

Effects of Systemic Administration of Oxytocin on Contextual Fear Extinction in a Rat Model of Post-Traumatic Stress Disorder

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ABSTRACT

Introduction: One of the hallmark symptoms of posttraumatic stress disorder (PTSD) is the impaired extinction of traumatic memory. Single prolonged stress (SPS) has been suggested as an animal model of PTSD, since SPS rats exhibited the impaired fear extinction. Oxytocin (OXT) has been recently suggested as a potential pharmacotherapy for treatment of PTSD. In this study, using SPS rats we investigated the effects of multiple systemic administration of OXT on contextual fear extinction.

Methods: SPS was conducted in three stages: restraint for 2 h, forced swim for 20 min, and diethyl ether anesthesia, and then left undisturbed in their home cage for 7 days. In the SPS group, 7 days after SPS treatment, contextual fear conditioning was performed (on day 0), and then extinction training was performed on each of four consecutive days following fear conditioning. In the sham group, the procedures were similar except that SPS treatment was not performed.

Results: During extinction trial (10 min) freezing behavior was recorded. OXT (1, 10, 100 and 1000 µg/kg) was administrated (I.P) immediately after each extinction trial. SPS rats exhibited significant impairment of contextual fear extinction as compared with sham rats. While there was no significant difference in the freezing levels between SPS and Sham rats 24 h after the fear conditioning, the freezing levels in SPS rats were significantly higher than those in sham rats after the second extinction training. Systemic OXT delayed fear extinction in sham rats as compared with sham-saline treated animals. No effect of OXT was found in SPS rats.

Discussion: These findings indicate that increasing OXT transmission during fear memory reactivation delays fear extinction, and thus, the recommendation of OXT for PTSD treatment should be considered with caution.

1. Introduction

Posttraumatic stress disorder (PTSD) is a psychiatric disorder that develops following the experience of life-threatening traumatic events, characterized by symptoms such as persistent re-experiencing of the traumatic event, avoidance of stimuli associated with the trauma, numbing of general responsiveness, and increased arous-

al (Pitman 1997). The neuronal mechanisms underlying fear conditioning and impaired fear extinction were suggested to be involved in the production of re-experiencing symptoms, such as intrusive memory and, in PTSD (Charney, Deutch, Krystal, Southwick, & Davis 1993). Thus, extinction learning (a reduction in conditioned fear response when the conditioned stimulus is repeatedly presented in the absence of an unconditioned stimulus) plays an important role in the treatment of PTSD.

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In fact, cognitive behavioral therapy (CBT), the most commonly used approach for the treatment of PTSD, relies on extinction-based mechanisms (Rothbaum & Davis 2003). Numerous studies have demonstrated CBT as an effective treatment for PTSD (Agorastos, Marmar, & Otte 2011, Olatunji, Cisler, & Deacon 2010, Roberts, Kitchiner, Kenardy, & Bisson 2009). However, many patients fail to achieve remission with CBT (Cloitre 2009, Devilly & Huthier 2008). Recent studies have suggested that adding some pharmacologic agents to CBT, particularly those involved in neural control of fear extinction, can augment treatment efficacy in PTSD patients (Davis, Ressler, Rothbaum, & Richardson 2006, Dunlop, Mansson, & Gerardi 2012).

Oxytocin (OXT), a nine-amino acid peptide, is synthesized in the hypothalamus and secreted into the blood stream in the neurohypophysis as a neuro-hormone (Gimpl & Fahrenholz 2001). As a hormone, it mainly regulates a variety of biological functions such as reproduction-associated processes (Ivell, Balvers, Rust, Bathgate, & Einspanier 1997), social recognition (Keverne & Curley 2004), maternal behavior (Pedersen, Ascher, Monroe, & Prange 1982), and neuroendocrine regulation of the stress response (Neumann 2002). In addition to endocrine functions, OXT acts as a neurotransmitter in a variety of brain structures including the septum, hippocampus, and central amygdala in response to various stressful stimuli (Bosch, Meddle, Beiderbeck, Douglas, & Neumann 2005, Neumann 2008). Exogenous OXT has anxiolytic effects in both animals and humans (Heinrichs & Domes 2008), inhibit the activity of the hypothalamic–pituitary–adrenal (HPA) axis (Neumann, Wigger, Torner, Holsboer, & Landgraf 2000), and reduces activation of the amygdala to threatening faces, thereby reducing the autonomic and behavioral manifestation of fear in healthy volunteers and patients with social anxiety disorder (Kirsch et al. 2005, Labuschagne et al. 2010). These findings suggest that OXT has anxiolytic and anti-stress effects in both humans and rodents. Since PTSD is marked by impairments in anxiety/stress regulation and hyperactivity of the amygdala (Rauch et al. 2000, Shin, Rauch, & Pitman 2006), OXT might be a good candidate for the treatment of PTSD (Olf, Langeland, Witteveen, & Denys 2010, Viviani et al. 2011).

