学位論文

Dexmedetomidine inhibits epileptiform activity in rat hippocampal slices

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Original Article

Dexmedetomidine inhibits epileptiform activity in rat hippocampal slices

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Abstract: Purpose: Our study aimed to investigate the effects of dexmedetomidine on basal synaptic transmission in the rat hippocampus. We also examined dexmedetomidine in an animal epilepsy model, with further investigation into the role of specific antagonists on the alpha-2 adrenoceptors and the imidazoline receptors. Methods: All of the experiments used the CA1 region of hippocampal brain slices prepared from Sprague-Dawley rats. Epileptiform discharges were induced by perfusing Mg^{2+}-free artificial cerebrospinal fluid (ACSF). We first investigated the effects of dexmedetomidine on population spike (PS) amplitudes and field excitatory postsynaptic potentials (fEPSP) amplitudes in normal ACSF. We then investigated the effects of dexmedetomidine on the amplitudes of the first three PSs and the discharge duration in Mg^{2+}-free ACSF or in normal ACSF containing 10 μM bicuculline. Results: Dexmedetomidine depressed PS amplitudes and fEPSP without affecting the paired-pulse inhibition in normal ACSF. Dexmedetomidine inhibited the epileptiform activity produced by Mg^{2+}-free ACSF in a dose-dependent manner. Dexmedetomidine completely abolished the epileptiform activity induced by bicuculline. In the presence of yohimbine, dexmedetomidine had no significant effect on epileptiform activity. In the presence of efaroxan and idazoxan, dexmedetomidine significantly ($P < 0.05$) increased and slightly attenuated the amplitude of the epileptiform activity, respectively. Conclusion: These results suggest that dexmedetomidine depresses the glutamatergic excitatory synaptic transmission, but may not affect the inhibitory synaptic transmission mediated via the $GABA_A$-receptor in rat hippocampal slices. The anticonvulsant action of dexmedetomidine is mediated mainly via alpha-2 adrenoceptors. In addition, imidazoline type 1 and type 2 receptors are also involved in the effect of dexmedetomidine on the epileptiform activity.

Keywords: Seizure, alpha-2 adrenoceptor, imidazoline type 1 receptor, imidazoline type 2 receptor, hippocampus

Introduction

Dexmedetomidine is a highly specific central alpha-2 adrenoceptor agonist with minimal influence on respiration and hemodynamics that has been used for sedation in clinical practice. However, its action on seizures is still controversial; for example, Kubota et al. [1] reported that dexmedetomidine induced epileptic seizures in a neonate, but dexmedetomidine has also been shown to be able to control the twitch-convulsive syndrome associated with uremic encephalopathy [2]. Furthermore, Talke et al. [3] showed that dexmedetomidine did not have any statistically significant effect on interictal epileptiform activity in epileptic patients. In animal studies, dexmedetomidine has also been reported to have both anticonvulsant and proconvulsant properties. In these experiments, investigators have shown that dexmedetomidine has an *in vivo* anticonvulsant action on seizures induced by electrical stimulation [4], local anesthetics [5, 6], or by a chemoconvulsant [7]. In contrast, other experimental epilepsy animal model studies have demonstrated that dexmedetomidine decreased the seizure threshold [8, 9].

In addition to its action on alpha-2 adrenoceptors, dexmedetomidine has an imidazoline structure and affinity for imidazoline receptors. Imidazoline receptors are widely distributed in the central nervous system [10, 11]. However, the physiological properties of imidazoline receptors are not fully understood. Several studies have provided evidence for the involve-

ment of dexmedetomidine's effect on the imidazoline receptors in the hippocampus. For example, Dahmani et al. reported that imidazoline type 1 receptors likely contribute to dexmedetomidine's effects on both the expression of phosphorylated extracellular signal-regulated protein kinases [12] and postconditioning properties against oxygen and glucose deprivation [13]. Takamatsu et al. [14] also showed that dexmedetomidine impairs long-term potentiation in the CA1 area via not only alpha-2 adrenoceptors but also imidazoline type 2 receptors. However, to our knowledge, no *in vitro* study has yet evaluated the effects of dexmedetomidine on seizures. In addition, little is known about the effects of dexmedetomidine on imidazoline receptors during seizure-like events.

