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ENHANCED RETENTION OF A SPATIAL DISCRIMINATION USING POSTTRAINING VASOPRESSIN INJECTION

by

MARK PAUL HAMMER

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

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DEDICATION

This thesis is dedicated to the blessed memory of my parents, who taught me that a little failure is nothing to be ashamed of and a thirst for knowledge was everything to be proud of. It is also dedicated to a scholar and humanist of the highest order - my best friend Leonard Greenberg, who faught the good fight, and whose courage and heart will see me through the next one.

ABSTRACT

The pituitary hormone vasopressin is believed to facilitate long-term retention of memory in animals. Published studies supporting this view have relied almost exclusively on the use of aversively motivated tasks. Attempted demonstrations of vasopressin enhancement of retention using appetitive tasks have yielded either negative outcomes or been confounded with various non-memorial factors. In light of this, some authors have suggested that vasopressin may only potentiate the learning or performance, but not long-term retention, of aversive tasks. This study demonstrates a limited enhancing effect of lysine-vasopressin (6ug/kg) on rats' long-term retention of a food-motivated spatial discrimination using retardation of reversal learning as the measure of retention. Drug treatment was found to interact with the amount of acquisition training subjects received. Appropriate methods for assessment of retention enhancement effects are discussed.

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Introduction

De Wied (1980) has claimed that the pituitary hormone vasopressin (VP) plays a role in normal memory storage and retrieval processes. Studies employing intraventricular injection (Davis, Pico & Cherkin, 1982; Koob, Le Moal, Gaffori, Manning, Sawyer, Rivier & Bloom, 1981; Bohus, Kovacs & De Wied, 1978), intranasal administration (Couk & Beckwith, 1982), and subcutaneous injection (Rigter, 1982; Vawter & Green, 1980; Ader & De Wied, 1972) of VP or its' synthetic analogs have generally reported some degree of improvement on various behavioural measures of retention and retrieval in animals, supporting De Wied's claim. The prevailing interpretation of these findings is that VP augments and enhances existing biological memory mechanisms. Although the exact neural mechanisms responsible for these effects have not yet been specified, preliminary evidence suggests that VP acts by facilitating transmission in central noradrenergic pathways originating from the locus coeruleus (Kovacs, Bohus & Vertseeg, 1979).

Due to the various criticisms that may be offered regarding both the administration regimens and assessment techniques employed, several authors (Gash & Thomas, 1983; Sahgal & Wright, 1983; Koob & Bloom, 1982) have questioned whether VP actually does have the effects on memory that have been claimed elsewhere in the literature. For example, claims of facilitation of retrieval are based on studies in

which subjects were treated with VP shortly before behavioural testing and demonstrated exaggerated responding on the behavioural measure of retrieval (e.g., Ader & De Wied, 1972). Support for a retrieval enhancement interpretation of these results would require that numerous performance effects, such as altered motor behaviour, are ruled out. Even though behaviourally effective doses of VP do not appear to bias the subject towards any particular response (Bohus, Ader & De Wied, 1972), one must be certain that no motivational component common to different responses is altered either.

Ettenberg, Van der Kooy, Le Moal, Koob and Bloom (1982) and Sahgal and Wright (1983) have recently suggested that peripheral injection of VP may produce an increase in arousal or an aversive state. Such a heightened state of arousal might increase the probability of any fear-motivated responding, regardless of the specific response requirements of the memory measure employed (e.g., freezing, cessation of drinking, running). Given a common motivational component, the independence of these various response measures may not be so easily assumed, and the validity of any claims for retrieval enhancement must be questioned.

Effects of VP on long-term retention (presumably reflecting the strength of initial memory formation) are typically assessed using either pre- or post-training drug

treatment. Retention testing follows after an interval deemed to be longer than the lifespan of the drug action. Heise (1981) noted that when a drug is administered prior to training, it may alter what the subject learns under the influence of the drug rather than how well the subject remembers what was learned. Consequently, where one is interested in long-term retention across days or sessions rather than effects on acquisition within a session, post-training injection is typically preferred. Post-training injection is assumed to influence only memory storage processes rather than the contents, and is generally accepted as a less ambiguous demonstration of putative memorial effects.

In the case of VP, objections have been raised to the use of post-training injection as well. Ettenberg, et. al., (1982) noted that post-trial injection of arginine-vasopressin (AVP - the form endogenous to rats) as a contingent unconditioned aversive stimulus, in the absence of any other aversive UCS (such as footshock or illness), would support appropriate passive avoidance behaviour in several different tasks.

One possible source of mediation for this action is the peripheral action of the hormone. Sharp, transient increases in systolic blood pressure have been noted in rats very soon after subcutaneous injection of AVP (Le Moal, Koob, Koda, Bloom, Manning, Sawyer & Rivier, 1981).

Chemical blockade of this peripheral effect either attenuates or markedly reverses the retention enhancing effect of AVP (Le Brun, Rigter, Martinez Jr., Koob, Le Moal & Bloom, 1983; Le Moal, et.al., 1981). Consequently, far from having an effect only on the strength of storage and not what is being stored, post-trial peripheral injection of VP may actually extend the training episode and be included in the training memory as an additional aversive UCS. As a contingent aversive stimulus, it would also be expected to show a a declining effect on subsequent performance as the training/treatment interval is increased. The possible similarity between a delay-of-reinforcement gradient and a memory consolidation time course would make it difficult to differentiate memorial from aversive effects of VP.

Appetitive Studies

The most obvious way to circumvent these problems and criticisms is to employ an appetitive task for the assessment of VP effects on memory. Ideally, responding for food or other reward should not be facilitated by conditioned or unconditioned fear, and should thus provide a useful measure of memory enhancement effects independent of effects on motivation. However, appetitive tasks may also be subject to confounding motivational effects. For example, Hostetter, Jubb, and Kozlowski (1977) trained rats

to solve a black/white T-maze discrimination problem and then measured extinction responding. The rats were injected with pitressin - a pituitary extract containing mostly VP - shortly before each session of either acquisition or extinction training. The authors reported a facilitation of retrieval (as measured by retarded extinction in subjects treated prior to extinction sessions) but no facilitation of acquisition or long-term retention (as determined by the extinction rate of subjects who received VP only prior to acquisition sessions). Oddly enough, enhanced retrieval was unique to the half of the VP-treated group that had initially been rewarded for running to the black goal arm.

