Chapter II

Historical Resume

Vasopressin (VP), a peptide synthesized by the neurons in the hypothalamus, has well defined peripheral actions in regulating fluid and electrolyte balance and at high physiological titers in the blood it has a significant pressor activity. Based on their studies with rats, de Wied and his associates (1965, 1975, 1980) have developed the thesis that VP also plays a major role in the central nervous system's mediation of memory process.

In 1965, de Wied found that removal of the posterior pituitary interfered with the maintenance of a two-way active avoidance response. Although the lesioned rats extinguished relatively quickly, an extract of crude pitressin alleviated the deficient. On the basis of these results de Wied concluded that the poor performance was due to the absence of some principle present in the extract. This principle was later identified as VP—a posterior pituitary hormone. Subcutaneous administration of VP to normal rats improved active avoidance learning and conferred resistance to
extinction; moreover it had a long-term effect in that further administration was not necessary.

In 1975, van Wimersma et al. reported a temporal effect of VP on retention. Intracerebral vasopressin analogs prolonged extinction time for active and passive avoidance. Resistance to extinction of an active avoidance response was influenced by Lysine Vasopressin (LVP) only if treatment was provided shortly before or after effective avoidance responding. Treatment administered as much as 6 hours before or after avoidance training was ineffective in modifying the behaviour. Similar temporal relationship holds for the retention of passive avoidance behaviour as well.

Attempts have been made to identify the locus of action of VP in the brain by microinjection of LVP into various brain structures (van Wimersma et al., 1975). Application of this peptide to the posterior thalamic area, including the parafascicular nuclei increased resistance to extinction of the pole-jumping response. Kovacs et al. (1979), also reported that local microinjections of VP into the hippocampal dentate gyrus, the dorsal septal nucleus and the dorsal raphe nucleus facilitated
retention. However, injections into other regions of the thalamus, substantianigra, reticular formation and dorsal hippocampal complex were ineffective (van Wimersma et al., 1975). Lesions in the parafascicular nuclei reduced, but did not abolish the behavioural response to treatment with LVP, while destruction of the dorsal hippocampus and the amygdaloid complex abolished the memory consolidating effects (van Wimersma et al., 1976, 1979). This indicates that VP acts upon mid-brain limbic circuits including the septal and hippocampal structures to facilitate the storage and retrieval of acquired behaviour.

An interesting hypothesis concerning the possible mechanism by which VP may be altering memory processes has been proposed by Kovacs et al. (1979), who reported that both pretreatment with α - methyl-p-tyrosine, an inhibitor of catecholamine synthesis, and destruction of the dorsal noradrenergic bundle by means of 6-hydroxydopamine blocked the effect of VP on memory consolidation (Telegdy and Kovacs, 1979).

Alternations of the catecholamine turnover were also observed after intraperitoneal injections of LVP and microinjection of Arginine Vasopressin (AVP) (Kovacs et al., 1979 b). These alternations appeared to be
restricted to a few brain areas and did not involve the whole set of catecholamine neurons in the brain. Results indicate that VP requires an intact coeruleo-telencephalic noradrenergic pathway to facilitate memory. Changes in catecholamine turnover have also been studied following icv injections of VP at doses as high as 10-100 ng (Tanaka et al., 1977; Schulz et al., 1980). However at these dose levels, a variety of effects unrelated to memory consolidation and retrieval are also induced and it is not evident that the observed neurochemical changes are related to memory processes.

Recently some opiate peptides i.e., endorphine and enkephaline have also been found to act as transmitters in the nociceptive synaptic pathways. Although both these opiate peptides are secreted by the brain cells their highest concentrations are present in the pituitary gland (Waston et al., 1977; Bloom et al., 1977; Akil et al., 1978). In 1980, Izquierdo et al. demonstrated that post training injections of Leu-enkephalin impairs memory of both habituation and shuttle avoidance training. Low doses of endorphin when administered, either centrally or systemically, prior to training impair retention (Kastin et al., 1976; Riley et al., 1980; Kobb et al., 1981; Kovacs and de Wied, 1981;
A physiological interaction has been demonstrated between VP and the opiate peptides. Intravenous administration of β-endorphin results in the release of VP (Weitzman et al., 1977). Bloom et al. (1978), reported the existence of an enkephalinergic supraoptic neurohypophysial tract. They observed that distinct fiber-like processes within the posterior pituitary react to enkephalin antiserum. Further support for the functional interactions between vasopressin and endorphins is provided by the finding of impaired development of tolerance to the analgesic effects of morphine in HO-DI rats (de Wied and Gispen, 1976). Thus the facilitative effect of VP on memory might be mediated via the opiate receptors.

