Psychological Medicine, 1987, **17**, 335–341
Printed in Great Britain

Vasopressin and memory: improvement in normal short-term recall and reduction of alcohol-induced amnesia

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SYNOPSIS The vasopressin analogue 1-desamino-8-D-arginine vasopressin (DDAVP) has been shown in healthy male volunteers to cause significant improvement in short-term memory and to reduce alcohol-induced amnesia. There was no significant effect upon semantic retrieval or simple reaction time. It was concluded that vasopressin benefited the initial processes of consolidation and learning, while the reduction of the amnesic effects of alcohol may support the contentions of other authors that the peptide improves memory in states of mild amnesia.

INTRODUCTION

Considerable research interest has focused upon the role of the neurohypophyseal hormone vasopressin in human memory processes. Interest has been encouraged by studies which have claimed that vasopressin can relieve the amnesia associated with various organic pathologies (Laczi *et al.* 1982, 1983; Legros *et al.* 1978; Oliveros *et al.* 1978), and facilitate memory in healthy volunteers (Beckwith *et al.* 1982, 1983; Weingartner *et al.* 1981). However, Fehm-Wolfsdorf and colleagues have pointed out that there are many negative findings which are directly contrary to those reported above (Fehm-Wolfsdorf *et al.* 1984, 1985; Franceschi *et al.* 1982: Jenkins *et al.* 1982).

It is difficult to determine the cause of such inconsistent results because of the great variation in treatment regimes, pathologies, memory tasks and vasopressin analogues examined in different studies. However, it will be argued here that many of the inconsistent effects of vasopressin may be due both to difficulties inherent in some experimental designs and the varying severity of amnesia in different patient groups.

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Methodological difficulties are illustrated by a number of studies. Beckwith *et al.* (1982) claimed to show a facilitative effect of DDAVP upon concept learning in normal subjects. However, the lack of baseline data in their separate-groups design does not determine whether the DDAVP group were simply better regardless of treatment. Baseline performance measures are essential for full evaluation of the effects of vasopressin in separate-groups designs.

In two studies, Laczi *et al.* (1982, 1983) claimed to demonstrate an improvement in visual, spatial and auditory memory due to lysine-8 vasopressin (LVP), 1-desamino-8-D-arginine vasopressin (DDAVP) and desglycinamide-arginine-8-vasopressin (DG-AVP) in normal and amnesic subjects. Their results conflict with those of Jenkins *et al.* (1982) who found that DDAVP had no effect on separate groups of healthy volunteers performing broadly similar tasks. However, vasopressin always followed placebo in the repeated-measures designs of Laczi *et al.* (1982, 1983) and the supposed beneficial effect of vasopressin may simply have been one of improved performance with continuing practice.

Beckwith *et al.* (1983) and Nebes *et al.* (1984) examined the influence of DDAVP upon short-term memory by use of the Sternberg recognition memory-scanning task (Sternberg, 1969, 1975). Sternberg (1975) suggests that recognition speed can be broken down into

separate components of retrieval, encoding and response selection time. Beckwith *et al.* (1983) and Nebes *et al.* (1984) concluded that DDAVP had its facilitative effect upon the retrieval component of the task, implying that the drug made retrieval faster. However, it should be noted that extensive research on the task has produced results which create serious difficulties for interpretation of recognition performance in terms of Sternberg's original concepts (see Baddeley, 1976). At best, therefore, the results of Beckwith *et al.* and Nebes *et al.* may suggest a non-specific cognitive-arousing effect, as implied by the study of LVP by Legros *et al.* (1978) which showed improvement across a number of cognitive abilities involving attention, reaction time, digit span and visual memory.

Nebes *et al.* (1984) also examined the effect of vasopressin upon long-term memory by use of a cued semantic recall task. As the authors pointed out, the very high error rates on the task, with both placebo and vasopressin, rendered the negative result inconclusive. However, semantic memory does provide a useful vehicle with which to examine the effect of vasopressin upon long-term retrieval because the subject is required to retrieve information which has been assimilated and stored prior to treatment with the drug. The problem of high error rates reported by Nebes *et al.* (1984) with their recall task, can be avoided by use of a semantic recognition task whose performance is characterised by low error frequencies. The latter task is employed in the present study.

