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Penile erectile dysfunction after brachial plexus root avulsion injury in rats

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Abstract

Our previous studies have demonstrated that some male patients suffering from brachial plexus injury, particularly brachial plexus root avulsion, show erectile dysfunction to varying degrees. However, the underlying mechanism remains poorly understood. In this study, we evaluated the erectile function after establishing brachial plexus root avulsion models with or without spinal cord injury in rats. After these models were established, we administered apomorphine (*via* a subcutaneous injection in the neck) to observe changes in erectile function. Rats subjected to simple brachial plexus root avulsion or those subjected to brachial plexus root avulsion combined with spinal cord injury had significantly fewer erections than those subjected to the sham operation. Expression of neuronal nitric oxide synthase did not change in brachial plexus root avulsion rats. However, neuronal nitric oxide synthase expression was significantly decreased in brachial plexus root avulsion + spinal cord injury rats. These findings suggest that a decrease in neuronal nitric oxide synthase expression in the penis may play a role in erectile dysfunction caused by the combination of brachial plexus root avulsion and spinal cord injury.

Key Words: *nerve regeneration; brachial plexus avulsion; spinal cord injury; peripheral nerve injury; penis; neuronal nitric oxide synthase; erectile dysfunction; rat model; neural regeneration*

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Introduction

Brachial plexus root avulsion (BPRA) is a type of serious injury of the upper limb peripheral nerve, and mostly results from traffic accidents or industrial injuries, affecting more male patients than female ones (Dubuisson and Kline, 2002; Kim et al., 2003; Kitajima et al., 2006; Kretschmer et al., 2009; Aras et al., 2013; Dodakundi et al., 2013; Gao et al., 2013; Franzblau and Chung, 2014). Our previous studies have demonstrated that some male patients suffering from BPRA have varying degrees of erectile dysfunction, and this seriously affects the sex life and quality of life of the patient's spouse (Fu et al., 2010). Besides the pain and anxiety caused by the trauma itself, whether neuropathophysiological effects are involved in ED in patients with brachial plexus injury has not yet been studied.

Penile ED refers to the persistent inability to achieve or maintain a suitable adequate for satisfactory sexual intercourse (Lue, 2000; Montorsi et al., 2006; Zhang et al., 2013). Depending on its etiology, ED can be classified as psychogenic, organic, or mixed ED (Cohan and Korenman, 2001; Grant et al., 2013; Barassi et al., 2014; Vodusek, 2014). Neuronal nitric oxide synthase (nNOS) is currently believed to play an important role in penile erection (Burnett et al., 1992; Hurt et al., 2012; Wang et al., 2012; Amany and Heba, 2013; Hu et al., 2014). Pathogenic factors may decrease NOS activity, subsequently reducing nitric oxide production and thereby leading to ED. One of these factors is spinal cord injury. Studies in rats have shown that spinal cord or cavernous nerve injury results in a significant reduction in penile nNOS activity and subsequently, ED (Burnett, 2004; Toda et al., 2005; Hannan et al., 2013; Tavukcu et al., 2014). However, changes in penile nNOS expression after brachial plexus injury have not yet been reported.

Brachial plexus injury combined with spinal cord injury (SCI) occurs in some patients (Chechick et al., 1982; Webb et al., 2002; Nordin and Sinisi, 2009; Moses et al., 2013). This multiple injury is rarely observed and often leads to a misdiagnosis with the patient missing the optimal time for treatment. Brachial plexus avulsion may also cause partial spinal

cord injury. Whether brachial plexus injury, particularly brachial plexus avulsion, leads to ED or whether penile nNOS is affected by brachial plexus injury, is unknown. Therefore, in this study, we evaluated the erectile function after establishing BPRA models combined with SCI to better understand the changes in nNOS changes in penile tissues after this injury and the neuropathophysiological etiology of ED.

