Neuroscience Vol. 4, pp. 1529 to 1537
Pergamon Press Ltd 1979. Printed in Great Britain

COMMENTARY

THE EFFECTS OF VASOPRESSIN ON MEMORY PROCESSES: THE ROLE OF NORADRENERGIC NEUROTRANSMISSION

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The effects of posterior pituitary neuropeptides on learning and memory processes
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THE EFFECTS OF POSTERIOR PITUITARY NEUROPEPTIDES ON LEARNING AND MEMORY PROCESSES

DE WIED & BOHUS (1966) presented the first evidence that an extract of the posterior pituitary gland (Pitressin) causes long-lasting alterations in central nervous system (CNS) processes: pitressin-treated rats exhibited a delay in the extinction of an active avoidance reaction, and thus these rats maintained the previously acquired behavioural response for a considerably longer period. Subsequent experiments in De Wied's laboratory clarified that the active substance of the crude extract with the ability to induce the behavioural effects was vasopressin, a nonapeptide of hypothalamo-pituitary origin. Accordingly, administration of synthetic lysine^8-vasporessin likewise caused a long-lasting delay in extinction, even after a single treatment with the peptide (DE WIED, 1971). In agreement with these findings, avoidance latencies of one-trial learning step-through (BOHUS, ADER & DE WIED, 1972) or step-down (KOVÁCS, VÉCSEI, SZABÓ & TELEGDY, 1977; KOVÁCS, VÉCSEI & TELEGDY, 1978) passive avoidance reactions were also increased upon vasopressin treatment. Since active and passive avoidance situations require completely different motor patterns for correct perfomance (in order to maintain active avoidance extinction, the motor activity must be kept high; while to increase passive avoidance latency, a previously acquired behavioural response should be inhibited) these experiments strongly suggested that the neuropeptide might affect CNS processes other than motor performance.

Electrophysiological findings also indicate an action of vasopressin on the central nervous system: the neuronal activities of the hypothalamus and cortex (SCHULZ, UNGER, SCHWARZBERG, POMMRICH & STOLZE, 1971; BARKER & GAINER, 1974) as well as the hippocampal theta rhythm (BOHUS, URBAN, VAN WIMERSMA, GREIDANUS & DE WIED, 1978*b*) are influenced by the peptide.

Analysis of the behavioural data described above led to the conclusion that vasopressin facilitates memory processes (DE WIED, VAN WIMERSMA GREIDANUS, BOHUS, URBAN & GISPEN, 1976). With single treatments with the peptide at various time intervals after the single learning trial, the 'critical period' of the effect of vasopressin could be determined.

Treatment given immediately after the learning trial appeared to be the most effective, and, if the challenge was postponed until a few hours later, the effect was reduced. Finally, the effect of the peptide disappeared 6 h after the trial (DE WIED *et al.*, 1976). Since consolidation of memory (the process by which information endures over time; input stage of memory processes; labile phase of information processing) takes place within the first few hours after learning, the conclusion that vasopressin facilitates memory consolidation was justified.

If the peptide was administered shortly before the retention trial, the passive avoidance latency was again increased, and thus the effect reappeared (DE WIED *et al.*, 1976). This means that vasopressin affects not only consolidation, but also retrieval processes (the process by which acquired information is made available during recall; output stage of memory; readout mechanism).

Further evidence of the influence of vasopressin on memory processes was given by studies on retrograde amnesia. Inhibition of cerebral protein synthesis in mice, as well as CO_2 inhalation (inducing hypoxia) and electroconvulsive shock in rats, cause retrograde amnesia, provided the treatment is given in the labile phase after learning (MCGAUGH, 1973; MCGAUGH,

Abbreviations: α-MPT, α-methyl-*p*-tyrosine; 6-OHDA, 6-hydroxydopamine.

GOLD, HANDWERKER, JENSEN, MARTINEZ, MELIGENI & VASQUEZ, 1979; FLOHR, 1979 and the references cited therein). All these treatments induce amnesia by impairing either consolidation and/or retrieval processes (FLOHR, 1979). In support of the memory hypothesis, vasopressin and structurally similar vasopressin analogues were found to protect against puromycin-induced amnesia in mice (LANDE, FLEXNER & FLEXNER, 1972; WALTER, HOFFMAN, FLEXNER & FLEXNER, 1975) and against CO_2- and electroconvulsive shock-induced amnesia in rats (RIGTER, VAN RIEZEN & DE WIED, 1974).