The results of Beckwith *et al.* (1983) also illustrate a further important methodological difficulty in many studies of vasopressin. In common with many other research workers, Beckwith *et al.* (1983) employed a crossover design to present placebo and vasopressin. While the latter design does offer some advantages with respect to economy in subject numbers and a reduction in error variation due to between-subject differences, it also carries a significant penalty when tasks of cognitive or psychomotor performance are involved. There is clear evidence that the order in which a treatment occurs in the treatment sequence (i.e. placebo–vasopressin versus vasopressin–placebo) can significantly alter the effect of the treatment and obscure its true influence upon performance (Armitage & Hills, 1982; Hills & Armitage, 1979; Millar, 1983; Poulton & Freeman, 1966; Poulton & Edwards, 1979). Such asymmetries in treatment effects are hard to predict, but they often act to reduce the difference between treatments (Millar & Wilkinson, 1981; Poulton & Edwards, 1979). Thus negative effects of vasopressin which are based on crossover designs may be difficult to interpret (Fewtrell *et al.* 1982; Franceschi *et al.* 1982).

One solution to the problem is to use between-group designs, or at least to analyse crossover data for the presence of an order effect. Commendably, the study of Beckwith *et al.* (1983) was one of four crossover-studies of vasopressin which did analyse for order effects (Nebes *et al.* 1984; Eisenberg *et al.* 1984; Jennekens-Schinkel *et al.* 1985). Of these studies, two (Beckwith *et al.* 1983, and Eisenberg *et al.* 1984) noted significant order effects underlying the supposed improvement in memory due to DDAVP. For example, Beckwith *et al.* (1983) observed that DDAVP only improved memory when subjects had first experienced a session with placebo. However, the majority of researchers fail to account for treatment-order effects and, given the illustration by Beckwith *et al.*, must render uncertain the reliability of any improvement due to vasopressin in their results (e.g. Weingartner *et al.* 1981).

The severity of the amnesic deficit may be a further factor in the inconsistent effects of vasopressin. In a comprehensive review, Jolles (1983) has observed that vasopressin may only benefit patients suffering relatively mild amnesia. The hypothesis is difficult to evaluate because methodological problems of the type described above may obscure any effects due to different severities of amnesia. Moreover, patients with severe amnesia may also suffer from other pathological conditions which might mask any beneficial effect of vasopressin. Fehm-Wolfsdorf *et al.* (1985) therefore attempted to examine the hypothesis, unconfounded by such difficulties, by inducing a supposed minimal amnesic effect in normal subjects by preventing elaborative encoding of material during learning. While no significant effect was found, it is arguable that the encoding manipulation may have induced a change in memorization strategy, rather than a state of amnesia *per se*. Their results therefore leave open the question of whether vasopressin may be beneficial in cases of mild amnesia.

The present study was designed to re-examine the effects of vasopressin upon normal human memory and to reconsider its effects upon a state of mild amnesia. Short- and long-term memory functions were assessed by tasks which are known to give consistent results across a broad range of experimental conditions, namely short-term free recall of verbal lists and semantic recognition. As noted above, the latter task has the advantage of low error rates when compared to the semantic recall task used by Nebes *et al.* (1984). The effects of vasopressin upon mild amnesia were examined by inducing a transient amnesic state in normal subjects by ingestion of alcohol. The method has the advantage that the amnesia is unconfounded by medication and other pathologies that may accompany amnesia in clinical samples.

It was beyond the scope of the present study to examine the influence of different treatment regimes and vasopressin analogues. Therefore, the design attempted some standardization by employing one of the most commonly-administered analogues (DDAVP) at a typical therapeutic dose.

METHOD

The study was approved by the local Medical School Ethical Committee.

Subjects

Thirty-six healthy male medical students gave their informed consent to participate in the study. None was currently taking any medication. The sample size was determined by those who volunteered spontaneously to participate in response to advertisements posted within the medical school. Subjects agreed to avoid alcohol in the 24 hours preceding and following the study, and to fast (water only) for the 6 hours preceding treatment with vasopressin and ingestion of alcohol.

Tasks

Memory was assessed by two tasks. The auditory short-term memory task involved free recall of 15 twelve-word lists recorded on tape and presented over headsets at one word per 2s with a 20s inter-list interval. During each interval, subjects wrote down on response sheets as many words as could be recalled from the previous list.

