ФИЗИОЛОГИЯ

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SEROTONINERGIC REGULATION OF SPINAL LOCOMOTION*

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In this study the neuropharmacological mechanisms of mammalian locomotion induced by epidural stimulation have been examined. Significance of serotoninergic system in regulation of locomotor behavior of spinal animals has been evaluated. It was demonstrated the different role of 5-HT2 and 5-HT1/7 receptors in initiation and regulation of locomotion.
Keywords: *central pattern generator, locomotion, spinal cord stimulation, serotonergic system.*

Introduction. The spinal network controlling stepping movements of the hindlimbs, i.e., the central pattern generator (CPG), is located in the lumbosacral segments of the spinal cord. This network can generate stepping patterns and adapt to external conditions [13]. In mammals it seems that the rhythmogenic capacity is distributed throughout the lumbar cord along a rostrocaudal gradient [12; 21]. Numerous pharmacological approaches have been shown to modulate locomotor activity in spinal subjects. Noradrenergic drugs (e.g., L-DOPA and clonidine) can trigger alternating rhythmic activity in antagonist nerves of paralyzed spinal cats [18; 26], and can initiate a locomotor-like pattern in adult cats after spinal cord transection [5]. Likewise, although they do not directly initiate stepping in the early stages after spinalization, serotonergic and glutamatergic agonists can modulate locomotion in chronic spinal animals [1; 5; 9; 10]. Recent findings point to the serotonergic system as a particularly attractive target for modulating locomotion [7; 25]. Jacobs and Fornel [18] hypothesized that 5-HT neurons can facilitate central pattern generation and activate α-motoneurons. These observations are consistent with the conclusion that 5-HT is an important and complex neuromodulator of locomotion, probably acting on a variety of neuronal populations and 5-HT receptor subtypes [28].

Recently, we have shown that stepping in complete spinal rodent can be markedly facilitated when quipazine (a broad but predominantly 5-

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HT2A/C agonist) administration is combined with step training [10; 12]. Here we hypothesize that epidural spinal cord stimulation following quipazine or 8-OHDPAT (5-HT1A/7 agonist) administration will differentially modulate the excitability of flexor- and-extensor related intraspinal neural networks in qualitatively unique, but complementary, ways while facilitating locomotion in spinal cord injured rats.

Methods. Data were obtained from nine adult female Sprague-Dawley rats (270 to 300 g body weight). The experimental procedures comply with the National Institute of Health Guide for the Care and Use of Laboratory Animals and were conducted in accordance with experimental protocols approved by the Animal Care Committee at the University of California, Los Angeles.

Surgical procedures. The rats were anesthetized deeply using a combination of ketamine (100 mg/kg) and xylazine (10 mg/kg) and maintained at a surgical level with supplemental doses of ketamine as needed. All surgeries were performed under aseptic conditions.

Headplug implant. A small incision was made at the midline of the skull. The muscles and fascia were retracted laterally, small grooves were made in the skull with a scalpel, and the skull was thoroughly dried. Two 12-pin amphenol headplugs with Teflon-coated stainless steel wires (AS632, Cooner Wire, Chatsworth, CA, US) were securely attached to the skull with screws and dental cement as previously described [27]. A small skin incision was made in the lower lumbar region and all wires were routed subcutaneously to this opening.

EMG implants. Skin and fascial incisions were made to expose the bellies of the medial gastrocnemius (MG) and tibialis anterior (TA) muscles, muscles semitendinosus (St), muscles vastus lateralis (VL) bilaterally. Two wires were routed subcutaneously from the back incision to each of the muscles. A small notch (~1 mm) of insulation was removed from each wire to form recording electrodes and the exposed regions were inserted and secured in the mid-belly of the deep region of each muscle as described previously [27]. Stimulation through the headplug was used to verify the proper placement of the electrodes in each muscle. The EMG wires were coiled near each implant site to provide stress relief.

