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Toward a Pharmacotherapy for Aphasia

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INTRODUCTION

Aphasia rehabilitation techniques should be designed to facilitate biologically possible recovery processes. Progress in neurobiology has provided two intersecting sets of data specifically important for understanding pharmacosystems and cognition. The first is the collection of detailed information concerning mechanisms of recovery following brain damage, such as "sprouting," "latent synapses," and "diaschisis" (1). For recovery of language function following brain damage, such neurobiological notions are no less critical than cognitive, psycholinguistic, or emotional issues. Modern techniques for aphasia treatment appear to be directed, to some extent, at stimulation of biological recovery. Melodic intonation therapy (2), visual action therapy (3), and visual communication therapy (4), for example, seem to facilitate the unblocking of latent synapses (5), bypassing damaged neurons in the zone of language. Luria et al. (6) have recommended the use of various chemical agents for "deinhibition" from diaschisis to restore higher cortical function. Pharmacotherapy for aphasia based on applied neurobiology may be one of the keys to successful treatment programs.

The second set of data relates to the emerging model of "neurocognitive

networks" (7–10). According to this model, complex human cognition and behavior are processed through an integrated neural network that consists of (1) widely distributed, but interconnecting, sets of neural pathways that underlie anatomically localized operations and (2) chemically addressed pathways for modulating behavioral tone. Selected cognitive skills are organized in association with distinct neurotransmitter profiles. For example, dopaminergic pathways play a selective role in working memory (11,12). Even in the highly complicated realm of speech and language, specific neurobehavioral mechanisms, such as verbal fluency and verbal memory, can be postulated as being related to particular neurochemical systems.

The line of argument presented here leads directly to the suggestion that manipulation of neuropharmacosystems may ameliorate a deficit in aphasia. Specifically, we propose the following three-part hypothesis: (1) that clinical signs of aphasia are dependent on more basic deficits (processing deficits) in underlying neurobehavioral mechanisms, (2) that those underlying deficits are influenced by specific pharmacosystems, and (3) replacement or supplementation therapy with selected neurotransmitters targeted at the underlying processing deficit will relieve that deficit and thereby ameliorate the clinical aphasic signs and symptoms. In this chapter, we first review the concept of selective pharmacotherapy targeted at specific language symptoms, with special reference to dopaminergic and cholinergic systems. A considerable number of studies demonstrate that speech and language output is at least partially dependent on dopaminergic networks, and verbal memory on cholinergic networks. We then discuss briefly nonspecific pharmacotherapy that may ameliorate behavioral problems that could hinder conventional speech and language therapy.

LANGUAGE-TARGETED PHARMACOTHERAPY

Historical Background

The idea of treating aphasia with pharmacological agents has historical roots dating to ancient times. One of the earliest known treatments for aphasia is cashews (*Anacardium*) (13). In the middle of this century, Linn and colleagues (14,15) and others (16,17) demonstrated a beneficial effect of intravenous sodium amytal on aphasia. Linn and Stein (14) speculated that sodium amytal worked by reducing anxiety. Smith and Turton (18) demonstrated improvement in aphasic symptoms utilizing a vasodilating drug. Juria and colleagues (19) advocated the use of cholinergic agents (anticholinesterase) and drugs of other pharmacodynamic groups (caffeine, vitamin B_{12}, glutamic acid, gentian) in the treatment of aphasia.

Roumanian investigators systematically explored the value of drugs. Solomonovici et al. (20) and Voinescu and Gheorghita (21) reported that the antidepressant imipramine improved language function. More recently,

Gheorghita and colleagues (22,23) investigated other pharmacological agents in the treatment of aphasia. They showed a differential effect of drugs on different components of language. Among drugs administered, pyrithioxine (encephabol) had a significant and specific effect on aphasic symptoms. In decreasing order of effect, it benefited repetition and naming, reading and reception, and, finally, writing. Voinescu and Gheorghita (23) hypothesized that pyrithioxine exhibits its effect via enhanced cortical metabolic activity. In Germany, Willmes et al. (24) conducted a double-blind, placebo-controlled pilot study in which patients with aphasia treated with piracetam, a nootropic drug, showed greater improvement than the control group in certain subtests of the Aachen Aphasia Test.

