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Dexamethasone induces alterations of slow wave oscillation, rapid eye movement sleep and high-voltage spindle in rats

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Glucocorticoids arising from chronic stress and long-term inflammatory treatment with corticosteroids are both associated with neuropathology and cognitive impairments. Many previous studies have focused on changes in brain morphology and deficits in learning behavior. However, effects of long-term exposure to stress hormones on electrical brain signaling and sleep-wake patterns have remained largely unexplored. This study aimed to monitor electroencephalographic (EEG) patterns induced by prolonged dexamethasone exposure. Adult male Wistar rats implanted with electrodes on the skull over the frontal and parietal cortices were intraperitoneally injected with either saline or dexamethasone (0.5 mg/kg) once daily for 21 consecutive days. Longitudinal EEG recording was performed on day 6, 11, 16 and 21. Fast Fourier transform was used for frequency power analysis. One-way ANOVA revealed significant increases in parietal EEG power of slow frequencies (delta, theta and alpha) particularly, with the dominant theta activity seen as early as day 11 of dexamethasone treatment. Sleep-wake analysis on day 21 confirmed a significant reduction of rapid-eye movement (REM) sleep and increased slow frequency oscillations mainly in the parietal cortex during the awake period. The number of high-voltage spindles (HVSs) (6-10 Hz EEG oscillation) was significantly increased during awake and slow wave sleep (SWS) periods following dexamethasone treatment. These findings demonstrated that distinct frequency oscillations, sleep-wakefulness and sleep spindles may be parameters of neuropathology produced by long-term dexamethasone exposure. Early detection of these parameters might be predictive of neuropathology in long-term corticosteroid users.

Key words: corticosteroid, dexamethasone, electroencephalography, EEG spectral power, rapid eye movement, high-voltage spindle

INTRODUCTION

Previously, mental and cognitive deficits known as steroid psychosis were found in cases of long-term anti-inflammatory drug treatment (Clark et al., 1952). In addition, daily life stress also increased corticosterone levels and induced hypothalamic–pituitary–adrenal (HPA) axis hyperactivity, anxiety-like behavior, impairments in learning and memory, dysfunction in balance and motor coordination and volume reductions in multiple brain areas, including rodent hippocampus (Jafari et al., 2018). Stress hormones produce neurobiological effects through glucocorticoid receptors generally localized in the brain. In humans, sympathoadrenal system hyperactivity is associated with impaired sleep continuity (Hubain et al., 1998). Different brain mechanisms are implicated in sleep disturbances experienced by people with different mental disorders (Staner et al., 2003). Many reports have consistently shown that stress hormones can cause impairments in sever-

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al cognitive functions in humans (Lupien et al., 1995; 2005). These findings suggested an association between long-term exposure and some adverse consequences of stress hormones.

It is important to monitor brain activity in a longitudinal study to detect possible neuropathological evidence as early as possible. Most neurodegenerative diseases have been diagnosed at late stages when pathological symptoms emerge. Many failed treatment trials for neurodegenerative diseases have been reported (Selkoe, 2011; Toyn, 2015). Treatment effectiveness appeared to be minimal in the late stage of the diseases, especially following the emergence of clinical symptoms (Laske, 2014). Effective disease-modifying therapies would likely be administered if a diagnosis was made at the earliest stage of brain pathology. It is possible for researchers to detect abnormal cerebrospinal fluid composition in people who do not yet have clinical symptoms but are at risk for Alzheimer's disease (Fagan et al., 2007). A similar potential application has been reported in studies of Parkinson's disease using PET scans (Garraux et al., 2013). Moreover, myelin basic protein in cerebrospinal fluid was also found to be a reliable indicator of myelin damage in multiple sclerosis (Sellebjerg et al., 1998). These reports hint at the possibility of early detection for neurodegenerative diseases with promising methods. However, these sophisticated techniques have been applied mostly at specialized research centers for neurodegenerative diseases. These findings have not had significant impact on neurodegenerative intervention for the mass population due to sparse availability of the techniques.

Subsequently, other non-invasive and non-expensive techniques have been researched. Among the various approaches, electroencephalography (EEG) has ained enormous attention. Originally, it was primarily used for epilepsy research and treatment (Minasyan et al., 2010). However, it has also been recognized as a useful tool for purposes including diagnosis of depression (Itil, 1983), attention deficit hyperactivity disorder (Snyder and Hall, 2006) and schizophrenia (Kwon et al., 1999; Uhlhaas et al., 2008). These reports have demonstrated that electrical brain signals are rich sources for assessing differential brain functions found in various conditions or diseases.

This study aimed to mimic neuropathology induced by prolonged dexamethasone therapy in a rat model. Therefore, EEG signals were recorded for frequency analysis by using Fast Fourier transform (FFT) to identify neural signaling and sleep disturbances induced by prolonged administration of dexamethasone in rats. Microanalysis of EEG signals was performed to detect changes in sleep-wake states and the occurrence of abnormal sleep spindles.

METHODS

Animal model

16 adult male Wistar rats (weighing 300-350 g, n=8 per group) were obtained from Southern Laboratory Animal Facility, Prince of Songkla University, Thailand. The rats were maintained at 22°C with a 12/12 dark/light cycle (light on at 7:00 a.m.). Standard commercial food pellets and filtered tap water were available *ad libitum*. The experimental protocols described in this study were approved and guided by the Animal Ethics Committee of the Prince of Songkla University.

