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Research Paper

Effect of chronic stress on capsaicin-induced dental nociception in a model of pulpitis in rats

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ABSTRACT

Objective: Chronic stress can alter nociceptive sensitivity. However, the effect of stress exposure on dental nociception has been less addressed. Therefore, the present study investigated the effects of chronic exposures to some social and psychological stresses on pulpal nociceptive responses.
Design: The stress groups were constructed as follows: forced swimming (n = 6), restraint (n = 6), and mild (n = 10) and severe (n = 15) crowding stresses. Rats were subjected to stress for 1 h per day for a week. At the end of the stress session, pulp irritation was induced by intradental application of capsaicin (100 μg). There were another capsaicin or capsaicin plus stress training groups that received articaine 5 min before the administration of capsaicin. Nociceptive responses were recorded for 40 min. The time (in s) of continuous shaking of the lower jaw and excessive grooming and rubbing of the mouth near the procedure site was measured as nociceptive behaviors. Data was analyzed using one-way analysis of variance (ANOVA) followed by post hoc Tukey's test.
Results: Significant nociceptive responses were evoked by the administration of capsaicin. Exposures to forced swimming ($p < 0.01$), restraint ($p < 0.001$), and both mild and severe crowding stresses ($p < 0.05$) exaggerated capsaicin-induced nociceptive reaction. There was, however, no significant difference in nociceptive reaction time between the different stress groups. Articaine buccal infiltration attenuated nociceptive time in capsaicin and capsaicin plus stress training groups ($p < 0.001$).
Conclusions: The current data support the association between chronic stress exposures and nociceptive behavior following intradental capsaicin administration.

1. Introduction

Dental pain arising from pulpitis is one of the major orofacial problems associated with significant neural deficiency and social disabilities (Sebring, Dimenäs, Engstrand, & Kvist, 2016; Sheiham, 2005). The dental pulp has a highly complex structure that is innervated by myelinated A and unmyelinated polymodal C fibers. Neuropeptide-containing nerves have also been found in the dental pulp. They synthetize and release sensory neuropeptides such as calcitonin gene-related peptide (CGRP) and substance P in response to noxious stimulations (Caviedes-Bucheli, Lombana, Azuero-Holguín, & Munoz, 2006; Manuja, Nagpal, Pandit, & Chaudhary, 2010). A number of sensory nerve fibers innervating human pulp express transient receptor potential vanilloid-1 (TRPV1) as a nonselective ligand-gated cation channel. TRPV1 can be activated in response to various types of stimuli including capsaicin, a bioactive compound of cellie paper (Chung & Oh, 2013). Activation of TRPV1 leads to burning and sturdy pain responses via cytosolic calcium increase and a subsequent induction of pro-inflammatory sensory neuropeptides in sensory neurons (Gouin et al., 2017; Kárai, Russell, Iadarola, & Oláh, 2004).

Stimulation of trigeminal nerves by capsaicin is a reliable experimental model for the study of pathophysiologic features of orofacial nociceptive responses in rat. Injection of capsaicin into the vibrissa pad of rat is associated with distinctive patterns of nociceptive responses (Pelissier, Pajot, & Dallel, 2002). Moreover, intradental administration of capsaicin causes significant dental inflammatory response in rats (Chidiac et al., 2002; Raoof, Esmaeili-Mahani, Nourzadeh et al., 2015). Capsaicin-stimulated CGRP release from dental pulp has been introduced as a pre-clinical model for the study of peripheral neuropeptide secretion in healthy tissue (Fehrenbacher, Sun, Locke,

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Henry, & Hargreaves, 2009).

Stress is an adaptive response to interruptions in normal physiologic state. It prompts a variety of neuroendocrine and immunological responses to maintain internal homeostasis (McEwen, 2007). Prolonged stresses are associated with structural and neurophysiological changes in brain (Czéh et al., 2001; McEwen et al., 2015). Interestingly, there is strong evidence to suggest that exposure to stress challenges may change the intensity of pain (Crettaz et al., 2013; Long, Sadler, & Kolber, 2016). The associations between stressful situations and perception of trigeminal nociception were also investigated in some clinical and preclinical studies (Bergamini et al., 2017; Nevalainen et al., 2016). Psychological stress has been shown to be associated with increased temporomandibular joint-evoked responses (Okamoto, Tashiro, Chang, Thompson, & Bereiter, 2012). However, it has been reported that acute restraint stress can diminish formalin-induced temporomandibular joint nociceptive responses in female rats (Botelho, Gameiro, Tuma, Marcondes, & Ferraz de Arruda Veiga, 2010).