Although this is ostensibly a food and not fear motivated task, the specificity of the drug effect is disturbing. Rats normally prefer and hide in dark places. If VP-treated rats increased their preference for the black arm during extinction training, this might be construed as a retrieval enhancement effect, but could just as easily be interpreted as performance mediated by increased arousal or fear. Clearly, appetitive tasks by themselves do not eliminate non-memorial interpretations nor do they provide unambiguous demonstrations of the behavioural effects of VP. As with aversive tasks, the design and specific outcome of any appetitive study is critical in determining what conclusions may be drawn.

Of the few published studies that have employed VP in

appetitive tasks, only eight have had design characteristics that might be deemed appropriate for assessing facilitation of long-term retention. Two of these studies have examined the effects of VP on acquisition of conditioned barpress responding for food reward. Alliot and Alexinsky (1982) trained rats to perform a barpress response for food using continuous reinforcement (CRF). A second group of subjects received CRF training and additional training on a GO/NO-GO discrimination using the established response, while a third group received CRF, GO/NO-GO and subsequent extinction training. Each group received saline or lysine vasopressin (LVP - a porcine form of vasopressin which is less peripherally active than AVP) injections immediately after each session in the terminal phase of the study for that group (CRF, GO/NO-GO or extinction). The authors reported that LVP administered after barpress acquisition sessions slowed acquisition, while LVP injected after extinction sessions hastened extinction. There was no drug effect on discrimination formation. Since LVP was injected post-session and each phase of the study required more than one session to complete, this study does not support the view that VP facilitates long-term retention.

Messing and Sparber (1983) examined the effects of peripheral injections of des-glycinamide lysine vasopressin (DGLVP - a peripherally inactive synthetic analog) on

acquisition and extinction of an autoshaped lever touching response. Although DGLVP was found to facilitate acquisition and retard extinction, drug treatment was prior to rather than following each session, making it difficult to use day to day performance as a compelling index of long-term retention effects. It should have been possible to assess long-term effects of pre-session DGLVP in acquisition on subsequent extinction sessions, but the authors neglected to include a group which received DGLVP only during acquisition. As a result, despite demonstrable influences on acquisition and retrieval, no conclusions about long-term retention may be drawn from this study.

Two studies have used nondiscriminative training. Koob, Ettenberg, Le Moal and Bloom (1982) injected nondeprived rats with AVP immediately after locating a drinking spout in a single "latent learning" trial in an open field. They noted a subsequent decrease in the latency to relocate a drinking spout when subjects were water deprived and placed back into the apparatus 48 hours later.

It is unclear whether decreased latencies necessarily reflect specific learning of the location of the water spout as opposed to some more general change in behavioural tendencies. VP has been shown to facilitate behavioural habituation to novel environments (Sadile, de Luca & Cioffi, 1978). Decreased latencies may have been due to habituation-related factors such as decreases in the

duration of each bout of exploration or simple reduction in irrelevent behaviours. Koob, et.al., did not report any data concerning activity or exploration by their subjects. Consequently, this study is also inconclusive despite its' positive outcome.

Garrud, Gray and De Wied (1974) trained rats to traverse a straight runway for food reward and failed to find any maintenance of rapid running in extinction when DGLVP was injected after each subsequent extinction session. Several reports (De Wied, 1971; King & De Wied, 1974) have noted that a single post-extinction injection of VP is successful in prolonging extinction responding. However, it is unclear, even if a study is successful, what one may conclude from this treatment regimen. Enhanced responding resulting from post-extinction treatment cannot rightly be considered a storage effect, since subjects are generally required to demonstrate a reasonable level of acquisition before proceeding to extinction (i.e., the target memory is already consolidated). On the other hand, post-extinction treatment occurs well before the next test session (usually at least 24 hours), making performance or retrieval effects unlikely. Just exactly what is being facilitated or impaired when VP is administered following extinction training, is a matter for speculation.

Four of the eight studies have employed a T-maze discrimination task to assess long-term retention effects.

Bohus (1977) trained male rats in a spatial (left/right) discrimination task using copulation reward and a combination of forced and free choice trials. Subjects were injected with saline or DGLVP immediately after each of four daily 4-trial sessions. Subjects were tested over the next two days without DGLVP in two 4-trial free choice sessions. Subjects treated with DGLVP after training sessions demonstrated better choice accuracy than controls.

There are several problems with Bohus' findings. Sara, Barnett and Toussaint (1982) noted that in Bohus' study, VP and control subjects behaved identically during the first three test trials. After the first three trials, however, saline performance drops well below chance, suggesting an avoidance of the rewarded side. Sara, et.al., question whether DGLVP has altered the subject's sexual activity or memory. Bohus' study may also be criticized on the grounds that drug and control subjects were not equated for performance levels prior to retention testing. It is possible that between group differences may have existed prior to drug treatment. Consequently, this oft-cited study does not provide strong evidence for enhancement of long-term retention.

The study by Hostetter, et.al., (1977), mentioned earlier, is flawed for reasons other than the specificity of the retrieval effect. In that study, the total number of trials required to reach an extinction criterion was used

as an index of retention. Subjects were given 10 trials per day, and if they chose the previously rewarded goal arm at least 6 times out of 10, they were automatically given 10 more trials the following day. Using this index, subjects scoring 6/10 on any given day would be automatically scored as having required at least 10 more trials to reach the extinction criterion than a subject scoring 5/10 for the same session. This method of scoring tends to inflate differences between similarly behaving subjects that are scoring only marginally above chance. This study, too, does not provide compelling evidence for either a storage or retrieval enhancing effect of VP.

Two of the maze studies employed a reversal learning measure. Discrimination reversal learning provides a useful measure of long-term retention. Impaired acquisition of a new and conflicting response may be taken as an index of a subject's tendency to remember (and thus perform) a previously rewarded response.

Reversal training has several important advantages over other methods of assessment. First, unlike avoidance tasks, subjects are forcibly exposed to the new contingency whenever they make a previously rewarded response. Second, unlike simple appetitive extinction, reinforcement is still available to the subject for correct reversal responses, and so may maintain vigourous responding. This would make it possible to distinguish between effects on choice

accuracy and effects on activity or motivation.