Long-term memory was assessed by semantic recognition (after Millar *et al.* 1980) where a category name, e.g. 'Animal' is presented on a VDU along with a test word, e.g 'Horse', 'Table' etc. Retrieval is measured by the speed and accuracy of the vocal binary decision response (detected by throat microphone and voice key) as to the category membership of the test word. Retrieval 'depth' can be manipulated by presenting test words of differing 'dominance' (familiarity) within the semantic hierarchy (Battig & Montague, 1969). Increases in physiological arousal favour retrieval of 'high dominance' words (Millar, 1979; Millar *et al.* 1980). There was a total of 120 trials, a random half of which required 'high-', and the remainder 'low-dominance' retrieval. Within the factor of retrieval dominance, a further random half of the trials required a positive, and the rest a negative decision.

A task of simple, unprepared visual reaction time requiring a manual response (30 trials) assessed any non-specific arousing effects of the vasopressin.

Vasopressin and alcohol treatments

Vasopressin was administered intra-nasally as 40 μg of 1-desamino-8-D-arginine vasopressin (DDAVP, Ferring Pharmaceuticals Ltd.). The placebo vasopressin was administered in an identical manner.

Alcohol was administered as vodka at 2ml per kilo body weight in an equal volume of fresh orange juice. For placebo, water replaced the alcohol, 4ml of alcohol was floated on the surface of the mixture, and the drinking surface of the vessel was swabbed with neat alcohol.

Experimental design and procedure

A between-group design was employed to avoid the possibility of asymmetry in treatment effects associated with crossover designs described in the introduction. Treatments were administered according to a single-blind routine. Subjects were allocated at random to one of four, equal-sized groups which received one of the following four treatment combinations, where V = vasopressin, A = alcohol and P = placebo: V+A, V+PA, PV+A, and PV+PA.

Testing occurred in the afternoon in order to control for the known circadian variation in memory efficiency (Millar *et al.* 1980). Subjects

first practised on the three tasks. Baseline performance measures were then taken using tests parallel to those to be administered in the experimental session. Tasks were performed in a fixed order by all subjects, with a 2–3 minute break between each task. The order and duration of the tasks were: semantic recognition (8 min), short-term memory (12 min), and reaction time (5 min).

Following the baseline session, subjects were administered vasopressin or its placebo and, 2 minutes later, alcohol or placebo. Subjects were instructed to consume the drink over a period of about 10 minutes. An absorption period of 45 minutes followed during which subjects sat quietly reading. Blood–alcohol concentrations were then assessed by electronic breath analysis (Lion Laboratories Alcolmeter SD2) prior to the experimental session where the tasks, but not the actual stimuli, were identical to those in the baseline session. On completion of the experiment, subjects were paid £3.00. Subjects who had received active vasopressin were instructed to drink no more than two pints of fluid in the following six hours because of the moderate antidiuretic effects of the drug. If necessary, subjects who had received alcohol were driven home.

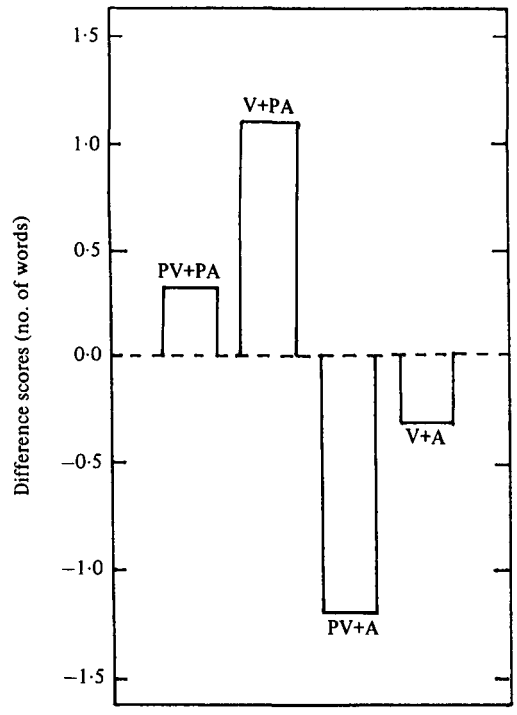

FIG. 1. Words recalled from short-term memory as a function of the treatment combinations of vasopressin (V), alcohol (A) and their placebos (PV and PA). Performance is expressed as difference scores between experimental and baseline sessions. Baseline = 0; positive difference scores indicate improvement in performance during the experimental session.