Surgical procedures were carried out according to a previous study (Cheaha et al., 2014). Briefly, animals were anesthetized with intramuscular injection of 60 mg/kg Zoletil® 100 (Virbac, Thailand Co. Ltd.). Stainless steel screw electrodes were implanted on the skull over the frontal cortex (AP; +3, ML; 3) and the parietal cortex (AP; -4, ML; 4) on the left side skull. The reference and ground electrodes were placed at midline above the cerebellum. Bipolar wire electrodes (PFA-coated stainless steel wire with coated diameter 139.7 µm (Catalog No. 79110A-M system) were inserted into the dorsal neck muscles for electromyography (EMG). All electrodes were secured in place with acrylic resin (Unifast Trad, Japan). After surgery, animals were individually housed in a single cage and observed for approximately 15 days to ensure full recovery. The antibiotic ampicillin (General Drug House Co., Ltd., Thailand) was applied (80 mg/kg, i.m.) for 4 days to prevent infection. Rats were randomly divided as control and dexamethasone groups for 21-day treatment. Control rats received 0.9% saline (i.p.) (n=8), whereas treated rats received 0.5 mg/kg dexamethasone (i.p.) (n=8). Injection was performed at 9:00 a.m. and EEG recording started at 1:00 p.m.

Dexamethasone preparation

Dexon® (General Drugs House co., Ltd.) was diluted in 0.9% saline to a final concentration of 0.5 mg/ml. Both control and dexamethasone groups were injected with a volume of 1 ml/kg.

EEG recording

The process of recording was performed as previously described (Cheaha et al., 2014). EEG signals of individual rats in a recording chamber were recorded for 2-h period through recording cables. EEG signals were amplified with a low-pass 60 Hz, high-pass 0.1 s and

digitized at 400 Hz by a PowerLab/4SP system (ADInstruments) with 12-bit A/D, and stored in a PC through the LabChart ADInstruments software. The EEG signals were processed through 1.25-45 Hz band pass filter. The digitized EEG data were segmented into 1,024 data points (50% overlap) and the signals were converted to power spectra by the FFT algorithm (Hanning window cosine transform). Then, the power spectra of 2.56-sec sweeps of a selected period were averaged to create the power spectra of the period. In each power spectrum, values were divided into 5 frequency bands: delta, 1.25-4.5 Hz; theta, 4.75-6.75 Hz; alpha, 7-12.5 Hz; beta, 12.75-30 Hz and gamma, 30.25-45 Hz. EEG powers in each frequency band of each group were averaged and expressed as power (μV^2) and power density (μV^2/Hz). EEG powers of animals were analyzed from 2-hr records on day 1, 6, 11, 16 and 21 following the start of dexamethasone treatment.

Analysis of sleep-wake cycle

EEG signals from the frontal and parietal cortices and EMG signals from the dorsal neck muscles were used to determine sleep-wake states of animals. Awake periods (AW) were identified by fast wave, low amplitude EEG and the presence of high EMG activity (Fig. 1A). The interchange among different sleep-wake periods can be displayed in spectrograms for visual inspection (Fig. 1B). Slow wave sleep (SWS) or non-rapid

