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# Dexmedetomidine Decreases Seizure Threshold in a Rat Model of Experimental Generalized Epilepsy

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**Background:** Dexmedetomidine (DEX) is a highly selective  $\alpha_2$  agonist with marked sedative and analgesic properties thought to be mediated *via* reduction of central noradrenergic transmission. Because an anticonvulsant effect is associated with increased noradrenergic activity, we investigated the possible proconvulsant effects of DEX in an experimental model of generalized seizures.

**Methods:** Male rats ( $n = 82$ ) were administered 0.9% saline as placebo ( $n = 18$ ) or pretreatment drug(s) before initiation of an infusion of pentylenetetrazol (PTZ) at  $5.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . The total dose of PTZ required to elicit electroencephalographic (EEG) and behavioral seizure activity was assessed. Blood samples were obtained 15 min after initiation of infusion ( $82.5 \text{ mg/kg}$ ) for determination of serum PTZ concentrations by gas chromatography. Pretreatment drug groups included DEX ( $20 \text{ } \mu\text{g/kg}$  [ $n = 11$ ],  $100 \text{ } \mu\text{g/kg}$  [ $n = 14$ ], and  $500 \text{ } \mu\text{g/kg}$  [ $n = 10$ ]); l-medetomidine ( $500 \text{ } \mu\text{g/kg}$  [ $n = 7$ ]); the  $\alpha_2$  antagonist atipamezole ( $500 \text{ } \mu\text{g/kg}$  [ $n = 9$ ]); and atipamezole ( $500 \text{ } \mu\text{g/kg}$ ) before DEX ( $100 \text{ } \mu\text{g/kg}$  [ $n = 7$ ] and  $500 \text{ } \mu\text{g/kg}$  [ $n = 6$ ]).

**Results:** In control animals, PTZ  $25\text{--}35 \text{ mg/kg}$  induced EEG evidence of epileptiform activity. The mean dose to EEG epileptiform activity and clonic convulsions was  $30 \pm 5.8$  (SE) and  $59 \pm 3.2 \text{ mg/kg}$ , respectively. Infusion of DEX at  $100$  and  $500 \text{ } \mu\text{g/kg}$  resulted in a marked sedative response and reduced the EEG seizure threshold of PTZ to  $18 \pm 1.5$  and  $7 \pm 1.8 \text{ mg/kg}$ , respectively ( $P < 0.05$  at both doses). The clonic convulsant threshold also was significantly decreased in both groups, to  $37 \pm 3.2$  and  $28 \pm 2.3 \text{ mg/kg}$  ( $P < 0.01$  at each dose). Before clonic convulsion, a significantly greater number of motor

seizure manifestations were scored in the DEX-treated animals at all three dose levels compared with the number scored in control animals. The proconvulsant action of DEX was not a result of alteration of PTZ kinetics, because serum concentrations did not differ between control and DEX-treated animals. Animals treated with l-medetomidine demonstrated more paroxysmal motor phenomena before clonic seizures than controls ( $P < 0.01$ ) although the clonic seizure threshold was not altered. Atipamezole alone did not alter background EEG, nor did it affect the clonic convulsant threshold. Atipamezole did, however, block the proconvulsant behavioral action at both doses of DEX, raising clonic seizure threshold from  $37 \pm 3.2$  to  $59 \pm 5.8 \text{ mg/kg}$  ( $100 \text{ } \mu\text{g/kg}$  DEX,  $P < 0.05$ ) and from  $28 \pm 2.3$  to  $59 \pm 6.9 \text{ mg/kg}$  ( $500 \text{ } \mu\text{g/kg}$  DEX,  $P < 0.01$ ).

**Conclusions:** DEX exerted a significant proconvulsant action in the PTZ experimental seizure model. The pharmacodynamic effect was dose-dependent and stereospecific and was blocked by the selective  $\alpha_2$ -receptor antagonist atipamezole. These data are consistent with previous data demonstrating that inhibition of central noradrenergic transmission facilitates seizure expression. Further evaluation of DEX for possible clinical proconvulsant effects may be warranted. (Key words:  $\alpha_2$ -Agonists. Dexmedetomidine. Pentylenetetrazol. Seizures.)

