetomidine on inflammatory hyperalgesia at 15 (*A*) and 30 min (*B*). Within each age group, the change in threshold after inflammation and before epidural injection is standardized as 100% change. The degree of change at subsequent time points is then represented as a proportion of the initial change produced by inflammation (mean ± SEM). At both time points, reversal of inflammatory hyperalgesia is obtained with 1 μg/kg dexmedetomidine in P3 pups, whereas 4 μg/kg is required in P10 and P21 pups. Analysis at these two doses reveals a significantly greater change in P3 pups compared with P21 pups. * $P < 0.05$, one-way analysis of variance with Tukey *post hoc* comparison; n = 6–8 in all groups.

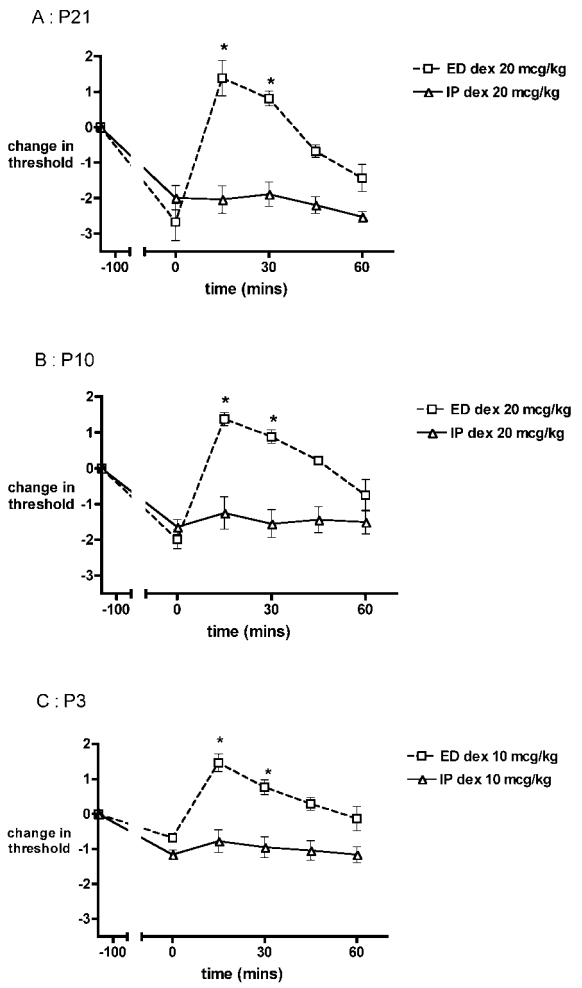

Fig. 4. Comparison of epidural and intraperitoneal administration of dexmedetomidine at P21 (*A*), P10 (*B*), and P3 (*C*). The change in threshold of the ipsilateral inflamed paw *versus* time is shown after epidural (ED dex; n = 6–8) or intraperitoneal (intraperitoneal dex; n = 4) administration of dexmedetomidine. Significant differences between the two routes were seen 15 and 30 min after administration. At each age, the reduction in threshold produced by inflammation was not altered by intraperitoneal dexmedetomidine * $P < 0.05$, two-tailed Student *t* test.

point mutation (D79N) of the α_{2A} receptor suggest that this subtype is important for antinociceptive effects.[26,27] α_{2A}-Receptor protein and messenger RNA (mRNA) have been isolated in rat dorsal root ganglia[28–30] and in the superficial dorsal horn.[26,31]

Dexmedetomidine has greater potency and increased selectivity for the α_2 receptor than clonidine.[32,33] In adult animals, dexmedetomidine produces dose-related antinociceptive effects in response to thermal and mechanical stimuli.[33,34] In our study, high doses of epidural dexmedetomidine increased the mechanical withdrawal threshold of the hind paw above baseline (*i.e.*, had an antinociceptive effect) at all ages. However, we also wished to determine whether selective reversal of inflammatory hyperalgesia could be achieved at lower doses without affecting sensory transmission in the contralateral paw. In adult animals, dexmedetomidine attenuates carrageenan-induced hyperalgesia[34,35] at doses lower than required to produce antinociceptive effects. Reversal of inflammatory hyperalgesia was achieved at all postnatal ages by doses of epidural dexmedetomidine that did not alter the threshold of the contralateral paw. This suggests that in early development, antihyperalgesic effects of α_2 agonists can be achieved at doses that have no effect on baseline sensory processing. In addition, the dose required for both antihyperalgesic and antinociceptive effects was lower in the youngest pups, suggesting an increased sensitivity to dexmedetomidine in early life.

