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Retrograde facilitation of verbal memory by trihexyphenidyl in healthy elderly with and without the APOE ε4 allele

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Abstract

Retrograde facilitation (RF) of information learned prior to acute oral administration of trihexyphenidyl, a preferential muscarinic M1 receptor antagonist which impairs new learning, was studied in 24 healthy elderly subjects. The relationship between the RF induced by this anticholinergic drug and the APOE ε4 allele was also examined. Acute adverse performance effects of trihexyphenidyl (1- and 2 mg) were determined using the Buschke Selective Reminding Test administered pre-drug and at 1, 2.5, and 5 h post-drug. Recall of pre-drug words at the end of the fifth hour neuropsychological assessment (end-of-session recall) was of primary interest. Words studied before drug administration were better recalled following 2 mg trihexyphenidyl compared to placebo, and this RF effect was not affected by the APOE ε4 allele. Better recall of pre-drug words following 2-mg trihexyphenidyl was associated with a greater amnestic effect of this dose. Our findings demonstrated that RF induced by trihexyphenidyl was related to anterograde amnestic effects of the drug and resulted in part from drug-induced reduction of retroactive interference.

1. Introduction

Numerous studies have demonstrated that administration of the cholinergic muscarinic receptor antagonist scopolamine produces impairments in the acquisition of new information while having little effect on retrieval of previously stored information in humans (Atri et al., 2004; Hasselmo, 1995; Hasselmo and Wyble, 1997; Crow and Grove-White, 1973) and animals (Aigner and Mishkin, 1986; Aigner et al., 1991; Buresova et al., 1986). In a study with rats, Winters et al. (2007) reported a paradoxical facilitation effect of scopolamine on object recognition memory. Winters et al. demonstrated that presentation of an interfering object between learning phase and test phase impaired recognition

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performance in the test phase, but that infusions of scopolamine into the perirhinal cortex (PRh) prior to the presentation of the interfering object significantly reduced this impairment as compared to the infusion of saline. It was suggested that intra-PRh infusions of scopolamine disrupted the acquisition of interfering information, and therefore facilitated object recognition memory for material presented prior to the scopolamine infusion.

The curious phenomenon reported by Winters et al. following the administration of an anticholinergic compound is commonly referred to as retrograde facilitation (RF). Acute administration of agents that produce anterograde amnestic effects results in enhanced recall of information presented prior to drug exposure. RF has been widely observed with alcohol (Bruce et al., 1999; Knowles and Duka, 2004; Lamberty et al., 1990; Mann et al., 1984; Mueller et al., 1983; Parker et al., 1980; Parker et al., 1981; Tyson and Shirmuly, 1993) and benzodiazepines (Cahill et al., 1986; Chaves et al., 1990; Coenen and van Luijtelaar, 1997; File et al., 1999; Fillmore et al., 2001; Hinrichs et al., 1984; Unrug-Neervort et al., 1992; Weingartner et al., 1995; Pomara et al., 2006; Reder et al., 2007). The most parsimonious explanation for the RF associated with the administration of alcohol and benzodiazepines appears to be the interference reduction interpretation (Postman and Underwood, 1973; Postman, 1976; Wixted, 2004). This explanation contends that the enhanced recall of pre-drug information is the result of the anterograde amnestic effect of the drug and the consequent reduction of interference from new learning. Interference reduction has been employed to explain the RF effect of alcohol or benzodiazepines in many studies (e.g. Hinrichs et al., 1984; Mueller et al., 1983; Reder et al., 2007; Pomara et al., 2006). Nonetheless, some studies have suggested that benzodiazepines produced RF by directly enhancing memory retrieval (File et al., 1999) or changing retrieval strategies (Weingartner et al., 1995; Fillmore et al., 2001). Wixted (2004) has argued that agents that produce RF through a direct enhancement of retrieval should produce anterograde facilitation as well. However, there is no clear evidence showing that either alcohol or benzodiazepines produce enhanced recall of post-drug information.