As mentioned above, it is well established that stress can alter orofacial nociceptive responses. However, stressor effects on the perception of pulpal nociception have received less attention. In the current study, by using forced swim, restraint, and social crowded test as animal models of social and psychological stress, the possible effects of chronic stress on capsaicin-evoked pulpal nociception was investigated in rats.

2. Materials and method

2.1. Animals

The experiments were performed on adult male Wistar rats (230–270 g). Animals were housed in a controlled room environment (23 ± 1 °C) and kept on a standard 12:12 h light/dark cycle. Food and water was provided ad libitum. The experimental protocol was approved by the Ethical Committee of Kerman University of Medical Sciences, Kerman, Iran. The rats were adapted to the laboratory environment in their home cages 1 h per day for 2 weeks prior to the initiation of any procedure manipulation and behavioral assessment.

2.2. Experimental groups

The rats were randomly divided into various experimental groups as follows: intact group (n = 6) which received no injection; capsaicin group (n = 6), which received a small cotton pellet dampened with capsaicin solution (100 μg) into a prepared cavity on the left mandibular incisor; capsaicin plus articaine-treated rats (n = 6), which received 0.1 mL of 4% articaine hydrochloride in the alveolar mucosa near the apex of the tooth prior to capsaicin administration; and different experimental stress groups including forced swimming (n = 6), restraint (n = 6), and mild (n = 10) and severe (n = 15) crowding stresses groups that also received cotton pellet dampened with capsaicin solution after exposure to stress. Moreover, to elucidate stress effects of nociceptive induction, the same stress groups that received no capsaicin injection were used. The calculation of an adequate sample size was based both on previous reports (Abbas, Naqvi, Mehmood, Kabir, & Dar, 2011; Gameiro et al., 2005; Hadigol & Rajaei, 2011) and a pilot study.

2.3. Forced swimming test

Forced swimming test is one of the most commonly used method for the assessment of antidepressant-like behavior and stress responses in rodents (Armario, Gavaldà, & Martí, 1995) .Each rat was placed in a Plexiglas container in a cylinder (60 cm high × 12 cm wide) filled to 50 cm with water at a temperature of 22 ± 1 °C. Rats were allowed to swim 5 min per day for seven successive days. At the end of the test, rats were removed from the container and lightly dried.

2.4. Restraint stress test

Restraint stress is well known as a useful method to investigate neurophysiological features of stress (Gregus, Wintink, Davis, & Kalynchuk, 2005). In the present study, the rats were restrained 1 h per day for a week in a plastic conical tube with 5 cm diameter and 12 cm height. The tube was fixed with ventilation holes, and it was plugged so that animals were unable to move/turn around.

2.5. Crowding stress test

Crowding stress is an imposed movement limitation, which is considered a psychosocial stress (Blanchard, McKittrick, & Blanchard, 2001). In this study, before being exposed to stress, the animals were kept in groups of five per cage (40 × 20 × 20 cm). To induce crowding stress, two groups of animals consisting of 10 (mild stress condition) and 15 (severe stress condition) rats per cage were used. The sample size calculation was conducted on the basis of both previous publications and a pilot study (Hadigol & Rajaei, 2011). Each groups exposed to crowding 1 h per day for 1 week. Following the stress cessation, animals were returned to their home cages.

2.6. Induction and management of nociceptive responses

On the day of testing for nociceptive behavior, rats were taken to the testing room and habituated for 30 min. After the induction of short-term anesthesia with carbon dioxide (CO2), a cavity ($2 \times 2 \times 2\ mm^2$) was prepared in the gingival one-third of the distal aspect of left mandibular incisors using a small fissure bur in a high-speed handpiece with water coolant. With the help of magnification (2.5×), pulp exposure was prevented. A small cotton pellet dampened with capsaicin solution (100 μg) was left in the cavity under a light-cured glass-ionomer (Fuji II, GC, Japan) restoration.

