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Dexamethasone induced changes of neural activity in the auditory cortex of rats

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ABSTRACT

Previous studies have suggested that elevation of glucocorticoid level can alter auditory processing and may have relevance for auditory hallucinations. However, the neural mechanism underlying the glucocorticoid induced sensory change remains unclear. To examine the effects of glucocorticoid on the neuronal spike activities of sensory cortex, we topically applied dexamethasone (DEX), a glucocorticoid receptor agonist, to the auditory cortical surface of rats while recording single-unit extracellular spike activities in response to sound stimuli. Our major findings are: (1) a topical administration of DEX increased the cortical neural responses to pure-tone stimuli from 10 to 60 min after administration, while the peak response enhancement occurred at 20–30 min; (2) DEX not only markedly increased the magnitude of tone-evoked responses, but also extended the response duration and the frequency range of the neural responses; (3) the enhancement of neural responses was more salient at the higher frequency band; (4) the ratio of spontaneous firing rate between post- and pre-administration was negatively correlated with the unit's spontaneous firing rate before treatment. Our data confirm that DEX can modulate the neural activity at the cortical level and provide more information for understanding the mechanism of glucocorticoid-induced alterations in auditory processing.

1. Introduction

Glucocorticoid hormones, released from the adrenal cortex in response to stressful stimuli, regulate a variety of important cardiovascular, metabolic, immunologic, and homeostatic functions (de Kloet, 1991; Munck et al., 1984). Glucocorticoids are also involved in the process of neuronal regeneration and death, and for regulating a variety of behaviors including learning, memory and adaptation (Bohn et al., 1994; Roozendaal, 2002; Roozendaal et al., 2009; Sandi and Pinelo-Nava, 2007). Several studies have suggested that glucocorticoids can influence the encoding and processing of auditory stimuli. Acute and sub-chronic administration of hydrocortisone transiently enhanced amplitude of auditory evoked potentials (AEPs) in normal human (Ashton et al., 2000; Born et al., 1989). Stress exposure or corticosteroid administration also altered the auditory sensitivity in human (Fehm-Wolfsdorf and Nagel, 1996; Hasson et al., 2013) and rodents (Maxwell et al., 2006; Mazurek et al., 2010). Interestingly, corticosteroid administration has been suggested to model schizophrenia-like sensory processing impairments (Stevens et al., 2001).

The neural mechanism underlying the glucocorticoid induced behavioral change remains unclear. To date, significant effort has been made to investigate how the glucocorticoid administration affects the synaptic potentiation (Alfarez et al., 2002; Diamond et al., 1992; Okuhara and Beck, 1998; Rey et al., 1994). However, most previous studies were conducted on brain slices and focused on hippocampus. Less is known about the effects of glucocorticoid on the neuronal spike activities of sensory cortex in vivo. Single-unit neuronal studies are critical for shortening the bridge from cellular to sensory changes. For this reason, we investigated the effects of glucocorticoid on the auditory cortex (ACx) of rats. We topically applied dexamethasone (DEX), a glucocorticoid receptor agonist, to the cortical surface while recording single-unit extracellular spike activities of the ACx. Pure-tone stimuli were applied to evaluate the fundamental characteristics of neuronal response including the latency, strength, duration and frequency-tuning. These neuronal characteristics were compared before and after drug application. The changes of spontaneous spike activities were also quantified.

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2. Materials and methods

All animals' works was carried out in strict accordance with National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23) revised 1996. All surgery was performed under anesthesia, and all efforts were made to minimize the number of animals used and their suffering.

2.1. Subjects

Recordings were made in the primary ACx of adult Wistar rats of either sex. Animals, weighing 250–350 g (8–10 weeks old), came from our own colony housed in a humidity-controlled (50–55%) and temperature-controlled (22–24 °C) facility on a 12 h light/dark cycle (lights on at 7:30 A.M.) with access to food and water ad libitum.

2.2. Surgical procedures

The animal was anesthetized by an initial injection of urethane (0.9 g/kg, i.p.) supplemented by additional doses if necessary (usually once or twice during the recording session). Temperature was monitored rectally and maintained at 37 °C using a feedback-controlled blanket. After placing the animal in a stereotaxic frame (SR-5R, Narishige, Tokyo, Japan), the cranium was exposed, four small holes were drilled over the parietal bone and fine jeweler's screws were inserted to serve as an anchor for a metal head-post holder that was cemented to the skull with dental acrylic. A craniotomy was performed above the ACx according to the coordinates of the Paxinos and Watson brain atlas: 3–7 mm posterior of bregma and 3–5 mm lateral to bregma (Paxinos and Watson, 1986). The dura above the ACx was removed under binocular control, and the cerebrospinal fluid was drained to prevent the occurrence of edema. At the end of the recording session, a lethal dose of pentobarbital (>200 mg/kg, i.p.) was administered to the animal.

