

Apomorphine effects on episodic memory in young healthy volunteers

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Abstract

Rationale: Dopamine (DA) modulates working memory. However, the relation between DA systems and episodic (declarative) memory is less established. Frontal lobe DA function may be involved. We were interested in assessing whether apomorphine (Apo), a drug used extensively in clinical research as a probe of DA function, has an effect on episodic memory test performance in healthy volunteers.

Objective: To investigate the effect of a presynaptic dose of Apo on episodic memory tests and on other tests thought to be sensitive to frontal lobe functions.

Methods: Twenty healthy subjects were treated with Apo HCl (5 µg/kg sc) or placebo (10 subjects/group) in a randomized, double blind parallel group design and performance on a battery of cognitive tests was assessed.

Results: Apomorphine significantly impaired performance on tests of source recognition (d.f. = 19, $p = 0.05$) and item recognition memory (d.f. = 19, $p < 0.05$), and memory interference (d.f. = 19, $p < 0.010$). No significant change was found on other tests (Go/no-Go Test, Categorized Words, Stroop, Trail Making Test, and verbal fluency).

Conclusion: Findings in this small sample of subjects suggest that dopaminergic transmission affects episodic memory functions.

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1. Introduction

Pharmacological studies in both humans and animals have established a link between working memory functions and dopamine (DA) activity in the brain (Brozoski, Brown, Rosvold, & Goldman, 1979; Fournet, Moreaud, Roulin, Naegele, & Pellat, 2000; Robbins, 2000). Working memory refers to a memory system involved in the temporary maintenance and manipulation of information for behavioral purposes (Baddeley, 1992). In healthy humans, the administration of DA receptor antagonists improves working memory abilities (Luciana & Collins, 1997; Mehta, Swanson, Ogilvie, Sahakian, & Robbins, 2001; Muller, von Cramon, & Pollmann, 1998), whereas, the admin-

istration of DA receptor antagonists impairs working memory (Luciana & Collins, 1997; Mehta, Sahakian, McKenna, & Robbins, 1999). The association between DA activity and other memory systems is less clear. Little is known for instance about the role of DA in episodic (declarative) memory, the memory system responsible for the explicit and conscious recollection of events (Tulving, 1983). There is reason to believe that there may be a relationship as many dopamine receptors are found in areas of the brain known to be implicated in episodic memory. For instance, DA receptors are found in the prefrontal cortex (Grace, 2002), subcortical regions (caudate, putamen, thalamus, amygdala) (Gurevich & Joyce, 1999; Schatzberg & Nemeroff, 1995), as well as hippocampal regions (Ryoo & Joyce, 1994). Numerous lesion and neuroimaging studies have shown these same regions to be involved in episodic memory processing (Exner, Weniger, & Irle, 2001; Lepage, Ghaffar, Nyberg, & Tulving, 2000; Rugg, Fletcher, Chua, & Dolan, 1999; Tulving, 2002). Thus, a closer exam-

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ination of the role of DA in episodic memory is clearly warranted.

To date, only a few studies in humans have explored the effect of DAergic agents on episodic memory performance. L-Dopa improves word learning in normal humans (Knecht et al., 2004). However, L-dopa, a precursor of both dopamine and norepinephrine increases the turnover of both these amines and decreases the turnover of serotonin so that the transmitter mechanism subserving the effect of L-dopa on word learning is unclear. Schuck et al. (2002) reported that in 12 healthy male volunteers, episodic memory (immediate and delayed free recall tasks) improved after the administration of pibedil (3 mg i.v.), a DA receptor agonist acting on D2 and D3 receptors. However, pibedil is also an antagonist at alpha-2-adrenoreceptors, a factor that may have contributed to its influence on cognition (Millan et al., 2001). In studies using apomorphine (Apo), a direct DA receptor agonist, Friston et al. (1992) found that Apo (5 and 10 µg/kg sc) impaired the free-recall performance of 24 healthy male subjects on a word list memory test. Using positron emission tomography (PET), these investigators showed that this effect was associated with an attenuation of prefrontal dorso-lateral brain activity. In medicated patients with melancholic depression ($N=7$) and controls ($N=5$), Apo (2.5 mg/subject sc in the presence of domperidone) had no effect on cognitive task performance including the Rey Auditory Verbal Learning Task (Austin et al., 2000). In studies with DA receptor antagonists, chlorpromazine (D2 antagonism > D1) in doses of 12.5 and 25 mg had no effect on free recall and word completion tests (Danion et al., 1992) whereas haloperidol (D2 antagonism \gg D1) in a dose of 3 mg p.o. had a detrimental effect on immediate and delayed free recall tests (Rammsayer, Rodewald, & Groh, 2000). Neither chlorpromazine nor haloperidol are selective for DA receptors, both bind to adrenergic receptors amongst others.