In an earlier report Donovan (1978) had reported that VP released within the brain and not that discharged into peripheral circulation seems to be important in influencing memory process, since intravenous administration of large amounts of antivasopressin serum, which brought about a marked increase in urine production, had no effect on passive avoidance. On the other hand intraventricular injection of the antiserum immediately after a learning trial, almost completely, abolished retention of passive avoidance behaviour.
However, a number of earlier investigators have reported the facilitative influence of VP even after peripheral administration. In 1969, de Wied reported that hypophysectomized rats showed marked impairment of learning and memory which could be reversed by peripheral administration of VP. Beneficial effect on avoidance, measured in terms of slower extinction and longer re-entry latencies were obtained with subcutaneous doses ranging from 20 ng to 5 μg (Ader and de Wied, 1972; Bohus et al., 1972, 1978; de Wied, 1976; Kovacs et al., 1979).

Later on, it was shown that either peripheral or intraventricular administration of VP shortly before or after a learning trial markedly delays extinction of active and passive avoidance in intact animal as well (Bohus and de Wied, 1966; de Wied, 1969, 1976; Ader and de Wied, 1972; de Wied et al., 1975). However, Hostetter et al. (1980), and Sahgal et al. (1981), found that subcutaneously administered LVP did not improve performance. Le Moal et al. (1981), studied the effects of peripheral administration of an AVP antagonist (1-deaminopencillamine - 2 - Co - methyltyrosine) arginine vasopressin, and found that this substance blocked the behavioural effects of AVP.

Although the results of investigations in which VP was administered peripherally appear to be conclusive in
themselves, the chance that the effect might be due to peripheral influence on other behavioural variables and not on centrally mediated memory processes cannot be ruled out. Peripherally administered VP does not cross the BBB (Vorherr et al., 1968; Zaidi and Heller 1974; Mens et al., 1980; Ermisch et al., 1982), at least not rapidly enough to be behaviourally effective (Pardridge, 1983).

However, a number of earlier investigators have reported that icv administration of VP into the lateral ventricle has about 1,000 fold greater behavioural potency as compared to peripheral administration (de Wied, 1976; 1977; Bohus et al., 1978). Resistance to extinction is also enhanced by icv administration of low amounts of VP, i.e. in the range 0.025-10 ng. These findings contradict the above view and indicate that the effects of both peripheral and central VP might be on the same mechanisms involved in mnemonic processing.

It has recently been reported that VP increases behavioural arousal, which, in turn, has an inverted U-shaped relationship with memory (Sahgal et al., 1982; Sahgal 1983; Sahgal and Wright, 1983). The arousal hypothesis postulated by Yerks and Dodson (1908) and expanded by Broadhurst (1957), Hebb (1966), Broadbent (1971), Eysenck (1982) and Sahgal (1982, 1983), proposes that VP administration
immediately after the learning trial increases arousal which thereby improves acquisition and consolidation of information in under-aroused subjects. Ettenberg et al. (1983), reported that low levels of arousal generally yield less effective performance as compared to moderate levels while a very high level disrupts test performance. Thus the visceral effect of peripherally administered VP can be viewed as an arousing event that only indirectly acts to improve learned performance.

An alternative way of describing the previously obtained results was put forth by Sahgal (1983). He observed that the peripheral and central effects of VP were quite distinct, but at times they sometimes produce identical results. Thus the peripheral administration of VP may be negatively reinforcing (aversive) thereby strengthening avoidance behaviour as measured by increased re-entry latencies. On the other hand, centrally administered VP may involve the central arousal mechanisms. This "dual model" hypothesis is consistent with the observations of Hebb (1966), Broadbent (1971), Eysenck (1982) and Sahgal (1982). Moreover, Bohus et al. (1978) found that oxytocin (OT) another neurohypophysial hormone had effects opposite to VP only when the peptides were administered into the ventricles. They argued that peripheral
administration may produce common metabolites, which then exert identical effects. Such findings indicate that distinction might have to be made between mechanisms affected by central and peripheral administration. The biological targets and underlying behavioural processes affected may be very different, although the observed effects may be similar.

