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Pharmacology of human memory and cognition: illustrations from the effects of benzodiazepines and cholinergic drugs

J. M. Danion¹, H. Weingartner², S. E. File³, R. Jaffard⁴, T. Sunderland³, E. Tulving⁶ and D. M. Warburton⁷

¹Département de Psychiatrie d'Adultes, Service de Psychiatrie I, Hôpitaux Universitaires de Strasbourg, 1 place de l'Hôpital, BP 426, 67091 Strasbourg Cedex, France, ²NIH/NIMH, Building 10, Room 3B19, and ⁵Room 3D41, Bethesda, MD, 20892, USA, ³Psychopharmacology Research Unit, UMDS, Division of Pharmacological Sciences, Guy's Hospital, London SE1 9RT, UK, ⁴Laboratoire de Neurosciences Comportementales et Cognitives, Avenue des Facultés, 33405 Talence Cedex, France, ⁶Rotman Research Institute, Baycrest Centre, 3650 Bathurst Street, North York, Ontario, M6A 2E1, Canada and ⁷Human Experimental Psychopharmacology, Building 3, Early Gate Whiteknights, Reading RD6 2AL, UK

The current research methods, findings and questions that are being addressed in studies of the pharmacology of human memory and cognition are reviewed. Memory is not a unitary function. Neuropsychological studies of brain-damaged memory-impaired patients, as well as neuroimaging and drug studies in normal individuals indicate that different forms of learning and memory are subserved by different brain systems. Animal drug studies have also provided evidence that, while distinct, memory systems are not independent, but operate in close interaction with one another. Recent human studies of benzodiazepines and of cholinergic drugs demonstrate the value of the psychological models and of the experimental paradigms that are available from cognitive sciences for exploring how drugs alter cognitive and memory functions. They also show how drugs can be used as tools for analyzing the distinct neurochemical mechanisms underlying independent cognitive processes, and so find effective drugs rationally from a knowledge of the neurochemical bases of cognition. This research leads to specific recommendations concerning treatments that may improve memory functioning, for instance in Alzheimer's disease.

Key words: memory; cognition; benzodiazepines; cholinergic drugs; human; Alzheimer's disease

Introduction

Cognitive neuroscience methods and theory have been increasingly useful for defining psychoactive drug-induced changes in memory and related cognitive functions. Unlike brain lesions, drugs provide us with a vehicle for producing reversible graded 'lesions' and, as such, subjects can be studied as their own controls under a variety of replicable experimental conditions. This is one of the reasons why psychoactive drugs are also useful tools for exploring the determinants and mechanisms of memory functions.

At a recent CINP symposium, the authors reviewed some of the current research methods, findings and questions that are being addressed in studies of the pharmacology of human memory and cognition. The focus of the presentations included a consideration of the research strategies that are useful for exploring how drugs, such as the benzodiazepines and cholinergic drugs, alter cognitive functions and the relevance of this research for understanding both normal and impaired memory functions. Some of this research is also useful in

considering the value of treatments that may improve memory functioning. We emphasized the value of using a multidisciplinary perspective, one that makes use of methods and theory that come from cognitive science and cognitive neuroscience, psychopharmacology, clinical neuropsychiatry and neuropsychology. The theme that was stressed by all of the symposium participants is that memory is not a unitary function. Different types of drug treatments can produce highly specific changes in some aspects of memory and related cognitive functions while sparing other memory domains. This is apparent in studies of unimpaired normal volunteers, cognitively impaired patients, as well as in rodents and other living organisms.

Specificity of memory effects

Models of human memory

A number of well developed models of human memory currently are being used and tested. All of them consider a variety of functions that make up memory, including

the acquisition, retention and retrieval of information, the use of habits, skills, knowledge and experiences. Evidence suggests that different forms of learning and memory are subserved by different brain systems.