At this point our understanding of the role of DA in episodic memory in man is limited by several factors. Such factors include the paucity of pharmacological studies, the subject population investigated (patients or normal subjects), selectivity of agents used to address DA function, and possible adverse action of drug side effects on memory performance. Also, some of the standardized memory tests used in previous studies may not have been optimal for the detection of subtle deficits. Given the density of DA receptors in the prefrontal cortex, memory measures that are thought to rely more heavily on prefrontal cortical functions may be more effective at detecting subtle between group differences. For example, source memory tasks, where subjects must retrieve (recollect) additional contextual information in order to make correct source recognition judgments, have been shown to rely on prefrontal cortical regions more than item memory tasks (Janowsky, Shimamura, & Squire, 1989; Mays & Daum, 1997). It is thus possible that measures of source memory would be more affected by an acute change in dopamine neurotransmission than measures of item memory. Similarly, other episodic memory tests, such as the AB-AC paired associate (memory interference) test and the categorized words test contain measures that have been shown to be sensitive to prefrontal cortical functioning (Gershberg & Shimamura, 1995;

Shimamura, Jurica, Mangels, Gershberg, & Knight, 1995). As such, these tests may be more informative about the relationship between DA and episodic memory than are other more traditional standardized memory tests.

In the present study, we evaluated the relationship between dopaminergic function and episodic memory using Apo (Lal, 1988). Apo is a highly selective agonist for D1-like (D1, D5) and D2-like (D2, D3, D4) receptors in animals (Seeman & Van Tol, 1994) and man (Tsang & Lal, 1977). Apo activates DA receptors at doses that do not affect norepinephrine (Butcher & Anden, 1969) or serotonin turnover (Lal, Sourkes, Missala, & Belendiuk, 1972). Apo stimulates both pre and postsynaptic DA receptors (Carlsson, 1977; de la Fuente-Fernandez et al., 2001). In man, Apo at low doses (3.5–5 µg/kg sc) (dose expressed as the salt, Apo HCl) stimulates presynaptically located DA receptors and thereby decreases DA release into the synaptic cleft, and hence, DAergic neuro-transmission whereas at doses of 7 µg/kg or higher Apo stimulates postsynaptically located DA receptors and increases DAergic neurotransmission (Lal et al., 1989).

We hypothesized that if DA function plays a role in episodic memory, then administration of a presynaptic dose of Apo would impair performance on tests of episodic memory. We did not test to see if postsynaptic doses of Apo would enhance episodic memory because such doses, especially 10.5 µg/kg, induce uncomfortable side effects (Lal et al., 1989) and hence adversely affect test performance. Also, we hypothesized that given the high concentration of DA receptors in the prefrontal cortex, DA function might subserve other prefrontal cognitive functions and therefore show impairment when DA neurotransmission is decreased.

We report our findings on the effect of Apo HCl (5.0 µg/kg sc) in healthy volunteers on three episodic memory tests (Source and item recognition test, Memory interference test, Categorized words test) and other cognitive tests thought to be sensitive to frontal lobe functions (Stroop Test, Go/no-Go, Trail Making Test, and Verbal Fluency). We expected to observe significant group by memory condition interactions on all three of our memory tests. More specifically, we expected the administration of Apo to lead to lower performance on source recognition relative to item recognition, memory interference relative to no memory interference, and on recall of categorized words relative to non-categorized words. With regards to the other cognitive tests, we expected measures of prefrontal function to be disrupted by Apo but not placebo.

2. Method

A double blind, placebo-controlled, parallel group study with planned randomization and stratification by gender to ensure equal numbers and sex distribution per group was undertaken.

2.1. Subjects

Twenty right-handed, healthy, paid volunteers (10 men and 10 women) participated in the study (Table 1). Selection criteria were: (1) no past or present psychiatric disorder as assessed with the Structured Clinical Interview for DSM-IV-TR, Non-Patient version (SCID-I NP) (First, Spitzer, Gibbon, & Williams,

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