Regardless of the mechanism by which a drug exerts its effect, these results suggest that pharmacological therapy may specifically influence language function in aphasic patients. In the United States, Benson (25) utilized dexedrine in the treatment of a small number of aphasic patients. Samuels (26) has routinely used L-dopa/carbidopa in the treatment of nonfluent aphasia. Thus, numerous investigators have demonstrated a beneficial effect on aphasia from a variety of pharmacological treatments, although no single agent stands out as clearly better than all others.

Dopaminergic Networks

Many of the drugs discussed above were considered to have their positive effect via the dopamine system. L-dopa/carbidopa specifically increases presynaptic dopamine synthesis and release within the central nervous system. Dexedrine increases activity within the catecholamine system, including dopamine and norepinephrine systems. The mechanism of pyrithioxine action is unknown, but some studies suggest that pyrithioxine may exert its effect by increasing dopaminergic activity within the central nervous system (27).

Dopaminergic activity may specifically mediate verbal fluency. This hypothesis results from both clinical and neurochemical findings. If this hypothesis is true, dopamine agonist therapy may be beneficial in the treatment of nonfluency in aphasia.

Clinical Observations

Parkinson's Disease. Strong evidence that dopamine mediates verbal fluency comes from clinical observations of speech and language in Parkinson's disease. Such deficits may include abnormalities of speech volume and timing, impaired verbal fluency, reduced phrasal and syntactic constructions, word-finding difficulties, paraphasias, and impaired verbal abstraction (28–30). Among these deficits, the most prominent features affected in Parkinson's disease seem to be reduced productivity, volume, phrase length, and prosody (31,32). Gotham et al. (33) found that verbal fluency in Park-

inson's disease varies with dopaminergic therapy while other cognitive deficits do not. Their patients with Parkinson's disease were impaired on a measure of verbal fluency only when off levodopa. These findings suggest that Parkinson's disease is associated with verbal fluency deficits, which may be partially reversed with dopamine replacement therapy.

Akinetic Mutism. In 1981 Ross and Stewart (34) described a patient with akinetic mutism following removal of a tumor of the anterior hypothalamus who responded to bromocriptine, a postsynaptic dopaminergic agonist. They concluded that akinetic mutism may arise from loss of dopaminergic input to the anterior cingulate cortex or related structures, and direct dopamine agonists can successfully ameliorate the akinetic mutism. Other cases with akinetic mutism or milder abulia were subsequently reported with successful effect of bromocriptine (35,36). Crimson et al. (37) described specific improvement in speech and language, including intelligibility, spontaneity, and articulation of speech in three patients following bromocriptine. These reports suggest that dopaminergic agonists improve speech and language output, although this improvement may be the consequence of increased spontaneity.

Stuttering and Tourette's Syndrome. The success of haloperidol, a dopamine antagonist, in the treatment of Tourette's syndrome and stuttering provides another perspective (32,38). Several authors have suggested that stuttering may be linked to a central imbalance in dopaminergic activity (32,39).

Neuroanatomical and Neurochemical Correlates

Dopamine Network Projection. Midbrain dopaminergic systems project to medial frontal areas (mesocortical system), as well as to caudate and putamen (nigrostriatal system). Dopaminergic projections have predominance in the frontal cortex and also in the left hemisphere (40). From this preference of dopaminergic distribution one could anticipate that speech output, which seems to depend on left frontal regions, may be linked to dopamine.

Supplementary Motor Area. The supplementary motor area (SMA) plays a major role in mediating production of sequential, voluntary motor activity, of which speech is by far the most complex (41). As discussed in Chapter 4, lesions of the left medial frontal area, specifically SMA, can result in the syndrome of transcortical motor aphasia (42,43). The SMA is the principal cortical structure in the neural network that mediates the initiating mechanism of speech (44). Electrical stimulation within the SMA elicits vocalizations in both humans and monkeys (45). Regional cerebral blood flow studies demonstrate dramatic activation of SMA associated with silent counting and spoken recitation of overlearned items (46). SMA, together with anterior cingulate, forms a link with midbrain dopaminergic centers, receiving an

important dopaminergic projection (40). Any site in this link, when lesioned, can produce transcortical motor aphasia. Naeser et al. (47) reported that severe nonfluency in aphasia was associated with combined lesions in the subcallosal fasciculus and periventricular white matter. The subcallosal fasciculus is a pathway of a dopaminergic system connecting SMA and anterior cingulate with striatal sites. Thus, SMA appears to regulate, through its network connections, both initiation of speech and its maintenance; dopamine is the facilitatory transmitter for this network. Impaired speech initiation and decreased verbal fluency may be due to interruption of the mesocortical dopaminergic projection.

