“Use of Pharmacotherapy to Improve Functional Outcome in Stroke”
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The American Speech Language and Hearing Association- Miami, FL November 16, 2006

Background: The possibility of accelerating and/or enhancing functional recovery with a pharmacologic agent days to weeks post injury could have wide ranging social impact. Exploration of the effects of medications that modulate neurotransmitters after brain injury extends work from the basic science laboratory. This research draws scientists/clinicians from diverse disciplines toward the ultimate goal of biologically based approaches to rehabilitation.

Changing Concepts of Recovery of Function: Neurologically based approaches to rehabilitation reflect changing concepts of neural specificity and plasticity, which have important implications for human rehabilitation (Juliano, 1998; Klein et al., 1997; Kilgard & Merzenich, 1998). Brain plasticity can be defined biologically on several different levels, but the term plasticity basically refers to the ability of the brain to change. Animal models provide growing evidence for cortical reorganization on a structural as well as functional level that is use dependent (Kilgard & Merzenich, 1998). Additionally, it has been shown that following cortical ischemic lesions there is a period of reactive synaptogenesis which may increase the susceptibility of the lesioned brain for adaptive change and recovery (Jones et al., 1996; Stroemer et al., 1993) and which may be influenced by pharmacologic modulation (Stroemer et al., 1998).

The Use Dependent/Learning Dependent Model: A large number of animal studies suggest that the amount and type of either sensory input or motor practice are critical determiners of recovery of function. In a series of experiments, Merzenich et al. (Merzenich et al., 1983,1984,1998; Jenkins et al., 1990) have observed that the type of input during recovery (days to months post injury) matters. Merzenich defines a type of brain reorganization (following median nerve section and digit amputation in the monkey) as a dynamic self-organizing process resulting from use dependent alteration of the cortical field. More recently, the term learning dependence (Plautz et al., 1995; Nudo et al, 1997) has been suggested for the activity dependent changes following motor and sensory injury in animal models of recovery. Practice over relatively long periods of time is required for brain reorganization paralleling behavioral changes. Nudo and colleagues (1997) observed that motor maps were altered by motor skill acquisition not by repetitive use alone. Topographic plasticity coincided with the acquisition of new motor skills in intact animals or the reacquisition of motor skills in lesioned animals.

Neuropharmacologic approaches in animals: Following stroke, animal models and a few human studies have shown reductions in catecholamines or their metabolites throughout the cerebrum, brainstem, cerebellum and cerebrospinal fluid (Reding, 1998). Reductions are most prominent on the side of the lesion but are also reduced throughout the brain. Feeney and colleagues have published a series of experimental studies that have used some type of central noradrenergic agonist to facilitate functional recovery of sensory, motor and visual deficits when paired with relevant experience or training. The importance of noradrenergic mediation of recovery is supported by the fact that drugs which act as noradrenergic antagonists have reinstated motor deficits in animals (Boyeson, et al., 1993) and hindered recovery from aphasia in humans (Porch et al., 1985). This could be related to this class of drugs facilitating learning and memory as they have been shown to affect long-term potentiation (Gold et al., 1984). Other experimental studies have explored such drugs as dopamine and acetylcholine.

Pharmacologic treatment in humans: Pharmacologic treatment as an adjunct to traditional
behavioral approaches to treatment is not a new idea. There are clinical reports dating back over 70 years that suggest the use of various agents in the treatment of both hemiplegia and aphasia (Scicoulouff, 1934; Luria, 1969). Most recently, the drugs explored for use in rehabilitation pharmacology are those that modulate the dopaminergic/noreadrenergic (Stefanatos et al. 2006) and acetylcholine systems (Berthier et al. 2003; Pashek & Backman, 2003). During the presentation this section will be elaborated.

Timing Windows/Limitations: The critical timing window after brain injury for initiation of use dependent practice or pharmacologic modulation is not known. Work in animals suggests that there are limits (Feeney & Hovda, 1985). Physiologic events following brain injury also complicate the timing for administration of various agents. Drugs that are effective in the very acute or subacute period following injury may be ineffective or even detrimental at later recovery periods (Goldstein, 1998).

REFERENCES:


patient with stroke-related aphasia and apraxia of speech. *Brain and Language*, 87 (1), 179-180.


