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3

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INTRODUCTION

The knowledge concerning the relation between acetylcholine and cognitive function mainly stems from three different sources. The first source is the cholinergic hypothesis of geriatric memory dysfunction (Drachman and Leavitt 1974). The purpose of this hypothesis is to explain cognitive deterioration with advancing age, and ultimately Alzheimer's disease (AD) as a result of cholinergic dysfunction. As a consequence of this hypothesis, treatments with cholinergic drugs, cognition enhancers, to prevent or halt cognitive deterioration are studied. The second source are studies into the cognition impairing anticholinergic side-effects of antidepressants (Davies *et al.* 1971). Since the introduction of more selective antidepressant drugs, anticholinergic effects impairing cognition are seen less and less and antidepressants have in some cases become cognition enhancing rather than cognition impairing drugs. The third source are studies in which cholinergic drugs are used as tools to study the neurochemical basis of human cognition (Warburton and Wesnes 1984). The psychology of anticholinergic drug effects addresses the question whether there is a direct association between anticholinergic effects and memory impairment, or whether this effect is mediated via early or late selection processes in attention, effort and resource reduction (Rusted 1994). For the purpose of this chapter we will

show that these three sources have in common that certain cognitive functions such as memory can be expressed, and manipulated, as a function of the degree of cholinergic stimulation.

The Cholinergic Hypothesis of Geriatric Memory Dysfunction

The four basic elements that constitute the cholinergic hypothesis of geriatric dysfunction (Bartus et al. 1982; Drachman and Leavitt 1974) are of a neurological, neuropsychological, experimental psychopharmacological and clinical psychopharmacological nature, respectively:

(1) Significant functional disturbances in cholinergic activity occur in the brains of aged and especially demented patients.
(2) These disturbances play an important role in memory loss and related cognitive problems associated with old age and dementia.
(3) Similar memory deficits can be artificially induced by blocking cholinergic mechanisms in young healthy subjects.
(4) Proper enhancement or restoration of cholinergic function by means of drugs acting upon the cholinergic system (so-called cognition enhancers) may significantly reduce the severity of the cognitive loss.

The cholinergic hypothesis has been a leading principle for the research into the etiology of cognitive ageing and dementia (Bartus et al. 1985). These were defined as a pathology of memory. Subsequently it was shown that cholinergic denervation played a role in the ageing of the central nervous system (CNS) and had a high prevalence in AD victims at autopsy. It was observed after the administration of anticholinergic anesthetic and antidepressant agents, signs of dementia, i.e. forgetfulness and in high doses confusion occurred (Cole et al. 1983; Davies et al. 1971; Rupreht and Dworacek 1990). Increased cognitive sensitivity of elderly persons to experimentally induced cholinergic blockade (Molchan et al. 1992; Ray et al. 1992) is consistent with the impression of clinicians that older persons are more sensitive than younger ones to anticholinergic adverse effects of drugs such as tricyclic antidepressants, inducing cognitive impairment. It is unclear whether normal aging results in a loss of cholinergic innervation to cerebral cortex and hippocampus, as in AD, but the prevailing evidence suggests that certain aspects of brain cholinergic function are diminished with advancing age (McEntee and Crook 1992). Cholinergic dysfunction many contribute to age-related decline of cognitive processing speed, but the enormous discrepancy between the small effects of scopolamine versus the large effects of age on cognitive speed (Riedel 1995) is more likely to be explained by age-related decline of other neurotransmission functions such as that of the catecholamines (McEntee and Crook 1990), serotonin (McEntee and Crook 1991), but also glutamate

(McEntee and Crook 1993). Furthermore, it is likely that these systems interact and hence that their influences on cognition, as well as on memory, are interactive and not independent.

Anticholinergic Effects of Antidepressants on Cognition

One of the most prominent central anticholinergic effects of antidepressants is that on cognitive function (Riedel and Van Praag 1995). Effects that occur after a single dose consist of sedation, psychomotor impairment and memory disturbances (Thompson 1991). After long-term administration, tolerance to sedation and psychomotor impairment is likely to develop, but not to memory disturbances (Sakulsripong *et al.* 1991).

Elderly patients can be assumed to be particularly sensitive to anticholinergic effects of antidepressants on cognitive functioning (Feinberg 1993; Marcopulos and Graves 1990; Nolan and O'Malley 1992; Tune *et al.* 1992). Drugs with anticholinergic properties, such as nortriptyline, maprotiline and amitriptyline, impair aspects of memory (Knegtering *et al.* 1994). Serum anticholinergic activity is correlated with greater cognitive impairment for amitryptiline (Richardson *et al.* 1994) and nortriptyline (Knegtering *et al.* 1994). Cognitive impairment induced by amitryptiline and nortriptyline during treatment might not be a transient effect, but may last as long as treatment continues. Amitriptyline, dothiepin, mianserin and trazodone impair attention and ability to concentrate. The second generation, or atypical antidepressants, and the newer selective serotonine (5-hydroxytryptamine; 5HT) reuptake inhibitors (SSRIs) are considered to be free from anticholinergic effects. Data regarding the effects of SSRIs on cognitive performance in the elderly indicate no detrimental effect (Knegtering *et al.* 1994). Monoamine oxidase (MAO) inhibitors hardly influence cognitive performance. The reversible inhibitors of monoamine oxidase MAO-A (RIMAs), may even improve cognitive function (Wesnes *et al.* 1989).

Cholinergic Drugs as Tools for the Study of Memory and Cognition

Scopolamine, which acts by blocking muscarinic acetylcholine receptors and nicotine, which acts by stimulation of nicotinic acetylcholine receptors, have been used to study the role of acetylcholine in attention and memory, and to model aspects of memory and other cognitive changes that occur with aging (Brandeis *et al.* 1992; Potter *et al.* 1992; Rusted and Eaton-Williams 1991; Rusted *et al.* 1991; Sahakian *et al.* 1989; Sunderland *et al.* 1988; Warburton and Wesnes 1984). Scopolamine impairs working memory (Rusted and Warburton 1988), and the selection and evaluation of environmental information (Callaway *et al.* 1991), and reduces the likelihood of

information presented being subsequently recalled or recognised (Rusted and Warburton 1989). Scopolamine causes sedation which may interfere with alertness, attention and vigilance and contribute to apparent memory impairment (Kopelman and Corn 1988; Wesnes *et al.* 1988). However, the disruptive effects of scopolamine on memory have been shown to be independent of sedative effects (Kopelman 1986; Molchan *et al.* 1992). In general, the scopolamine induced cognitive dysfunction can be reversed when nicotine (Riedel *et al.* 1995; Wesnes and Revell 1984) or other drugs that stimulate the cholinergic system are administered concomittantly (Duka *et al.* 1992; Jones *et al.* 1991; Molchan *et al.* 1990; Preston *et al.* 1992, 1989; Wesnes *et al.* 1987, 1991a,b; Wesnes and Warburton 1984). However, this effect is not always found with CNS stimulants (Bartus *et al.* 1982; Molchan *et al.* 1992), another indication that anticholinergic effects are specifically related to impaired memory functions.