The analgesic effects of α_2 agonists are achieved at lower doses after spinal as compared with systemic administration in adults.[36] Epidurally administered dexmedetomidine is rapidly absorbed into the cerebrospinal fluid[37] and reaches binding sites in the spinal cord.[33] The dose required for epidural administration is approximately 5 times less than that required with systemic

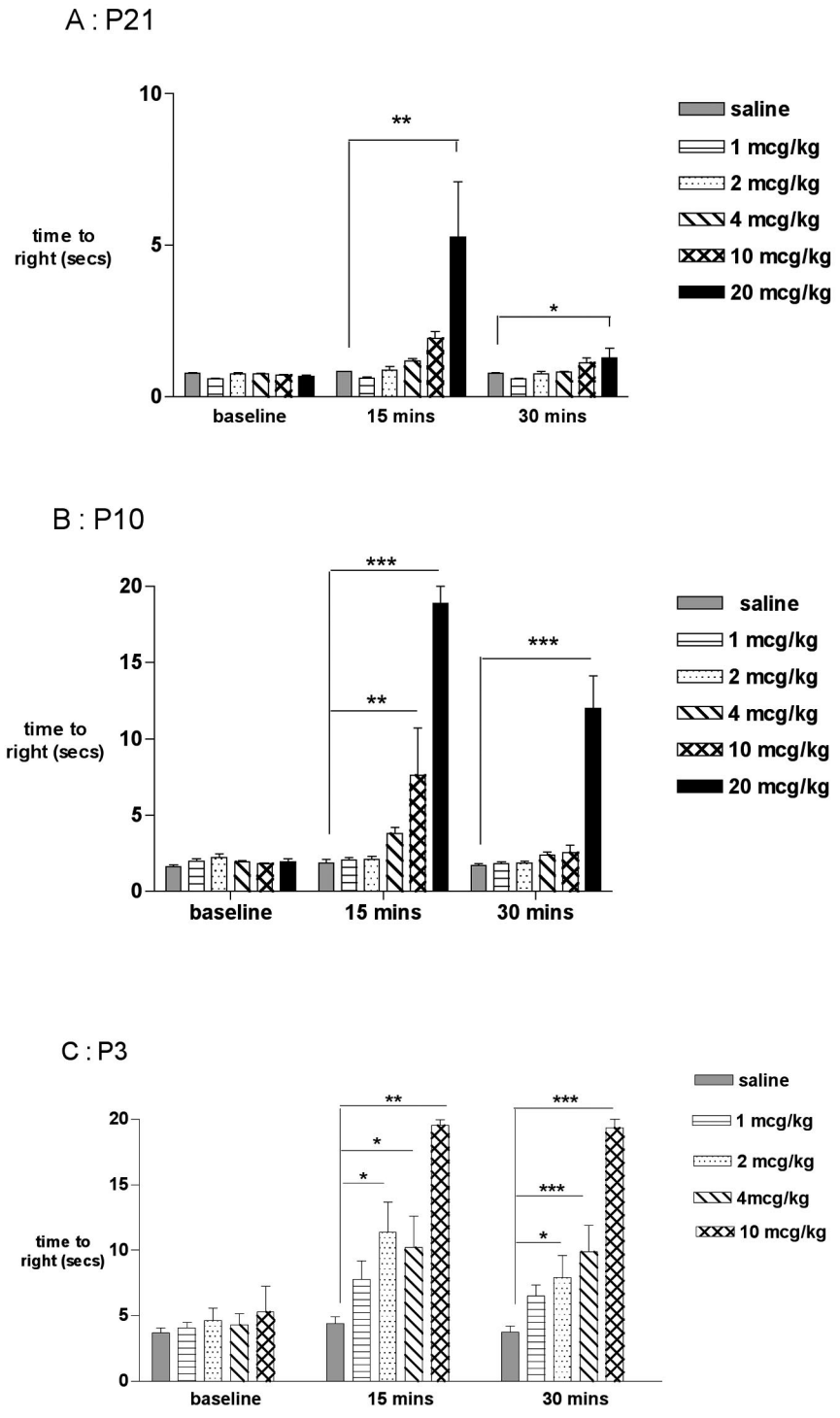

Fig. 5. Duration of the righting reflex at baseline and after epidural dexmedetomidine. The duration of the righting reflex in each treatment group is shown at baseline and 15 and 30 min after epidural injection (*bars* = mean ± SEM) in P21 (*A*), P10 (*B*), and P3 (*C*) rat pups. The duration is significantly prolonged by lower doses of dexmedetomidine in the youngest pups. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, one-way analysis of variance with Tukey *post hoc* comparison.

administration.[33,37,38] In all age groups, the maximum epidural dose had no effect on mechanical withdrawal thresholds or inflammatory hyperalgesia when given by the intraperitoneal route, suggesting that the effect of epidural dexmedetomidine is spinally mediated.

A major advantage of the decreased dose requirement with spinal administration is the potential for reduced side effects when compared with systemic administration. Several studies have shown that the therapeutic window is narrow after systemic administration of α_2 agonists, because sedative and motor side effects often occur within the same dose range as analgesia.[36,38,39] Because both analgesia and sedation are mediated by the α_{2A} receptor, development of a subtype selective drug is unlikely to decrease the likelihood of side effects.[27] In the current study, doses of epidural dexmedetomidine

that reversed inflammatory hyperalgesia did not significantly prolong the righting reflex. The righting reflex has been used in previous studies with adult animals to assess the sedative effects of dexmedetomidine.[39,40] Other methods of assessing sedative or motor activity, such as the rotarod[36] or activity in an open field,[34] are not applicable to P3 pups, which have a low level of spontaneous activity. Although the righting reflex is less coordinated in young pups and the baseline time to right is longer, a dose-related increase with higher doses of dexmedetomidine could be seen at all ages.