RESULTS

Prior to analysis of variance, performance on each task was expressed as the difference between baseline and experimental scores in order to reduce inter-subject variability (Hills & Armitage, 1979; Millar, 1983).

The factorial design of the experiment involved the following analyses. The short-term memory data conformed to a three-factor experiment with repeated measures on the factor of serial position. The analysis was identical to the 'case II' analysis described by Winer (1970, p. 337). The semantic memory data involved a similar analysis, the repeated measures being on the factor of retrieval dominance. Analysis of the reaction time data was for a simple two-factor experiment as described by Winer (1970, p. 228).

Short-term memory

The factor of serial position was not significant, nor did it interact with either of the between-group factors of vasopressin or alcohol. Therefore, for clarity, the data presented in Fig. 1 have been averaged across the factor of serial position, such that recall is shown simply as a function of vasopressin and alcohol treatment.

Fig. 1 reveals that vasopressin improved the short-term memory performance of the placebo–alcohol and alcohol groups when compared to groups treated with placebo vasopressin. The significant main effect of vasopressin ($F\ 1,32 = 4{\cdot}90$, $P < 0{\cdot}05$) and its lack of interaction with alcohol indicates that the facilitation by vasopressin was equivalent for the alcohol and placebo–alcohol groups relative to their control conditions. Reference to Fig. 1 confirms that the improvement in the memory of non-intoxicated subjects is largely similar in magnitude to the degree to which vasopressin reduces the memory deficit in alcohol-treated subjects.

Treatment with alcohol produced a mean

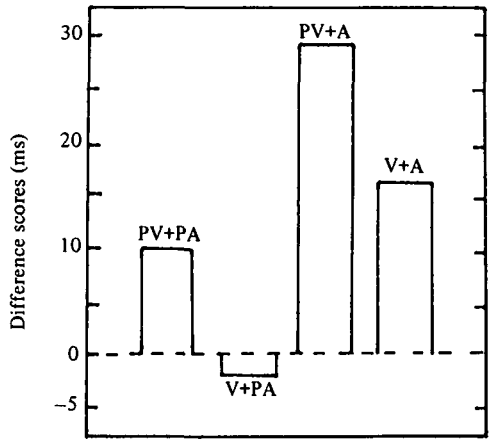

FIG. 2. Reaction time expressed as difference scores in ms between experimental and baseline sessions as a function of the treatment combinations of vasopressin (V), alcohol (A) and their placebos (PV and PA). Baseline = 0; positive difference scores indicate impaired performance during the experimental session.

blood–alcohol concentration of 65·5 mg prior to the experimental session. The two alcohol-treated groups did not differ significantly in their blood–alcohol levels. The significant main effect of alcohol ($F\,1,32 = 17{\cdot}10$, $P < 0{\cdot}005$) confirms many previous findings in demonstrating the adverse effect of the drug upon short-term memory.

Semantic recognition

Neither vasopressin nor alcohol exerted a significant effect upon semantic recognition, although decision latencies became generally longer with alcohol. The results are not considered further here.

Reaction time

Fig. 2 illustrates the significant increase in simple reaction time due to alcohol (main effect: $F\,1,32 = 10{\cdot}20$, $P < 0{\cdot}01$), a result that replicates many previous findings. Although some advantage can be seen for groups treated with vasopressin, neither the main effect of the factor ($F\ 1,32 = 3{\cdot}34$, $P < 0{\cdot}1 > 0{\cdot}05$) nor the interaction with alcohol ($F < 1{\cdot}0$) was significant.

DISCUSSION

The results confirm that a single treatment with 40 μg DDAVP can significantly facilitate human short-term memory processes. Use of the separate-groups design precludes asymmetries in performance that have obscured the results of previous studies which used repeated-measures designs. However, it should be noted that while the between-group design does obviate the problem of asymmetrical transfer of treatment effects associated with a crossover design, the practice period offered by the baseline session may serve partially to insulate subsequent performance from the treatment effects. It is, for instance, well-known that practice tends to blunt the sensitivity of a task to performance impairment (see Millar, 1983, 1986; Wilkinson, 1969). Therefore, the advantage of the between-group design must be balanced against a possible reduction in sensitivity to treatment effects due to practice. The same is, of course, true of the crossover design, where the effects of practice may also interact and become confounded with the treatment effects as the subject encounters one treatment after another.

