

CEREBRAL AGEING, NEUROTRANSMITTERS AND THERAPEUTIC IMPLICATIONS

SYNOPSIS

Cerebral ageing may progress to the stage of senile dementia in 5-10% of elderly over 65 years old. Recent evidence suggests that central cholinergic deficits may contribute to the cognitive decline in Alzheimer's disease while in normal elderly a less impaired cholinergic tone may manifest as benign senile forgetfulness. Similar but less pronounced deficits have also been demonstrated in the noradrenergic and serotonergic systems in pathological and normal cerebral ageing. The use of cholinergic and adrenergic agonists is still experimental while more established neuromodulators such as ergoloids have been used extensively for idiopathic decline of cognitive function in the elderly. With the rapid development of geriatric neurosciences, early detection and more effective pharmacological intervention of Alzheimer's disease may in future help to arrest the progression of the disease.

INTRODUCTION

Aging may be associated with intellectual deterioration of varying severity. While most elderly people have mild memory losses, only 5-10% of cases progress to the more malignant phase of senile dementia. (1) Clinically it is often difficult to distinguish normal cerebral ageing from the early phase of senile dementia. The qualitative changes of plaques and neurofibrillary tangles typical in Alzheimer's disease may also occur in small numbers in normal cerebral ageing. However, once a certain threshold level of plaques and tangles is exceeded, the cognitive deficits of the disease may become manifest. (1) Senile dementia of the Alzheimer's type which accounts for 50-60% of the dementias, is a primary neuronal degenerative condition associated with neurotransmitter deficits especially in the cholinergic system. Such losses have also been reported in normal cerebral ageing. The nature of these deficits and the therapeutic implications are now discussed.

Cholinergic deficits

Acetylcholine, a major neurotransmitter, is synthesised from acetylco-enzyme-A and choline under the influence of the enzyme choline acetyltransferase (ChAT). Once released the acetylcholine acts on the muscarinic receptors while some of it is hydrolysed by acetylcholinesterase (ACE) to acetate and choline. Normal cerebral ageing is associated with a mild decrease in ChAT enzyme but this deficit is more pronounced in Alzheimer's disease (2). The enzyme is confined to the cholinergic neurons and as it is relatively stable after death it is a useful marker of the integrity of the cholinergic system. (3) In Alzheimer's disease the deficit occurs in areas where the histological features of plaques and tangles are most noticeable in the frontotemporal cortex and the hippocampus (4). Cholinergic neurons from the nucleus basalis of Meynert and the adjacent medial septate nucleus, project to the hippocampus and the neocortex via the ascending projection system. The decrease in the cholineacetyltransferase activity in the two latter areas is due to increased cell loss from the basal forebrain nuclei (5). This cholinergic deficit is closely linked to the severity of dementia at the time of death (6).

While ChAT activity is located in the nerve terminals the decrease in the acetylcholinesterase activity (ACE) reflects damage to the nerve cell bodies (7). ACE is also decreased in Alzheimer's disease but is normal in those without senile dementia (7). However this deficit is not significantly linked to the decline of cognitive function.

In normal cerebral ageing, the muscarinic receptor sites are decreased but this is relatively preserved in Alzheimer's disease (7). Nicotinic receptors have been less extensively studied in the human neocortex but they account for only 2% of the cholinergic binding sites.

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Noradrenergic deficits

Noradrenergic terminals within the cerebral cortex arise from an ascending system originating in the locus coeruleus nuclei in the dorsal brainstem (5). The decrease in noradrenergic terminals occurs in normal ageing but is more accentuated in Alzheimer's disease (8). The loss of these cells correlates with the number of plaques (9) and the degree of mental impairment (10). This noradrenergic deficit may affect the microcirculatory flow and the permeability to metabolites through its action on the capillary pericyte (11). The accumulation of aluminium has been postulated as one of the etiologic hypothesis of Alzheimer's disease. (12)

Other Neurotransmitters

Serotonin, dopamine, gamma-aminobutyric acid and somatostatin have been reported to be decreased in Alzheimer's disease (5). However, the abnormalities in these systems are not so clearly defined as the cholinergic and the noradrenergic deficits and their significance is questionable.

Therapeutic implications of neurotransmitter deficits

The major cognitive deficiencies in Alzheimer's disease have been ascribed to the loss of cholinergic activity in the neocortex and the hippocampus. This has given rise to three possible therapeutic concepts.

The first possible mode of treatment involves the use of acetylcholine precursors, choline or lecithin to increase the synthesis and release of cerebral acetylcholine. The second concept involves the inhibition of acetylcholine hydrolysis by esterase-blockers such as physostigmine. In the third pharmacological approach, direct cholinergic agonists such as Arecholine are used to substitute for the natural transmitter as the muscarinic receptors are present at normal concentrations even in advanced Alzheimer's disease.