However, the effect of VP is not limited only to aversively motivated tasks. It also has a facilitative effect on positively motivated tasks. Bohus (1977), and Kobb et al. (1981) reported that VP and its analogues can improve performance in a water rewarded and copulation rewarded tasks respectively. Although VP does not significantly affect memory consolidation in a food rewarded task when injected at the time of training, it does improve memory retrieval when administered during the extinction period (Hostetter et al., 1977). Ettenberg et al. (1983), reported positive effect of VP on open field activity behaviour. These investigations support the hypothesis that VP may influence memory by modulation of related states of emotionality, motivation, attention or arousal rather than by direct involvement in the retrieval and consolidation of information.
This memory modulatory role of VP is further evident from studies in which VP was reported to reverse the amnesia caused by a number of amnestic agents. It has been reported that VP and its analogues can protect against or reverse retrograde amnesia induced experimentally by Co$_2^+$ protein and noradrenaline synthesis inhibitors and electro convulsive shock (Lande et al., 1972; Flexner et al., 1977, 1978; Pfeefr and Bookin, 1978; Asin et al., 1980; Martin et al., 1981). Also, antivasopressin serum is capable of inducing an amnesia for passive avoidance training when injected into the brain (van Wimersma et al., 1976).

These investigations confirm the contention that VP modulates memory. This conclusion is further strengthened by a comparison of independent groups of mice, both of which received the effective dose of VP and differed only in their training procedure. Only mice receiving VP before testing and a specific pairing of shock with the dark side of the passive avoidance apparatus during training show a high latency to enter that side during the test session, indicating that VP did not non-specifically suppress behaviour.

This information, coupled with the evidence that VP affects the catecholamine systems in the brain (Kovacs et al., 1979; Telegdy and Kovacs, 1979), suggest that the
functional effect of endogenous VP on mammalian behaviour may be to enhance the ability of an animal to retrieve and utilize stored information. This idea has encouraged research both in animal (Ader and de Wied, 1972; Lande et al., 1972; Rigter et al., 1974; de Wied et al., 1976; Asin et al., 1980; Cooper et al., 1980), and human (Legros et al., 1978; Oliveros et al., 1978; Weingartner et al., 1981) subjects with congenital or functional disorders.

With the discovery of the brattleboro strain of rats which exhibits congenital hypothalamic diabetes insipidus (Valtin, 1967), another possible test of the hypothesis that VP is involved in memory processes became available. In rats of the brattleboro strain, severe hypothalamic diabetes insipidus is determined by a single autosomal locus. Homozygous diabetes insipidus (HO-DI) animals lack the ability to produce VP and its associated neurophysin (Valtin, 1962; Morris et al., 1977). As revealed by radioimmunoassay, the posterior pituitary of homozygous diabetes insipidus animals contains virtually no VP content of HE-DI rats is approximately 40% of that of normal brattleboro rats (van Wimersma and Wied, 1977) while the HO-DI rats lack cerebral VP (Dogterom et al., 1978). Thus the HO-DI rats seem to be a more suitable animal model for the study of the behavioural effects of VP than neurohypophysectomized rats.
De Wied et al. in 1975 reported that memory function of HO-DI rats for a single trial passive avoidance behaviour was impaired when tested 24 hours or more after training. VP administered immediately after the single acquisition trial restored the disturbed behaviour. This favours the idea that memory rather than learning is disturbed in the absence of VP. Indeed, full retention of passive avoidance behaviour is obtained in HO-DI rats when retention is tested shortly after the acquisition trial. Thus, the main disturbance is in the maintenance of an acquisition itself. This is also illustrated by the observation that HO-DI rats are able to acquire a conditioned avoidance response in multiple trial paradigms, albeit the rate of acquisition is slightly slower than in the HE-DI rats (Bohus et al., 1975; Miller et al., 1976).

Although the maintenance of acquired behaviour is severely disrupted in the HO-DI rats, it does not disappear completely (de Wied et al., 1975). The HO-DI rats display a certain level of passive avoidance response even at 24 hours after acquisition, although the retention is extremely weak. Bohus et al. (1975) explained that HO-DI rats display a pituitary-adrenal response during passive avoidance performance which shows a marked relationship with the avoidance behaviour. This suggests that the

The lack of an absolute retention deficit in passive avoidance behaviour is more clearly illustrated by the experiments of Bailey and Weiss (1979). The results of their experiments show that passive avoidance behaviour of HO-DI rats is poorer than HE-DI rats, but that the absence of VP is not associated with a total impairment. They suggest that factors other than the total deficiency of VP such as chronic elevation of plasma oxytocin levels (Valin et al., 1965; Dogterom et al., 1977) and the alternations in the adrenocortical function in growth and metabolism (Sokal and Sise, 1973; Dlouha et al., 1977; Laycock, 1977; Bailey and Waiss, 1981) might explain the behavioural characteristics of HO-DI rats.

