Chemico-Biological Interactions 203 (2013) 361–364

Contents lists available at SciVerse ScienceDirect

Chemico-Biological Interactions

journal homepage: www.elsevier.com/locate/chembioint

Effect of cholinesterase inhibitors on attention

Giancarlo Pepeu [a,*], Maria Grazia Giovannini [a], Laura Bracco [b]

[a] Department of Preclinical and Clinical Pharmacology, University of Florence, Viale Pieraccini 6, 50139 Florence, Italy
[b] Department of Neurological Science and Psychiatry, University of Florence, Policlinico di Careggi, Viale Morgagni, Street No. 85, 50134 Florence, Italy

ARTICLE INFO

Article history:
Available online 6 October 2012

Keywords:
Acetylcholine
Alzheimer's disease
Attention
Cholinesterase inhibitors

ABSTRACT

Advantages and limits of the use of cholinesterase inhibitors (ChEI) in Alzheimer's disease (AD) are well established. Their effects result from an increase in extracellular acetylcholine (ACh) whose hydrolysis is prevented by cholinesterase inhibition. In this way, the cholinergic deficit which characterizes AD may be corrected. This overview discusses which components of the cognitive process are improved by ChEI administration. In animal experiments, the increase in ACh release, detected in brain areas during behavioral tasks designed to tax attentional processes, demonstrates that an activation of cholinergic neurons underlies arousal and attention. Since arousal and attention depend on activation of the forebrain cholinergic system, it is to be expected that the loss of cholinergic neurons occurring in AD may lead to impairment of the attentional processes. Indeed, a consensus exists that attention is the first non-memory domain to be affected in AD, before deficits in language and visuo-spatial functions. The difficulties with daily living, which occur even in mild AD, may be related to attentional deficits. ChEIs, by restoring the cholinergic activity, should improve attention. If the cognitive changes resulting from ChEI treatment in AD patients are assessed with appropriate tests or selected items of the scales, a predominant effect on attention and executive functions emerges. In a group of 121 subjects with mild to moderate AD, (MMSE score 21.88 ± 3.63) followed in the Alzheimer Unit in Florence, after a year of treatment with standard doses of ChEIs, it was observed a stabilization of the disease, characterized by no changes of the tests evaluating attention and executive functions but a worsening of those involving memory mechanisms. These findings suggest that ChEI treatment preserves attention more than memory. Finally, the electrophysiological and neurochemical mechanisms through which the activation of the cholinergic forebrain neurons enhance attention and create the condition for information acquisition are reviewed.

1. Introduction

Thirty years after the introduction of tacrine in the treatment of Alzheimer's disease (AD), followed by donepezil, rivastigmine and galantamine, these drugs are still the mainstay of symptomatic AD therapy. In the meantime, a large and continuously expanding literature has made and makes us aware of the advantages and limits of these drugs [1–4]. Observational studies suggest that these drugs show symptomatic effects that delay cognitive deterioration for up to a year and may delay the time to nursing home placement [5,6]. However, only 40% of the patients are thought to be improved [7,8]. According to a recent behavioral and morphometric study [9], the response appears to depend on the degree of degeneration of the cholinergic system whose activation is the main effect of ChEIs.

Through which neuronal circuits and molecular mechanisms the activation of the cholinergic system is involved in information acquisition and memory formation is still an open question. As Michaux and Marighetto recently wrote [10], between acetylcholine (ACh) and memory there is a long, complex and chaotic but still living relationship. A relationship which begins with the possibility to disrupt the cognitive processes in man and animals by the administration of drugs blocking ACh receptors [11] and ends with the attempts to improve cognition with ChEIs in healthy subjects (see Refs. in [12]).

2. Attention and the cholinergic system

Attention is the cognitive process of focusing on one aspect of the environment while ignoring others and is the key to successful encoding of information [13]. Several types of attention can be recognized [14]. Selective attention is the process of rapidly selecting more relevant from less relevant stimuli for further cognitive processing. Divided attention refers to the ability to attend to more than one stimulus, modality or process at one time.

Sustained attention (vigilance) may be defined as a state of continuous readiness to respond to unpredictable events.

* Corresponding author.
E-mail addresses: giancarlo.pepeu@unifi.it (G. Pepeu), mariagrazia.giovannini@unifi.it (M.G. Giovannini), bracco@neuro.unifi.it (L. Bracco).

0009-2797/$ - see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.cbi.2012.09.016

It has been known for a long time that arousal and attention are associated with electroencephalographic (EEG) activation characterized by fast, low voltage waves in the cortex [15], and by theta waves in the hippocampus [16]. Both patterns can be modulated by stimulation of the cholinergic nuclei or by the administration of cholinergic drugs, a demonstration of the connection between the cholinergic system and attention [17].

Much evidence [18–20] demonstrates that attention depends on the activation of the forebrain cholinergic neurons. These neurons form four groups of cells, intensely stained for choline acetyltransferase, located in the nucleus basalis of Meynert, and the nuclei of the septum and diagonal band [21]. Their nerve endings constitute a dense network in the cerebral cortex and hippocampus forming synaptic contacts with glutamatergic neurons by which in turn they are activated [22].

