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Association of Increased Pain Threshold by Noise with Central Opioid Neurons

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Abstract

Several studies indicated that stress would induce analgesia. Noise, one of the stressors, was assumed to be one of the elements to enhance the threshold of pain tolerance. Since noise might affect human's daily life, it is important to know the mechanism underlying this phenomenon. The objective of this study was to explore the possible mechanism which was trying to explain how the noise affects central nervous system and the possible relationship between this effect and the involvement of opioid neurons. In the preliminary study, the analgesic effect was corroborated in ICR mice in a formalin study. The results are as follows: [1] Naloxone (a μ-opioid receptor antagonist; 1 mg/kg, i.p.), β-FNA (a δ-opioid receptor antagonist; 5, 10 mg, i.c.v.) and naltrindole (a δ-opioid receptor antagonist; 1, 5 mg/kg, i.p.) were found to reduce antinociceptive effect. [2] nor-BNI (a κ-antagonist; 1 μg, i.c.v.) had much effect on noise induced analgesic. In conclusion, this study suggests that noise stress enhanced the threshold of analgesia, which might be related to μ- and δ-opioid receptors in the central nervous system.

Key Words: noise, antinociception, opioid neurones

Introduction

By definition, noise was considered as unwanted or undesirable sound. However, this definition could be very different depends upon individual, social and cultural factors. Early in 600 D.C., the Greeks had discovered that noise would impact on human beings' health and resulted in prohibiting the existence of heavy metal factories in the city (18, 19). Noise could impact daily life on several aspects, such as working efficacy, communication, social skills, sleep quality and so on (13, 26). The extent of the impact on these aspects could vary based upon the noise intensities, frequency, and environmental factors (15). Individual factors, such as age, sex, health, susceptibilities, and genetics were found to be the crucial factors (8).

Study showed that the noise has a great impact on individual daily activities. For example, it affected kids' concentration in school and would reduce their learning efficacy (15). Noise also affects workers' emotion. They would become anxious and could not concentrate on their works. In the end, their working efficacy and performance would be drastically diminished. Furthermore, the masking effect due to the noise was another serious problem worth investigation (15). Although the threshold of pain tolerance was increased due to the noise, the efficiency of communication and information delivery was affected under a noisy environment as well. It might mask the danger signals which might contribute to some crucial and/or undesired damages or injuries. Several studies indicated that the noisy

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working environment contributed the higher rate of accidents or errors, and low production. Although the masking effect due to high volume noise was not directly related to these results, more studies are needed to further examine the possible evidence and the possible mechanisms (20).

Recently, several studies indicate that both physiological and psychological stresses such as forced swimming stress, restraint stress, electric foot shock, psychological stress and startle are able to enhance the pain threshold in animal studies (1, 9, 29, 30, 31, 33, 34). In the meantime, the noise is considered as one of the stressors (11, 24). Different intensities of noise (60-110 dB (A)) can enhance the pain threshold, which is dose-dependent. Although several studies indicate that the noise result in physiological damage, evidence is still lacking for the relationships between the analgesic neuron systems (4, 7). Besides, possible mechanisms are still unclear. Therefore, in this study, the formalin test was performed to explore the noise mechanisms regarding the central nervous system and peripheral nervous system. Furthermore, in the formalin test, various opioid antagonists (naloxone, β-funaltrexamine, naltrindole and norbinaltorphimine) were chosen to examine the mechanisms of how noise affected central nervous system.

Materials and Methods

Animals

18-25 g ICR strain mice were located in a chamber with a constant temperature of 22-24°C for 24 h. Waters and food were supplied freely. To avoid other undesired environmental stress, the mice were located in the noise chamber and observed for 30 minutes prior to the experiment.

Equipments and Apparatus

In this study, the noise chamber was an 84 × 57 × 57 cm square chamber with a 14 × 27 cm glass window on top of it, which was used to observe the mice. Random noise generator (SF 05 R10N Company), which was connected by transducer to the speaker in noise chamber, was placed outside of the chamber. The mice were placed separately in iron rages within the chamber. 'White noise' was used and was measured *via* the level meter, TES 1350, which was precisely corrected before use.

Drugs

The following drugs were used in the experiment: Naloxone HCl (opioid receptor antagonist), which was purchased from Sigma company, St. Louis, MO, USA, β-Funaltrexamine (β-FNA; μ-opioid receptor antagonist), naltrindole (δ-opioid receptor antagonist) and nor-binaltorphimine 2HCl (nor-BNI; κ-opioid receptor antagonist), which were obtained from RBI company (Natick, MA, USA).