DEXMEDETOMIDINE (DEX), the dextroenantiomer of 4(5)-{1-(2,3-dimethylphenol)-ethyl} imidazole, is a highly selective agonist at the  $\alpha_2$ -adrenoceptor. Several recent studies have demonstrated the potential benefits of this potent agent in anesthetic practice. Through its action of reducing central noradrenergic activity, dexmedetomidine induces a high degree of sedation and analgesia.<sup>1-3</sup> It has also been shown to potentiate the effects of the volatile anesthetics as well as to reduce the sympathetic response to endotracheal intubation.<sup>3</sup> There is also evidence that this  $\alpha_2$  agonist improves outcome after cerebral ischemic injury.<sup>4</sup> DEX may thus prove to be a useful adjunct in the clinical anesthetic armamentarium.

It has been known for the past three decades, however, that the central noradrenergic system plays an important role in the expression of seizure activity.<sup>5-7</sup> Most of the studies support the hypothesis that central depletion of norepinephrine has a facilitatory effect on seizure expression. Clinical data suggest that distur-

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bances of this transmitter system may contribute to the pathophysiology of some forms of human epilepsy.<sup>8</sup>

The possibility therefore exists that systemic administration of DEX may facilitate seizure expression *via* its action to decrease central noradrenergic activity. We investigated this hypothesis through the evaluation of the effects of DEX on seizure threshold in a standard animal model for human generalized epilepsy.

### Materials and Methods

All experimental procedures and protocols utilized in this investigation were reviewed and approved by the Animal Care and Use Committee of the authors' institution, which is fully accredited by the American Association for Accreditation in Laboratory Animal Care. Male rats (Sprague-Dawley, Charles River, 250–350 g,  $n = 82$ ) were briefly anesthetized with 2–3% halothane in O<sub>2</sub> by face mask for placement of four epidural screw electrodes (Plastics One, Roanoke, VA) fixed to the cranium with dental cement (Durelon, ESPE-Premier, Norristown, PA), a jugular venous catheter (all animals), and a femoral arterial catheter ( $n = 5$ ) using P-50 plastic tubing (Becton-Dickenson, Parsippany, NJ) attached to a heparinized saline-filled syringe. After a minimum 2-h recovery period with access *ad lib.* to food and water, the animals were placed in a large clear plastic container with sloping side walls that allowed freedom of movement and close observation, while protecting the animal from injury during convulsions.

Animals were administered either 0.9% saline (control,  $n = 18$ ) or pretreatment drug(s) dissolved in saline *via* an infusion pump (Harvard Apparatus, Southnatick, MA) over a 15–20 min period before the continuous infusion of the chemical convulsant pentylenetetrazol (PTZ) (20 mg/ml in 0.9% saline; Sigma Chemical, St. Louis, MO). The convulsant was infused at a rate of  $5.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  which, in control animals, resulted in the elicitation of generalized seizures within 10–18 min. Blood samples were obtained 15 min after initiation of infusion (82.5 mg/kg) for determination of serum PTZ concentrations by using gas chromatography (National Medical Services, Willow Grove, PA). A continuous cortical electroencephalogram (EEG) was recorded (79D EEG chart recorder, Grass Instruments, Quincy, MA), and the PTZ dose required to elicit paroxysmal EEG and behavioral activity was noted.

Clinical seizure events were scored by a modified scale of Racine.<sup>9</sup> The scale was selected from among several seizure scales because it accurately reflects the

stereotypic progression of paroxysmal motor activity after PTZ. A score of  $R = 0$  was assigned for no motor seizure activity;  $R = 1$ , oral-facial movements only;  $R = 2$ , head nodding;  $R = 3$ , myoclonic jerk movements;  $R = 4$ , forelimb clonus;  $R = 5$ , rearing;  $R = 6$ , rearing and falling. EEG epileptiform activity before full clonic convulsions ( $R = 6$ ) was notable for single high-voltage spikes and sharp waves ( $>250 \mu\text{V}$ , 20–70 and 70–200 ms duration, respectively) and brief epileptiform burst activity (crescendo-decrescendo 50–200- $\mu\text{V}$  sharp-wave complexes, 0.5–2.0 s duration). Repetitive hypersynchronous discharges (RHD) (repeated trains of  $>250 \mu\text{V}$  spikes, frequency  $> 2 \text{ Hz}$ ) were observed in control animals only during severe clonic seizures ( $R = 6$ ).