Single prolonged stress (SPS) has been proposed as a valid animal model of PTSD, since rats exposed to SPS illustrate enhanced negative feedback of the HPA axis (Kohda et al. 2007), a sustained exaggeration of the acoustic startle response, increased anxiety-like behavior in the elevated plus maze, and increased contextual fear (Yamamoto et al. 2009). These responses resemble

the clinical symptoms observed in PTSD patients (Pitman 1997). In the present experiments, OXT was administered systemically at different doses to investigate its effects on the extinction of fear response in a rat model of PTSD.

2. Methods

2.1. Animals

Male Wistar rats (200-300g) were housed five per cage, maintained on a 12-h light/dark cycle (light on from 08:00 to 20:00), and fed and watered ad libitum. All procedures were conducted in agreement with the National Institutes of Health Guide for Care and Use of Laboratory Animals. All behavioral experiments were done between 9am to 2pm.

2.2. Drugs

OXT (Sigma-Aldrich, USA) was dissolved in saline and administered interaperitoneally at doses of 1, 10, 100, or 1000 $\mu\text{g}/2\text{ml}/\text{kg}$. The choice of doses was based on pilot and previous studies (Kovács, Vécsei, & Telegdy 1978, Missig, Ayers, Schulkin, & Rosen 2010, Petersson, Hulting, & Uvnäs-Moberg 1999).

2.3. SPS Procedure

SPS is an animal model of PTSD that first proposed by Liberzon, Krstov and Young (1997). According to this method, SPS was conducted in three stages: restraint for 2 h, forced swim for 20 min, and diethyl ether anesthesia. Each rat was restrained for 2 h by placing it inside a disposable clear polyethylene cone bag with only the tail protruding. The wide end of the cone was closed with tape at the base of the tail. The bag size was adjusted according to the size of the rat in order to achieve complete immobilization. A hole in the narrow end of the cone allowed the rats to breathe freely. After immobilization, the rats were individually placed in a clear acrylic cylinder (240 mm D, 500 mm H), filled two-thirds from the bottom with water (24 °C), and forced to swim for 20 min. Following 15 min recuperation, they were exposed to diethyl ether (Sigma-USA) until loss of consciousness and then left undisturbed in their home cages for 1 week. Sham rats were left undistributed in their home cage prior to the contextual fear conditioning.

2.4. Contextual fear Conditioning and Extinction Training

An automated rodent fear conditioning system (TSE, Bad Homburg, Germany) was used to study contextual

fear conditioning of each rat. Contextual fear conditioning took place in a conditioning box. The walls and the ceiling of the box were constructed of clear Plexiglass. The floor of the box was made of 25 stainless steel rods (6 mm in diameter, 12 mm apart) through which footshock could be delivered from a constant current source. The box was enclosed in a sound attenuating chamber. The chamber was illuminated by a single house light, and was cleaned with 5% ethanol before and after utilization. Ventilation fans provided continuous background noise (68 dB) during the experiment. A software program was used to control the test in the box, and to collect, display and store all experimental data for “off-line” analysis.

General procedures for contextual fear conditioning have previously been described (Abrari, Rashidy-Pour, Semnani, & Fathollahi 2008). Briefly, contextual fear conditioning took place in a conditioning box. On day 1, the rats were placed into the chamber and after 3 min received two footshocks at 30 s intervals. Each shock was 1.5 mA and 4 s duration. Rats were left in the conditioning box for 30 s after termination of the procedure and returned to their home cage.

