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NICOTINE AS A COGNITIVE ENHANCER

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Contents

Abstract

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1 Nicotine improves attention in a wide variety of tasks in healthy volunteers.
2. Nicotine improves immediate and longer term memory in healthy volunteers.
3. Nicotine improves attention in patients with probable Alzheimer's Disease.
4. While some of the memory effects of nicotine may be due to enhanced attention, others seem to be the result of improved consolidation as shown by post-trial dosing.

Keywords: acetylcholine, Alzheimer's Disease, attention, cholinergic, memory, nicotine, scopolamine.

Abbreviations: Alzheimer's Disease (SDAT)

1. Introduction

The primary aim of research on cognitive enhancers is the treatment of senile dementia of the Alzheimer type (SDAT). SDAT is associated with disruption of function in a large number of brain neuro-transmitter systems, but the single transmitter system which has received the most attention is the cholinergic system. The clinical severity of SDAT correlates both with cognitive decline (Cutler and Narang, 1986) and decline in activity of choline acetyltransferase, a marker of cortical cholinergic activity (Perry et al, 1978) and with chronic loss of subcortical cholinergic cell bodies in the basal forebrain (Whitehouse et al, 1982).

The cholinergic system has long been considered to have a modulatory role in information processing, attention and memory (Warburton, 1975), and the emphasis on impaired cognitive functioning as an early and progressive symptom of SDAT appeared to support the significance of the relationship between the two (Sahakian et al. 1989). Consequently, psychopharmacological treatment strategies for the cognitive dysfunction in SDAT have examined the potential of direct enhancement of cholinergic function to counteract the loss of cholinergic neurons in the basal forebrain.

Early studies involving treatment with precursors of acetylcholine, such as choline or lecithin, were not very successful in producing significant improvements in cognitive performance (see review by Bartus et al. 1982). The results with cholinesterase inhibitors, such as physostigmine, have been marginally better. Kopelman (1986) provides a succinct review of experimental studies; small benefits have been reported in the better designed studies, but the effects are far from dramatic. The potential of the compounds in clinical practice is limited by the narrow therapeutic window for effective doses, and the adverse side effects associated with chronic administration.

Finally, attempts to stimulate the cholinergic receptors with the administration of post-synaptic muscarinic agonists, such as arecoline and RS86, failed to produce reliable improvements on objective tests of cognitive performance (Palacios and Spiegel, 1986), although there are claims that the compounds improve global functioning (Harbaugh et al, 1984) and affect (Tariot et al, 1988).

Increased understanding of the cholinergic system and the mechanisms of action within this system has suggested alternative strategies. For example, Warburton (1981), Sahakian et al (1989) and Sarter et al (1990)

have suggested pharmacological strategies, which focus on the amplification of presynaptic activity, rather than direct influence on the normal patterning of cholinergic transmission.

An interesting new focus in cholinergic research, and one which is relevant to the present discussion, is the interest in the nicotinic receptors of the cortical cholinergic system. The ascending pathway from the nucleus basalis deteriorates in SDAT. While muscarinic receptor numbers and function remain stable over the course of the disease, it is said that there is a significant loss of nicotinic receptors in all cortical laminae (Kellar et al, 1987). At first sight, this damage would seem to prevent effective enhancement of cognitive function via this route in SDAT patients. However, there is some indication that the extent of cholinergic cell loss may have been overestimated. Lams et al (1988) have suggested that the cholinergic neurons survive despite significant loss of acetylcholine-associated enzymes, which have previously been interpreted as a measure of neuron density.

In addition, recent work has suggested that instead of a reduced number of nicotinic binding sites, high affinity nicotinic binding sites are converted into low affinity sites in the course of the disease (Nordberg et al, 1988), and that this increased number of low affinity sites could result in enhanced functioning of residual cholinergic neurons (Sarter et al, 1990).

Consequently, it seems sensible to re-evaluate nicotine as a cognitive enhancer. The drug could be useful in its own right as an enhancer, or as an indicator of the class of drugs which may be useful in the future for the amelioration of the cognitive deficits which are characteristic of SDAT.

2. Nicotine and Attentional Processing

It has frequently been pointed out that attention cannot be thought of as a unitary concept and it is suggested that we must consider alertness, selectivity and processing capacity as separate components of attention (Posner and Boies 1971, Kinchla, 1980). Kinchla (1980) suggested three classes of experiment which were relevant to the issue of selectivity in information processing; namely, sustained attention tasks, attentional switching tasks, and selective attention tasks.

2.1 Sustained Attention

One classical type of sustained attention test is the vigilance task. In vigilance tasks, attention is directed to one or more sources of input for long periods of time and the subject is required to detect and respond to brief, infrequent changes in input. During a typical vigilance session, the detection rate decreases, a change called the vigilance decrement. We have used the Mackworth Clock task (Mackworth, 1950) as a task which produces a reliable vigilance decrement. In this task, the volunteer has to detect brief pauses in the movement of the minute hand of the clock. In healthy volunteers, beneficial effects of nicotine on sustained attention have been consistently documented. Nicotine tablets held in the mouth for five minutes reduced the vigilance decrement which occurs over time in the Mackworth clock task (Wesnes et al., 1983).

