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Anti-nociceptive Mechanisms of Testosterone in Unilateral Sciatic Nerve Ligated Male Rat

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Abstract

BACKGROUND: Neuropathic pain is a chronic condition which is mediated by complex mechanisms exerted by the release of nerve neurotransmitter. A correlation exists between the sex hormones and neuropathic pain, however many aspects of this correlation still remain unclear.

OBJECTIVES: The aim of the current study was to determine the anti-nociceptive activity of testosterone and its interaction with the opioidergic, GABAergic, and dopaminergic receptors in sciatic nerve-ligated male rats.

METHODS: In this study, 170 adult male rats were randomly allocated into the 4 experimental groups following the sciatic nerve ligation. In the experimental group 1, the animals were injected intraperitoneally (i.p.) with saline, testosterone (10 and 15 mg/kg), and morphine (5 mg/kg), and 30 minutes later with formalin into the plantar surface of the right paw. In the experimental group 2, the animals were injected with saline, testosterone (15 mg/kg), naloxone (2 mg/kg), and testosterone (15 mg/kg)+naloxone (2 mg/kg). In the groups 3 and 4, flumazenil (5 mg/kg) and yohimbine (2 mg/kg) were injected instead of naloxone. Then, the time spent for paw licking was monitored for the first and second phases after the formalin injection.

RESULTS: According to the results, the injection of testosterone in a dose dependent manner decreased the time of licking and biting in the injected paw compared to the control group (P<0.05). Likewise, pretreatment with naloxone or flumazenil significantly decreased the anti-nociceptive effect of testosterone (P<0.05). While pretreatment with yohimbine significantly increased the anti-nociceptive effect of testosterone (P<0.05).

CONCLUSIONS: These results suggested testosterone has an anti-nociceptive activity and this effect is mediated by the opioidergic, GABAergic, and dopaminergic receptors in the sciatic nerve-ligated male rat.

KEYWORDS: Anti-nociceptive, Dopaminergic, GABAergic, Rat, Sciatic nerve injury, Testosterone

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Introduction

Neuropathic pain is a chronic condition that can happen at the peripheral and central nervous systems (Migita *et al.*, 2018). Its symptoms include an unpleasant sensation of burning or tingling, increased sensitivity to the noxious stimuli (hyperalgesia), and pain due to tissue damages or infections (allodynia) (Vahdati Hassani *et al.*, 2015). Numerous factors such as tissue damages, injury, or infections are associated with neuropathic syndromes (Trevisan *et al.*, 2016). Following the nerve injury, the activation and production of pro- and anti-inflammatory cytokines lead to the activation of the injured nerve and spinal cord which contribute to the peripheral and central sensitization (Xu *et al.*, 2018). A prolonged condition may lead to a serious disability in walking and even hinder the quality of life. Experimental sciatic nerve injury and ligature are useful techniques to determine the pathophysiology of neuropathic pain (Sumizono *et al.*, 2018). The appropriate management of neuropathic pain should be considered since pharmacological treatments have a positive effect in half of the patients afflicted with this problem (Tsuda, 2016).

Growing evidence on sex differences and the anti-nociceptive activity of the opioidergic system in non-human primates and rodents has demonstrated that males are more sensitive than females (Khakpay and Khakpai, 2020). Observed differences are related to hormonal, physiological, psychological, neuro-immunological, and sociocultural factors (Nasser and Afify, 2019). There is information about the anti-nociceptive role of testosterone in males, where gonadectomy leads to a decrease in morphine-induced nociception (Beshkani *et al.*, 2017). Testosterone plays an analgesic role in temporomandibular joint pain/damage in male rats (Sharma *et al.*, 2019). It was reported that clonidine (α_2 adrenoceptor agonist) alone, in a dose-dependent manner, reduced the nociceptive responses in both the first and second phases in a mouse orofacial formalin model (Yoon *et al.*, 2015). Moreover, the α_2-adrenoceptor-induced anti-nociception in the trigeminal area was mediated by testosterone in a male rat (Nag and Mokha, 2016). The anti-nociceptive effects of clonidine and orphanin/FQ were mediated by testosterone in the spinal cord (Nag and Mokha, 2009). Furthermore, higher levels of testosterone propionate (1 mg/kg for 7 days) decreased the temporomandibular joint-induced pain using formalin in the male rats (Fischer *et al.*, 2007).