Noise-Induced Analgesic Experiments-Formalin Test

Then, the noise-group and non-noise group mice were given with 25 μl 1% formalin subcutaneously in their right hind foot using microsyringes. After that, the mice were located into the chamber in order to record their licking time. The first 5 min after formalin injection was recognized as early phase or first phase, whereas the 5 to 40 min after formalin injection was considered as late phase or second phase.

Noise-Induced Analgesic Mechanism Study

ICR mice were divided into noisy group and non-noisy group, and both were divided into experiment group and control group. Each experiment group was given different drugs and each control group was given the same volume of 0.9% NaCl solution. With respect to the experiment examining the mechanism of opioid-receptor antagonists to noise-induced analgesic, the mice were given naloxone (1 mg/kg, i.p.), β-funaltrexamine (β-FNA; 5, 10 μg, i.c.v.), naltrindole (1, 5 mg/kg, i.p.) and norbinaltorphimine (nor-BNI; 1 μg, i.c.v.) in the 35 min, 24 h, and 30 min, respectively, before the formalin test. Under the same condition, the control groups were given the same volume of 0.9% NaCl solution. The experiment groups were located in the noisy chambers and exposed to white noise 20 min before the formalin test and the control groups were observed without the exposure to the white noise.

Statistical Analysis

The one-way ANOVA was used to analyze the noise-induced analgesic effect associated with different dosages of drugs. Subsequently, Dunnett's test was used to compare the differences of effects in each group. Furthermore, two-way ANOVA was chosen to determine the effect of noise and drugs. One-way ANOVA was repeated to analyze the differences of effects between each group. Then, Dunnett's test was performed to compare the minor differences in each group. Nevertheless, the noisy and non-noisy groups which were given the same volume of drugs were compared using Student's *t*-test. If $P < 0.05$, it was statistically significant.

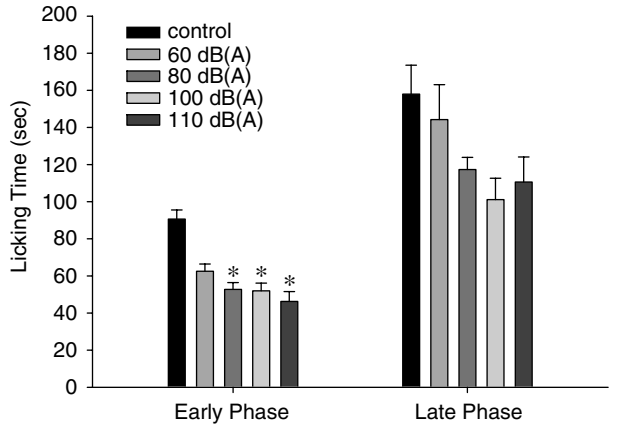

Fig. 1. The effects of different intensities of white noise on the early and late phases of the formalin test in mice. Data are shown as means ± S.E. (n = 7). *$P < 0.05$ compared with control group.

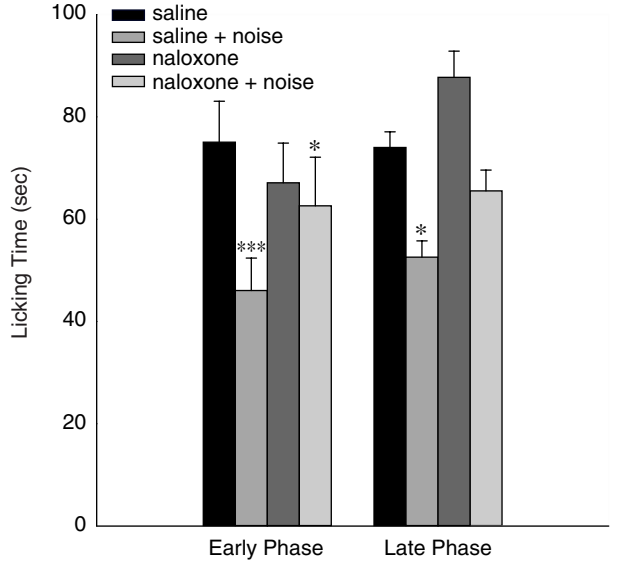

Fig. 2. The effects of naloxone (1 mg/kg, i.p.) on the early and late phases of formalin test in mice with or without 100 dB(A) white noise exposure. Data are shown as means ± S.E. (n = 8). *$P < 0.05$, ***$P < 0.001$ compared with control group.