Dopaminergic Therapy for Nonfluent Aphasia

Based on both clinical and anatomicochemical evidence that supports the hypothesis of dopaminergic mediation in verbal fluency, our research team undertook an open-label study of the effect of bromocriptine on nonfluent aphasia. Initially, we reported a patient with residual moderate transcortical motor aphasia following left frontal intracerebral hemorrhage who demonstrated dramatic improvement in speech and language during treatment with bromocriptine (48). His major fluency problems, including impaired initiation and hesitancies (long response latencies) of speech, responded well to pharmacotherapy. Both the number and proportion of pauses between and within utterances diminished significantly during free conversation. After cessation of drug therapy his language returned to baseline.

We also reported two additional cases (one with stable mixed anterior aphasia, the other with severe Broca's aphasia) who showed an increased use of novel words and an increased likelihood of conversation initiation at home, although they did not demonstrate obvious changes on formal testing (49). In addition to the mesocortical dopamine pathway discussed above, Bachman and Morgan (49) suggested an important role of the limbic system in influencing language function via dopaminergic pathways.

Subsequently, other studies described the beneficial effect of bromocriptine on fluency in aphasia. Gupta and Mlcoch (50) reported two nonfluent aphasia patients (one with Broca's aphasia, the other with transcortical motor aphasia) who showed considerable improvement in fluency after treatment with bromocriptine. Sabe et al. (51) noted that three patients with moderate nonfluent aphasia showed a significant improvement in language deficits after treatment with 30 to 60 mg per day of bromocriptine, while this improvement did not occur in four patients with severe nonfluent aphasia.

So far, all these clinical studies have methodological weaknesses, as noted in the original papers. The studies were uncontrolled; the subject samples were small; the drug trials were unblinded; and no placebo phases were included. MacLennan et al. (52) conducted a placebo-controlled study to verify

the effect of bromocriptine on speech and language deficits. Although the number of words produced by their subjects increased during bromocriptine administration, the authors concluded that bromocriptine did not significantly affect any specific speech and language functions, and they cautioned against uncritical acceptance of bromocriptine treatment for improving communication capabilities of aphasic patients. We fully agree that a further placebo-controlled study with large numbers of subjects is warranted. In any future study, at least the following factors should be taken into account: aphasia type and severity, selection of dopaminergic agent, optimal dose, and side effects.

Aphasia Type and Severity. All patients who reportedly benefited from dopamine agonists had nonfluent aphasia. However, it is quite clear that not all patients with nonfluent aphasia improve with drug administration. Cases so far reported indicate that patients with transcortical motor aphasia respond more readily to dopaminergic agents than patients with other types of aphasia. This observation is consistent with the notion that transcortical motor aphasia may result from damage interrupting the mesocortical dopaminergic projection.

However, even patients with transcortical motor aphasia, who are theoretically most suited, may not always respond to treatment (52). In our laboratory, for example, one patient with transcortical motor aphasia did not show significant improvement with bromocriptine. This 70-year-old male who received bromocriptine 12 months after onset of aphasia did not respond to medication in any language-output measure, including average pause length, meaningful words per utterance, and meaningful words per total words. His aphasia-severity rating scale on the Boston Diagnostic Aphasia Examination (53) indicated severe dysfluency, and this severity may have been a reason for nonresponsiveness. Another possibility is that some subtype of transcortical motor aphasia could respond specifically well to bromocriptine, as transcortical motor aphasia may have variations according to lesion extension.

