Dexmedetomidine, Acting Through Central Alpha-2 Adrenoceptors, Prevents Opiate-Induced Muscle Rigidity in the Rat

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The highly-selective alpha-2 adrenergic agonist dexmedetomidine (d-MED) is capable of inducing muscle flaccidity and anesthesia in rats and dogs. Intense generalized muscle rigidity is an undesirable side effect of potent opiate agonists. Although the neurochemistry of opiate-induced rigidity has yet to be fully elucidated, recent work suggests a role for a central adrenergic mechanism. In the present study, the authors determined if treatment with d-MED prevents the muscle rigidity caused by high-dose alfentanil anesthesia in the rat. Animals (n = 42) were treated intraperitoneally with one of the following six regimens: 1) l-MED (the inactive L-isomer of medetomidine), 30 μg/kg; 2) d-MED, 10 μg/kg; 3) d-MED, 30 μg/kg; 4) d-MED (30 μg/kg) and the central-acting alpha-2 antagonist, idazoxan (10 μg/kg); 5) d-MED (30 μg/kg) and the peripheral-acting alpha-2 antagonist DG-5128 (10 mg/kg) or; 6) saline. Baseline electromyographic activity was recorded from the gastrocnemius muscle before and after drug treatment. Each rat was then injected with alfentanil (ALF, 0.5 mg/kg sc). Alfentanil injection resulted in a marked increase in hindlimb EMG activity in the l-MED treatment group which was indistinguishable from that seen in animals treated with saline. In contrast, d-MED prevented alfentanil-induced muscle rigidity in a dose-dependent fashion. The small EMG values obtained in the high-dose d-MED group were comparable with those recorded in earlier studies from control animals not given any opiate. The high-dose d-MED animals were flaccid, akinetic, and lacked a startle response during the entire experimental period. The elimination of opiate rigidity by d-MED was completely blocked by the coadministration of the central alpha-2 antagonist, idazoxan, but only marginally by the peripheral alpha-2 antagonist, DG-5128. These results suggest that subanesthetic doses of the highly selective alpha-2 agonist dexmedetomidine may be clinically effective in preventing the muscle rigidity and augmenting the anesthesia produced by moderate to high doses of opiates. These effects appear to be due to the activation of central alpha-2 adrenoceptors. Selective alpha-2 adrenergic agonists show increasing clinical promise as anesthetic adjuvants. (Key words: Anesthetics, intravenous: alfentanil. Complications: muscle rigidity. Sympathetic nervous system, alpha2 agonist: dexmedetomidine.)

Activation of the alpha-2 adrenoceptor produces many physiological effects, including analgesia, sedation, bradycardia, lowered blood pressure, decreased salivary secretions, hypothermia, mydriasis, and relief of anxiety. Given this desirable physiological profile, potent alpha-2 agonists could be quite useful as anesthetic adjuvants. In fact, we and others have recently demonstrated that the highly-selective alpha-2 adrenergic agonist, dexmedetomidine (d-MED) is an anesthetic in both dogs and rats. Another selective alpha-2 agonist, azepoxide, has similar anesthetic properties. Vickery et al. showed that d-MED decreased the minimum alveolar concentration (MAC) of halothane in dogs to a greater extent than any other pharmacological intervention previously reported. At the highest dose studied in dogs (10 μg/kg), d-MED was essentially a complete anesthetic with a duration of action of nearly 1 h. This effect was stereospecific (levomedetomidine [L-MED], the L-isomer, was inactive) and was reversible with the specific alpha-2 antagonist, idazoxan. In a similar study by Bloor and coworkers, 20 μg/kg (iv bolus) of dexmedetomidine reduced isoflurane MAC by 91% in spontaneously ventilating dogs.

