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Sound conditioning protects hearing by activating the hypothalamic–pituitary–adrenal axis

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Sound conditioning primes the auditory system to low levels of acoustic stimuli and reduces damage caused by a subsequent acoustic trauma. This priming activates the HPA axis resulting in the elevation of plasma corticosterone with a consequent upregulation of glucocorticoid receptors (GR) in the cochlea and the paraventricular nucleus (PVN) of the hypothalamus in the mouse. This protective effect is blocked by adrenalectomy or pharmacological treatment with RU486+ metyrapone. Sound conditioning prevents GR down-regulation induced by acoustic trauma and subsequently enhances GR activity in spiral ganglion neurons. Increased SRC-1 expression, triggered by sound conditioning, positively correlates with the upregulation of GR in the cochlea. These findings will help to define the cellular mechanisms responsible for protecting the auditory system from hearing loss by sound conditioning.
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Introduction

Sound conditioning is a well-studied paradigm where prior exposure to low levels of acoustic stimuli reduces the subsequent damage to the auditory system caused by acoustic trauma (Campo et al., 1991; Canlon et al., 1988; Ryan et al., 1994; Wang and Liberman, 2002). The clinical significance of the sound conditioning paradigm has been established in young adults (Miyakita et al., 1992). In spite of sound conditioning being a documented method of protecting against hearing loss, the underlying mechanisms have not been well characterized. Several mechanisms have been suggested to play a role in auditory protection by sound conditioning including the activation of antioxidant enzymes (Harris et al., 2006; Jacono et al., 1998), inhibition of apoptosis (Niu et al., 2003), increased tyrosine hydroxylase activity in the lateral efferent system (Niu and Canlon, 2002), and glucocorticoid activation (Yoshida and Liberman, 2000).

In addition to sound conditioning, the auditory system has been shown also to be resistant to acoustic trauma when pretreated with a variety of different stressors. Pre-treatment with acute stressors such as restraint (Wang and Liberman, 2002), or heat shock (Yoshida et al., 1999) protects against subsequent acoustic trauma. These stressors are acting systemically, and protect the physiology and hair cell loss in the cochlea against subsequent trauma. Pre-treatment with restraint stress induces an elevation of plasma corticosterone that is correlated to defending the cochlea from damage (Wang and Liberman, 2002). It has recently been demonstrated that glucocorticoid-dependent transcription factors regulate the effects of restraint stress in the cochlea (Tahera et al., 2006). In addition, heat stress induces transcription of heat shock proteins that are known to regulate the activity of glucocorticoid receptors (Basu et al., 2003; Cvoro et al., 1998), one of the prime targets for glucocorticoids. In response to stress, glucocorticoids are released as the main mediator of the hypothalamic–pituitary–adrenal axis (HPA). Despite the well-documented protective effect of different stressors (i.e., restraint, heat shock, sound conditioning) against acoustic trauma, it is not known if the HPA axis modulates and protects the sensitivity of the auditory system. One factor that may be common with these different stressors that prime the auditory system is glucocorticoid receptors. Here we utilize a sound conditioning paradigm followed by acoustic trauma to determine how the HPA axis modulates glucocorticoid signaling in the cochlea to alter hearing sensitivity. To date, there is little knowledge regarding the interactions between the HPA axis and the auditory system.

Methods

Animals

A total of 100 CBA male mice (B and K, universal AB Sweden), aged 10–12 weeks (25–29 g) without any evidence of middle ear pathology were used in this study. Before the experimental start, the animals were allowed to acclimatize to

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the animal facility for at least 2 weeks after delivery. The animals were housed in groups of five animals per cage on an artificial light/dark cycle (12/12 h, lights on at 07:00 h), with free access to food and water. The cage was bedded with sawdust and contained environmental enrichment (a paper nest and shredded paper). The Ethical Committee at the Karolinska Institute approved the care and use of animals in this experiment.

Experimental design

The animals were divided into seven groups: (1) an unexposed control group that received a vehicle injection (Control), (2) vehicle and acoustic trauma (Trauma), (3) vehicle+sound conditioning (SC) followed by acoustic trauma (SC+Trauma), (4) RU486 and metyrapone (MET) followed by SC and acoustic trauma; (RU486+MET+SC+Trauma), (5) sham operated followed by sound conditioning and acoustic trauma (Sham+SC+Trauma), (6) adrenalectomy followed by sound conditioning and acoustic trauma (AdX+SC+Trauma), and (7) adrenalectomy with supplemented corticosterone (CORT) followed by sound conditioning and acoustic trauma (AdX+CORT+SC+Trauma). Baseline hearing was determined by auditory brainstem response (ABR) measurements prior to any treatment. The experimental design is summarized showing treatment and the temporal aspects for the different groups (Fig. 1).