Pretreatment drug groups included DEX at total doses of 20 ( $n = 11$ ), 100 ( $n = 14$ ), and 500 ( $n = 10$ )  $\mu\text{g}/\text{kg}$  (20–100  $\mu\text{g}/\text{ml}$ ); L-medetomidine (L-MED) (the levospecific isomer of medetomidine) 500  $\mu\text{g}/\text{kg}$  ( $n = 7$ ) (20  $\mu\text{g}/\text{ml}$ ); the selective  $\alpha_2$  antagonist atipamezole (APZ) 500  $\mu\text{g}/\text{kg}$  ( $n = 9$ ) (500  $\mu\text{g}/\text{ml}$ ); and APZ 500  $\mu\text{g}/\text{kg}$  before DEX 100 ( $n = 7$ ) and 500 ( $n = 6$ )  $\mu\text{g}/\text{kg}$  (500  $\mu\text{g}/\text{ml}$ ). All adrenergic drugs were provided by Orion-Farmos Pharmaceuticals (Turku, Finland). Doses of the above drugs were selected based on previously published experimental data in the rodent model.<sup>2</sup> After the experiments, the animals were killed with intravenous pentobarbital.

Data evaluation was performed by comparing the threshold for clinical and EEG seizure events between pharmacologically treated animal groups and controls. Statistics were derived using a one-factor analysis of variance model with Scheffé's *post hoc* comparison test. Data were presented as significant if  $P < 0.05$ . Levels of greater significance were presented where appropriate for comparison. For the determination of a significant difference between animal groups in the scoring of behavioral seizures (R score) during continuous PTZ infusion, the method of least-square-means comparison for repeated measures was applied.

### Results

In control animals, continuous infusion of PTZ at  $5.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  resulted in a stereotypic progression of CNS stimulation. The earliest evidence of PTZ convulsant activity was the elicitation of brief, 1-s, medium-voltage sharp-wave bursts on cortical EEG after a dose of 25–35 mg/kg (4–6 min of infusion) (fig. 1). No clinical manifestation of seizure activity was ever pres-

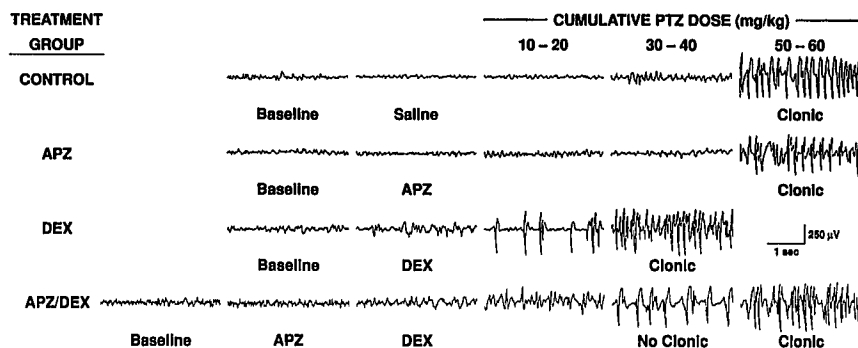


Fig. 1. Stages of the electroencephalogram during baseline, drug pretreatment period, and during continuous infusion of the convulsant pentylenetetrazol (PTZ). Comparison is among control, dexmedetomidine (DEX) (100  $\mu\text{g}/\text{kg}$ ), atipamezole (APZ) (500  $\mu\text{g}/\text{kg}$ ), and APZ (500  $\mu\text{g}/\text{kg}$ ) followed by DEX (100  $\mu\text{g}/\text{kg}$ ). In control animals, behavioral clonic seizures and electroencephalographic repetitive high-voltage discharges (RHD) occurred with 50–70 mg/kg PTZ.  $\delta$ -Wave activity appears during DEX pretreatment in association with clinical sedation. Pretreatment with DEX resulted in the facilitation of PTZ seizure expression with clonic seizures and RHD at 30–40 mg/kg total dose of PTZ. The RHD activity observed on the APZ + DEX EEG after 30–40 mg/kg PTZ infusion was not associated with major motor seizure activity.

ent during this period ( $R = 0$ ). After several more minutes of drug infusion, the EEG gradually changed to include single high-voltage spike or multiple spike and sharp-wave complexes lasting up to 1 s. On occasion, these bursts were associated with minor motor phenomena ( $R = 1-2$ ). Thereafter, a rapid progression to a full clonic seizure ( $R = 6$ ) would occur after 50–80 mg/kg PTZ (mean  $59 \pm 3.2$  SE mg/kg) and associated with RHD activity on EEG. Control animals never displayed RHD without concomitant clonic activity. Continued PTZ infusion resulted in a second, more severe clinical and EEG seizure after a total dose of 90–120 mg/kg. This latter seizure usually included tonic forelimb extension. The dose after which all control animals would succumb to the effects of continued seizures was 75.1 mg/kg.