In addition to loss of consciousness and analgesia, pilot studies in rats reveal that d-MED produces muscle flaccidity. These properties could make d-MED an ideal adjuvant to high-dose opiate anesthesia because intense generalized muscle rigidity is an undesirable side effect of potent opiate agonists. Furthermore, d-MED may also augment other beneficial opiate actions such as analgesia and sedation. The mechanisms whereby opiates induce muscle rigidity have yet to be elucidated, although recent work suggests a role for central adrenergic mechanisms. Work with the type-2 serotonin antagonist, ketanserin, suggests a serotoninergic component to alfentanil-induced rigidity in the rat. Several studies have documented the close physiological and anatomical relationships between adrenergic, serotoninergic, and opioid neural pathways, particularly in brainstem areas known to mediate many of the behavioral and physiological manifestations of opiate anesthesia.
In the present study, we evaluated whether treatment with the selective alpha-2 agonist, dexmedetomidine, could prevent alfentanil-induced muscle rigidity in the rat. In addition, using pharmacological manipulations, we sought to determine if dexmedetomidine's effects on alfentanil rigidity were due to activity at central alpha-2 adrenoceptors.

Materials and Methods

ANIMALS

The subjects were 43 male albino Wistar rats (Charles River Laboratories, Wilmington, MA) weighing 215–325 gm. The animals were studied in groups of 8–12 over a 4-month period. They were housed three to four per cage, with food and water available continuously, in a temperature-controlled room. Rats were handled prior to the experimental days to minimize potential effects of stress on the results. Every animal was conditioned to the experimental apparatus, a cylindrical holding cage, at least twice prior to the actual study.

The conduct of this study conformed to the Guiding Principles in the Care and Use of Animals and the study was approved by our institutional Animal Care Committee.

Experimental Protocol

Rats were assigned to one of six groups (table 1). Animals were injected intraperitoneally with either levomethadomine (the inactive L-isomer of methadone), 30 μg/kg, [L-MED, n = 7]; dexmedetomidine, 10 μg/kg [d-MED (10), n = 7]; D-MED, 30 μg/kg [D-MED (30), n = 8]; the combination of D-MED, 30 μg/kg, and the central-acting alpha-2 antagonist, idazoxan, 10 mg/kg [IDZ, n = 7];3 or the combination of D-MED, 30 μg/kg, and the hydrophilic peripheral alpha-2 antagonist DG-5128, 10 mg/kg [DG, n = 6].4 A separate group of eight rats was treated with physiological saline [SAL] and then underwent a similar experimental protocol.

Generally, four rats were studied each day between the hours of 9 A.M. and 3 P.M. Two animals, from randomly-assigned treatment groups, were studied concurrently by blinded observers. The animals were placed in barred cylindrical holding cages which allowed free movement of the extremities as well as easy access to injection and recording sites. Pilot studies in our laboratory suggested that, with prior conditioning, this minimal restraint has no effect on EMG recordings, cardiorespiratory status, or animal behavior. Two monopolar (10 mm × 100 μm diameter) platinum recording electrodes (Grass E2) were placed percutaneously into the left gastrocnemius muscle, while a third (ground) electrode was inserted subcutaneously into the right hindlimb. Leads were secured with cellophane tape in a manner that allowed unimpeded joint mobility. Both animals were placed inside the soundproof box (Coulbourn Instrument Co., Lehigh Valley, PA), a cardboard partition was put between the cages, and an electric fan was run continuously to provide white noise. Actual muscle potentials were differentially amplified 200 times and band-pass filtered from 10 Hz to 3 kHz (Grass P511K, Grass Instrument Co., Quincy, MA). The resulting signal, viewed on an oscilloscope (Tektronix 7633, Tektronix Inc., Beaverton, Ore.), was then converted with a root-mean-squared (RMS) voltage rectifier (t½ = 3 s) to produce a time-varying analog deflection on a 200-mV meter (Triplet 820-M) from which data in microvolts were obtained. Full-scale deflection of the meter corresponded to 200 μV of RMS EMG activity.12,17

Electromyographic (EMG) activity was assessed over a 15-min baseline (pretreatment) period, with readings taken at 5, 10, and 15 min. At the end of the 15-min pretreatment period, each animal received an intraperitoneal injection of either L-MED, D-MED, or D-MED plus one of the two antagonists. EMG activity was then recorded for an additional 15 min in order to assess the effects of the various drug treatments on muscle tone and animal behavior. Note that in the Saline group, in contrast to the other groups, EMG activity was not recorded until after the saline injection.