In the present study, we first investigated the effects of dexmedetomidine on basal synaptic transmission in the Schaffer collateral-commissural pathway of rat hippocampal slices. We then examined the effects of dexmedetomidine in an *in vitro* model of epilepsy. Finally, we also studied the effects of dexmedetomidine in an *in vitro* model of epilepsy with specific antagonists in order to further evaluate the role of alpha-2 adrenoceptors and imidazoline receptors.

Material and methods

All of the experimental procedures used in this study were carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals. This study was also reviewed and approved by the Animal Care and Use Committee of our institute. All efforts were made to minimize suffering and to use as few animals as possible to achieve sufficient power of the results. All of the experiments used the CA1 region of hippocampal brain slices prepared from 3- to 6-week-old Sprague-Dawley rats (80-150 g, either sex). The rats were first anesthetized with isoflurane and then decapitated. The brain of each rat was then rapidly removed from the skull and placed in a cold (3-4°C), oxygenated, sucrose-based artificial cerebrospinal fluid (ACSF). The constituents of the sucrose-based ACSF were as follows: sucrose (220 mM), KCl (3.0 mM), $MgSO_4$ (2.0 mM), NaH_2PO_4 (1.25 mM), $NaHCO_3$ (26 mM), $CaCl_2$ (2.0 mM), and glucose (10 mM). The brain was immersed in oxygenated sucrose-based ACSF, and while immersed, slices were cut with a vibrating tissue slicer (DTK-3000; Dosaka EM, Kyoto, Japan). A sucrose-based slicing medium was used because it has been shown to increase the *in vitro* cell viability. The brain slices, each 350 μm thick, were immediately transferred to a holding chamber filled with normal ACSF through which a gas mixture of 95% O_2 and 5% CO_2 was bubbled. The constituents of the normal ACSF were as follows: NaCl (124 mM), KCl (5.0 mM), $MgSO_4$ (2.0 mM), NaH_2PO_4 (1.25 mM), $CaCl_2$ (2.0 mM), $NaHCO_3$ (22 mM), and glucose (10 mM). After a 1-h incubation period, a single brain slice was placed on the center of a MED probe (each electrode: 50 × 50 μm, interpolar distance: 300 μm; MED-P530AP, Panasonic, Osaka, Japan) and positioned to cover the 8 × 8 microelectrode array. Slices were continuously perfused with oxygenated, warmed ACSF (32 ± 1°C, pH 7.4) at a constant rate of 2 ml/min. For the electrophysiological recordings, the MED probes containing the slices were connected to the stimulation/recording component of the MED 64 multi-electrode system (Panasonic). One of the electrodes in the Schaffer collateral fibers was selected as the stimulating electrode. Single or paired pulses (pulse width, 0.1 ms; frequency, 0.083 Hz) were delivered to the preparation. The interstimulus intervals of paired stimuli varied from 10-60 ms. The stimulus intensity (30-150 μA) was adjusted for each experiment to yield field excitatory postsynaptic potentials (fEPSPs) or population spikes (PSs) that were 80% of the maximal responses. The evoked field potentials at 63 other sites were simultaneously recorded by the system using a 20-kHz sampling rate. Epileptiform discharges were induced by perfusing Mg^{2+} free ACSF.

In the first step of the experiment, we investigated the effects of dexmedetomidine on the PS amplitudes and the fEPSP amplitudes in normal ACSF. Next, we investigated the effects of dexmedetomidine on the amplitudes of the first three PSs (PS1, PS2, PS3) and the discharge duration (DD) in Mg^{2+}-free or normal ACSF containing 10 μM bicuculline. The amplitude of each fEPSP was measured as the peak negativity from the baseline, while the amplitude of each of the PS measurements was determined as follows: Briefly, a sloping baseline was drawn between the two upward peaks, and the amplitude of the PS was calculated as the length of the vertical line drawn from the

