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Amphetamine and other pharmacological agents in human and animal studies of recovery from stroke

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ABSTRACT

Neuromodulation with pharmacological agents, including drugs of abuse such as amphetamine, when paired with behavioral experience, has been shown to positively modify outcomes in animal models of stroke. A number of clinical studies have tested the efficacy of a variety of drugs to enhance recovery of language deficit post-stroke. The purpose of this paper is to: (1) present pertinent animal studies supporting the use of dextro-amphetamine sulfate (AMPH) to enhance recovery after experimental lesions with emphasis on the importance of learning dependent activity for lasting recovery; (2) briefly review neuropharmacological explorations in the treatment of aphasia; (3) present a pilot study in aphasia exploring a drug combination of AMPH and donepezil hydrochloride paired with behavioral treatment to facilitate recovery; and (4) conclude with comments regarding the role of adjunctive pharmacotherapy in the rehabilitation of aphasia, particularly AMPH.

1. Introduction

Neuromodulation with pharmacological agents, including drugs of abuse such as dextroamphetamine sulfate (AMPH), when paired with behavioral experience has been shown to modify outcomes after experimental lesions in animals (Barbay et al., 2006; Bütefisch et al., 2002; Feeney et al., 1982; Hovda and Feeney, 1984; Stroemer et al., 1998). A number of clinical studies have tested the efficacy of a variety of drugs to enhance recovery from post stroke deficits including aphasia (Ashtary et al., 2006; Berthier et al., 2006; Kessler et al., 2000; Pashek, 2006; Sabe et al., 1995; Szelies et al., 2001; Tanaka et al., 2001; Walker-Batson et al., 2004). Evidence regarding critical periods of plasticity post-injury, theories of learning and the enhancing effects of certain drugs has application to biologically based approaches for human rehabilitation. The purpose of this paper is to: (1) present pertinent animal studies supporting the use of AMPH to facilitate recovery following experimental lesions with emphasis on the importance of learning dependent activity to for lasting recovery; (2) briefly review clinical studies employing a range of pharmacologic agents to facilitate recovery of post-stroke aphasia; (3) present a pilot study exploring a drug combination of AMPH and donepezil hydrochloride paired with language treatment to facilitate recovery of aphasia; and (4) conclude with comments regarding the role of adjunctive pharmacotherapy in the rehabilitation of aphasia, particularly AMPH.

2. Evidence from the basic science laboratory

There is an impressive literature in animal models of stroke exploring pharmacological agents to facilitate recovery after injury. Much of this literature has focused on the noradrenergic and dopaminergic systems. A number of experiments have investigated the hypothesis that modulation of brain catecholamines might influence recovery of motor function. One of the primary agents explored was AMPH (Boyeson and Feeney, 1993; Feeney et al., 1982; Hovda and Feeney, 1984;). An important finding from these studies was that recovery was greater when targeted behavioral experience was paired with the drug intoxication phase and not drug administration alone. AMPH facilitated recovery has also been reported for binocular depth perception (Feeney and Hovda, 1985) and sensory motor integration (Hurwitz et al., 1991) with limits to the AMPH effect in terms of lesion location (Boyeson and Feeney, 1993) and time post-injury (Hovda and Feeney, 1984). Recently other groups have reported positive findings in post-lesioned animals after AMPH administration (Atkins and Jones, 2005; Barbay et al., 2006; Bütefisch et al., 2002; Papadopoulos et al., 2009; Stroemer et al., 1998). Previous research studied the relationship between behavioral recovery and expression of proteins involved in neurite growth and synaptogenesis (Stroemer et al., 1998). AMPH and placebo treated rats were exposed to beam walking as a motor activity. AMPH treated rats had accelerated recovery compared to the placebo treated rats at two time periods: at the early assessment period, which

Abbreviations: AMPH, dextro-amphetamine sulfate; PICA, Porch Index of Communicative Ability; WAB-R, Western Aphasia Battery-R; MCA, middle cerebral artery; ST, speech therapy; OLCT, open label clinical trial.

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the authors have suggested could be due to resolution of diaschisis and at a later period, which was suggested to contribute to neuronal remodeling. Papadopoulos et al. (2009) studied how differing levels of motor treatment paired with short term AMPH administration enhanced forelimb function in rats. Results showed that short term pairing of AMPH with specifically focused activity induces long-term improvement. The anatomical data suggested that cortico-efferent plasticity of axonal sprouting contributes to improved motor recovery. These authors emphasize that sufficiently focused physical activity (dosing) is needed to realize the therapeutic benefits of AMPH recovery. This implies that the amount and specificity of rehabilitation paired with neuromodulation are of utmost importance.

The type of behavioral treatment needed to facilitate neuroplasticity and lasting recovery has been well studied in the laboratory with implications for translation to human rehabilitation. Post-lesion plasticity of sensory and motor systems has been studied in adult monkeys. The term learning dependent (Plautz et al., 1995) has been suggested to describe the type of treatment required for changes in cortical plasticity to occur following motor and sensory injury. Nudo et al. (1997) observed that motor maps are altered by motor skill acquisition and not by repetitive use alone. Topographic plasticity paralleled the reacquisition of motor skills in lesioned animals and the acquisition of new motor skills in intact animals. Plasticity of the somatosensory cortex was studied by Xerri et al. (1998) who found that post-lesion remodeling was influenced by activity that was idiosyncratic to each animal. This research suggests that the specificity of the behavioral treatment following brain injury with or without pharmacologic modulation critically determines the type of recovery that occurs.

