

ANALGESIC EFFECT OF ENVIRONMENTAL NOISE : A POSSIBLE STRESS RESPONSE IN RATS

N. SHANKAR,* N. AWASTHY, H. MAGO
AND O. P. TANDON

*Department of Physiology,
University College of Medical Sciences & GTB Hospital,
Dilshad Garden, Delhi - 110 095*

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Abstract : Environmental noise is a known stress, which induces alterations of various physiological responses in individuals exposed to it. Stress has been shown to cause changes in the perception of various sensations including pain and stress-induced analgesia has been observed following exposure to a diverse set of stimuli. To examine the analgesic behavior of rats exposed to loud environmental noise, for long duration, we used an environment simulating chamber and conducted the tail flick test for the assessment of pain. The rats were divided into groups and subjected to loud noise for test sessions lasting 1 h, 2 h or 3 h in trials of 5 consecutive days. The noise was of two kinds - a continuous shrill noise (pure tone 92 dB & 98 dB) and an intermittent heavy artillery noise (white noise 102 dB). 15 min before and after each test session, tail flick latencies (TFL) were recorded at 5 min interval. The TFL recorded were normalised to an Index of Analgesia (IA) and the readings statistically analyzed using the F test (ANOVA), the significance being obtained by Tukey's test (at 5% level). The results revealed a significant increase in the TFL and the IA ($P < 0.0001$) in all the test groups demonstrating a significant analgesic response in rats subjected to noise stress. The analgesia was maximum immediately after noise exposure and declined with time. It was found to be directly related to the duration of exposure, the intensity and the characteristics of the noise with loud intermittent (white) noise and longer duration of exposure producing more analgesia.

Key words : environmental noise stress-induced analgesia
tail flick latency

INTRODUCTION

Over the past three decades it has been convincingly established that brain contains circuitry for the inhibition of painful sensation which can be activated by electrical (1, 2) or chemical stimulation (3)

as well as by environmental changes (4, 5). The presence of noxious or otherwise aversive stimuli in an animal's environment results in a series of stimulus-relevant behavior and physiological responses with abundant evidence to suggest that environmental stress powerfully activates

*Corresponding Author

these analgesia systems, a phenomenon commonly referred to as 'stress-induced analgesia' (SIA) (6-8). This has been demonstrated in many species, and may be elicited by a wide range of stressors. In humans, conditions of war, emergency situations requiring flight, accidents and similar stressful conditions have been known to produce SIA. Analgesia after exposure to a variety of aversive events is well known in animals. The cold water swim is a commonly used stressor in studies of SIA (9, 10). Conversely, Christee et al (11) found that exposing mice to a 3 min swim in 32°C, a warm water swim, significantly increased TFLs for upto 4 min following the termination of the swim. Inescapable foot shock, immobilisation, exposure to extremes of temperature, exposure to predators and vaginal stimulation in females, also induced analgesia in rats (12-15). A variety of research protocols have indicated multiple analgesia systems with overlapping components and pathways. As with stimulation - produced - analgesia, both opioid and non-opioid forms of SIA exist (16-17).

Noise, which is an unwanted, untimely, and unpleasant sound, is an environmental pollutant and biological stressor that causes both auditory and extra-auditory effect on the body over a period of time (18-20). An important extra-auditory effect is an elevation of blood pressure. In humans, several studies have shown that acute stimulation by noise leads primarily to a diastolic blood pressure elevation caused by increased peripheral resistance. The basis of the proposed relationship between noise and hypertension is grounded in the 'stress response' resulting in the release of several

chemical substances in the body such as catecholamines and corticosteroids (21). Prolonged exposure to loud noise in everyday life leads to a sustained activation of the autonomic nervous system and the pituitary adrenal axis with many far reaching ill effects on the wellbeing of the individual exposed to it (22). Similar studies in rats have shown that noise alone can produce blood pressure elevation and accelerates the development of permanent hypertension thereby indicating the potentiality of noise as a biological stressor. Deaf rats do not respond, indicating that the blood pressure response is truly auditory, involving auditory pathways and their interaction with other pathways in the brain stem (23).