Extinction training was defined as the repetitive exposure to the contextual box in the absence of footshock. One-day after contextual training, rats were placed for 10 min in the same context and the percentage of time animal spent freezing (characterized by the absence of all visible movement except respiration) was measured using automated procedures. Time threshold for freezing

behavior was set on 3 second and. freezing was interpreted whenever the animal was not moving for more than this duration. In a similar way, extinction training was performed on each of four consecutive days following fear conditioning (Fig. 1)

2.5. Locomotor Activity Measurement

Locomotor activity of animal was measured using an automated activity monitor system (TSE infraMot, TSE, Bad Homburg, Germany) as previously described elsewhere (Rashidy-Pour, Sadeghi, Taherain, Vafaei, & Fathollahi, 2004). Spontaneous locomotor activity of each rat was measured for five 2-min intervals. Only one animal was placed in each activity chamber per measurement time.

2.6. Statistical Analysis

Data were expressed as a means \pm SEM and were analyzed with analysis of variance (ANOVA) with repeated measure and the unpaired-Student t-test. All post hoc comparisons were made using Tukey's multiple comparison test. Values of $P < 0.05$ were considered significant.

2.7. Experiments

2.7.1. Effects of SPS on Spontaneous Motor Activity

In this experiment, we examined influence of SPS on spontaneous motor activity. Seven days after SPS, the lev-

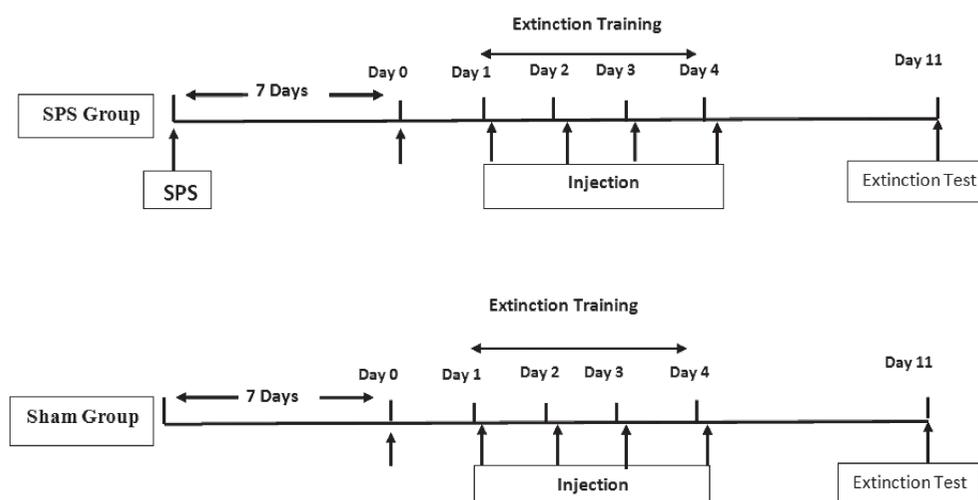


Figure 1. Experimental groups and treatment procedures. In the SPS group, 7 days after SPS treatment, contextual fear conditioning was performed (on day 0), and then extinction training was performed on each of four consecutive days following fear conditioning. In the sham group, the procedures were similar except that SPS treatment was not performed.

els of spontaneous motor activity of sham and SPS rats were measured according to procedures explained above.

2.7.2. Effects of SPS on Fear Extinction

In the first experiment, we investigated influence of SPS on fear extinction. Rats were randomly divided into two SPS and sham groups ($n=8-10$ in each group). Sham group: animals of this group were left undisturbed without handling in their home cages. SPS group: SPS procedure was performed on these animals according to the procedures described above. Fear conditioning and extinction training were performed as described above. Immediately following each extinction trial, each rat received physiological saline. In addition, to examine the sustained effect of saline upon fear extinction, we evaluated the freezing responses of animals of each group one week after the fourth extinction training period (Fig. 1).

2.7.3. Effect of systemic OXT on Fear Condition.

Animals were randomly divided into 4 sham and 4 SPS groups. Fear conditioning and extinction training were

performed as described above. Immediately following extinction, each group of rat was administrated 1, 10, 100, or 1000 $\mu\text{g}/2\text{ml}/\text{kg}$ of OXT or saline (Fig. 2).