Studies on human patients too confirmed the memory hypothesis. LEGROS, GILOT, SERON, CLAESSENS, ADAMS, MOEGLEN, AUDIBERT & BERCHIER (1978) and OLIVEROS, JANDALI, TIMSIT-BERTHIER, REMY, BENGHEZAL, AUDIBERT & MOEGLEN (1978) reported that treatment of human patients with lysine^8-vasopressin improves the ability to remember and substantially alleviates the clinical symptoms of amnesia (Korsakoff's psychosis, traumatic amnesia, etc.).

It is of interest to note that vasopressin is not the only peptide of the posterior pituitary gland that influences learning and memory processes. The other physiologically secreted neuropeptide, oxytocin, facilitates the extinction of an active avoidance reaction (SCHULZ, KOVÁCS & TELEGDY, 1974) and attenuates passive avoidance behaviour in various one-trial learning avoidance paradigms (KOVÁCS *et al.*, 1978; BOHUS, KOVÁCS & DE WIED, 1978*a*, BOHUS *et al.*, 1978*b*; TELEGDY & KOVÁCS, 1979*a*; DE WIED & BOHUS, 1979); thus, the two neuropeptides—oxytocin and vasopressin—affect behavioural processes in opposite ways. Behavioural analysis revealed that the effect of oxytocin too has a 'critical period' and that oxytocin interferes with both the memory consolidation and retrieval processes (BOHUS *et al.*, 1978*b*).

The opposite actions of the two neuropeptides have similarly been observed on other CNS processes, such as the brain-stimulation reward (SCHWARZBERG, HARTMANN, KOVÁCS & TELEGDY, 1976), hypothalamic neuronal activity (SCHULZ *et al.*, 1971), hippocampal electroencephalogram (EEG) (BOHUS *et al.*, 1978*a*) or heroin self-administration (VAN REE & DE WIED, 1977). Experiments on human patients are necessary, however, to study the clinical significance of the opposite effects of posterior pituitary neuropeptides on CNS processes.

CHANGES IN BRAIN CATECHOLAMINE METABOLISM FOLLOWING VASOPRESSIN TREATMENT

In spite of the well-documented observation that vasopressin facilitates learning and memory processes, relatively little is known about the biochemical mechanism by which the neuropeptide affects the central nervous system. In an early publication LANDE *et al.* (1972) reported that vasopressin treatment restores the memory in puromycin-induced amnesia. These authors concluded that the peptide affects memory processes by facilitating cerebral protein synthesis. More recently, this conclusion has been questioned by DUNN, IUVONE & REES (1976), who found that vasopressin did not influence the incorporation of [^{3}H]-lysine into brain proteins, while other neuropeptides (e.g. corticotrophin) did.

An alternative hypothesis has been proposed independently by KOVÁCS *et al.* (1977) and by TANAKA, VERSTEEG & DE WIED (1977*b*). These authors have shown that peripheral administration of lysine^8-vasopressin (KOVÁCS *et al.*, 1977) and intraventricular microinjection of arginine^8-vasopressin (TANAKA *et al.*, 1977*b*) affected the steady-state levels and the α-methylparatyrosine-induced disappearance of norepinephrine and dopamine from the striatum and some limbic midbrain areas. In the majority of these brain regions, the neuropeptide facilitated the rate of disappearance of catecholamines, which is thought to be proportional to the nerve impulse flow of catecholaminergic neurons. A detailed follow-up study by TANAKA, DE KLOET, DE WIED & VERSTEEG (1977*a*), using a sensitive microassay for catecholamines in individually dissected brain nuclei (PALKOVITS, 1973), revealed that the effect of arginine^8-vasopressin on the rate of disappearance of norepinephrine was restricted to 7–8 limbic midbrain and lower brain stem nuclei out of the 45 nuclei investigated (viz. in the dorsal septal nucleus, medial forebrain bundle, parafascicular nucleus, dorsal raphe nucleus, nucleus ruber, locus coeruleus, nucleus tractus solitarii). The rate of disappearance of dopamine was facilitated in two extrahypothalamic structures: the striatum and the dorsal raphe nucleus. These data suggested a relatively specific influence of the neuropeptide on catecholaminergic activity in certain limbic midbrain structures. That the peptide-induced alterations in cerebral catecholamine metabolism might be related to the action of the neuropeptide on memory processes was further substantiated by results of pharmacological experiments, using a submaximal dose of α-methyl-*p*-tyrosine (α-MPT), an inhibitor of tyrosine hydroxylase (SPECTOR, SJOERDSMA & UDENFRIEND, 1965). The drug lowered the norepinephrine and dopamine levels in the brain and prevented the facilitatory action of lysine^8-vasopressin on passive avoidance behaviour (KOVÁCS *et al.*, 1977) and on the extinction of active avoidance behavior (TELEGDY & KOVÁCS, 1979*a*). None of these data, however, specifically indicated the brain nuclei in which the peptide-induced changes in catecholaminergic neurotransmission are directly linked to the facilitation of memory processes.