Recent studies have identified a role for the central and spinal γ-aminobutyric acid (GABA) receptors in pain modulation (Witkin *et al.*, 2019; Ness *et al.*, 2020). The spinal $GABA_A$ receptors have an important role in the management of inflammatory and neuropathic pains (Bravo-Hernández *et al.*, 2016). Despite the fact that the anti-nociceptive activity of testosterone has been well documented, its analgesic activity in sciatic nerve injury remains unclear. Additionally, its neurological connection to the central nervous system (CNS) has been investigated in several types of research (Yoon *et al.*, 2015; Nag and Mokha, 2016), however, limited information exists on its role in the peripheral nervous system (PNS). Therefore, the primary aim of the current study was to determine the anti-nociceptive mechanisms of testosterone in the sciatic nerve-ligated male rat. The secondary purpose was to determine its interaction with the opioidergic, GABAergic, and dopaminergic (DAergic) receptors in the sciatic nerve-ligated male rat.

Materials and Methods

Animals and Surgical Procedure

In this study, 170 adult male Wistar rats (200-250 g) were used in 4 experimental procedures (4 groups in each). Anesthesia was induced by the combination of ketamine HCL (60 mg/kg) and Xylazine HCL (10 mg/kg). The skin on the right paw was shaved and prepared with 10% povidone-iodine solution. A partial sciatic nerve ligation was performed using a tight ligature with a surgical suture, around 1/3 to 1/2 of the diameter of the sciatic nerve located in the right-paw side (Zimmermann, 1983; Kim *et al.*, 2014; Koga *et al.*, 2017). In experimental group 1, animals were injected intraperitoneally (i.p.) with saline, testosterone propionate (Iran hormone, Tehran, Iran) (10 and 15 mg/kg), and morphine (5 mg/kg), and 30 minutes later with 1% formalin (10 µL) into the plantar surface of the right paw (Mahdian Dehkordi *et al.*, 2019). The test was performed according to a protocol proposed by Hunskaar and Hole (1987). Thirty

minutes after formalin injection, the time spent for licking the injected paw was considered as the first (0-5 minutes) and second (15-30 minutes) phases (Hajhashemi *et al.*, 2011). In the experimental group 2, the rats were injected (i.p.) with saline, testosterone (15 mg/kg), naloxone (2 mg/kg), and testosterone (15 mg/kg) + naloxone (2 mg/kg). In the group with two injections, first, antagonist was injected and 15 minutes later testosterone (15 mg/kg) and 15 minutes later formalin (10 µL of the 1% solution) were injected. Then, the time spent for paw licking was monitored in both phases. In the experimental group 3, saline, testosterone (15 mg/kg), flumazenil (5 mg/kg), and flumazenil (5 mg/kg) + testosterone (15 mg/kg) were injected. In the experimental group 4, the rats received saline, testosterone (15 mg/kg), yohimbine (2 mg/kg), and yohimbine (2 mg/kg) + testosterone (15 mg/kg). The doses of the drugs used were selected based on the previous reports (Hasanvand *et al.*, 2018; Hassanpour *et al.*, 2020) as well as a preliminary pilot study. The experimental procedures were followed according to the Guide for the Care and Use of Laboratory Animals to investigate the experimental pain in the animals. The study was approved by the Ethics Committee of Faculty of Veterinary Medicine, Science and Research Branch, Islamic Azad University, Tehran, Iran (IAU 42546).

Statistical Analyses

Data was analyzed by the one-way analysis of variance using the SPSS software version 18.0 (PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.) and presented as mean ± standard error (SE). The Tukey post-hoc test was also used for the differences between the groups. P-value <0.05 was considered to indicate a significant difference.

Results

In experimental group 1, the injection of testosterone (10 and 15 mg/kg, i.p.) in a dose dependent manner decreased the time of licking and biting in the injected paw compared to the control group (P<0.05). Likewise, morphine (5 mg/kg, i.p.) significantly decreased the time of licking and biting in comparison to the control group (P<0.05) (Figure 1).