A third advantage is that one should still be able to assess retention enhancement even if such effects occurred in tandem with drug-induced changes in arousal or conditioned fear (there is no a priori reason to assume that such combined effects cannot occur). For example, post-session VP treatment may conceivably produce a generalized conditioned fear of the apparatus (via its' aversive peripheral effect). Although there may be a reduction in the overall rate of responding due to fear-induced freezing, one would still expect some ratio of correct to incorrect responses to be preserved. Conversely, a reduction in overall rate of responding without any alteration of choice behaviour during reversal would suggest very strongly that VP only has a punishing or aversive effect.

Couk and Beckwith (1982) trained rats to a performance criterion (9/10 correct) first on a black/white T-maze discrimination, and then on the reverse discrimination. Subjects received DDAVP (a more stable analog of AVP) intranasally 15 minutes prior to each session in both phases of training. Five days after reaching the reversal criterion, subjects were tested for long term retention of the reverse discrimination by giving them additional reversal training and examining rate of relearning. No drug was given during this phase. The authors reported a

nonsignificant trend towards facilitated acquisition of the original discrimination, and an initial impairment of reversal learning. There was no drug influence on relearning of the reverse discrimination. While providing some support for VP enhancement of retrieval (as suggested by initial impairment of reversal learning), there was no evidence to support the view that VP enhances long-term retention.

Sara, et.al., (1982) trained rats to solve a light/dark discrimination in a Y-maze. Nineteen days following discrimination training, subjects were given a retention test (relearning session). Twenty-four hours after relearning, subjects were trained to a performance criterion on the reverse discrimination. LVP was injected ninety minutes prior to each session throughout the entire study. Sara, et.al., found that LVP facilitated acquisition and impaired reversal of the light/dark discrimination but had no effect on long term retention of the original discrimination after nineteen days. Unfortunately, the study did not include any subjects which were tested on reversal learning without LVP. Although, this study demonstrates sound evidence of facilitated acquisition and retrieval, like the Messing and Sparber (1983) study, it also fails to demonstrate facilitation of long term retention.

Methodological Issues

As this brief review indicates, there is little clear evidence from appetitive studies to support De Wied's (1980) claim that VP facilitates memory storage and subsequent long-term retention. This does not necessarily imply that alternative interpretations such as those offered by Sahgal and Wright (1983) or Ettenberg, et.al., (1982) provide complete accounts of the available literature, whether appetitive or aversive. Rather, there may be certain procedural aspects of aversive tasks which are more appropriate for demonstrating retention enhancing effects.

For instance, examination of the aversive and appetitive literatures indicates that the tasks used in appetitive studies frequently require many more training trials than the tasks used in aversive studies. Passive step-through avoidance, a task frequently used in assessing VP effects, typically does not require more than three to five trials (including pretraining) to establish. This stands in contrast to the studies by Hostetter, et.al., (1977) or Couk and Beckwith (1982), in which many subjects received in excess of 60-100 training trials during acquisition. The lengthy training requirements of some appetitive tasks may impose certain conditions which are not conducive to either producing or demonstrating a retention enhancing effect.

One such factor may be the distribution of drug treatments. Where a particular task or the performance criterion employed in a study require that many trials be given, training and concommitant drug treatment is often split up into many sessions. For example, in the Hostetter, et.al., (1977) study, subjects received daily training session for up to seven days in some instances. Alliot and Alexinsky (1982) trained their subjects every day for 12 days of acquisition, while Couk and Beckwith (1982) trained subjects every day for an average of about 4-6 days during original learning and an average of about 12 days during reversal training. VP was administered in conjunction with every training session in these three studies and all of these studies failed to demonstrate any robust enhancement effects on either acquisition or retention.

One may justifably question whether VP administered repeatedly during the early stages of training has an effect equivalent to a single injection when training is confined to a single session or trial. It may be assumed that at each point in training prior to reaching the performance criterion, a subject is learning different aspects of the task and training situation, some of which may be irrelevent. If VP actually does facilitate memory, there is no reason why it should not facilitate irrelevent as well as relevent memories. Viewed in this manner, VP could conceivably impair acquisition if injected early on

in training (as in the Alliot and Alexinsky study). It is important to note that aversive studies typically employ a single drug treatment, regardless of the task or when the drug is administered (before or after training or extinction sessions). The difference in degree of success between aversive and appetitive studies, then, may be related to when and how often the drug is received rather than the motivational basis of the task used in assessment.

A second difference between successful and unsuccessful VP studies concerns the distribution of training. With two exceptions, appetitive studies typically require many training sessions. Sara, et.al. (1982), observed a facilitative effect of VP on acquisition, and an impairment of reversal. Unlike Alliot and Alexinsky (1982), Couk and Beckwith (1982) or Hostetter, et.al., (1977), Sara, et.al., employed a single injection and massed training session to assess VP effects on acquisition. Messing and Sparber (1983) also obtained enhancement of acquisition using massed training in conjunction with VP. The success of these two studies suggests that some types of VP enhancement effects (neither of these studies clearly demonstrated an effect on long-term retention) may require, or at least be favoured by, massed rather than distributed training.

One of the advantages that massed training may offer is that the subject may be expected to learn much about the

task within a single session. The change in acquisition level within the session occuring in conjunction with VP treatment may be crucial to producing retention enhancement effects.

There is some support for the notion that a subject should learn some minimum amount about the task in order for VP to be effective. King and De Wied (1974) varied the number of active avoidance trials subjects received (1-10) an hour after LVP injection. They found that added training potentiated the long-term effect of VP on avoidance retention and concluded that "...some measure of associative strength must be present before LVP is behaviourally effective in an active avoidance situation." (1974, p.1017).

In some active avoidance studies (e.g., De Wied, 1971; Koob, et.al., 1981), subjects are injected following the first extinction session and subsequently tested for continued avoidance responding in subsequent extinction sessions. These subjects are usually screened such that only subjects with 70% or more successful avoidances in the first (pre-drug) extinction session are treated and used for the remainder of the study. This type of screening assures that VP and saline control groups are both performing similarly, but it also inadvertently assures that subjects meet the "associative strength" criterion stated by King and De Wied (1974), since only subjects with

some mastery over the task are treated with VP and then tested.