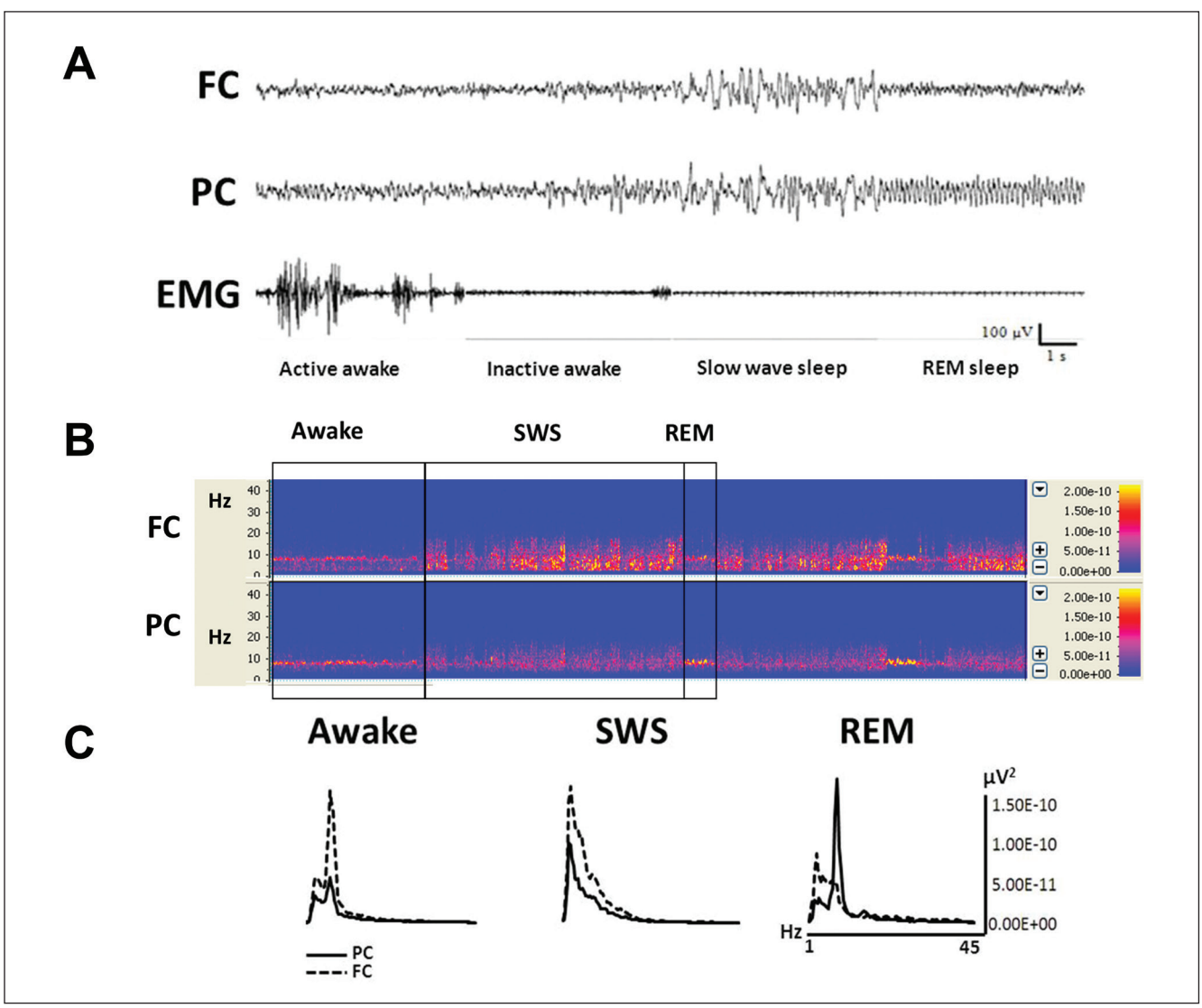

Fig. 1. Determination of sleep-wake states from frontal (FC) and parietal (PC) EEG signals. Raw EEG and EMG signals were used to identify awake, slow wave sleep (SWS) and (rapid eye movement (REM) sleep periods (A). The spectrograms displaying spectral power are expressed and referenced with color codes of frequency (Y axis) in time domain (X axis) (B). Each sleep-wake state was confirmed with specific characteristic of EEG power densities (C).

eye movement sleeps (non-REM sleep) were identified with slow wave and high amplitude EEG. REM sleeps were detected with fast wave, low amplitude EEG and the absence EMG activity. Specific characteristics of the EEG power spectrum were examined by using FFT for quantitative data (Fig. 1C). Awake signals were identified with peaks at theta wave for frontal and parietal EEG. On the other hand, SWSs were recognized with peaks specifically within delta range for both frontal and parietal EEG. The most unique characteristic was detected during REM sleep when parietal EEG exhibited dominant theta peak whereas frontal EEG had relatively overall low power.

Data analysis

Power densities (μV^2/Hz) of frontal and parietal EEG during baseline and post-treatment period were calculated. Baseline values were set to 100% and changes of post-treatment values were documented as percent of baseline values. For spindle investigation, frontal EEG was scanned through 6-10 and 10-14 Hz filters from a 2-hr recording for HVSs and regular sleep spindles, respectively. Numbers of occurrences of spindles were counted from loops or peaks of EEG power density of filtered signal. Therefore, data were normalized and expressed as numbers of spindle per hour.

All data were expressed as mean ±S.E.M. Effects of treatment were determined by using one-way ANOVA followed by the Student Newman Keuls test for multiple comparison. T-test was used for the analysis of two-set data. *, ** and *** indicate p<0.05, 0.01 and 0.001, respectively, for statistically significant differences.

RESULTS

Effects of repeated dexamethasone exposures on EEG power spectrum

The broad spectrum of EEG power was divided into 5 frequency bands: delta, theta, alpha, beta and gamma. Therefore, values of different time points were analyzed for each frequency range. All data were normalized with baseline values obtained before the start of dexamethasone treatment and expressed as percent baseline (% baseline). Data were shown in comparison to controls. Frontal EEG analysis revealed no significant change was induced by the dexamethasone in any duration of any frequency band (Fig. 2A). However, the analysis of parietal EEG signals indicated that dexamethasone significantly increased powers of slow waves which included delta, theta and alpha bands (Fig. 2B). Multiple comparisons indicated that significant changes were observed only on day 21 for delta band. In theta band, significant changes were confirmed as early as day 11 and until day 21. Alpha powers were also significantly increased on day 16 until day 21.

Effects of dexamethasone on sleep-wake patterns

Sleep-wake patterns were analyzed from EEG signals recorded on day 21 of dexamethasone treatment. Hypnograms were created to display dynamic appearances of sleep-wake parameters which included awake, slow wave sleep (SWS) and rapid eye movement (REM) in time domain (Fig. 3A). Time fragments of each parameter during a 2-hr period of recording

