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Effect of prenatal chronic excessive sound exposure on auditory filial imprinting area of chick forebrain

*Alpana G. Kesar**

Department of Anatomy, All India Institute of Medical Sciences, Delhi, India

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ABSTRACT

Aim: Noise acts as an environmental stressor and can lead to neurodegenerative changes in the brain and in the ear. The present study was undertaken to investigate the effect of chronic noise on growth and development of nervous system during the sensitive period of embryonic life. In this study, we determined the neuronal nuclear diameter and density of neurons in MNH region (a higher auditory association area in chick forebrain) along with the body weight and brain weight following prenatal chronic noise exposure.

Method: Fertilized eggs of domestic chicks were exposed to chronic excessive acoustic stimulation with frequency of the sound ranging from 30 to 3000 Hz with peak at 2700 Hz was given at 110 dB sound pressure level from embryonic day (E) 10 until hatching.

Results: An appreciable decrease in the neuronal nuclear diameter in MNH region was evident in the experimental group exposed to chronic excessive acoustic stimulation. Almost a two-fold increase in the density of neurons was observed compared to the control group. The brain weight was significantly less in the experimental group.

Conclusion: Functional development in brain causes neuronal number to decrease and size of neurons to increase. In the present study, a reduction in the size of neuronal nuclear diameter and increase in neuronal density in each frame could be an indicator of growth and developmental retardation, following foetal exposure to chronic noise.

1. Introduction

Hearing begins early in embryonic life. Acoustic stimuli between 36 and 40 weeks gestational age elicited a foetal response to the external auditory stimulation, in a magnetoencephalographic (MEG) study.[1]

In birds, responses to airborne sound were compared with responses to direct columella footplate stimulation of the cochlea. Cochlear ganglion neurons exhibited a profound insensitivity to airborne sound from E12 to E16 (stages 39–42) though they responded to direct stimulation through footplate. Responses to sound and frequency selectivity emerged at about E15. Frequency selectivity matured rapidly from E16 to E18 (stages 42 and 44). Thus, two periods of ontogeny have been proposed. First is a pre-hearing period (E12–E16) of endogenous cochlear signalling that provides neurotrophic support and guides normal developmental refinements in central binaural processing pathways followed by a period (E16–E19) wherein the cochlea begins to detect and encode airborne sound.[2]

* Department of Anatomy, PDM Dental College, Bahadurgarh, Haryana, India. Tel.: +91 9811809560.
E-mail address: alpanakesar@rediffmail.com.

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Studies show that the prenatal exposure to sound can mould the learning process. Exposure to ambient environmental sounds like voice of mother and soothing music has a positive effect on growth and development in premature human neonates.[3] Prenatal exposure to music induced a rapid advance in motor ability such as sitting and standing in human neonates.[4]

Morphological studies carried out to assess changes in the structure of auditory nuclei in brainstem and forebrain, show that prenatal exposure to ambient sounds like species specific and music leads to increase in the size of neuronal nuclei. Significant increase in volume of second and third order brainstem auditory nuclei – n. magnocellularis (NM) and n. laminaris (NL) attributable to increase in length of nucleus, number and size of neurons, number of glia as well as neuropil was observed in response to both species specific and music sound over-stimulation given during the critical period of development.[5] Exposure to 65 dB of comfortable music in rats for 1 h once a day starting from 15th day of pregnancy until the delivery, caused increased neurogenesis in the hippocampus in CA1, CA2, CA3 regions as seen by BrdU immunochemistry and enhanced spatial learning ability tested in radial arm maze test in pups on day 21 after birth.[6]

There is a growing concern over the hazardous effects of noise pollution in the modern society and both physiological as well as morphological studies have been conducted to study the effect of acoustic trauma. Exposure to loud noise leads to an acoustic traumatisation with a temporary threshold shift initially and, with increasing exposure, intensity and duration, a permanent hearing loss. Chronic traffic noise (cars, trains, air planes) is usually not threatening to the ear, but it may represent a considerable subjective annoyance and a stress factor leading to psychosomatic disturbances, neuro-vegetative symptoms and sleeping disorders.[7] Noise could impair the micromechanics of the outer hair cells in the lateral wall and might consequently impair the electro-motility to induce threshold shift.[8] A1 organization is shaped by a young animal's exposure to salient, structured acoustic inputs and implicates noise as a risk factor for abnormal child development.[9] Cell density was significantly reduced in all subdivisions of the MGB and in layers IV–VI of AI in mice after exposure to noise.[10]

