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L-dopa Effect on Frequency-Dependent Depression of the H-reflex in Adult Rats with Complete Spinal Cord Transection

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Abstract

This study investigated whether L-dopa (DOPA), locomotor-like passive exercise (Ex) using a Motorized Bicycle Exercise Trainer (MBET), or their combination in adult rats with complete spinal cord transection (Tx) preserves and restores low frequency-dependent depression (FDD) of the H-reflex. Adult Sprague Dawley rats (n=56) transected at T8-9 had one of five treatments beginning seven days after transection: Tx (transection only), Tx+Ex, Tx+DOPA, Tx+Ex+DOPA, and Control (Ctl, no treatment) groups. After 30 days of treatment, FDD of the H-reflex was tested. Stimulation of the tibial nerve at 0.2, 1, 5, and 10 Hz evoked an H-reflex that was recorded from plantar muscles of the hind paw. No significant differences were found at the stimulation rate of 1 Hz. However, at 5 Hz, FDD of the H-reflex in the Tx+Ex, Tx+DOPA and Ctl groups was significantly different from the Tx group ($p<0.01$). At 10 Hz, all of the treatment groups were significantly different from the Tx group ($p<0.01$). No significant difference was identified between the Ctl and any of the treatment groups. These results suggest that DOPA significantly preserved and restored FDD after transection as effectively as exercise alone or exercise in combination with DOPA. Thus, there was no additive benefit when DOPA was combined with exercise.

Keywords

H-reflex; hyperreflexia; spasticity; spinal cord injury; exercise; DOPA; low frequency-dependent depression

1. Introduction

At least 250,000 Americans suffer from spinal cord injury (SCI), and each year 10,000 new cases occur in the U.S.A.[1]. SCI produces numerous deficits of the motor and sensory systems, one of which is spasticity. Spasticity is a major motor deficit that interferes with the

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quality of life of patients with SCI. One of the major components of spasticity is hyperreflexia [2] that develops over time following SCI [3, 4]. While the pathophysiology of hyperreflexia is not completely defined, numerous components have been identified [4]. These include decreased pre-synaptic inhibition of Ia afferents [5, 6], upregulation of postsynaptic receptors [4], terminal sprouting [4], changes in intrinsic properties of motor neurons [7], and recently, changes in gap junctions between spinal cord neurons [8, 9]. These most likely produce the clinical findings of decrease of reflex threshold and increase of reflex amplitude.

The Hoffman reflex (H-reflex), the electrical analogue of the classic tendon tap reflex, has been widely used as a measure of hyperreflexia. It is a compound electromyographic (EMG) response evoked by nerve stimulation. In intact animals and humans, the H-reflex demonstrates marked low frequency-dependent depression (FDD) once stimulus frequencies exceed 1 Hz [10-12]. Reduction of FDD of the H-reflex is thought to be due to decreased inhibition following SCI [6, 13, 14]. Treatments that reduce hyperreflexia after SCI have been shown to improve gait in humans [15, 16]. Previously, we reported the ability of long-term passive exercise therapy, called motorized bicycle exercise training (MBET), to preserve and/or restore FDD of the H-reflex in adult rats with complete spinal cord transection [9, 11, 17]. In these studies in rats with a model of SCI using complete transection of the spinal cord, MBET therapy for only 30 days prevented the development of hyperreflexia. The effect of passive exercise was evident in a duration-dependent manner in transected, exercised rats [17]. This methodology also was found to normalize FDD of the H-reflex in a human patient with a SCI [12]. In addition, active bicycle training has been shown to normalize reflex depression for patients with incomplete SCI [18].

In addition, pharmacological therapy has shown promising results in the treatment of SCI. Dopaminergic agonists have been implicated in the initiation and maintenance of locomotion. The dopamine precursor, L-dopa (DOPA), is capable of inducing locomotor activity of long duration in decerebrate neonatal rats [19], and triggering locomotor movements in paraplegic mice [20]. In mid-thoracic spinalized adult cats, DOPA initiated hind-limb locomotion when the hind-limbs were placed on a moving treadmill [21, 22]. In addition, dopaminergic agonists have been found to ameliorate motor deficits in animals and humans following brain injury. After cerebral frontal cortex injuries in animals, amphetamine increased the rate of recovery of beam-walking ability in rats and in cats [23, 24], an effect that was blocked by haloperidol [25]. Also in cats, both amphetamine and apomorphine improved the rate of recovery of tactile placing following motor cortex injury [26]. While the recovery rate was accelerated with treatment, the end result, however, was about the same.