Interruption of HPA axis by adrenalectomy or pharmacological manipulations

To remove the source of corticosterone (CORT) synthesis, adrenalectomy was done under ketamine (50 mg/kg) and xylazine (10 mg/kg) anesthesia 1 week prior to the start of the experiment. Drinking water was replaced with 0.9% NaCl. Corticosterone (Sigma, St. Louis, MO) supplement was given by 7 daily injections at a dose of 20 mg/kg.

Animals were given the glucocorticoid synthesis inhibitor metyrapone (2-methyl-1, 2-di-3-pyridyl-1-propanone) (Sigma, St. Louis, MO), dissolved in de-ionized water (200 mg/kg, intraperitoneally), and the glucocorticoid receptor antagonist RU486 (Roussel Uclaf, Romainville, France) dissolved in vegetable oil (100 mg/kg, subcutaneously). Vehicle treatment consisted of two injections; de-ionized water injected intraperitoneally, simulating metyrapone injection, and vegetable oil injected subcutaneously, simulating the RU486 injection. All injections were given in a constant volume of 0.1 ml each. After 1.5 h animals were placed in a sound-proof box with or without sound conditioning for 15 min.

Sound conditioning

Unanesthetized animals were placed into wire mesh cages (one animal per cage) in a sound proof box and exposed to a sound conditioning stimulus (8–16 kHz, 89 dB, 15 min). The vehicle only group was treated in exactly the same manner (i.e., in a cage and then in the sound proof box) but without sound conditioning. The sound conditioning itself does not cause any change to auditory thresholds at any frequency (data not shown).

Acoustic trauma protocol

Twenty-four hours after sound conditioning, animals were exposed to acoustic trauma by being individually placed into a small wire mesh cage (10 cm^3) that was then placed inside an open field acoustic chamber (225×120×100 cm). During the exposure the animals did not have any access to food or water. Free field broad-band noise (8–16 kHz, 100 dB SPL, 2 h) was produced by a noise generator (Hewlett Packard, 33120 A), and delivered by 4 Lansing speakers that was placed in the upper corners of the acoustic chamber. Calibration of the sound-exposure levels was performed with a 12.5 mm condenser microphone (Bruel and Kjaer model 2213) within the region of the wire mesh cages.

Corticosterone and ACTH analysis

Animals were sacrificed and blood was collected in the same time of day to avoid circadian variation. Plasma was separated by centrifuging at 6000 rpm at room temperature and immediately stored at −20°C until the corticosterone assay was performed. All samples were taken at the same time of day to minimize the circadian variation (between the hours of 11:00 and 12:00). The plasma corticosterone concentrations were determined by ELISA (Assay Designs Correlate-EIA™, Assay Designs, Inc., Ann Arbor, MI) with a sensitivity of 5 pg/ml. The plasma ACTH concentrations were determine by ELISA (MD Biosciences, catalogue ACTH.96, Zurich, Switzerland) with a sensitivity of 0.46 pg/ml.

Auditory brainstem response (ABR)

Auditory sensitivity was assessed with ABR thresholds for the frequency of 8, 12.5, 16 and 20 kHz after being anesthetized with an intraperitoneal injection of ketamine (50 mg/kg) and xylazine (10 mg/kg). The body temperature of the animals was maintained at 38°C using light heating and cotton coverings. ABR thresholds were recorded with subcutaneously stainless steel electrodes as the potential difference between an electrode on the vertex and an electrode on the mastoid, while the lower back served as ground, as

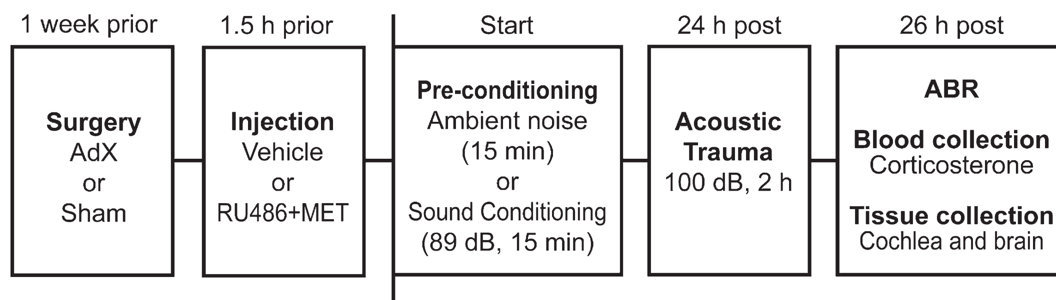

Fig. 1. Schematic diagram indicating the experimental paradigm. AdX— adrenalectomy, ABR—auditory brain stem response.

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