Earlier data with electrolytic lesioning of brain structures or with local implantation of the peptide (VAN WIMERSMA GREIDANUS, BOHUS & DE WIED, 1972; VAN WIMERSMA GREIDANUS, 1975; VAN WIMERSMA GREIDANUS & DE WIED, 1976) pointed at a role of limbic midbrain structures (septum, hippocampus, thalamus, etc.) in vasporessin-induced facili-

tation of memory processes. Limbic midbrain structures were shown to play a role in the attenuation of memory processes following oxytocin treatment, too (KOVÁCS, BOHUS, VERSTEEG, DE KLOET & DE WIED, 1979*b*). Therefore, the primary interest focused on the changes of catecholamine metabolism in limbic midbrain areas.

In a combined behavioural and biochemical experiment, KOVÁCS *et al.* (1979*b*) studied the effects of minute amounts of arginine^8-vasopressin (25–50 pg) on passive avoidance behaviour and on the α-MPT-induced disappearance of catecholamines in individual brain nuclei. Vasopressin, microinjected immediately after a single learning trial into the dorsal septal nucleus, the dentate gyrus or the midbrain dorsal raphe nucleus, facilitated passive avoidance behaviour. Injected into the central nucleus of the amygdala or the locus coeruleus (A_6 catecholaminergic cell group), vasopressin failed to alter the passive avoidance reaction (Table 1). The α-MPT-induced disappearance of norepinephrine and dopamine was estimated 1 week after the behavioural experiment following a repeated microinjection of the peptide. Injected into the dentate gyrus (Table 2) or into the dorsal septal nucleus (Table 3), the neuropeptide caused *in situ* changes in the rate of disappearance of norepinephrine and facilitated norepinephrine metabolism in the midbrain red nucleus. Additional experiments (KOVÁCS *et al.*, 1979*b*) indicated that the increased rate of disappearance of norepinephrine in the nucleus ruber is a biochemical correlate of the facilitated avoidance behaviour, rather than a direct effect of the neuropeptide. These studies support the notion that noradrenergic neurotransmission in limbic midbrain structures is important for the effects of the neuropeptide on memory. In keeping with this suggestion, TANAKA *et al.* (1977*a*) and VAN REE, BOHUS, VEERSTEEG & DE WIED (1978) concluded that the altered catecholamine metabolism in lower brain stem structures (e.g. nucleus tractus solitarii), observed after intraventricular administration of the peptide, is related to other, non-behavioural effects of vasopressin, e.g. its action on blood pressure regulation.

THE ROLE OF THE COERULEO-TELENCEPHALIC NORADRENERGIC SYSTEM: LESION STUDIES WITH NEUROTOXIC COMPOUNDS

Although the previous experiments strongly suggested noradrenergic neurotransmission played an important role in the facilitated memory consolidation caused by vasopressin, this hypothesis needed further proof. The role of the coeruleo-telencephalic (dorsal noradrenergic) pathway was therefore studied in more detail, for two reasons:

(a) The cerebral sites in which local microinjection of vasopressin facilitates consolidation processes (dentate gyrus, dorsal septum, dorsal raphe nucleus), as well as the majority of the sites of the peptide-induced changes in norepinephrine metabolism after intraventricular (TANAKA *et al.*, 1977*a*) or intracerebral

TABLE 1. FACILITATION OF PASSIVE AVOIDANCE BEHAVIOUR FOLLOWING INTRACEREBRAL MICROINJECTION OF ARGININE^8-VASOPRESSIN

Site of injection	No. of rats	24 h Avoidance latency (median in seconds)
1. Dentate gyrus		
Saline	8	132
AVP	7	300*
2. Dorsal septal nucleus		
Saline	8	84
AVP	10	300*
3. Dorsal raphe nucleus		
Saline	8	76
AVP	10	274*
4. Central amygdaloid nucleus		
Saline	7	70
AVP	6	72
5. Locus coeruleus		
Saline	9	44
AVP	7	40

One-trial learning passive avoidance behaviour (ADER, WELINEN & MOLEMAN, 1972) was tested 10 days after implantation of cannulae. Arginine^8-vasopressin (AVP) was injected to the free-moving, alert animals immediately after the learning trial and the avoidance latency was measured 24 h following injection. The peptide was given bilaterally (25–25 pg in 0.5 μl), except in the dorsal raphe nucleus (50 pg unilaterally).