Materials and Methods

Animals and surgical procedure

Twenty-seven 6-week-old male Sprague-Dawley rats, weighing 250–350 g, were provided by the Laboratory Animal Center of the First Affiliated Hospital of Sun Yat-sen University, China (license No. SYXK [Yue] 2010-0108). The study was approved by the Animal Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University, China. The rats were fed with water and food *ad libitum* until 12 hours before the operation. They were randomly and evenly divided into three groups: BPRA, BPRA + SCI, and sham-operation. The rats were secured in a prone position, and a straight incision 4 cm in length was made along the posterior midline of the neck from the occiput to the upper corner of the scapula. Positioned using the 2nd thoracic vertebra, the right longest muscle of the head, semispinalis muscle of the neck, and digastric muscle of the neck were pulled outward. The small muscles adhering to the spinous process and vertebral lamina were stripped off until the small articular processes of C_4–T_1 were exposed. Laminectomy on the right side of C_4–T_1 was performed using a purpose-made vertebral lamina rongeur. The medulla spinalis was opened to the left using a custom-made microscopic neural hook until the dorsal and the ventral roots of C_4–T_1 were exposed, then the dura mater and arachnoid around the medulla spinalis were exposed and separated.

Avulsion of the corresponding C_5–T_1 nerve roots was performed under the microscope on rats in the BPRA group. After the avulsion of C_5 and C_6 in rats of the BPRA + SCI group, part of the medulla spinalis white matter was observed to overflow. If the spinal cord was not completely injured, the medulla spinalis was separated and the medulla spinalis capsula was slightly damaged and stretched until part of the medulla spinalis substantia alba overflowed. BPRA caused the forelimbs to droop flaccidly. Furthermore, these rats did not move independently, and were observed to limp when crawling. SCI was evaluated by observing the overflow of medulla spinalis white matter, as well as flaccid paralysis of the affected hind limb, impaired movement, and the appearance of limping while crawling. The presence of hind limb ulceration in certain rats was also used as further verification.

In the sham-operation group, only the vertebral lamina was removed (**Figure 1**). After the operation, the incision was closed and covered with an aseptic dressing. All surgical instruments were appropriate for use on experimental animals. The tested animals naturally regained consciousness after the operation, underwent routine breeding, and their movement was not restricted. Each rat received a daily intramuscular injection of 20,000 U gentamicin for 1 week after the operation. The activities and survival of the rats were observed periodically.

Detection of penile erection function

Fifteen days after injury, the rats were weighed and the experiment performed (in the observation room) according to Heaton et al. (1991). The indoor temperature was set between 22–24 °C and the relative humidity was approximately 50%. Silence was maintained in the room, and the light was dimmed to a minimum which still allowed for the observations to take place. The rats were individually placed inside the transparent testing cage and were administered with apomorphine (APO; 100 μg/mL; injection volume adjusted to 80 μg/kg) (Sigma-Aldrich, St. Louis, MO, USA) subcutaneously into the neck after 10 minutes of environmental adaptation. APO was dissolved in normal saline containing 0.5 mg/L vitamin C.

The effects of APO were observed 5–10 minutes after injection and were no longer present after 30 minutes. Each rat was observed for 30 minutes after injection using the Cambridge A60pro USB camera, and the following events were recorded: penile erection, the number of erections, and the number of yawns. The engorgement of the glans penis with blood and the appearance of the tip of the penis was counted as one erection. Flexion-extension and involuntary mouth opening accompanied by appropriate breathing movements was counted as one yawn. The observation indexes were latent period of penis erection and number of erections.

Immunohistochemistry for nNOS in penile tissue

After testing penile erectile function, the rats were killed by decapitation 21 days after the operation. Middle sections of the penile tissues were obtained and embedded in optimum cutting temperature (OCT) compound, and then sliced (5–10 μm). Immunohistochemistry for nNOS was then performed. Sections were incubated with 2.5% bovine serum albumin at room temperature for 30 minutes. Thereafter, penile sections were incubated with rabbit anti-nNOS (Beijing Biosynthesis Biotechnology Co., Ltd., Beijing, China; 1:400) at 4°C overnight. The tissues were subsequently incubated with biotinylated goat anti-rabbit IgG (Boster, Wuhan, Hubei Province, China; 1:150) for 2 hours at room temperature. The streptavidin-biotin complex was used for immunohistochemical staining. The sections were observed under a light microscope (Shanghai optical instrument factory, Shanghai, China) at 400 × magnification and then photographed. Ten fields of view showing the greatest expression of positive fibers were assessed, and subsequent counts of these fibers determined the average number of nNOS-positive fibers.

Statistical analysis

All data are expressed as the mean ± standard deviation (SD), and were analyzed by one-way analysis of variance followed by the least significant difference test. Significance was reached at values of $P < 0.05$. The SPSS 18.0 statistical package was used for analysis.