Since stress alters perception of pain and noise is a well known stressor, independent groups of rats were exposed to brief auditory stimuli at different intensities and their analgesic response studied. In 1974, Davis (24) produced in rats a state of behavioral sensitization or non-associative fear similar to that produced by foot shock by exposing them to 80 dB white noise for a few minutes. Other workers also observed similar aversive or stress related behavioral response on exposure of rats to auditory stimuli of intensities generally not considered noxious or painful (25, 26). Later, Cranney (27) showed that exposing rats to a series of short duration 110 dB noise bursts was sufficient to produce a form of analgesia similar to that seen after exposure to shock. Single 60 s presentation of white noise resulted in a time dependent elevation of radiant heat tail flick latency that varied as a function of stimulus intensity and the noise stress analgesia in response to the 90

dB stimulus was blocked by pretreatment with opioid antagonist naltrexone (28). In view of these findings the aim of the present study was to re-examine the stressor potentiality of noise by giving the rats a longer exposure in the controlled environment of the ESC and to study not only the effects of noise intensity and duration but also the effect of the characteristics of the noise on the analgesic response.

METHOD

Animals: The study was conducted in 40 male Wistar rats (bw 150 - 200 g). During the course of the study the animals were housed in pairs in the animal house with food and water ad libitum and kept under standard environmental conditions for light (12: 12 h light: dark cycle) temperature (27°C) and noise levels (40-45 dB (A)). On the days of the test the rats were brought to the laboratory and placed in an Environment Simulating Chamber (ESC).

Environment Simulating Chamber: This is a perspex box of the dimensions of 48"x 48"x 36", so constructed to enable various environmental conditions to be simulated, while maintaining the other environmental conditions at standard levels. The chamber has the provision for altering & maintaining the inside temperature at the desired level (via a temperature regulating device and fan), composition of the air (via an inlet tube for gases), and level of illumination in the chamber (via a light source). During this study, the environment inside the chamber was maintained at standard levels for light (daylight), atmospheric pressure, temperature (between

26-27°C) and composition of air as exists normally in an experimental laboratory, the only variable that was altered was the intensity of noise (dB level).

Noise: In the ESC, using an audio device, Sony FH7 MKII Compact Hi-Density Component System with 280 watts output and an audio recording, the rats were subjected to the following 3 types of noise.

Pure tone 1 KHz 92 dB,

Pure tone 2 KHz 98 dB and

White noise 102 dB.

Both pure tones were shrill and continuous noise. The white noise used was intermittent (artillery) noise. The intensity of noise was measured using a hand held Sound Level Meter (SLM) B&K 2209, Bruel and Kjaer, Copenhagen with a 1/3 octave filter set Type 1616, a built in microphone and a linear display of noise intensity in decibels. It was held about 36 inches from the audio device, the same distance as that between the test rats and the audio device. The duration of noise exposure of various groups was 1 h, 2 h or 3 h respectively in each test session for a trial of 5 consecutive days.

Tail Flick Latency: The perception of pain was assessed using the tail flick latency (TFL) test in which changes in the latency of the tail flick escape from noxious heating of the tail skin was used to determine the analgesic response. The device used for this was the Ephaptex Heater Timer Unit. The TFL recording procedure has been described by us earlier (29). Briefly, the rat was placed in a clear plastic rat holder from which the

tail protruded. A part of the tail, between 4 and 6 cm from the tip, was placed onto a nichrome wire at room temperature. A calibrated current was passed through the coil so as to raise its temperature and cause normal rats to flick the tail away from the source of heat between 2.5 - 4 sec. If no response occurred, the current was automatically cut off after 10 sec and the tail removed from the coil to prevent tissue damage. Scores were normalized according to the following formula:

$$\text{Index of Analgesia (IA)} = \frac{\text{TFL} - \text{baseline TFL}}{10 - \text{baseline TFL}}$$

where baseline TFL was the average of three readings taken at 5 min interval before putting the rat in the ESC, while TFL was the latency recorded following the exposure to ESC and ESC + noise (depending on the group) at 0 min, 5 min, 10 min and 15 min duration. 10 represents the cut off time of 10 sec. The readings were taken on all 5 days of the trial and pooled independently, to give the average value for each rat, for each time interval.