* $P < 0.05$. (Results are taken from the publications of KOVÁCS *et al.*, 1979*a*,*b*, with editorial permission).

TABLE 2. CATECHOLAMINE DISAPPEARANCE/RATE/TURNOVER/FOLLOWING LOCAL MICROINJECTION OF ARGININE[8]-VASOPRESSIN INTO THE DENTATE GYRUS

Brain nuclei	Norepinephrine turnover (%)	Dopamine turnover (%)
Locus coeruleus	91	83
Nucleus raphe dorsalis	93	103
Nucleus ruber	149*	98
Nucleus caudatus	n.d.	94
Nucleus parafascicularis	93	92
Dentate gyrus	138*	n.d.
Subiculum	106	n.d.
Nucleus septalis dorsalis	89	100
Nucleus septalis medialis	77	82

This table is based on the results given in the paper by KOVÁCS *et al.* (1979*b*). Repeated microinjection of 25–25 pg arginine[8]-vasopressin bilaterally into the dentate gyrus. The peptide was administered 30 min after an i.p. injection of 300 mg/kg DL-α-methyl-*p*-tyrosine, and the rats were decapitated 3 h after arginine[8]-vasopressin treatment. After isolated removal of brain nuclei (PALKOVITS, 1973), the catecholamine content was estimated with the radioenzymatic method, described by VAN DER GUGTEN, PALKOVITS, WIJNEN & VERSTEEG (1976). Norepinephrine turnover is expressed as percentage of the saline-treated controls. Higher values indicate facilitated disappearance (turnover).

* Significantly different from control; n.d., not detectable.

(KOVÁCS *et al.*, 1979*b*) administration of the neuropeptide coincide with brain regions which receive noradrenergic innervation from the A_6 noradrenergic cell group via the coeruleo-telencephalic pathway (DAHLSTRÖM & FUXE, 1964; UNGERSTEDT, 1971; JONES & MOORE, 1977; KODA, WISE & BLOOM, 1978).

(b) The coeruleo-telencephalic noradrenergic pathway plays a basic role in learning and memory processes (CROW, 1968; KETY, 1970). Although recent publications of MASON & IVERSEN (1975; 1977) tended to reject the importance of the dorsal noradrenergic bundle as a specific substrate of memory, these latter authors too concluded that the pathway is important in filtering out irrelevant stimuli.

Since the neuropeptide affects dopaminergic (TANAKA *et al.*, 1977*a,b*; KOVÁCS *et al.*, 1977; 1979*b*; TELEGDY & KOVÁCS, 1979*a*) and under certain circumstances serotoninergic (RAMAEKERS, RIGTER & LEONARD, 1977) neurotransmission as well, these mechanisms were also investigated. A lesion of the coeruleo–telencephalic projection by 6-hydroxydopamine (6-OHDA) results in a selective degeneration of noradrenergic neurons and in selective depletion of forebrain and brain stem norepinephrine levels, but not of the dopamine content (ROBERTS, PRICE & FIBIGER, 1976; MASON & IVERSEN, 1977; KOVÁCS, BOHUS & VERSTEEG, 1979*a*). This lesion completely prevented the facilitation of the passive avoidance be-

TABLE 3. CATECHOLAMINE DISAPPEARANCE (TURNOVER) FOLLOWING LOCAL MICROINJECTION OF ARGININE[8]-VASOPRESSIN INTO THE DORSAL SEPTAL NUCLEUS

Brain nuclei	Norepinephrine turnover (%)	Dopamine turnover (%)
Locus coeruleus	78	71
Nucleus raphe dorsalis	86	78
Nucleus ruber	130*	120
Nucleus caudatus	n.d.	106
Nucleus parafascicularis	93	71
Dentate gyrus	78	n.d.
Subiculum	114	n.d.
Nucleus septalis dorsalis	66*	112
Nucleus septalis medialis	96	87

For legend see Table 2.

haviour which occurs in normal rats following administration of the neuropeptide immediately after the learning trial (KOVÁCS *et al.*, 1979*b*). Thus, the action of the neuropeptide on consolidation processes depends on the intact coeruleo-telencephalic pathway. When the peptide was administered shortly (1 h) before the retention trial, vasopressin facilitated the passive avoidance behaviour significantly, although its effect was partially attenuated by the lesion of the dorsal bundle. 6-OHDA-induced destruction of the mesolimbic accumbens nucleus, or 5,6-dihydroxytryptamine-induced lesion of the dorsal raphe nucleus failed to interfere with the effect of vasopressin given peripherally, immediately after the learning trial (Table 4).