The most persistent effects of muscarinic blockade on human cognition are the impairment of short- and long-term memory (Kopelman 1986). For this reason, it has been assumed that the memory effects of scopolamine could be attributed to cholinergic blockade of neurons particularly involved in memory functions. However, it was not clearly resolved whether the memory impairments induced by scopolamine were brought about by the disruption of storage processes, or retention processes, or retrieval processes in memory (Wesnes *et al.* 1988). The comparison of the effects of scopolamine on memory functions in healthy volunteers using clinical neuropsychological assessments similar to those used in Alzheimer's disease and Korsakoff's disease patients, led to the conclusion that cholinergic blockade, induced by scopolamine, is a model for cholinergic depletion and not for clinical amnesia such as in Alzheimer's disease and Korsakoff's disease (Kopelman and Corn 1988). The discussion has shifted towards the view that scopolamine induced sedation and impaired attention and hence impaired memory indirectly, rather than directly impairing memory processes such as storage, retention, or retrieval (Dunne and Hartley 1986). Scopolamine impaired working memory and its impairing effects were attributed to a decrement at the level of the central executive mechanism rather than at the subsystems under its control (Rusted and Warburton 1988). Scopolamine was found to impair early processes in the selection of attention which led to the contention that scopolamine disrupted the automatic capture of attention, inducing more serial processing (Brandeis *et al.* 1992). Scopolamine was also found to broaden the focus of attention, thus hampering focused attention in particular (Callaway *et al.* 1992). The opposite, i.e. the association of cholinergic dysfunction with divided attention deficits, has also been suggested (Sarter 1994). The resource interpretation of the effects of scopolamine on cognition includes the attribution of the impairing effects of scopolamine on controlled information

processing, presumably due to a reduced availability of resources, rather than on automatic information processing (Rusted 1994).

MODELS AND PARADIGMS TO STUDY CHOLINERGIC FUNCTION AND COGNITION

Cholinergic receptors can be divided into two types: nicotinic and muscarinic. The vast majority of cholinergic receptors in the brain are of the muscarinic subtype, and these receptors appear to be involved in memory and attentional functions. Outside the brain, muscarinic receptors are located in various organ systems such as the gastrointestinal tract, where they are involved in smooth muscle contraction. Nicotinic receptors however, are also involved in memory and attentional functions. Basically, the methods to study the cognitive effects of manipulations that affect acetylcholine receptors in humans are the administration of acetylcholine agonists and antagonists. Antagonists of muscarinic and nicotinic receptors produce somewhat different patterns of cognitive impairment, although it must be kept in mind that the selectivity of these compounds is most probably dose-dependent; in lower doses muscarinic and nicotinic antagonists selectively block these receptor subtypes, whereas in higher doses antagonists of either acetylcholine receptor subtypes may block both subtypes. Furthermore, selectivity can be further extended into the five subtypes of muscarinic receptors, named M1 to M5, respectively. The M1 receptors are widespread in the brain whereas M2 receptors primarily play a role in the cardiovascular system (Larson *et al.* 1991). Recently, specific antagonists and agonists of the muscarine M1 receptor have become available. The best known, non-specific, muscarinic receptor antagonist is scopolamine, while biperiden is the best known specific muscarinic M1 receptor antagonist. Several antidepressant drugs have also significant non-specific muscarinic receptor antagonizing properties.

Agonists of muscarinic and niotinic acetylcholine receptors generally lead to improved performance on cognitive tasks, even in healthy individuals. Muscarinic and nicotinic agonists are developed for the treatment of AD, but also yield insight in the pharmacological mechanisms involved in attention, learning and memory formation.

In the following paragraphs the effects of cholinergic blockade induced by muscarinic antagonists, including antidepressants, and nicotinic acetylcholine receptor antagonists are discussed, followed by those of cholinergic stimulation which are induced by muscarinic and nicotinic agonists and cholinesterase inhibitors. Finally, a paragraph is devoted to other factors that may lead to cholinergic stimulation, such as precursors of acetylcholine, vitamins, hormones and drugs that indirectly facilitate acetylcholine turnover such as the methylxanthines and 5HT.

Cholinergic Blockade

The term 'anticholinergic' refers to the blockade of acetylcholine receptors in general, while the term 'antimuscarinic' refers specifically to blockade of muscarinic cholinergic receptors (Richelson 1987).

Clinical anticholinergic effects are mediated by a competitive antagonism of muscarinic acetylcholine receptors in the central and peripheral nervous system (Baldessarini 1996; Heller Brown and Taylor 1996). The most potent anticholinergic drugs are the belladonna alkaloids atropine and scopolamine. The antidepressants that have the most potent anticholinergic effects are the tricyclic antidepressants (TCAs) amitryptiline and protriptyline. Although these drugs possess about one-tenth of the antimuscarinic receptor binding affinity of atropine, the clinical antimuscarinic effect of them can be more prominent than that of atropine. This is because the therapeutic dose range exceeds that of atropine 25- to 100-fold, for amitriptyline and 10- to 20-fold for protriptyline (Richelson 1987). Moreover, because the concentrations of anticholinergic drugs are dependent on dose regimen and pharmacokinetic parameters (such as distribution time and elimination half-life) anticholinergic effects can emerge as a consequence of slow accumulation after repeated dosing.

Muscarinic blockade

The effect of muscarinic blockade on cognition is mostly obtained using the nonselective muscarinic receptor antagonist scopolamine. Recently a selective antagonist of M1 muscarinic acetylcholine receptors, biperiden, is also used to investigate effects of blockade of M1 muscarinic acetylcholine receptors on cognition. In the following section, the effects of scopolamine on cognitive functions are illustrated with results obtained in our laboratory. Subsequently, effects of scopolamine on measures of regional cerebral blood flow (rCBF) are discussed. The relevance of the scopolamine model to screen the cognitive enhancing potential of new cognition enhancing drugs is discussed in the next paragraph. A brief overview of the effects of muscarinic blockade using the selective antagonist of M1 muscarinic acetylcholine receptors, biperiden, is then given. The, mostly unwanted widespread muscarinic blockade in the brain caused by antidepressants, is illustrated in the last paragraph on muscarinic blockade.

Nonselective muscarinic receptor antagonists: scopolamine

Scopolamine is the best known muscarinic receptor antagonist. Although there exist many more muscarinic receptor antagonists, in this section, mainly the effects of scopolamine on cognition and brain function, will be discussed.

The effects of scopolamine on cognition The effects of scopolamine on cognition are illustrated by data recently obtained in our laboratory. An emphasis is placed on the interaction of scopolamine with task factors. As far as possible, we do not look at single parameters of cognitive performance, but try to establish the effect of muscarinic blockade on psychological processes as reflected by task factors, such as the serial position effect in word learning, the target/nontarget similarity and memory load factors in the memory search paradigm, the number of response choices and S-R compatibility in a choice reaction time paradigm, time-on-task in a signal detection task and degree of automaticity in responding to different subsets of the Stroop task. Scopolamine 0.5 mg s.c. was administered to 16 healthy volunteers (25–35 yr). The effects of scopolamine on cognition 2 hours after administration, was evaluated using a neuropsychological test battery, and was compared to baseline performance.