Exposure of the chick cochlea to intense acoustic overstimulation led to rapid changes in the structural organization of hair cells and supporting cells in chick basilar papilla (Cotanche et al, 1991)[11] and loss of hair cells and damage along the cochlear basilar membrane.[12] Reduction in the volume of the anteroventral cochlear nucleus (AVCN) (Aarnisalo, 2000)[13]; decrease in neuronal cell area in nucleus magnocellularis (Saunders et al 1998)[14] and change in the tonotopic organization of the nucleus magnocellularis (NM) (Cohen, 1994)[15] have been observed in the chick following exposure to noise.

Most studies on noise exposure have been conducted on adult and neonatal animals. The few studies in prenatal period have examined the cochlea, brainstem, thalamic nuclei and cortex of the auditory pathway. The higher auditory areas have not been studied. The higher auditory association area in chick forebrain, i.e. medio-rostral neostriatum/hyperstriatum ventrale region (MNH), is involved in juvenile auditory filial imprinting. This region of the forebrain medio-rostral

Fig. 1 – Egg Incubator.

neostriatum/hyperstriatum ventrale (MNH), includes the medial portion of the neostriatum (now termed nidopallium) adjoining the lateral ventricle located dorsal to ventral pallial lamina (vpl) and the adjoining part of hyperstriatum ventrale (currently called mesopallium) which lies ventral to vpl in the rostral forebrain.[16]

The studies on separation paradigm (Muller and Scheich, 1986)[17] showed that playback of auditory imprinting stimulus produces higher activation of MNH as compared to normal, and chicks imprinted on rhythmic tones with electrolytic lesion of MNH had difficulties in deciding towards which loud speaker to head (Weiberg, 1986),[18] thereby confirming that the MNH area in the rostral forebrain is involved in auditory imprinting.

The MNH receives its main sub-telencephalic afferents from the dorsal thalamic nuclei, n. dorso-medialis anterior, n. dorso-medialis posterior and n. dorso-lateralis anterior (Wallhausser-Franke, 1987[19]; Heil and Scheich, 1991[20]; Metzger et al, 1996[21]) and has reciprocal intra-telencephalic connections with the neostriatum dorso-caudale (Ndc).[22]

In earlier experiments conducted in our laboratory, the MNH region of chick forebrain was studied, following prenatal sound stimulation given to chick embryos by species specific and music sounds (sitar). The sound stimulation protocol was found to cause an appreciable increase in the neuronal nuclear area.[23] However, there are no studies on the MNH region following prenatal chronic excessive sound stimulation.

Hence, in the present study we have attempted to investigate the effect of prenatal chronic excessive sound stimulation on the morphology of neurons in MNH, involved in auditory filial imprinting. Density of neurons was also evaluated along with the body weight and brain weight of chicks exposed to noise during the developing period.

2. Materials and methods

The number of animals used and procedures to minimize the suffering of the animals are in accordance with the ethics committee on animal experiments of All India Institute of Medical Sciences, Delhi.

2.1. Incubation conditions

Fertilized eggs of White Leghorn chickens (*Gallus domesticus*), weighing between 50 and 60 g, were obtained from a registered poultry farm. The eggs were incubated in a specially designed, double-walled, insulated, sound proof incubator (Widson Scientific Works Ltd.) (Fig. 1). Incubation conditions were maintained at 70–80% humidity and temperature of 37 °C (36–38 °C). The eggs were tilted four times a day and exposed to a photo-period of 12-h light and 12-h dark cycle, controlled by automatic timer devices. Aeration was provided with a force draft of air.

A background sound of 40 dB, emanating from the motor two to three times in an hour, will be audible to all the groups and cannot be eliminated.

2.2. Experimental groups

2.2.1. Control (Group I)

The incubating eggs which served as control received no additional auditory stimulus.

2.2.2. Experimental (Group II)

The incubating eggs were exposed to chronic excessive acoustic stimulation (unpatterned sound as noise) from E10 till the day of hatching.

2.3. Auditory stimulation protocol

The auditory stimuli were given for 15 min per hour, over the period of 24 h, beginning from day 10 and continued till the day of hatching. This was achieved through two built in speakers connected to a stereo sound system provided with automatic setting with an electronic timer device.

