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INTRODUCTION

CHOLINOMIMETICS AND ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the progressive loss of memory, judgement, and language and motor functions, which affects aged individuals exclusively and culminates in the death of the patient. The lack of proven therapies and the ever-increasing life expectancy of Western societies presage a bleak future unless truly efficacious medications are discovered. Although much is known about the neuropathology of AD, the true etiology of the disease remains unknown. In fact, AD may represent a collection of pathologically similar, but etiologically diverse conditions. Multiple genetic, environmental, infectious and immunological theories about the etiology of AD have been proposed; however, there is no general consensus on any of them. On the other hand, certain biochemical deficiencies and pathological changes have been well documented in AD brains. Most consistent among them is the selective loss of certain neuronal populations. In particular, the cholinergic neurons that project from the basal forebrain to the cerebral cortex and the hippocampus are at risk in AD.[1] This selective cholinergic neurodegeneration, which may be the result of a variety of biochemical processes, forms the basis for the so-called "cholinergic hypothesis of AD".[2]

The Cholinergic Hypothesis of Alzheimer's Disease

The cholinergic hypothesis of AD, which is now in its second decade of existence, contends that cholinergic deficiencies in the brains of AD patients are directly related to their cognitive impairment, and it rests on the following observations:

[1] The selective atrophy of cholinergic neurons in the nucleus basalis, the medial septum and other basal forebrain areas, and the pathological changes (senile plaques and neurofibrillary tangles) observed in the hippocampus and cerebral cortex of AD patients are well established.[1,3] Decreases in the levels of cholinergic neuronal markers [acetylcholine (AcCh),[4] acetylcholinesterase (AcChE) and choline acetyltransferase (ChAcT),[5] and high affinity choline uptake (HAChU)[6]] have been documented in AD. Furthermore, the decline in cognitive function in AD patients correlates well with the loss of cholinergic activity in the cortex and hippocampus.[7]

[2] Muscarinic antagonists (atropine, scopolamine) produce cognitive deficits in animals[8] and humans.[9] Similar deficits can be obtained by experimental lesions of central cholinergic projections in animals.[10]

[3] Cholinomimetics, such as the muscarinic agonists arecoline and oxotremorine, improve cognitive function in aged animals.[11]

Cholinomimetic Therapy

Given the central role played by the cholinergic system in AD neuropathology, it may be possible to alleviate the cognitive and behavioral deficits of AD by enhancing or supplementing cholinergic neurotransmission. Conceptually, **cholinomimetic therapy** is analogous to the activation of striatal

dopamine receptors by dopaminergic agents (L-DOPA, bromocriptine), successfully used in Parkinson's disease to compensate for the neurodegeneration of substantia nigra dopamine neurons.[12] In some clinical trials, cholinomimetic therapy has been shown to be of some benefit in AD patients.[13] However, the cognition-enhancing effects of cholinomimetic agents in humans are not clear. This may be a reflection of the specific compounds taken to the clinic, or it may be due to the heterogeneity of the AD population. In general, the study of cholinomimetics in AD has been hindered by the poor pharmacokinetic profiles and small therapeutic ratios of available agents.[14]

Types of cholinomimetics

The neurotransmitter AcCh activates two types of receptors: nicotinic receptors, ligand-gated ion channels, and muscarinic receptors, membrane-bound receptors coupled to GTP-binding proteins that utilize inhibition of adenylate cyclase or stimulation of phosphatidyl inositol hydrolysis as second messenger systems. Cholinergic neurons possess muscarinic as well as nicotinic receptors. The postsynaptic component of the cholinergic synapse appears to be muscarinic in nature. It has been shown that postsynaptic muscarinic receptors are unaffected in AD.[15] Cholinomimetic therapy has primarily been aimed at increasing the level of cholinergic stimulation at these postsynaptic muscarinic receptors.

In organizing this Symposium-in-Print, we have chosen to use the term "cholinomimetic" in the broadest possible sense, including compounds that either directly or indirectly enhance cholinergic neurotransmission. Useful cholinomimetic agents may mimic AcCh and act directly at muscarinic receptors, stimulate the synthesis and/or release of AcCh, block its breakdown, or indirectly potentiate the effects of endogenous AcCh.