Following the 15-min post-treatment baseline, each rat was injected in situ subcutaneously with alfentanil (0.5 mg/kg). EMG readings were obtained 1 and 5 min post-injection, and then at 5-min intervals over the course of the 60-min observation period. During data collection, care was taken to eliminate the effects of transient-movement artifacts, thereby permitting an assessment of tonic rather than phasic muscle activity. This was performed during experimental observation by not recording transient increases in EMG activity which directly correlated with hindlimb movement.

Immediately before and after alfentanil injection, and then at regular intervals of every 10–15 min throughout the experimental period, animals were subjectively assessed for spontaneous movement (present/absent), muscle tone (rigid/flaccid/neither), and acoustic startle reflex (present/absent). Muscle tone was determined by gently
feeling the resistance to a small movement of the hindlimb and the tail. A startle response was elicited by the observer opening the soundproof box and clapping hands together once. In prior studies, it was noted that normal rats generally flinched while narcotized rats usually exhibit more prominent startle responses consisting of truncal and limb movement associated with transient increases in EMG activity.

**DRUGS**

The drugs used were levomedetomidine (Farmos Group Ltd., Turku, Finland), dexmedetomidine (Farmos), DG-5128 (Daichi Seiyaku Co. Ltd., Tokyo, Japan), idazoxan (Reckitt and Colman, Kingston-upon-Hull, England) and alfentanil hydrochloride (Janssen Pharmaceutica, Piscataway, NJ). All drugs, obtained as powders, were dissolved in 0.9% sterile physiological saline and injected in a volume of 1 ml/kg. The alfentanil dose used throughout the study was 0.5 mg/kg; this dose has been successfully employed in previous work examining the neurochemical basis of opiate rigidity in the rat. 19,20

**STATISTICAL ANALYSIS**

Data from each animal's 15-min pretreatment baseline (except those in the Saline group), 15-min post-treatment (pre-alfentanil) baseline, and 60-min postalfentanil experimental period (all groups) were recorded. The raw data values were plotted over time and the total area under the EMG-activity-versus-time (after ALF injection) curve was calculated as a measure of the overall degree of ALF rigidity during the experimental period. Statistical differences between treatment groups were determined using two-way analyses of variance (ANOVA) with repeated measures on one factor (time). Newman-Keuls a posteriori tests were performed to determine differences between treatment groups at individual time points, as well as differences over time within individual treatment groups. 18

**Results**

There were no differences between groups with respect to pretreatment baseline EMG activity. None of the drug treatment regimens produced a significant alteration in baseline EMG activity and in none of the groups was the post-treatment baseline different from that of the SAL group. The group receiving the 30 µg/kg dose of D-MED alone appeared more flaccid and reacted less to subsequent subcutaneous injection than animals in the other groups. One animal in the D-MED/DG-5128 group died shortly after receiving the ALF injection; his death was not readily explicable.

ALF resulted in a marked increase in hindlimb EMG activity in the group treated with the inactive isomer, L-MED. This degree of rigidity was essentially indistinguishable from that observed in the group treated with saline (fig. 1). In both groups, EMG activity rose to more than three times the pre-ALF level within 5 min of opiate injection. This level of EMG activity persisted for at least 60 min. As described in previous studies, 19,20 increases in EMG activity closely correlated with subjective measures of opiate-induced muscle rigidity.

In addition to rigidity, ALF administration also resulted in akinesia, an absence of corneal and pinnae reflexes,
Fig. 2. Dexmedetomidine treatment dose-dependently antagonizes alfentanil rigidity. This figure presents the effects of dexmedetomidine (D-MED, 10 or 30 μg/kg) on alfentanil-induced rigidity. Hindlimb muscle tone is represented on the Y-axis by EMG activity (μV RMS) and time is presented along the X-axis (min). Alfentanil (0.5 mg/kg, ALF) was administered 15 min after experimental drug pretreatment. Rats treated with the lower dose of D-MED (at Rx) were statistically indistinguishable from rats treated with the inactive l-isomer of medetomidine (l-MED). In contrast, 30 μg/kg of D-MED caused a significant (P < 0.01) attenuation of alfentanil-induced muscle rigidity beginning at 1 min after alfentanil injection. Data are plotted as mean ± SEM.

and a significant slowing of respiratory rate in both the L-MED and saline groups. Despite being in a trance-like state consistent with complete anesthesia, these rats consistently responded to loud auditory stimuli with generalized flinching, a reflex commonly referred to in the behavioral literature as "explosive motor behavior." Nevertheless, when left undisturbed, all animals in the L-MED and saline groups remained motionless for 30–40 min after ALF injection. Thereafter, some animals occasionally twitched or moved their heads from side-to-side. By the end of the 60-min experimental period, many animals showed evidence of partial recovery from the opiate’s effects. This was reflected by decreased hindlimb EMG values and increased spontaneous movement.