Groups: The rats were divided into control and test rats as follows (n = 10 in each group). Each group was subjected to 3 trials in the ESC with a minimum rest period of 21 days in between each trial.

Group I: Control rats not exposed to any noise but the standard conditions of ESC for 3 trials of 1 h, 2 h and 3 h duration per test session.

Group II: Test rats exposed to noise for 1 h per test session.

Group III: Test rats exposed to noise for 2 h per test session.

Group IV: Test rats exposed to noise for 3 h per test session.

Since each test group was exposed to all 3 intensities of noise during the course of the 3 trials the groups were further designated as:-

Groups IIa, IIIa, IVa: when rats exposed to 92 dB noise.

Groups IIb, IIIb, IVb: when rats exposed to 98 dB noise.

Groups IIc, IIIc, IVc: When rats exposed to 102 dB noise.

Therefore, in the grouping, the numerals II, III & IV represent the duration of noise exposure (in hours) while the alphabets a, b & c represent the intensity of noise (in dB).

Statistical analysis: Graphs were prepared of mean IA values against time, for all groups of animals, and the mean area under the curve was calculated. The data were statistically analyzed using the F test (ANOVA) for the control and the three test groups, (1 h, 2 h & 3 h noise exposure), for 92 dB, 98 dB and 102 dB, and the significance obtained by Tukeys' test at 5% level of significance. Similarly, the significance was also tested for the three noise levels (92 dB, 98 dB and 102 dB) for the three time duration.

RESULTS

In the control rats, the TFLs recorded after the exposure to the ESC (without the noise) did not differ significantly from the average pre-exposure baseline TFLs in all

3 trials ranging from 1 h - 3 h duration per test session. The data was hence pooled and the IA and mean area under the curve calculated to give the common control values. This finding indicates that the exposure to the ESC alone does not have any significant analgesic effect.

The test groups, however, show an analgesic response to noise, as evidenced by an increase in TFLs, from the baseline values and as compared to the control values. On calculation, the IA and the mean area under the curve was found to be

significantly increased ($P < 0.0001$). (Table I). As depicted by Fig 1 there was a significant increase ($P < 0.0001$) in the analgesic response, denoted by the mean area under the curve, with the increase in time duration of noise exposure in all the test groups, except for 102 dB in which the difference in analgesia was not found to be significantly different between 1 h & 2 h test sessions. It was also seen that for each time duration, exposure to 102 dB (white noise) showed a significantly higher ($P < 0.0001$) analgesic response as compared to the exposure to 92 dB and 98 dB (pure

TABLE I : Analgesic response (Mean \pm SD of mean area under the curve), the relationship between the time duration of exposure (h) and the amplitude of noise (dB) in control (I) and test groups (II, III, IV), and the significance by Tukey's test (n=10 in each group).