The requirement of some minimal amount of learning may also be pertinent to passive avoidance studies. Noting that several studies which failed to demonstrate VP enhancement of passive avoidance retention also used minimal pretraining, Rigter (1982) varied the amount and kind of pre-exposure rats received for two days prior to a single passive avoidance training trial and post-trial AVP injection. He found that increased pre-exposure to the apparatus potentiated the enhancing effects of VP on long-term retention. Although this study used only a single training trial, making the distinction between massed or distributed training inappropriate, there are several aspects which Rigter's study might still have in common with both King and De Wied's study and the appetitive studies mentioned above.

Lewis (1976), noted that in studies using electro-convulsive shock to produce retrograde amnesia for passive avoidance, pre-exposure to the training apparatus drastically reduced the severity of the amnesia. He suggested that pre-exposure plays a two-fold role. First, pre-exposure permits the subject to acquire sensory information about the apparatus and general context of the task, reducing the amount of information the subject has to acquire on the subsequent training trial. Secondly, this-

sensory information provides a knowledge base or context within which the subject can nest new information. Both of these factors would tend to facilitate learning during a single passive avoidance training trial and reduce the disruptive effects of the ECS that follows the trial. Applying Lewis' analysis to Rigter's study, increased pre-exposure may increase the efficiency of subjects' learning on the single training trial preceding AVP injection, providing the measure of associative strength described by King and De Wied (1974).

Overall, then, VP appears most likely to facilitate retention in aversive tasks if there is a significant amount of learning prior to or shortly after the drug is administered. This learning can be potentiated by relevent pretraining, initial acquisition training without drug treatment prior to critical training and treatment or by massed training in conjunction with VP treatment. In appetitive tasks, VP appears most likely to facilitate acquisition, although not necessarily retention, if subjects receive a single drug treatment and undergo massed rather than spaced training.

Reversal and Retention Assessment

The elements of a study designed to produce enhancement of long-term retention in an appetitive task, then, would include a food-rewarded discrimination task with a choice component, with training confined to a single session, and

a single VP treatment immediately following the training session. Retention enhancement may be best assessed by examining discrimination reversal learning in a single session some period of time after drug effects are known to dissipate.

In visual discrimination tasks, reversal learning may be impaired, unaffected, or facilitated as training on the initial discrimination is increased, depending upon the task and training parameters employed (Sperling, 1965; Lovejoy, 1966; Mackintosh, 1969). Given these multiple effects, it is unclear in what direction a VP-treated subject's performance ought to go during reversal. To the extent that retention enhancement may mimic the effects of added training, the direction of drug effects on reversal may be ambiguous in some instances. If reversal of a visual discrimination is facilitated by post-acquisition VP treatment, it is unclear whether this would be due to enhancement and positive transfer, or to amnesia and reduced interference. Conversely, under some conditions, VP treatment could also impair reversal, relative to saline controls, for similar reasons (reduced transfer or increased interference). The concerns about amnesic effects are very real given that several laboratories have noted amnesia-like effects using high doses of VP (Gold & Van Buskirk, 1976; Cooper, McNamara, Thompson & Marsh, 1980; Hagan, Bohus & De Wied, 1982).

For these reasons, the choice of discrimination task and training/reversal parameters is of special importance. Literature reviews (Sperling, 1965; Lovejoy, 1966; Mackintosh, 1969) and direct tests (Mackintosh, 1969) have noted that, over a fairly wide range of values, facilitation of reversal by overtraining - the overtraining reversal effect or ORE - is only likely to occur if subjects are trained on a fairly hard discrimination with a large reward. The ORE is rarely found when using a small reward and has not been found in subjects trained on an easy task such as a spatial (left/right) discrimination (Sperling, 1965). If anything, overtraining of a spatial discrimination using a small reward typically retards reversal (Sperling, 1965; Mackintosh, 1969).

By using an easy task such as a spatial discrimination in conjunction with small reward, retention enhancement by VP would more than likely be reflected by retardation of reversal compared to saline controls at the same training level - a considerably less ambiguous outcome. A spatial discrimination task would therefore be the choice task of preference for assessing enhanced retention using a reversal measure. In addition to avoiding the dilemma of ambiguous results, spatial discriminations also have the advantage of being acquired quite rapidly, permitting massed training and psychologically meaningful variations in the amount of training within a single session. (The

comparison between VP enhancement and overtraining need not imply that VP specifically mimics the effects of increased training. Rather, the comparison between training and VP effects on reversal may serve primarily a heuristic value in suggesting other relevent variables for study.)

Although not a sufficient condition to compel an enhancement of retention interpretation, it is nonetheless a necessary condition that a target memory, capable of being enhanced, be demonstrable. In the absence of such a demonstration, drug effects may not be legitimately described as memory enhancement. Therefore, a subject trained on a discrimination task prior to VP treatment should be trained to some reasonable behavioural criterion which reflects at least a minimum level of acquisition of the task (e.g. 8/10 consecutive correct).

METHODS

Subjects

Fifty-one adult male Holtzman rats (300-400gm) were maintained at approximately 80% free-feeding weight in individual cages. Sixteen of the animals had served as subjects in a taste aversion study several weeks previously, while the remaining animals were experimentally naive. All animals were handled every day for one week prior to the start of the study. One subject was deleted from the study due to illness.

Apparatus

Subjects were trained and tested in a wooden T-maze measuring 73cm x 12.5cm x 14cm along the stem and 63cm x 12.5cm x 14cm along each of the arms. The entire maze was painted grey. Manually operated guillotine-style doors situated in the stem and at the entrance to each of the goal arms were lowered behind the subject once all four of its limbs had entered a goal arm.

Food reward (one 45mg Noyes food pellet) was placed in a small glass dish (6cm across) located at the end of the correct goal arm. An unbaited dish was located at the end of the incorrect arm. Masking noise was provided by a loudspeaker in one corner of the room.

Drugs

Lysine-vasopressin (LVP) was the VP analog chosen for several reasons. First, LVP has been found to be behaviorally effective in many different tasks using a fairly standard dosage of approximately 6ug/kg. Second, LVP has roughly one third the pressor activity of AVP, reducing (although not eliminating) the possible role that peripheral effects may play. Finally, LVP is readily obtainable from commercial sources.