Results

Noise-Induced Analgesic in Formalin Test

After the mice exposed to different intensities of noise, we found that the licking time induced by formalin were markedly inhibited in the early phase in noise-group. When the intensity was larger than 80 dB(A), the licking time was significantly different (Fig. 1). However, the noise was not affective in late phase.

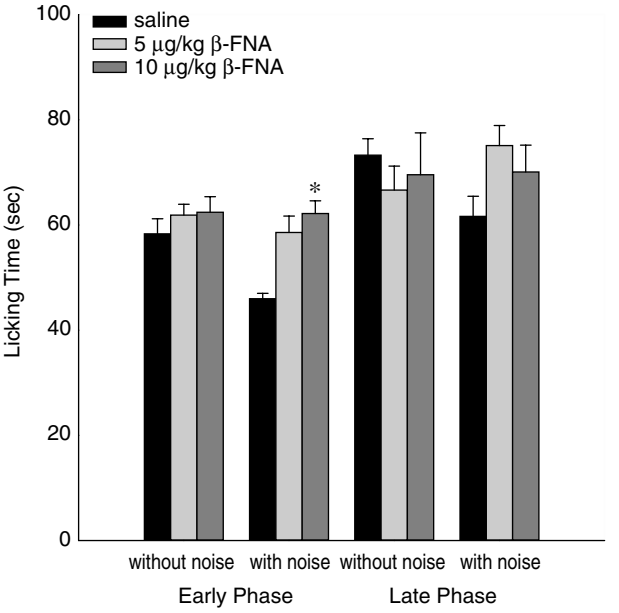

Fig. 3. The effects of different doses of β-funaltrexamine (β-FNA, i.c.v.) on the early and late phases of formalin test in mice with or without 100 dB(A) white noise exposure. Data are shown as means ± S.E. (n = 8). *$P < 0.05$, as compared with the control group.

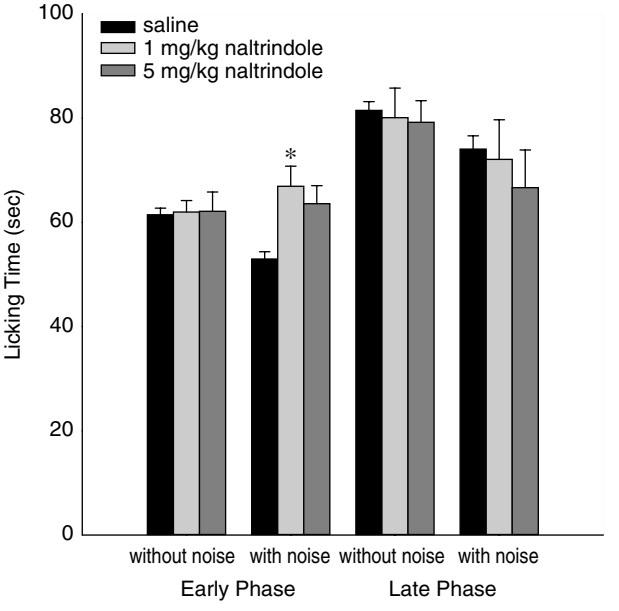

Fig. 4. The effects of different doses of naltrindole (1, 5 mg/kg, i.p.) on the early and late phases of formalin test in mice with or without 100 dB(A) white noise exposure. Data are shown as means ± S.E. (n = 10). *$P < 0.05$, as compared with the control group.

Effects of Opioid Antagonists on Noise-Induced Antinociception

Naloxone (1 mg/kg, i.p.), β-FNA (5, 10 μg, i.c.v.), naltrindole (1, 5 mg/kg, i.p.) and nor-BNI (1