Amplitude (dB)	I-Control Mean \pm SD	II-1 h Mean \pm SD	III-2 h Mean \pm SD	IV-3 h Mean \pm SD	P-value (F-test)	Significance Tukey's test at 5%
a-92 dB	0.82 \pm 0.32	4.83 \pm 1.10	7.43 \pm 1.03	11.17 \pm 1.20	<0.0001	Control is signif. diff. from 1h, 2h and 3h 1h is signif. diff. from 2h and 3h 2h is signif. diff. from 3h
b-98 dB	0.82 \pm 0.32	5.46 \pm 2.12	7.38 \pm 1.30	11.46 \pm 1.66	<0.0001	Control is signif. diff. from 1h, 2h and 3h 1h is signif. diff. from 2h and 3h 2h is signif. diff. from 3h
c-102 dB	0.82 \pm 0.32	9.04 \pm 1.06	9.94 \pm 1.19	14.46 \pm 0.97	<0.0001	Control is signif. diff. from 1h, 2h and 3h 1h is signif. diff. from 3h 2h is signif. diff. from 3h
P-value (F-test)	—	<0.0001	<0.0001	<0.0001	—	—
Significance Tukey's Test at 5%	—	102 dB is signif. diff. from 92 dB and 98 dB	102 dB is signif. diff. from 92 dB and 98 dB	102 dB is signif. diff. from 92 dB and 98 dB	—	—

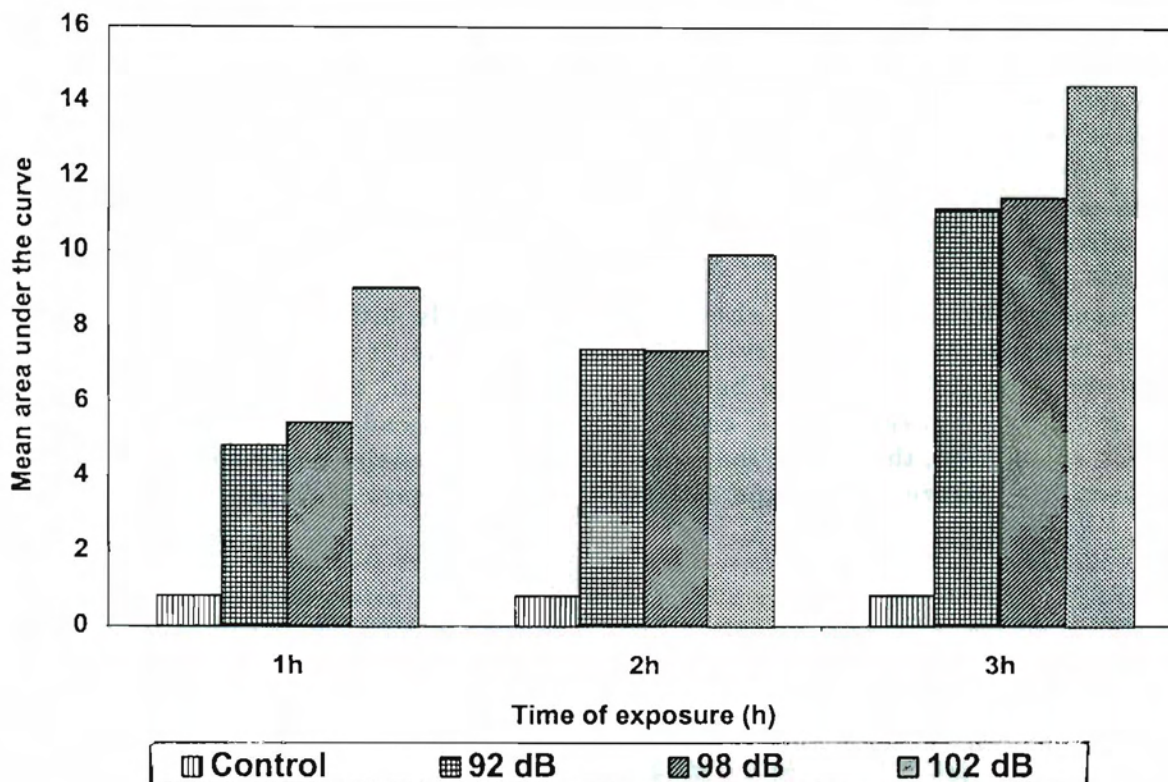


Fig. 1: The magnitude of the analgesic response, as represented by the mean area under the curve, in all 4 groups of rats tested ($n = 10$ in each group), with respect to time duration of exposure (h) and the intensity of noise (dB).