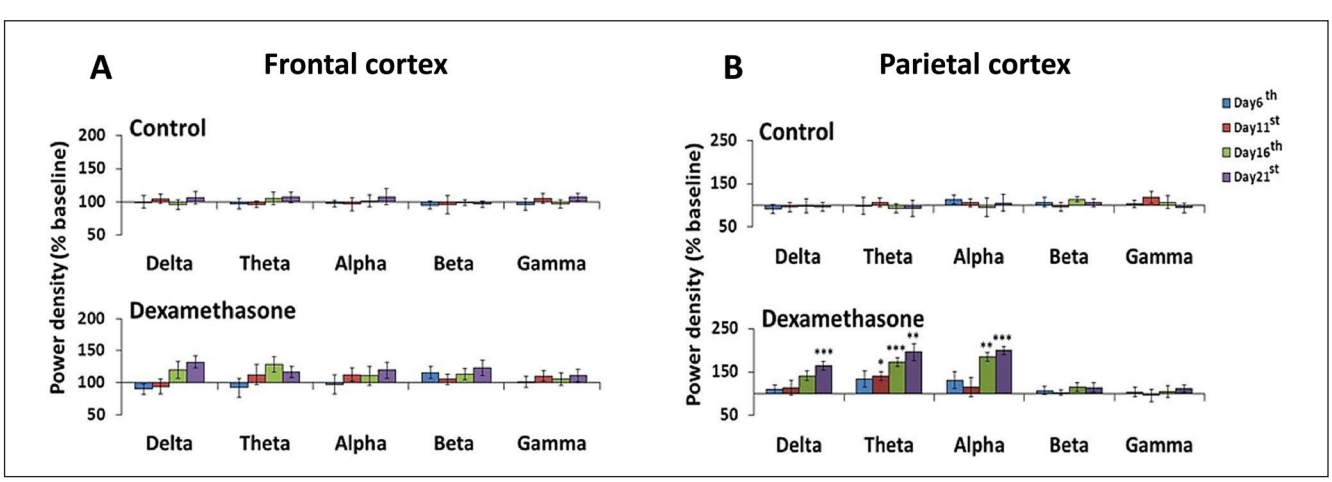

Fig. 2. Effects of repeated dexamethasone treatment on EEG powers in the frontal (A) and parietal (B) cortices. Baseline activities were evaluated from 2-hr recordings on the first day before drug administration. After the administration, EEG was recorded for 2 h on each assigned day. EEG power spectra were divided into 5 frequency ranges: delta, theta, alpha, beta and gamma. Data are expressed as mean ± S.E.M. of power density (% baseline). *p<0.05, **p<0.01, ***p<0.001 compared with control values.

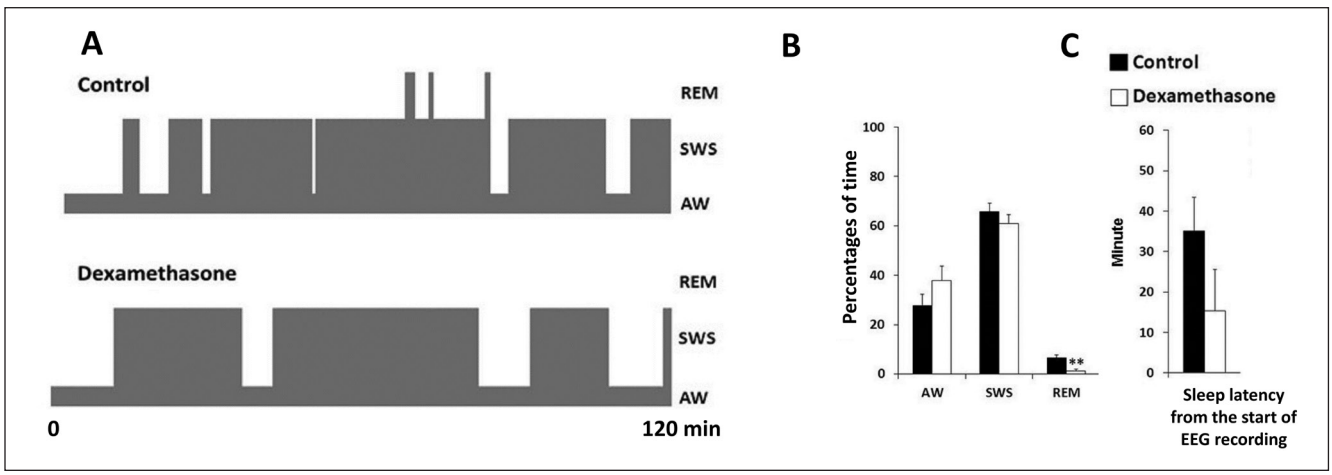

Fig. 3. Effects of repeated dexamethasone exposures on sleep-wake cycle. Hypnograms of representative rats from control and dexamethasone groups were created to show the dynamic presentation of sleep-wake states (A). Mean of time spent in each brain state and sleep latency are shown (B and C, respectively). Sleep-wake data were analyzed from EEG signals recorded for 2 h on day 21 of the treatment. $^{**}p<0.01$ compared with control levels.

were summed. Total times spent in awake periods, SWS and REM sleep were analyzed and expressed as percent of total (Fig. 3B). The results showed that chronic dexamethasone exposure significantly decreased the percentage of REM sleep (Dx=1.22±2.04 and control=6.42±0.59 (t_{14}=-6.926, P<0.001)). No change in time spent was seen for awake and SWS periods. The analysis of sleep latency also revealed no significant change induced by dexamethasone (Dx=16.17±12.49 min and control=36.22±8.31 min (t_{14}=-3.780, P<0.01)) (Fig. 3C).