Infusion of DEX, especially at 100 and 500  $\mu\text{g}/\text{kg}$ , resulted in a high degree of behavioral sedation which correlated with the increase in  $\delta$ -wave activity on EEG (fig. 1). The animals remained awake and upright, but displayed a reduction in spontaneous motor activity and were clearly less responsive to external stimuli (cage shaking or loud noises) than controls. Hemodynamic monitoring in five animals demonstrated a moderate increase in mean arterial pressure (130–140 mm Hg from 100–110 mm Hg).

The earliest EEG phenomenon in DEX-treated animals after initiation of the PTZ infusion was a replacement of the slow wave forms with predominantly low-voltage fast activity. This EEG change correlated with behavioral arousal. Thereafter, a relatively rapid progression toward EEG and behavioral seizure manifestations oc-

curred in animals pretreated with DEX at 100 and 500  $\mu\text{g}/\text{kg}$ . At the largest dose of DEX, the threshold for elicitation of EEG burst activity was reduced to  $6 \pm 1.8$  mg/kg PTZ compared to  $30 \pm 5.8$  mg/kg in controls ( $P < 0.05$ , fig. 2). With respect to the behavioral manifestations induced by PTZ, animals treated with DEX at 20, 100 and 500  $\mu\text{g}/\text{kg}$  demonstrated greater seizure scores before the expression of clonic convulsions than controls (fig. 3). The threshold to clonic activity at the

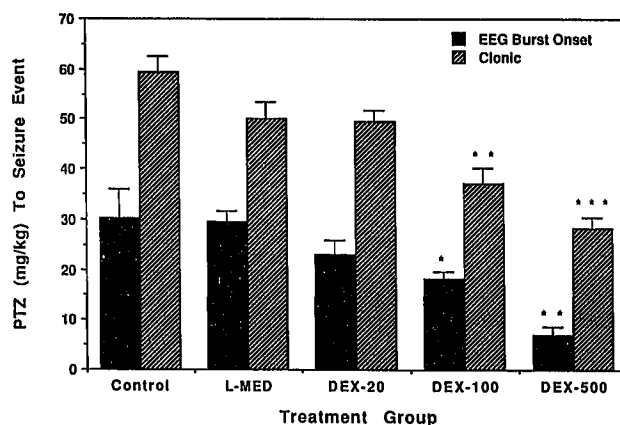


Fig. 2. Comparison of means ( $n = 7-18$ ,  $\pm$  SE) demonstrating the dose-response effect of dexmedetomidine (DEX) pretreatment on the elicitation of early electroencephalographic epileptiform activity and clonic seizures ( $R$  score = 6) induced by the continuous infusion of pentylenetetrazol. Statistically significant differences were noted between the mean for electroencephalographic burst onset and clonic seizure threshold of the control group versus groups given DEX 100 or 500  $\mu\text{g}/\text{kg}$  (\* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ ; one-way analysis of variance and Scheffé's *post hoc* comparison test).

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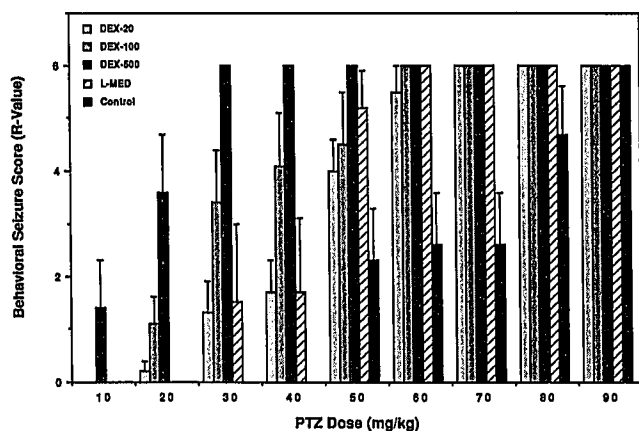