There is as yet no general agreement as to how memory systems are to be classified. One possible classification scheme that makes sense in the light of available data, comprising five major systems, is summarily presented in Table 1. It represents an extension and elaboration of several early dichotomies, such as those between short-term and long-term memory (e.g. Shallice and Warrington, 1970; Waugh and Norman, 1965), episodic and semantic memory (Tulving, 1972), and procedural and declarative memory (Cohen and Squire, 1980). The five-system classification has been discussed by Weiskrantz (1987), Tulving (1991) and Tulving and Schacter (1992). It includes (1) procedural memory, (2) perceptual representation system (PRS) (Schacter, 1990; Tulving and Schacter, 1990), (3) short-term memory, (4) semantic memory and (5) episodic memory. Episodic and semantic memory share important features and may, for certain purposes, be grouped together under the category of declarative memory (Tulving, 1983; Squire, 1987).

Memory systems are described and differentiated from one another in terms of the kinds of behavior or cognitive information they support, their operating characteristics and their neural basis (e.g. Sherry and Schacter, 1987; Squire, 1987; Tulving, 1984; Tulving and Schacter 1990; Weiskrantz, 1987, 1990). Each of the five major systems shown in Table 1 encompasses a number of subsystems, not shown in the table. Different systems seldom operate independently. Indeed, they usually collaborate in the execution of tasks that confront the individual, in real life as well as in the laboratory. The untangling of the web of the intricate system/task interactions is a major objective of the systems-oriented research. The relevant evidence is gleaned from experimental and clinical observations, by practitioners in different divisions of neural, behavioral/cognitive and computational sciences. Pharmacological analyses have come to play an increasingly important role in this multidisciplinary endeavor.

Another frequently used classificatory distinction is that between implicit and explicit memory (Schacter, 1990). These terms designate two different forms of memory retrieval. Explicit memory designates retrieval

of stored information with, and implicit memory retrieval without, subjective awareness of the spatio-temporal source of the information. Thus retrieval from procedural, PRS and semantic memory is classified as implicit, that from short-term memory and episodic memory is classified as explicit.

The procedural system, with its numerous subsystems, is in a class by itself in that it is an action system whose operations are expressed in the form of changes in overt behavior, independently of cognition. The other four are cognitive systems that may function independently of overt behavior, although their operations are frequently revealed through behavior, including verbal reports. PRS is critically involved in perceptual identification of objects, as well as in perceptual priming, that is, the enhancement of the efficacy of such identification through experience. Perceptual priming—the non-conscious, early-developing, pre-semantic perceptual learning—was only recently discovered (for a brief history, see Polster, Nadel and Schacter, 1991). It is currently under intense experimental and theoretical study in cognitive neurosciences. Short-term memory, also referred to as primary memory or working memory, registers and retains cognitive information in a special state of ready accessibility, usually just for a short period of time after the admission of the information into the system. This readily accessible information can be used by central executive processes in ongoing cognitive operations (Baddeley, 1986).

Semantic memory makes possible the acquisition, retention and use of factual information about the world in the broadest sense. It also is believed to mediate conceptual priming. Episodic memory enables individuals to remember their personal past, that is, to consciously recollect experienced events and their settings as embedded in the complex matrix of other happenings in subjectively apprehended space and time.

The evidence relating to the neuroanatomical and neurochemical identity of the putative memory systems is still sparse, although some reasonably encouraging, suggestive data, converging on these systems, has been provided by studies of brain-damaged memory-impaired patients, as well as neuroimaging and drug studies in normal individuals. The currently available evidence suggests that the medial temporal lobe and diencephalic structures play a role in episodic and semantic memory, that extrastriate occipital regions may be involved in visual guided perceptual priming and that prefrontal regions probably participate in the operations of episodic memory.

