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Brain Research

Research Report

Efficacy of dexamethasone on penicillin-induced epileptiform activity in rats: An electrophysiological study

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ARTICLE INFO

Article history:
Accepted 24 January 2014
Available online 1 February 2014

Keywords:
Dexamethasone
Phenytoin
Levetiracetam
Experimental epilepsy
Penicillin
Rat

ABSTRACT

Corticosteroids are extensively used in treatment of many diseases. In neurosurgery practice, dexamethasone (DEX) is commonly used particularly in cerebral edema secondary to brain tumors, head trauma, and central nervous system infections. There are some uncertainties surrounding the secure use of DEX in patients with epilepsy or seizures induced by diseases of the central nervous system such as head trauma and brain tumors. Despite its extensive use, the effect of DEX on epileptiform activity is unclear. In this study the effect of DEX on epileptiform activity was investigated in rats. The effects of 1, 3, and 10 mg/kg DEX on epileptiform activity was compared with effects of antiepileptic drugs commonly employed in treatment of epilepsy, namely phenytoin (PHT) 50 mg/kg and levetiracetam (LEV) 50 mg/kg that were administered intraperitoneally for 1 week. All groups were administered intracortical penicillin (500 IU) to induce epileptiform activity. DEX at the doses of 3 mg/kg and 10 mg/kg significantly reduced spike frequencies compared to the initial values. In conclusion, we think that DEX can effectively decrease the epileptiform activity.

1. Introduction

Corticosteroids consist of hormones secreted from adrenal cortex, such as cortisol and aldosterone, and their analogs obtained by synthesis. They are commonly used in neurosurgery practice for treatment of the central nervous system (CNS) disorders, spinal cord injuries, and cerebral edema (Fehlings, 2001; Galicich et al., 1961). Glucocorticoids (GCs) improve neoplastic and inflammatory CNS edema and strengthen blood–brain barrier by inhibiting pathological endopeptidase activities and preserving structural integrity of proteins (Reichardt et al., 2006). GCs have been used for treatment of convulsions such as infantile spasm and Lennox–Gastaut syndrome for years (Aird and Woodbury, 1975;

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http://dx.doi.org/10.1016/j.brainres.2014.01.040
0006-8993

Chutorian, 1982; Pieretti et al., 1992; Snead et al., 1983). They have also been used in carcinomatous meningitis and CNS lymphoma (Todd et al., 1986). It has been reported that dexamethasone (DEX) has led to a dramatic decrease in morbidity and mortality following its routine use especially in treatment of peritumoral edema of brain tumors (Galicich et al., 1961).

Epilepsy is a neurological disorder characterized by unprovoked and spontaneously recurring seizure activity (Shneker and Fountain, 2003). Data from epidemiological studies have shown that conditions including brain trauma, CNS infections, vascular diseases of brain, brain tumors, degenerative CNS diseases, physical and mental developmental disorders, and febrile convulsions increase the incidence of epilepsy. In 70% of cases, however, the cause of epilepsy cannot be determined (Annegers, 1994). On the other hand, in a third of patients seizure activity cannot be controlled by available medications (Kwan and Brodie, 2000). Posttraumatic epilepsy varies between 4% and 53% and may develop at both early and late stages (Frey, 2003). DEX is a drug with a powerful glucocorticoid activity, which is commonly used in neurosurgery practice. The relationship between epilepsy, a commonly encountered disorder in neurosurgery practice, and DEX which is also a commonly used medication in the same practice setting remains largely unknown. Moreover, there is no commonly accepted practice information regarding use of DEX in patients with epilepsy.

Although there are a few studies that have investigated the effect of GCs on epileptic seizures and mentioned a dose- and time-dependent effect, this subject has been incompletely clarified (Al-Shorbagy et al., 2012; Sagratella et al., 1995). In this context, Sagratella et al. (1995) suggested that there is the in vitro antiepileptic activity of DEX on the CA1 epileptiform activity induced by sodium penicillin in rat hippocampal slices. However, there are no studies in literature examining the effect of GCs in vivo penicillin model of epilepsy. Elucidating if GCs have any effect on epilepsy, and, if any, assessing that effect clinically require novel studies using experimental epilepsy models. In the present study it was aimed to investigate the effects of DEX on epileptiform activity in a penicillin-induced experimental epilepsy model in Wistar rats in comparison with commonly used antiepileptic medications phenytoin (PHT) and levetiracetam (LEV).