Spinal cord transection and epidural stimulation electrode implants. A mid-dorsal skin incision was made between T6 and L4 and the paravertebral muscles were retracted as needed. A partial laminectomy was performed at the T8-T9 level and the dura mater was opened longitudinally. Lidocaine was applied locally and the spinal cord was transected completely as described previously [29]. Two surgeons verified the completeness of the spinal cord transection by lifting the cut ends of the spinal cord with fine forceps. Partial laminectomies then were performed to expose spinal cord segments L2 and/ or S1 for implantation of epidural stimulating electrodes. Wire from the back incision were tunneled subcutaneously to the exposed

region of the spinal cord. A small notch (~1 mm) of insulation was removed from one wire, and this wire was affixed to the dura at the midline at the S1/L2 spinal segments with the exposed surface facing the spinal cord using 9.0 suture as described previously [16]. The exposed region of the wire served as the stimulating electrode. The wire was coiled in the back region to provide stress relief. The Teflon-coating was stripped from the distal cm of the second wire that then was inserted subcutaneously in the back region and served as a common ground.

All incision areas were irrigated liberally with warm, sterile saline and closed in layers, i.e., the investing fascia and then the skin. All closed incision sites were cleaned thoroughly with saline solution. Analgesia was provided by Buprenex (0,5 to 1,0 mg/kg i.m., TID). The analgesics were initiated prior to completion of the surgery and continued for a minimum of 2 days. The rats were allowed to fully recover from anesthesia in an incubator. The rats were housed individually and the bladders of the spinal rats were expressed manually three times per day for the first two weeks after surgery and twice per day thereafter. The hindlimbs of the spinal rats were moved passively through a full range of motion once per day to maintain joint mobility.

Stimulation and recording procedures. Testing procedures began one week after surgery and were performed weekly for 7 weeks post spinal cord transection. All testing was performed when the rats were fully awake. The raw EMG signals were amplified and filtered (10 to 10,000 Hz band-pass). Stimulation was performed using a Grass S88 Stimulator (Grass Instruments) and a stimulus isolation unit (Grass SIU5, Grass Instruments). Continuous epidural stimulation at S1 from 30 Hz to 40 Hz and at a pulse duration of 0.2 ms was used to induce bipedal stepping.

During the testing of locomotor ability, the spinal rats were secured in an upper body harness support system and the hindlimbs were placed on a moving treadmill as described previously [16]. The automated body weight support system was used to provide the amount of body weight support necessary to enable walking. EMG activity was collected during stepping using a custom-made LabView program.

A four-camera system with retro-reflective markers placed on bony landmarks at the iliac crest, greater trochanter, lateral condyle of the femur, lateral malleolus, and the distal end of the fifth metatarsal on both legs was used to record the kinematics of the hip, knee, and ankle joints. Video analysis of the kinematics of the stepping movements was performed using a SIMI Motion Analysis System and was used to produce stick diagrams and trajectories of the limb movements.

The 5HT treatment. Dose-response testing (0,1 to 1 mg/kg) have been performed to verify of the optimal dose of quipazine in combination with ES facilitating coordinated, alternating plantar stepping on a treadmill belt. To manipulate the locomotor networks pharmacologically, we administrated

quipazine (0,3 mg per kg of body weight, intraperitoneal), a predominantly 5-HT2A/C receptor agonist, and 8-OHDPAT (0,1–0,3 mg per kg, subcutaneous), a 5-HT1A/7 receptor agonist, the 5-HT2 antagonist ketanserin (2–4 mg/kg), 5-HT1A antagonist WAY 100.635 (0.5 mg/kg) and 5-HT7 antagonist (SB 269970).

Statistical analyses. All data are reported as mean ± SEM. Statistically significant differences were determined using a one-way repeated measures analysis of variance (ANOVA). Normality of the data was evaluated using the Kolmogorov-Smirnov test. Values that were not normally distributed were analyzed using the nonparametric Kruskal-Wallis rank test. The criterion level for determination of statistical significance was set at $P<0,05$ for all comparisons.

Results. The dose-dependent effect of quipazine on bipedal stepping facilitated by ES in spinal rats was initially studied. Quipazine (a primarily 5-HT2 agonist) (i.p.) was tested at doses of 0,1, 0.2, 0.3, 0,4, and 0,5 mg/kg. Rats were placed in a body weight support system, allowing them to walk bipedally on a moving treadmill belt (7 cm/s). Locomotor movements were recorded for three conditions: ES alone, quipazine alone, and their combination. It was found that quipazine alone, ES alone, and their combination were all capable of stimulating the spinal cord to generate stepping movements when rats were placed on a moving treadmill belt. The stepping characteristics, however, were different for each condition. The combination treatment produced significantly greater numbers of plantar steps and improved quality of stepping compared to either intervention alone. Both number and quality of stepping peaked at the intermediate dose of around 0,3–0,4 mg/kg (Fig. 1).