Upon capsaicin administration, each rat was placed in the transparent Plexiglass container (30 × 30 × 30 cm) with a mirror positioned at a 45° angle below the floor to allow unbarred observation of the animals. The nociceptive responses were monitored using a digital video camera for 40 min. The measured parameter for nociceptive behavior was the cumulative time (seconds) spent in continuous shaking of the lower jaw, excessive grooming, and rubbing of the mouth near the procedure site (Raoof, Esmaeili-Mahani, Abbasnejad et al., 2015). In the orofacial capsaicin test for rats, the nociceptive response peaks about 15 min after the administration of capsaicin and then gradually decreases (Pelissier et al., 2002). Therefore, the time course of nociceptive behavioral response was divided into eight blocks of 5 min to specify distinctive patterns of capsaicin-induced nociceptive behaviors. Following the assessment of nociceptive responses, the rats were euthanized by exposure to high concentrations of CO2.

2.7. Statistical analysis

Data are presented as means ± standard error of mean. Statistical analysis of nociceptive behavior was performed using one-way analysis of variance (ANOVA) followed by post hoc Tukey's test. Differences were considered significant if $p < 0.05$.

3. Results

3.1. Orofacial capsaicin test

Intradental application of capsaicin produced nociceptive behavior that was characterized by shaking of the lower jaw, scratching, and rubbing of the injected site. The highest nociceptive response time was recorded within 10–15-min intervals following capsaicin administration. The cumulative nociceptive time during 40 min was 856 ± 13.1 s (Fig. 1).

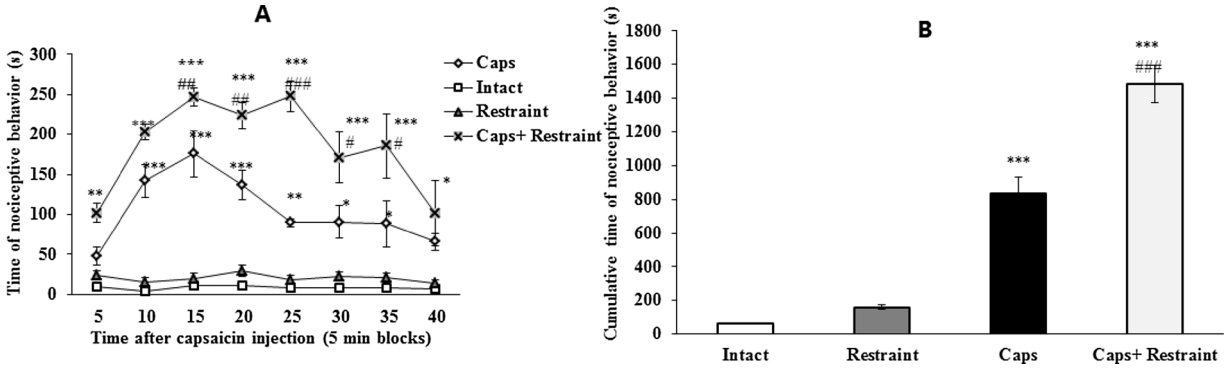

Fig. 1. Effects of restraint stress on the time of nociceptive behavior at each time block (A) and cumulative time of nociceptive behavior (B). Data are presented as mean ± SEM. ***p < 0.001, **p < 0.01, *p < 0.05 versus intact and restraint groups, ###p < 0.001, ##p < 0.01, and #p < 0.05 versus capsaicin (Caps) group.

3.2. Effects of restraint stress on capsaicin-induced pulpal stimulation

Fig. 1A shows the time course of the effect of restraint stress on capsaicin-induced pulpal nociception. In capsaicin-treated rats, the cumulative duration of nociceptive time significantly increased when compared to intact (65.16 ± 3.23) and restraint stress (161 ± 14.62) ($p < 0.01$) groups. In rats submitted to restraint stress before the administration of capsaicin, nociceptive responses significantly increased at 15–35 min intervals after capsaicin stimulation. When compared to other groups, the cumulative duration of nociceptive responses significantly increased in restraint plus capsaicin-treated rats (1489 ± 109.34 s) ($p < 0.001$) (Fig. 1B).

