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Tualang honey improves memory performance and decreases depressive-like behavior in rats exposed to loud noise stress

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Abstract

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Recent evidence has exhibited dietary influence on the manifestation of different types of behavior induced by stressor tasks. The present study examined the effects of *Tualang* honey supplement administered with the goal of preventing or attenuating the occurrence of stress-related behaviors in male rats subjected to noise stress. Forty-eight adult male rats were randomly divided into the following four groups: i) nonstressed with vehicle, ii) nonstressed with *Tualang* honey, iii) stressed with vehicle, and iv) stressed with honey. The supplement was given once daily via oral gavage at 0.2 g/kg body weight. Two types of behavioral tests were performed, namely, the novel object recognition test to evaluate working memory and the forced swimming test to evaluate depressive-like behavior. Data were analyzed by a two-way analysis of variance (ANOVA) using IBM SPSS 18.0. It was observed that the rats subjected to noise stress expressed higher levels of depressive-like behavior and lower memory functions compared to the unexposed control rats. In addition, our results indicated that the supplementation regimen successfully counteracted the effects of noise stress. The forced swimming test indicated that climbing and swimming times were significantly increased and immobility times significantly decreased in honey-supplemented rats, thereby demonstrating an antidepressant-like effect. Furthermore, cognitive function was shown to be intensely affected by noise stress, but the effects were counteracted by the honey supplement. These findings suggest that subchronic exposure to noise stress induces depressive-like behavior and reduces cognitive functions, and that these effects can be attenuated by *Tualang* honey supplementation. This warrants further studies to examine the role of Tulang honey in mediating such effects.

Keywords: *Antioxidants*, *behavior*, *brain*, *cognitive*, *depression*

Introduction

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Numerous reports have shown that noise exposure affects cognitive performance and induces behavioral changes. Increased noise levels have been associated with decreases in intentional, incidental, and recognition memory in children,[1,2,3] a result that has been paralleled in rats.[4,5,6] Chronic noise exposure in industrial workers and individuals living near major transportation routes has been associated with depression and feelings of aggression.[7,8] Noise may also be fear-inducing,

as evidenced by a more prominent tonic immobility response in noise-stressed hens.[9,10]

Tualang honey is a multifloral honey produced by the rock bee species (*Apis dorsata*) that builds hives high up in the branches of the *Tualang* tree (*Kompassia excelsa*). Recent studies revealed that the consumption of honey may reduce anxiety and improve spatial memory in middle-aged rats.[11] It is also reported that honey is used in natural preventive therapies for both cognitive decline and dementia, as it possesses antioxidant properties and enhances the brain's cholinergic system and circulation.[12] In closely related studies, it was demonstrated that *Tualang* honey was able to improve memory performance in stressed ovariectomized (OVX) rats[13] and postmenopausal women.[14] To our knowledge, no previous research had been done regarding the effects of *Tualang* honey on cognitive functions and depression in rats exposed to loud noise stress. Therefore, this study aimed to evaluate the efficacy of *Tualang* honey in improving cognitive functions and reducing depressive symptoms.

Materials and Methods

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Experimental animals

Forty-eight male Sprague-Dawley rats (2 months old, weighing 200-250 g) were used in this study. The animals were housed under a reversed 12-h light/dark cycle (lights off at 8 AM) at a consistent room temperature of ±27°C, with free access to commercial rat chow (Gold Coin Ltd., Kuala Lumpur, Malaysia) and water. Rats were allowed to acclimatize to the holding room for 24 h before the behavioral procedures. The procedures in this study were approved by the Animal Ethics Committee of the Universiti Sains Malaysia (USM/Animal Ethics Approval/2013(85)(444).