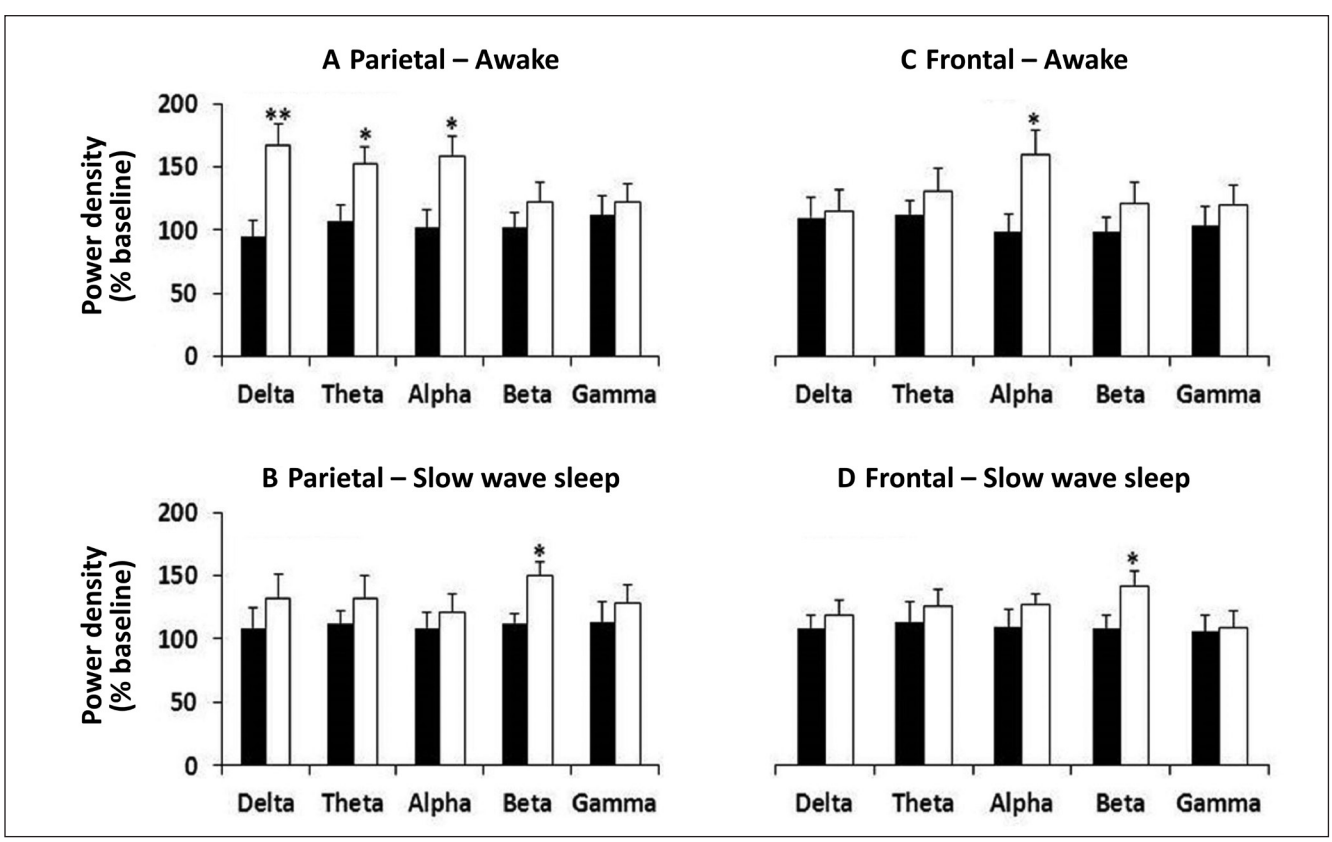

Fig. 4. Effects of repeated dexamethasone treatment on power of Delta (A), Theta (B), Alpha (C), Beta (D) and Gamma (E) waves. EEG powers of 5 frequency waves were analyzed from parietal (PC) EEG and frontal (FC) EEG on day 21 of dexamethasone treatment. Data were taken from 5-min continuous periods of awake and slow wave sleep (SWS) brain states for separate analysis.

Effects of repeated dexamethasone treatment on EEG powers during awake and slow wave sleep periods

EEG powers were separately analyzed with regard to specific awake and SWS periods. Signals were taken from the first 5-min recording of the first appearance of awake or SWS periods after dexamethasone treatment for 21 days. EEG power analysis was performed for 5 frequency ranges. Awake EEG analysis confirmed that dexamethasone significantly induced increases in power of slow frequency bands which included delta, theta and alpha activity for parietal EEG (Fig. 4A) and only alpha activity for frontal EEG (Fig. 4C). However, the analysis of EEG signals during SWS revealed the only significant change seen was within beta band for both parietal and frontal EEG (Fig. 4B and 4D, respectively).

Effects of repeated dexamethasone treatment on EEG spindles

The distribution of spindles was determined from raw EEG signals. Types of EEG spindles were characterized by power spectrum analysis of frontal EEG signals using FFT. Raw EEG signals were filtered for 6-10 and 10-14 Hz oscillations to extract EEG spindles and inspect their features. Two main types of spindles were characterized. Sleep spindles were recognized from frontal EEG with relatively low power when filtered for 10-14 Hz activity (Fig. 5A). When filtered for 6-10 Hz activity, HVSs were detected. They exhibited high amplitude loops with peak frequency in the range. Therefore, numbers of both types of EEG spindle were counted from a 2-hr period of EEG recordings after dexamethasone treatment for 21 days. The results showed that