As far as severity is concerned, Sabe et al. (51) documented that patients with severe nonfluency did not respond well to bromocriptine treatment. Our experience also confirms this notion; none of our patients with very severe nonfluent or global aphasia has yet been successfully treated with bromocriptine. Of note, the case reported by Albert et al. in 1988 (48), who responded exceptionally well to bromocriptine, had an initial aphasia severity rating of 3.5 on the Boston Diagnostic Aphasia Examination, indicating only mild to moderate communication difficulty. Thus, at this early stage in our understanding of pharmacotherapy for aphasia, bromocriptine appears relatively less effective in situations in which dopaminergic postsynaptic receptors are severely damaged.

With a special interest in the correlation between lesion site and effect of pharmacotherapy, we reanalyzed the CT scan of our initial case (unpublished data) according to the method of Naeser et al. (47). This 62-year-old patient had a large left frontal lesion that partially included Broca's area. The lesion extended across to the lateral border of the left frontal horn. A large superior lesion extension was noted into the premotor and motor cortex areas, with patchy deep extension into the anterior one-third of the periventricular white matter (PVWM). The middle one-third PVWM (deep to motor and sensory cortex area for the mouth) was largely spared. There was a patchy lesion in the subcallosal fasciculus (ScF), but the supplementary motor area (cortical origin of the ScF pathway) was largely spared. We then analyzed the CT of another patient who showed overall improvement with bromocriptine treatment, a 55-year-old man who had a persistent Broca's aphasia 49 months post-onset. His CT scan showed no lesion in SMA, but a lesion rated half in the ScF and more than half in the middle one-third of the PVWM. Taking these two cases together, we conclude that for improvement to occur following bromocriptine therapy at least part of the supplementary motor area should remain intact, with some preservation also of its related subcortical pathways, the ScF and the PVWM.

Selection of Drug. Among dopaminergic agonists, bromocriptine is currently most widely used in pharmacotherapy for aphasia. This is an ergot derivative and a selective postsynaptic D2 receptor agonist. L-dopa increases presynaptic dopamine synthesis and release, and requires preserved presynaptic functions (54). The argument in favor of bromocriptine over L-dopa is that the former does not necessarily require presynaptic function. However, insufficient study has been done to confirm a preference of one drug over the other.

Liebson et al. (55) described a patient with multifocal head injury with residual severe dysarthria. Introduction of bromocriptine and carbidopa/L-dopa 2 and 3 years, respectively, after the injury resulted in extraordinary improvement in speech and motor functions. It was not until carbidopa/L-dopa was added to bromocriptine that dramatic improvements were seen. One explanation for this effect is that long-term low-dose bromocriptine primed the central nervous system, improving cell function sufficiently to facilitate response to carbidopa/L-dopa. Another is that the carbidopa/L-dopa by itself was the therapeutic agent, and that this drug combination effects a better delivery of dopaminergic activity to the central nervous system. We evaluated another patient who sustained a severe closed head injury as the result of a fall. This 20-year-old soldier also had a residual dysarthria, and his speech was unintelligible although he did not have other aphasic symptoms. We first administered L-dopa, then superimposed bromocriptine. Although L-dopa significantly improved his intelligibility, additional bromocriptine did not influence his speech functions.

Relation of Language to Other Cognitive Functions. Dopaminergic agents may affect not only speech and language functions but other cognitive functions as well. Indeed, the beneficial effect of dopamine on speech and language may be the fortunate, but nonspecific, consequence of the effect of dopamine on nonlinguistic functions. A considerable body of evidence supports the role of dopamine as a mediator of attention, memory, and motor function (12,56–58). No study has yet been published to determine if dopamine has a primary, direct effect on speech and language or a secondary effect working through its influence on other cognitive domains.

Optimal Dosage and Side Effects. Most of the open-label studies administered bromocriptine in both relatively low dose (10–20 mg) and relatively high dose (30–40 mg). Some cases demonstrated dose-dependent effect on fluency (50; case 1). However, the second patient of Gupta and Mlcoch (50) improved at 10 mg but got worse at 30 mg. They speculated that optimal dose might vary from person to person.

From the clinical point of view, a gradual increase in dose with careful observation is recommended. Maximum dosage so far reported for patients with chronic aphasia is 40 mg. Much higher doses (up to 110 mg per day) were administered in cases of akinetic mutism (34,36).