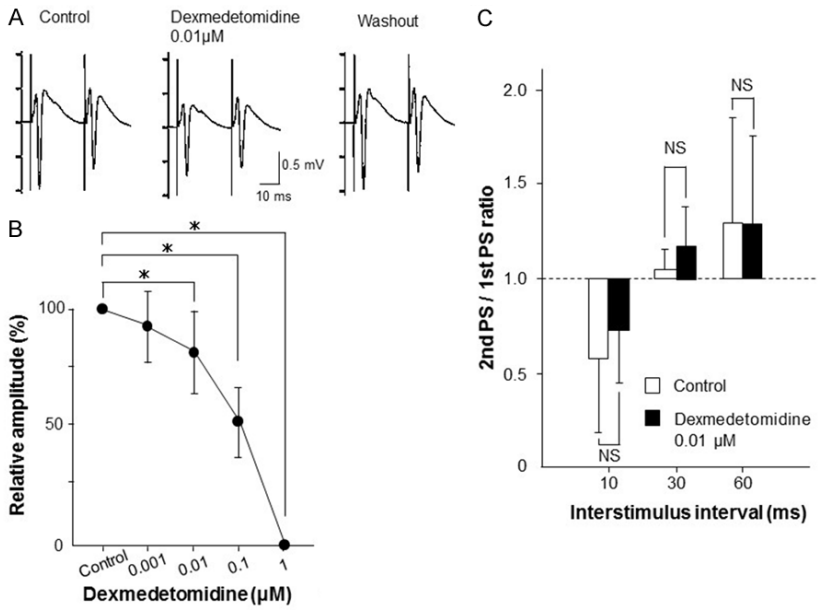

Figure 1. Effects of dexmedetomidine on basal synaptic transmission. A: The effect of 0.01 μM of dexmedetomidine on population spikes (PSs) in normal artificial cerebrospinal fluid. The PSs were elicited with a paired-pulse stimulus (interstimulus interval = 30 ms). B: Concentration-response relationship for dexmedetomidine on the amplitude of the first PS. Dexmedetomidine produced an inhibitory effect on the PS amplitudes in a concentration-dependent manner (n = 4 for 1 μM of dexmedetomidine; n = 8 for all of the other concentrations; *P < 0.05, analysis of variance). C: The effect of 0.01 μM of dexmedetomidine on the 2nd PS/1st PS ratios at various interstimulus intervals. The data are expressed as the mean ± SD (n = 6; NS: not significant when compared with the control, unpaired *t*-test).

downward peak to the sloping baseline. The effect of dexmedetomidine on the epileptiform activity was evaluated based on the amplitudes of PS1, PS2, and PS3 and on the duration of the spike discharges. The duration was measured from the first to the last PS that had an amplitude exceeding 0.2 mV. All of the responses were normalized as a percentage of the control. All drugs except dexmedetomidine were obtained from Sigma (St. Louis, MO, USA). Dexmedetomidine (Precedex®) was purchased from Maruishi Pharmaceutical Co., Ltd. (Osaka, Japan). All drugs were applied to the slices extracellularly through the superfusing ACSF without alteration of the perfusion rate and temperature.

The data are expressed as the mean ± SD. All analyses were performed with R statistical software, version 3.0.1. The dose-response effects of dexmedetomidine on the PS amplitudes and the duration were assessed using a one-way analysis of variance (ANOVA) with repeated measures and the Scheffe *post hoc* test. The statistical significance of any difference in the data between the two groups was determined using Student's *t*-test (unpaired or paired). The data obtained in the presence of yohimbine, efaroxan, and idazoxan were compared using a one-way ANOVA with repeated measures followed by Tukey's method. Differences were considered significant when $P < 0.05$.

Results

Effects of dexmedetomidine on basal synaptic transmission

We first investigated the effects of dexmedetomidine on PS and fEPSP in normal ACSF. Dexmedetomidine depressed the PS amplitudes in a dose-dependent manner. **Figure 1A** shows representative recordings of the effect of the 0.01 μM dexmedetomidine on the PSs (interstimulus interval = 30 ms). Dexmedetomidine 0.01 μM decreased the first PS amplitude to 81.3 ± 15.4% of the control (n = 6, P < 0.05, **Figure 1B**). **Figure 1B** summarizes the concentration-effect relationship between dexmedetomidine (0.001, 0.01, 0.1, 1 μM) and the first PS amplitudes. The paired pulse paradigm was used to evaluate the effects of a drug on $GABA_A$-mediated synaptic inhibition in the hippocampus. Therefore, we studied the effect of dexmedetomidine on the paired pulse inhibition (PPI). **Figure 1** also shows that dexmedetomidine had no influence on the PPI. Dexmedetomidine 0.01 μM did not affect the second PS/the first PS ratios at intestimulus intervals of 10, 30, and 60 ms (control vs. dexmedetomidine; 10, 30, 60 ms: 0.59 ± 0.38 *vs.* 0.72 ± 0.27; 1.03 ± 0.11 *vs.* 1.18 ± 0.22; 1.30 ± 0.54 *vs.* 1.29 ± 0.47; n = 6, for each, with no significance found between the ratios, **Figure 1C**). Dexmedetomidine also depressed the fEPSP. Representative recordings of the effects of dex-