To ensure that the embryos receive the auditory stimuli, a portion of the shell of approximately 3 mm size over the air sac will be removed on day 9.5 of incubation, maintaining the membranes intact.

2.4. Auditory stimuli characteristics

The recorded cassettes were pre-screened with sound analyser at the National Physical Laboratories (CSIR, New Delhi) to determine the frequency range and modulation. An AD-3521 FFT analyser was used to visualize sound wave pattern and measure the frequency at every point of the wave pattern with the aid of a stylus (Fig. 2). The frequency of the sound ranging from 30 to 3000 Hz with peak at 2700 Hz was given at 110 dB sound pressure level.

2.5. Tissue collection

Chicks from the control and the experimental group were collected on the day of hatching (referred to as post-hatch day 1). The chicks after ether anaesthesia were weighed. They were decapitated and the brain along with the brainstem was removed from the skull by severing all the cranial nerves and vessels at the base. The whole brain was weighed (Table 1).

2.6. Tissue processing

Immediately after the tissue was obtained, it was immersion fixed in 4% paraformaldehyde at 4 °C for 2 weeks. The forebrains were dehydrated, infiltrated and the blocks were prepared by embedding in paraplast. Serial coronal sections of 7 μm thickness were cut with a rotary microtome. Starting from a distance of 1 mm from the rostral end of the forebrain, 150 serial coronal sections, covering the MNH region were taken. The sections were mounted on egg albumin coated glass slides and subsequently stained for Nissl substance with 1% buffered thionin.

2.7. Quantification

The thionin stained serial sections from five forebrains each of the control and the experimental groups were quantitatively

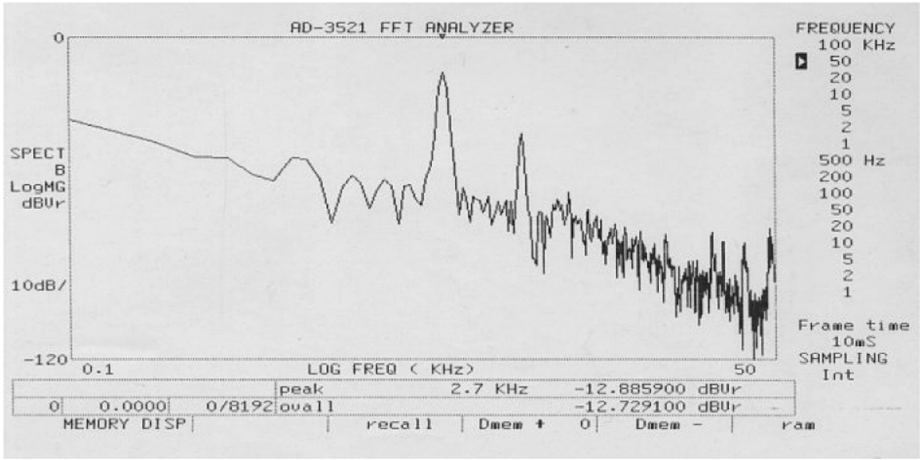

Fig. 2 – Curve showing the frequency distribution of 110 dB sound.

Table 1 – Body and brain weight of chicks.

Variable	Median (min–max)		
	Control	Experimental	*p*-value
Body weight (in grams)	38.76 (32.32–46.11)	34.43 (30.72–35.96)	0.047
Brain weight (in grams)	0.88 (0.85–0.94)	0.80 (0.77–0.85)	0.011

Two-sample Wilcoxon rank-sum (Mann–Whitney) test for body and brain weight.

evaluated. For estimation of neuronal nuclear size, every 15th section in the series was considered. Thus, ten sections from each of the 10 forebrains were used for quantification. In every section, on either side of ventral pallial lamina (vpl), beginning 100 μm lateral to the ventricular ependyma, four frames of standard area (21702 μm^2) were selected in a uniform systematic manner, to cover the region of MNH.

Neurons selected for measurement within the standard frame were those having clear identifiable nuclear and cytoplasmic borders, Nissl substance and prominent nucleolus. The nuclear area of MNH neurons was determined on both sides of each sample, using an image analysing system Leica Q500MC (Fig. 3).