Scopolamine impairs immediate and delayed free recall memory for word lists (see Fig. 1). The lack of effect of scopolamine on the measures of subjective organization in short- and long-term memory may indicate, that scopolamine does not, or in any case not severely, affect acquisition, or storage into secondary memory. The delayed recognition of learned words is as good as undisturbed by scopolamine, which can be taken to indicate that all words are still stored in memory, but muscarinic blockade disrupts its active recall and not its passive recognition from memory. The learning curves of the word lists in Fig. 1 show that the probability of free recall is quantitatively, rather than qualitatively impaired after scopolamine. The serial position curves of the word lists (see Fig. 2) show that the recall probabilities of words that are presented last in the list are not affected by scopolamine. This effect can be explained by the distinction between primary and secondary memory. The latter is impaired by scopolamine leaving the former unaffected. Retrieval is also quantitatively impaired by scopolamine, as assessed by prolonged recognition reaction times. It can also be interpreted as difficulties associated with accessing information which is processed less deep when it is stored in memory (Rusted 1994).

The search time in short-term or working memory is clearly prolonged after scopolamine (see Fig. 3). This finding lends further support to the observation that processes of search in memory are particularly disrupted by muscarinic blockade. The response time of the memory search task increases as a function of the number of letters to be held in memory as a target. Only the slope of this function, and not the intercept, is affected by scopolamine. This finding indicates, that in a condition with almost no memory load, neither visual encoding time (blurred vision apparently did not handicap the subjects), nor response execution time, are affected by scopolamine.

Discrete responses obtained in choice reaction time paradigms (see Fig. 4) show that both decision and movement reaction time (RT) were impaired by
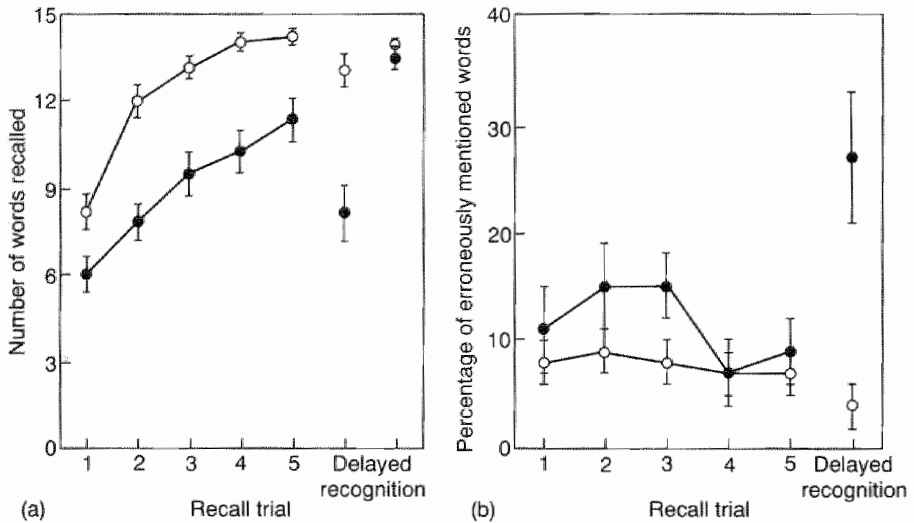
Figure 1. The effect of scopolamine on word learning. The word learning task con-
sists of five presentations of a list of 15 unrelated monosyllabic words, matched for
frequency. After each presentation, free recall yields the number of words remem-
bered (a) and the percentage of intrusions (b). Following a delay of 20 min, the sub-
jects perform another trial without presentation (delayed recall). Finally, the word list
is presented at a rapid pace (1 word/2 s) as a recognition trial in which subjects have
to identify learned words (targets) from distractors. The figure shows that scopola-
mine impairs learning considerably. However, the storage of words in memory seems
not to be qualitatively affected. Also, passive recognition does not discriminate scopo-
lamine from baseline, but recognition reaction time (not shown) is drastically pro-
longed after scopolamine. Upon delayed free recall, however, the strongest expression
of the scopolamine effect appears to be the combination of the impaired correct recall
of words and the sharp increase in the percentage of intrusions. Subjects do not seem
to be sedated; they mention the same number of words after scopolamine and at
baseline, but it seems as if their signal–noise ratio in actively retrieving the correct
words from their memory is impaired drastically. (○) baseline; (●) scopolamine

scopolamine. The interaction effect of scopolamine and the number of
response choices on decision RT yield significantly prolonged decision RT.
This suggests that scopolamine has persistent cognitive and perceptual-
motor effects. On the other hand, scopolamine consistently has no influence
on variables reflecting processes of response inhibition. This is apparent as
to the absence of an interaction effect of scopolamine with stimulus-response
compatibility on decision and movement reaction times and also as to the
absence of an effect of scopolamine on color–word interference in the
Stroop task (Fig. 5). It suggests that the effects of scopolamine on cognition
are selective (i.e. memory functions pertinent to free recall from secondary
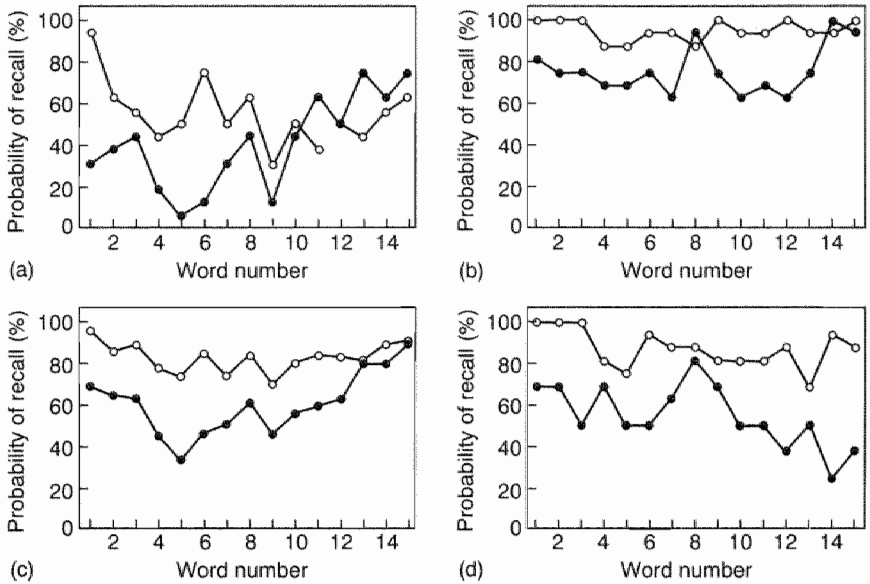(long-term) memory are markedly impaired, just as search in short-term