Developmental changes in nociceptive processing, receptor distribution, and descending inhibitory mechanisms[8,41] may influence the response to α_2 agonists. The relative contribution of primary afferent, spinal cord, and descending pathway mechanisms to α_2-adrenergic analgesia has not been determined during development. Descending inhibitory pathways in the dorsolateral funiculus do not inhibit dorsal horn activity in the first postnatal week,[42] and although noradrenergic-immunoreactive fibers are visible in the dorsal horn at P3, the density of innervation does not reach adult levels until P30.[43] However, radioligand binding of the agonists [^{3}H]RX821002 and [^{3}H]rauwolscine demonstrate a predominance of α_{2A} binding sites in both neonatal and adult spinal cord,[44] and binding sites for [^{3}H]dexmedetomidine have been identified in neonatal spinal cord (P1–2).[45] Messenger RNA for the α_{2A} receptor is present in prenatal dorsal horn cells,[46] and moderate levels have been detected in dorsal horn slices at P1–3 and P21 and high levels have been detected at P5–14.[47] The effect of postnatal age on the density and distribution of 2A receptor protein expression in the spinal cord or the expression of α_2-adrenergic receptor mRNA and protein in the dorsal root ganglion has not been systematically investigated. Postnatal changes in receptor distribution may contribute to developmental changes in sensitivity to analgesics, as shown for opioids.[20] In adult animals, comparison of effects after intracerebroventricular and intrathecal administration suggests the spinal cord as the predominant site mediating analgesia.[48,49] In isolated neonatal spinal cord (P0–6), dexmedetomidine depresses the ventral root potential evoked by substance P[18] or electrical stimulation of the dorsal root.[19] This suggests that local spinal cord mechanisms may mediate analgesic effects in early development, but dose-related effects at different postnatal ages have not previously been tested *in vivo*. Our study demonstrates reversal of inflammatory hyperalgesia by epidural dexmedetomidine at all postnatal ages, with an increased functional sensitivity in the youngest pups.