The measurements were made under a 100× objective lens such that pixel size was 0.51 μm. A total of 50 MNH neurons on each side of the section were sampled. Hence, 100 neurons in each of the 10 sections of 5 forebrains amounting to 5000 neurons in each group-control and experimental were measured.

2.8. *Data analysis*

Wilcoxon rank-sum (Mann–Whitney) test was applied to compare the body and brain weight of the control with experimental chicks. To test the statistical significance of change in the neuronal nuclear area of MNH neurons of right and left sides of the control and experimental groups the 2-tailed paired *t*-test was used. Further statistical analysis on the pooled data to assess the difference, if any, in the two groups studied – normal and experimental was done using *t*-test. Frequency distribution was analysed using Fisher's exact test.

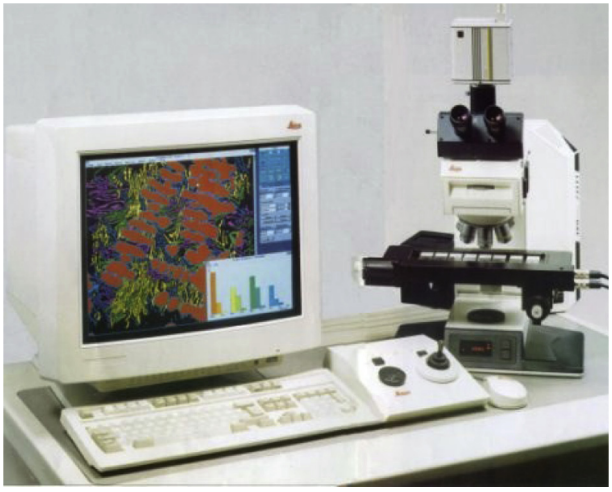

Fig. 3 – Image analysis system showing the microscope, CCD camera and computer components with the image analysis software.

3. Results

3.1. *Egg weight, embryo weight, brain weight*

The weight of the eggs was almost the same for control and experimental groups ranging between 50 and 60 g. The body weight was reduced in the experimental group but was not significantly less than the control group. However, the brain weight was significantly less in the experimental group compared to the control group (Table 1).

3.2. *Location, extent and cell type of MNH neurons*

The auditory imprinting area in the chicks is the MNH region which includes the medial portion of the neostriatum/nidopallium and adjacent part of the hyperstriatum ventrale/mesopallium on either sides of ventral pallial lamina adjoining the lateral ventricle in the rostral forebrain (Fig. 4).

In the Nissl stained coronal sections of the chick forebrain at post-hatch day 1, the MNH region extended over 150 sections. The neurons of the MNH region had round to ovoid soma with a centrally or eccentrically placed nucleus with one or two nucleoli (Fig. 5). The nuclear area of the neurons in the region varied between 10 and 50 μm^2 and the diameter between 3.5 and 8.5 μm. These neurons have been shown to vary from small type III with short bushy dendrites and medium type II with 4–6 stem dendrites to large type I with 6–12 stem dendrites.[24]

3.3. *Density of neurons*

In the experimental group exposed to chronic excessive acoustic stimulation, almost a two-fold increase in the density of neurons was observed in all the four frames of standard area (21702 μm^2) that were selected in a uniform systematic manner, to cover the region of MNH (Fig. 5).

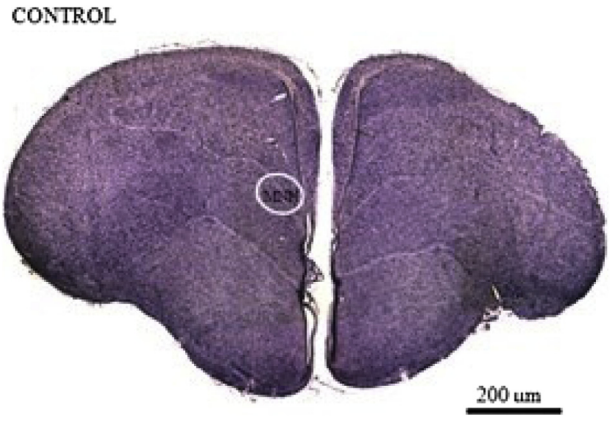

Fig. 4 – Coronal section of forebrain from post-hatch day 1 chick of the control group.