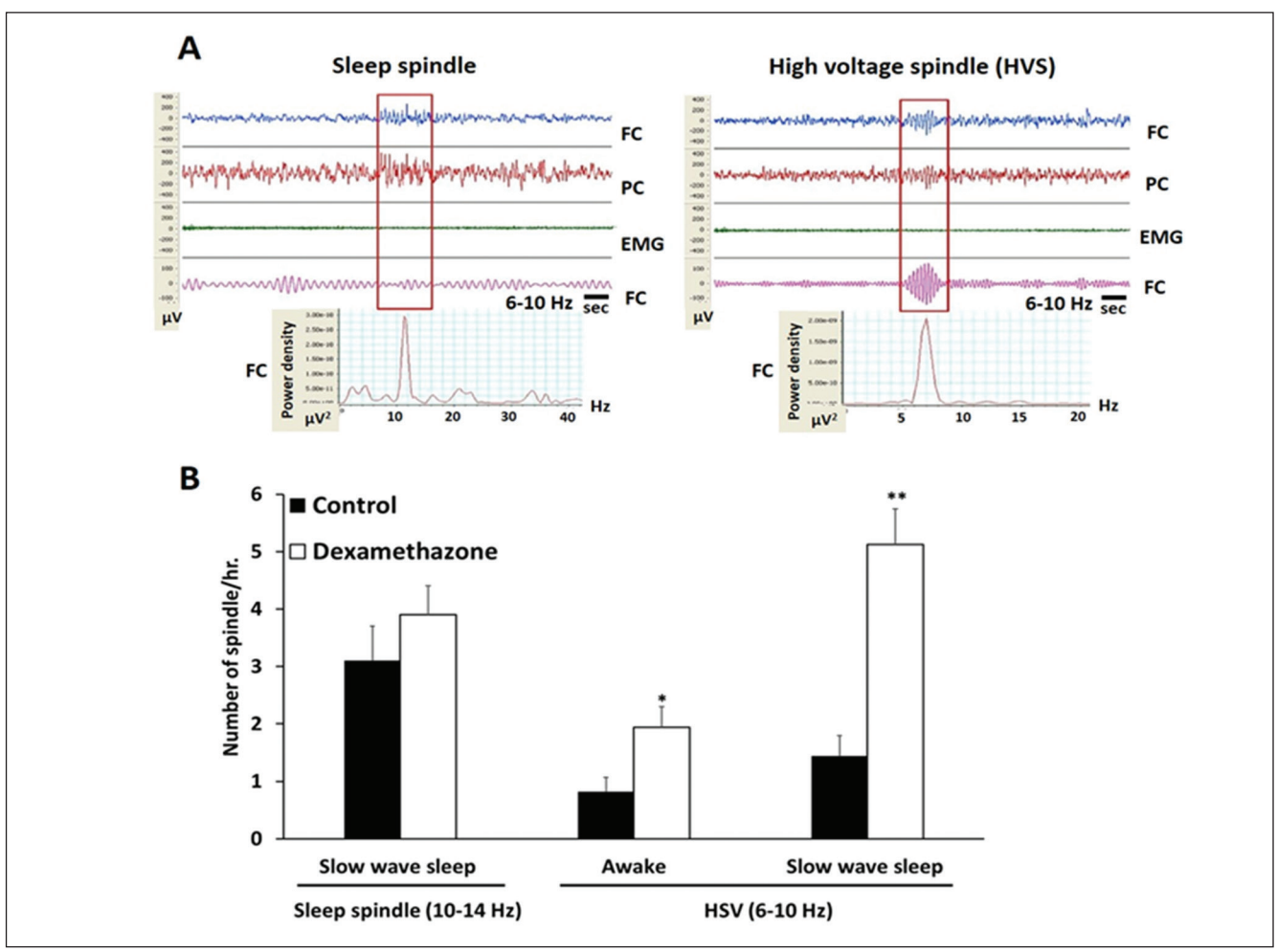

Fig. 5. Effects of repeated dexamethasone treatment on sleep-wake cycle. Identification of normal sleep spindles and high-voltage spindles (HVSs) was performed by using EEG signals recorded on day 21 of dexamethasone treatment (A). EEG signals were filtered and EEG spindles were identified from power density of frontal EEG signals. There are 2 types of EEG spindle according to their features and EEG power densities: regular sleep spindle (10-14 Hz) and HVS (6-10 Hz). Numbers of spindles during slow wave sleep (SWS) and awake (AW) periods were analyzed (B). Data are expressed as mean ± S.E.M. number of spindle (times/h). *p<0.05, **p<0.01 compared with control levels.

repeated exposure to dexamethasone had no effect on normal sleep spindles analyzed during SWS brain state (Fig. 5B). However, it was found to significantly increase the number of HVSs per hour both during awake and SWS states (AW: Dx=1.94±0.36 and control=0.82±0.25 (t_{14}=7.228, P<0.001) and SWS: Dx=5.13±0.62 and control=1.44±0.36 (t_{14}=14.558, P<0.001)).

Correlations between HVSs and EEG power

Regression analyses between type of spindle and EEG power of each band of frequency waves were performed. No significant correlation was seen for the normal sleep spindle (data not shown). In contrast, positive correlations were found between number of HVSs and EEG powers. During the awake period, the number of HVSs was positively correlated with only Theta power (Fig. 6A). Relatively greater relationships were seen during the SWS period. Significant correlations between numbers of HVSs and EEG power of delta, theta and alpha waves were found (Fig. 6B-D, respectively). The distributions of slow frequency powers against numbers of HVSs completely distinguished between the values of control and dexamethasone groups.