Results

Establishing rat models

From the 27 rats, 21 were used for final analysis (BPRA group, $n = 6$; BPRA + SCI group, $n = 7$; sham-operation

group, $n = 8$; all with a success rate of 72% [13/18]). In the BPRA group, three rats died of hemorrhagic shock. In the BPRA + SCI group, two rats died from anesthesia overdose. In the sham-operation group, one rat died of anesthesia overdose. Rats in the BPRA and BPRA + SCI groups showed poor nutritional status and dull hair, but weight change was insignificant. Furthermore, the forelimb on the injured side showed a limping gait but had no ulceration. The severity of SCI was evaluated by observing the overflow of the medulla spinalis white matter during the operation and the movement of the hindlimb on the injured side, as well as the ulceration in some rats. In the BPRA + SCI group, six rats had forelimb dysfunction, dragging of the hindlimb on the injured side, and movement impairment, and one rat showed ulceration of the hind limb. Rats in the sham-operation group showed no limping and had good grabbing responses.

Effect of APO injection

APO usually took effect after 6–8 minutes. Piloerection, stretching, yawning, exposure of the glans penis, licking of the glans, and penile erection occurred in all three groups. There was no significant difference in the latent period of penis erection between the three groups. The number of the erections in 30 minutes for the rats in the BPRA group and BPRA + SCI group was significantly ($P < 0.05$) decreased compared with the sham-operation group (**Figure 2**).

nNOS changes in penile tissue

nNOS immunoreactive nerve fibers were diffusely distributed throughout the penis, and were usually observed in the periphery of the dorsal nerve of the penis. nNOS immunoreactivity was highest in two of the three erectile columns, particularly in the area surrounding the tunica albuginea, whereas the corpus spongiosum had the least immunoreactivity of nNOS. nNOS-immunoreactive nerve fibers were darkly stained in the three groups. A larger number of nNOS-immunoreactive nerve fibers were stained brownish yellow (**Figure 3**). The number of nNOS-immunoreactive nerve fibers in the rat penis was significantly ($P < 0.05$) lower in the BPRA + SCI group compared with the BPRA and sham-operation groups (**Figure 2**).

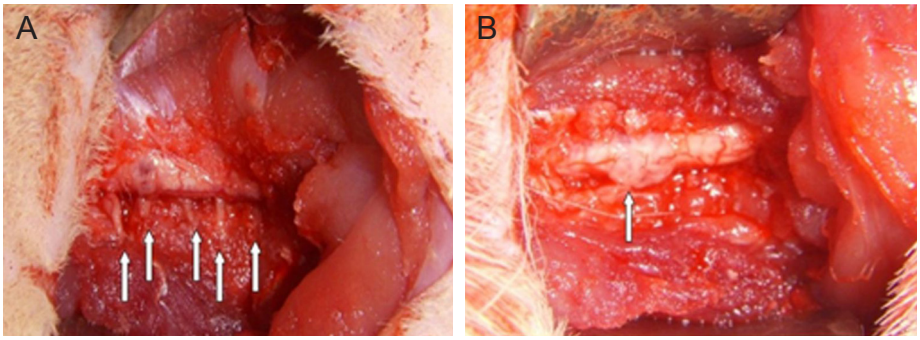
Discussion

The present study demonstrated that the erectile function of male rats was significantly decreased after BPRA. Furthermore, we found that the expression of nNOS-immunoreactive nerve fibers was significantly decreased in the BPRA + SCI group. BPRA is a kind of special peripheral nerve injury that affects a patient's life severely. Moreover, in males, it leads to ED (Kitajima et al., 2006; Kretschmer et al., 2009; Fu et al., 2010). However, the specific pathophysiological mechanisms underlying ED remain unclear. To better understand these mechanisms, animals have been exposed to BPRA to investigate its effect on erectile function. Rats have a similar anatomy to humans with the advantage of being less expensive and easier to handle than other animal models. Rat models are efficient, economical, and accurate for studying the mechanisms of ED caused by brachial plexus injures.