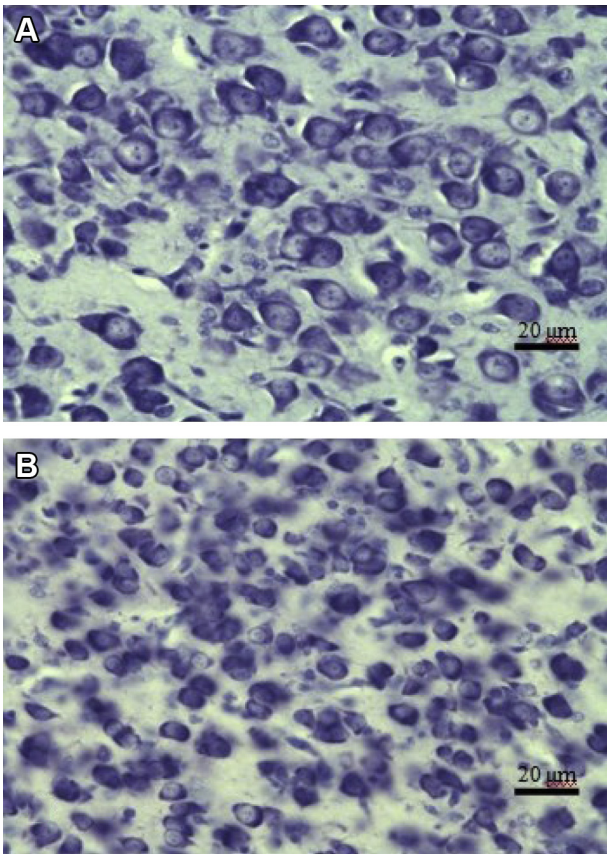

Fig. 5 – Neurons in MNH region of chick in the control group (A) and the experimental group (B). Compare the diameter and density of the neurons in the two groups. Scale Bar = 20 μm.

3.4. *Nuclear diameter and area of neurons in the control and experimental groups*

An appreciable decrease in the neuronal diameter was evident in the experimental group exposed to chronic excessive acoustic stimulation as compared to the control (Fig. 5).

The nuclear diameter and area of neurons determined on the left and right sides in the control and the experimental groups were not significantly different ($p > 0.05$), as analysed by the 2-tailed paired *t*-test. This indicated that there was no difference in these parameters on the two sides of the brain. Hence, the data of the two sides – left and right for nuclear diameter and area studied in the MNH region of each group, was pooled.

The mean neuronal nuclear diameter in μm ± S.D. for control and experimental groups was 6.50 ± 0.71 and 4.84 ± 0.54 respectively. The mean neuronal nuclear area in μm^2 ± S.D. for control and experimental groups was 32.57 ± 6.27 and 18.96 ± 4.24 respectively. Comparison of the experimental group exposed to chronic excessive sound stimulation with the control showed a significant decrease in the neuronal nuclear diameter and area (*t*-test; $p < 0.001$) (Table 2).

In the control group, 386 neurons had nuclear diameter between 3.5 and 5.5 μm, 4169 neurons between 5.5 and 7.5 μm and 445 neurons within the range of 7.5–8.5 μm. On the other hand, in the experimental group 4434 neurons had nuclear diameter between 3.5 and 5.5 μm, 566 neurons between 5.5 and 7.5 μm and 0 neurons within the range of 7.5–8.5 μm (Table 3, Fig. 6). In the control group, 589 neurons had nuclear area between 10 and 25 μm^2, 3740 neurons between 25 and 40 μm^2 and 671 neurons were between 40 and 50 μm^2. On the other hand, in the experimental group 4579 neurons had nuclear area between 10 and 25 μm^2, 419 neurons between 25 and 40 μm^2 and 2 neurons were between 40 and 50 μm^2 (Table 4, Fig. 7).

Table 2 – Neuronal nuclear diameter and area of control with experimental.

Groups ($n = 5000$)	Mean neuronal nuclear diameter (in μm ± S.D.)	Mean neuronal nuclear area (in μm^2 ± S.D.)
Control	6.50 ± 0.71	32.57 ± 6.27
Experimental	4.84 ± 0.54	18.96 ± 4.24

Two-sample *t*-test with equal variances for area and diameter.

4. Discussion

The present study was undertaken to investigate the effects of prenatal chronic excessive sound exposure on the MNH region of chick forebrain. This region is the auditory imprinting area that includes the medial portion of the neostriatum/nidopallium adjoining the lateral ventricle located dorsal to ventral pallial lamina (vpl) and the adjoining part of hyperstriatum ventrale/mesopallium which lies ventral to vpl in the rostral forebrain.