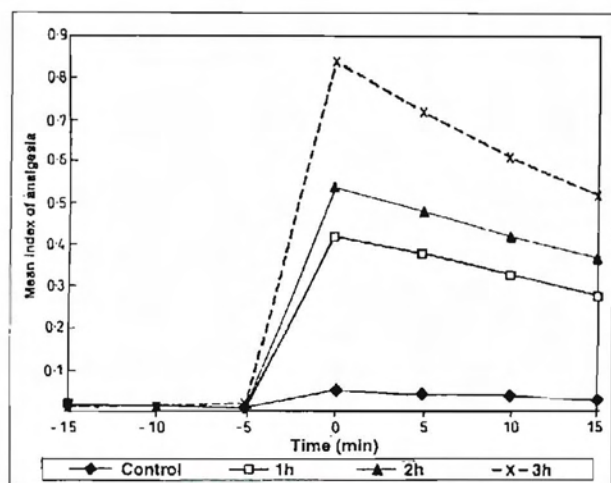


Fig. 2: Graph showing the magnitude of the analgesic response, as represented by the mean IA values, with time (min) for 102 dB noise

tones) which did not differ significantly from each other.

The response, when plotted with respect to time, showed a peaking immediately after the noise exposure followed by a decline with the passage of time. Fig. 2 depicts the time course of the response for 102 dB intensity of noise showing the maximum response at 0 min i.e. immediately after the noise exposure followed by a decline in the

intensity (Group IIc, IIIc & IVc) as compared to the control group (Group I). On the time scale, -15, -10 and -5 reading denote the baseline IA values before the exposure to ESC or ESC + noise, 0 reading denotes the IA value immediately after the exposure followed by post-exposure IA values for the next 15 min.

response in the next 15 min. It also depicts the significant difference of the response from the baseline IA values and those of the control group.

Thus we observed that a greater exposure, both in terms of time duration or intensity of noise, as well as, intermittent (white) noise as compared to continuous noise (pure tone), produced a significantly greater analgesic response in rats.

DISCUSSION

The results of the present study have affirmed that the presence of loud noise in the rat's environment produces an analgesic response. It is directly related to the duration of exposure, the intensity and the continuous or intermittent characteristics of the noise with loud intermittent (white) noise and longer duration of exposure producing more analgesia. It supports the idea that analgesia is expressed by rats in response to the non-noxious auditory stressor and that this response is in several respects similar to the inhibition of pain-related behavior seen during its exposure to a wide variety of stressors and aversive stimuli. Exposing rats to any one of these stressors results in the activation of specialised neural systems capable of modulating noxious input from the periphery (30). The biological significance of this endogenous analgesic system is to allow the animal, under emergency conditions, to focus its attention on the life preserving strategies of fight or flight, undisturbed by pain (31).

Noise is an important environmental stress factor in industrialized societies, and

hence, has been investigated as a probable stressor in studies of SIA. A study conducted by Andren et al (32) showed that industrial noise of 95 dB is a well-defined stress factor causing significant elevations in diastolic blood pressure. Previous reports indicate that exposure to intense (e.g. 100 to 115 dB) noise results in a decreased response to noxious somatosensory stimuli in rats (27, 33) and in human volunteers (34). The application of auditory stressors to rats may result in many of the same defensive reactions that normally follow electric shocks but, unlike shocks, auditory stimuli of intensities below 130 dB are not generally considered noxious or painful (25, 26). It is, therefore, interesting to note that presentation of such non-nociceptive auditory stimuli has been shown to result in the expression of stress-induced analgesia. Helmstetter and Bellgowan (28) have shown that a single presentation of 90 dB white noise results in a state of unconditional fear or sensitization that is expressed through the activation of an opioid sensitive form of analgesia.