In addition, we have used a completely different sustained visual attention task in which a series of digits is presented sequentially on a computer screen at a rapid rate (100 digits per minute). Volunteers are required to detect three digit sequences of odd or even numbers as they occur. Measures of both speed and accuracy of detection are taken. Nicotine gum produces dose-related increases in the number of correct detections and decreases in reaction time to make those correct detections on the rapid visual information processing task (Rusted and Warburton, unpublished data). In an earlier study using nicotine tablets (Wesnes and Warburton, 1984a), 1.5 mg nicotine produced a similar performance improvement in terms of both speed and accuracy on the rapid visual information processing task which closely resembled the improvement produced by smoking a single cigarette (Wesnes and Warburton, 1984b).

The improvement in both speed and accuracy are important because it shows that this was not a consequence of speed-accuracy trade-off in performance, but that there was an overall improvement in attentional processing efficiency.

2.2 Attentional Switching

In an attentional switching task, volunteers must attend to more than one source of information and process material from both sources. A study of divided attention (cited in Warburton and Walters 1988), used a test which was based on the rapid visual information task (Wesnes and Warburton 1984a). Subjects were presented with digits at a rate of 50 per min. in both the visual and auditory modality, a different sequence for each

modality. The detection of sequences in both modalities improved significantly after 10 hour deprived smokers smoked a cigarette, in comparison with not smoking; an improvement of seven percent. Smoking a cigarette also prevented the increase in reaction times that occurred in the non-smoking condition.

2.3 Selective Attention

A task which demonstrates selective attention and perceptual intrusions from unattended material is the Stroop task (Stroop, 1935). This is a complex information processing task in which volunteers are required to process information under conditions of distraction. Typically, a list of colour words may be presented, with the words written in different coloured inks. The ink colours are incongruent with the written words, for example, the word YELLOW may be written in red ink, and the word RED in green ink. The task is to move down the word list naming the colour of the ink in which each word is written, ignoring the actual printed word.

The Stroop effect is the name given to the distracting effect of the to-be-ignored distractor stimuli on the processing of the attended material. Naming the print colour of incongruently printed colour words takes much longer than ink colour naming of non-colour words written in different inks. The difference in time required for these conditions provides a measure of the volunteer's capacity to selectively attend to the relevant dimension (the ink colour) while ignoring the irrelevant one (the printed word).

Oral doses of 1.0 mg and 2.0 mg nicotine reduced the size of the Stroop effect in both deprived smokers and nonsmokers (Wesnes and Warburton, 1978), indicating enhanced selective attention for relevant information and suppression of irrelevant information.

3. Nicotine and Event-Related Potentials

Another indicator of improved information processing with nicotine is the changes which are observed in the P_3 wave. The occurrence of the P_3 wave depends on the completion of certain stimulus evaluation processes (Donchin, 1984). Smoking decreases the latency of the P_3 component of the event-related brain potentials during the rapid visual information processing task (Edwards et al. 1985). A reduced latency of the P_3 indicates quicker stimulus evaluation i.e. more efficient processing. It is important that cholinergic antagonists like scopolamine have the opposite effect (Callaway et al. 1985).

4. Nicotine and Memory Enhancement

A review of the literature shows that the effects of nicotine on short term memory have not been robust. An early study by Andersson and Hockey (1977) provided weak evidence that smoking may enhance storage of information, but only of information intentionally encoded for recall. One interpretation of this finding is an attentional one; the group who smoked may be more efficient at selecting the relevant information.

In contrast, Peeke and Peeke (1984), who studied the effects of smoking on immediate memory in two hour deprived smokers, found that recall of a 50-word list was improved immediately after learning. In a complementary study of a low and a high nicotine cigarette, the high nicotine cigarette produced improved recall, while the low nicotine cigarette was less effective. In agreement with the last study, when testing was given once just after the input, we found evidence of improved immediate memory (Warburton et al. 1986). After smoking a 1.4 mg cigarette at their own pace (nine puffs every 38 secs on average), the subjects were shown a list of 48 nouns and were immediately asked to write down as many as they could. There was better immediate recall after smoking in comparison with not smoking.

In another study, we used 1.5 mg nicotine tablets in the state-dependent design in which smokers were deprived for over 10 hrs (Warburton et al. 1986). After the tablet, the subjects listened to 48 words and then did successive subtractions for one minute to prevent rehearsal. As we have said earlier, immediate recall was improved. One hour later, the subjects were given either nicotine or placebo tablets, depending on their group. They were asked to recall as many of the words as they could in another ten minutes free recall test. Long term recall was significantly better when subjects had taken nicotine prior to learning but not when taken prior to recall. A significant interaction term gave evidence for a state dependent effect of nicotine and showed that nicotine was facilitating the input of information to storage but had no direct effect on retrieval.

