Cholinergic deficiency and inflammation in cognitive dysfunction
Lemstra, A.W.

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Chapter 2

The cholinergic deficiency syndrome and its therapeutic implications

A.W. Lemstra
P. Eikelenboom
W.A. van Gool

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ABSTRACT

Cholinesterase inhibitors are licensed for treatment of dementia in Alzheimer's disease. However, the effects of these drugs on the cognitive symptoms of dementia are very small. We suggest that symptoms like impairment of attention and concentration, anxiety, restlessness and hallucinations, delineate a specific central cholinergic deficiency syndrome (CDS), that may be a much better target for such treatment. Changes in the quantitative electroencephalogram, muscarinic subtype radioimaging and serum anticholinergic activity may potentially help to diagnose the CDS. CDS is suggested to occur in various neurodegenerative diseases like Alzheimer's disease, Dementia with Lewy bodies and Parkinson's disease and to respond well to cholinesterase inhibitor therapy.
INTRODUCTION

World-wide cholinesterase inhibitors (CEIs) like donepezil, rivastigmine and galantamine have been licensed for symptomatic therapy in Alzheimer’s disease (AD). This development has brought a little hope in a previously desperate clinical situation, but the therapeutic response to CEIs and the severity of side-effects vary widely between AD patients. If strict responder criteria are used, CEI therapy is successful in only 5 to 15% of AD patients. On the other hand, case-reports and a single randomised controlled trial suggest that neuropsychiatric symptoms like hallucinations, anxiety and agitation in patients with Dementia with Lewy bodies (DLB) or Parkinson’s disease (PD) may respond well to this type of drug. Therefore, despite their official label stating that CEIs are licensed for ‘the treatment of mild to moderate dementia of the Alzheimer’s type, it is highly questionable if the cognitive deficits of dementia represent the most appropriate target of CEIs and also if use of these drugs should be restricted to AD only.

The cholinergic hypothesis in Alzheimer’s disease

AD is a devastating neurodegenerative disorder characterised by neuritic plaques, neurofibrillary tangles and loss of neurons and synapses. Since the early 1970s, brains of patients with AD have been extensively examined hoping to find a neurochemical deficit underlying the disease, analogous to PD and dopamine. The first clues on specific neurochemical systems affected in AD, became available when Drachmann and Leavitt showed that cognitive impairments resembling the deficits observed in elderly people with primary degenerative dementias, could be produced by antagonists of muscarinic acetylcholine receptors (for example scopolamine).

The cholinergic transmission is one of the most important neuromodulating systems in the brain. All sectors of the human cerebral cortex receive dense cholinergic input. The origin of this projection is located in the magnocellular neurons of the basal forebrain, the nucleus basalis of Meynert and the substantia innominata. These extensive cholinergic projections influence nearly all aspects of cognitive functions, especially the domains of attention, memory and emotion. Several laboratories demonstrated a significant reduction in markers of cholinergic transmission in AD, including the synthetic and degradative enzymes choline acetyltransferase (ChAT) and acetylcholinesterase (AChE), respectively. Subsequent discoveries of reduced choline uptake, acetylcholine (ACh) release, and loss of cholinergic cells in the septal nuclei and basal forebrain established the cholinergic hypothesis of AD. According to this hypothesis, the cholinergic dysfunction in AD is mainly due to loss of cholinergic innervation, rather than to reduction in postsynaptic receptivity to the effects of ACh release.
The cholinergic hypothesis as an explanation for the syndrome of dementia in AD has been challenged over the last 20 years. Indeed, numerous studies have documented important cholinergic deficits in AD\textsuperscript{10,19}. However, by their nature, most postmortem studies were performed in AD patients with end-stage disease. Recent studies of AD patients representing the complete spectrum of disease indicate that loss of cholinergic markers can not be detected in individuals with mild AD and is not present until relatively late in the course of the disease\textsuperscript{22-24}. Many other neurotransmitter deficits have been identified in AD brain tissue. It became increasingly clear that AD did not involve degeneration of a single neurotransmitter but was highly heterogeneous. Currently, beta-amyloid and presenilins are considered by many to be important factors in the process that leads to widespread degeneration of cortical networks underlying dementia in AD. At the moment it is widely acknowledged that loss of cholinergic transmission alone cannot account for the whole clinicopathological picture of AD. The lack of robust clinical benefit in most patients treated with cholinergic drugs is consistent with these insights\textsuperscript{25}.