DISCUSSION

The present findings have demonstrated that analysis of EEG spectral powers and sleep components yielded differential parameters for control and dexamethasone-treated rats. Longitudinal study of EEG also allowed for the detection of changes in slow wave as early as day 11 of dexamethasone treatment. These parameters may be of particular significance for EEG studies when repeated measures are possible and convenient. The suppression of REM sleep and the detection of HVSs induced

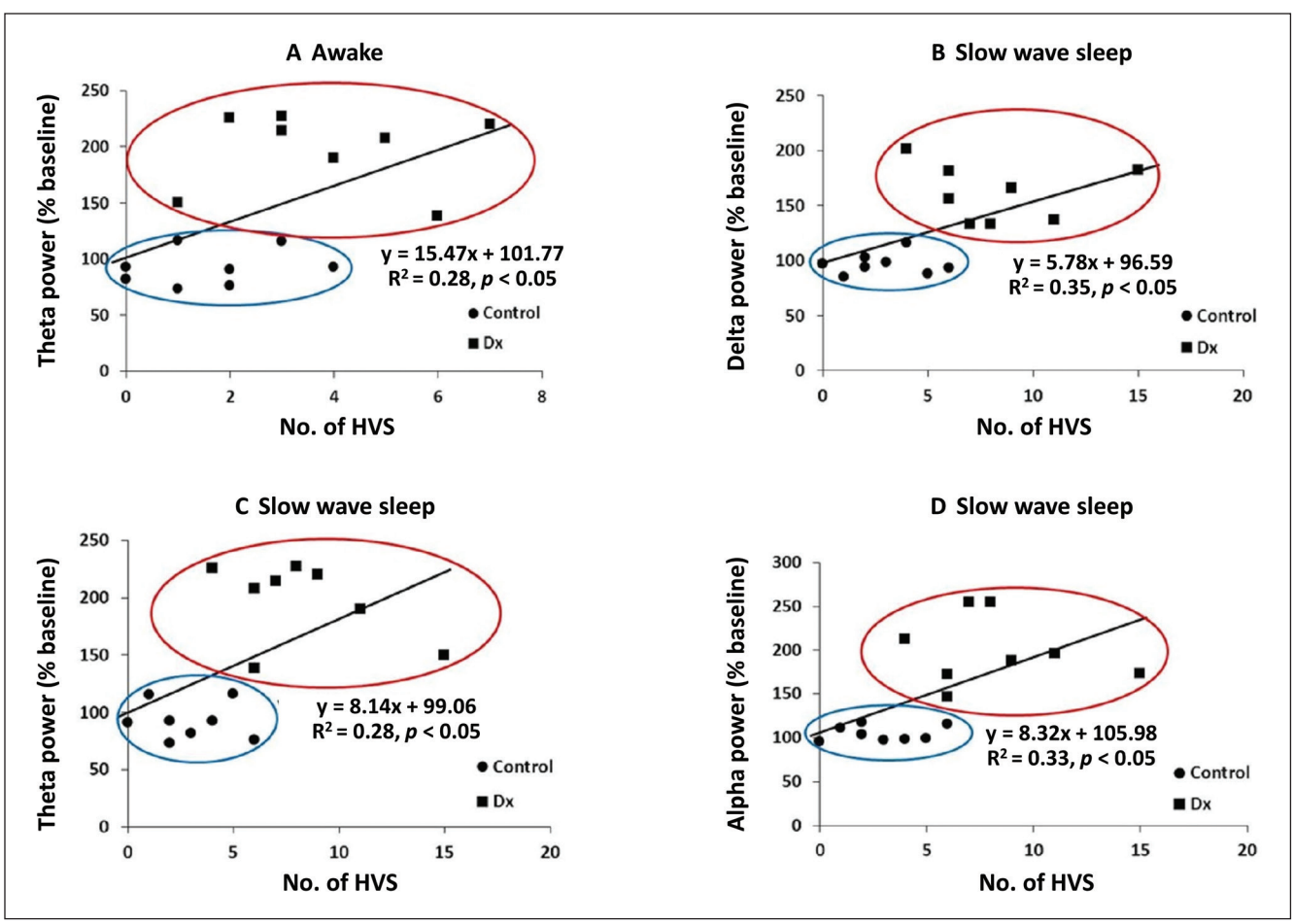

Fig. 6. Linear regression analyses of relationships between EEG power and number of high-voltage spindles (HVSs) during awake and slow wave sleep brain states. Relationships between Theta and HVS during awake (A), Delta and HVS during SWS (B), Theta and HVS during SWS (C) and Alpha and HVS during SWS were analyzed from EEG signals of control and dexamethasone-treated rats. Correlations are expressed as R-square (R^2) and linear equation and statistically confirmed with p values.

by long-term treatment with dexamethasone also clearly distinguished electrical brain signals between groups.

Dexamethasone is a synthetic steroid with high glucocorticoid activity. It is widely used due to its anti-inflammatory effects (Leggas et al., 2009; Choksi et al., 2013). However, its use has been linked with mechanisms that increase oxidative stress through long-lasting upregulation of reactive oxygen species (Schafer et al., 2005; Kraaij et al., 2011). Down-regulation of genes involved in the mitochondrial respiratory chain and those that encode antioxidant enzymes were induced by dexamethasone (Mutsaers and Tofighi, 2012). Therefore, oxidative stress induced by dexamethasone has been extensively used as a model for evaluation of protective effects of novel therapeutic substances (Hu et al., 2009; Gao et al., 2010).