3.3. Effects of forced swimming stress on capsaicin-induced pulpal stimulation

In capsaicin-treated rats, each time block and cumulative time of nociceptive responses significantly increased as compared to both intact (65.16 ± 3.23) and forced swimming stress (149 ± 56.59) groups (Fig. 2A and B). In rats subjected to forced swimming stress, nociceptive responses significantly increased at 20, 25, 30 and 40 min interval times following capsaicin administration (Fig. 2A). Moreover, the total time of nociceptive responses within 40 min of the test period significantly increased in rats treated with forced swimming stress plus capsaicin (1234.1667 ± 115 + 53) when compared to capsaicin (856 ± 13.1) group ($p < 0.05$) (Fig. 2B).

3.4. Effects of crowding stress on capsaicin-induced pulpal stimulation

As shown in Fig. 3A, significant increases in nociceptive responses during different test blocks were observed in capsaicin or capsaicin plus crowding stresses groups as compared to intact and stressed groups. Moreover, in rats submitted to crowding stress (mild or severe) before capsaicin administration, nociceptive behavior slightly, but not significantly, increased at each time block when compared to capsaicin-treated rats (Fig. 3A). Cumulative times of nociceptive behaviors, however, significantly increased in both mild (1165 ± 161.08) and severe (1139.16 ± 32.02) crowding-stress groups as compared to capsaicin group (856 ± 13.1) ($p < 0.05$) (Fig. 3B).

3.5. Comparison of capsaicin-induced nociceptive response between stress training groups

There were no statistically significant differences regarding capsaicin-induced nociceptive behaviors among groups of animals subjected to different stressors. However, restraint rats showed longer cumulative nociceptive time (1489 ± 109.34 s) than animals exposed to other stresses (Fig. 4).

3.6. Effect of articaine on capsaicin-induced nociceptive behaviors in stress training groups

At each time block and cumulative nociceptive time, the administration of articaine hydrochloride 4% could attenuate capsaicin-induced nociceptive stimulation of pulp in all stress groups (Fig. 5A and B).

4. Discussion

The data of the present study showed that repeated exposures to various social and psychological stressors including forced swimming, restraint, and crowding stresses could enhance capsaicin-induced nociceptive stimulation of pulp. Intradental application of capsaicin has been shown to be a valuable tool in measuring nociceptive behaviors

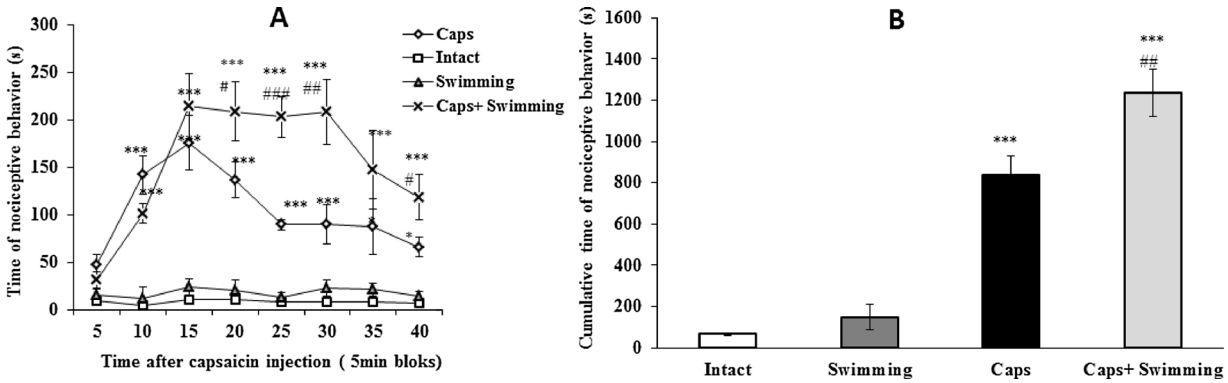

Fig. 2. Effects of forced swimming stress on the time of nociceptive behavior at each time block (A) and cumulative time of nociceptive behavior (B). Data are presented as mean ± SEM. ***p < 0.001, *p < 0.05 versus intact and swimming forced groups, ###p < 0.001, ##p < 0.01, and #p < 0.05 versus capsaicin (Caps) group.