Pharmacological studies in rodents have made a significant contribution to the understanding of different forms of memory and learning, and to the brain systems subserving them. These studies have also provided evidence converging on the idea that, while distinct,

Table 1 Classification of human memory systems

Major memory systems	Other terms	Retrieval
1. Procedural	Non-declarative	Implicit
2. Perceptual representation	Quasi-memory (QM)	Implicit
3. Short-term	Primary working	Explicit
4. Semantic	Knowledge	Implicit
5. Episodic	Autobiographical	Explicit

memory systems are not independent but operate in close interaction with one another. Thus, for instance, the very same treatments that facilitate acquisition in certain tasks can disrupt acquisition in others. These task-dependent bidirectional effects suggest that, in certain circumstances, one memory system can inhibit another one. This assumption is further reinforced by similar findings using either brain lesions (Eichenbaum *et al.*, 1988) or examination of training-induced alterations in hippocampal neurobiological markers i.e. synaptic excitability (Jaffard and Jeantet, 1981; Green, McNaughton and Barnes, 1990) or protein kinase C (Bank *et al.*, 1988; Olds *et al.*, 1990). Moreover, pharmacological experiments have shown that the effect of cholinergic drugs on retention performance depends highly on the retention interval (Deutsch, 1971; Stanes, Brown and Singer, 1976). Together with post-training lesioning experiments that result in extended temporally-graded retrograde amnesia (Cho, Béracochea and Jaffard, 1993), this suggests that, as time passes, brain mechanisms that sustain retrieval of the same information can change drastically. These findings indicate that memory systems cannot be viewed as stable entities over time. They illustrate both the interactive and fluid nature of memory systems.

Benzodiazepines and memory

Several groups of investigators have exploited cognitive methods in human studies of the effects of benzodiazepines on memory. Their research efforts have had two goals, one, to characterize the behavioral response to different benzodiazepines and, two, to use benzodiazepines as pharmacological tools that can be used to explore and test various models of memory. Some researchers have also tested whether the benzodiazepine-induced changes in memory mimic the types of memory dysfunctions that are expressed in cognitively impaired neuropsychiatric patients. The benzodiazepines might simulate, or model, the form of memory dysfunction, i.e. impaired acquisition of information in explicit memory tasks, normal priming and skill learning and normal semantic memory, that is expressed in the typical amnesic patient (File, 1992; Danion *et al.*, 1992; Weingartner *et al.*, 1992; Wolkowitz *et al.*, 1987). Damage to frontal lobe may mediate some of these selective memory effects in the amnesic syndrome. Interestingly, there is also some evidence that benzodiazepines may impair some frontal functions, e.g. recency judgements (File, Sharma and Shaffer, 1992). However, whereas benzodiazepines have been repeatedly shown to spare various forms of motor, perceptual and cognitive skill learning (Lister, 1985; Curran and Birch, 1991; Danion *et al.*, 1992), studies of the effects of these drugs on perceptual priming, and on retrieval processes, are more controversial. While diazepam seems devoid of action on perceptual priming

(Fang, Hinrichs and Ghonheim, 1987; Danion *et al.*, 1989, 1990), lorazepam does have a deleterious effect (Brown, Brown and Bowes, 1989; Knopman, 1991; Danion *et al.*, 1992), suggesting that the two benzodiazepines might have differential memory effects (Sellal *et al.*, 1992). In addition, there is evidence from recent studies with the benzodiazepine antagonist, flumazenil, that some benzodiazepines may have some disruptive effect on retrieval of information from episodic memory, even though this retrieval effect is much smaller than the impact of benzodiazepines on acquisition functions. The effects that are expressed at the time of retrieval depend on the task and the level of training and the time at which memory is tested. Also, the demonstration of a memory retrieval effect depends on the difference between the performance of benzodiazepine-treated groups given either placebo or intravenous flumazenil. Thus, it is crucial that effects are assessed after a sufficiently high dose of flumazenil to antagonize the benzodiazepine dose employed, and at a short enough interval after flumazenil administration to ensure its effects have not worn off (File, Skelly and Girdler, 1992). There was also some evidence that benzodiazepines may even disrupt retrieval of information from semantic memory (File, Sharma and Shaffer, 1992). However, this possibility needs further investigation and the effect is likely to be only minor. File suggested that the apparent sparing of semantic memory after administration of benzodiazepines could relate to the fact that benzodiazepines mainly impair acquisition. Unfortunately, there have been no systematic experiments on their effects on acquisition of semantic memory.