The most common side effects include dizziness, drowsiness, and faintness. Nausea, vomiting, and gastrointestinal discomfort are reported in some patients. All these symptoms are usually transient and frequently resolve if therapy is continued. Decrease in systolic blood pressure is reported in nearly 30% of patients upon initiation of therapy with bromocriptine (59). This decrease in blood pressure is often asymptomatic but requires regular blood-pressure examination. More serious side effects occur very rarely. These include exacerbation of a pre-existing psychosis, exacerbation of pre-existing movement disorder, confusion and disorientation, seizures, hypertension, and urinary dysfunction. Sabe et al. (51) reported severe dystonia in her four patients although this subsided after cessation of the treatment. We observed dose-related muscle cramps and spasms in the paretic leg of one aphasic patient. Caution is warranted in the use of dopaminergic drugs with brain-injured patients, as the long-term effects of these drugs in a nonparkinsonian brain are not yet well documented. It has been suggested that long-term use of dopaminergic agents may result in disturbances of visuospatial function (60).

Available data, thus, do not justify the routine administration of bromocriptine or other dopaminergic agents in the treatment of aphasia. However, there is little question that some patients with nonfluent aphasia improve with bromocriptine. Our current impression is that mild to moderate nonfluent aphasia may respond to bromocriptine, especially transcortical motor aphasia, and especially if the supplementary motor area is not com-

pletely destroyed. Further research studies are not only warranted but highly desirable.

Cholinergic Networks

Pharmacotherapy for fluent aphasia may also be feasible, utilizing cholinergic agents. Abundant data indicate that cholinergic pathways mediate verbal memory and spatial synthesis. Our hypothesis is that cholinergic agonists can improve selected aspects of naming deficit and comprehension dysfunction in aphasia to the extent that these aphasic disorders are influenced by verbal memory and spatial synthesis.

Neuroanatomical and Neurochemical Correlates

Acethylcholine is ubiquitous in the nervous system. Cerebral nuclei such as the nucleus basalis of Meynert and the substantia inominata have been demonstrated to be primary sources of cortical cholinergic innervation (61). In humans, cholinergic innervation may be asymmetrical, greater on the left than on the right, because choline acetyltransferase (ChAT) activity was found to be significantly higher in the left superior temporal gyrus than in the right (62). This study demonstrated that the ChAT activity in Brodmann area 22 had a greater left than right prevalence of enzymatic activity in cortical layers II and IV. From this dense and preferential cholinergic innervation in the left temporal lobe, it would be reasonable to suggest that cholinergic pathways might play a major role in verbal functions. Indeed, we already know that in dementia of Alzheimer's type, in which cholinergic activity is reduced (63), a significant verbal memory deficit is a characteristic feature (64).

Cholinergic System, Memory, and Language

Anticholinergic agents, such as scopolamine, impair verbal memory, with increased verbal intrusions/perseverations in healthy volunteers (65). The effect of anticholinergic agents on memory is consistent: they impair the ability to store new information in long-term memory, the ability to retrieve information from long-term memory, and the functioning of working memory systems (66,67). Deficits produced by anticholinergics (anticholinergic amnesia) have been considered as a model of memory deficits in elderly patients and in Alzheimer's disease (68,69), although the link between cognitive deficits and neurotransmitter deficiencies in Alzheimer's disease is clearly complex, and tied to multiple neuromodulators (70,71). Fuld et al. (72) demonstrated that patients with Alzheimer's disease frequently show verbal intrusions, correlated with verbal memory deficits, and that these verbal intrusions were also correlated with low levels of ChAT and high numbers of senile plaques.

Additional evidence of a cholinergic effect on verbal functions comes from a study of side effects of psychotropic agents. Five patients presented speech blockage after being treated with tricyclic antidepressants (73). The authors concluded that their patients' speech and language problems were the consequence of a tricyclic-exerted, central anticholinergic effect on higher cortical functions. They did not encounter the same language-related side effect when using desmethylimipramine, which causes fewer anticholinergic effects.

From these research results, and others not reported here, one can infer that cholinergic systems influence verbal memory processes. In contrast, dopamine pathways showed no significant effect on verbal memory (74,75).