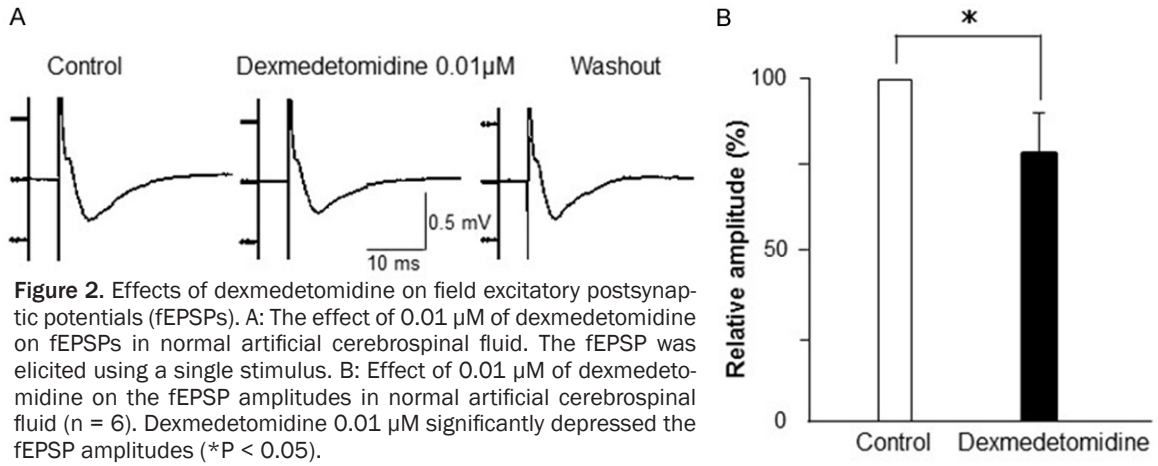

Figure 2. Effects of dexmedetomidine on field excitatory postsynaptic potentials (fEPSPs). A: The effect of 0.01 μM of dexmedetomidine on fEPSPs in normal artificial cerebrospinal fluid. The fEPSP was elicited using a single stimulus. B: Effect of 0.01 μM of dexmedetomidine on the fEPSP amplitudes in normal artificial cerebrospinal fluid (n = 6). Dexmedetomidine 0.01 μM significantly depressed the fEPSP amplitudes (*P < 0.05).