Fig. 3. Dose-response effect of dexmedetomidine (DEX) pretreatment on the elicitation of paroxysmal motor phenomena induced by continuous infusion of pentylentetrazol (PTZ) with comparison to appropriate control groups. Seizure score for each group ( $n = 6-18$ ) represents the mean ( $\pm$ SE) with a possible range of  $R = 0-6$ . Statistical analysis was performed by analysis of variance with the method of least squares for repeated measures. Statistically significant differences were noted for all comparisons between control and DEX 500  $\mu$ g/kg within the PTZ dose range of 20-70 mg/kg ( $P < 0.001$ ); DEX 100  $\mu$ g/kg within the range of 30-70 mg/kg ( $P < 0.01$ ); DEX 20  $\mu$ g/kg within the PTZ dose range of 30-70 mg/kg ( $P < 0.01$ ); L-medetomidine within the PTZ dose range of 50-70 mg/kg ( $P < 0.01$ ).

larger doses of DEX was also significantly less than in controls (fig. 2). In fact, the mean for clonic threshold at 100 or 500  $\mu$ g/kg (37.1 and 28.2 mg/kg respectively) was less than any single value ever observed in control animals. Measurement of serum concentrations of PTZ at an identical infusion time point (15 min, 82.5 mg/kg total PTZ dose) in control ( $n = 6$ ) and DEX-treated ( $n = 6$ ) animals demonstrated no significant difference in drug concentrations ( $141 \pm 7.9$  SE  $\mu$ g/ml vs.  $151 \pm 7.5$   $\mu$ g/ml respectively).

Pretreatment with L-MED, the levoisomer of medetomidine, did not have a noticeable sedative effect nor did it alter the threshold of EEG or clonic seizures. However, animals administered L-MED before PTZ did express more motor seizure phenomena than controls ( $P < 0.05$ ) before reaching the threshold for clonic convulsions (fig. 3). APZ, administered alone as an infused dose of 500  $\mu$ g/kg, did not appreciably alter the background EEG or behavior. Challenge with PTZ subsequent to APZ infusion resulted in a similar response as in the control PTZ-alone group.

Pretreatment with APZ alone facilitated the onset of minor motor seizure phenomenon at low doses of PTZ (10-40 mg/kg) compared to controls ( $P < 0.05$ ) but

not at the larger doses where clonic seizures were expressed (50-70 mg/kg). In the DEX-treated animals, APZ partially reversed the sedative action of DEX and diminished the amount of  $\delta$ -wave activity on EEG (fig. 1). Behaviorally, APZ decreased the seizure score ( $P < 0.05$ ) and inhibited the DEX-induced decrease in the clonic seizure threshold in both the DEX 100 and 500  $\mu$ g/kg groups (fig. 4).

Of interest, a dissociative effect on behavior and EEG was observed after initiation of PTZ in the APZ + DEX animals. At doses of the convulsant that triggered clonic and EEG ictal activity in the DEX-only pretreated group (25-40 mg/kg), APZ blocked the behavioral seizure correlate without inhibiting RHD activity seen on EEG (fig. 1). Periods of RHD were common before any behavioral convulsions ( $R < 3$ ) in these animals. This EEG manifestation of paroxysmal activity was not observed in controls without concomitant clonic or tonic seizures.

## Discussion

The above data demonstrate that DEX, through its action as an agonist at the  $\alpha_2$ -receptor, had a significant facilitatory action on PTZ seizures when systemically administered in rats. The proconvulsant activity was