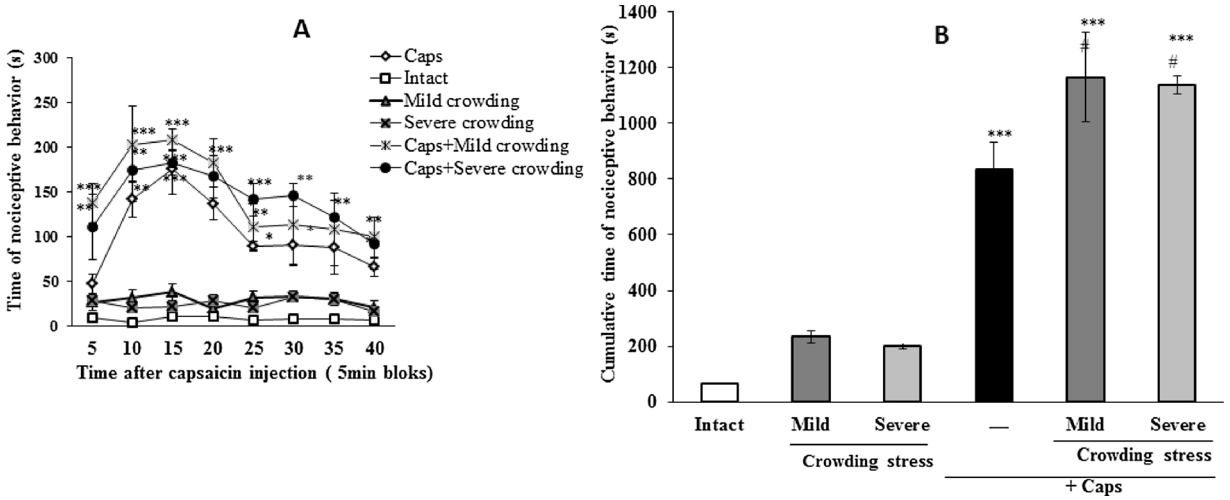

Fig. 3. Effects of crowding stress on the time of nociceptive behavior at each time block (A) and cumulative time of nociceptive behavior (B). Data are presented as mean ± SEM. ***p < 0.001, **p < 0.01, and *p < 0.05 versus intact and crowding stress groups, #p < 0.05 versus capsaicin (Caps) group.

related to the trigeminal system. This method produces more pronounced nociceptive scores than that observed with other chemical compounds such as formalin (Chidiac et al., 2002; Raoof, Esmaeili-Mahani, Abbasnejad et al., 2015).

This is the first study that addresses increased nociceptive behavior following stress induction in an animal model of capsaicin-induced pulpal stimulation. It has already been indicated that swimming and prenatal stresses enhance nociceptive responses in formalin test (Butkevich & Vershinina, 2003; Quintero et al., 2000). Chronic forced swim stress can also increase complete Freund's adjuvant-induced thermal hyperalgesia and c-Fos induction in the insular cortex of rats (Imbe, Kimura, Donishi, & Kaneoke, 2014). Moreover, repeated sound stress is found to increase bradykinin-evoked inflammatory reaction in rats (Khasar, Green, & Levine, 2005).

As shown in Fig. 4, all the stressors showed similar excitatory effects on nociception induction. Interestingly, a similar pattern of nociceptive behavior was found in different stress groups. In almost all groups, the highest nociceptive scores were recorded within 10–25 min after capsaicin administration. However, the nociceptive behaviors were more noticeable in animals of the restraint stress group. It is an established laboratory method for the study of biochemical and neurophysiological aspects of stress responses. Surprisingly, a recent study indicated that repeated restraint stress enhances nociceptive perception in rats with dentin hypersensitivity (Bergamini et al., 2017). It has also been reported that chronic restraint stress can induce masseter hyperalgesia and c-fos induction in neurons and astrocytes of spinal subnucleus caudalis as a critical brain center is involved in the transmission and processing of trigeminal signals (Lin et al., 2017). In general, chronic stress is associated with dysregulation of autonomic and endocrine systems. In particular, it has been indicated that immune and inflammatory responses are disturbed following stressful challenges (Glaser & Kiecolt-Glaser, 2005; Pace et al., 2006). It has been indicated that the level of pro-inflammatory cytokines in certain brain regions of stressed rats is overexpressed. It may be causally linked to prompt nociceptive hypersensitivity (Johnson, O'Connor, Watkins, & Maier, 2004; Yang et al., 2015). However, the underlying mechanism(s) of stress-induced nociceptive sensitivity can be very complex and is highly dependent on the nature, intensity, and duration of the stressor (Blanchard et al., 2001). For example, the effects of repeated stress on inflammatory pain-related behavior are not the same in stress normo-responsive and stress hyper-responsive rat strains (Jennings, Okine, Olango, Roche, & Finn, 2016).