In contrast to the effects of L-MED or saline treatment, D-MED prevented ALF-induced muscle rigidity in a dose-dependent fashion (fig. 2). The group that received the highest dose of D-MED (30 μg/kg) had significantly lower EMG values (P < 0.01) beginning 1 min after ALF and continuing for the entire 60-min study period (figs. 2, 3). The low EMG values obtained in the high-dose D-MED group were comparable with those recorded in earlier studies from control animals given saline alone without any opiate. The high-dose D-MED animals were noticeably flaccid in both the limbs and tail. In addition, these animals appeared to be completely anesthetized—they were akinetic and lacked an acoustic startle response during the entire 60-min experimental period. This is in contrast to animals in the other treatment groups that, despite obvious muscle rigidity and some signs of opiate anesthesia, still manifested a significant acoustic startle response.

At the end of the 90-min experiment, the high-dose D-MED rats had a slow but intact righting reflex despite persistent flaccidity. The lower D-MED dose (10 μg/kg) failed to produce any significant effects on ALF rigidity at any time throughout the experiment.

The addition of the central alpha-2 antagonist, idazoxan, eliminated D-MED’s blockade of ALF-induced muscle rigidity (fig. 3). In contrast, the hydrophilic peripheral alpha-2 antagonist, DG-5128, had only a limited effect on D-MED’s antagonism of ALF rigidity. Examination of figure 3 suggests little difference in EMG activity between the DG-5128 plus D-MED group and the group receiving D-MED alone; that is, both groups failed to exhibit appreciable muscle rigidity after alfentanil. However, when the area of the EMG-activity-versus-time curve over the entire experimental period was analyzed, there was a small but significant [P < 0.05] increase in muscle activity after ALF in the DG-5128/D-MED group compared with the group receiving D-MED alone (fig. 4).

Discussion

The results of this study demonstrate that treatment with dexmedetomidine prevents opiate-induced muscle rigidity in the rat in a dose-dependent fashion. The central antagonist, idazoxan, completely reverses dexmedetomidine’s attenuating effect while only slight reversal is seen with the peripheral antagonist, DG-5128. These data suggest that dexmedetomidine is acting principally via central alpha-2 adrenoceptors to attenuate ALF-induced muscle rigidity. Furthermore, the addition of dexmedetomidine (30 μg/kg) to alfentanil (500 μg/kg) results in
a complete anesthetic state, greater than that produced by either agent alone.

Moderate to high-dose opiate anesthesia has gained widespread popularity because of its lack of significant cardiovascular depression, particularly in critically ill patients. Unfortunately, with each of the potent opiate agonists presently available, the profound analgesia is invariably accompanied by significant respiratory depression and generalized muscle rigidity. This opiate-induced muscle rigidity most commonly occurs upon anesthetic induction,20,21 not infrequently before the patient loses consciousness. With the onset of opiate rigidity, the ability to ventilate is compromised and hemodynamics are adversely affected.21 While the rigidity can be ameliorated by pretreatment with full paralyzing doses of muscle relaxant drugs, this is not always clinically desirable. Studies suggest that pretreatment with a variety of agents, including low-dose muscle relaxants and a number of CNS depressants, is ineffective at preventing opiate rigidity.22 Of those agents studied thus far in humans, only benzodiazepines23,24 and barbiturates22 appear to significantly (although not always completely) attenuate opiate-induced rigidity. However, the concurrent use of these CNS depressants along with high-dose opiates frequently results in adverse hemodynamic changes.26 Thus, optimal pretreatment regimens do not yet exist.