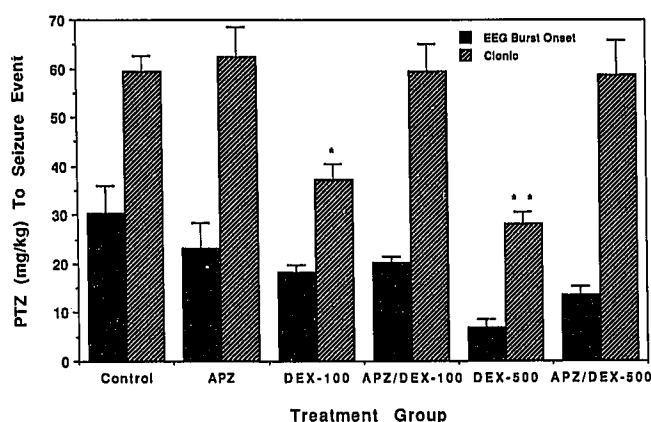


Fig. 4. Comparison of means ( $n = 7-18$ ,  $\pm$ SE) demonstrating the effects of atipamezole (APZ) (500  $\mu$ g/kg) pretreatment on the proconvulsant action of dexmedetomidine (DEX) (100 and 500  $\mu$ g/kg) during continuous infusion of pentylentetrazol. Clinical thresholds are electroencephalographic epileptiform burst activity and clonic seizures ( $R = 6$ ). \* $P < 0.05$  for the comparison of the mean dose to clonic seizures between groups given DEX 100  $\mu$ g/kg and APZ + DEX 100  $\mu$ g/kg; \*\* $P < 0.01$  for the comparison of the mean dose to clonic seizures between DEX 500  $\mu$ g/kg and APZ + DEX 500  $\mu$ g/kg (one-way analysis of variance and Scheffé's *post hoc* comparison test).

dose-dependent, stereospecific, and was blocked by the selective  $\alpha_2$ -receptor antagonist APZ. In addition, the lack of any change in serum PTZ concentrations with DEX pretreatment compared to controls supports a pharmacodynamic mechanism of action leading to a facilitation of seizure activity by DEX rather than a DEX-induced alteration in PTZ pharmacokinetics.

Experimentally, it has been well documented that perturbation of brain noradrenergic transmission, specifically to inhibit norepinephrine release and turnover at synaptic terminals, has an effect on seizure threshold.<sup>10</sup> Pretreatment in animals with reserpine or  $\alpha$ -methylparatyrosine has been demonstrated to lower the threshold for electroshock or PTZ-induced convulsions.<sup>5,11,12</sup> Animals treated with 6-hydroxydopamine, which depletes brain norepinephrine and dopamine, have an exacerbated response to convulsant stimuli.<sup>6,13,14</sup> This effect appears to be due to norepinephrine depletion rather than dopamine as selective microinjection of 6-hydroxydopamine into noradrenergic fiber bundles within the brain, but not dopamine fiber bundles, results in facilitation of seizures in the kindling model of epilepsy.<sup>6</sup> Similarly, disruption of normal noradrenergic transmission in brain *via* lesion of the locus ceruleus facilitates the onset of seizures in a variety of animal seizure models.<sup>7,15</sup> Conversely, electrical stimulation of locus ceruleus in animal and human studies has been correlated with a diminished response to convulsant challenges.<sup>16,17</sup>

The mechanism by which central noradrenergic-mediated transmission exerts an anticonvulsant influence is not entirely clear. There is some evidence to suggest that norepinephrine may indirectly augment the inhibitory action of  $\gamma$ -aminobutyric acid.<sup>18-20</sup> It has also been shown that when administered iontophoretically to various brain regions, norepinephrine exerts a differential depressant action on evoked *versus* spontaneous discharges.<sup>21,22</sup> The net effect has been likened to "enhancing the signal-to-noise ratio" of synaptic activity.<sup>23</sup> Suppression of aberrant synaptic activity may thus be a mechanism by which paroxysmal transmission is effectively prevented from spreading and becoming clinically manifested as a seizure. Normally, this suppressive characteristic appears to play a role in an animal's ability to remain attentive even toward weak afferent stimuli. Indeed, enhanced norepinephrine transmission has been demonstrated during periods of arousal and vigilant activity.<sup>24,25</sup>

With respect to its effect on seizure threshold, DEX appears to act clinically in a fashion distinct from sev-

eral other  $\alpha_2$  agonists such as guanfacine, lofexidine, and most notably, clonidine.<sup>26</sup> The latter drug has been demonstrated to have an anticonvulsant action when tested in several animal seizure models, including amygdaloid kindling and PTZ.<sup>26,27</sup> The difference in their effects on seizures between clonidine and DEX may be due to several factors. DEX, having approximately 10 fold greater selectivity for the  $\alpha_2$ - than  $\alpha_1$ -receptor compared to clonidine, represents the most selective  $\alpha_2$  agonist yet tested in seizure models. Therefore, the anticonvulsant action seen with clonidine could represent action at the  $\alpha_1$ -receptor, although several reports suggest an opposite action of  $\alpha_1$ -receptor agonists on seizure expression.<sup>28,29</sup> In addition, clonidine and DEX are regarded as partial and full agonists, respectively, and this difference may result in disparate effects on seizure expression. Antagonism at the  $\alpha_2$ -receptor, for example, has been associated with a proconvulsant effect.<sup>29</sup> Alternatively, the known presence of  $\alpha_2$ -receptors on both pre- and postsynaptic membranes suggests that the pharmacologic action of agonist drugs may relate to their respective selectivity at each membrane site. Preferential binding to postsynaptic membranes by an  $\alpha_2$  agonist would enhance norepinephrine-mediated postsynaptic activity, contrary to the presynaptic effect.