Immediately following the last training trial, subjects were injected subcutaneously in the nape of the neck (1ml/kg bodyweight) with freshly prepared lysine vasopressin (Sigma Chemicals; 6ug/kg bodyweight) solution or isotonic saline vehicle. Drug solutions were prepared by dissolving commercial LVP solution in plastic vials containing bacteriostatic saline not more than 90 minutes prior to injection. Injections were randomized by another person such that the experimenter ran each subject blind with respect to drug condition for the duration of the study.

Procedure

The overall sequence consisted of five phases over seven days; magazine training on Days 1-3, runway training on Day 4, discrimination training on Day 5, no treatment on Day 6, and reversal training on Day 7.

All subjects received magazine training consisting of three daily presentations of 10 food pellets in a glass dish in the home cage followed by reinforced runway training in the maze on the fourth day. Subjects were runway trained in the stem of the T-maze in squads of four. Each subject was placed in the start box and permitted to run to the end of the stem where it received 3 food pellets in a glass dish. This training continued until subjects required less than 10 seconds to reach and consume the food pellets on each of any two consecutive trials. Magazine training continued for a minimum of 4 and a maximum of 8 such trials. Animals which were reluctant to leave the start box or consume the food reward within 8 trials (n=6) were deleted from the remainder of the study.

The day following runway training, subjects received acquisition training on a spatial (left/right) discrimination in the T-maze. Each group was approximately counterbalanced for the number of subjects to be rewarded in the left or right maze arms. All subjects were trained in squads of 4 (two saline and two LVP) until they reached a criterion of 8 correct out of 10 consecutive trials (LOW training condition). Inter-trial intervals were approximately 2-5 minutes depending upon running speed. Immediately following the last training trial in either of these conditions, subjects were injected with either lysine vasopressin (LVP condition) or saline (SAL condition),

placed in the carrying cage, and returned to the home cage once all other subjects in that squad had completed training and been injected. Subjects with especially long choice latencies during acquisition (greater than 5 minutes) were deleted from the remainder of the study (n=4).

Half of the subjects were given an additional 20 overtraining trials (HIGH training condition) in an attempt to examine whether LVP enhancement would vary with the amount of training prior to drug treatment as in King and De Wied's (1974) study. Pilot data indicated that 20 trials would roughly double the number of training trials provided. In addition, the extra 20 trials could be used to confirm whether 8/10 correct was a valid index of acquisition and subsequent performance. Due to time constraints imposed by the preparation of the drug, each squad consisted of LVP and SAL subjects from only one training condition (LOW or HIGH).

Forty-eight hours after acquisition training, all subjects were trained in the same T-maze on the reverse discrimination. Reversal training was continued in the same manner as acquisition training until subjects reached a more stringent criterion of 9/10 correct.

RESULTS

One LVP/HIGH subject was deleted from both the acquisition and reversal analyses due to extreme scores. Using the Chebyshev correction (Larsen & Marx, 1981), this subject was found to be approximately 6.4 standard deviations from the recomputed mean for its' group (the probability of this occuring is assumed to be <.025). This, combined with the fact that its' deprivation weight was substantially lower than anticipated (below 70%) was felt to be sufficient grounds for deleting the subject. Deletion restored the homogeneity of variance for the 4 groups.

Acquisition

Overall, subjects required an average of 17.4 ($\pm$5.9) trials to reach the acquisition criterion. Within each training condition there were no differences in rate of initial acquisition between drug and control subjects (see Table 1). LOW subjects required slightly more training to reach the acquisition criterion than HIGH subjects (18.9$\pm$5.9 vs. 15.8$\pm$5.5 trials), but this difference was not significant, $F(1,35) = 2.88$, $p=.099$. The 20 additional training trials received by the HIGH training groups roughly doubled the amount of training they received relative to the LOW training groups. Performance by the HIGH training groups was maintained and in many instances improved, across the 20 additional training trials (mean of

86.9% correct), indicating that training to a criterion of 8/10 provides a valid index of some basic level of acquisition of the original disrimination. There were no differences in the number of errors committed up to completion of the criterion run during acquisition across either of the treatment variables. Left and right rewarded subjects did not differ in the number of trials to criterion (18.3±5.8 vs. 16.4±5.9).

Reversal

A two-way analysis of variance for the number of trials required to reach the reversal criterion of 9/10 correct (see Table 2) revealed a significant two-way interaction between drug and training, $F(1,35) = 4.72$, $p=.037$, but no main effect of either training ($F=1.12$) or drug ($F=1.24$). The interaction was reliable in that it also occurred earlier in reversal with less stringent criteria (e.g., 8/9, 7/8, etc.). Planned comparisons indicated that there was a significant drug effect in the LOW training condition, $F(1,35) = 5.23$, $p=.028$, but not in the HIGH training condition ($F<1$). A planned comparison between the two saline groups (SAL/LOW vs. SAL/HIGH) indicated that the added training was effective in producing impairment of reversal in saline controls, $F(1,35) = 5.36$, $p=.027$.

The fact that the two-way interaction was almost exclusively due to a single divergent group (SAL/LOW)

suggested that perhaps the two training levels did not introduce differing levels of acquisition. A main effect of training, however, was supported by the finding that SAL/LOW and SAL/HIGH groups differed significantly in the numbers of trials required to reach the reversal criterion (18.9 vs. 24.5) . Effects of training level were also supported by a two-way ANOVA for the number of errors committed during reversal up to and including the criterion run (see Table 3). This indicated a significant effect of training level, $F(1,35) = 6.201$, $p=.018$, but no interaction or effect of drug treatment.

Because groups differences may have existed early but not later in reversal, as suggested by Couk and Beckwith's (1982) study, an additional two-way ANOVA was performed on the number of errors committed during the first 10 reversal trials. This also revealed a main effect of training, $F(1,35) = 11.55$, $p=.0017$, but no effect of drug treatment or drug by training interaction ($F<1$ for each).