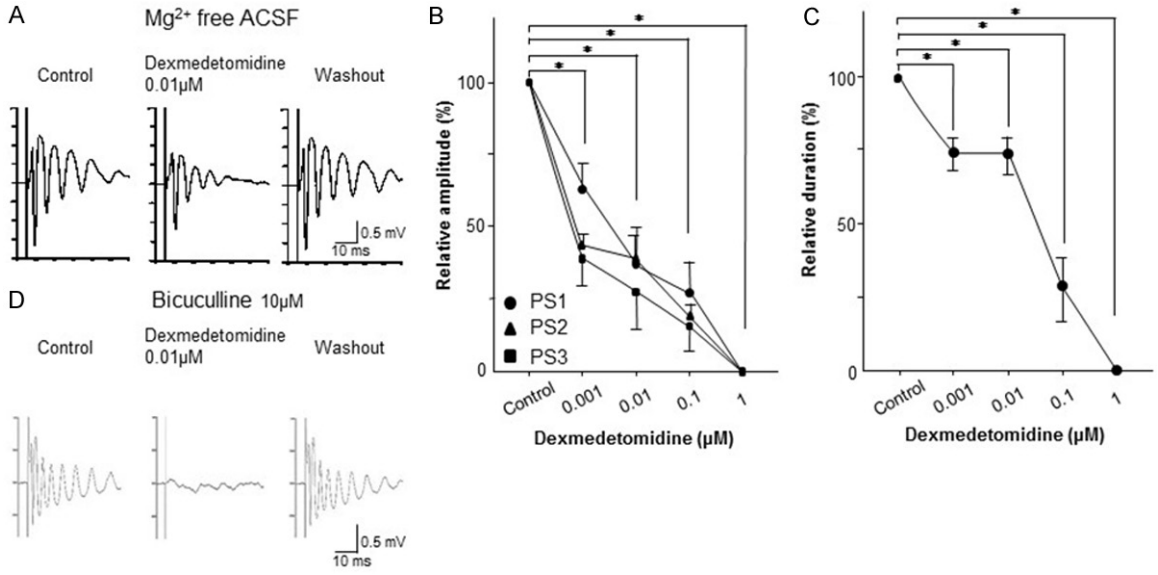

Figure 3. Effects of dexmedetomidine on the epileptiform activity induced by Mg^{2+}-free artificial cerebrospinal fluid (ACSF) or in normal ACSF containing 10 μM bicuculline. A: Representative response of the effect of 0.01 μM of dexmedetomidine on the epileptiform activity induced by Mg^{2+}-free artificial cerebrospinal fluid. B: Concentration-response relationship for dexmedetomidine on the amplitude of the first three population spikes (PS1, PS2, PS3). Dexmedetomidine produced an inhibitory effect on the PS amplitudes in a concentration-dependent manner (n = 4 for 1 μM of dexmedetomidine; n = 8 for all of the other concentrations; *P < 0.05, analysis of variance). C: Dexmedetomidine decreased the duration of epileptiform activity in a dose-dependent manner (n = 4 for 1 μM of dexmedetomidine; n = 8 for all of the other concentrations; *P < 0.05, analysis of variance). D: Representative response of the effect of 0.01 μM of dexmedetomidine on the epileptiform activity by normal ACSF containing 10 μM bicuculline.

medetomidine 0.01 μM on fEPSP are shown in **Figure 2A**. Dexmedetomidine 0.01 μM decreased the fEPSP amplitude to 78.5% ± 12.1% of the control (n = 6, P < 0.05, **Figure 2B**).

Effects on epileptiform activity

We next investigated the effects of dexmedetomidine on the epileptiform activity. **Figure 3A** presents representative recordings of the effects of dexmedetomidine 0.01 μM on the epileptiform activity induced by Mg^{2+}-free ACSF. Dexmedetomidine depressed the epileptiform activity produced by Mg^{2+}-free ACSF in a dose-dependent manner. Dexmedetomidine 0.01 μM decreased the amplitude of PS1, PS2, and PS3 to 55.2% ± 18.8%, 41.8% ± 21.3%, and 32.2% ± 19.6% of the control, respectively (n = 8, P < 0.05, **Figure 3B**). **Figure 3B** summarizes the concentration-effect relationship between