One should also note that while vasopressin does facilitate auditory short-term memory performance, the result provides relatively limited insight because overall improvement in recall does not indicate which of the many processes in short-term memory may underlie the effect. Even if the serial position effect had interacted with vasopressin treatment, there would be reservations attached to unequivocal interpretation of primacy and recency effects in terms of long- and short-term memory processes respectively. Learning, and hence retrieval, also depend upon such processes as elaboration and articulation of material during encoding. Such processes may be affected in unpredictable ways when the subject is in an altered state due to drug treatment. Further experimentation would be required to manipulate systematically each process in order to determine its relevance to the present results.

When the significant effect of DDAVP upon short-term memory is contrasted with its non-significant effect upon long-term semantic recognition, the net result does imply a selective effect of DDAVP upon the initial process of learning or storage of material in memory. The non-significant effect of vasopressin upon semantic recognition is similar to that reported by Nebes *et al.* (1984) with a task of cued semantic recall but, at first sight, may be more reliable due

to the low error rates inherent in the recognition task. One should note, however, that the two tasks also differ in their retrieval requirements. In semantic recognition, presentation of the category name and test word are themselves retrieval cues to the word's representation in memory. The task of semantic recognition is then rather simpler than that of cued semantic recall and, as a consequence, may be slightly less sensitive to factors that may impair retrieval efficiency. Moreover, the recall of amnesic patients is known, under certain circumstances, to benefit from partial cueing (Graf *et al.* 1984; Meudell & Mayes, 1984). Consequently, the present negative result may not be entirely conclusive. Further experimentation might concentrate upon (non-semantic) recognition and recall tasks which are known to be sensitive to the amnesic deficit and which might more readily distinguish the effect of vasopressin.

The non-significant effect of DDAVP upon reaction time, when contrasted with the positive effect upon short-term memory, would seem to provide further support for a specific memory facilitation by DDAVP. However, DDAVP was associated with overall faster simple reaction times and the results of other research have indicated a more general facilitative effect of vasopressin upon alertness, attention and cognitive processes (Beckwith *et al.* 1982, 1983; Eisenberg *et al.* 1984; Fehm-Wolfsdorf *et al.* 1984; Legros *et al.* 1978). Nevertheless, one should note that vasopressin was not associated with any facilitation of response *speed* on the semantic recognition task, implying that any beneficial effect may extend only to basic reaction processes rather than to those concerned with memory retrieval.

The reduction by DDAVP of amnesia due to a moderate dose of alcohol may support some research workers (e.g. Jolles, 1983) who argue that vasopressin benefits cases of mild amnesia. The conclusion should be guarded because treatment with vasopressin did not interact with that of alcohol; the improvement due to vasopressin was similar in magnitude in both sober and intoxicated subjects. Moreover, it is evident that the transient amnesia induced by alcohol will not have the same basis as that due to many states of organic pathology. The result also leaves open the question of whether more profound amnesia is resistant to similar facilitation. One could not validly employ a high dose of alcohol to simulate such amnesia because of confounding with the inevitable adverse motor and emotional side-effects of severe alcoholic intoxication. While alcohol may, therefore, serve a useful function as an experimental model of amnesia, further studies must be required with clinical populations suffering closely-defined organic damage (van Wimersma Greidanus *et al.* 1983).

A final point attaches to the implications of the significant facilitation by DDAVP of short-term memory in the present normal sample. It is probably incorrect to regard DDAVP as a drug that evokes 'super-memory' performance without a cost. Facilitated consolidation of material due to DDAVP may bear the penalty of stronger proactive interference with later learning. Thus, for example, in a paired-associate learning task the vasopressin-treated subject may well learn the initial word pairings more efficiently but find it harder to learn new associations to the word pairs. Further studies of vasopressin in normal subjects might therefore consider the possibility that the beneficial effects of the peptide may only encompass a restricted range of experimental conditions.

Ferring Pharmaceuticals Ltd. kindly supplied the vasopressin and placebo. We are grateful to Dr Tj. B. van Wimersma Greidanus for helpful advice.

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