3. Clinical explorations of neuropharmacological agents in the treatment of aphasia

Research reports exploring various neuropharmacological agents as an adjunct in the treatment of aphasia date back over 80 years. As would be expected, there is considerable variability in study design and outcome measures employed over this period. Differences include time post-stroke of study initiation, drug administered alone or paired with behavioral treatment, timing of the behavioral treatment (e.g. during the peak period of drug action), intensity and dosing of the behavioral treatment, and measures assessing lasting behavioral effects at follow-up.

Table 1 provides an overview of the diversity of the drugs that have been explored to facilitate recovery of aphasia. The search strategy used key phrases on search engines along with PudMED and PsychInfo. Older publications not identified on search engines were part of personal libraries or specifically requested. As seen in Table 1 the greatest percentage of studies have been open label or cross over design with small numbers and few double blind comparisons. Drugs showing moderately positive effects include Piracetam, acetylcholinesterase inhibitors, and dextroamphetamine sulfate.

4. Combined AMPH/donepezil in the treatment of aphasia: a pilot study

Influenced by previous explorations of cholinesterase inhibitors (Berthier et al., 2006; Tanaka et al., 1997; Tanaka et al., 2001; Pashek, 2006), the asymmetry of acetylcholine in the left temporal lobe (Amaducci et al., 1981), coupled with our experience (Unwin and Walker-Batson, 2000; Walker-Batson et al., 2004) and that of others (Benson, 1970) administering AMPH to facilitate recovery from aphasia, we were curious if a drug combination might have more impact than a single drug alone. The purpose of this Phase I pilot study was two-fold: to investigate the safety of the drug combination of AMPH and donepezil sulfate and to determine if this combined drug regimen when paired with 36 h of language treatment showed clinically significant effects which were maintained at follow-up long after drug treatment ceased.

4.1. Methods and procedures

4.1.1. Subjects

Eight consecutively entered patients with aphasia due to a single left middle cerebral artery (MCA) occlusive infarction participated in the study. Written informed consent was obtained from all subjects before the study was initiated. The research protocol was approved by the Institutional Review Boards for Human Subjects at the participating centers. Participants were recruited from medical centers in a metropolitan area and entered in a consecutive manner. Over a two-year period the medical charts of approximately 320 patients were screened. The primary reasons for exclusion were history of a previous stroke or aphasia either too mild or too severe to meet our inclusion criteria.

All patients were native English speakers. Diagnosis was based on radiological and neurological examination. Either CT or MRI confirmed the presence of a single infarction at entry. The National Institute of Health Stroke Scale (NIHSS) (Brott et al., 1989) was administered to provide a baseline score of the degree of neurological involvement. Exclusion criteria specified that none of the subjects have a terminal medical condition such as AIDS or cancer, other coincident neurological disease, history of psychiatric illness, extensive alcohol or drug abuse, unstable cardiac dysrhythmia, hypertension not controlled by medication (<160/100 mm HG) or untreated hyperthyroidism. Participation was limited to persons not older than 80 years and not receiving alpha-adrenergic antagonists or agonists, major or minor tranquilizers. The Porch Index of Communicative Ability-PICA (Overall Score) (Porch, 1982) and the Western Aphasia Battery—WAB-R (Aphasia Quotient) (Kertesz, 2006) were the dependent measures and were obtained within three days of study initiation. The presence of aphasia was defined as a score of 15 to 70 on the Overall Score on the PICA. The primary outcome measure was the PICA Overall Score at the one week off drug assessment. Patients were closely monitored during the six week treatment period and follow-up in an attempt to eliminate any confounding medications that might have a deleterious effect on recovery.

4.1.2. Procedures

This was an open label study designed to evaluate the effects of combining AMPH and donepezil to enhance recovery from aphasia. All participants received a 1.5 hour language therapy session four days per week, Monday through Thursday (36 hours total) for six weeks. On Monday and Thursday only, an oral dose of 10 mg of AMPH was administered 30 min prior to the treatment session for a total of 12 doses of AMPH over the six week study period. Every day, the participant took 5 mg of donepezil. Therapeutic protocols for each participant were individually designed using cognitive linguistic approaches which targeted the most complex language behaviors (Thompson et al., 2003; Raymer and Rothia, 2008; Kiran and Thompson, 2003) that could be elicited by the therapist. Blood pressure was checked each treatment day before AMPH administration and at the end of the 1.5 hour treatment session. A log of any negative side effects was kept by each subject or significant other and monitored bi-weekly.

4.2. Data preparation

The Porch Index of Communicative Ability—PICA (Overall Score) (Porch, 1982) and the Western Aphasia Battery—WAB-R (Aphasia Quotient) (Kertesz, 2006) were the dependent measures. The PICA Overall score at the one week off treatment (gain scores from Time 1 to Time 3) was considered the primary outcome measure. We chose to administer two standard aphasia batteries used in research settings both for reliability and to compare our data to other published studies. PICA Overall and Verbal scores were obtained at baseline, mid-

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