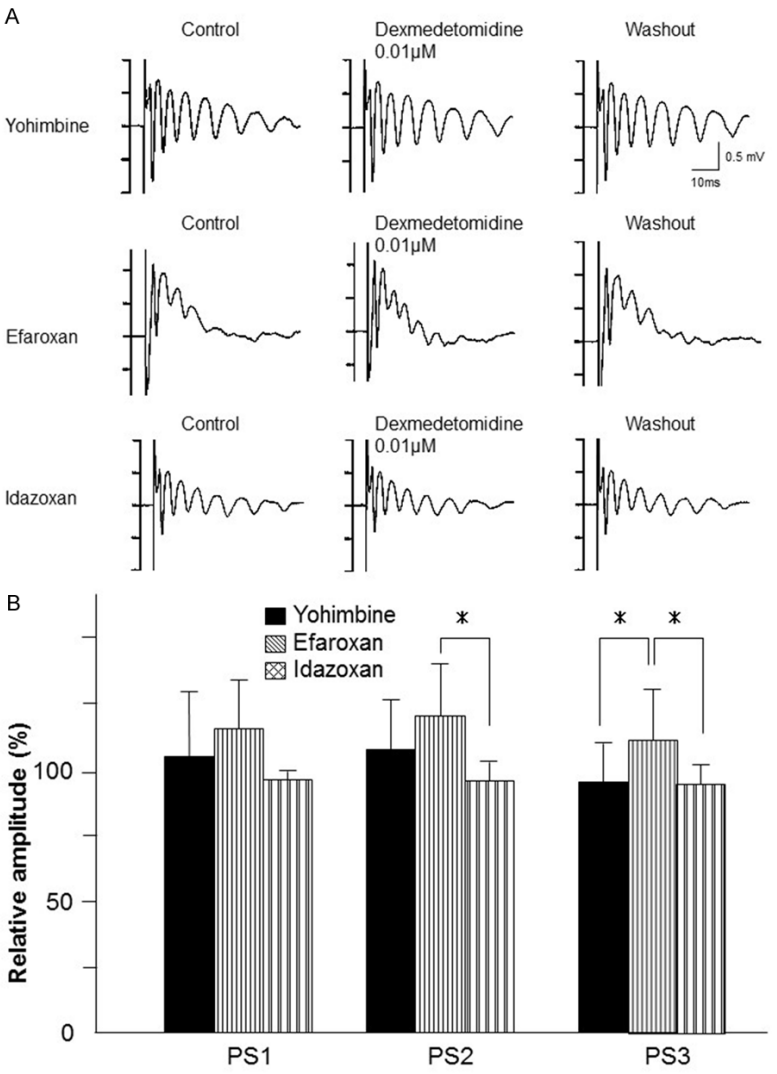

Figure 4. Effects of dexmedetomidine on the epileptiform activity induced by Mg^{2+}-free artificial cerebrospinal fluid in the presence of specific antagonists. A: Representative recordings showing the effect of 0.01 μM of dexmedetomidine on the epileptiform activity in the presence of 2 μM of yohimbine (upper trace), 10 μM of efaroxan (middle trace), and 10 μM idazoxan (lower trace). B: Effects of dexmedetomidine on the amplitudes of the epileptiform activity in the presence of yohimbine, efaroxan, and idazoxan (*P < 0.05, analysis of variance, *post hoc* analysis used Tukey's method).

dexmedetomidine (0.001, 0.01, 0.1, 1 μM) and the amplitudes of the PS1, PS2, and PS3. The duration of the epileptiform activity was also reduced by dexmedetomidine 0.01 μM to 59.1 ± 25.2% of the control (n = 8, P < 0.05). The concentration-effect relationship between dexmedetomidine (0.001, 0.01, 0.1, 1 μM) and the DD is summarized in **Figure 3C**.

We also investigated the effects of dexmedetomidine on the epileptiform activity induced by the $GABA_A$ receptor antagonist bicuculline 10 μM. **Figure 3D** presents representative recordings of the effects of dexmedetomidine 0.01 μM on the epileptiform activity induced by bicuculline. Dexmedetomidine completely abolished the epileptiform activity induced by bicuculline. Dexmedetomidine 0.01 μM decreased the amplitude of PS1, PS2, and PS3 to 1.1% ± 2.6%, 2.0% ± 4.5%, and 0% ± 0% of the control, respectively (n = 6, P < 0.05).

It is well known that dexmedetomidine is a selective alpha-2 adrenoceptor agonist. Accordingly, we examined the effects of dexmedetomidine on the epileptiform activity in the presence of yohimbine, an alpha-2 adrenoceptor antagonist. Typical records, presented in **Figure 4A** (upper trace), show the effects of dexmedetomidine on the epileptiform activity induced by Mg^{2+}-free ACSF containing of 2 μM yohimbine. Yohimbine almost completely antagonized the effects of dexmedetomidine on the epileptiform activity. In the presence of yohimbine 2 μM, dexmedetomidine 0.01 μM had no significant effect on the amplitude of PS1, PS2, PS3, or the DD (107.4% ± 28.7%, 113.8% ± 18.3%, 96.4% ± 15.9%, and 117.3% ± 45.6% of the control, respectively [n = 8, **Figure 4B**]).

