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Effect of a serotonin antagonist on delay in grip muscle relaxation for persons with chronic hemiparetic stroke ☆

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HIGHLIGHTS

- Our findings support the supposition that monoaminergic brainstem pathways may be disinhibited following stroke.
- Disinhibited monoaminergic brainstem pathways appear to result in increased delays in muscle relaxation.
- Treatments to reduce delay in muscle relaxation may facilitate hand rehabilitation in persons with stroke.

ABSTRACT

Objective: To investigate if, following stroke, sustained involuntary activity after voluntary contraction (e.g., grip) of the long finger flexor muscles of the paretic hand is attributable to augmented serotonin release from brainstem pathways, affecting excitability of spastic motoneurons.
Methods: This single-dose placebo-controlled study examined whether a serotonin receptor (5-HT2) antagonist, cyproheptadine hydrochloride, could reduce delay in muscle relaxation of a key paretic long finger flexor muscle immediately after grip for persons with stroke. Time to initiate the long finger flexor muscle contraction, grip and pinch strengths, and clinical hand function scores (the Action Research Arm Test and the Box and Block Test) were also assessed.
Results: Cyproheptadine hydrochloride reduced mean delays in finger relaxation ($n = 13$; from 7.2 to 4.1 s; SEM = 1.2 s; $p = .026$) in comparison to placebo, while leaving grip and pinch strengths and time to initiate the muscle contraction largely unaffected. Reduction in the relaxation time alone did not lead to increased clinical hand function scores.
Conclusions: The findings support the supposition that monoaminergic brainstem pathways may be disinhibited following stroke, thereby resulting in increased delays in muscle relaxation.
Significance: Treatments to reduce delay in muscle relaxation may facilitate hand rehabilitation in persons with stroke.

1. Introduction

Stroke is the leading cause of long-term disability, affecting more than 6.5 million people in the US, with a total economic impact of $68.9 billion a year (Lloyd-Jones et al., 2009). Each year, more than 795,000 people suffer a stroke in the US (Lloyd-Jones et al., 2009). More than half of all individuals with chronic stroke were found to be dependent on others for help in activities of daily living (Wade, 1994). Chronic motor and sensory impairments following stroke (Woodson, 2002) are especially prevalent in the hand (Kamper et al., 2003; Trombly, 1989), which significantly diminishes the capacity to perform activities of daily living and lowers stroke survivors' functional independence.

Disability arising from stroke results not only from a reduced ability to activate certain muscles (Clark et al., 2006; Jonkers et al., 2009), but also from difficulty in controlling the excitation of others.

☆ The planning and experiment was performed in the Coleman Hand Rehabilitation Laboratory at the Sensory Motor Performance Program at the Rehabilitation Institute of Chicago. Analysis and manuscript preparation were primarily done at the University of Wisconsin-Milwaukee.

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Spasticity (Kamper and Rymer, 2000; Woldag and Hummelsheim, 2003), abnormal synergies (Dewald et al., 1995), and excessive coactivation (Kamper et al., 2003) have all been reported to contribute to impairment. Another manifestation of stroke that has significant functional ramifications but has not been as thoroughly studied is difficulty with terminating muscle activation. Upon gripping an object with the paretic hand, stroke survivors routinely have difficulty letting go of the object (Kamper et al., 2003; Trombly, 1989). This study is concerned with the ability to relax paretic hand muscles immediately after contraction for persons with stroke.

Using the surface electromyogram (EMG), sustained involuntary muscle activities after a voluntary contraction of paretic muscles for persons with stroke have been recorded in muscles of the forearm (Seo et al., 2009), wrist (Chae et al., 2002), and lower limb (Chae et al., 2006). For example, delay in relaxing one of the long finger flexor muscles after a maximum grip was, on average, 5 s for the severely impaired paretic hand as opposed to 0.4 s for age-matched individuals without neurological disorders (Seo et al., 2009). In some cases, the relaxation time was longer than 20 s. This delay is indicative of the difficulty persons with stroke can exhibit in terminating activity in the forearm muscles. The sustained activity leads to even greater difficulty when trying to open the hand after closing it. Delays in grip muscle control following stroke can also contribute to inefficient grip force scaling during grip-and-lift tasks (Nowak et al., 2007; Nowak et al., 2003), deficits in timing and coordination of movement (Nowak et al., 2007), and thus to decreased motor function (Chae et al., 2006; Chae et al., 2002).