One of the unresolved issues in the study of the effects of drugs, particularly of benzodiazepines, on memory is the dependence of such memory effects on non-cognitive changes, such as the sedative effects of drugs. While in the amnesic syndrome there is usually little or no sedation or impairment of attention (Squire, 1986), the administration of a benzodiazepine to normal volunteers induces a dose-dependent increase in self-rated sedation as well as a dose-dependent impairment in explicit memory, these two effects being highly correlated (Hommer, Matsou and Wolkowitz, 1986). Thus it is possible that the cognitive effects of benzodiazepines as well as other drugs may be secondary to sedation and impaired attention (Curran, 1991). However, several recent studies as well as previously reported research would suggest that the sedative and memory impairing effects of benzodiazepines can be dissociated from one another (Hommer, Weingartner and Breier, 1993; Ghoneim *et al.*, 1981; File and Lister, 1982; Lucki, Rickels and Geller, 1986; Thiebot, 1985; Gentil, Tavares and Gorenstein, 1989; O'Boyle *et al.*, 1983; Dunton, Schwam and Pitman, 1988; Ghoneim, Dembo and Block, 1989; Birch and Curran, 1990).

Cholinergic system and allocation of resources

A somewhat different scheme for describing memory in normal volunteers, in cognitively impaired patients and in response to the administration of psychoactive drugs is based upon evaluations of the resources that must be allocated and used under a variety of information processing conditions. This approach to the study of memory considers the limitations of the resources available for information processing. Allocation of resources is under the control of the central executive system which is responsible for assigning resources for information processing in attention and working memory (Baddeley, 1986).

Warburton and his co-workers have shown that cholinergic blockade by scopolamine impairs performance on tasks involving sustained and selective attention. These effects can be interpreted as the drug depleting central executive resources in working memory (Rusted, 1988). In studies of long-term memory, it has been demonstrated that cholinergic blockade impairs acquisition and active retrieval, but not recognition of information from durable storage (Rusted and Warburton, 1988). Drawing these studies together, the effects of cholinergic blockade on human cognition can be accommodated within a resources model. The central executive mechanism has been linked not only to working memory, but to the supervisory attentional system and to the organization of information for durable storage. This is consistent with the theory that the cholinergic system is controlling the functional state of the cortex for processing.

Stimulation of the cholinergic system, by administration of nicotine, improves performance on tasks of sustained and selective attention (Warburton, 1992), and facilitates durable storage of information under conditions of both pre- and post-trial administration (Warburton *et al.*, 1986; Warburton, 1992). Warburton and co-workers have examined the extent to which these memory improvements are associated with enhancement of attention, rather than memory *per se*, by looking at the action of the compound under carefully constrained conditions (Rusted and Eaton-Williams, 1991; Rusted and Warburton, 1992). These studies indicate that the effects of nicotine on memory performance can also be accommodated within a resources model, whereby the enhanced processing efficiency can be explained in terms of nicotine increasing the available resources. An analysis of individual performance suggests that the deployment of these additional resources is under the strategic control of the individual. In summary, cholinergic drug-induced manipulations of cognitive performance provide more than confirmatory evidence of the modulatory role of that neurotransmitter system in human information processing. They show how drugs can be used as tools for analyzing

the neurochemical mechanisms underlying behavior and so find effective drugs rationally from a knowledge of the neurochemical bases of behavior.

In search of drugs that would improve memory

Cognitive enhancers is a term used loosely in the field of psychopharmacology to describe drugs which may enhance human memory in any of a number of conditions, ranging from normal forgetfulness to Alzheimer's disease. Until recently, discussions of cognitive enhancers focused primarily on three drug classes: vasodilators, metabolic enhancers and cholinergic agents. Today, this classification has been expanded greatly to include numerous neurotransmitter-specific agents, peptides, nutrients, vitamins, channel blockers, second messenger modulators, xanthenes and many other drugs.