DISCUSSION

The results of this study indicate that injection of lysine vasopressin following acquisition training in a spatial discrimination task results in impaired reversal learning of that task, provided that subjects are not overtrained on the original discrimination. By examining choice behaviour, rather than simple GO/NO-GO responding as in some types of avoidance or appetitive extinction, enhancement effects are not confounded with effects on general activity or motivation. Moreover, because the use of an acquisition criterion means that subjects will have performed a run of correct responses immediately prior to injection, any punishing effects of drug injection should be reflected in a decreased occurence of the "punished" response. This latter effect was not apparent. No subject displayed any behaviour that could be construed as an avoidance of the previously correct goal arm. Therefore, these results are congruent with the view that vasopressin can enhance storage and retention of recently acquired information.

The positive outcome of the study is also congruent with the notion that VP is more likely to be effective when subjects receive massed training immediately prior to or shortly after injection. Sara, et.al., (1982) obtained a facilitation of acquisition using massed training but

failed to find a concommitant long-term effect. Although the outcomes of Sara, et.al., and the present study differ, this difference may be due to the retention intervals employed in the two studies. Sara, et.al., tested subjects for long-term retention 19 days after training and treatment, whereas the present study examined retention following a 48 hour interval. It is possible that the 19 day interval employed by Sara, et.al., was sufficient to produce substantial forgetting in saline and drug groups alike. The use of a 2 day retention interval in the present study may have eliminated such a floor effect on retrieval performance.

The most salient result of this study is the fact that the LVP/LOW, SAL/HIGH, and LVP/HIGH groups do not differ. One possible cause of this is that neither drug nor training condition produced any alteration of reversal, but between group differences may have existed prior to training which led to one group (SAL/LOW) being divergent. This is unlikely for several reasons. First, SAL/LOW and LVP/LOW did not differ with respect to intial acquisition rates (18.8 vs. 19.0 trials to criterion). Subjects for the study were collected over three separate replications with approximately equal distribution among all four drug/training groups in each replication. Consequently, any factor which may have differentiated subjects within any replication would only account for a fraction of the

subjects in any one group making it unlikely that the SAL/LOW or LVP/LOW constituted an aberrant and homogeneous group quite apart from treatment or training.

A second possibility concerns the likelihood that any group consistently received an improperly prepared drug solution. This is unlikely given that separate drug solutions were prepared for each squad of 4 subjects (two SAL + two LVP) over the entire course of the study (10 different batches of LVP solution).

In view of how the study was conducted, it seems unlikely that either the enhancing effect in the LOW condition or the null effect in the HIGH groups was due to either sampling error or differential drug treatment. In the absence of any alternative explanation, the interaction between drug and training may be assumed to be reliable.

A second potential reason for the presence of a drug effect only in the LOW condition is a simple ceiling effect. This constraint may take several forms. There may be a biological limit to how much memory consolidation may be facilitated. There may also be a limit as to how much the subject may learn during initial training. Alternatively, the strength or durability of storage may be unlimited for all intents and purposes, but the task is so easily acquired during reversal that large degrees of impairment (more than 25-30 trials) simply do not occur.

Hence, an important question to be answered is just how

much impairment is possible in general, whether by overtraining or other means? Mackintosh (1969) trained rats on a spatial discrimination using spaced (10 trials per day) training and a small (52mg) food reward until they reached a criterion of 9/10 correct and gave either 0 or 100 trials of overtraining. The acquisition scores were roughly comparable to the present study (approximately 19-20 trials to criterion), but the reversal scores were substantially higher with most subjects requiring more than 50 trials to reach 9/10 correct in reversal (at 10 trials per day). Overtrained subjects required slightly more trials (67 vs. 56) to reach the reversal criterion but this difference was not significant. Hill and Spear (1963) trained rats to a 9/10 criterion using two 10-trial sessions per day and noted that 140 trials of overtraining significantly increased the number of trials required to reach an identical reversal criterion from about 24 to 33.

Although these two studies demonstrate that overtraining of a spatial discrimination does not result in an ORE, they also suggest that even large amounts of overtraining (as in Hill & Spear, 1963) do not necessarily produce substantially greater retardation of reversal. However, it should be considered that use of a more stringent 9/10 criterion in acquisition will generally result in more trials being required to establish the initial discrimination than an 8/10 criterion such as in

the present study. In this case overtraining may only be be a relevent factor when compared against much lesser levels of acquisition.

Mackintosh's (1969) results indicate that simple left/right discriminations are not learned so easily that reversal is always rapid. In the present study, a minimal amount of overtraining was sufficient to produce increased impairment of reversal in saline controls (18.9 vs. 24.5 trials to criterion). These two factors suggest that at least some additional impairment may be possible with even greater training. Several factors such as the retention interval, and spacing of acquisition training differ between these three studies, though, making them difficult to compare (e.g., Mackintosh began reversal in the same session that the subject reached the acquisition criterion). Most unfortunately, the lack of a second level of overtraining in all three of these studies leaves the original question unanswered. Would a third group receiving greater overtraining in the present study (e.g., 60-80 trials) display even greater impairment of reversal as a result of overtraining? If so, would LVP-treated subjects be equivalent to controls? Although the use of a single overtraining group in the present study is, perhaps, a better design choice for demonstrating a simple two-way interaction, it limits hypotheses about why this interaction occurs and why there appears to be a limit to

VP's effects in the present study. Consequently, the interaction between LVP and additional amounts of training would be worth exploring in a further study.

Overtraining and Automaticity

A third, and somewhat more novel, interpretation of the limited nature of LVP effects in this study concerns the role of the post-session interval in potentiating LVP enhancement. The effects of post-training VP have been shown to decline as the training-treatment interval increases (De Wied, 1971; King & De Wied, 1974; Bohus, Kovacs & De Wied, 1978; Rigter, 1982). This time course has been interpreted as evidence for a physiological effect upon time-dependent memory consolidation processes (De Wied, 1980). Many authors, however, have questioned the general validity of conventional time course data as reflecting the period of neural fixation of long-term memory. Instead, it has been suggested that memory fixation is almost immediate, and followed by a variable interval during which the target memory is said to remain in an "active" state (Lewis, 1979; Spear, 1981). Within this framework, time dependent alterations of memory (amnesia or hypermesia) are presumed to reflect the duration of the interval during which it remains in this active state. At least part of what is added to the target memory during this interval may be said to result from the subject's own

rehearsal processes (for want of a better description, self-generated retrieval) immediately following the training episode (Spear, 1981).

