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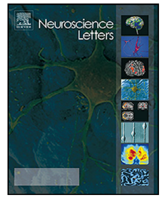

Research article

Dexmedetomidine promotes the recovery of the field excitatory postsynaptic potentials (fEPSPs) in rat hippocampal slices exposed to oxygen-glucose deprivation

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HIGHLIGHTS

- Induction of OGD conspicuously reduced fEPSP amplitude in the hippocampus.
- Treatment with 10 μM DEX did not reduce fEPSP in the normal hippocampus.
- Pre-, co-, and post-treatment with 10 μM DEX facilitated recovery of fEPSP in OGD.
- DEX may be used as a therapeutic agent for hypoxic-ischemic brain damage.

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ABSTRACT

Dexmedetomidine (DEX), a selective α_2 adrenergic agonist, is an anesthetic and sedative agent, and is reported to exert neuroprotective effects after hypoxic ischemia. However, there are few studies on the electrophysiological effect of DEX in hippocampal slices under ischemic conditions. The effects of DEX on field potential in hippocampal slices exposed to oxygen-glucose deprivation (OGD) were evaluated. Hippocampal slices were prepared from rats, and the evoked field excitatory postsynaptic potentials (fEPSPs) were recorded using the MED 64 system. Hypoxic-ischemia was induced by perfusion with glucose-free artificial cerebrospinal fluid (aCSF) bubbled with 95% N_2 and 5% CO_2, and hippocampal slices were perfused with DEX-added aCSF before, during, and after OGD induction. In the normal hippocampal slices, perfusion with 1 and 10 μM DEX did not significantly decrease the normalized fEPSP amplitude, but 100 μM DEX significantly reduced the fEPSP amplitude compared with its baseline control. The induction of OGD remarkably decreased the fEPSP amplitude, whereas the pre-, co-, and post-treatment of 10 μM DEX gradually promoted recovery after washing out, and consequently the amplitude of fEPSP in DEX pre-, co-, and post-treated OGD slices were significantly higher than that in the untreated OGD slices at 10 min and 60 min after washing out. In particular, co-treatment with DEX conspicuously promoted the recovery of the fEPSP amplitude at the beginning of washing out. These results suggest the possibility of DEX as a therapeutic agent to prevent hypoxic-ischemic brain damage and promote functional recovery after ischemia.

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1. Introduction

Dexmedetomidine (DEX), a highly selective α_2 adrenergic agonist, is regarded as an important adjunct to anesthesia for surgical, endoscopic and imaging procedures [1,2]. Anesthetic agents are generally thought to be detrimental to the brain because they cause widespread apoptotic neurodegeneration in the developing brain and induce hippocampal synaptic dysfunction, consequently

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impair learning ability and memory function [3]. In particular, ketamine and isofluraneare reported to initiate apoptosis and impair brain function in the developing brain of rats, on the other hand, DEX significantly attenuates the neurotoxicity induced by ketamine and isoflurane [4,5]. Such neuroprotective effect of DEX has been reported in other clinical and animal studies [6–8]. In particular, Zhang and Kimelberg [9] reported that DEX improved the histomorphological and neurological outcome after cerebral ischemia.

Cerebral ischemia is related to an increase in catecholamine, especially massive release of norepinephrine. An increase in circulating and extracellular norepinephrine may play a crucial role in modulating the development of ischemic neuronal damage [10,11]. For example, stimulation of the cerebral metabolic rate for oxygen by norepinephrine exaggerates the imbalance of the ratio between cerebral oxygen demand and oxygen supply [12], and high norepinephrine increases the sensitivity of pyramidal neurons to excitatory neurotransmitters, resulting in excitotoxicity [13]. Thus, prevention of excessive norepinephrine release may be considered neuroprotective, and DEX alleviates neuronal damage caused by ischemia through the inhibition and/or reduction of norepinephrine [10,14]. DEX is also reported to exert a neuroprotective effect by suppressing the excessive release of glutamate during cerebral ischemia via activation of the α_{2A} adrenergic receptor [15,16]. There is increasing evidence linking the neuroprotective effect of DEX to important cellular effects, such as phosphatidyl-inositol 3 kinase (PI3-kinase), protein kinase C and extracellular signal-regulated protein kinase 1 and 2 (Erk1/2), which play a role in the survival of neuronal tissue [1,2,17]. For instance, DEX increases the expression of hypoxia-inducible factor (HIF-1α), vascular endothelial growth factor (VEGF) and regulated in development and DNA damage responses 1 (RTP801) through activation of the I2 imidazoline receptor-PI3K/Akt pathway to protect against oxygen-glucose deprivation (OGD)-induced injury in rat glioma C6 cells [1].