Social crowding is defined as a psychophysiological stressor that can be associated with significant changes in emotional state, sympathetic reactivity, and nociceptive sensitivity (Gadek-Michalska & Bugajski, 2003; Tramullas, Dinan, & Cryan, 2012). In a laboratory setting, animals are housed in crowded conditions with insufficient space for applying crowding stress. Unfortunately, because of a shortage of adequate data and absence of a detailed procedure protocol, there is no exact definition of crowded housing conditions. (McKittrick, Blanchard, Hardy, & Blanchard, 2009). In this study, similar to a previous work, we had two-fold and three-fold increases in the number of animals per cage

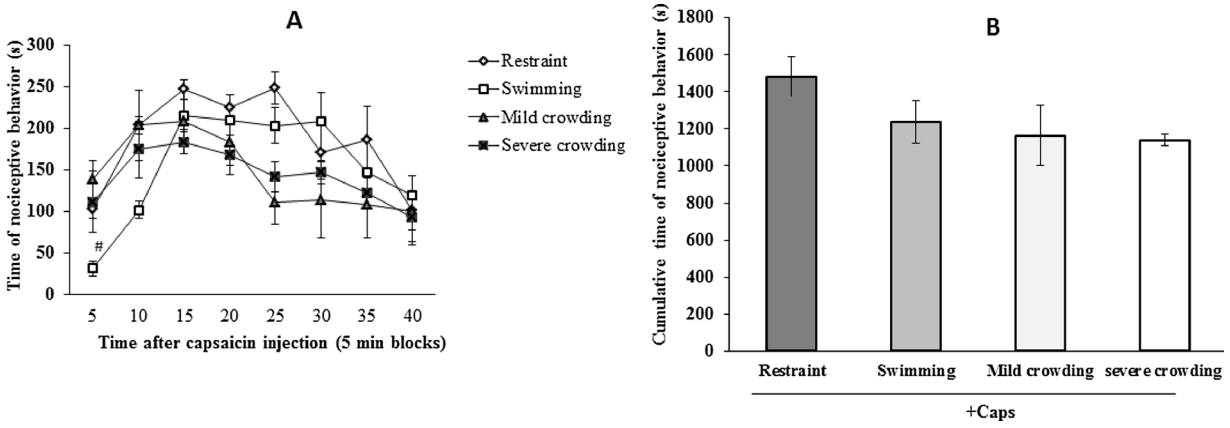

Fig. 4. Time of nociceptive behavior at each time block (A) and cumulative time of nociceptive behavior (B) in rats subjected to different chronic stress models. Data are presented as mean ± SEM.

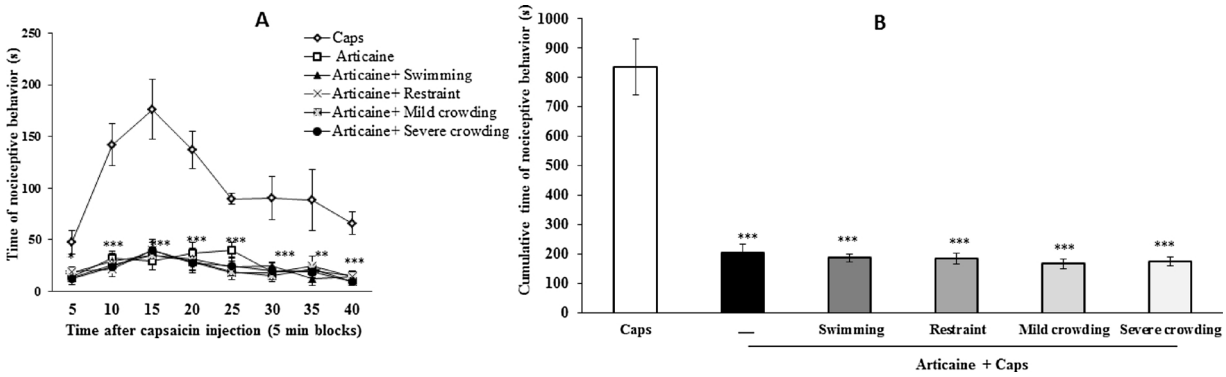

Fig. 5. Effects of administration of articaine on the time of nociceptive behavior at each time block (A) and cumulative time of nociceptive behavior (B) in capsaicin and capsaicin plus stress training groups. Data are presented as mean ± SEM. ***p < 0.001, versus capsaicin (Caps) group.

to simulate mild and severe crowded situations (Hadigol & Rajaei, 2011). Surprisingly, the result showed that the intensity of crowded stress did not significantly affect the nociceptive response. This could probably be correlated with the protocol used to induce stress, including the number of animals and stress duration. However, additional work is required to further investigate this issue.