An interesting observation was made in the experiments involving the APZ-alone and APZ + DEX pretreatment groups when challenged with PTZ. During the early stages of PTZ infusion, APZ exerted a facilitatory action on motor seizure phenomenon compared to controls. At a larger dose of PTZ, APZ reversed the proconvulsant action of DEX with respect to the motor, but not EEG component of seizure expression. In fact, APZ alone or the combination of APZ + DEX demonstrated RHD without clonic activity after challenge with PTZ. Such an EEG manifestation was never observed in control animals receiving PTZ. As noted above, antagonists at the  $\alpha_2$ -receptor have been reported to be proconvulsants. Although APZ alone in our model did not alter the clonic seizure threshold from control values, the lack of EEG spike suppression and the facilitatory effect on the expression of minor motor paroxysms may be an element of the proconvulsant nature of  $\alpha_2$ -receptor antagonism.

In our experiments, pretreatment with L-MED resulted in a higher behavioral seizure score before clonic convulsion than observed in the control group. Two explanations may be considered. The first is that the  $\alpha_2$ -receptor exhibits some functional binding affinity for

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the levoisomer of medetomidine. The second possibility is that the L-MED sample used, in fact, contained a small contaminant fraction of the dextroisomer. Of the two, the latter explanation is the more likely in light of previous work having demonstrated that the dextroenantiomer possesses the pharmacologic activity of medetomidine.<sup>30</sup> In its pure form, L-MED does demonstrate some small degree of sedative and analgesic properties, but they are manifested at three or more orders of magnitude larger doses than DEX or medetomidine.<sup>30</sup> The results from our study reveal that L-MED was similar in its proconvulsant tendency as 20  $\mu\text{g}/\text{kg}$  DEX (figs. 2 and 3). This approximation of clinical effect between 20  $\mu\text{g}/\text{kg}$  DEX and 500  $\mu\text{g}/\text{kg}$  L-MED supports a contamination of dextroisomer in the L-MED sample rather than an intrinsic effect of the levoisomer of medetomidine.

The chemical convulsant PTZ was primarily selected for study because it is a commonly used experimental model of human generalized epilepsy.<sup>31</sup> Its action to facilitate CNS excitation appears to be a result of several possible mechanisms, including a reduction in transmitter-induced  $\text{Cl}^-$  conductances,<sup>32</sup> alteration of depolarization  $\text{Na}^+$  spike currents,<sup>33</sup> and selective antagonism of  $\gamma$ -aminobutyric acid at the  $\text{Cl}^-$  channel.<sup>34</sup> As a model for human epilepsy, it has been extensively used by the pharmaceutical industry for the development of clinically effective anticonvulsant drugs. In animal studies, PTZ is particularly popular because of its titratable clinical response, stereotypic EEG and behavioral manifestations, and antagonism of effects by clinically used anticonvulsant compounds. More importantly, facilitation of PTZ seizures by pharmacologic agents tested against this model has been correlated with clinical proconvulsant effects.<sup>31,35</sup>

In summary, DEX was demonstrated in a receptor-mediated fashion to reduce the threshold for the elicitation of EEG and motor ictal phenomenon in the rat PTZ seizure model. These results are consistent with previous data supporting the concept that inhibition of central noradrenergic transmission has a facilitatory action on seizure expression. The inability of DEX alone, however, to induce seizures even at large doses argues against a direct convulsant action of the drug. Nevertheless, further evaluation of this  $\alpha_2$  agonist is recommended to establish whether the proconvulsant effect of DEX in the PTZ model has any clinical implications for use in patients. Particularly of interest would be to evaluate any proconvulsant tendency of DEX in patients at risk for seizures as well as to define any

additive proconvulsant effects and risks between DEX and other anesthetic agents such as ketamine, enflurane, and etomidate that have central nervous system excitatory properties.

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