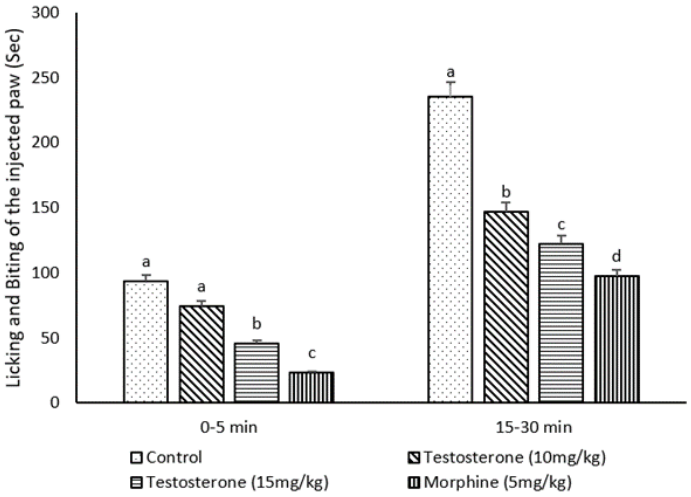

Figure 1. Effect of testosterone and morphine on licking and biting time of the injected paw in sciatic nerve ligated male rat (n=50). Data are expressed as mean ± SE. Different letters (a-d) indicate significant differences between treatments (P<0.05).

In experimental group 2, naloxone (2 mg/kg, i.p.) had no significant effect on the time of licking and biting in comparison to the control group (P>0.05). This is while testosterone (15 mg/kg, i.p.) significantly decreased the time of licking and biting compared to the control group (P<0.05). Moreover, pre-treatment with the opioid receptor antagonist significantly decreased the anti-nociceptive effect of testosterone compared to the group injected with testosterone alone (P<0.05) (Figure 2).

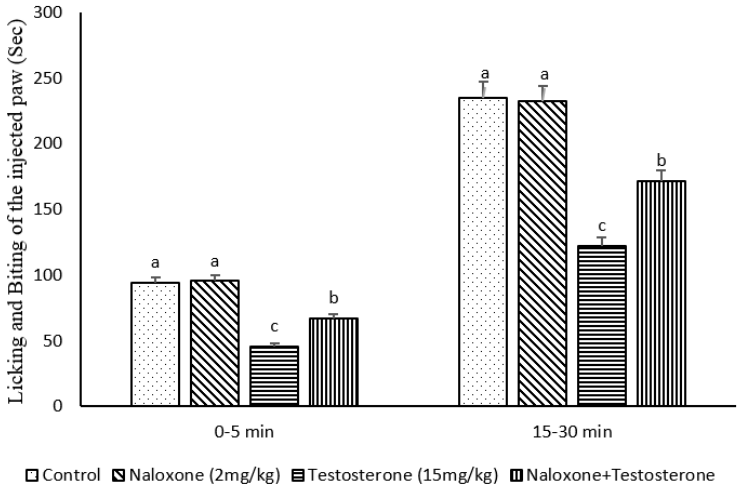

Figure 2. Effect of testosterone, naloxone and their co-injection on licking and biting time of the injected paw in sciatic nerve ligated male rat (n=40). Naloxone: opioid receptor antagonist. Data are expressed as mean ± SE. Different letters (a-c) indicate significant differences between treatments (P<0.05).

Regarding experimental group 3, flumazenil (5 mg/kg, i.p.) had no significant effect on the time of licking and biting in comparison to the control group (P>0.05). While testosterone (15 mg/kg, i.p.) significantly reduced the time of licking and biting compared to the control group (P<0.05). Similar to the previous group, the pre-treatment with the selective $GABA_A$ antagonist significantly diminished the anti-nociceptive effect of testosterone compared to the solely testosterone-injected group (P<0.05) (Figure 3).