Noise is probably a stronger 'stress factor' for animals than for humans as hearing is often essential for the survival of animals. Thus non familiar noise could produce a fully developed defense-alarm reaction with haemo-dynamic and hormonal adaptation, for fight and flight (35). It has been observed that sudden intense sounds will evoke the startle response the magnitude of which is related directly to the loudness of the sound and inversely to its rise time but is also affected by its unexpectedness and by the level of the background ambient noise. It has been seen that 2 s bursts of a 1KHz tone increased

the muscle tensing response dramatically between levels of 90 & 120 dB. Repetition of the sound usually result in a reduction of the response, although such habituation may not become complete while there is a complete lack of habituation to some sounds, especially to gunfire (36).

Even a sudden or impact noise with a level as little as 30 dB above the background level is likely to cause a startle response and subsequent stress reaction. In our study as soon as the noise was started this sudden intense sound evoked the startle response: an immediate contraction of the orbital eye muscle and the flexor muscles of the legs, arms and back, manifested as an eye blink and a crouching movement with the animal moving as far as possible from the source of noise. This startle response was followed by an orientation reflex in which the animal turned the head and eyes toward the source of sound. It has been shown that the startle response produces complex physiological responses typically associated with stress, including pupil dilation, increase adrenaline secretion and elevation of blood pressure. The extent of these physiological reactions tends to increase when the noise is intense, when it is aperiodic, or when it is uncontrolled (37). In the present study the rats were exposed to loud noise of two kinds – a continuous shrill noise (pure tone 92 dB and 98 dB) and an intermittent heavy (artillery) noise (white noise 102 dB) and our results support the fact that the intermittent heavy noise and that which lasted for a longer duration produced more analgesic response. There was no significant difference in the analgesic response between the 2 pure tones.

In most of the previous studies reported, the auditory stimuli were brief bursts (a few ms to a few min) of loud noise (upto 115 dB) and the analgesia produced was attributed to the initial startle response (38). In this study we have chosen to subject the rats to prolonged loud noise by exposing them for 5 consecutive days in longer test sessions, to different high amplitude noise of varying characteristics, in an attempt to produce the subsequent stress reaction as well, and to observe its effect on the TFL. Our observations affirm that even with longer exposure the analgesic response still remains intensity- and duration-related together with being characteristics-related. Earlier studies have shown that stimulus duration may also be an important factor in the expression of analgesia because opioid antagonists appear to block analgesia resulting from a series of brief noise pulses (27) and from a single 60 sec stimulus presentation, but not from the antinociceptive effect of 5 min of noise used in the Szikszay et al. (33) study. Longer periods (i.e. seconds to minutes) of continuous exposure to noise result in a state of behavioral sensitization that is typically considered to be a non-associative form of fear or anxiety and Davis (39) reported that the maximum elevation of startle amplitude caused by exposure to 80 dB background white noise was seen after 35–40 min of continuous stimulation and that this form of sensitization rapidly dissipated after the noise was turned off. Our observations also showed a peaking of response following noise exposure with a gradual tapering off with time. However, the readings were taken only for 15 min after the noise exposure and hence the

duration of the response could not be measured.

By using the ESC we maintained standard environment conditions as normally encountered by the animal, except for the noise. Thus, since no other discreet stimuli are presented to the rat within our experimental model we must assume that in the present study the representation of noise is critical for producing analgesia. The present study was also conducted on adult male rats as several previous studies have reported sex differences in baseline pain sensitivity and SIA magnitude in rodents presumably associated with hormonal cyclicity in females and neurochemical difference in SIA mechanism between the sexes (40, 41). In addition, it is also evident that the age of the animal plays a significant role in the expression of endogenous analgesia mechanisms (31).

In conclusion, this study reaffirms that noise is a stressor which has a significant

effect on the behavior of an animal exposed to it, producing among others, a profound analgesic response. The findings indicate that, during exposure to noise the auditory pathway, in the brain stem, may interact with the pain inhibiting pathway leading to its excitation and consequent analgesia. The release of adrenaline during this noise stress response may also sensitize the system. However, the neural pathway and mechanism responsible for the analgesic response merits further electro-physiological and hormonal investigation.

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