Figure 2. The effect of scopolamine (●) compared to baseline (○) on the probability of recall of learned words as a function of serial position in the word list. Because six parallel versions of word lists were used, effects pertaining to particular words are ruled out. Probability of recall refers to the percentage of subjects who recall the word at a given serial position. The serial position effect in short-term memory experiments is due to increased attention of earlier items (primacy effect) and the easy recall of late items (recent effect) from primary memory (Norman 1976). The memory impairing effect of scopolamine at immediate recall is due to the decreased recall probabilities of the words presented at the beginning of the list and not to the words presented last in the list. After the first presentation of the word list, the recall probabilities of the last five words are even higher after scopolamine relative to baseline, but recall probabilities of the first ten words are decreased (a: first immediate recall trial). After the fifth presentation of the word list, recall probabilities have drastically improved, showing that memory impairment after scopolamine is quantitative rather than qualitative, but selectively spares the recall probabilities of the last two words (b: fifth immediate recall trial). This pattern becomes more clear when looking at the recall probabilities calculated over the total of five immediate recall trials; the scopolamine-induced memory impairment is due to the first twelve words in the list. The last three words are apparently still in the unaffected 'primary memory' (c: immediate recall over five trials). This seems to be consistent with the finding that after delayed recall (when the list is not presented again) subjects can not utilize this 'recent effect' and the last words in the list appear to have the lowest probability of recall (d: delayed recall trial)
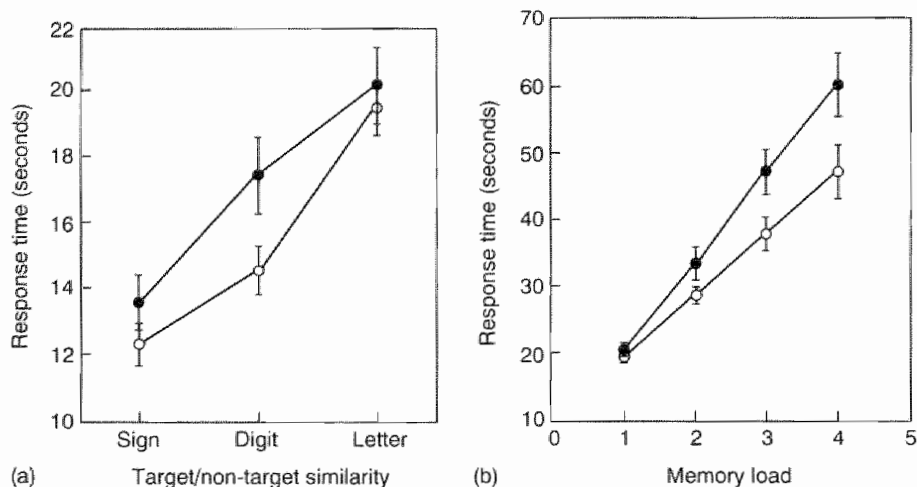
Figure 3.   The effect of scopolamine on memory search employing various target memory sets (a: one sign, one digit, one letter; b: one–four letters) while non-targets are always letters. The subject is shown one or more target items (the memory set) which he or she has to memorize. Subsequently the subject has to mark the target items on a sheet of paper containing 20 target items and 100 non-target letters which are spaced in 10 rows of 12 items. Scopolamine impairs the perceptual identification of one target sign (%) and on target digit among non-target letters, but not of one target letter among non-target letters. This is an illustration of the impairing effect of scopolamine on perceptual processes based on the automatic capture of attention, while a more difficult, controlled, perceptual process—the detection of a target letter among letters is not impaired. However, when an increasing amount of letters have to be kept in working memory (memory load), scopolamine proportionally impairs response time. Hence, scopolamine on the one hand prolongs the response time needed to discriminate signs and digits among letters and on the other hand it specifi-cally prolongs memory search time (slope of the memory search function) without prolonging response time related to controlled perceptual or motor processes (inter-cept). ($\circ$) baseline, RT $+$ 19.42 $+$ 9.26 $\times$ memory load; ($\bullet$) scopolamine, RT $=$ 20.17 $+$ 13.39 $\times$ memory load

memory and choice reaction time, but executive functioning such as inhibit-ing a dominant response by ignoring distracting or conflicting input stimuli, appeared unaffected by scopolamine).

The effects of scopolamine on cerebral blood flow   Positron emission tomo-graphy studies of scopolamine's regional metabolic effects showed a reduction in the functional activity of the thalamus (Blin *et al.* 1994; Cohen *et al.* 1994). Scopolamine's effects on the functions of thalamic, cingulate and basal ganglia are the likely causes of scopolamine's well-described attention-altering properties. Alterations in these same brain structures could
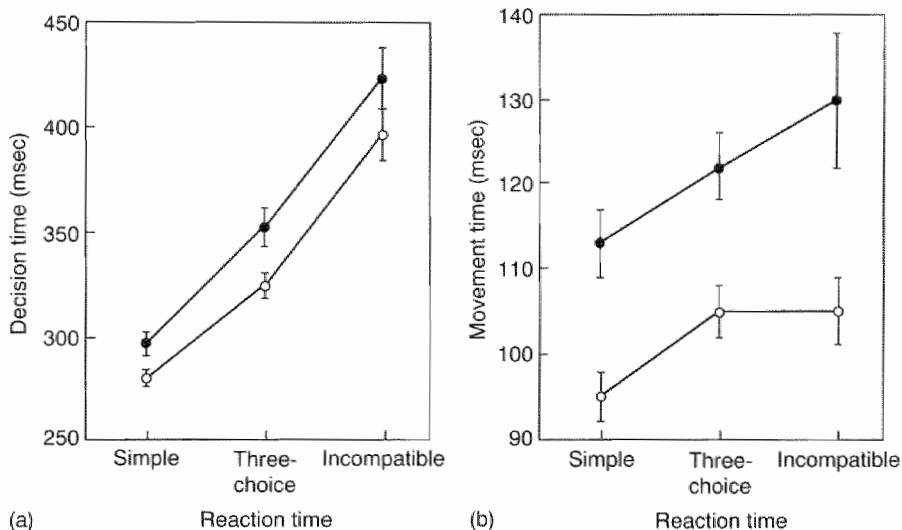
Figure 4.   Reaction time (a: decision time; b: movement time) as a function of the number of response alternatives and stimulus–response compatibility (simple, one response; three-choice, one of three response alternatives; incompatible, response adjacent to one of three response alternatives). Scopolamine delayed overall speed of both response initiation and movement. Furthermore, scopolamine delayed the three-choice decision reaction time in such a way that it specifically interfered with the process of response choice. Scopolamine did not interfere with S–R compatibility. (○) baseline; (●) scopolamine.

be responsible for scopolamine's effects on other cognitive function, e.g. memory. Alternatively, scopolamine's effects on other brain structures such as the hippocampus and frontal cortex could underlie scopolamine's effects on these other cognitive functions (Cohen *et al.* 1994). The cerebral blood flow effects of scopolamine in older volunteers are generally not consistent with changes seen in AD. Deficits in muscarinic system function may contribute to some but not all of the hypometabolic changes seen in AD patients (Molchan *et al.* 1994; Sunderland *et al.* 1995). Despite induction of a dementia-like state, scopolamine does not produce blood flow abnormalities in parietotemporal cortex, but does produce frontal cortex flow reduction (Gitelman and Prohovnik 1992).