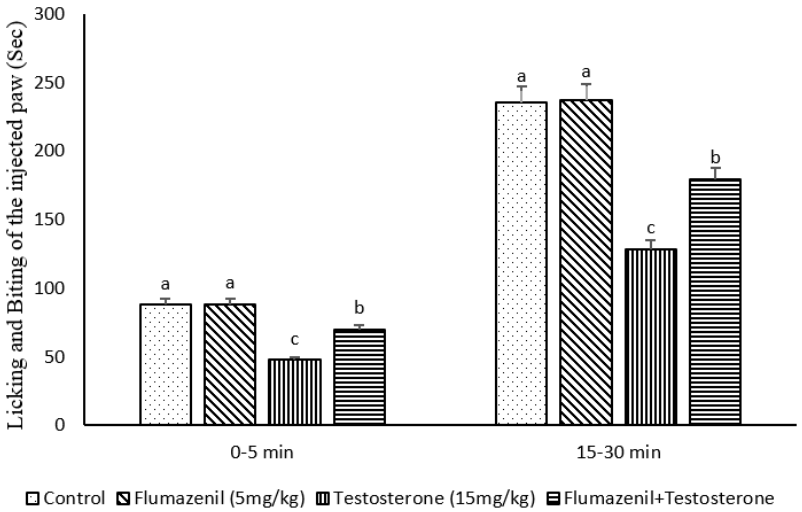

Figure 3. Effect of testosterone, flumazenil and their co-injection on licking and biting time of the injected paw in sciatic nerve ligated male rat (n=40). Flumazenil: selective $GABA_A$ antagonist. Data are expressed as mean ± SE. Different letters (a-c) indicate significant differences between treatments (P <0.05)

Considering the experimental group 4, yohimbine (2 mg/kg, i.p.) had no significant effect on the time of licking and biting in comparison to the control group (P>0.05). While testosterone (15 mg/kg, i.p.) significantly reduced the time of licking and biting compared to the control group (P<0.05). despite the

previous two groups, the pre-treatment with the α-adrenergic receptor antagonist (yohimbine) significantly improved the anti-nociceptive effect of testosterone compared to the group injected with testosterone alone (P<0.05) (Figure 4).

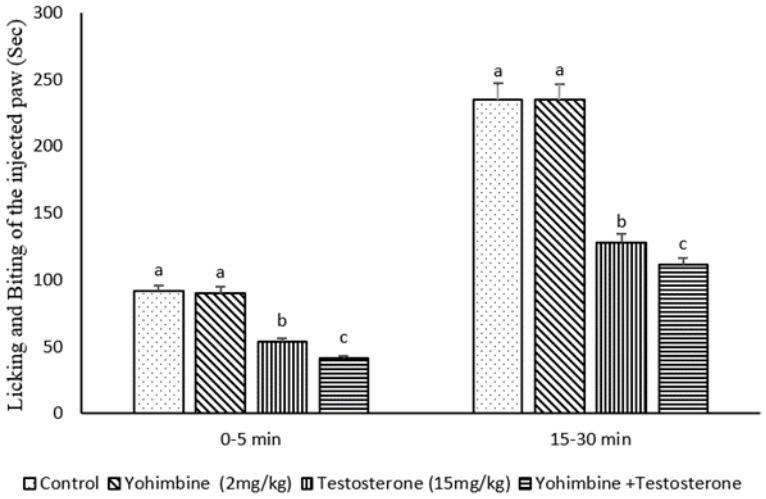

Figure 4. Effect of testosterone, clonidine and their co-injection on licking and biting time of the injected paw in sciatic nerve ligated male rat (n=40). Yohimbine: α-adrenergic receptor antagonist. Data are expressed as mean ± SE. Different letters (a-c) indicate significant differences between treatments (P <0.05).

Discussion

The central and peripheral mechanisms of neuropathic pain consist of the changes in the ion channel expression and nerve neurotransmitter release (Trevisan *et al.*, 2016). Pain acts via several chemical mediators released during this process and leads to nociceptive sensitization. The mechanism underlying the formalin-induced pain behavior involves a series of events including peripheral and central biphasic responses (Shi *et al.*, 2011). Acute pain serves as a warning system that signals imminent tissue damage. Whereas chronic pain has no protective role and persists for a long time after injury without reflecting a definite lesion or disease (Labuz *et al.*, 2016). The formalin test is a reliable and sensitive behavioral biphasic model of nociception (Vahdati Hassani *et al.*, 2015) that is used to determine the mechanism of action of testosterone. The rats subjected to the formalin test do not usually display any pain response between the two phases, as observed in the current study. Actually, the interphase is the result of hyperpolarization and transient inactivation by formaldehyde of the surviving neurons (Fischer *et al.*, 2014).