Direct injections of methylxanthine (MN), a quaternary opiate antagonist, into the area of the pontine reticular formation of the rat brainstem were extremely effective at preventing alfentanil-induced rigidity.12,26 This brain region contains a number of interconnected midline (raphe) nuclei that have been implicated in mediating a variety of physiological processes, including motor behavior and analgesia.27 The raphe nuclei are the major source of serotonergic neurons in both the rat and the human brains.28 These nuclei also contain significant alpha-2 adrenergic binding sites.29 There appear to be close physiological and anatomical relationships between adrenergic, serotonergic, and opioid neural pathways, particularly in brainstem areas known to play a role in the analgesia, respiratory depression, and muscle rigidity associated with high-dose opiates.13,14
The data from this study provide strong evidence that central alpha-2 adrenoceptors are responsible for dexametomidine’s antagonism of ALF rigidity. The effect was stereospecific, dose-dependent, and reversible with the central-acting alpha-2 antagonist (idoxanox) but not the peripheral antagonist (DG-5128). Dexametomidine binds to the alpha-2 adrenoceptor approximately 1600 times more avidly than it binds to the alpha-1 adrenoceptor. It is therefore approximately 27 times more selective for alpha-2 receptors than is clonidine and is significantly more potent.

Idoxanox is a potent, selective alpha-2 antagonist which readily crosses the blood-brain barrier. The dose of idoxanox used in this study (10 mg/kg) was higher than that used in earlier behavioral studies. However, recent work has demonstrated the existence of at least two subtypes of alpha-2 adrenoceptors (isoreceptors) and higher doses of idoxanox are necessary to completely and selectively block all of these brain alpha-2 isoreceptors. Idoxanox has recently been shown to also bind to nonadrenergic sites in rabbit urethral smooth muscle tissue. The significance of this finding to the present study involving live rats is unclear. It is possible that idoxanox alone might have effects on opiate rigidity but this was not examined in the present study.

DG-5128 is a relatively hydrophilic compound with an approximately 7 times greater affinity for alpha-2 than alpha-1 receptors. The fact that the systemic co-administration of DG-5128 resulted in a partial reversal of d-MED’s attenuation of ALF rigidity could be most readily explained by a small amount of drug crossing the blood-brain barrier resulting in mild central alpha-2 antagonism. The dose chosen was, in fact, significantly higher than that used by Eisenach (1 mg/kg) to demonstrate the peripheral alpha-2-mediated respiratory effects of clonidine in sheep.

Alpha-2 adrenergic agonists, when given in isolation, produce some effects similar to those seen after opiate administration; i.e., analgesia, decreased sympathetic outflow, sedation, etc. On the other hand, alpha-2 agonists appear to produce less respiratory depression than the opiates and they increase systemic vascular resistance via activation of peripheral alpha-2 adrenoceptors resulting in vasoconstriction and thereby preventing a significant fall in systemic blood pressure. Nevertheless, it is quite interesting that while high doses of opiates like alfentanil result in profound centrally-mediated muscle rigidity, the alpha-2 agonist, dexametomidine, clearly produces muscle flaccidity. The fact that the opiates and potent, selective, alpha-2 agonists produce counteracting effects on muscle tone suggests that such a combination (e.g., alfentanil plus dexametomidine) could produce good anesthetic conditions and surgical muscle relaxation with a significantly reduced need for neuromuscular blocking agents.

Other drug classes which appear to have some ability to attenuate opiate-induced muscle rigidity, such as the benzodiazepines, barbiturates, and type-2 serotonin antagonists, all have intrinsic sedative effects. The anesthetic-inducing properties of these drugs could be responsible for some or all of their beneficial effects on opiate rigidity. The D-MED dose shown in this study to be sufficient to antagonize ALF rigidity (80 μg/kg) is approximately the ED50 for its halothane MAC-reducing effect.

It is possible that, in the present study, CNS hyperperfusion contributed to the etiology of dexametomidine’s attenuation of ALF-induced rigidity. However, severe brain ischemia generally results in decerebrate rigidity rather than flaccidity. In addition, in combination with volatile anesthetics, D-MED appears to have minimal effects on blood pressure. At 1 MAC of halothane, D-MED (10 μg/kg) produced a 50% reduction in heart rate and cardiac output in dogs without any change in mean arterial or central venous pressures. At a higher dose (20 μg/kg), in the presence of isoflurane, D-MED again produced a significant decrease in heart rate and cardiac output but this was associated with significant increases in blood pressure and systemic vascular resistance. The cardiovascular effects of D-MED appear to vary depending on the dose studied, the route of administration, the animal species, the presence of concomitant drugs, and the underlying physiological condition of the animal. In preliminary studies in our laboratory, the addition of D-MED to high-dose alfentanil produced minimal changes in the degree of opiate-induced depression of heart rate or blood pressure.