Spinal neuron excitability can be modulated by monoamines such as serotonin (Hounsgaard et al., 1988; Hounsgaard and Kiehn, 1989). Addition of monoamine agonists induced increased Ia-mediated motoneuronal excitation and increased stretch reflexes in cat preparations in vivo (Lee and Heckman, 2000; Miller et al., 1996). Increases in neuromodulator availability in the spinal cord could generate an increase in firing activity (Hornby et al., 2002). More specifically, administration of monoamines such as serotonin was shown to elicit depolarization (or increases of inward current) in a majority of motoneurons (Wang and Dun, 1990) and to enhance plateau behavior (Hornby et al., 2002) in animal models. Therefore, it is plausible to consider that the large delay in muscle relaxation could be attributable to increased serotonergic influence in the spinal cord, resulting from disinhibition of monoaminergic brainstem pathways following stroke (Kamper et al., 2003; Kline et al., 2007; Matsuyama et al., 2004).

The aim of this study was to determine if delayed muscle relaxation following stroke is attributable to the actions of disinhibited monoaminergic brainstem pathways. It follows that administration of drugs that suppress the influence of monoaminergic pathways such as serotonin receptor antagonists may decrease persistent inward ion currents into spinal motoneurons, and subsequently decrease delay in muscle relaxation in persons with stroke. One such agent, cyproheptadine hydrochloride, has been shown to block the depolarizing effect of serotonin on motoneurons in neonatal rats (Wang and Dun, 1990). In summary, we hypothesize that delay in grip relaxation for the paretic hand of persons with stroke will decrease after administration of cyproheptadine in comparison with placebo.

2. Methods

2.1. Study participants

Thirteen individuals with chronic hemiparesis subsequent to stroke participated in this study. The inclusion criteria were: (1) the occurrence of a single hemispheric stroke at least 9 months prior to the study and (2) severe hand impairment as indicated by a rating of stage 2 or 3 for the Stage of Hand section of the Chedoke-McMaster Stroke Assessment (Gowland et al., 1995). The exclusion criteria were: (1) inability to comprehend experimental tasks; (2) history or clinical signs of concurrent medical problems such as upper extremity injuries and orthopedic conditions; and (3) concurrent usage of pharmacological agents targeting amines such as selective serotonin reuptake inhibitors. The study participants were composed of 8 males and 5 females with the mean age of 54 years (standard deviation = 11 years, with a range from 38 to 80 years). Time since stroke ranged from 3 to 23 years. The study protocol was approved by the University Institutional Review Board and all study participants signed the approved consent form prior to beginning participation in the study.

2.2. Procedure

The acute effect of a single-dose cyproheptadine hydrochloride (8 mg of Periactin®) on delay in grip relaxation, delay in grip initiation, grip and pinch strength, and clinical hand function scores was investigated in a double-blinded placebo-controlled randomized study. This dosage falls within typical usage levels (Greaves, 2001). Cyproheptadine is an antiserotonergic and antihistaminic drug directly targeting 5-HT2 receptors. It inhibits motoneurons by attenuating the excitatory effects of serotonin on spinal and supraspinal centers. Cyproheptadine has been shown to attenuate clonus in persons with spinal cord injury and multiple sclerosis (Barbeau et al., 1982). Side effects of cyproheptadine are well tolerated for the dose levels typically administered. Adverse reactions are related to central nervous system depression resulting from anticholinergic properties of the drug such as sedation and dry mouth (Adkinson, 2003).

This study consisted of two days of experiments (one day for cyproheptadine and one day for placebo control) for each study participant. Each day had two testing sessions (before and after administration of a pharmaceutical agent). The two experiment days were held one week apart to ensure washout. The order of placebo and cyproheptadine administration was blinded and randomized such that about one half of all of the study participants received placebo on the first day of the experiment, and the rest received cyproheptadine on their first day of the experiment.

Cyproheptadine (8 mg) was administered orally. Peak plasma concentration occurs about 4 h after administration, and effects are maintained up to eight hours after administration (Greaves, 2001). Thus, we measured delay in grip relaxation, delay in grip initiation, grip and pinch strength, and clinical hand function scores prior to and 3.5 h after ingestion of the pill (cyproheptadine or placebo). Each testing session lasted for one hour. Each experimental day lasted for approximately 5.5 h.

Hand function was evaluated using both the Box and Block Test (BBT) (Desrosiers et al., 1994; Mathiowetz et al., 1985) and the Action Research Arm Test (ARAT) (Lang et al., 2006). Lateral pinch strength was recorded using an electronic pinch gauge (Baseline BIMS pinch gauge, Fabrication Enterprises, Inc., White Plains, NY). Study participants performed maximum pinch grip using the thumb and the lateral aspect of the index finger for five seconds. For measurement of delay in grip relaxation, delay in grip initiation, and grip strength, study participants grasped an electronic grip dynamometer (Baseline BIMS hand dynamometer, Fabrication Enterprises, Inc., White Plains, NY). To perform these measurements, study participants were seated with the elbow flexed approximately at 90° and the forearm resting on the table. Study participants were instructed to keep the hand relaxed for the initial 5 s until they heard a computer-generated audible tone at which time they gripped maximally, maintained that grip for the duration of the tone (5 s), and then relaxed the hand as soon as the tone stopped (see Fig. 1). Study participants were instructed to grip