The auditory stimuli in the present study were given at 110 dB sound pressure level with the frequency of the sound ranging from 30 to 3000 Hz with peak at 2700 Hz. This is the level of sound encountered in many industrial work places, busy traffic intersection and discos. These unpatterned sounds are considered as noise. Hence the sound delivered to the chick embryos in the present study amounted to noise.

The noise stimulus in the present study was given for 15 min per hour, over the period of 24 h, beginning from day 10 and continued till the day of hatching. This auditory stimulation protocol was based on the knowledge that in the basilar cochlear papillae of chick (*G. domesticus*), afferent synapses appear on the hair cells by about embryonic day E8.[25] It is also

Table 3 – Distribution of neurons based on nuclear diameter.

Groups	Neuronal nuclear diameter (μm) $N = 5000$		
	3.3–5.5	5.5–7.5	7.5–8.5
Control	386	4169	445
	7.72%	83.38%	8.90%
Experimental	4434	566	0
	88.68%	11.32%	0%

Fisher's exact test $p < 0.001$.

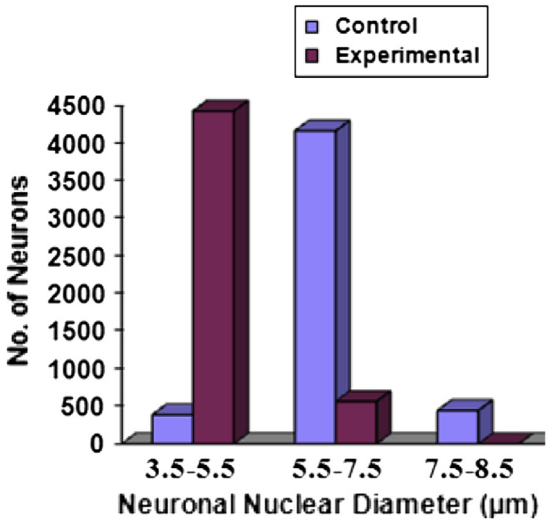

Fig. 6 – Distribution of neurons based on nuclear diameter.

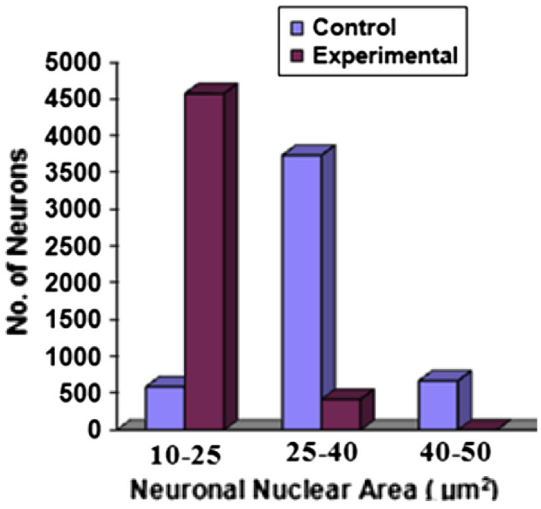

Fig. 7 – Distribution of neurons based on nuclear area.

known that the cochlear nucleus of the chick responds to electrical stimulation from day E11 of incubation.[26] Thus the auditory apparatus and the pathway are functional early in development and hence the initiation of the present protocol by E10.

In the present study, the chronic excessive sound stimulation [at 110 dB and high frequency of 2700 Hz (30–3000 Hz)] was given throughout the period of embryonic development. It has been demonstrated that during normal development the auditory evoked responses in the chick mature in a systematic pattern, by responding first to low frequency sounds prior to hatching and high frequency sounds after hatching.[26] Thus in the present study, as opposed to developmental norms, the embryos have been subjected to high frequency sound throughout their embryonic period.

Following the prenatal sound exposure, a significant decrease was observed in the nuclear diameter and area of the neurons in the MNH region, which is the higher auditory association area in the chick forebrain. Saunders et al (1998)[14] reported a reduction in neuronal nuclear area in the brainstem auditory nuclei of the chick following acoustic over-stimulation given to neonatal chicks. From the present study, it is evident that chronic noise given in the prenatal period also influences the higher regions of the auditory pathway in the chick.