Honey supplement

The *Tualang* honey used was from a single batch of honey supplied by the Federal Agricultural Marketing Authorities (FAMA), Malaysia. The honey was filtered by FAMA to remove solid particles, concentrated in an oven at 40°C, and evaporated to achieve a water content of about 20%. It was then subjected to γ irradiation at 25 kGy at SterilGamma (M) Sdn. Bhd. (Selangor, Malaysia) for sterilization and bottled 230 g per jar. The final concentration of the bottled *Tualang* honey was 1.3 g/mL. *Tualang* honey (0.2 g/kg body weight) was dissolved in distilled water and given once a day via oral gavage over a period of 35 days. The dissolution of *Tualang* honey was freshly done before the administration. The control groups received an identical volume of distilled water (vehicle) as placebo.

Experimental design

The animals were randomly assigned to the following groups (n = 12):

1. Nonstressed with vehicle,
2. Nonstressed with *Tualang* honey,
3. Stressed with vehicle, and
4. Stressed with *Tualang* honey.

As illustrated in Figure 1, honey supplementation was started on day 1 and continued for a period of 35 days. On days 22-35, the noise stress procedure was implemented. The behavior tests were conducted following the final day of stress exposure. The novel object recognition tests were conducted from day 36 to day 38, followed by the forced swimming test from day 39 to day 41. The animals were killed by decapitation upon completion of the behavioral tests. Individual body weights were recorded weekly using electrical balance.

Figure 1
Methodology timeline

Noise stress exposure

The animals of the test groups (iii and iv) were exposed to white noise for 4 h (9 AM-1 PM) daily for 14 days. Noise was recorded from the generator and amplified by speakers in a separate room. Speakers were located 30 cm above the cages. The noise level was set at 100 dB(A) and intensity was measured by sound level meter CENTER 325 (range: 80-130 dB(A); accuracy: +1.5 dB(A); made in Taiwan). Sound levels were verified at the center of the cage before each exposure and varied by less than 1 dB(A) in the space the cage occupied. The control groups were kept in the same room for the same period of time without switching on the noise.

Behavioral tests

All the behavioral tests were conducted after the noise stress procedure. Two types of behavioral tests were performed, namely, the novel object recognition test to evaluate working memory and the forced swimming test to evaluate depressive-like behavior. The behavioral tests were carried out in a separate room that was ventilated, soundproof, and maintained at a constant temperature (±27°C). The animals were brought into the test room 1 h before the tests began to minimize the arousal caused by the transference. All behavioral tests were performed during the active period of the animals (dark phase) between 9 AM and 2 PM. All the animals were tested in a random order. The trained observer remained blind to the treatment group of the rats until scoring was completed.

Novel object recognition test

The test employed was similar to that described elsewhere.[15] The test was conducted in an open box made of transparent plastic 60 cm × 60 cm × 30 cm. Training sessions were conducted on two successive days, with the animals allowed to explore the arena for 10 min each day. In each training session, two identical sample objects were placed in the field in a symmetrical pattern about 10 cm away from the wall. The objects discriminated were made of plastic and varied in shape and color. Between tests, the objects were cleaned with a 10% ethanol solution to mask any olfactory cues. All combinations and locations (left and right) of the objects were alternated in order to prevent potential bias due to preferences for particular locations or objects.

After the two successive training sessions, testing/retention sessions were conducted. The retention sessions consisted of two sessions, for short-term memory and long-term memory, in which the retention intervals for short-term memory and long-term memory were 2 h and 24 h, respectively, after the last training session. In the retention session, rats were placed back in the same field, where one of the familiar objects used in the training session was replaced by a novel object, and the rats were allowed to explore for 5 min. The times spent exploring each object were video-recorded. Exploration of an object was defined as directing the nose toward the object at a distance of 2 cm or less. Climbing and leaning on an object was not considered exploratory behavior.

The total exploration time of the familiar and novel objects were used to calculate discrimination index. The discrimination index is an index of measures of discrimination between the familiar and the novel objects corrected for exploratory activity. It is calculated as: (time spent on novel object − time spent on familiar object)/(time spent on novel obejct + time spent on familiar object). The discrimination index can range from −1 to 1, with −1 indicating complete preference for the familiar object, 0 indicating no preference for either object, and 1 indicating complete preference for the novel object.