The memory dysfunction associated with Alzheimer's disease (AD), the most common cause of dementia in the elderly, is thought to be related in part to central cholinergic system pathology (Bartus et al., 1982; Coyle et al., 1983). Post-mortem studies have indicated that the activity of choline acetyltransferase (ChAT), the biosynthetic enzyme for acetylcholine, and acetylcholinesterase (AChE), the enzyme that hydrolyses acetylcholine, are significantly reduced in the cerebral cortex and hippocampus of patients with AD compared to age-matched controls (Davies and Maloney, 1976; Perry et al., 1978; Davies, 1979). More recent studies have reported that the reduction of cortical ChAT activity or loss of cholinergic neurons may not be present until relatively late in the course of AD and that the cognitive decline in mild cognitive impairment (MCI) and mild AD may not be associated with these cholinergic deficits (Davis et al., 1999; DeKosky et al., 2002; Gilmor et al., 1999). Additionally, some studies based on patients who had advanced disease reported that AD patients who are carriers of the APOE ε4 allele, the major genetic risk factor for AD, have greater reduction in ChAT activity in the hippocampus, temporal and frontal cortex compared to AD patients without the allele (Poirier et al., 1995; Allen et al., 1997; Soininen et al., 1995), and that the reduction in ChAT activity in the hippocampus and frontal cortex was even greater in AD patients homozygous for the APOE ε4 allele (ε4/ε4) than AD patients who were heterozygous (ε4/ε3 or ε4/ε2) (Poirier et al., 1995; Soininen et al., 1995). However, other studies have found no clear relationship between the APOE ε4 allele and the reduction of cortical ChAT activity (Tiraboschi et al., 2004).

Cholinergic muscarinic receptor antagonists, such as scopolamine and trihexyphenidyl, have been used to model aspects of the memory and other cognitive alterations that occur with aging and AD. Older people appear to be more sensitive to the adverse effects of anticholinergic drugs on memory compared to the younger people (Tariot et al., 1996; Ray et al., 1992; Zemishlany and Thorne, 1991; Molchan et al., 1992; Flicker et al., 1992). Further, patients with AD are even more sensitive than normal elderly to the cognitive effects of anticholinergic drugs (Sunderland et al., 1987, 1988). These findings presumably reflect some reduction in central cholinergic function with aging and AD that may not be necessarily reflected by changes in cortical ChAT activity. Our previous study investigating the effects of the preferential muscarinic M1 receptor antagonist trihexyphenidyl on memory in healthy elderly with and without the APOE ε4 allele indicated that acute oral 1 mg dose trihexyphenidyl produced impairments only in individuals with the APOE ε4 allele and that 2 mg dose produced impairments in both APOE groups. Moreover, the memory impairments induced by the 2 mg dose of trihexyphenidyl were greater in individuals with the APOE ε4 allele as compared to those without the allele (Pomara et al., 2004). The greater sensitivity to the cognitive effects of trihexyphenidyl in cognitively intact elderly with the APOE ε4 allele may also reflect greater cholinergic abnormalities in this population or a less efficient compensatory CNS response to anticholinergic challenge associated with this allele (Pomara et al., 2004). Support for the potential clinical significance of our findings was provided by the results from a recently published multi-center study involving a very large number of community-dwelling non-demented elderly showing that the APOE ε4 positive females on long-term anticholinergic drug treatment experienced greater global cognitive decline than non-carriers during longitudinal follow-up (Carriere et al., 2009).

In the present study, we examined the performance effects of acute oral doses of trihexyphenidyl compared to placebo in healthy elderly to determine if RF occurred and if this phenomenon was influenced by the APOE ε4 allele. According to the interference reduction interpretation of RF, we predicted that the dose of trihexyphenidyl that produced anterograde amnestic effect would also produce enhanced recall of pre-drug words and that the RF effect might be more evident in the APOE ε4 carriers because, compared to the non-carriers, they experienced greater drug-induced anterograde amnestic effects possibly leading to greater suppression of retroactive interference.

2. Methods

2.1. Participants

The study was approved by the Institutional Review Board at the Nathan S. Kline Institute for Psychiatric Research and performed