Lower doses of epidural dexmedetomidine prolonged the righting reflex in the youngest pups, suggesting an age-related sensitivity to side effects. The sedative effects

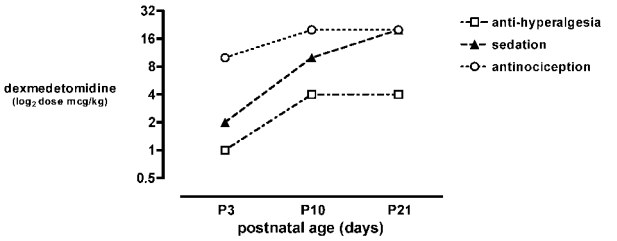

Fig. 6. Schematic representation of dose-related effects according to age. The lowest dexmedetomidine dose associated with reversal of hyperalgesia (antihyperalgesia), significant prolongation of the righting reflex (sedation), and significant increases in the mechanical withdrawal threshold of the contralateral paw (antinociception) 15 min after epidural injection is represented for each age group. The dexmedetomidine dose is charted on a $\log_2$ scale to allow differentiation of the effects at lower doses.

of α_2 agonists are mediated in the locus ceruleus,[17] and therefore, an increased pharmacodynamic sensitivity, increased central redistribution, or increased dural penetration may contribute to this effect. The blood–brain barrier is functional at birth,[50] and no age-related differences in dural penetration after epidural morphine were found in rat pups.[51] The locus ceruleus is a specific area with high expression of α_2 mRNA throughout postnatal development,[47] and levels of α_2-receptor binding are high and already near adult levels at P1.[52] The relatively high level of α_2 receptor in the developing brainstem may contribute to increased sedative effects in early life. In P3 pups, although the dose of epidural dexmedetomidine that reverses hyperalgesia is less than that associated with sedation (1 *vs.* 2 μg/kg), the therapeutic window is relatively narrow. With increasing postnatal age, there was a change from a 2- to a 10-fold difference between the dose associated with reversal of hyperalgesia and the dose that produced sedation (as illustrated in fig. 6). Sedation was also produced at doses lower than required for antinociception, suggesting a specific increased sensitivity to sedation in early life that differs from a nonspecific effect on sensory processing. By P21, only doses that have antinociceptive effects produce sedation and are much higher than the dose required for reversal of inflammatory hyperalgesia. Some overlap between analgesia and side effects is seen in infants and children because caudal clonidine (1–2 μg/kg) prolongs analgesia and is associated with mild sedation,[5,11] whereas clinically significant sedation and cardiovascular changes are produced by higher doses (5 μg/kg).[53] However, a tendency to increased side effects from epidural α_2 agonists in early life is reflected in clinical reports of apnea, oxygen desaturation, and bradycardia in neonates[13–15] given doses of caudal clonidine (1.25–2.2 μg/kg) that are tolerated by older children. Although these side effects cannot be specifically attributed to caudal clonidine, particularly because two of the neonates were born preterm (32 and 36 weeks' postconcep-

tional age), there is a trend for increasing side effects with higher doses, and the youngest neonate had previously undergone hernia repair with caudal local anesthetic alone without problems.[15]

Changes in the developing nervous system have a significant impact on the response to injury and analgesic agents.[41] At all postnatal ages, epidural dexmedetomidine reverses inflammatory hyperalgesia at doses that have no effect on baseline sensory processing in the contralateral paw. The effect of epidural dexmedetomidine is developmentally regulated, because the dose required to reverse hyperalgesia is lower in early life. This suggests that the mechanisms required for analgesia are present and functional in early development. However, sensitivity to the sedative effects of epidural dexmedetomidine is also increased, and therefore, the therapeutic window is narrow in early development. α_2 Agonists may be effective epidural analgesics in infants at doses lower than those required in older children. Controlled clinical trials are required to establish the efficacy and risk–benefit profile of epidural α_2 agonists in neonates and infants.

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