To investigate whether or not the depressant effects of dexmedetomidine on the epileptiform activity could be attributed to imidazoline receptors, we studied the effects of dexmedetomidine on the epileptiform activity in the presence of specific imidazoline receptor antagonists. **Figure 4A** (middle trace) shows representative findings regarding the effects of 0.01 μM dexmedetomidine on the epileptiform

activity in the presence of efaroxan (an imidazoline type 1 receptor and alpha-2 adrenoceptor antagonist). Efaroxan strongly antagonized the effects of dexmedetomidine on the epileptiform activity. In the presence of efaroxan 10 μM, dexmedetomidine 0.01 μM increased the amplitude of PS1, PS2, PS3, and the DD to 114.7% ± 20.1%, 121.7% ± 20.1%, 113.1% ± 18.7%, and 129.5% ± 35.1% of the control, respectively (n = 8, **Figure 4B**). **Figure 4A** (lower trace) also shows representative findings regarding the effects of 0.01 μM dexmedetomidine on the epileptiform activity in the presence of idazoxan (an imidazoline type 2 receptor and alpha-2 adrenoceptor antagonist). Idazoxan nearly abolished the effects of dexmedetomidine on the epileptiform activity. In the presence of idazoxan 10 μM, dexmedetomidine 0.01 μM slightly decreased the amplitude of PS1, PS2, PS3, and the DD to 96.9% ± 4.9%, 95.0% ± 8.1%, 96.6 ± 8.0%, and 90.9% ± 10.8% of the control, respectively (n = 8, **Figure 4B**). There were significant differences in the effects of dexmedetomidine on the amplitude of PS2 and PS3 among yohimbine, efaroxan, and idazoxan (n = 8, $P < 0.05$, ANOVA). Efaroxan significantly increased the amplitudes of PS2 and PS3 compared to idazoxan, and also increased the amplitudes of PS3 compared to yohimbine (n = 8, $P < 0.05$, **Figure 4B**).

Discussion

This study provides the first demonstration that dexmedetomidine inhibits the epileptiform activity in the rat hippocampus *in vitro*. The anticonvulsant action of dexmedetomidine has been mainly attributed to the activation of the alpha-2 adrenoceptors. Imidazoline type 1 and type 2 receptors are also involved in the effect of dexmedetomidine on the epileptiform activity.

Effects on basal synaptic transmission

In the present study, we found that dexmedetomidine depressed the PS amplitudes and fEPSP amplitudes in a dose-dependent manner. The depression of the PS amplitudes indicates that dexmedetomidine suppresses neuronal excitability. The depression of the fEPSP amplitudes shows that dexmedetomidine inhibits glutamatergic excitatory synaptic transmission. This inhibitory action of dexmedetomidine is probably involved in both the alpha-2 adrenoceptor- and the imidazoline receptor-mediated responses. In the central nervous system, alpha-2 adrenoceptors exist at both presynaptic and postsynaptic sites. Chiu et al. [15] demonstrated that dexmedetomidine inhibits glutamate release from rat cerebrocortical nerve terminals. Therefore, it appears that dexmedetomidine's effect on excitatory synaptic transmission results in a decrease in the transmitter release from the presynaptic terminals. Furthermore, a patch clamp study [16] revealed that dexmedetomidine induced outward currents in the presence of tetrodotoxin in rat substantia gelantinosa neurons. Another patch clamp study [17] showed that the alpha-2 adrenoceptor agonist guanfacine inhibited an evoked excitatory postsynaptic current, which was blocked both by yohimbine and the Gi inhibitor NF023 in the medial prefrontal cortex. These previous studies showed that dexmedetomidine exerted a considerable postsynaptic effect. With regard to the imidazoline receptors, an *in vitro* study [18] using rat hippocampal slices revealed that the endogenous imidazoline receptor agonist imidazole-4-acetic acid-ribotide reduced the slope of the fEPSPs. Thus, it is likely that dexmedetomidine depresses excitatory synaptic transmission through an imidazoline receptor-mediated mechanism in the rat hippocampus. In contrast to our results, Takamatsu et al. [14] demonstrated that dexmedetomidine 50 nM had no effect on either the slope of the fEPSPs or the paired-pulse facilitation in mouse hippocampal slices. This discrepancy could be related to the species that were used in the studies and/or the experimental conditions.

The PPI was enhanced by a drug that facilitates GABA action [19] and attenuated by drugs that block GABA transmission. In the present study, we found that dexmedetomidine had no effect on the PPI. Thus, our results suggested that dexmedetomidine probably does not influence the $GABA_A$ receptor-mediated synaptic inhibition. Kan et al. [4] also showed that there was no effect detected with regard to the levels of GABA in the hippocampus after an intraperitoneal administration of dexmedetomidine. Therefore, it is unlikely that dexmedetomidine enhances $GABA_A$ receptor-mediated synaptic inhibition in the hippocampus.