Capsaicin prompts a burning pain through the activation of TRPV1 receptors on C and A fibers of trigeminal nerves (Caterina et al., 2000). TRPV1 receptors play an important role in the modulation of both stress and nociceptive responses (Ho, Ward, & Calkins, 2012; Ishikura et al., 2015). Forced swim stress-induced depression-like behavior was inhibited following the central antagonism of TRPV1 receptors in rats (Manna & Umathe, 2012). Yu and colleagues reported that chronic water avoidance stress is associated with hyperalgesia and TRPV1 expression in dorsal root ganglion of rats (Yu et al., 2010). It has been also demonstrated that TRPV1 activation is associated with hyperexitability of sensory peptidergic neurons, which may be reflected by pain hypersensitivity (Weitlauf et al., 2014). In the present study, the excitatory effect of chronic stress on TRPV1 receptors, at least in part, may contribute to further enhancement of nociceptive transmission following capsaicin irritation. However, further studies are needed to elucidate this issue in more detail.

Stress exposure is frequently associated with dysregulation of excitatory and inhibitory synapses mediators, which are involved in the regulation of emotional state and nociceptive responses (Bretin et al., 2016; Maguire, 2016). It has been reported that stress exposure prompts satellite glia cell activation and substance P induction in the trigeminal ganglion of rats (Zhao et al., 2015). Stress may also influence the release of inhibitory neuropeptides, predominantly through GABAergic transmission. Forced swimming stress-induced hyperalgesia has been shown to decrease GABA inhibitory current through the activation of NMDA receptors in the spinal cord of rats (Quintero, Cardenas, & Suarez-Roca, 2011). In the literature, there are no reports indicating the effects of stress on the induction of pain neuromodulators in pulp sensory nerves. An attempt to deepen our understanding of the underlying mechanisms for the effect of stress on elevated nociceptive behaviors in response to pulp irritation may be beneficial.

Trigeminal nerve stimulation activates different areas of the brain, some of which are also involved in stress responses (Bantick et al., 2002). It might be another explanation for the effect of stressors on pulpal nociception. For instance, the limbic system, being the predominant purveyor of emotional processing, can also play a role in pain states (Sinha, Sharma, Mathur, & Nayar, 1999; Vogt, 2005).

Stressful situations are commonly accompanied by increases in pro-apoptotic and oxidant markers, which may induce neurological toxicity. It has shown that social stresses induce increases in reactive oxygen species and lipid peroxidation in rat brain (Fontella et al., 2005). Additionally, forced swimming stress prompts imbalances in oxidant and anti-oxidant markers (Lucca et al., 2009). Capsaicin also increases reactive oxygen species and apoptosis, which may reflect the toxic effects of capsaicin (Pramanik, Boreddy, & Srivastava, 2011; Raoof, Esmaeili-Mahani, Nourzadeh et al., 2015). However, evaluating such important effect needs supplementary studies.

In this study, injection of articaine prior to capsaicin administration could prevent nociceptive behavior in all stress-training groups. Unlike other anesthetics, which have benzene as their aromatic ring, articaine has a thiophene ring providing greater liposolubility and higher concentration. This helps articaine to diffuse better through soft tissue and bone and achieve higher anesthesia success than other anesthetics such as lidocaine (Vree & Gielen, 2005; da Silva et al., 2010).

5. Conclusions

The present data indicate that chronic exposures to stressful challenges are correlated with increased nociceptive behaviors following intradental administration of capsaicin. All the stressors showed similar excitatory effects on nociception duration. Interestingly, a similar pattern of nociceptive behavior was found in different stress groups. Further study is necessary to define a shared mechanism(s) underlying their effects.

Conflict of interest

The authors report no conflicts of interest.

Acknowledgments

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