The use of the scopolamine model in the screening of cognition enhancers   It has been suggested that scopolamine-induced amnesia is a potential predictor of clinical response to cholinergic cognition enhancing drugs (Hall *et al.* 1990). The model has indeed, in the past 5 years, frequently been used
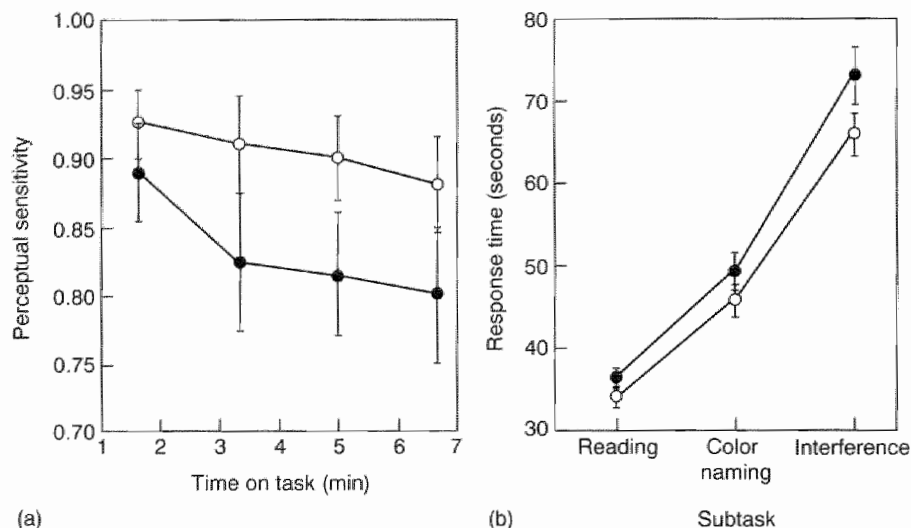
Figure 5. The effect of scopolamine and time on task on perceptual sensitivity in the signal detection test (a) and the effect of scopolamine on reading and naming of congruent and incongruent color-words in the Stroop test (b). In the signal detection test the subjects are shown a random pattern of dots appearing on a computer screen. Each time a set of four dots constitute a square, a response button has to be pressed as fast as possible. Using the proportion of correct detection and the proportion of false alarms, the perceptual sensitivity is calculated. Scopolamine impaired perceptual sensitivity and this effect slightly increased as a function of time on task. In the Stroop test the subjects are shown 10 lines of 10 colors. In the first trial color names are written in black ink and the subject has to read these as fast as possible. In the second trial colours are denoted as colored patches. In the third trial color words are printed in incongruently colored ink. In the second and third trials the subject has to name the color of the ink as fast as possible while ignoring the verbal content of the color words. Scopolamine only affected overall speed of the performance on the Stroop test and did not interfere with the incongruity factor. This is somehow consistent with the interpretation that scopolamine impairs perceptual processes that normally utilize the automatic capture of attention. (○) baseline; (●) scopolamine.

in the process of screening the effects of cognition enhancers in humans. Despite many criticisms, particularly with respect to the validity of the scopolamine model as a model of dementia or age-related cognitive decline (Parrott and Deary 1992; Schifano and Curran 1994), the number of studies on the effects of scopolamine on human cognition and its use as a screening model for cognition enhancing drugs, is still increasing rapidly. In only the past 5 years 21 studies have been published in which the scopolamine model was used as a screening model for putative cognition enhancing drugs (Riedel and Jolles, 1996).

Selective M1 muscarinic acetylcholine antagonists: biperiden

Currently, only one selective M1 muscarinic acetylcholine antagonist, biperiden, has been demonstrated to be active in humans (Salin *et al.* 1993) and to impair information processing (Dierks *et al.* 1994) and memory (Silver and Geraisy 1995). The impairment of memory by biperiden was observed in schizophrenic patients who receive antimuscarinic treatment primarily to combat extrapyramidal symptoms induced by concomitant neuroleptic treatment. The significance of this finding however, is that biperiden, because of its M1 selectivity, might be the successor of scopolamine to study the effects of muscarinic blockade on attention, learning and memory. The advantage of a selective M1 antagonist, would be its relative lack of cardiovascular effects which are supposedly primarily induced by blockade of M2 receptors.

Muscarinic antagonism induced by antidepressant drugs

Antidepressant drugs have clinically important interactions with muscarinic receptors, while nicotinic receptors are not affected by these drugs. Confusional states (induced by antimuscarinic actions) occur in as many as 13% of psychiatric patients receiving tricyclic antidepressants (TCAs) and other anticholinergic drugs (Davies *et al.* 1971; Tune *et al.* 1982; Walkup 1991). Few studies explicitly describe the relationship between anticholinergic effects and cognitive function (Curran *et al.* 1998; Sakulsripong *et al.* 1991) Many equate the occurrence of anticholinergic effects with the presence of sedation, memory problems and other effects such as dry mouth, without analysing whether these effects are actually related to cholinergic dysfunction. For example, sedation can be induced by blockade of cholinergic, histaminergic, α_1-adrenergic and γ-aminobutyric acid (GABA) receptors, and impaired performance on psychomotor- and cognitive performance can occur as a consequence of sedation. For this reason, drugs with very different pharmocological actions may lead to apparently the same net effect on behavior.

Tricyclic antidepressants cause moderate to severe effects on cognitive functioning, inducing symptoms such as forgetfulness, slowness of thought and difficulty in concentrating (more specifically, difficulty in focussing attention on one source of information while ignoring others). These effects are attributed to anticholinergic activity, but could also be caused by blockade of histaminergic and α-adrenergic receptors. Both strongly (amitriptyline) and weakly (trazodone) anticholinergic antidepressants induced a high degree of sedation that was associated with many different types of psychomotor and cognitive impairments, but memory was more impaired by anticholinergic antidepressants (Curran *et al.* 1988; Sakulsripong

et al. 1991). Thus, forgetfulness qualifies as the most prominent cognitive effect differentiating antidepressants with and without anticholinergic activity.

The atypical antidepressants trazodone and mianserin are considered to lack anticholinergic activity, but are highly sedating (Rudorfer and Potter 1989) due to antagonism of histamine H_1-, α_1-adrenergic and possibly $5HT_2$-receptors, to which tolerance does not readily develop. The successor of trazodone, nefazodone, also lacks anticholinergic affinity (Eison *et al.* 1990). The selective serotonin reuptake inhibitors (except paroxetine) and the reversible MAO-A inhibitors are devoid of anticholinergic as well as antihistaminergic and α-blocking effects, and hence do not induce sedation after single or repeated administration.