Direct acting cholinomimetics

At least five distinct molecular subtypes of the human muscarinic receptor have been identified to date.[16] Within the CNS, m1 receptors predominate in cortical and hippocampal areas, while the m2 subtype is believed to be a pre-synaptic inhibitory autoreceptor, found on cholinergic nerve endings.[17] Direct activation of postsynaptic m1 receptors by highly specific agents (i.e. muscarinic agonists) represents the most direct type of cholinomimetic therapy. Such compounds might be effective regardless of the number and condition of the remaining cholinergic neurons. The main problem encountered so far in the clinical testing of muscarinic agonists such as arecoline, oxotremorine, RS-86, etc., has been the lack of good subtype selectivity, which may account for the large incidence of peripheral side effects, and poor pharmacokinetic parameters. The search for m1-selective muscarinic agonists is an area of intense current research.

Indirect acting cholinomimetics

1. AcCh precursor loading. AcCh precursor loading has been tried in animal and human subjects with generally disappointing results. Large doses of choline and lecithin have been claimed to improve cognitive function, but other investigators have been unable to replicate these results.[18]

2. AcCh release enhancers. Several distinct pharmacologic mechanisms result in the enhancement

of AcCh release in the CNS:

m2 antagonists

Blockade of m2 autoreceptors on cholinergic terminals stimulates evoked release of AcCh from cholinergic neurons.[19] Thus, selective m2 antagonists might be useful as AcCh releasing agents. However, since m2 receptors are widely expressed in gastrointestinal and cardiac tissues, the potential for peripheral side effects would appear to be high. No compounds from this approach have been studied in humans.

nicotinic agonists

Activation of presynaptic receptors by nicotinic agonists increases basal release of AcCh from cholinergic nerve terminals.[20] Once again, the wide distribution of nicotinic receptors in and outside the CNS raises the question of selectivity for potential drug candidates. Sporadic reports have appeared suggesting a beneficial effect of nicotine in AD patients.[21] However, at the present time there appear to be no nicotinic agonists in large scale clinical trials for AD.

Other release enhancers

Over the years, a number of compounds have been described that stimulate the release of AcCh. Currently in clinical trials is DuP 996 (linopirine), which enhances the evoked release of AcCh and other neurotransmitters via interaction with a novel receptor site.[22]

3. AcChE inhibitors. Acetylcholinesterase (AcChE) is the enzyme responsible for extracellular catabolism of AcCh. Inhibition of AcChE retards AcCh breakdown and thus amplifies the effect of endogenous AcCh. As with other indirect cholinomimetics, AcChE inhibitors rely on the release of AcCh from existing neurons, and thus they may be most useful in the early stages of the disease, when neuronal damage is still relatively small. The two AcChE inhibitors most widely tested in humans are the alkaloid physostigmine and the synthetic compound tacrine (tetrahydroaminoacridine, THA). Although multiple investigators have documented the cognition enhancing properties of both compounds,[23] physostigmine has very poor oral activity, brain penetration, and pharmacokinetic parameters, and tacrine appears to possess some hepatotoxic liability. Peripheral side effects have generally limited the doses of AcChE inhibitors used in clinical trials.[24] There are numerous AcChE inhibitors in clinical development.

4. Miscellaneous. In addition to the above approaches, a number of mechanisms appear to possess the potential for enhancing the efficiency of central cholinergic neurotransmission. These include HAChU enhancers,[25] ACTH and TRH analogs,[26] and ACE inhibitors,[27] among others.

A large number of compounds, based on these and other pharmacological rationales, find themselves at different stages of clinical testing. The process toward gaining regulatory approval for any drug in this area is certain to be a difficult one, due to the complexities of the disease and the difficulties in defining and quantifying cognitive function. The purpose of this **Symposium-in-Print on Cholinomimetics and Alzheimer's Disease** is to provide a forum for the latest medicinal chemistry related to cholinergic neurotransmission, with a particular emphasis on the discovery of potential new drugs for the treatment of AD. Ultimately, validation of the cholinergic hypothesis of AD hinges on the selectivity, potency, and safety of novel cholinomimetic agents, such as those described herein.