Data obtained by Bohus et al. (1975) in multiple learning trial paradigms also show that HO-DI rats are able to acquire fear-motivated responses. Acquisition of a pole jump avoidance response is approximately similar in HO-DI and HE-DI rats. HO-DI rats display avoidance behaviour in shuttle box as well, although their rate of acquisition in this two-way active avoidance behaviour is slightly slower than that of HE-DI rats. Miller et al. (1976), also confirmed these results.
In contrast, Celestian et al. (1975) reported an unimpaired maintenance of a multiple trial conditioned avoidance response in HO-DI rats. Differences in behavioural performance were observed between HO-DI rats and HE-DI rats. The HO-DI rats did not achieve the high level reached by the HE-DI ones. However, HO-DI rats which did reach the learning criterion of conditioned avoidance responding retained more conditioned avoidance responses, reflected in a retarded rate of extinction of the response.

Experiments on human subjects also indicate that VP has a physiological role in learning and memory process. In the first investigation of the efficacy of VP in cognitively impaired subjects (Moeglen et al., 1977), VP was administered to three amnesic patients by means of intranasal spray. One male patient suffered from a syndrome reminiscent of Korsakoff's disease. This syndrome is often seen in subjects with a prior history of excessive and prolonged alcohol intake, and its primary feature is amnesia. Treatment with VP was prescribed at a dose of 11 I.U./day, divided among four nasal sprays. There was an improvement in both retrograde and anterograde amnesia within days and no relapse was observed even after termination of the treatment.
The use of VP in studies of memory function in humans, without clinical or with measured biochemical disturbances has suggested that intranasal administration of 16 I.U. of lysine-8-vasopressin significantly improved the performance of 12 patients on attention tasks, motor performance, and usual retention recognition and recall (Legros et al., 1978). VP has also been used with some success in the treatment of alcoholic as well as posttraumatic amnesia (Oliveros et al., 1978), Korsakoff's syndrome (Le Boeuf et al., 1978) and senile dementia (Oliveros et al., 1978).

Weingartner et al. (1981), studied four depressed patients, who had impaired cognition related to their disordered moods. After completing a period of baseline assessment of learning, memory and mood, the 1-desamino-8-D-arginine vasopressin (DDAVP) treatment was started. Three of the four patients demonstrated significant cognitive enhancement beginning two days after treatment (Gold et al., and Weingartner, 1979) and this continued for two weeks. This cognitive improvement was independent of changes in mood. Serial learning, a particularly difficult task for these patients (few reached criterion), was not similarly altered after DDAVP treatment. Only 4 weeks after active drug treatment had ceased did patients return to their baseline learning and memory performance. These changes in learning
and memory were not significantly correlated with changes in the severity of clinical depression, although some patients did spontaneously report feeling more activated while being treated with DDAVP. A second group of cognitively less-impaired mood disorder patients treated with DDAVP for much shorter period of time demonstrated a less robust and more variable learning-memory response to DDAVP treatment. DDAVP has also been found to reverse ECS induced retrograde amnesia (Gold et al., 1981).

Anderson et al. (1979) and Ehrensing et al. (1982), studied the effect of DDAVP on acquisition of avoidance tasks. They found that DDAVP improved learning in children suffering from the LesNyhan syndromes, and in adults who wished to give up smoking. Thus clinical reports appear to support the evidence from animal studies that VP and its analogues exert beneficial effect on memory.

Vojtěchousky et al. (1981), reported the effect of a vasopressin analogue N-alpha-glycyl-glycyl-glycyl-8-lysine vasopressin on amnesia. They administered this analogue to 6 male alcoholic Korsakoff's patients (aged 30-70) for 4 weeks. Findings from a visual memory test administered before and after treatment show significant improvement in spontaneous recall and discrimination in subjects treated with the vasopressin analogue.
Burish (1981), reported improved cognitive function of central diabetes insipidus patients when treated with a vasopressin analogue. Results indicate that subjects showed little change in their emotional functioning but significant improvement in some aspects of their cognitive functioning was observed.

From the above reviewed researches, it is evident that VP affects the acquisition and retention of a wide variety of appetitive and aversive tasks. It also helps in counteracting the amnesia associated with diabetes insipidus and Korskoff's syndrome both in animals and human beings. Although it does have a varied effect on the organism i.e. enhancement of motor activity, increases emotionality and attentional processes, its effect on memory appears to be due to an influence on the centrally mediated mnemonic processing.

We may now pass on to the next chapter dealing with the problem and hypothesis of present investigation.