2.3. Recording

Recording experiments were conducted in an electrically shielded, soundproofed room. During the recording experiments, the earbars were removed. The rat's head was fixed through the head-post holder implanted on the skull. Four-channel extracellular recordings were obtained from an array of 2 × 2 Teflon-insulated tungsten microelectrodes (50 μm diameter; impedance: 0.5 MΩ at 1 kHz; A-M Systems, Carlsborg, WA). The distance of two neighbor electrodes was approximately 300 μm. A silver wire, used as ground, was inserted between the temporal bone and the dura mater on the contralateral side. The electrodes were mounted on a custom-built holder which was lowered stepwise with a pulse motor-driven manipulator (SM-20, Narishige, Tokyo, Japan). The electrode penetration, perpendicular to the cortical surface, was made under visual guidance via an operating microscope. Inserting electrodes in the cortical tissue usually induced a deformation of the cortex. At least a 30 min recovering time lapse was allowed for the cortex to return to its initial shape, and then the electrodes were slowly lowered. The recording depth was approximately 400–800 μm from the pial surface, which corresponds to the thalamorecipient layers (layer III/IV) of rat ACx. Tucker-Davis Technologies (Alachua, FL) neurophysiology hardware (RA16PA, RZ-2) and software (OpenEx) were used for signal filtering (0.3–5 kHz), amplification and data acquisition. Action potentials were detected on-line by threshold crossing, and waveforms were stored to hard disk. Single-unit spike activities were sorted off-line using the same principal component analysis (OpenSorter, TDT, Alachua, FL) before and after drug application.

2.4. Acoustic stimuli

Acoustic stimuli were digitally generated by custom-built programs under MATLAB (Mathworks) environment and delivered via a free-field speaker (K701; AKG). The speaker was placed at the horizontal plane 1 m from the pinna and 45° contralateral to the recording hemisphere. Frequency and intensity calibrations were done with a Bruel & Kjaer 1/2″ condenser microphone with a preamplifier 2669 situated at the rat's ear. Sound pressure level (SPL) was expressed in decibels relative to 20 μPa. A set of 125 pure-tone stimuli (ranging from 0.1 to 32 kHz in logarithmic scale) was presented at 60 dB SPL in a random sequence. The duration of each tone was 160 ms including 5 ms rise/fall time. The inter-stimulus interval randomly varied between 1 and 2 s. The total duration of one stimulus set was 3–4 min.

2.5. Drug application

We applied the drug for 5 min via a filter paper (1 × 2 mm) saturated with DEX (1 or 10 μM, Sigma, St Louis, MO, USA) or vehicle (saline), placed in close vicinity to the electrode array. DEX was freshly dissolved in saline and kept at 38 °C until application on the cortical surface. Topical application allows application of pharmacological agents on cortical areas and has been used previously in several brain regions (Caesar et al., 2003; Gaucher et al., 2013; Jones and Barth, 2002; Riquimaroux et al., 1992, 1991; Wang et al., 2009; Yu et al., 2008). Here, this technique was used because we aimed at assessing the consequences of glucocorticoid over the whole cortical area. The glucocorticoid receptor antagonist RU38486 (11β,17β-11 [4-(dimethylamino) phenyl]-17-hydroxyl-17-(1-(propynyl)-estra-4, 9-dien-3-one) (catalog #M8046, Sigma, St Louis, MO, USA) was dissolved in HCl and diluted 1:1000 with oxygenated artificial CSF to yield a final concentration of 5 μM, followed by readjustment of the pH to 7.2 with NaOH.

2.6. Experimental protocol

When the electrodes reached the target depth, and clear sound-evoked neural responses were obtained, we repeated the recording of neural activities in response to the 125 pure-tone stimuli every 10 min. Until the neural responses showed similar patterns at least in three successive recordings, we started the protocol by applying saline for 5 min. If the neural responses remained unchanged 30 min after the application of saline, we applied DEX for 5 min and then recorded the neural responses to pure-tone stimuli at 10, 20, 30, 60 and 90 min after the drug application. We also recorded 3 min of spontaneous activity after each time of stimulus presentation. In some recordings, we topically applied RU38486 for 5 min before the application of DEX to investigate whether the effect of DEX can be blocked by the glucocorticoid receptor antagonist.

2.7. Data analysis

Spike activities driven by pure-tone stimuli were aligned along the stimulus onset, constructing a raster plot of each tone frequency (Fig. 1A). The peri-stimulus time histogram (PSTH), counting the spikes across the 125 trials of different frequencies, was computed in 1-ms bin width and smoothed by Gaussian function with 5 ms SD (Fig. 1B). The spontaneous firing rate for 500 ms before stimulus onset was considered as background. The height of PSTH was transformed into the "driven rate" by subtracting the background firing rate. The analysis time window to access a stimulus-evoked response was set from stimulus onset to 50 ms after stimulus offset (210 ms duration), in order to include both onset and offset responses. Duration of the excitatory response was the summation of time bins, at which the height of PSTH was higher than the