Cholinergic System, Spatial Synthesis, and Grammatical Comprehension

Visuospatial deficits in normal aging and Alzheimer's disease have also been attributed to hypocholinergic function (76). Patients with Alzheimer's disease or progressive supranuclear palsy have been reported to show improvement on visuospatial, constructional, or spatial attentional abilities following treatment with the anticholinesterase agent physostigmine (77). Meador et al. (78) recently demonstrated that scopolamine impairs performance on visuospatial information processing, such as judgment of line orientation and complex figures, which require constructive skills. Zemishlany et al. (79) also noted that elderly subjects consistently showed impairment in constructional praxis following administration of scopolamine. Luria et al. (6) proposed that deficits in auditory comprehension of complex logicogrammatical constructions is a verbal manifestation of impaired spatial relationships. This deficit in comprehension of grammatical aspects of language, they argued, followed left parietal lesions, and frequently gave rise to a picture of semantic aphasia. Following Luria, we would speculate that comprehension of grammatical aspects of highly complex sentences and spatial synthesis may have a common neurochemical basis, mediated, in part, by cholinergic networks.

Cholinergic Therapy for Cognitive Disorders

Based on neurobiological findings that indicate that cholinergic pathways influence human memory and cognition, studies on pharmacological treatment of cognitive deficits began to appear in the 1970s and 1980s. Short-acting cholinergic agents such as physostigmine and arecholine have been demonstrated to enhance memory function transiently in various human conditions (76,80). Results of subsequent research focused on cholinergic therapy for memory difficulties in aging or primary degenerative dementia have been mixed. Some have reported positive results with physostigmine (81), physostigmine plus lecithin (82,83), and arecholine (84).

Thal et al. (82), for example, reported that six of eight patients with early Alzheimer's disease treated with oral physostigmine and supplemental lecithin demonstrated improvement in total recall and retrieval from long-term storage, with a decrease in verbal intrusions. The neuropsychological observations were highly correlated with inhibition of cholinesterase activity in cerebrospinal fluid, suggesting that the degree of improvement in memory function was related to the amount of physostigmine that reached the brain. Other neurotransmitters and metabolites in cerebrospinal fluid were unaffected by the physostigmine therapy, suggesting a specific effect of physostigmine on the cholinergic system. They concluded that small oral doses of physostigmine combined with lecithin ingestion have therapeutic benefit for some patients with Alzheimer's disease.

However, many others have reported negative results with long-term administration of cholinergic substances in different clinical conditions: elderly subjects (85), Alzheimer's disease (86,87), and progressive supranuclear palsy (88). Theoretical and methodological problems that remain to be resolved include the following: (1) cholinergic agents might not improve cholinergic function in patients with Alzheimer's disease who may not have sufficient cholinergic structures to respond; (2) improved memory with a single dose of physostigmine does not necessarily imply that long-term treatment would continue to produce such improvement; (3) cognitive deficits in brain disorders are undoubtedly due to dysfunction in several neuromodulator systems, and cannot be reduced to dysfunction in a single neurotransmitter system; and (4) dose-response relationships remain to be clarified. Similar methodological and theoretical problems must be addressed as we attempt to develop pharmacological approaches to therapy of aphasia.

Cholinergic Therapy for Fluent Aphasia

From the clinical and neurochemical evidence discussed above, we suggest that some aspects of language, specifically those based on anatomical networks regionalized to left posterior brain areas, may be mediated, in part, by the cholinergic system. Naming and comprehension in aphasia are partially dependent on verbal memory, and these language features may benefit from cholinergic supplementation.

Little research has looked directly at the effect of cholinergic agents on speech and language functions. Luria et al. (6) utilized "galanthamine," a powerful anticholinesterase agent, to obtain a "deinhibitory" effect on complex gnostic, praxic, and speech functions in brain damage. Galanthamine is said to have improved a wide range of cognitive dysfunctions. Electroencephalography (EEG) was used during treatment with galanthamine to obtain evidence of the changes in cortical neurodynamics. Activation of cortical function, as measured by EEG, following administration of galanthamine

was found to take place only if the anatomical connections between the cortex and the mesencephalon remained intact. This observation suggested that galanthamine acted through cholinergic structures in the reticular formation of the mesencephalon, and that the activating effect of galanthamine might be nonspecific. However, they also noted a particularly strong effect on speech and language functions. Galanthamine improved motor speech problems including articulatory deficits, paraphasias, aphonia, and impaired fluency and tempo. In these studies, cholinergic medication was also effective in sensory disorders of speech; the range of acoustic perception of patients became wider, their understanding of speech was improved, the phenomena of alienation of word meaning were diminished, phonemic hearing was improved, and the time required for naming objects was shortened.