REFERENCES

1. (a) J. T. Coyle, D. L. Price, M. R. DeLong; Science **1983**, 219, 1184. (b) P. J. Whitehouse, D. L. Price, R. G. Struble, A. W. Clark, J. T. Coyle, M. R. DeLong; Science **1982**, 125, 1237.
2. R. T. Bartus, R. L. Dean, III, B. Beer, A. S. Lippa; Science **1982**, 217, 408.
3. (a) P. Davies, A. J. F. Maloney; Lancet **1976**, 2, 1403. (b) E. K. Perry, R. H. Perry, G. Blessed, B. E. Tomlinson; Lancet **1977**, 189.
4. T. D. Bird, B. S. Stranahan, S. M. Sumi, M. Raskind; Ann. Neurol. **1985**, 14, 284.
5. (a) P. Davies; Brain Res. **1979**, 171, 319. (b) E. K. Perry, B. E. Tomlinson, G. Blessed, K. Bergmann, P. H. Gibson, R. H. Perry; Brit. Med. J. **1978**, 2, 1457.
6. R. J. Rylett, J. M. Ball, E. H. Colhoun; Brain Res. **1983**, 289, 169.
7. R. M. Marchbanks; J. Neurochem. **1982**, 39, 9.
8. (a) J. M. Whitehouse; J. Comp. Physiol. Psychol. **1964**, 57, 13. (b) R. T. Bartus, H. R. Johnson; Pharmacol. Biochem. Behav. **1976**, 5, 39.
9. (a) D. A. Drachman, J. Leavitt; Arch. Neurol. **1974**, 30, 113. (b) W. W. Beatty, N. Butters, D. S. Janowsky; Behav. Neural Biol. **1986**, 45, 196.
10. C. A. Johns, V. Haroutunian, B. S. Greenwald, R. C. Mohs, B. M. Davis, P. Kanof, T. B. Horvath, K. L. Davis; Drug. Dev. Res. **1985**, 5, 77.
11. R. T. Bartus, R. L. Dean, III, B. Beer; Psychopharmacol. Bull. **1983**, 19, 168.
12. D. B. Calne; Clin. Neuropharmacol. **1982**, 5 (Suppl. 1), S38.
13. C. Hermann, R. G. Stern, M. F. Losonzcy, S. Jaff, M. Davidson; Drugs & Aging **1991**, 1, 144.
14. (a) V. Kumar, M. Calache; Int. J. Clin. Pharmacol. Ther. Tox. **1991**, 29, 23. (b) For a recent review on cholinergic neuropharmacology: J. M. Palacios, H.W.G.M. Boddeke, E. Pombo-Villar; Acta Psychiatr. Scand. **1991**, (Suppl. 366), 27.
15. P. Davies, A.H. Verth; Brain Res. **1978**, 138, 385.
16. (a) T. L. Bonner, N. J. Buckley, A. C. Young, M. R. Brann; Science **1987**, 237, 527. (b) T. L. Bonner, A. C. Young, M. R. Brann, N. J. Buckley; Neuron, **1988**, 1, 403.
17. D. C. Mash, D. D. Flynn, L. T. Potter; Science **1985**, 228, 1115.
18. E. Hollander, R. C. Mohs, K. L. Davis; Br. Med. Bull. **1986**, 42, 97.
19. P. A. Lapchak, D. M. Araujo, R. Quirion, B. Collier; Brain Res. **1989**, 496, 285.
20. D. M. Araujo, P. A. Lapchak, B. Collier, R. Quirion; J. Neurochem. **1988**, 51, 292.
21. B. Sahakian, G. Jones, R. Levy, J. Gray, D. Warburton; Br. J. Psychiatry **1989**, 154, 797.
22. S. W. Tam, D. Rominger, V. J. Nickolson; Mol. Pharmacol. **1991**, 40, 16.
23. (a) L. J. Thal, P. A. Fuld, D. M. Masur, N. S. Sharpless; Ann. Neurol. **1983**, 13, 491. (b) W. K. Summers, L. V. Majovski, G. M. Marsh, K. Tachiki, A. Kling; N. Engl. J. Med. **1986**, 315, 1241.
24. R. E. Becker, E. Giacobini; Drug Dev. Res. **1988**, 12, 163.
25. K. Ninomiya, K. Saito, M. Sugano, A. Tobe, Y. Morinaka, T. Bessho, H. Harada; Eur. Patent 427636 A2; Chem. Abstr. **1991**, 115(13): 136076e.
26. M. Yamamoto, M. Shimiau; Naunyn-Schmied. Arch. Pharmacol. **1988**, 338, 262.
27. B. Costall, J. Coughlin, Z. P. Horovitz, M. E. Kelly, R. J. Naylor, D. Tomkins; Pharmacol. Biochem. Behav. **1989**, 33, 573.