In a study of short duration, a single dose of amphetamine or placebo was given to stroke patients followed within 3 hrs by a single physical therapy session. The next day, motor scores were significantly improved in patients receiving amphetamine [27]. Also in a single dose study, DOPA given to patients with SCI suppressed all muscle reflexes induced by large muscle afferents with the peak reduction occurring at 1 hour [16]. In stroke rehabilitation in human patients over a 6-week period, motor recovery improved significantly beginning at 2 weeks when DOPA was administered 30 minutes prior to physical therapy [28]. This effect was maintained for the duration of the test period, i.e. 3 weeks after treatment ceased.

In this study, we tested the effect of DOPA for treatment of hyperreflexia (FDD of the H-reflex) compared to exercise alone and in conjunction with exercise. DOPA was chosen because it is a drug with proven safety in the treatment of motor diseases [29]. Studies in

humans have led to the speculation that DOPA could become a standard adjunct to rehabilitation of patients with brain or spinal cord injuries [16, 28].

2. Materials and Methods

Fifty-six adult, female Sprague-Dawley rats were assigned randomly into five groups: spinal transection only (Tx, n=15), transection and exercise (Tx+Ex, n=16), transection and DOPA (Tx+DOPA, n=7), transection and DOPA and exercise (Tx+DOPA+Ex, n=7), and control (Ctl, intact, no treatment, n=11)

Surgery

Rats (Harlan, 200-250 g) were anesthetized with Ketamine (60 mg/Kg, i.p.) and Xylazine (10 mg/Kg, i.p.), and body temperature was maintained at 36 ± 1 °C. A laminectomy was performed at T8-T9 and a complete transection of the spinal cord was made using aspiration. Surgery and postsurgical care was performed as previously described in [8, 17]. All procedures were approved by the Institutional Animal Care and use Committee and met the standards of the NIH Guide for the Use and Care of Laboratory Animals.

L-Dopa (DOPA)

The Tx+DOPA and Tx+Ex+DOPA groups received oral administration 5 days/week of DOPA in combination with a decarboxylase inhibitor, carbidopa (Sinemet, 1.4 mg/Kg) from crushed tablets in 1% methyl cellulose. A similar dose was effective in modulating the monosynaptic reflex in cats (38) and in improving motor recovery in human patients following stroke (Scheidtmann, et al, 2001). We followed the Scheidtmann, et al (2001) protocol (28) for humans by giving rats DOPA 30 minutes prior to exercise therapy in order to take advantage of the peak time of the DOPA effect. Studies of the effects of monoaminergic agents in rats following unilateral motor cortex ablation indicate that the motor recovery occurs only if physical training is performed during the peak of drug availability [30].

Exercise

Beginning 7 days post-transection, animals in the Tx+Ex and Tx+Ex+DOPA groups were suspended in a sling and the hind paws loosely taped with surgical tape to the pedals of a motorized bicycle exercise trainer (MBET) that simulated a bicycling motion of the hind-limbs. The pedaling motion (40 cpm) flexed one hind-limb and simultaneously extended the contralateral one. A full range of flexion and extension of the hip, knee, and ankle is evident with this exercise. Previous studies have shown that animals tolerate this procedure well [8, 11, 17]. Exercise consisted of two 30-minute bouts of cycling with a 10 min rest for five days/week for 30 days. Animals in the Ctl group were intact and did not receive exercise or DOPA. The Tx and Tx+DOPA groups did not receive exercise training.

Reflex Testing

After 24 hours but within 3 days after the last exercise/DOPA treatment, animals were anesthetized with Ketamine (60 mg/Kg, i.p.) and Xylazine (10 mg/Kg, i.p.). A bipolar electrode was placed on the surgically exposed tibial nerve beneath the calcaneal tendon for stimulation (0.1 msec pulses, cathode proximal). A wire electrode was inserted subcutaneously over the 4th and 5th interosseous muscles for EMG recording and referenced to a clip applied to the distal skin on the digits. A ground electrode was attached to the skin of the tail. Recordings were amplified x500 and filtered at 3-3K Hz. Responses to the stimulus were digitized and averaged using a GW Instrument (Somerville, MA) digitizer

module and SuperScope^R software. At the end of the experiment, animals were euthanized with an overdose of barbiturate (Nembutal) and the Tx was confirmed visually.