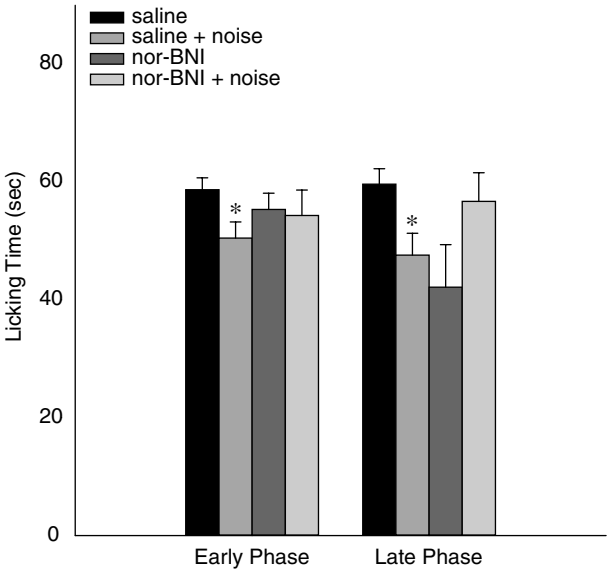

Fig. 5. The effects of different doses of nor-binaltorphimine (nor-BNI, 1 μg/kg, i.c.v.) on the early and late phases of formalin test in mice with or without 100 dB(A) white noise exposure. Data are shown as means ± S.E. (n = 8). *$P < 0.05$, as compared with the control group.

μg, i.c.v.), which was given separately, did not have any significant effects on the formalin test. However, the early phase analgesic was inhibited by naloxone, β-FNA and naltrindole but not during the late phase (Fig. 2-4). However, nor-BNI could not influence noise stress-induced analgesia in either phase (Fig. 5).

Discussion

Stress can enhance the threshold of analgesic effect. In 1970s, several studies indicate that the enhanced pain threshold due to the noise is related to both opioid and non-opioid pathways (2, 11, 22). Non-opoiod pathway might include the changes of neurotransmitters such as serotonin, dopamine, acetylcholine, norepinephrine and GABA (3, 7, 9, 16, 30, 35). However, different stimulations of stress, designed experiment models, animals' species might affect the analgesic outcomes and the possible mechanisms (3, 10, 16, 17, 22, 29, 35).

Because noise becomes one of the stressors to humans, many studies have found that noise would interrupt humans' physiological and psychological functions (15, 24, 26, 28). With different intensities, characteristics, exposure time, and measuring methods of noises, the results could be varied. Anyhow, the study of noise as a stressor was still limited (7, 24). In 1995, SD rats are exposed under 115 dB noise for 5 min in Szikszay's study. After that, tail flick test and hot plate test are performed to examine the impact of analgesic effect. Noise is found to enhance the pain threshold in hot plate test but have no effect in tail flick test. Furthermore, in 1994, similar results are obtained in Helmstetter and Bellgowan's study, in which they expose the mice in 60-95 dB(A) noise for 60 seconds (12). According to these studies, the intensities of the noise and the enhanced pain threshold are considered as dose-dependent. The present study had similar results with these two studies, and further confirmed that noise could actually enhance the threshold of pain by using different intensities of noise, exposure time and experiment models.

The formalin test was suggested by Dubuisson and Dennis in 1977 (6). Formalin solution is given to the animals' foot to induce pain, and the pain was measured *via* the licking reaction time. However, in 1987, a biphasic licking reaction is established in the formalin test by Takahashi (29). The first licking reaction period is observed in the first 5 min, which is classified as early phase, and the other 15-30 min, categorized as the late phase. The early phase is presumed to be related to the release of direct-pain stimulants such as substance P and bradykinin, whereas the late phase might be caused by the inflammatory, which can be induced by formalin solution (25). The late phase might be related to some of the neurotransmitters, such as histamine, serotonin, prostaglandin, and kinin. Generally speaking, the early phase is presumed to mediate *via* central nervous system (CNS), and the late phase might be associated with the peripheral nervous system (PNS). In this study, it was found that the licking time was significantly inhibited in early phase, but not in late phase. It showed that the antinociception of noise was mainly *via* central nervous system.

While exposing the mice to the noise, the mice were observed through the glass on top of the chamber. In the beginning of the noise exposure, the mice were startled and running up and down in the chamber. It seemed that they were trying to escape because they intended to get rid of the noise. However, some of the mice were running around, some were biting the chamber, and some seemed anxious to the environment. After a period of time, some of them were still active, but some began to calm down, and some hid in the corner until the end of the experiment. All of the aforementioned observations seemed similar to those in Segal's study, which has been carried out in 1989 and indicated that the impact on mice's activities due to noise were drastically increased during the first 5 min, and then diminished (23). The uses of various intensified noises are considered in the animal model, in which the cause of seizure disorders is examined (21). From those animals' reactions, the noise has been proven to influence the CNS reactions.