Forced swimming test

The test employed was similar to that described elsewhere,[16,17] with slight modification. The alterations consisted of increasing the water depth from 15-18 cm in the original to a depth of 30 cm and moving from a cumulative timing measure to a time-sampling technique wherein the predominant behavior over each 5-sec period of the 300-s test was rated.[18] All the animals were individually placed in a transparent plastic cylinder (40 cm in height × 18 cm in diameter) filled with water (25-27°C) to a level of 30 cm. The experimental session consisted of two trials: The conditioning trial and the test trial.[17] During the conditioning trial, the rats were placed in the water-filled cylinder for 15

min. After the trial, the rats were dried and placed in a warm cage with paper towels for 10-15 min before being returned to their home cages. Twenty-four hours later, the animals were placed again in the cylinder for a 5-min test session, that is, the test trial.

The test sessions were videotaped for subsequent quantitative behavioral analysis. The frequency and/or total duration was calculated for each of the predominant behaviors: Climbing (intense movements with all four limbs, with the two forepaws breaking the surface of the water and being directed against the walls of the cylinder); swimming (rigorous horizontal movements throughout all radiuses of the cylinder); and immobile (the animal remaining in water with all four limbs motionless except for the occasional alternate movement of paws and tail necessary to prevent sinking and to keep the head/nose above water). The water was changed before the next animal was placed in the water tank.

Statistical analysis

The data obtained were analyzed using a two-way analysis of variance (ANOVA), with stress treatment (no noise vs loud noise) and honey treatment (control vs honey) as fixed factors. All analyses were performed using IBM SPSS version 18. Statistical data were reported as mean ± SEM, and a result was deemed to be statistically significant if $P < 0.05$.

Results

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Novel object recognition test

The results are depicted in Figure 2. The univariate ANOVA revealed the significant main effects of stress on short-term memory [$F(1,46) = 6.77$, $P < 0.05$] and long-term memory [$F(1,46) = 40.25$, $P < 0.01$]. The loud noise stress-exposed rats exhibited a significantly lower mean discrimination index in both short-term and long-term memory compared to nonexposed rats, which indicates deteriorated memory. Interestingly, there were significant main effects of honey treatment on short-term memory [$F(1,46 = 18.45$, $P < 0.01$] and long-term memory [$F(1,46 = 34.7$, $P < 0.01$]. Rats given the honey supplement showed a significantly higher mean discrimination index in both short-term and long-term memory compared to the control rats, indicating better memory performance. However, there was no significant interaction effect between stress and honey treatment.

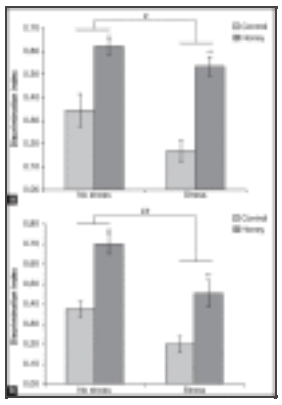

Figure 2

The effects of loud noise stress and honey supplementation on discrimination index of (a) short-term memory and (b) long-term memory in the novel object recognition test. Data are displayed as mean ± SEM. Significant main effects of loud noise **...**

Forced swimming test

The results were depicted in Figure 3. The univariate ANOVA revealed the significant main effects of stress on durations of climbing [$F(1,43) = 5.64$, $P < 0.01$], swimming [$F(1,43) = 8.09$, $P < 0.01$], and immobility [$F(1,45) = 14.55$, $P < 0.01$]. The rats exposed to loud noise stress exhibited significantly lower climbing and swimming durations and higher immobility durations compared to nonexposed rats, which indicates depressive-like symptoms. In addition, the analyses revealed significant main effects of honey treatment on durations of climbing [$F(1,43 = 6.27$, $P < 0.01$], swimming [$F(1,43 = 11.32$, $P < 0.01$], and immobility [$F(1,45 = 19.65$, $P < 0.01$]. Rats treated with the honey supplement showed significantly a higher duration of climbing and swimming and significantly lower duration of immobility, which reflected honey's antidepressant-like effects. However, there was no significant interaction effect between stress and honey treatment.