According to the results, the injection of testosterone in a dose dependent manner decreased the time of licking and biting in the injected paw. Moreover, the pre-treatment with naloxone significantly decreased the anti-nociceptive effect of testosterone in the sciatic nerve-ligated male rat. In the present study, 14 days after the unilateral sciatic nerve ligation, hyperalgesia to the thermal stimulation was significantly observed (pilot study for the accuracy of ligation protocol). Testosterone and its metabolites have an anti-nociceptive effect on the inflammation-induced mechanical allodynia. In addition, the replacement of testosterone reversed the inflammation-induced sensitivity in the gonadectomized rat (Nasser and Afify, 2019). Furthermore, the testosterone replacement improved the responses to morphine in the castrated rats (Hosseini *et al.*, 2011). Despite several types of research, the cellular and molecular mechanisms underlying the regulatory activity of testosterone on opioid analgesia remain still unclear (Nasser and Afify, 2019).

The Effect of adrenoceptors on pain has been well documented as the administration of clonidine attenuates the nociception and hyperalgesia in the animal models of acute and chronic pain (Nag and Mokha,

2009). As observed in the current study, pre-treatment with yohimbine increased the anti-nociceptive effect of testosterone in the sciatic nerve-ligated male rat. On the contrary, the pre-treatment with flumazenil decreased the anti-nociceptive effect of testosterone in the sciatic nerve-ligated male rat. During the prolonged chronic pain, mediators such as bradykinin and substance P were released into the nerve terminals. The analgesic activity of α- adrenoceptors were mediated by a decrease in the levels of glutamate and substance P in the spinal cord (Claiborne *et al.*, 2006). Testosterone plays a key role in the expression of anti-nociception induced by α_2-adrenoceptor in the trigeminal region of the male rats and our findings in terms of sciatic nerve-ligated male rat was similar to this report. The testosterone replacement in the ovariectomized rats improved the anti-nociceptive effect of clonidine (Nag and Mokha, 2009). It is assumed there is a correlation between the anti-nociceptive effects of testosterone and α-adrenoceptors. A similar report about the requirement of testosterone for the expression of α-adrenoceptors in the spinal cord and trigeminal region implies the importance of the trigeminal region as a relay center for the nociceptive signals of lower area such as temporomandibular joint (Jahanshahi *et al.*, 2018). Perhaps testosterone and α-adrenoceptors act via decreasing the release of pain mediators; however, more investigations are required to determine the accuracy of this phenomenon.

The effect of the GABAergic system on neuropathic pain is clear (Zeilhofer *et al.*, 2012). The blockade of spinal $GABA_A$ receptors decreases the tonic excitability of primary afferent fibers (Loeza-Alcocer *et al.*, 2013), as well as decreases the inflammatory and neuropathic pain (Bravo-Hernández *et al.*, 2016). The central and spinal $GABA_A$ receptors inhibit the basal synaptic transmission and increase the pain thresholds in mice (Xue *et al.*, 2017). However, because of the limitations of the current study, we were not able to determine the interaction of testosterone with specific adrenergic and GABAergic receptors. The nociceptive response in the formalin test was higher in the mice lacking the α5-$GABA_A$ receptors (Perez-Sanchez *et al.*, 2017). Furthermore, the GABA receptors play a crucial role in different nuclei of the CNS such as the parabrachial nucleus as a nociceptive relay between the spinal laminas and intralaminar thalamus that mainly project to the prefrontal cortex (Roeder *et al.*, 2014). There is an interaction between testosterone and GABA in the regulation of several physiologic and pathophysiologic conditions. The anxiolytic effects of testosterone are mediated by the $GABA_A$ receptors and this effect is blocked by the administration of picrotoxin (a $GABA_A$ receptor antagonist) in the female rats (Flores-Ramos *et al.*, 2019).