The shrinkage in cell size throughout the MNH area may be due to a reduction in spontaneous activity in the cochlear nerve fibres caused by the acoustic injury to the chick basilar papilla and its subsequent effects on the auditory pathway. As demonstrated by Cousillas and Rebillard (1988)[27], and Rubel and Ryals (1993)[12], in the adult and neonatal chick, exposure to intense noise is known to cause damage to the hair cells of the basilar papillae. The status of the hair cells of the basilar papillae after prenatal chronic excessive sound exposure, however, still needs to be determined.

The reduction in cell size could also be attributed to developmental retardation caused by stress due to chronic excessive sound exposure during the sensitive and critical phase of foetal development.

In the adult brain, stress related neuronal changes such as suppressed neurogenesis of dentate gyrus granule neurons and atrophy of dendrites in the CA3 region of hippocampus (McEwen and Magarinos, 2000)[28] as well as spine synapse loss in the neurons in medial prefrontal cortex (Cook and Wellman, 2004)[29] have been demonstrated. Prenatal stress administered by restraining pregnant rats in a small cage for 240 min daily for three days (gestational day 15–17) results in enhanced corticotropin-releasing factor (CRF) messenger RNA expression and a significant decrease in the size of neuronal processes of the hypothalamic paraventricular nucleus in the 18 day old rat foetus.[30]

Thus stress as indicated by increase in mRNA and plasma levels of stress hormones can cause decremental changes in the central nervous system.

Noise too acts as an environmental stressor as has been demonstrated by increased brain acetylcholinesterase activity as well as elevated plasma corticosterone and ACTH levels in healthy adult rats, following acute and chronic exposure to noise of 100 dB sound pressure level.[31–33]

Following prenatal exposure to chronic excessive sound, the post-hatch day one chicks also showed a decrease in the brain weight. A similar growth retardation in pups indicated by decreased body weight was observed by Kim et al (2006)[6] following prenatal exposure to noise of 95 dB from supersonic sound machine for 1 h once a day starting from 15th day of pregnancy in rats until the delivery. In their study on the rats, Kim and his colleagues (2006)[6] also demonstrated

Table 4 – Distribution of neurons based on nuclear area.

Groups	Neuronal nuclear area (μm^2) N = 5000		
	10–25	25–40	40–50
Control	589	3740	671
	11.78%	74.80%	13.42%
Experimental	4579	419	2
	91.58%	8.38%	0.04%

Fisher's exact test $p < 0.001$.

decreased neurogenesis in the CA1 region of hippocampus by BrdU immunochemistry, as well as impaired spatial learning ability in the pups assessed by radial arm maze test.

In additional to the observation of decrease in brain size and weight in the present study, we have interestingly noted an apparent increase in the neuronal density throughout the MNH region. This apparent increase in the neuronal density needs to be quantitatively assessed. It would indeed be also essential to determine the total neuron number in order to be definitive whether there is an increase or decrease in total neuronal population of the MNH after prenatal chronic excessive sound exposure. However, since the extent of MNH area is not definable, it may be difficult to ascertain the total neuronal count of MNH.

The functional development in normal brain causes neuronal number to decrease and size of neurons to increase. Nevertheless, in the present study a reduction in the size of neurons and increase in neuronal density, could be an indicator of developmental retardation as well as positive growth due to developmental plasticity, following foetal exposure to chronic noise.

A study by Hardie and Shepherd (1999)[34] conducted on neonatally, bilaterally, deafened adult cats, demonstrated a decrease in spiral ganglion cell density to 17% of normal, and a 37% increase in the neuronal density in the anteroventral cochlear nucleus.

The present study was undertaken in continuity to the study of Panicker et al (2002)[23] in our laboratory, in which a significant increase in neuronal nuclear area in MNH region was observed following auditory stimulation by species specific sound and music. Hence, while the ambient patterned environmental sounds during prenatal period resulted in an increase of neuronal nuclear area in MNH region in the neonates, on the other hand, exposure to prenatal noise caused a significant decrease.

The findings of the present study indicate that the neurons of the higher auditory association area of chick forebrain, MNH are susceptible to alterations in response to the sensory experience during the prenatal period. Thus while the enriched environment augments the growth of neurons, the noise related stress can retard growth and development, indicating that this issue has considerable theoretical and clinical significance.

Conflicts of interest

The author has none to declare.

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