Other consequences of CNS anticholinergic effects that sometimes occur during treatment with antidepressants include disturbance of judgement (Walkup 1991), and delirium and confusion (Davies *et al.* 1971). These effects are primarily thought to be associated with accumulated or toxic concentrations of agents with anticholinergic properties. They symptoms may also be the emergent signs of a more severe disruption of memory and information processing functions. They rarely occur as a consequence of antidepressant therapy, but the syndrome is known from anesthesia where it is described as the central anticholinergic syndrome. The prevalence of the syndrome after anesthesia is thought to be augmented by antidepressant use.

The memory impairment induced by anticholinergic antidepressants does not necessarily hamper their clinical effects, but memory impairment seems an inappropriate side effect during antidepressant therapy, while sedation, often accompanied by psychomotor slowness, may be a welcome side effect. It has been stated that these effects on memory and psychomotor speed reflect diffuse aspects of the same underlying alterations of neurotransmission induced by antidepressant treatment (Volz and Sturm 1995). In this manner, any change in cognitive or psychomotor performance is an indicator of any change in the final common path of brain function, be it changes in serotonergic, noradrenergic, cholinergic, or other neurotransmission. On the other hand, a carefully controlled comparison between the clinical and cognitive effects of an anticholinergic antidepressant, amitryptiline, and an antidepressant without anticholinergic effects, fluoxetine, unequivocally showed that amitryptiline treatment impaired verbal learning while fluoxetine treatment did not (Richardson *et al.* 1994). This difference was not related to changes in clinical improvement, but rather appeared to be associated with serum anticholinergic levels.

Experimental data, obtained in studies into the cognitive effects of antidepressants and scopolamine and alcohol after acute administration and compared with placebo yields an interesting pool of observations. In all these experiments the Sternberg memory search paradigm was employed.

The memory search paradigm is designed to study the speed of memory processes. The underlying principle is that the extra time needed to complete a test in which there is a stepwise increase in the amount of information to be kept in memory, is a measure of the ease at which information is processed in working memory (Sternberg 1975). The reaction time as a function of memory load across subtasks can be expressed as a linear regression function (see also Fig. 3: right graph) in which the intercept is associated with nonmemory search stages of information processing, whereas the slope of the function represents the extra time needed to compare a test item to one item in memory. As memory load increases, RT increases by the time represented by the slope of the memory search function times the memory set. In Fig. 6 drug–placebo differences of intercepts and slopes of memory search functions obtained in different experiments with antidepressants are compared. In this way it can be seen that within the Sternberg task paradigm amitryptiline is even more impairing than scopolamine. This is because of the combined impairment of intercept and slope of the memory search function after amitryptiline. The proposition that the slope of the memory search function is cholinergically determined, whereas the intercept is determined, mainly by impairments in other neurotransmitters, finds its basis in the observation that scopolamine selectively impairs the slope of the memory search function. A way to investigate this proposition is shown in Fig. 7 in which the acute impairments of slope and intercept of memory search function, induced by several antidepressants, are plotted as a function of their anticholinergic potencies (Eison *et al.* 1990; Voltz and Sturm 1995). As for the relation between anticholinergic potency and slope, this seems to confirm that the slope of the memory search function is a behavioral indicator of cholinergic function, whereas the intercept may be determined by histaminergic, noradrenergic and α-adrenergic function.

Nicotinic blockade

Acute blockade of nicotinic receptor function by the nicotinic antagonist mecamylamine can produce measurable and significant cognitive impairment, even in non-smoking normals (Newhouse *et al.* 1992). Furthermore, an age-related increase in sensitivity to nicotinic blockade by mecamylamine has been demonstrated (Newhouse *et al.* 1994).

Mecamylamine yields rCBF changes similar to those seen in AD, a perfusion deficit in parietotemporal cortex, despite producing only minimal cognitive effects on its own. The rCBF and behavioral manifestations in AD may therefore reflect the functional loss of nicotinic receptors in addition to alterations in other receptor systems (Gitelman and Prohovnik 1992).
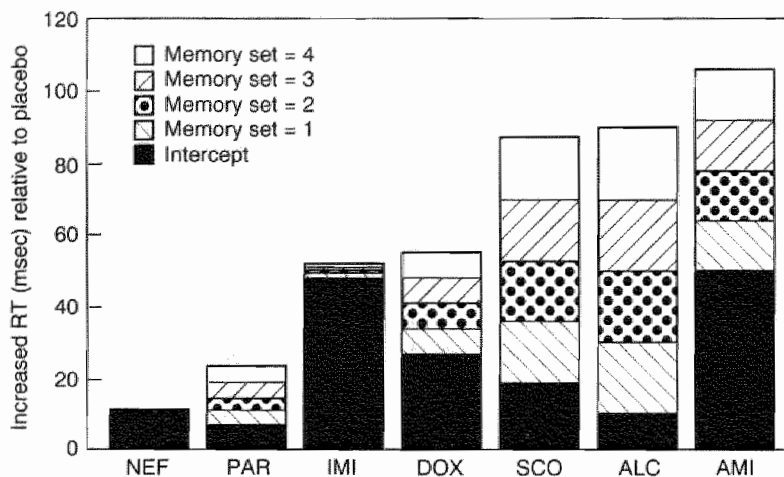
Figure 6. The effects of several antidepressants in comparison with scopolamine and alcohol in information processing using the Sternberg task (Sternberg 1975). The Sternberg memory search paradigm consists of a memory set which has to be kept in memory by the subject and sequentially compared with a series of test stimuli. The subject responds as fast as possible by pressing 'Yes' if the test stimulus belongs to the memory set, otherwise the subject responds by pressing 'No'. The dependent variable, Reaction Time, can be expressed as search time per item times the memory set size (slope, shaded bars) plus a constant time (intercept; black bars). The bars denote drug-placebo differences which are composed of a psychomotor impairment component (black portion of the bars) and memory search impairment components (striped portions of the bars). Evidently, the latter are far more important for daily life memory functioning as their influence increases proportionally with memory load. Results were obtained in various placebo-controlled studies. As to the data obtained after scopolamine treatment, scopolamine was compared to baseline. These data were obtained in a similar paradigm using pencil and paper version of the memory search paradigm. Percentual impairments of intercepts and slopes of scopolamine and baseline regression functions of memory search were taken which were subsequently converted to difference scores in reaction times. ALC = alcohol 50 g (Riedel et al. 1990); DOX = doxepine 25 mg (Robbe et al. 1991); NEF = nefazodone 100 mg; IMI = imipramine 50 mg (Van Laar et al. 1995); PAR = paroxetine 20 mg; AMI = amitryptiline 50 mg (Robbe and O'Hanlon 1995); SCO = scopolamine 0.5 mg s.c. (Riedel et al. 1995)