Then we demonstrated that epidural stimulation combined with quipazine administration and step training enables stepping in spinal rats. The combination of ES and quipazine provided conditions that are sufficient for generating weight-bearing stepping in spinal animals. Furthermore, we have shown that the extent of locomotor recovery obtained in chronic spinal rats given this combination treatment was a function of their training state. Spinal rats that were administered quipazine, provided with ES at the S1 spinal segment (40 Hz) and step trained daily (20 min/day, 7 days/wk, for 6 wks) recovered the ability to step bipedally on a treadmill. These rats executed stepping patterns that were highly coordinated, displaying plantar foot placement and partial weight bearing (Fig. 2). In contrast, non-trained rats were typically unable to bear weight, and the cycle period of their stepping movements was significantly shorter than in the trained rats. Also, the amplitudes of the EMG bursts in the hindlimb muscles were significantly smaller in non-trained vs. trained spinal rats.

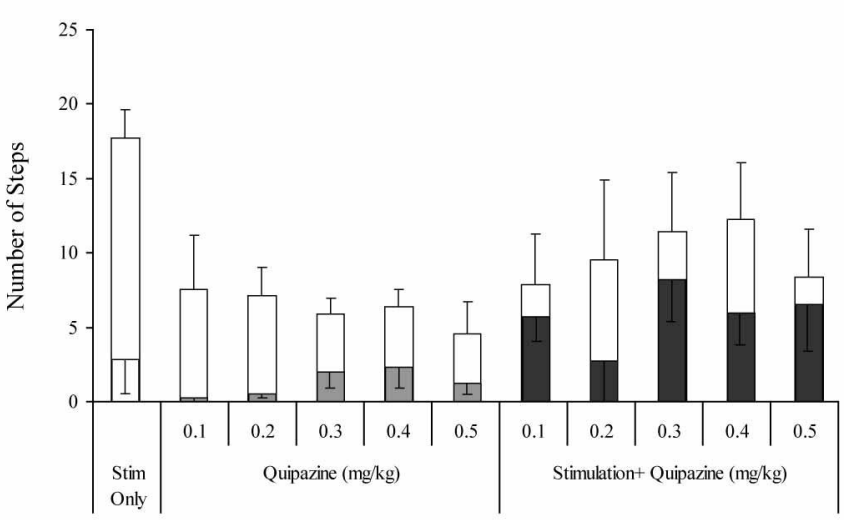

Fig. 1. Total number of locomotor movements (open bars) and plantar steps (filled bars) for each intervention and each dosage of quipazine:
As a group, stimulation alone produced a significantly greater number of locomotor movements ($p<0,001$). However, as a group, the combination of stimulation and quipazine produced a significantly greater number of plantar steps than either quipazine alone or stimulation alone ($p<0,001$)