The central antinociceptive systems, including

pereaqueductal gray area, raphe magnus nucleus and dorsal horn were possibly mediated through opioid receptors, noradrenergic neurons or serotonergic neurons (32). It is unclear whether these pathways related to the enhancement of noise-induced analgesic effects. Stress-induced analgesic effects are related to endogenous upload peptides (2, 35). The anti-nociceptic effects are induced by various stimuli, and these pathways are mostly related to endogenous opioids. Most of the stimulations are probably related to pain. Although the startle stimuli are assumed to be nonpainful stimuli, it might be related to the endogenous opioid substances (5). In 1985, Szikszay *et al*. suggest that naloxone (2 mg/kg, s.c.) has no effects on noise and is not tolerant to morphine. It is then indicated that noise-induced analgesic effects have nothing to do with opioid receptors (28). Three years later, Cranney *et al*. find that naloxone (4 mg/kg, i.p.) can reduce the noise-induced analgesic effects. In addition, Watkins *et al*. suggest that naloxone is found to antagonize other stimuli-induced pain threshold (36). The naltrexone (0.1-7.0 mg/kg, i.p.) is used in Helmstetter's study, in which the noise-induced analgesic effect is reduced, whenever the dose is greater than 3.0 mg/kg (12).

Respectively, the opioid receptor antagonist was considered in this study to examine the relationship between the endogenous opioid substances. Naloxone (1 mg/kg, i.p.) was found to reverse the noise-induced analgesic effect in the formalin test during the early phase. However, these findings were inconsistent with other studies, which might be due to the various dosage and models. In addition, the intensities of noise in use were also one of the influencing factors. Therefore, noise-induced analgesic effects might be closely related to opioid pathway. Furthermore, μ-, κ-, and δ- opioid subtype receptors are considered to examine their antagonist effects in this study. Kamei's study in 1993 finds that naltrindole; a δ-receptor antagonist, reverse the late phase analgesic effect in formalin test throughout the examination of the antinociceptive effects, which are induced in forced swimming stress. It is also found that the supraspinal δ-opioid receptor might be affected by the higher dose of naltrindole (14). In 1992, Vanderah suggest that analgesia, induced by cold water stress in the tail-flick test, is antagonized by δ2-opioid receptor antagonists, and was not influenced by δ1-opioid receptor antagonists (*e.g*. D-Ala 2, Leu 5, Cys 6), enkephalin, μ-opioid receptor antagonist, β-FNA and nor-Binaltorphimine, a κ-opioid receptor antagonist (34). A larger dose of naltrindole also has an influence on the δ-opioid receptors in the supraspinal cord (27).

In this study, naltrindole, a δ- opioid receptor antagonist and β-FNA, a μ-receptor selective antagonist were found to reverse the analgesic effect in the early phase in the formalin test. This result showed that noise-induced analgesic effect was closely related to opioid receptors in CNS. However, nor-BNI, a κ-receptor antagonist, was found to have no effect on the enhancement of pain tolerance threshold. In fact, it was found that the nor-BNI affected psychological stress, which induced pain tolerance threshold antagonist, and had no effects on foot shock stress and forced swimming stress. This might be due to different stimuli, which were acting through different mechanisms.

As a matter of fact, three pathways related to antinociceptive effects, including noradrenergic neuron, serotonergic neuron and opioid receptors, are taken into account in the whole study related to the noise. Using the drugs related to these three pathways, the enhancement of noise-induced analgesic effect was examined using the formalin test. The noise-induced analgesic threshold was enhanced, and this might be related to the monoamine serotonergic neurons and noradrenergic neurons. However, the extent of effects associated with the noradrenergic neuron and serotonergic neuron was not reported because it was beyond the scope of this study.

As in other developed countries, Taiwan has been well-developed in the recent years, but the majority of workers are still exposed to noisy environments. Noise could affect humans psychologically and physiologically and incur the masking effect that might place workers in dangerous situations. With respect to the incurred minor injuries, which are always ignored by people in a noisy environment, it might result in undesired, various extent of disasters. Based on the findings of this study, it is suggested that employers and employees in the working environment should be aware of the influence of productivity and workers' health problems related to noise. They should cooperate to build a safer working environment in Taiwan.

In conclusion, given that several studies have established the effects of noise on human health, noise was considered as one of the dangerous factors that affect daily life. Although the performed hot plate test and tail flick test found that hot plate tolerance was prolonged by noise but had no effects on tail flick test, in the present study, it was found that the acting mechanism of noise-stress was mainly in the CNS. The results demonstrated that the enhancement of the pain threshold induced by noise-stress was associated with μ- and δ-opioid receptors.

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