**Cholinergic therapy**

Development of CEIs was inspired by the cholinergic hypothesis of AD stating that selective degeneration of cholinergic neurons in the basal forebrain is responsible for dementia in this disease. However, the prior probability that all cognitive deficits of dementia would respond favourably to CEI therapy is low, considering the discussion above. In general, the rationale behind the choice for a specific therapeutic target is based on a clear description of the disease or complex of symptoms, but this has not been the case for the use of CEIs in AD\textsuperscript{26}. In his original description of Auguste D., Alzheimer emphasised aphasia, apraxia, agnosia and acalculia in addition to memory deficits\textsuperscript{27}. A neurologically based model of human cognition, as suggested by Albert, distinguishes between instrumental functions such as language, perception and praxis, and fundamental functions such as set shifting, attention, concentration, and rate of information processing\textsuperscript{28}. This instrumental/fundamental dichotomy, that was later expanded by Cummings to include anatomic, ontogenetic and neurochemical dimensions, may be helpful in characterising the symptoms of AD\textsuperscript{29}. Thus, Auguste, as the prototypical patient with AD, suffered mainly from impairments of instrumental functions with relatively intact fundamental functions, as is the case in most patients with AD. The consistent, albeit small effects of CEIs in AD, can be understood by the limited contribution of cholinergically mediated fundamental functions to the symptoms of AD (figure 1). Rather than serving specific instrumental cortical functions, the
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Diffusely organised cortical cholinergic input system serves the more fundamental role of detection, selection, discriminating and processing of sensory stimuli and higher processes\textsuperscript{13,30}. Substantial evidence has accumulated in support of the notion that demands in attentional processing are mediated via cortical cholinergic inputs\textsuperscript{31}. Deficiencies in these inputs impair discriminatory processes, the efficiency of cortical processing and responsiveness to relevant and new stimuli. Performance on neuropsychological tasks requiring perception, language or praxis can be modulated by factors such as motivation, attention and concentration. Therefore, in addition to extensive cortical damage in AD resulting in severe instrumental impairments, some deficits in the fundamental processes associated with degeneration in the cholinergic projection system, may to some extent also contribute to the symptomatology of AD (figure 1).

From the recent clinical trials with CEI it can be concluded that patients with AD can be divided in at least two different groups: responders and non-responders to CEI\textsuperscript{26}. Although small, the effects of CEIs on cognitive test scores in groups of AD were statistically significant and very consistent across various trials with different CEIs in AD\textsuperscript{1-4}. Liberini et al note in a comprehensive review on cholinergic therapy...
that the variability of the response to CEI may be related to individual differences in the pharmacokinetics. On the other hand the differential response to CEI may be related to the clinical heterogeneity of degenerative dementia.

Neurochemical reductions in cholinergic enzymes and/or loss of neurons from the basal nucleus are apparent in many other brain disorders associated with neuropsychiatric symptoms like DLB, PD, progressive supranuclear palsy and Down’s syndrome. Neuropathological studies show that the neuronal damage to the nucleus basalis of Meynert of DLB patients is greater than in that of patients with Alzheimer disease. In addition, neurochemical examinations of autopsy material from DLB cases have shown an extensive deficit in cholinergic input to the frontal, parietal and temporal cortices, with reductions in ChAT activity greater than those seen in AD. The basal nucleus is also severely depleted in PD patients with dementia. The cholinergic deficits in PD and DLB are not accompanied by widespread cortical changes and they may even exceed the changes in the cholinergic system found in AD.

In a clinical trial with rivastigmine in DLB patients significant reductions of apathy, anxiety, delusions and hallucinations that exceeded the changes on cognitive test scores. Hallucinations and confusional states are frequent and disabling complications also of PD. Although, excess of dopamine resulting from pharmacotherapy is usually presumed to cause hallucinations, several observations cast doubt on this explanation. Hallucinations in PD are known from the time before dopamine therapy became available, the relationship between high levels of levodopa and neuropsychiatric manifestations has never been documented directly, and Goetz et al. failed to provoke hallucinations with a high-dose intravenous challenge with levodopa in PD patients. In PD anticholinergics may elicit confusional states and hallucinations whereas preliminary observations suggest that CEI therapy does not increase parkinsonism and can be benificial.

Conventional antipsychotics are associated with considerable side effects in these patients, therefore, CEI therapy deserves consideration also for the neuropsychiatric symptoms associated with PD.