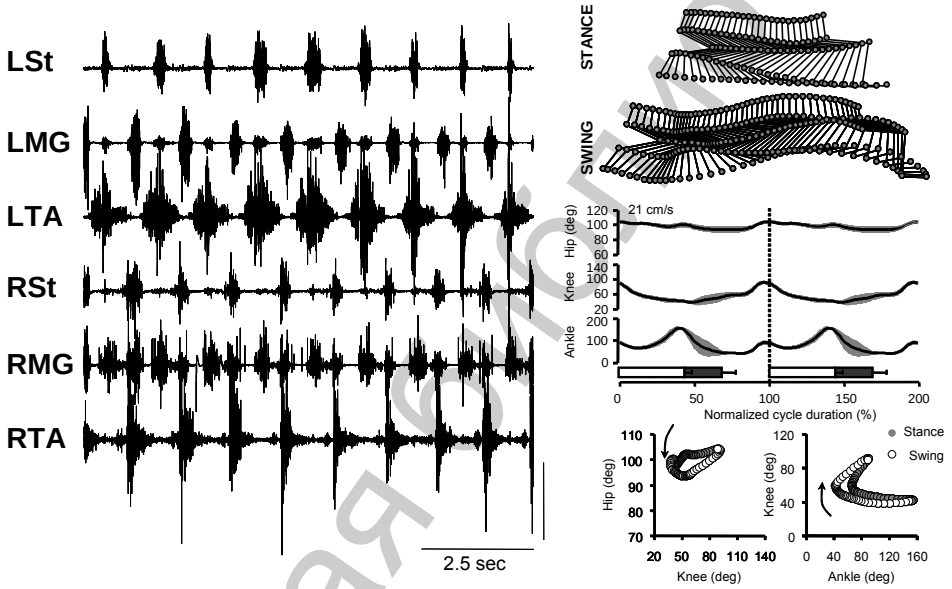

Fig. 2. EMG and kinematics data of the rat during epidural stimulation + quipazine administration are presented:
Representative stick diagram decompositions of hindlimb (left) movements during the stance and swing phases of gait are shown. Mean waveforms of each joint angle for the left hindlimb are plotted vs. the normalized gait cycle duration. The horizontal bars at the bottom indicate the mean value of the stance phase and foot drag duration. Angle-angle plots showing the coupling between the hip and knee (left) and knee and ankle (right) are shown. Filled and empty circles represent the stance and swing phases of gait, respectively

Epidural stimulation (40–50 Hz, 0.2 ms, 1–4 V) at L2 together with S1 initiated modest EMG bursting patterns in the hindlimb muscles with partial but limited body weight support (BWS) (Fig.3 A). Administration of 8-OHDPAT (0,1–0,3 mg per kg, subcutaneous) alone induced predominantly erratic hindlimb movements in response to treadmill motion. Combination of ES and administration of 8-OHDPAT evoked more stable stepping pattern with reduction of dragging duration (Fig. 3B) and increase in predominantly EMG activity of distal flexor muscles with higher level of body weight support. Thus, combined 5HT1A/7 pharmacological treatment and ES interventions after a complete interruption of supraspinal input, could induce functional states that would enable higher level of stepping capacities with specific properties.

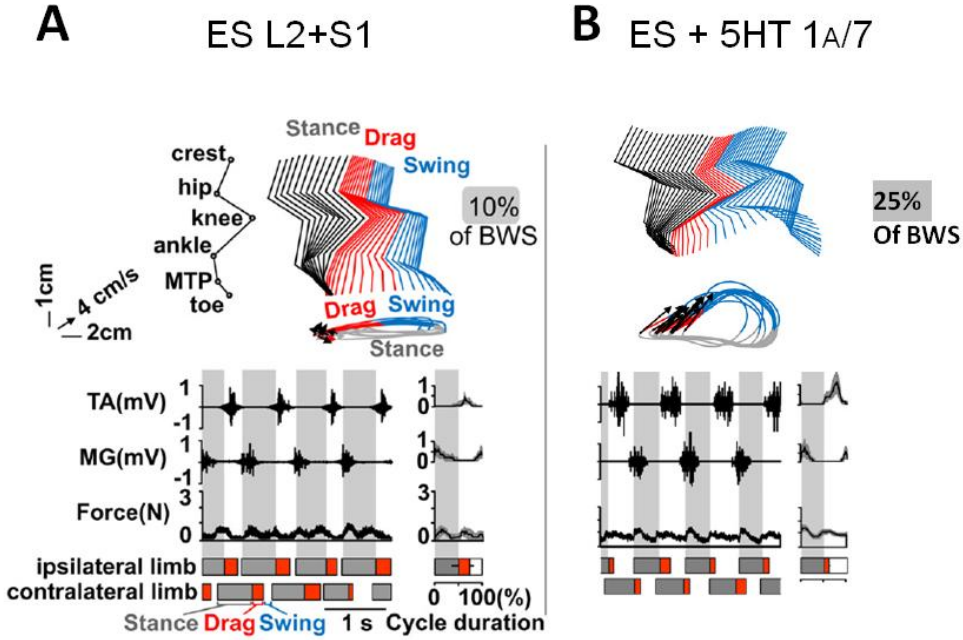

Fig. 3. The stepping patterns enabled by ES (A) and ES + 8-OHDPAT (B) in spinal rats:

Representative stick diagram decomposition of hindlimb motion during stance, paw dragging, and swing is shown for each condition together with successive (n=10) trajectories of the limb endpoint (MTP marker). In these drawings, the arrows represent the direction and intensity of limb endpoint velocity at swing onset. A sequence of raw EMG activity from the TA and MG muscles and the changes in vertical ground reaction forces is shown at the bottom. The boxes indicate the duration of stance and drag phases bilaterally, while open areas indicate the duration of the swing phase. Averaged (n=10 steps) rectified EMG activity, vertical forces, and stance period durations are displayed nearby the raw data in the right most plots

Administration of antagonists of 5-HT1A (WAY 100.635) and 5-HT7 (SB 269970) distributed the stepping rhythm and marginally depressed flexor activity (Fig. 4B). Administration of 5-HT2 antagonist (ketanserin)

significantly reduced extensor activity and consequently severely impaired stepping (Fig. 4C). These results are in agreements with data obtained in vitro experiments on newborn rats [19] that 5-HT1A/7 receptors are responsible for rhythm regulation whereas 5-HT2 receptors are responsible for pattern formation.

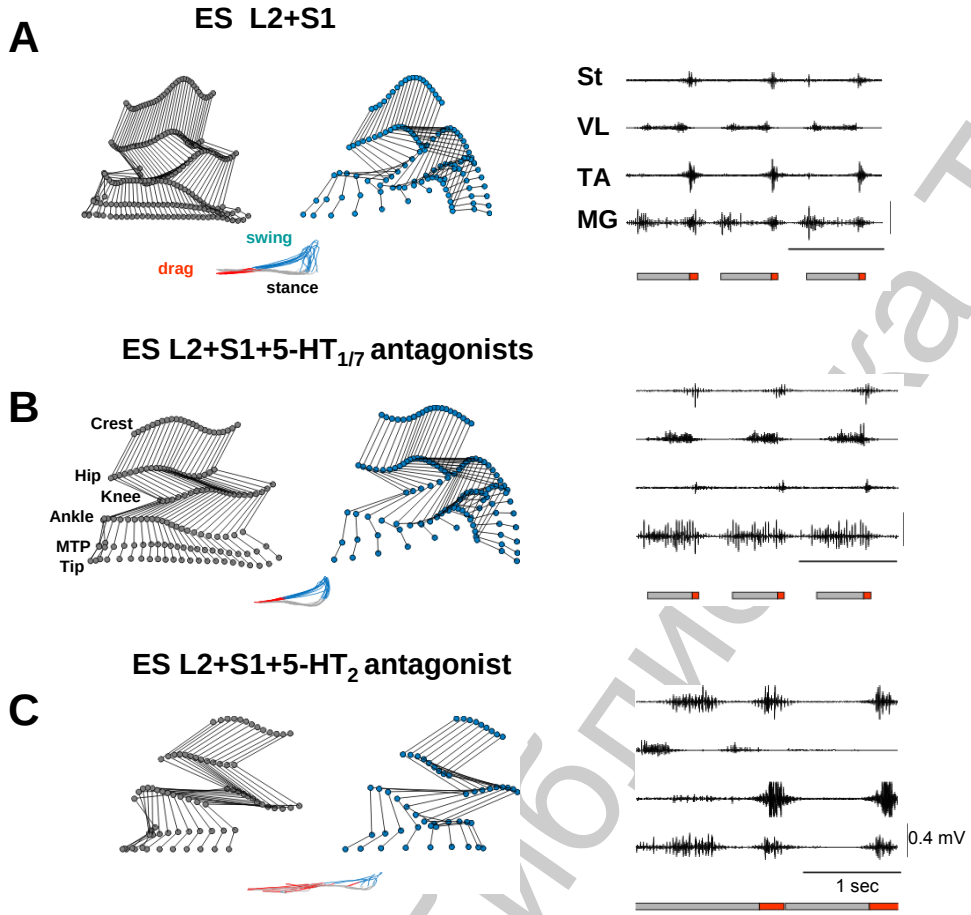

Fig. 4: Effect of 5-HT antagonists on stepping movements elicited by ES in adult spinal cord transected rats:
Kinematic and EMG data are presented. EMG was recorded from m.semitendinosus (St), m. vastus lateralis (VL), m. tibialis anterior (TA) and m. medial gastrocnemius (MG). ES L2+S1 (A), ES L2+S1+WAY 100.635+SB-269970 (B) and ES L2+S1 + ketanserin (C) are shown. Porizontal bar shows the stance and drag phases, unfilled bar demonstrates the swing phase.