In a recognition study (Warburton et al. 1986), smokers who were deprived of cigarettes for over 10 hrs were given a 1.4 mg nicotine cigarette, or nothing, immediately before serial presentation of a set of Chinese ideograms. Subjects were divided into four groups - a quarter who did not smoke prior to learning or recall; a quarter who did not smoke prior to learning but had a cigarette prior to recall; those who had a cigarette prior to learning and recall; and those who had a cigarette prior to learning but none prior to recall. Subjects who smoked prior to

learning had significantly better recognition scores than the subjects who did not smoke in the first part of the experiment. There was no effect of smoking on recall performance itself. A significant interaction term indicated that changing the chemical state interfered with recognition i.e. state dependency.

The effects of smoking a low (0.7 mg) and a middle (1.3 mg) nicotine yield cigarette on learning to associate pairs of words and retention was examined by Mangan (1983). Cigarettes improved retention in the paired-associate learning, and performance during learning suggests that improvement is produced by smoking on longer term memory rather than shorter term memory. Mangan and Golding (1983) also studied the effects of smoking on longer term memory. After one month subjects who smoked a 0.8 mg and 1.3 mg nicotine cigarette were better than non-smokers.

It seems clear that nicotine can improve longer term storage of information in some circumstances. One explanation may be that their memory task had an attentional component. In a typical memory task, attention to the words is controlled by instruction. The list is short and so attention does not play a part. However, the list in the Warburton et al (1986) study was 48 items long, and that in the Peeke and Peeke (1984) study was 50 words long, in comparison with the eight word lists in the Andersson and Hockey (1977) study and the nine digit list of Williams (1980), for example. In this regard, it is interesting that nicotine did produce a slight improvement in the Andersson and Hockey study when subjects had to remember words, word order and location on the computer screen i.e. 24 items.

Rusted et al (In press) have tested this hypothesis directly in a recent study involving immediate free recall of either 10 or 30 word lists following ingestion of a 1.5 mg nicotine tablet. In accordance with the attentional hypothesis, nicotine significantly improved free recall of 30 item lists, but not of 10 item lists. Crucially, co-administration of the same dose of nicotine did not reverse the scopolamine-induced recall deficits observed for both 10 and 30 item lists, in contrast to the effective reversal of scopolamine-induced deficits on a sustained attention task, reported by Wesnes and Revell (1984).

Nevertheless, animal studies have demonstrated that information storage is improved in animals. Posttrial nicotine treatment has been shown to result in facilitated retention of a variety of tasks (Garg and Holland, 1968; Garg, 1969; Battig, 1970; Evangelista et al., 1970; Erickson, 1971). Post-learning smoking also improved recall in one human study (Mangan and Golding, 1983).

Since this is the only example in the literature, we believed that further work was needed to resolve the issue. Accordingly, we designed a word list so that a list of 32 words was presented in blocks of four words. After each presentation of a block, subjects were instructed to puff on a cigarette and to rehearse the material. After the presentation of all eight blocks, there was an interval of 10 min during which the subjects did successive subtractions of seven from a large number to prevent further rehearsal. The subjects were given five minutes for recall.

The data were analyzed by examining the serial position curve. We predicted that if nicotine was improving memory indirectly via attention, then the recall should be better in the later blocks of the list at a time when lapses in concentration would occur due to the length of the list. On the other hand, if nicotine was enhancing consolidation, then improved performance would occur in the early portions of the list. The results demonstrated a significant improvement on the early blocks of the list which indicated that nicotine could improve memory at a time when attention should have been at a maximum.

5. Nicotine and the Cognitive Deficits of Alzheimer's Disease

In the light of the findings of enhanced cognitive performance in healthy volunteers, it was of interest to know whether nicotine would have any effect on patients in the early stages of SDAT. Of significance for the therapeutic potential of nicotine, Wesnes and Revell (1984) had reported that nicotine antagonizes the scopolamine-induced deficits on the rapid visual information processing task and the Stroop task, a positive indication that nicotine may improve information processing in a deficient system.

In a study completed at the Institute of Psychiatry in London, the effects of subcutaneous doses of nicotine on information processing performance of patients with SDAT were examined (Sahakian et al, 1989; Jones, et al in press). Nicotine produced a dose-related improvement in performance in the detection of signals in the rapid visual information processing task, such that the performance of patients approached the performance of the healthy elderly control group. Nicotine also produced improvements in reaction times relative to baseline and placebo performances on this task. In a critical flicker fusion test run on the same patients, nicotine produced a dose-related improvement in the frequency with which the patients saw the lights as fused. Higher resolution of flashes is interpreted as improved cortical functioning.

The improved attention performance in this patient sample is the behavioural consequence of nicotine's effects on cortical functioning. Nicotine sustains release of acetylcholine at the cortex, and consequently lapses of attention and the concomitant variations in information processing normally observed (particularly in the patient group) are reduced. In a sense, nicotine "locks" the brain into a state appropriate for efficient information processing (Warburton, 1986; 1990).

6. Concluding Comments

The pattern of effects reported in experimental studies with young adults, the healthy elderly and patients with senile dementia of the Alzheimer type, is consistent with the view that nicotine can act as a cognitive enhancer.

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