Cholinergic Stimulation

Cholinergic receptors in the brain are of the muscarinic or nicotinic type. There are muscarinic and nicotinic agonists, that stimulate these two subtypes of acetylcholine neurotransmission, respectively. Furthermore, there are inhibitors of acetylcholinesterase, the enzyme that normally degrades
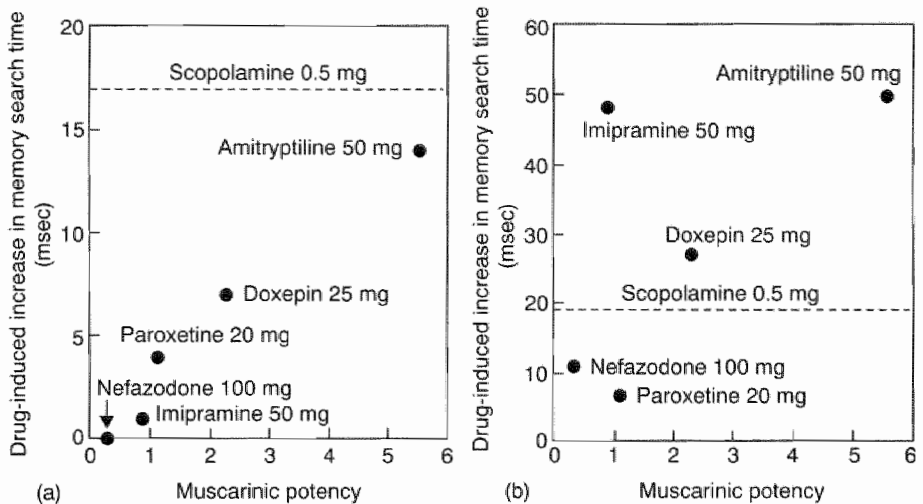
Figure 7. The effect of several antidepressants of varying muscarinic potency in comparison with the anticholinergic drug scopolamine on information processing using the Sternberg memory search task (Sternberg 1975). Muscarinic potencies were obtained from Volz and Sturm (1995). Results express drug-placebo differences (impairments) which were obtained in various controlled studies of acute drug effects in healthy volunteers. DOX = doxepin 25 mg (Robbe et al. 1991); NEF = nefazodone 10 mg; IMI = imipramine 50 mg (Van Laar et al. 1995); PAR = paroxetine 20 mg; AMI = amitryptiline 50 mg (Robbe and O'Hanlon 1995); SCO = scopolamine 0.5 mg s.c. (Riedel et al. 1995)

acetylcholine. Inhibition of acetylcholinesterase thus stimulates acetylcholine neurotransmission. Precursors of acetylcholine are choline and lecithin. They are necessary for the formation of acetylcholine. Increased intake of these precursors could lead to increased acetylcholine turnover. Finally, many substances such as nootropic drugs, neurohormones, vitamins and methylxanthines, have been tested for their indirect influence on acetylcholine neurotransmission.

Cholinergic agonists

Muscarinic agonists

Clinical experience with muscarinic agonists in the symptomatic treatment of Alzheimer's disease includes studies of the effects of arecoline (Soncrant *et al.* 1993), bethanechol (Harbaugh *et al.* 1989; Read *et al.* 1990), pilocarpine, oxotremorine and RS 86 (Gray *et al.* 1989). Although the results are

somewhat conflicting, there is evidence that a subgroup of patients may respond with an improvement of cognitive and/or behavioral function. The existing agents tend to induce adverse effects due to the stimulation of peripheral muscarinic receptors. Furthermore, they reduce (at least *in vitro*) acetylcholine release by an action on presynaptic receptors. Strategies to overcome these problems include the development of potent agonists with high blood–brain barrier penetration, the search for agents selective for muscarinic receptor subtypes (using cloned receptors as tools) and the identification of agents acting as presynaptic receptor antagonists, to increase acetylcholine release (Gray *et al.* 1989).

Examples of these are the more potent and selective compounds milameline and xanomeline that are specific muscarine agonists. Xanomeline is even specifically aimed at the M1 receptor subtype. Studies in humans have been reported to show the selectivity and specificity of these agents, but unfortunately reports on their cognitive effects in humans are lacking (Bodick *et al.* 1994).

Nicotinic agonists

The main development in nicotinic agonists is reflected by the interest in the influence of nicotine on cognition. The effects of nicotine on cognitive functions have been extensively studied in healthy persons, smokers, non-smokers, subjects with scopolamine-induced cholinergic blockade, and in patients with AD (Jones *et al.* 1992; Rusted and Eaton-Williams 1991; Wesnes and Parrott 1992). The mechanism by which nicotine exerts its effects on cognition is by agonism of nicotinic acetylcholine receptors. Recently, it has also been established however, that nicotine stimulates glutamate release (McGehee *et al.* 1995), which would be the primary neuronal candidate mechanism for memory consolidation. This mechanism of fast excitatory synaptic transmission could indicate that nicotine stimulates long-term potentiation (LTP), an explanation which could account for the observation that nicotine also improves memory formation after 'post-trial' administration (Rusted *et al.* 1995). Furthermore, it has been stated that nicotine use might play a role in the prevention of AD by maintaining cholinergic function better in old age (Levin 1992).

Numerous compounds are known which activate neuronal nicotinic acetylcholine receptors and which might serve as lead compounds toward the development of such agents (Holladay *et al.* 1995). The diversity of nicotinic acetylcholine receptors suggests the possibility of developing selective compounds, which would have more favorable side-effect profiles than the existing agents. ABT-418 may be the first cognitive enhancing nicotine agonist, possessing a substantially reduced side-effect profile compared to nicotine (Arneric *et al.* 1995).

Cholinesterase inhibitors

Cholinesterase inhibitors, increase acetylcholine neurotransmission by means of inhibiting the activity of the enzymes that normally degrade acetylcholine. Cholinesterase inhibitors are currently in the focus of interest since tacrine has been registered as the first drug against dementia of the Alzheimer type (Wagstaff and McTavish 1994). This has stimulated research with cholinergic agents in general and cholinesterase-inhibitors in particular, a second and third generation of these compounds are currently being studied and developed, respectively (Giacobini and Becker 1994). Furthermore, it can be noted that experiments using the scopolamine model of cognitive dysfunction have shown that cholinesterase inhibitors can completely reverse cholinergic deficits in humans (Wesnes *et al.* 1991b), whereas the influence of most other substances tested using this model are reported in terms of a significant attenuation.

Cholinergic precursors

Precursors of acetylcholine are aimed to increase the synthesis of acetylcholine in the brain. The best known precursors of acetylcholine are choline and lecithin. Several trials have been carried out with dietary choline and lecithin to improve cognitive function in elderly people and Alzheimer patients, generally without much success (Growdon *et al.* 1986), but a small additional effect of lecithin on cognition in AD patients was reported when lecithin was administered simultaneously with tacrine (Holford and Peace 1994). Unfortunately, it has been shown that increased intake of choline does not lead to increased acetylcholine synthesis in the brain, whereas depletion of choline does lead to decreased synthesis of acetylcholine in the brain (Wecker 1988).