Choline and Lecithin

Oral ingestion of choline salts have been shown to increase the plasma and brain choline levels (13) with subsequent increased synthesis and release of acetylcholine. (14) As the muscarinic receptors remain intact, the acetylcholine from the remaining undamaged neurons may help to correct the cognitive deficits. Our natural foods contain very little choline salts; most of it is found in the form of lecithin (phosphatidyl choline) in egg yolks, meat, fish and soya beans. Lecithin ingestion increases the acetylcholine levels more than the ingestion of choline salts (15). Lecithin has also been shown to improve tardive dyskinesias in the elderly by correcting the cholinergic deficiencies (16). However, controlled trials so far have not shown convincing results in Alzheimer's disease (17, 18, 19, 20) though definite improvement in memory of normal volunteers has been reported (21).

Physostigmine, a centrally active acetylcholinesterase inhibitor, has been shown to improve the long term memory and reverse the scopolamine induced memory deficits in normal subjects (22, 23). In Alzheimer's disease, Smith and Swash demonstrated a decrease in the number of intrusion errors in treated patients though the memory storage system remained unaffected. (24) Unfortunately, both physostigmine and direct agonist such as arecholine have serious limitations as they produce severe muscarinic side-effects and their

duration of action is short. (25)

Future studies should test the use of pure lecithin over a longer period of time and utilise better neuropsychologic evaluation sensitive to cholinergic manipulation. The problem of dosage of choline has also to be resolved. Choline has a biphasic cholinergic effect on the memory system. A little cholinergic stimulation may improve memory but a slight excess may impair it. (25) There are no published data that relate plasma choline to clinical effects.

Noradrenergic agonists

In two separate experimental studies, Levodopa improved the cognitive function in Alzheimer's disease without Parkinson's disease. (26, 27) The beneficial effect of L-Dopa was attributed to the preferential modulation of noradrenaline system.

Other adrenergic drugs have been tried such as Ritain and Metrazol. However, these studies have inconclusive evidence and their effect of alleviating cognitive function have been postulated to be secondary to adrenergic 'mood elevation'. (28)

Other neuromodulating drugs for cerebral ageing

Hydergine has been extensively studied and used for cognitive decline associated with ageing. The concept of hydergine as a cerebral vasodilator has been changed in favour of its metabolic enhancing activities. Cerebral blood flow is decreased both in normal ageing and in Alzheimer's disease. (29) In the latter, the decrease in flow is secondary to a decrease in metabolic demands due to parenchyma damage. Thus any vasodilatation causing an increase in cerebral blood flow will only create a state of luxury perfusion. (29) In multi-infarct dementia, the initiating cause is a decrease in blood supply causing parenchymatous damage and decreased metabolic demands which further decreases the blood supply. The vessels in multi-infarct dementia are often sclerosed with decreased reactivity to carbon dioxide stimulus and they are only capable of moving inwards. (30) Thus the so-called vasodilators do not improve cognitive functions by their effects on the cerebral blood flow.

Though the mode of Hydergine is uncertain, it is postulated that it has a positive enhancing effect on the noradrenergic, dopaminergic and serotonergic systems. (31) It has a high affinity for noradrenergic receptors in the brain and increases the cyclic denosine monophosphate at the receptor level. Thus the primary effect of Hydergine is to improve the metabolic functioning of the brain cells and increase the cerebral blood flow secondarily.

Hydergine is mainly indicated for mild to moderate dementia after excluding the treatable causes and depressive illnesses. It has been shown to improve the cognitive functions, self-care abilities, motivation and mood disorders in the elderly. A recent study by Yoshikawa et al showed that the 6mg daily dose is superior to the conventional 3mg dose in improving subjective, psychiatric and neurological symptoms in 550 elderly with cerebrovascular disease. (34)

Nootrophil, a cyclic derivative of gamma-aminobutyric acid has also been shown to be useful for improving the cognitive deficits in mild to moderate Alzheimer's disease without the troublesome side effects of other neuromodulating drugs. It increases the energy stores in the brain and promotes interhemispheric transfer of information. (35)

Vasopressin may be the first neuropeptide substance to be of use clinically for improving the cognitive decline in the elderly. Vasopressin nasal

spray has been shown to improve the memory of amnesic and demented patients. (36, 37) Its beneficial effects on memory may be due to the stimulation of ACTH secretion which in turn improves the attention-arousal system in the elderly. (37) It may also influence the biogenic amines and the release of other peptide modulators such as endorphins. (38)

CONCLUSION

Pharmacological treatment of senile dementia and geriatric memory loss remains in its infancy. Many cerebral enhancers and cholinomimetic drugs have been tried with variable results and future large scale and long term studies are necessary. Ultimately the ideal pharmacological intervention must not only involve symptomatic management but also the specific treatment of the disease process itself and perhaps the possibility of prophylaxis. Geriatric neurosciences may in future uncover the reasons for the transition from benign cerebral ageing into the malignant phase of senile dementia. It is in the initial stages of the disease that the best opportunities present themselves for effective intervention to prevent further damage to the ageing brain.

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