Exposure to neurosteroids increases the open probability of the $GABA_A$ receptor and leads to a Cl^- influx and decreases neuronal excitability (Wang *et al.*, 2016). Reddy and Jian (2010) reported that testosterone-derived metabolites such as rostanediol can activate the $GABA_A$ and $GABA_C$ receptors. Additionally, the $GABA_C$ receptors have an interaction with the anxiolytic effect of testosterone. Perhaps the findings of this study also is regulated by these interactions though because of limitations of the current study, we were not able to determine the interaction of testosterone with specific receptors. Hence, further researches are needed to determine the accurate neurologic mechanisms involved in the anti-nociceptive activity of testosterone in unilateral sciatic nerve ligation. The limitations of the current study hampered us to determine the anti-nociceptive activity of the central testosterone and its interconnections with the opioidergic, GABAergic, and DAergic systems.

Conclusion

In conclusion, these results suggested testosterone has an anti-nociceptive activity and this effect is mediated by the opioidergic, GABAergic, and DAergic receptors in the sciatic nerve-ligated male rat.

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Conflict of Interest

The authors declared no conflict of interest.

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اثرات ضددردی تستوسترون در انسداد یک طرفه عصب سیاتیک در موش صحرایی نر

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چکیده

زمینه مطالعه: درد نوروپاتیک شرایط مزمنی است که با مکانیسم‌های پیچیده از طریق میانجی‌های عصبی انجام می‌شود. ارتباطی بین هورمون‌های جنسی و درد نوروپاتیک وجود دارد ، اما بسیاری از جنبه‌های این پدیده هنوز نامشخص است.

هدف: بنابراین، هدف از مطالعه حاضر اثرات ضد دردی تستوسترون و تأثیر متقابل آن با گیرنده‌های اوپیوئیدی، گاباارژیک و دوپامینرژیک در موش صحرایی نر متعاقب لیگاتور عصب سیاتیک بود.

روش کار: مدر این مطالعه ۱۷۰ موش صحرایی نر بالغ متعاقب لیگاتور عصب سیاتیک به‌طور تصادفی در ۴ گروه آزمایش قرار گرفتند. در آزمایش ۱، به حیوانات به‌واسطهٔ سرم فیزیولوژی، تستوسترون (۱۰ و ۱۵ میلی‌گرم در کیلوگرم) ، مورفین (۵ میلی‌گرم در کیلوگرم) تزریق شدند و ۳۰ دقیقه بعد تزریق فرمالین به سطح کف پای راست انجام شد. در آزمایش ۲ ، سرم فیزیولوژی، تستوسترون (۱۵ میلی‌گرم در کیلوگرم)، نالوکسان (۲ میلی‌گرم در کیلوگرم) و تستوسترون (۱۵ میلی‌گرم در کیلوگرم) + نالوکسان (۲ میلی‌گرم در کیلوگرم) تزریق شد. در آزمایشات ۳ و ۴ فلومازنیل (۵ میلی‌گرم در کیلوگرم) و یوهیمبین (۲ میلی‌گرم در کیلوگرم) به جای نالوکسان تزریق شد. سپس زمان صرف لیسیدن پنجه در مرحله اول و دوم پس از تزریق فرمالین تعیین شد.

نتایج: براساس یافته‌ها، تزریق تستوسترون به روش وابسته به دوز باعث کاهش زمان لیسیدن و گاز گرفتن در پنجه در مقایسه با گروه کنترل شد ($P<۰/۰۵$). پیش تزریق نالوکسان یا فلومازنیل به‌طور قابل توجهی اثر ضد درد تستوسترون را کاهش داد ($P<۰/۰۵$). پیش‌تزریق با یوهیمبین به‌طور قابل توجهی اثر ضد درد تستوسترون را افزایش داد ($P<۰/۰۵$).

نتیجه‌گیری نهایی: نتایج نشان‌دهندهٔ این است که تستوسترون دارای فعالیت ضد دردی بوده و این اثرات از طریق گیرنده‌های اوپیوئیدی، گاباارژیک و دوپامینرژیک در موش نر متعاقب لیگاتور به عصب سیاتیک انجام می‌شود.

واژه‌های کلیدی: ضددرد، دوپامینرژیک، گاباارژیک، موش صحرایی، آسیب عصب سیاتیک، تستوسترون

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