Although numerous studies have established animal models of ED *via* BPRA (Fullarton et al., 2000, 2001, 2002; Spinner et al., 2000; Knakiewicz et al., 2009; Lu et al., 2013; Soldado et al., 2014), the combined effect of BPRA and SCI, namely on ED, has not been reported. In the present study, we found that anterior surgery was simpler, easier in exposure, and less traumatic for inducing BPRA compared with the posterior cervical spine operation. However, anterior surgery has a low rate of success, is less reliable, and is unsuitable for establishing a rat model of ED involving C_8 and T_1. The posterior approach may be better owing to the higher rate of accuracy and success compared with the anterior approach. This method is an ideal choice for modeling C_8 and T_1 simultaneously or full BPRA injuries. Liu et al. (2009) have reported a positive correlation of each C_5–T_1 nerve root at the angles of 45°–90° and 90°–135°. Under a maximum load, each nerve root mainly showed a post-ganglionic rupture at 90°, and a pre-ganglionic rupture at 45°–90° and 90°–135°. However, it was irregular for C_5, C_6, and C_7 at 0°–45° and 135°–180°, although C_8 and T_1 mainly showed pre-ganglionic rupture. In the present study, we found that posterior laminectomy required a wider range when resecting vertebral lamina and articular processes, otherwise fully exposing the anterior root of the brachial plexus was difficult. Therefore, use of an appropriate microscope and gentle operative techniques was required. Furthermore, selecting adult rats that were strong and heavy for the posterior operation to produce BPRA was necessary, as well as custom-made fine bipolar electric coagulation devices to reduce the bleeding and surgery time. Rotation of the medulla spinalis to form a 90° traction angle was sufficient. Excessive traction may have caused more bleeding and blurred vision, thus affecting the surgical results. Maintaining an intact capsula of the medulla spinalis to establish a combined SCI is very important. Adequate separation of the medulla spinalis capsula and then counter traction of the nerve root was found to significantly reduce the damage to the surface of the medulla spinalis. The stretched residual root appeared flocculent without overflow of medulla spinalis white mater, but still showed abundant bleeding. To maintain a complete medulla spinalis capsula, more external force was needed. In contrast, the residual root that was removed appeared irregular, and the overflow of the medulla spinalis white substance was different. Furthermore, assessing the damage to each plane of the nerve root of the medulla spinalis was difficult.

Clinically, the combination of BPRA with SCI is usually not obvious, and thus the diagnosis and the optimal choice and timing of treatment will often be missed (Webb et al., 2002; Macyszyn et al., 2010; Rhee et al., 2011; Moses et al., 2013). Patients who have suffered from BPRA may neglect the resultant SCI because of a slow onset, resulting in a missed opportunity for treatment. This study successfully established the BPRA model of ED. However, we found no significant difference in the detumescence of the erection between the three groups. This effect may be due to incomplete SCI, which is different from the ED caused by complete SCI.

At present, the decrease in NOS is considered to mediate neuropathic ED (Azadzoi et al., 1998). Wang et al. (2010) have reported that nNOS-positive nerve fibers in the penis



(A) The brachial plexus root avulsion (BPRA) group (arrows indicate the avulsed brachial plexus root). (B) Partial overflow of medulla spinalis white matter (arrow) in rats with BPRA + spinal cord injury during the surgery.

Figure 1 Brachial plexus root and spinal cord using the posterior approach.