Cognition enhancers with possible cholinergic mechanisms of action

Methylxanthines

Improved performance on psychological tasks has been reported frequently after caffeine intake in normal subjects, even with dosages as low as 32 mg (Lieberman *et al.* 1987), in placebo-controlled double-blind studies, whereas only a few studies report detrimental effects on psychological task performance (Nehlig *et al.* 1992; Stavric 1992). The observed effects are described in terms of increased vigilance, arousal, activation, alertness, psychomotor speed, and mood. Learning and memory were improved by caffeine in one study (Loke 1988) but impaired in another (Terry and Phifer 1986). An

interesting study describing a positive effect of caffeine on cognitive function, including memory, involved 7414 people distributed over age groups of about 20, 30, 40, 50, and 60 years (Jarvis 1993). A positive linear relationship existed between the daily coffee consumption and cognitive performance. Older people appeared to be more susceptible to the performance-improving effects of caffeine than were younger people. Adenosine antagonism is assumed to be the most important mechanism for explaining the stimulating effects of the methylxanthines on behavior (Nehlig *et al.* 1992; Stavric 1992). Potential cognition enhancers include adenosine A_1-antagonists since inhibitory adenosine A_1-receptors have been found on cholinergic terminals in the hippocampus and the cortex (Briley 1990). If this mechanism is involved in caffeine's mode of action, then the cognition enhancing rather than merely the activating properties of caffeine would underlie the beneficial effect of caffeine on learning and memory performance. The possibility that caffeine stimulates acetylcholine was shown by caffeine's attenuation of scopolamine-induced cognitive dysfunction in human subjects (Riedel *et al.* 1995).

Vitamins

The association of vitamin B_1 deficiency with memory dysfunction and cognitive disorders has been related to an impairment of cholinergic activity (Micheau *et al.* 1985), and this association was shown in man using the scopolamine-model (Meador *et al.* 1993). Vitamin B_1 (sulbutiamine) has been advocated for the treatment of cognitive dysfunction and fatigue of central origin (asthenia), prevalent after prolonged physical exercise in endurance athletes (Consolis and Mas 1988), but also in aging (Israel *et al.* 1989). It has been suggested that the cognition enhancing potential of thiamine in AD is equivalent to that of physostigmine and due to its general lack of adverse effects would deserve the benefit of the doubt (Meador *et al.* 1993).

Serotonergic agents

The theory of indirect cholinergic facilitation by the $5HT_3$-antagonists is very well-described (Barnes *et al.* 1990) and seemed to explain the positive results obtained in their application with the scopolamine-model of cognitive dysfunction (Preston *et al.* 1992) and also in the treatment of age-associated memory impairment (Crook and Lakin 1991) However, cholinergic facilitation by $5HT_3$-antagonists could not be replicated, whereas m-CPP, a mixed 5HT agonist/antagonist tended to worsen the scopolamine-induced cognitive dysfunction, thereby suggesting that 5HT agonists decrease acetylcholine turnover (Little *et al.* 1995).

Hormones

Several neuropeptides, namely the ACTH- and TRH-analogs, have been shown to exert significant effects on motivational, learning and memory processes (Frostl and Maitre 1989). TRH has been demonstrated to attenuate scopolamine-induced cognitive dysfunction (Molchan *et al.* 1990). The administration of estrogens, especially to those who are presumably low on estrogen, improves memory (Phillips and Sherwin 1992). The administration of estrogens to elderly humans with memory complaints may halt or prevent cognitive decline or AD (Fillit 1994), presumably by means of facilitating the cholinergic system.

Phospholipids

Phosphatidylserine (PS) is a component of brain phospholipids displaying a manifold pharmacological action in both *in vitro* and *in vivo* animal models. PS is an essential component of cell membranes; neuronal excitability is—among other things—dependent upon the amount and nature of PS in the membrane. PS is particularly essential to the functioning of nerve cells, including neurotransmitter release and synaptic activity, in the brain. Clinical studies have suggested that treatment with PS, 300 mg daily, can play an important role in counteracting age-associated cognitive decline (Crook *et al.* 1991). One of the proposed mechanisms of action which leads to enhancement of cognitive functions by PS in (elderly) humans is a facilitation of cholinergic pathways in the CNS. Animal studies have shown that PS increases acetylcholine release *in vitro* (Pedata *et al.* 1985; Vannucchi and Pepeu 1987), while it reverses scopolamine-induced amnesia *in vivo* (Zanotti *et al.* 1986). Until recently, PS was only available from animal sources (brain), and occurred in commercial lecithins only in trace amounts. However, alternative sources for PS have been developed. These include an alternative animal source (egg) and a plant (soy) source. Therefore, it can be expected that the interest in this substance will increase during the coming years.

Nootropic drugs

Claims entailing the cholinergic effects of nootropic drugs mainly refer to attempts to attenuate the scopolamine-induced cognitive dysfunction. Piracetam and intravenous aniracetam did not succeed in this manner (Wesnes *et al.* 1990), while oral aniracetam (Wesnes *et al.* 1990) oxiracetam (Preda *et al.* 1993) and pramiracetam (Mauri *et al.* 1994) did.

DISCUSSION AND CONCLUSION

The cholinergic hypothesis briefly entails that cholinergic agonists positively affect cognitive function while cholinergic antagonists have an impairing influence on cognitive function. These predictions have been confirmed by experimentation, perhaps more than any other hypothesis in human psycho-pharmacology. However, this does not mean that we know which precise neurochemical and psychological mechanisms are at stake. With respect to the observations that nicotine and caffeine both facilitate glutamate release in vitro (McGehee et al. 1995; Silinsky, 1989) and both attenuate aspects of scopolamine-induced cognitive dysfunction in humans (Riedel et al. 1995) and post-trial administration of nicotine facilitates learning (Rusted et al. 1995), we may ask ourselves whether scopolamine, or cholinergic blockade in general, is associated with impaired glutamate neurotransmission possibly through blockade of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor which would consequently impair LTP (Artola and Singer 1987). The only pharmacological evidence available that scopolamine might do so in humans is the observation that D-cycloserine, a partial agonist at the strychnine-intensive neuronal glycine receptor which positively modulates the NMDA excitatory amino acid receptor and hence might promote LTP, attenuated scopolamine-induced cognitive dysfunction (Jones et al. 1991). The interaction of the cholinergic and the glutamatergic systems has led to the hypothesis that stimulation of both acetylcholine and NMDA receptors simultaneously might prove more effective than individual activation of either receptor (Ingram et al. 1994). In terms of behavioral observations, the serial position effect of scopolamine, seen in word list learning, resembles what impaired LTP might look like.

In the future, the scopolamine model will probably be replaced by more selective and specific muscarinic M1-antagonists, with less side effects, such as biperiden, to model aspects of (age-related) cognitive dysfunction. At the same time more specific agonists of muscarinic and nicotinic receptors are developed and promise new prospects for more specific cholinergic cognition enhancement effects, i.e. with less or no cardiovascular or peripheral side effects.

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