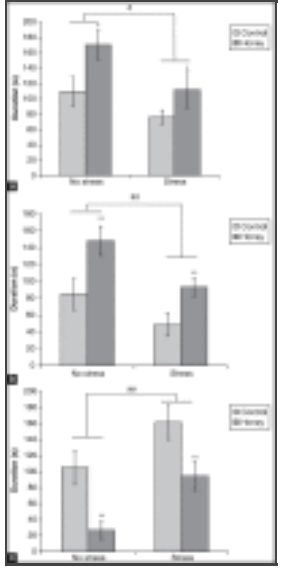

Figure 3

The effects of loud noise stress and honey supplementation on durations of (a) climbing, (b) swimming and (c) immobility behavior in the forced swimming test. Data are displayed as mean ± SEM. Significant main effects of loud noise stress (#, **...**

Discussion

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Stress responses are considered to play an important role in mental disorders.[19] Evans *et al*., (1995) [20] pointed out that chronic noise exposure is associated with cognitive as well as affective disorders of psychological stress. According to the definition of chronic stress proposed by Burchfield (1979), [21] chronic stress can be interpreted as a succession of repeated acute stressors. Two animal behavior models, the novel object recognition test, and the forced swimming test were selected in this study to investigate the effects of noise stress on cognitive performance and depressive-like behavior in rats.

The novel object recognition test has been shown to be an effective model for assessing learning and memory across species, including mice,[22] hamsters,[23] rats,[24] and pigs.[25] It is widely accepted that noise is a stressful environmental stimulus, and stress has been previously shown to impair cognition, such as the acquisition of memory, consolidation, and recall.[26,27] In the present study, it was observed that the noise-exposed rats demonstrated significantly lower cognitive performance compared to the nonexposed groups. The decrease of the mean discrimination index in both short-term and long-term memory sessions of the rats exposed to noise compared to control reflected a memory deficit in the recognition task. The adverse effects of noise exposure observed on spatial and recognition memory are in agreement with the findings of other researchers.[28,29,30]

The hippocampus plays an important role in spatial memory for both humans and rodents.[31,32] The hippocampus is also connected to the hypothalamic-pituitary-adrenal (HPA) axis and is particularly susceptible to stress.[33,34] With prolonged chronic stress, the HPA axis is hyperactivated, resulting in the release of adrenocorticotropic hormone (ACTH) and corticosterone, thus resulting in structural changes, cell atrophy, and neuronal loss in the hippocampus.[33,35,36] Thus, it is postulated that the deterioration of memory noted in the noise-exposed rats is due to stress, which then activates the HPA axis, triggers the release of ACTH and corticosterone levels, and consequently causes hippocampal neurodegeneration.

The HPA axis dysregulation has also been closely linked to the maintenance and triggering of depression.[37] The forced swimming test as originally reported by Porsolt and colleagues[16,17] has become the most widely used model for assessing antidepressant-like activity in rats. The test is based on the observation that when rats are exposed to water from which there is no escape, after initial intense escape-directed behavior, such as swimming and climbing, they stop struggling and show passive, immobile behavior. The immobile behavior is believed to reflect either a failure to persist in escape-directed behavior after stress (i.e., behavioral despair) or the development of passive behavior that disengages the animal from active forms of stress coping.[38,39,40,41] In the current study, the rats exposed to noise demonstrated a significant decrease in climbing and swimming durations as well as increased immobility duration, indicating depressive-like behavior. These findings are consistent with a previous study where exposure to loud noise for 15 days caused a longer immobility duration. [42] Brain neurotransmitters play an essential role in the pathophysiology of depression. Noise stress has been shown to diminish dopamine levels after 15 days of noise exposure.[43] Hence, it is suggested that noise stress causes reduced dopamine levels, thus resulting in diminished dopamine neurotransmission, and further promotes depressive disorders.