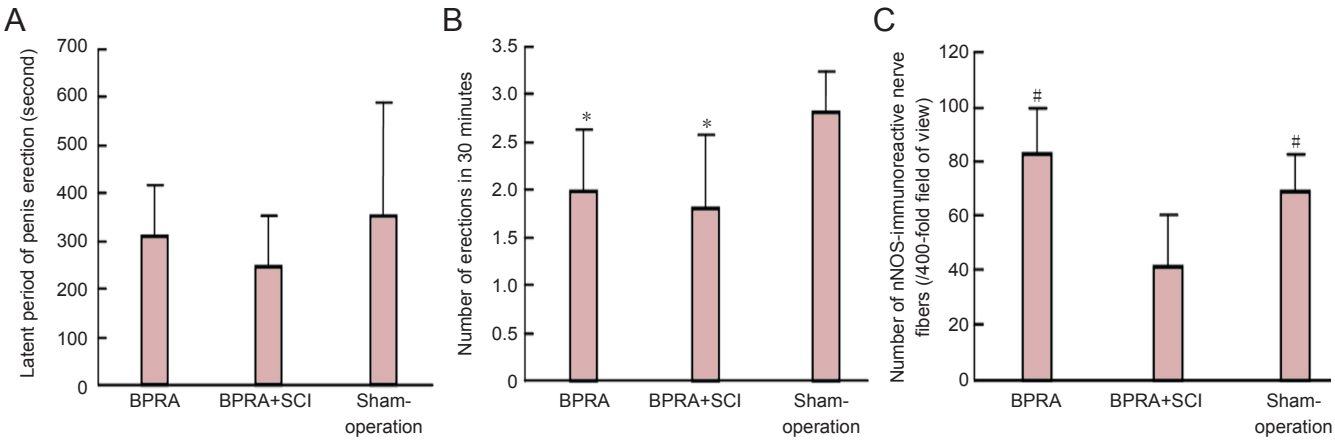


Figure 2 Comparison of erectile function and number of neuronal nitric oxide synthase (nNOS)-immunoreactive nerve fibers in penile tissues in each group.
(A, B) Erectile function; (C) nNOS-immunoreactive nerve fibers in penile tissues. $*P < 0.05$, *vs.* sham-operation group; $\#P < 0.05$, *vs.* BPRA + SCI group. All data are expressed as the mean ± SD, and were analyzed by one-way analysis of variance followed by the least significant difference test. BPRA: Brachial plexus root avulsion; SCI: spinal cord injury.

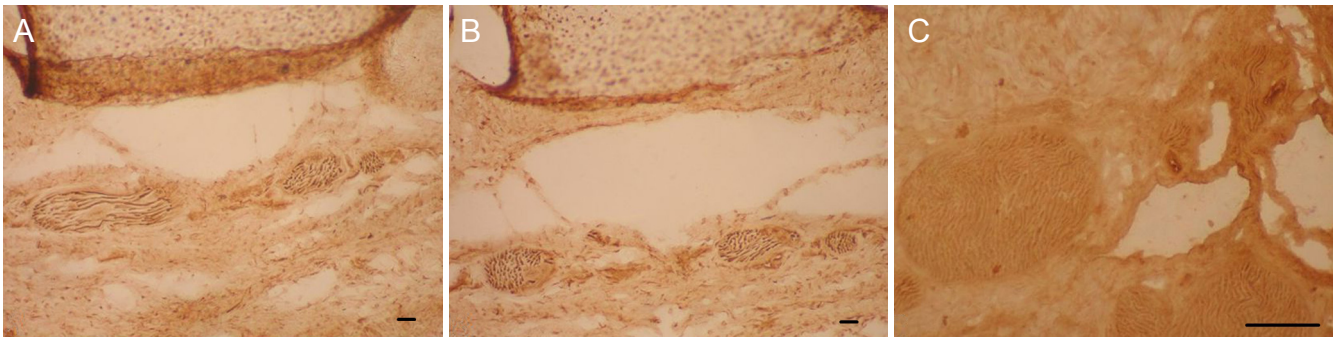


Figure 3 Expression of nNOS-immunoreactive nerve fibers in penile tissues in BPRA rats.
Immunohistochemical staining using the streptavidin-biotin complex. nNOS appears as a brownish-yellow color and as circular or granular deposits, with a variable degree of staining. Bars: 50 μm. (A) BPRA group, (B) sham-operation group, and (C) BPRA + SCI group. nNOS: Neuronal nitric oxide synthase; BPRA: brachial plexus root avulsion; SCI: spinal cord injury.

are mainly expressed in the periphery of the dorsal nerve of the penis. Furthermore, the number of the nNOS-positive nerve fibers decreases rapidly after SCI, with very weak expression in the dorsal nerve of the penis. This result suggests that the significant decrease of the nNOS-positive nerve fibers in the rat penile tissues after SCI in our study may be one of the main mechanisms causing ED after SCI. Tavukcu et al. (2014) have shown the number of nNOS-positive nerve fibers significantly decreases after SCI. This result suggests that the level of nitric oxide that affects the erectile tissue decreases rapidly after SCI. This change may be the main cause for SCI-mediated ED rather than cell death in the erectile tissue. The current study showed that the expression of nNOS in nerve fibers was only significantly decreased in the BPRA + SCI group, suggesting that incomplete SCI also affects the expression of penile nNOS in rats with BPRA.

This study successfully proved the occurrence of ED in a rat model *via* posterior laminectomy-mediated BPRA. Overall, reduced expression of penile nNOS may play a role in ED when SCI is combined with BPRA.

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Conflicts of interest: *None declared.*

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