Increases in slow wave activity have been typical findings in neurodegenerative disease (Coben et al., 1983; Kwak, 2006). Global cortical dysfunction was also found to be associated with increased theta activity in EEG spectra and a significant increase in delta power was observed in later stages of deterioration in Alzheimer's disease (Prichep et al., 1994; Helkala et al., 1996). Neuronal loss is proposed to underlie the increased slow wave oscillation. In urethane-anesthetized rats, high doses of cholinergic agonist or cholinesterase inhibitor were demonstrated to decrease slow wave activity including low frequency power (Toth et al., 2012). Basically, acetylcholine is primarily synthesized in the nucleus basalis of Meynert and basal forebrain and are the major sources of cholinergic afferents terminating in many brain regions, including the areas involved in learning and memory processes and the neocortex, that would impact neocortical EEG as well as sleep-wake stages (Selden et al., 1998; Semba, 2000). Moreover, increased delta and theta amplitudes in rats were induced by lesioning of the nucleus basalis and, therefore, reversed by anticholinesterase and pilocarpine (Riekkinen Jr. et al., 1991). Elevated acetylcholine release is associated with low-voltage fast oscillation during wakefulness and REM sleep, while a reduction in its release is found during SWS when Delta waves dominate the EEG (Kanai and Szerb, 1965; Celesia and Jasper, 1966). Degeneration of cholinergic basal forebrain has been commonly found in Alzheimer's diseases (Grothe et al., 2014). Moreover, monoamines also have a role in these actions as combined cholinergic-monoaminergic stimulation resulted in stronger effects in reversing learning impairments and EEG slowing than cholinergic enhancement alone in a rat model (Dringenberg, 2000). EEG analysis in Alzheimer's patients also revealed slowed mean frequency activity and reduced interplay among cortical regions (Jeong, 2004). Previously, a loss of neurons and glial cells in regions of the hippocampus was observed following long-term dexamethasone treatment (Issuriya et al., 2014). These consistent reports suggest possible links between elevated slow wave EEG power and degeneration of neuronal substrates that may also underlie neuropathology induced by long-term dexamethasone treatment.

In addition to EEG abnormalities, sleep disturbances have also been widely reported in cases of neurodegenerative diseases (Gagnon et al., 2002; Jackson and Snyder, 2008). Mostly, sleep disruption is detected before the onset of relevant neuropsychological impairments (Tranah et al., 2011; Ju et al., 2013). In Alzheimer's disease, sleep disturbances are positively correlated with amyloid deposition (Ju et al., 2013). In particular, REM sleep deprivation was hypothesized to be linked with an impairment in learning recent information (Christos, 1993). A decrease in REM sleep was among changes in parameters found in mild cognitive impairment subjects and to a greater extent in Alzheimer's patients (Maestri et al., 2015). In animal models of Alzheimer's disease, a reduction of REM and changes in EEG spectra were observed earlier than the occurrence of behavioral changes (Schneider et al., 2014). It was hypothesized that loss of REM in patients and mouse models is associated with a decrease in cholinergic tone and donepezil, a cholinesterase inhibitor, was demonstrated to restore some normal sleep in animals (Wisor et al., 2005) and Alzheimer's patients (Mizuno et al., 2004).

The present study analyzed features of spindles. 6-10 Hz and 10-14 Hz EEG oscillations were specifically investigated. Significant increases were observed for 6-10 Hz but not 10-14 Hz activity. Previously, sleep spindles relatively similar to 6-10 Hz EEG oscillation have been characterized in rats (Marini et al., 2008). This type of electrical activity, known as HVSs, was seen in rats with dopamine depletion (Ge et al., 2012) or systemic blockade of dopamine D2-like receptor (Yang et al., 2013). In a rat model of Parkinson's disease induced by 6-hydroxydopamine lesioning, high frequency stimulation of the sub-thalamic nucleus, a brain region involved in the cortical-basal ganglia loop, was found to restore the HVSs and motor deficits to normal states (Yang et al., 2015).

In terms of mechanisms, long-term treatment of dexamethasone might be proposed to affect at least cholinergic and dopaminergic groups of neurons in the brain. Glucocorticoid receptors are present on dopaminergic cells (Harfstrand et al., 1986) and found to mediate several essential processes of cholinergic neurons in the brain (Guijarro et al., 2006). Prolonged dexamethasone administration likely leads to hyperactivation of these neuronal cells through glucocorticoid receptors, ultimately causing cell death and neurodegenerative symptoms that might mimic those induced by oxidative stress.

Finally, the present study pointed out several correlations between EEG powers and HVSs in a rat model. These findings highlighted several indicative parameters of neuropathology for possible application at the clinical level. Through longitudinal monitoring of EEG signals, the analysis of slow frequency could allow for early detection of neuropathologies. Though the reduction of REM sleep was also an obvious and consistent parameter in previous reports, it only became evident relatively late when most of the symptoms had already emerged. Additionally, it is of particularly interest that the excessive appearance of HVSs especially during SWS was strongly correlated with increased theta oscillation.

CONCLUSIONS

Taken together, the present data demonstrated that changes in slow frequency oscillation appeared to be sensitive to prolonged dexamethasone treatment. REM suppression and HVSs also emerged at later stages. These findings clearly confirmed that long-term exposure to the corticosteroid led to changes in electrical brain activity. Moreover, this animal model may be useful for testing novel neurodegenerative disease-modifying drugs or substances.

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