Discussion. In the present study we have shown that epidural stimulation combined with pharmacological activation of 5HT2A/C or 5HT1A/7 receptors is an effective tool for facilitating spinal locomotion and can promote the generation of rhythmic, coordinated motor patterns between extensor and flexor hindlimb muscles in otherwise paralyzed spinal adult rats.

In vitro experiments performed with a neonatal rat spinal cord

preparation demonstrate that both the L1-L2 and the L6-L7 spinal cord segments can generate motor activity, and that stimulation at these two sites induces different forms of rhythmic behavior [2; 4; 6; 8; 22]. There is a strong coupling between these two networks [3]. It has been suggested that the rostral segments of the lumbar cord are critical for the initiation of stepping movements [23]. Studies of the caudal segments have shown that intraspinal microstimulation (ISMS) of the lumbosacral enlargement (L7-S1) also can elicit alternating movements in the hindlimbs in spinal cats [24], although it is unclear whether these movements are a result of direct activation of caudal networks, or are mediated by indirect activation of rostral networks.

Jacobs and Fornal [17] hypothesized that 5-HT neurons can facilitate central pattern generation and activate α-motoneurons. These observations are consistent with the conclusion that 5-HT is an important and complex neuromodulator of locomotion, probably acting on a variety of neuronal populations and 5-HT receptor subtypes [28]. There is growing evidence that a functional segregation of 5-HT receptor subtypes exists in the spinal cord, and recently, clusters of specific subtypes have been identified. Using synthesized receptor antibodies, dense populations of cells that are positive for the 5-HT7 receptor subtype have been localized in the low thoracic-high lumbar spinal cord [15; 19]. Thus, 5-HT7 seems to have an active role in the region of the spinal cord suggested to be responsible for the generation of rhythmic stepping [4]. In a double-labeling experiment using the 5-HT7 receptor antibody and the locomotor activity-dependent label sulforhodamine, the concentration of 5-HT7- positive cells that were active during fictive locomotion was more than four-fold higher in the upper (rostral) lumbar spinal cord than in the lower (caudal) segments [15]. Similar results were produced using c-fos as the activity-dependent label [20].Using an isolated neonatal rat brainstem and spinal cord preparation, Jordan et al. showed that blocking 5-HT7 receptors in the rostral segments of the lumbar cord with clozapine resulted in a decrease in step cycle duration, whereas blocking the 5-HT2 receptors in the caudal segments of the lumbar cord with ketanserin reduced the amplitude of ventral root discharges without influencing step cycle duration [24].

In this study we demonstrated that 5-HT1A/7 receptors improved intralimb and interlimb coordination, the reproducibility of stepping, as well as flexion components whereas the activation of 5-HT2A/C receptors enhanced extension and weight-bearing capacities but had a modest influence on rhythmic components. It also is highly likely that there will be important interactive effects when quipazine and epidural stimulation treatments are combined. We have observed that the stepping generated in response to several weeks of training in the presence of serotonergic agonists and epidural stimulation is significantly superior to that achieved in response to either intervention alone suggesting that there are some uniquely activated

neurons in response to each intervention. Together, these results evidence that 5-HT1A/7 and 5-HT2A/C receptors is highly integrated and synergistic system that can generate a range of specific gait patterns when recruited in different combinations.

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РОЛЬ СЕРОТОНИНЭРГИЧЕСКОЙ СИСТЕМЫ В РЕГУЛЯЦИИ СПИНАЛЬНОЙ ЛОКОМОЦИИ

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Статья посвящена исследованию нейрофармакологических механизмов локомоции у млекопитающих. Изучалось участие серотонинэргической системы в регуляции локомоторного поведения спинальных животных. Показано, что локомоция, вызванная электрической стимуляцией спинного мозга, имеет определеннную специфичность при активации отдельных типов серотониновых рецепторов.

Ключевые слова: *центральный генератор движений, локомоция, стимуляция спинного мозга, серотонинэргическая система.*

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