Some recommendations

What do all these drug classes have in common? The answer is that they share very little; in fact, the nomenclature surrounding cognitive enhancers has become increasingly vague and unscientific. To correct this confusing situation, Sunderland suggested several recommendations. First, it is important to specify carefully the target illness and dependent variables whenever one is discussing cognitive or memory-enhancing drugs. It should not be sufficient to call a drug a cognitive enhancer without stating explicitly the conditions involved in the drug study, as there is no intrinsic reason why a drug which helps the memory disorder in stroke-related dementia should also be helpful in Korsakoff's disease or normal aging. Second, the population heterogeneity of patients suffering from nominally the same disease such as Alzheimer's dementia must be taken into account. This is one persistent problem that has hindered progress in development of drugs that may improve memory. Therefore it is not surprising that in many studies some patients improve, others are unaffected and some actually get worse in response to some drug manipulations. Third, the time course of a drug's effect should be emphasized in any discussion of memory enhancement. For example, a drug which improves the free recall memory of a normal elderly subject may show very different results in Alzheimer subjects when administered chronically, given that most memory problems of old age are longstanding and often progressive. The issue of time course is particularly important because therapeutic trials are likely to be chronic. Fourth, the range of drug effects across a spectrum of cognitive tests is extremely valuable in evaluating the general usefulness of any potential

memory-enhancing drug. Without such broad information, an isolated positive cognitive finding in either a human or an animal experimental model might be quite misleading. For example, where positive drug effects are apparent, improvements in memory may be attributable to changes in other cognitive functions such as attention rather than to a direct result of effects on the memory system; these effects may also be attributable to alterations in non-cognitive domains such as motivation and arousal. Whether cognitive memory-altering effects of drugs are a direct result of alterations in systems that are involved in memory, or are the indirect consequence of changes in other types of behavior, such as mood or attention, continues to be an important issue in current psychopharmacological research.

In summary, the study of cognitive enhancers is currently diffuse and poorly organized. Since memory problems are often the end-stage clinical symptoms of broad and pervasive pathophysiological processes, it is reasonable to predict that the etiologic underpinnings will be varied from one illness to the next. However, etiologic variability also suggests that pharmacologic treatments must be individualized, and one cannot assume that a single cognitive enhancer would be efficacious across multiple human conditions. Future study in this field must therefore recognize this tremendous diversity and focus on carefully-selected cognitive questions in well-identified populations.

Prospects and conclusions

A major challenge for brain research lies in the integration of our knowledge of memory processes gained from functional analyses of normal and memory-impaired individuals with our knowledge of brain structure, neurochemistry and neurophysiology. At this time, the neuroanatomical correlates and neurophysiological-neurochemical mechanisms of different forms of human learning and memory are still largely unknown, and the evidence that is available tends to be indirect. It is our view that pharmacological studies, in combination with neuropsychological studies of brain-lesioned patients, will become increasingly useful in uncovering those brain systems that play a role in mediating and modulating different forms of memory. Furthermore these drug manipulations in both normal volunteers as well as in memory-impaired patients will also provide us with additional information about how structures that are known to be important in memory are expressed in the acquisition, retention and retrieval of experience.

During the coming years what we know about the differentiated view of memory and other cognitive functions will also be put to good clinical use, especially when combined with the methods of neuropsycho-

pharmacology. For example some of the areas of research that are likely to benefit through the use of combinations of cognitive and pharmacological methods include: (1) pharmacological modeling of neuropsychiatric disorders such as dementias, amnesias and anxiety disorders; (2) the development of pharmacological challenge paradigms for helping to establish more precise neuropsychiatric disorder diagnosis; (3) the use of various brain imaging techniques in combination with specific cognitive and pharmacological challenges; (4) the development of memory-enhancing drugs using specific memory methods and measures that are crucial for interpreting whether a compound is likely to be useful; (5) the development of research strategies that can be used to bridge human and other animal research.

Address for correspondence

J. M. Danion
Département de Psychiatrie d'Adultes
Service de Psychiatrie I
Hôpitaux Universitaires de Strasbourg
1 place de l'Hôpital
BP 426
67091 Strasbourg Cedex
France

or

H. Weingartner
NIH/NIMH
Building 10
Room 3B19
Bethesda
MD 20892
USA

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