3. Results

3.1. SPS does not Impair Spontaneous Motor Activity

The locomotor activity results are shown in Fig. 2A. There were no significant differences between groups in total activity recorded for 10 min period ($t_{12}=0.25$; $P=0.80$). A two-way ANOVA (group \times time) of locomotor activity at each two min interval of the 10 min test showed no significant effect of groups ($F_{1,12}=0.06$; $P=0.80$), a significant effect of time ($F_{4,56}=6.66$; $P=0.0002$), and no significant interaction between both factors ($F_{4,56}=0.75$; $P=0.55$). Post-hoc analysis indicated that in all groups locomotor activity was increased during the first two min interval ($P<0.05$ for all comparisons). These results indicate that SPS did not affect spontaneous locomotor activity.

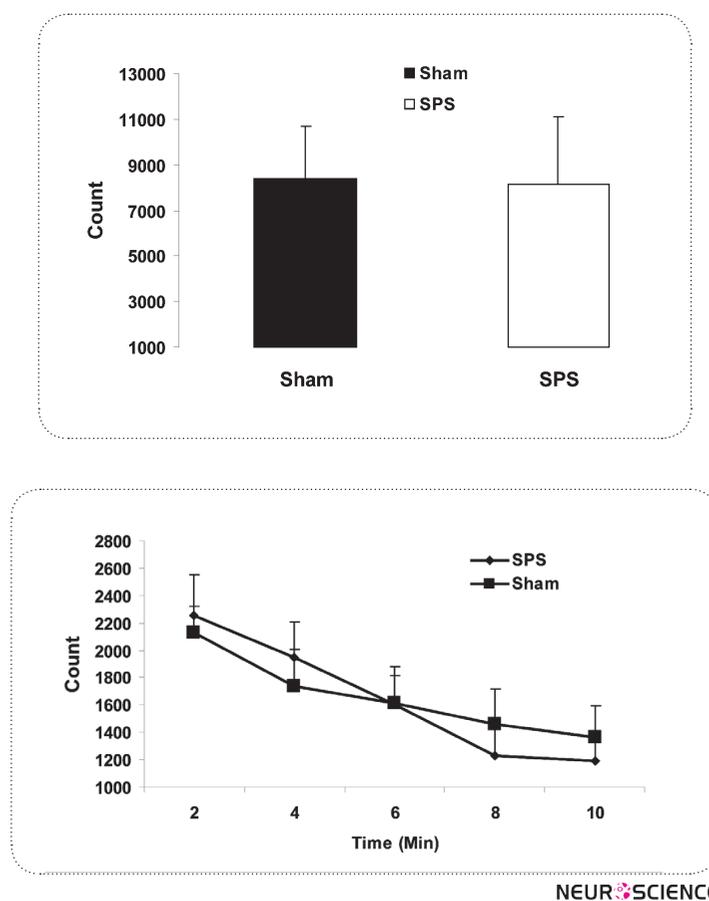


Figure 2. Effects of SPS procedures on spontaneous motor activity. (A) mean (\pm S.E.M.) total locomotor activity for a 10-min period; (B) mean (\pm S.E.M.) locomotor activity over the 10-min test (2-min interval).

3.2. SPS Impairs Contextual Fear Extinction

Fig. 3 shows freezing responses of Sham and SPS groups across the multiple extinction training. Two-way ANOVA with repeated measures on data from experiment 2 indicated a significant main effect of day ($F_{4,64}=14.67, P=0.0001$), stress ($F_{1,16}=5.77, P=0.029$), and no significant interaction between day and stress ($F_{(4,72)}=$

$1.2, P=0.8$). Post-hoc comparison using the unpaired Student's t-test indicated that the freezing levels of SPS and sham groups did not differ on day1, suggesting that CFC was successful in both groups. During extinction training, however, a significant difference in the freezing levels was found on days 4 ($P<0.01$), and 11 ($P<0.001$) between both groups (Fig. 3).