The H-reflex

Stimulation of the tibial nerve produced two responses: an early M-wave (latency 3-4 msec) due to direct activation of motor fibers in the tibial n. and a later H-wave (latency 6-8 msec) due to activation of type Ia muscle spindle afferents in the tibial n. that synapse monosynaptically on plantar motoneurons. Using stimuli of 1.4-1.6 times threshold, the first 5 responses were discarded in order to average 10 trials of the stabilized reflex [3]. Averages were obtained at 0.2, 1, 5, and 10 Hz. For a data series to be kept, the H-wave in a repeat average at 0.2 Hz had to be within $\pm 10\%$ of the initial one. The amplitude of the H-wave at each frequency was normalized to the amplitude of the H-wave at 0.2 Hz in order to compare results between animals.

Measurements and statistical tests

The amplitude of the H-wave was measured from the preceding baseline to its peak [17]. Results from treatment groups were compared using a repeated measures ANOVA model. Significant differences between groups with corresponding adjusted p-values were calculated using the Tukey *post hoc* comparison procedure. Results were considered significant at the $p < 0.05$ level.

3. Results

Low FDD (inhibition or habituation) of the H-reflex amplitude for all groups (Ctl, Tx, Tx +DOPA, Tx+Ex, and Tx+DOPA+Ex) following stimulation at 0.2, 1, 5, and 10 Hz is shown in Fig. 1. Multiple comparisons among treatment groups were performed at 1, 5, and 10 Hz frequencies. Data at the 0.2 Hz frequency were not included in the analysis because the response at this frequency was set to the 100% level and there is no variation. The repeated measures ANOVA showed significance for main effect factors of treatment ($p < 0.0002$, $df = 4, 51$, $F = 8.77$) and frequency ($p < 0.0001$, $df = 2, 102$, $F = 281.14$). The interaction of treatment and frequency factors was not significant ($p = 0.10$, $df = 8, 102$, $F = 1.75$). At 5 Hz the Ctl ($p = 0.0086$), Tx+Ex ($p = 0.0053$), and Tx+ DOPA ($p = 0.0016$) groups were different from the Tx group (Fig. 1); however, the Tx+Ex+ DOPA group was not different. At 10 Hz, all treatment groups; Ctl ($p < 0.0001$), Tx+Ex ($p < 0.0001$), Tx+ DOPA ($p = 0.0026$), and the combination group Tx+Ex+ DOPA ($p = 0.0013$), were different from the Tx group.

4. Discussion

In this study, all treatments were effective in reducing loss of FDD of H-reflex amplitude compared to that of the untreated, transected (Tx) group, but not at all frequencies tested. At 5 Hz, only the combined treatment group Tx+Ex+DOPA was not statistically different from the Tx group. At 10 Hz, all treatment groups and the Control group were different compared to the Tx group. Thus, DOPA treatment was as effective as exercise in preserving and/or restoring FDD to the H-reflex after SCI. The combined treatment of exercise and DOPA was not more effective than either treatment alone. The lack of a combined effect could occur if exercise and DOPA for 30 days each caused a maximal (floor) effect. This issue should be addressed in future studies.

In the period 7-14 days *post* transection, the first indication of hyperactivity of the H-reflex was detected as an average loss of FDD of about 10% at 10 Hz [8, 31]. In untreated transected animals, the FDD loss increased in a linear fashion such that at day 30 the loss of FDD was about 35% [8, 17, 31]. Thus, all treatments effected 1) a preservation of FDD by

preventing its loss from attaining the maximum level of 35% at day 30, and 2) a restoration of FDD at day 30 to a level indistinguishable from that of the intact Ctl group, i.e. the pre-transection level for all animals in this study.

4.1 L-dopa in animals

The majority of studies on the effect of DOPA on spinal reflexes in acutely spinalized preparations reported facilitation of the monosynaptic reflex [31-34], although Anden, et al. [32] reported that DOPA had an inconsistent effect on the monosynaptic, while consistently inhibiting polysynaptic and flexor, reflexes. Few studies have examined the effects of DOPA on spinal reflexes in chronically spinalized preparations. Anden, et al. [33] tested DOPA in adult spinalized animals (cats) at 2-4 weeks. While DOPA exerted a strong inhibitory effect on flexion reflex afferent-induced reflexes in acute preparations, in chronically spinalized animals, the effect was reduced. The results of these studies on the effects of DOPA are essentially in agreement with those using stimulation of the locus coeruleus, i.e. facilitation of the monosynaptic reflex. Thus, the facilitatory effect could be due to DOPA conversion to noradrenaline (NA).