Gordon (1983) has described the modification of the target memory during an active state as "updating", implying that subjects will add attributes to a target memory as time passes and thus insure its' recall through a multiplicity of retrieval cues. If overtraining alters post-training rehearsal, it might be expected to influence the extent and contents - the "updating" - of the target memory, and its' subsequent retrieval at the time of test. Thus overtraining may influence enhancement of the target memory.

In the human learning literature, prolonged training on a particular task frequently (but not always) produces the transition from "controlled" to "automatic" processing of events (Schneider & Shiffrin, 1977). "Automatic" behaviour is characterized by a reduction in rehearsal and attention (Schneider & Shiffrin, 1977) and a frequent decline in retention of automatically processed material (Kolers, 1975). To some degree, the behaviour of overtrained subjects could be described as having become more automatized. In this study, informal observation of subjects' behaviour revealed that upon completing the 8/10 criterion in acquisition, subjects tended to make their responses hesitantly, and frequently oriented, at the

choice point, alternately to each of the goal arms before choosing one. This is not an uncommon observation. By the end of overtraining, however, subjects ran immediately and directly to the correct goal arm (as might be expected of well-trained subjects).

Obviously one cannot infer equivalent cognitive processes in humans and rats on the basis of informal observation, however, prolonged training does produce changes in human information processing and may conceivably produce changes in animals as well. Aside from the number of trials received, the major pre-test dimension on which LVP/LOW and LVP/HIGH subjects differed was in their behaviour at the end of their respective training sessions. This may reflect underlying processes produced by differential training which, in turn, influence the effects of LVP. Whether the assumption of "automaticity" in rats is justified or not, the effect of overtraining on LVP enhancement remains open to empirical testing and should be examined over a broader range of greater and lesser amounts of initial training. Such an effect could conceivably account for the discrepancy between aversive and appetitive studies.

Arousal Mechanisms

How does this study address the questions raised about VP influencing memory via arousal processes? The authors

who have suggested an arousal interpretation (Sahgal & Wright, 1983; Gash & Thomas, 1983; Koob & Bloom, 1982) have not explicitly characterized their respective uses of the concept of arousal. The closest approximation, though, is perhaps that of a general stress-related behavioural arousal akin to Duffy's (1962) concept of "activation".

Sahgal and Wright (1983) noted bimodal effects (enhancement and impairment) of VP in passive avoidance and suggested that subjects would be differentially affected by VP injection, depending upon individual differences in arousal level prior to treatment. Specifically, underaroused subjects would benefit from an increase in arousal, whereas optimally aroused subjects would be impaired by a further increase in arousal. This is reflected by long and short passive avoidance latencies in their studies.

How might this observation be adapted to the present study? One might propose that the interaction between drug and training in the present study is due to subjects in the LOW condition being underaroused while HIGH subjects were at some higher point which is unaffected by an increase in arousal. As evidenced by spontaneous activity or other behavioural indices of arousal, there were no apparent differences in arousal between LOW and HIGH subjects in this study. Although choice latencies in the last 5 acquisition trials, had they been measured, would have

revealed a large difference between LOW and HIGH subjects, such differences are accounted for by time spent making false entries (fewer than 4 limbs) into each of the maze arms by LOW subjects rather than by any difference in overall activity.

Drug induced arousal may enhance retention by prompting task-related processing. Riccio and Ebner (1981) have suggested that some post-training hormonal treatments may mimic the internal "state" of the animal during training and facilitate memory by acting as a reminder or retrieval cue which would sustain task-related processing and rehearsal once the formal training episode is over. Indeed, this influence would easily provide an outcome consonant with the "aversive consequence" model of AVP effects (Ettenberg, et.al., 1982) without necessarily having to be a contingent punishing stimulus.

Post-session LVP could conceivably act in this manner, by maintaining an internal "state" similar to training but there is no obvious reason why it wouldn't act similarly at the higher training level as well. Moreover, in general, a VP "state" does not seem to be a crucial aspect of the training memory. Sara, et.al., (1983) found that subjects injected with VP prior to both training and retention testing did not show enhanced retrieval relative to subjects injected with VP prior to only training or testing.

Perhaps the simplest explanation of arousal effects would be that VP-induced arousal enhances consolidation processes via a direct or indirect biochemical action. If so, why wouldn't it do so at both training levels? One might suggest that consolidation reaches some asymptote between the LOW and HIGH levels of training, but the fact that the measure of consolidation - the rate of reversal - is subject to so much variation (in both directions), within the overtraining literature makes this hypothesis difficult to test, particularly within the framework of the present study.

Alternatively, one may discuss arousal at a more physiological level without invoking concepts deemed to be applicable to all events, such as consolidation. VP may conceivably influence, via its' noradrenergic modulatory action, the activity of pathways which mediate memory for the task. Kovacs, et.al., (1979), in reviewing the available literature, concluded that exogenous VP exerted its' memorial action at the forebrain terminals of noradrenergic cells emerging from the locus coeruleus (LC). Norepinephrine, and in particular, the dorsal noradrenergic bundle emerging from the LC and projecting to the cortex and cerebellum, has been implicated as having a role in some aspects of learning (Crow, 1968), although the nature of this role has been challenged (Mason, 1979) recently.

Tucker and Williamson (1984) have recently described a

different approach to noradrenergic cortical arousal mediated by LC activity. They suggest that norepinephrine (NE) does not potentiate a general cortical arousal, but rather, "enables responsivity to environmental stimulation, this form of neural control is inherently linked to external input...Because locus coeruleus neurons respond specifically to novel stimuli, some sort of habituation mechanism must influence either the afferents to the locus coeruleus or the responsivity of the locus coeruleus itself." (1984, pp.190). Thus, NE activity in higher centres (and presumably, VP modulation of it) may be determined by the novelty of current sensory input. Although VP does not exert its' action at the LC itself, VP potentiation of noradrenergic transmission would be modulated by whatever types of sensory input are likely to produce fluctuations in LC activity.

It is important to distinguish this type of arousal from other types. This gating action which Tucker and Williamson describe is not specific to any type of task or motivation, but might be influenced by events that are typical of certain training procedures. Indeed, facilitation or "arousal" of specific NE pathways is quite capable of occuring in parallel with, and relatively independent of, general behavioural arousal.