2. Results

The present study was designed to examine the effect of DEX on penicillin-induced epileptiform activity in rats. The animals were administered daily intraperitoneal DEX doses or antiepileptic drugs for 6 days. Craniotomy was performed under anesthesia at day 7, followed by recording a basal ECoG and 500 IU penicillin injection (i.c). Thirty minutes after penicillin injection, DEX doses or the final doses of antiepileptics were administered. Then, a 120 min ECoG recording was performed. Simultaneous ECoG recordings were obtained from 8 animals using 8 channels. A 10-min basal ECoG recording was performed in rats placed on the stereotaxic apparatus. Post-experiment examination revealed no spontaneous epileptiform activity on the basal ECoG recording. Intracortical penicillin injection at a dose of 500 U was performed to initiate epileptiform activity. All animals demonstrated an epileptiform activity 3–5 min after penicillin injection. Thirty minutes after penicillin injection the spike frequency of the epileptiform activity in control, 1 mg/kg DEX, 3 mg/kg DEX, 10 mg/kg DEX, 50 mg/kg PHT, and 50 mg/kg LEV groups were 34 ± 1, 31 ± 4, 35 ± 3, 34 ± 5, 30 ± 2, and 36 ± 4 spikes/min, respectively. In addition, the spike amplitudes of the epileptiform activity 30 min after penicillin injection were 822 ± 103, 1014 ± 218, 1023 ± 314, 932 ± 231, 604 ± 110, 976 ± 295 μV in the control, 1 mg/kg DEX, 3 mg/kg DEX, 10 mg/kg DEX, 50 mg/kg PHT, and 50 mg/kg LEV groups, respectively.

Analysis of 120 min epileptiform ECoG activity following final injection of DEX and antiepileptics revealed that DEX at the doses of 3 mg/kg and 10 mg/kg reduced the spike frequency of the epileptiform activity. As compared with the initial value (before point), the effect of 3 mg/kg DEX started 70 min after injection of the final dose and lasted until the end of the experiment (Figs. 1 and 2). In the 3 mg/kg DEX group, the spike frequency of the epileptiform activity at 70th, 80th, 90th, 100th, 110th and 120th minutes were 21 ± 3, 23 ± 3, 20 ± 3, 17 ± 3, 17 ± 3 and16 ± 3 spikes/min, respectively. The significance levels at 70th, 80th, 90th, 100th, 110th and 120th minutes were $p=0.009$, $p=0.024$, $p=0.007$, $p=0.001$, $p=0.002$, and $p=0.002$, respectively (Fig. 2). On the other hand, 3 mg/kg DEX injection significantly increased the mean frequency of epileptiform activity at the 20th minute (49 ± 3; $p=0.031$; Fig. 2). As compared with the initial value (before point), the effect of 10 mg/kg DEX started 80 min after injection of the final dose and lasted until the end of the experiment (Figs. 1 and 2). In the 10 mg/kg DEX group, the spike frequency of the epileptiform activity at 80th, 90th, 100th, 110th and 120th minutes were 13 ± 1, 14 ± 1, 14 ± 4, 12 ± 3 and 10 ± 2 spikes/min, respectively. The significance levels at 80th, 90th, 100th, 110th and 120th minutes were $p=0.015$, $p=0.024$, $p=0.041$, $p=0.029$, and $p=0.09$, respectively (Fig. 2). The spike frequency obtained from 50 mg/kg PHT group, on the other hand, significantly decreased compared with the initial value (before point) between 30th and 120th minutes. In the 10 mg/kg DEX group, the significance levels at 30th, 40th, 50th, 60th, 70th, 80th, 90th, 100th, 110th and 120th minutes were $p=0.025$, $p=0.01$, $p=0.003$, $p=0.001$, $p=0.004$, $p=0.003$, $p=0.007$, $p=0.015$, $p=0.005$ and $p=0.001$, respectively (Fig. 2). In the 50 mg/kg LEV group, on the other hand, the spike frequency was significantly reduced as compared with the control group between 70th and 90th minutes and at 120th minute ($p=0.027$, $p=0.034$, $p=0.038$ and $p=0.047$; Fig. 2).

In the control group, the spike amplitudes were decreased at 90th and 120th minutes compared with the initial value ($p=0.041$ and $p=0.022$). In the 1 mg/kg DEX group, the spike amplitudes were decreased at 60th, 90th and 120th minutes compared with the initial value ($p=0.022$, $p=0.046$ and $p=0.047$). In the 3 mg/kg DEX group, the spike amplitudes were decreased at 60th, 90th and 120th minutes compared with the initial value ($p=0.017$, $p=0.001$ and $p=0.006$). In the 10 mg/kg DEX group, the spike amplitudes were decreased at 120th minute compared with the initial value ($p=0.001$). In the 50 mg/kg PHT group, the spike amplitudes were decreased at 90th and 120th minutes compared with the initial value ($p=0.045$ and $p=0.021$; Table 1).