Effects on epileptiform activity

There have been no *in vitro* studies that have shown dexmedetomidine to have any effect on

experimentally induced seizures. In the present study that examined rat hippocampal slices, we clearly demonstrated that dexmedetomidine dose-dependently inhibited epileptiform activity induced by Mg^{2+}-free ACSF. The EC50 value of the anticonvulsant action of dexmedetomidine in our study was about 0.01 μM. In humans, it has been reported that the plasma concentration required maintaining optimal sedation after a continuous infusion of dexmedetomidine is about 0.4-8 nM [20]. Therefore, dexmedetomidine is a suitable anesthetic that can be used to prevent seizure-like events. Dexmedetomidine depressed both the amplitudes and duration of the epileptiform activity. Given dexmedetomidine's effects on basal synaptic transmission, we speculate that the anticonvulsant effects of dexmedetomidine result from inhibiting the glutamatergic synaptic transmission. In a rat model of self-sustaining status epilepticus with constant amygdala stimulation, dexmedetomidine decreased the number and cumulative duration of repeated seizures, along with reducing the level of glutamate in the hippocampus tissue [4]. These findings suggest that dexmedetomidine might attenuate the epileptiform activity by inhibiting the synaptic release of the excitatory neurotransmitter glutamate. We examined the effects of dexmedetomidine on the epileptiform activity induced by the $GABA_A$ receptor antagonist, bicuculline 10 μM and found that dexmedetomidine 0.01 μM completely abolished the epileptiform activity induced by bicuculline. This finding suggests that the anticonvulsant effects of dexmedetomidine might not be due to potentiation of the $GABA_A$-mediated synaptic inhibition.

To clarify the mechanisms of the anticonvulsant action of dexmedetomidine in a Mg^{2+}-free model of epileptiform activity, we examined the effects of dexmedetomidine in the presence of yohimbine, efaroxan, and idazoxan. Yohimbine almost completely abolished the effects of dexmedetomidine on the epileptiform activity. Previous studies have reported that the reduction in both the local anesthetic- and kainic acid-induced convulsions by dexmedetomidine was significantly reversed by alpha-2 adrenoceptor antagonists [5, 7]. These results suggest that the anticonvulsant action of dexmedetomidine is mainly mediated through the alpha-2 adrenoceptors. Noradrenaline has been shown to increase the rate of discharge produced by high-potassium-concentration-induced epileptiform activity in the CA3 region of rat hippocampal slices [21]. This further suggests that the mechanism of the anticonvulsant action of dexmedetomidine may result from a decrease in the noradrenaline levels via the activation of alpha-2 adrenoceptors.

Furthermore, efaroxan significantly increased the amplitudes of the epileptiform activity compared to idazoxan and yohimbine, suggesting that dexmedetomidine enhances the epileptiform activity via imidazoline type 2 receptors. Therefore, imidazoline type 2 receptor activation would likely lead to seizures. As in the present study, the imidazoline type 2 receptor ligands 2-BFI and BU224 have also been shown to produce epileptic seizures in mice *in vivo* [22]. The discrepancies that were observed for dexmedetomidine's effects on seizures both *in vivo* and *in vitro* could be related to the activation of the imidazoline type 2 receptors. However, the mechanism by which imidazoline type 2 receptors enhance the epileptiform activity remains unknown. The ligands 2-BFI and BU224 have also been shown to similarly increase the extracellular noradrenaline levels in the rat frontal cortex [23]. Thus, the increase in the noradrenaline levels via imidazoline type 2 receptor activation might enhance the epileptiform activity. In addition, idazoxan tended to reduce the amplitudes of the epileptiform activity.

There are several limitations associated with this study. First, we did not show the direct effects of dexmedetomidine on GABAergic modulation. Second we did not examine the imidazoline 3 receptor.

Conclusion

We demonstrated that dexmedetomidine depressed the glutamatergic excitatory synaptic transmission but might not affect the inhibitory synaptic transmission mediated via the $GABA_A$-receptor in rat hippocampal slices. Dexmedetomidine also inhibited the epileptiform activity induced by Mg^{2+}-free ACSF mainly via the alpha-2 adrenoceptors. Furthermore, imidazoline type 1 and type 2 receptors also appear to be involved in dexmedetomidine's effect on the epileptiform activity.

Disclosure of conflict of interest

None.

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