Training Regimen

It is of some concern that while one of the hypotheses of this study was that increased training would potentiate the enhancing effects of VP as in previous avoidance studies (Rigter, 1982; King & De Wied, 1974), the opposite result was obtained. This discrepancy may be at least partly attributed to what constituted "more" and "less" training in each of these studies. In Rigter's (1982) study, training consisted of a single step-through shock avoidance trial following various types of pre-training. Thus all subjects received the minimum amount of formal training that could be given. In King and De Wied's (1974) study, rats received between 1 and 10 active avoidance trials 60 minutes after LVP injection. An additional group of subjects was trained until they performed the first successful avoidance (to a maximum of 10 trials). VP-treated subjects receiving 10 training trials or trained until the first successful avoidance demonstrated enhanced retention compared to saline controls and all other VP groups. That is, simply beginning to acquire the avoidance was sufficient to potentiate VP enhancement.

In these two studies, the most training subjects received was little more than the minimum amount of acquisition training required to establish conditioning. In the present study, the minimum amount of training received was that deemed to represent a reliable index of

acquisition, with overtrained subjects being trained past this point. Where previous studies have examined variations in lesser amounts of training, the current study is concerned with greater amounts of training. The suggestion from this is that VP enhancement may be potentiated by extra training up to some point, but that memory will not be benefitted by VP once some degree of behavioural competence is reached.

In previous studies, there have been suggestions that VP enhancement depends upon the ease of the task employed, however these studies may have confounded task difficulty with amount of training. Sara, et.al., (1982) noted in their study that subjects trained to run to a dark maze arm for food reward did not show any evidence of facilitation of acquisition while subjects rewarded in a light arm did. Further analysis indicated that, overall, black rewarded subjects reached the acquisition criterion appreciably faster than white rewarded subjects. Sara, et.al., concluded from this that VP would benefit acquisition when a task was not easily learned. Hostetter, et.al., (1977) found that retrieval enhancement occurred for subjects which required fewer trials to acquire the task (black-rewarded). In each of these studies, the measure of task difficulty was essentially the number of acquisition trials the subject received. In the present study, the use of a left/right discrimination which was presumably devoid of

"preferred" cues (e.g., a dark goal arm) served to dissociate the task difficulty component from the degree of training component.

Comparing Aversive and Appetitive Studies

In comparison to the available literature employing aversive techniques, the results of this study are not especially robust. This may be construed as partial support for the hypothesis that VP's behavioural effects are mediated by its' aversive peripheral effects. Although there are sufficient logical and empirical grounds for rejecting aversive peripheral effects as the main factor in all forms of VP enhancement, there is no a priori reason why aversive peripheral effects of some analogs of VP could not co-exist with centrally mediated cognitive effects since there are both central and peripheral receptor sites for VP. The peripheral effects of VP, particularly analogs with greater pressor activity (AVP, DDAVP), may very well summate with true cognitive enhancement to maintain a bias in favour of aversively motivated behaviour, while not excluding less robust but "purer" memory effects in appetitive studies.

Alternatively, differences in assessment procedures used in appetitive and aversive tasks may be responsible for the differences in the magnitude of the VP effect. For example, in passive avoidance studies, a subject which has

wandered unharmed into a chamber where it was previously shocked may be more likely to wander in again the next time. A subject which remains outside the chamber until the cutoff time (typically 180 seconds) does not have any opportunity to discover the absence of shock and will likely remain outside the chamber the next time. In this manner, what may begin as a small difference (or no difference at all) at the beginning of testing, may result in substantially larger differences later in testing. Indeed, successful VP studies are frequently successful not in showing greater initial avoidance after VP treatment, but rather more sustained avoidance responding over tests. Thus, appetitive tasks (including this one) may not necessarily result in less robust enhancement. Rather, appetitive tasks (and the procedural differences between aversive and appetitive tasks) may simply provide a less biased measure of enhancement.

To summarize and conclude, subcutaneous injection of sine vasopressin immediately after a single session of food-rewarded spatial discrimination training in rats tend to result in retarded acquisition of the reverse discrimination 48 hours after training and treatment. This is congruent with the view that vasopressin and its' analogs can facilitate long-term retention of information independent of the motivational basis of the retention measure. Facilitation was absent in subjects receiving

extended acquisition training prior to drug treatment, suggesting that VP may not have any effect on memory when subjects are highly trained. These results prompt further investigation of the relationship between VP effects and amount of training in both appetitive and aversive situations.

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APPENDIX 1

GROUP MEANS AND STANDARD DEVIATIONS

TABLE 1

Trials to Criterion in Acquisition

	DRUG CONDITION	
	SALINE	LVP
TRAINING		
LOW	mean = 18.8 s.d. = 5.7 n = 10	mean = 19.0 s.d. = 6.4 n = 10
HIGH	mean = 16.8 s.d. = 7.3 n = 10	mean = 14.7 s.d. = 2.2 n = 9

TABLE 2

Trials to Criterion in Reversal

	DRUG CONDITION	
	SALINE	LVP
TRAINING		
LOW	mean = 18.9 s.d. = 6.1 N = 10	mean = 24.6 s.d. = 6.1 N = 10
HIGH	mean = 24.5 s.d. = 4.2 N = 10	mean = 22.7 s.d. = 4.9 N = 9

TABLE 3

Errors to Criterion in Reversal

	DRUG CONDITION	
	SALINE	LVP
TRAINING		
LOW	mean = 6.5	mean = 8.3
	s.d. = 3.1	s.d. = 4.1
	n = 10	n = 10
HIGH	mean = 10.5	mean = 9.4
	s.d. = 3.1	s.d. = 2.2
	n = 10	n = 9

APPENDIX 2

Analysis of Variance Summaries

TABLE 4

ANOVA SUMMARY - Trials to Criterion in Reversal

Source	df	MS	F-ratio	probability
train	1	32.7	1.118	0.298
drug	1	36.4	1.243	0.272
drug x training	1	138.04	4.719	0.037
error	35	29.25		

TABLE 5

ANOVA SUMMARY - Errors to Criterion in Reversal

Source	df	MS	F-ratio	probability
training	1	64.38	6.201	0.017
drug	1	1.35	0.129	0.721
drug x training	1	19.83	1.911	0.176
error	35	10.38		