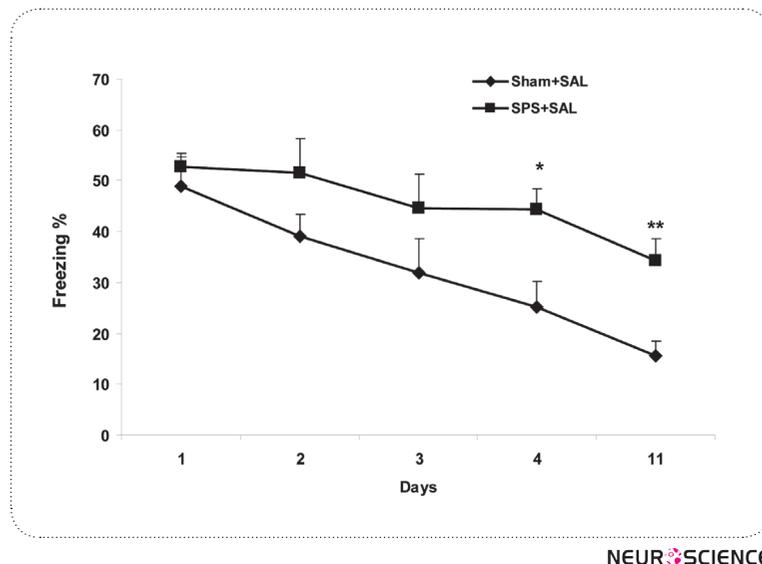


Figure 3. Effects of SPS on contextual fear extinction. Data are expressed as mean \pm SEM. Results indicated that the freezing levels of SPS and sham groups did not differ on day1, suggesting that CFC was successful in both groups. During extinction training, however, a significant difference in the freezing levels was found on days 4, and 11 between both groups.

3.3. Effect of OXT on Fear Extinction in Sham and SPS Rats

A three-way ANOVA with repeated measure showed significant effects of groups ($F_{1,348}=9.731, P=0.002$), of treatments ($F_{4,348}=7.89, P=0.0001$) and of days ($F_{3,348}=4.14, P=0.007$). Post-hoc comparisons indicated that freezing levels of sham rats receiving doses of 10,100 or 1000 $\mu\text{g}/\text{kg}$ of OXT were significantly higher than those rats receiving saline in day 2 to day 5 (all, $P<0.05$). No significant differences was found between saline and OXT-treated SPS rats.

4. Discussion

Using an animal model of PTSD, we investigated the effects of OXT on the impaired fear extinction in SPS and sham rats. While there was no significant difference in the freezing levels between SPS and sham rats 24 h after the fear conditioning, the freezing levels in SPS rats

were significantly higher than those in sham rats after the fourth, and fifth extinction training. Moreover, we found no differences in locomotor activity between SPS and sham groups. These findings rule out the possibility that the impaired extinction of SPS rats is due to disturbances of motor function.

Our findings are in agreement with previous studies indicating that SPS impairs contextual fear extinction, but does not disrupt sensory-motor function (Iwamoto, Morinobu, Takahashi, & Yamawaki 2007, Yamamoto et al. 2007). We found that repeated OXT administration slowed down the extinction of contextual fear in sham rats. In fact, sham rats receiving doses of 10,100 or 1000 $\mu\text{g}/\text{kg}$ of OXT showed higher freezing levels in subsequent testes than sham rats receiving saline. This effect was also found 7 days after the fourth extinction training. However, in SPS rats, OXT had no impairing effect. One possible interpretation is that SPS rats have already displayed the impaired extinction and thus, the