4.2. Dopamine synthesis in chronic SCI

In the chronically transected spinal cord, DOPA probably is converted to dopamine (DA) and used locally. After spinal cord transection in rats, NA was almost completely absent at day 15, while DA was moderately increased at day 3, but by day 9 it too was almost completely absent, along with 5-HT [34]. In another study, adult rats transected at T6 retained the ability to metabolize DOPA in the isolated spinal cord caudal to the transection. At 10 days *post*-transection, the spinal cord was able to synthesize 50% as much DA from exogenous DOPA as did the intact spinal cord. In contrast, at the same time, synthesis of NA was decreased by a factor of 40 to very low levels. By day 100, the synthesis of DA had returned to pre-transection levels while the synthesis of NA remained at the same reduced level [35]. The newly synthesized DA was metabolized to the usual metabolites, dihydroxyphenylacetic acid, and homovanillic acid. While synthesis of NA from DOPA requires terminals of NA descending fibers, synthesis of DA takes place in capillary endothelial cells [36], and in neurons that contain the decarboxylase enzyme [37]. Thus, after transection, the spinal cord can effectively synthesize DA from exogenously supplied DOPA. This was also demonstrated in isolated lumbar spinal cord after injection of DOPA in chronically transected (3 weeks) cats increased the cord content of DA from 0.26 μ g to 8.5 μ g, approximately a 32-fold increase, while NA increased only slightly [38], corroborating the finding that NA essentially cannot be synthesized in the isolated spinal cord.

Commissiong and Sedgewick [39] concluded that DOPA induced facilitation of the stretch reflex in rats after being converted to DA. This was demonstrated using D2 receptor antagonists. Of interest to our results is the finding that DA was shown to modulate the number of gap junctions in the retina, both the connexin 43 (Cx43) [40] and Cx36 types [41].

Recently, a possible mechanism for hyperactivity of the H-reflex involving gap junction and electrical coupling was proposed [42]. Gap junctions are known to synchronize subsets of neurons through electrical coupling [43, 44], and functional groups of interneurons in the spinal cord are coupled by gap junctions [45]. The desynchronization of EMGs during stepping that results from spinal cord transection [19] could be due in part to a reduction of gap junctions. Thus, a decrease in the number of gap junctions after SCI, especially between inhibitory interneurons, could lead to hyperreactive motoneurons. In support of this hypothesis, the drug modafinil, which is known to increase number of gap junctions [46],

preserved and restored normal frequency-dependent inhibition in SCI rats [42]. Therefore, DA may have an effect in spinal cord similar to that observed for modafinil.

In this study, DOPA most likely was converted into DA in the isolated spinal cord and became available for local use, such as modulating reflexes acutely, and apparently for inducing longer lasting changes in spinal cord circuitry. This was evidenced by the preservation and/or restoration of FDD of the H-reflex. Even though it is difficult to compare acute and chronic studies using somewhat different tests, it appears that the effect of DOPA in this study in spinalized animals is basically in agreement with the effect on the patellar reflex following direct application of DA to the spinal cord of intact animals [47]. Hence, DOPA administered over a 30-day period appeared to reorganize spinal cord circuitry such that functionally it resembled that of the intact animal. This reorganization was equivalent to that induced by exercise that requires movements resembling the locomotor pattern. It is not possible to discern from this study whether exercise and DOPA affect the same, separate or overlapping mechanisms in the spinal cord in effecting their preservation and/or restoration of FDD of the H-reflex following SCI. The question of mechanism will be addressed in future studies.

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Abbreviations

DOPA	L-dopa
FDD	frequency-dependent depression
Tx	transection
Ex	exercise
Ctl	control

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Figure 1.

Low frequency-dependent depression of the H-reflex as a function of frequency. Averages $\pm$ S.E. of H-reflex amplitudes are shown as a percent of the amplitude at the lowest frequency (0.2 Hz) at 0.2, 1, 5, and 10 Hz for Ctl (intact control, black circles), Tx (transection only, blue squares), Tx + DOPA (transection + DOPA, green triangles), Tx + Ex (transection + exercise, red diamonds), and Tx + DOPA + Ex (transection + DOPA + exercise, brown diamonds). Frequency-dependent depression of the H-reflex at 0.2 Hz was designated 100%. Statistical comparisons to the Tx group at 5 Hz are: A Tx+Ex+DOPA ns, B Tx+ DOPA $p=0.0016$, C Tx+Ex $p=0.0053$, and Ctl $p=0.0086$. At 10 Hz, E Tx+ DOPA $p=0.0026$, F Tx +Ex+ DOPA $p=0.0013$, G Tx+Ex $p=0.0001$ and H Ctl $p<0$. Ex = exercise, Tx = transected. ns=not significant