The changes in ACh extracellular level, investigated by microdialysis [23] or by *in vivo* voltammetry [24] in a given brain area, are considered indicators of the degree of activation of the cholinergic neurons whose endings are close to the probes. Therefore, the increase in ACh release, detected in several brain areas during the performance of behavioral tasks designed to explicitly tax attentional processes, demonstrates an increased activity of the cholinergic neurons underlying arousal and attention. Indeed, environmental situations which induce arousal, EEG activation and elicit attention, and tasks whose performance needs attention, evoke a strong increase in ACh release [25] which involves the entire cortex and hippocampus with a highest increase in specific receptive areas [26]. An increase in ACh release, lasting minutes, was detected in the frontal cortex and hippocampus, during exploratory activity [27], the acquisition of a passive avoidance response [28], the presentation of a sensory stimulus including a novel taste [29,30]. The increase is smaller in aging rats in which a cognitive impairment can be detected. Conversely, a transient cholinergic activation, lasting few seconds, is detected, by voltammetry, as choline release in the prefrontal cortex each time that a rat successfully performs an operant task, for instance lever pressing, requiring an attentional effort for cue detection [31]. Two subpopulations of forebrain cholinergic neurons, characterized by early or late firing, have been demonstrated [32] and their activity may correspond to the tonic and phasic ACh releases related to the attentional demand. It has also been shown that the more difficult the task the higher is the tonic ACh release [33] indicating a more intense involvement of the cholinergic neurons.

3. Attention deficit in patients affected by Alzheimer's disease

According to the extensive review on attention and executive deficits in AD by Perry and Hodges [14], attention is the first non-memory domain to be affected in AD, before deficits in language and visuo-spatial function, and it is possible that difficulties with daily living, which occur in even mildly demented patients, may be related to attentional deficits. It appears that divided attention and aspects of selective attention are particularly vulnerable while sustained attention is relatively preserved in early stages of AD. Baddeley et al. [34] also showed that attentional control of executive functions declines during the early stages of Alzheimer's disease and observed a marked impairment in the capacity of AD patients to combine performance on two simultaneous tasks, in contrast to preserved dual-task performance in a normal elderly group. It was also observed that in mild and very mild AD, deficits in executive functions can be detected using the Stroop test, the Trail Making test, the Dual task and the Phonemic fluency which depend on an attentional effort [35]. In a population of 3800 subjects with a clinical diagnosis of mild to moderate AD, attention problems were detected in 86% of them [36]. A consensus seems therefore to exist that attention deficit is an early symptom in AD and that subtypes of attention such as divided and sustained attention are particularly affected by the disease. According to Mohr [37], a quantitative reduction of attention can be detected in all forms of dementia but the loss of selective attentional processing is characteristic of AD, and to some extent of Huntington's dementia.

Since the seminal papers of Davies and Maloney published 36 years ago [38], which demonstrated a choline acetyltransferase decrease in *post mortem* brains of subjects affected by AD, and of Sims et al. [39] showing that ACh synthesis was strongly reduced in cortical biopsies taken from AD patients, it is well known that the cholinergic is the most affected, among the different neurotransmitter systems, in this form of dementia. For a review of the literature on the cholinergic deficit in AD see [40,41].

Since arousal and attention depend on the involvement of the forebrain cholinergic system, as discussed in the previous paragraph, it is to be expected that the cholinergic deficit, which characterizes AD, leads to an impairment of the attentional processes and that, in turn, ChEI administration may bring about an improvement of attention. According to Brousseau et al. [42] an enhanced level of attention in AD patients, induced by ChEI administration, is followed by an improvement of global cognitive measures and a better control of psychiatric symptoms. In this regard, a positron emission tomography (PET) study visualizing AChE loss, in patients with mild to moderate AD, showed that the mean cortical AChE activity, an indicator of the conditions of the cholinergic system, was significantly associated with performance on a test of attention and working memory but not with delayed short or long term memory functions [43].

4. Cholinesterase inhibitors and attention

Improvement of attention following ChEIs administration can be demonstrated in mouse models of AD [44]. It was observed that 3xTgAD mice, evaluated in a 5-choice serial reaction time test of attention, show an attentional impairment comparable to that of AD patients in two aspects: first, they failed to sustain their attention over the duration of the task; second, the ability to sustain attention was enhanced by the ChEI donepezil.

In most studies investigating the efficacy of ChEI treatment in AD patients, global evaluations of the cognitive changes are used such as the Mini Mental Scale Evaluation (MMSE), the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), the Global Deterioration Scale. If the cognitive changes are assessed with appropriate tests or selected items of the scale are considered, a predominant effect of ChEIs on attention and executive functions emerges. Gautier et al. [36], in their naturalistic, prospectic, observational study, evaluating the effects of rivastigmine on 3800 subjects with a diagnosis of mild to moderate AD, observed that loss of attention was the most frequent symptom and was the symptom improving in the largest number of patients, about 47% after 6 months of treatment. In subjects affected by AD, assessed with a set of computerized tests of visual attention and executive functions, ChEI treatment for 3 months consistently improved specific components of attention while it did not affect accuracy and completion [45]. In the Alzheimer's Unit of the Department of Neurological Science and Psychiatry, University of Florence, a group of 121 (M/F 42/79) subjects with a diagnosis of mild to moderate AD, showing a MMSE score of 21.88 ± 3.63, treated with standard doses of donepezil (n93), rivastigmine (n18) and galantamine (n9), was followed for one year (Bracco et al. manuscript in preparation). At the end of the year, there was a small, statistically significant but clinically meaningless, decrease of 1.13 point of the MMSE score, similar to that observed in 205 patients treated for