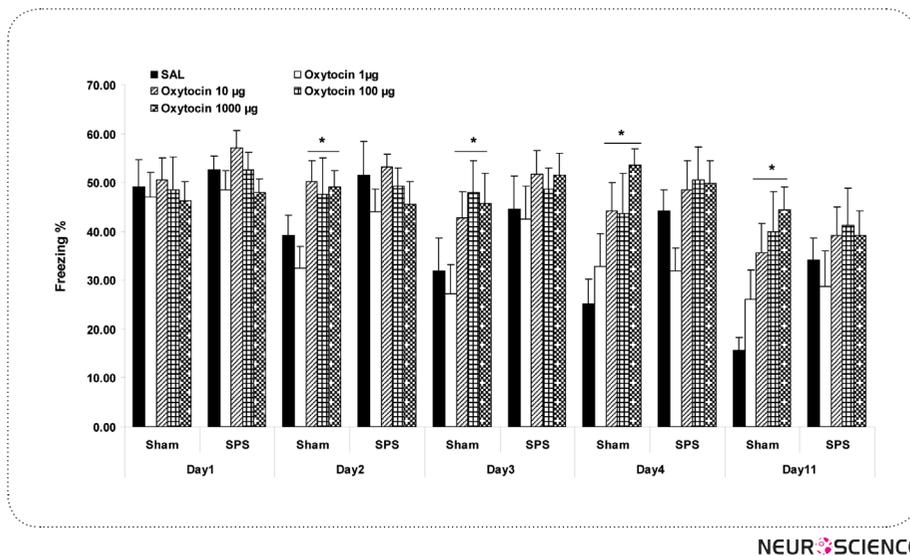


Figure 4. Effects of multiple injections of oxytocin on the extinction of fear response in sham and SPS rats. Data are expressed as mean \pm SEM. * $P < 0.01$, ** $P < 0.001$ as compared with saline-treated sham rats in the same day.

freezing level of SPS rats might reach a ceiling and this prevents us from detecting the impairing effect of oxytocin. Our findings are in agreement with a recent study showing that central administration of OXT impairs cued fear extinction in both rats and mice (Toth, Neumann, & Slattery, 2012). In that study, OXT was injected before extinction training, and thus, the drug influenced the acquisition of extinction. OXT administration before extinction training not only influences the acquisition of extinction, but also affects post-training consolidation process. We injected OXT immediately following each extinction training. In this time, the memory is active and the consolidation process is occurring. Thus, the injected OXT influenced the consolidation of extinction learning. The lower dose of OXT ($1\mu\text{g}$) was ineffective. The impaired extinction was not a result of reduction in general locomotor activity because OXT was injected following each extinction trial and the animals retested 24 h later. Given that the half-life of OXT is very short, during this interval the injected OXT is metabolized and eliminated from the plasma. Additionally, we found no differences in general locomotor activity between saline, OXT-treated, sham and SPS animals (data not shown).

Our findings are in contrast with previous studies showing that administration of OXT before extinction training facilitated fear extinction. For example, injection of OXT into the central amygdala before extinction training facilitated the fear extinction (Viviani et al. 2011, Wisema, Sluyter, & Driscoll 1992). The central amygdala coordinates the behavioral and physiological correlates

of fear expression (LeDoux, Iwata, Cicchetti, & Reis 1988). In this study, however, OXT was administered systemically, which is likely to explain the inconsistent results. Despite the fact that peripherally administered OXT may reach and influence the central amygdala, it may not do so in a concentration adequate to enhance fear extinction. Additionally, it is likely to influence brain areas which increase fear responses, such as the basolateral amygdala (BLA) and hippocampus. Both structures play an important role in fear modulation and have oxytocin receptors (Phillips & LeDoux 1992, Vaccari, Lolait, & Ostrowski 1998). Much more research is needed to determine the role of these structures in the impairing effects of oxytocin on fear extinction.

In general, peptides, including OXT, pass the blood-brain barrier with difficulty (Zaidi & Heller, 1974). Thus, central content of OXT should not be affected significantly by the alteration of peripheral peptide concentration following its systemic administration (Engelmann, Wotjak, Neumann, Ludwig, & Landgraf 1996). These findings suggest that intraperitoneally administered OXT may alter fear conditioning without directly influencing brain systems. A possible mechanism that may mediate the effects of OXT on fear extinction is the inhibition of glucocorticoid release from the adrenal glands by OXT (Pettersson et al. 1999). Previous studies have shown that decreasing corticosterone levels before extinction training by icvtracerebroventricular and BLA administration of metyrapone, a blocker of glucocorticoid synthesis blocks fear extinction (Barrett

& Gonzalez-Lima 2004, Jin, Lu, Yang, Ma, & Li 2007, Yang, Chao, Ro, Wo, & Lu 2006). Conversely, injections of glucocorticoid receptor agonists before extinction training facilitate fear extinction training (Yang, Chao, & Lu 2005, Yang et al. 2006)

In conclusion, our study shows that increasing OXT transmission at time of memory reactivation delays the extinction of conditioned fear response, and thus, much attention is required before commencing OXT for treatment of PTSD. Future research is required to determine the underlying mechanisms of oxytocin inhibitory effects on fear extinction. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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