**Central cholinergic deficiency syndrome**

It seems somewhat paradoxical to restrict use of symptomatic therapy to a single nosological entity. Symptomatic therapy with hypnotics, antipsychotics and antidepressants is prescribed for sleep, psychotic or affective disorders irrespective of the specific disease a patient is suffering from. So why not treat all patients with an apparent deficit of the cholinergically mediated fundamental functions with CEIs irrespective of the neurodegenerative disorder they are suffering from? The question is, if there is something like a clinical syndrome that results from central
cholinergic deficiency how can clinicians recognise it? There is not a clear description of the clinical picture of cholinergic deficiency which could be distinguished in patients with various neurodegenerative disorders. Despite the numerous trials with CEIs, factors that might a priori predict a response to cholinesterase inhibitors have not yet been identified. Symptom profiles of neurodegenerative diseases affecting the cholinergic system are not very well suited to define exactly the functional consequences of cholinergic impairment, because these effects are difficult to separate from additional neuropathological ramifications that are sometimes only partially known. Therefore, for this purpose it may be better to refer to other sources of knowledge.

In their 1958 paper advocating atropine coma as a safe alternative for insulin coma in the treatment of psychosis, Forrer and Miller described ‘restlessness, occasionally mild excitement, confusion’ as a result of anticholinergic treatment and at higher doses ‘memory disturbance, disorientation, clouded consciousness, illusions and most frequently visual hallucinations’. Itil and Fink reported depression, impaired consciousness, perceptual distortion, disturbances of thought and association, severe anxiety and restlessness. Interestingly, they report that upon administration of the CEI tetrahydroaminoacridine, currently better known as tacrine, this neuropsychiatric syndrome completely reversed within minutes. At that time, ‘broadening of attention’ indicating difficulties with filtering out distracting stimuli was identified as the most salient effect of anticholinergic treatment. These descriptions of the cholinergic deficiency syndrome (CDS) caused by anticholinergic treatment resemble more closely the state of delirium or acute confusion than that of dementia in AD. The emphasis is more on global behavioral symptoms rather than on specific focal cognitive disturbances as in AD. This is consistent with the extensive literature on the role of the cholinergic system in delirium, however the CDS in neurodegenerative diseases is of a more gradual onset and longer duration.

**HYPOTHESIS**

Here, we propose that to the benefit of patients a neuropsychiatric syndrome can be delineated that develops as a consequence of cholinergic deficiency in the central nervous system. The CDS is characterised clinically by loss of attention, impaired concentration and reduced capacity to detect and select relevant stimuli. As a consequence, patients become restless, anxious and confused. Maybe as a result of impaired binding with the real world, there is a propensity to develop misidentifications, pseudo-hallucinations or frank hallucinations and delusions. On formal tests of cognition, test scores are impaired, but on closer examination there are no outstanding focal cortical deficits.
The specific features of cholinergic deficiency may be quantified and/or qualified by a limited set of neuropsychological tests. This set of tests can measure vigilance, selective and sustained attention etc. In neurodegenerative diseases CDS may coincide with dementia, but for treatment purposes it should be distinguished from focal cortical deficits (figure 1). We speculate that ancillary investigations may help to characterise this CDS. Reductions of the power in the alpha2-band on quantitative analysis of the electroencephalogram (qEEG) following administration of scopolamine, suggest that central cholinergic dysfunction is associated with specific EEG changes49. Analogous effects in animal experiments on low voltage fast EEG activity of either atropine injection or lesions of the substantia innominata support this notion50. Other methods that are potentially of interest in attempts to characterise the functional status of cholinergic system in patients are imaging of presynaptic muscarinic (M2-)subtype receptor with radiolabelled ligands or measurements of serum anticholinergic activity48,51.

Direct testing of our hypothesis would require prospective studies of patients from various disease categories that are subjected to CEI therapy. Our hypothesis would predict that a beneficial therapeutic response will be associated with the presence of clinical symptoms of CDS outlined above independent of the presence of important focal cognitive deficits, reductions of alpha2-frequency in the qEEG, low M2-receptor subtype binding and presence of serum anticholinergic activity, irrespective of the specific disease that was diagnosed before initiating therapy.

To summarise, ‘dementia’ may be a poor descriptor of the target for CEI therapy and the same holds for a diagnosis of AD. Perhaps patients have much to gain if the indication for CEI treatment is based on the identification of a specific clinical syndrome, rather than a single disease category. A syndrome characterised by impairments of attention and concentration, restlessness, hallucinations and anxiety, as symptoms of the CDS could be a much better indication for this kind of treatment. Cognitive deficits may be secondary to this CDS, but the syndrome is sometimes superimposed on the dementia in AD. Acute delirium shares many features with CDS and future studies will have to clarify to what extent they overlap and if CEIs may be effective also in this condition. There may be a new role for qEEG, radioimaging of presynaptic cholinergic markers or measurement of serum anti-cholinergic activity in diagnosing CDS, thus helping to identify patients across different classical disease categories that may benefit optimally from CEI therapy.
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