![Figure 4: Dexametomidine’s effects on alfentanil rigidity are due to central alpha-2 adrenoceptor activity. This histogram presents the mean (±SEM) area under the EMG-versus-time curves of the treatment groups graphed in figure 3. Two can clearly see that d-MED (30 μg/kg) treatment produced a marked decrease in EMG activity over time compared with the group treated with the inactive L-isomer of metemidoline (L-MED)*, P < 0.01]. While d-MED’s attenuation of ALF-rigidity was completely reversed by idoxanox, a large dose of DG-5128 was much less successful at blocking d-MED’s effects on ALF rigidity. The mean EMG activity in the DG-5128 group after the entire experimental period falls between that of the L-MED and the d-MED groups, being statistically different from both ***, P < 0.05].

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pressure in spontaneously ventilating rats [unpublished data].

Because respiratory variables were not measured in this study, it is also possible that differences in ventilation among the treatment groups contributed to differences in the degree of muscle rigidity. However, all of the animals maintained spontaneous ventilation (at rates of 50–100 breaths/min) throughout the experiment period. Bloor and coworkers have convincingly demonstrated that D-MED produces minimal respiratory depression when administered alone or in combination with volatile anesthetics.6,7,34 Dogs given D-MED (20 µg/kg iv) were completely anesthetized for over 1 h and, breathing spontaneously, exhibited no increase in end-tidal carbon dioxide tensions compared with baseline.5 The addition of D-MED (20 µg/kg iv) to spontaneously ventilating dogs receiving one MAC isoflurane had no effect on end-tidal CO2.6 In a companion study, CO2 response curves were significantly steeper, arterial CO2 was lower, and arterial PO2 was higher after medetomidine (20 µg/kg) than during isoflurane anesthesia in spontaneously ventilating dogs.34 It should also be noted that preliminary data indicates that the addition of D-MED (30 µg/kg) will not significantly worsen alfentanil-induced respiratory depression in spontaneously ventilating rats [unpublished data].

In the present study, there were statistically significant differences in mean body weights between treatment groups because different batches of animals were studied at different weights and randomization was only between two different treatments at any one time. However, since all animals were 215–325 g, and since drug dosage was based on body weight, these weight differences between groups should not significantly alter the results of the study.

In early clinical trials in healthy human volunteers, the racemic mixture of medetomidine (D and L isomers mixed together) was shown to be nontoxic and relatively safe at low to moderate doses.46 Intravenous injection of subanesthetic doses rapidly produced significant sedation, reduced vigilance, decreased salivation, and yet produced only modest decreases in blood pressure, heart rate, and cardiac output. In addition, the drug dose-dependently reduced plasma concentrations of norepinephrine and increased growth hormone secretion. There were no effects on other hormone levels, ECG, temperature, or clinical chemistry tests. A double-blind, cross-over, placebo-controlled clinical trial of the use of medetomidine premedication in surgical third molar extraction under local anesthesia has recently been reported.57 Intravenous medetomidine (50 µg) administered 30 min before surgery significantly reduced patient anxiety compared to placebo. Eighty percent of the patients preferred medetomidine to placebo.

In conclusion, the results of this study suggest that subanesthetic doses of the highly selective alpha-2 agonist dexmedetomidine may be clinically effective in preventing the muscle rigidity caused by high-dose opiates. This effect appears to be due to the activation of central alpha-2 adrenoceptors. The precise physiological relationship between D-MED's activation of central alpha-2 receptors and the reversal of opiate rigidity must still be determined. Dexmedetomidine appears to produce a number of physiologic effects such as loss of righting reflex, analgesia, bradycardia, anxiolysis, and skeletal muscle relaxation which would make it a desirable anesthetic adjuvant.

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