Interestingly, they observed no "deinhibitory" action by neostigmine therapy, while a drug of the same pharmacological group (galanthamine) clearly exhibited an effect. A possible explanation was that galanthamine, a tertiary amine, penetrates faster and to a greater degree into the central nervous system than neostigmine, a quaternary amine. Luria et al. (6) advocated that rehabilitation measures should include an attempt at pharmacological treatment with galanthamine (or other anticholinesterase drugs).

Moscowitch et al. (89) reported that a cholinergic agent (ameridin, an anticholinesterase agent) selectively improved language performance in semantic aphasia. Eight patients with semantic aphasia who were administered ameridin showed improvement after treatment compared with 13 control patients (age- and severity-matched) in comprehension of grammatical structures and in naming. Encouraged by this result, we have now performed an open-label trial of physostigmine in one patient with fluent aphasia. In this highly preliminary pilot study, the patient clinically improved in comprehension and naming following pharmacotherapy.

BEHAVIOR-TARGETED PHARMACOTHERAPY

More than 20 neurochemical substances have been identified as neurotransmitters in the human brain. Some of these substances appear promising as "cognitive enhancers," which may secondarily and nonspecifically have a beneficial effect on speech and language. These include noradrenaline, serotonin (5HT), peptides (e.g., substance P and opioid peptides), and amino acids (e.g., glutamic acid) (90). Adrenergic and serotonergic systems have shown much less evidence than dopaminergic and cholinergic systems of having direct effects on specific language functions. Both appear to be more implicated in mood and emotional aspects of behavior, although recent studies have demonstrated their influence on cognition (91,92). The possible effects of these drugs on speech and language remain intriguing challenges

for future research and are not discussed here. Suffice it to say that we should open our minds to the possibility that drugs that influence limbic system function may have a nonspecific, beneficial effect on speech and language.

Patients who suffer from aphasia following brain damage may also display serious behavioral and psychiatric dysfunction. Although clinicians may not wish to consider treating these disorders pharmacologically as a first resort (93), medications occasionally ameliorate behavioral problems that could hinder language rehabilitation. Antidepressant agents, for example, may be useful adjuncts in aphasia therapy. Recently, beta-adrenergic antagonists (beta-blockers, such as propranolol) and serotonin agonists (selective serotonin reuptake inhibitors, such as fluoxetine, or 5HT A1 receptor agonists, such as buspirone or trazodone) have been reported to have a significant effect on aggressive and impulsive behavior (94,95). Administration of these medications may, in some cases, facilitate conventional speech and language therapy.

CONCLUSIONS

Cognitive functions cannot be explained by a reductionist approach to a single neurotransmitter system. Nevertheless, selected linguistic capacities, including verbal fluency and verbal memory, appear to be influenced by specific neurotransmitter systems. In light of this recognized chemicocognitive influence, it would be a mistake, we believe, to ignore the possibility that selected aphasic signs and symptoms may be ameliorated by targeted therapy with specific pharmacological agents. At this moment, we are aware of no neurochemical agent that has yet been rigorously proven to ameliorate specific language signs or symptoms, and it would be inappropriate to offer false hope to aphasic patients and their families.

The purpose of pharmacotherapy for aphasia would not be to replace traditional language therapy. Rather, when confronted with the devastating effects of loss of language on the person with aphasia and his or her family, one should employ all therapeutic possibilities based on each patient's condition. Both nonspecific (behavior-targeted) and specific (language-targeted) pharmacotherapy should be kept in mind as a potential adjunctive program. Clinicians and researchers should continue to seek any measure that can promote biological and functional recovery following brain damage. In this sense, pharmacotherapy for aphasia may be an important new avenue for discovery.

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