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It is also important to note that overexposure to intense sound may cause the destruction of cochlear hair cells, damage to the mechanosensory hair bundles, and loss of spiral ganglion cells and the cell bodies of the cochlear afferent neurons.[44,45] This noise-induced peripheral neurodegeneration may lead to changes in brainstem circuitry and cortical reorganization, and further result in abnormal auditory behavior, including tinnitus- and hyperacusis-like behavior.[46] Hence, it is also possible that the inner ear damage caused by overexposure to loud noise may have caused the behavioral changes seen in the rats. However, so far, there is no evidence suggesting a relationship between noise-induced inner ear damage or peripheral neurodegeneration and behavioral changes related to memory and depression. Therefore, further studies are required to examine the ear condition of the noise-exposed rats followed by observation of the behavioral changes.

Interestingly, this study revealed the potential of *Tualang* honey in improving memory and reducing depressive symptoms induced by loud noise stress. In the novel object recognition test, it was observed that the rats supplemented with *Tualang* honey exhibited significantly higher memory scores compared to the control rats. In addition, the rats demonstrated significantly higher duration of climbing and swimming and a lower duration of immobility in the forced swimming test.

Previously, it was reported that *Tualang* honey causes a significant reduction in ACTH and corticosterone levels, as well as depressive-like behavior in OVX rats exposed to social instability stress.[47] Apart from that, *Tualang* honey-treated stressed OVX rats exhibited elevation in brain-derived neurotrophic factor (BDNF) concentration.[47] Decreased expression of BDNF has been proved to contribute to hippocampal atrophy and neuronal loss in experimental animals[48] and was further evidenced by decreased hippocampal volume in depressed patients.[49,50] Hence, it is suggested that *Tualang* honey exhibits its antidepressive-like effects via restoration of HPA axis and enhancement of brain BDNF concentration. As *Tualang* honey is a phytoestrogen rich in flavonoids, it is possible that the mechanisms of antidepressive-like actions are similar to other phytochemical foods rich in flavonoids, such as green tea, blueberry, and *Ginkgo biloba*, which have been shown to increase hippocampal BDNF levels.[51,52,53,54,55]

It is also assumed that the improvement in memory and reduction of depressive symptoms in the stress-induced rats caused by *Tualang* honey are due to its antioxidant capacity, which is attributed to the aforementioned flavonoid contents. Honey has been reported to possess a high flavonoid content (of flavonoids such as quercetin, luteolin, kaempferol, apigenin, chrysin, and galangin), which ranges 60-460 μg/100 g of honey.[56] Other types of antioxidants also present in honey include both enzymatic (catalase, glucose oxidase, and peroxidase) and nonenzymatic substances (ascorbic acid, α-tocopherol, carotenoids, amino acids, proteins, Maillard reaction products, and phenolic acids).[57,58,59] It is possible that the antioxidant content of the honey may have contributed to the decrease of depressive-like behavior and improved the recognition memory of these rats. This would be in keeping with studies that have demonstrated that dietary antioxidants improve cognitive performance in clinical studies[60,61] as well as in animals.[62,63,64] In addition, studies by Chepulis *et al*. (2009)[11] reported that honey-fed rats exhibited better memory performance and decreased anxiety, compared to sucrose-fed rats. This suggests that the better performance seen in the honey-fed rats was not due to the sugar content alone but may have involved other components, possibly antioxidants, of the honey.

Conclusion

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The data in this study strongly suggest a negative role for loud noise stress on the cognitive performance and depressive symptoms of male rats. Moreover, it was shown that daily supplementation with *Tualang* honey may reverse the damage caused by stress exposure. Due to the promising effects of *Tualang* honey, further studies are warranted to identify the possible mechanism of its action.

Footnotes

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Conflict of Interest: None declared.

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