For OGD in which an ischemic episode continues for more than a few minutes, neurotransmission rapidly diminished and synaptic responses irreversibly disappeared. These OGD episodes also cause the appearance of anoxic depolarization, which induces various molecular events that contribute to neuronal cell injury and death [18,19]. Despite such electrophysiological features of OGD, the electrophysiological effect of DEX in hippocampal slices exposed to OGD has not been well-studied, although some studies have reported an influence of DEX on hippocampal long-term potentiation (LTP) in rats and mice [20,21]. Therefore, in the present study, we investigated the effect of DEX on synaptic transmission under hypoxic ischemia by measuring the field potential in hippocampal slices exposed to OGD, an in vitro ischemia model.

2. Materials and methods

2.1. Hippocampal slice preparation

Male Sprague-Dawley rats (3–4 weeks old) were anesthetized with Zoletil 50® (10 mg/kg, i.p.; Virbac Laboratories, Carros, France) and decapitated by guillotine. All of the experimental procedures were performed in accordance with the animal care guidelines of the National Institutes of Health (NIH), and this study was approved by the Institutional Animal Care and Use Committee of Kyung Hee University (KHUASP[SE]-15-053). The brain was rapidly removed from the skull and placed for 30 s in cold artificial cerebrospinal fluid (aCSF) containing 124 mM NaCl, 5 mM KCl, 1.2 mM KH_2PO_4, 1.3 mM $MgSO_4$, 2.4 mM $CaCl_2$, 10 mM glucose, and 24 mM $NaHCO_3$ (pH 7.4), bubbled with 95% O_2 and 5% CO_2. The brain was trimmed to expose the hippocampus, and transverse hippocampal slices (350-μm thickness) were prepared using the vibrating tissue slicer (DTK-1000; DSK, Tokyo, Japan). Three to four slices from the medial hippocampus of each rat were transferred to a recovery chamber containing aCSF supplied with 95% O_2 and 5% CO_2 for at least 1 h.

2.2. Electrophysiological recordings

Electrophysiological recordings were obtained using the 64 channel multi-electrode dish (MED) of the MED 64 system (Panasonic Co., Tokyo, Japan) according to a previously described method [22]. Briefly, individual hippocampal slices were placed on the center on the MED probe, which had been treated with a coating solution containing 0.1% polyethylenimine (PEI; Sigma-Aldrich, St. Louis, MO, USA) in 25 mM borate buffer adjusted to pH 8.4 for 8 h at room temperature, and then positioned to cover the 8×8 microelectrode array (interpolar distance 150 μm; Alpha MED Science, Berkeley, CA, USA) and photographed using an inverted microscope (Nikon, Melville, NY, USA). The MED probe was placed on the MED connector, and aCSF oxygenated with 95% O_2 and 5% CO_2 was continuously infused at 2 mL/min (at 34 °C) using a microinjecting pump (Harvard Apparatus, Holliston, MA, USA). Evoked field excitatory postsynaptic potentials (fEPSPs) at the 64 sites were simultaneously recorded after selecting one recording site and two stimulation sites within the striatum radiatum of CA1 of the hippocampal slice (Fig. 1A). To record the evoked fEPSPs, a pair of single planar microelectrodes delivering bipolar constant current pulses (45–95 μA, 0.2 ms) was applied, and baseline fEPSPs were experimentally set between 50% and 60% of the maximum amplitude for each slice. Slices exceeding more than 20% fluctuation during the stabilization period (at least 20 min) were discarded. Once the slice was stabilized, fEPSPs were recorded for an additional 15-min period in the absence of any drug to establish a baseline control (i.e., 100% baseline). Subsequent fEPSPs during drug application were recorded for a minimum of 30–40 min. MED64 Performer™ equipment (Panasonic Co.) was used for data recording and analysis, and all of the data were normalized with respect to a 15-min baseline preceding drug application.

2.3. Experimental procedures

Injectable dexmedetomidine hydrochloride (Fig. 1B) purchased from Hospira Korea (Hospira Korea, Seoul, Korea) was added directly to the aCSF oxygenated with 95% O_2 and 5% CO_2, at final concentrations of 1, 10, and 100 μM, and applied using a microinjecting pump for the measurement of fEPSPs on the rat hippocampal slices under normal conditions. Hypoxic-ischemia was induced by perfusion with 95% N_2 and 5% CO_2 bubbled glucose-free aCSF (OGD) for 10 min [23], after which oxygenated and glucose-containing aCSF was re-perfused. To investigate the effect of DEX on the fEPSPs in the hippocampus slices exposed to OGD, transverse hippocampal slices were perfused with 10 μM DEX before, during, and after OGD induction. Throughout this article, the term 'untreated OGD slices' refers to the hippocampal slices exposed to OGD for 10 min in the absence of DEX. 'Pre-treated OGD slices', 'co-treated OGD slices', and 'post-treated OGD slices' refer to the hippocampal slices in which 10 μM DEX was pre-treated for 10 min before OGD induction, co-treated for 10 min with OGD induction, and post-treated for 60 min after OGD induction, respectively.

2.4. Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics software (ver. 22.0; IBM Corp., Armonk, NY, USA). First, the Kolmogorov–Smirnov test was conducted to determine the normality of distribution for the examined variables. Because the data in this study were not normally distributed, the Kruskal-Wallis test

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