From these experiments it can be concluded that:

(1) The effects of vasopressin on memory consolidation and on memory retrieval processes most probably involve different neurotransmitter mechanisms: a lesion of the coeruleo–telencephalic pathway completely disrupts the consolidation effect and only partially attenuates the retrieval effect.

(2) The role of the coeruleo-telencephalic noradrenergic pathway in the consolidation effect seems to be rather specific: destruction of the dopaminergic or serotoninergic nuclei does not interfere with this action of the posterior pituitary neuropeptide.

NORADRENERGIC TERMINALS VERSUS CELL BODIES

Studies with local intracerebral microinjection of the peptide led to the hypothesis that noradrenergic terminals, rather than the cell bodies, are primarily involved in the vasopressin-induced alterations of norepinephrine metabolism and are thus responsible for the effect of the peptide on memory consolidation processes. This notion is based on the observation that vasopressin facilitates avoidance behaviour when injected into certain terminal regions of the dorsal bundle (dentate gyrus, dorsal septum, dorsal raphe), but not if administered into the locus coeruleus, the cell body area of the projection (KOVÁCS *et al.*, 1979*a*,*b*).

For further analysis of this hypothesis, the dorsal raphe nucleus seemed to be a suitable model system because: (1) the neuropeptide facilitates passive avoidance behaviour when injected into this area (KOVÁCS *et al.*, 1979*b*); (2) the serotoninergic cell bodies of this nucleus receive noradrenergic afferents from the locus coeruleus, and these noradrenergic terminals modulate the activity of the indolaminergic system (LOIZOU, 1969; JOUVET, 1969; KOSTOWSKI, SAMANIN, BAREGGI, MARC, GARATTINI & VALZELLI, 1974; ROIZEN & JACOBOWITZ, 1976; ANDERSON, PASQUIER, FORBES & MORGANE, 1977; PASQUIER, KEMPER, FORBES & MORGANE, 1977).

The effect of 50 pg arginine^8-vasopressin, administered into the dorsal raphe nucleus immediately after the learning trial, has been tested in chronically operated animals. A neurochemical lesion of the serotoninergic cell bodies by microinjection of 5,6-dihydroxytryptamine prevented the facilitation of passive avoidance behaviour otherwise caused by the peptide. Similarly, the effect of the peptide was abolished by destruction of the noradrenergic terminals in the

TABLE 4. NEUROCHEMICAL LESIONS OF VARIOUS NEUROTRANSMITTER PATHWAYS AND THE EFFECT OF ARGININE^8-VASOPRESSIN ON MEMORY PROCESSES

Lesioned pathway*	Neurotoxin† used	Monoamine‡ depleted	Time of AVP§ treatment	Memory process‖ affected by the neuropeptide	Facilitatory effect of the neuropeptide
Dorsal noradrenergic bundle	6-OHDA	NE	Post-trial	Consolidation	Absent
Dorsal noradrenergic bundle	6-OHDA	NE	Pre-retention	Retrieval	Partially attenuated
Nucleus accumbens	6-OHDA	DA	Post-trial	Consolidation	Present
Nucleus raphe dorsalis	5,6-DHT	5-HT	Post-trial	Consolidation	Present

Detailed data upon which this table is based published by KOVÁCS *et al.* (1979*b*).

* Lesioning of the pathways 10 days prior to the behavioural testing.

† 6-OHDA was injected bilaterally in doses of 10–10 μg; 5,6-DHT was given in an amount of 10 μg.

‡ Catecholamine (NE and DA) levels were measured 21 days after the operation and the monoamine content was estimated by the radioenzymatic microassay of VAN DER GUGTEN *et al.* (1976). The 5-HT depletion was controlled by the *in vitro* uptake of [^{3}H]5-HT in brain tissue slices, according to BLACKBURN, FRENCH & MERRILS (1967).

§ 5 μg arginine^8-vasopressin was administered sc. immediately after the single learning trial (post-trial treatment) or 1 h before the 24 h retention test (pre-retention treatment). Passive avoidance behaviour was tested in both cases 24 h after the learning trial.

‖ In normal animals vasopressin facilitates memory consolidation processes (input stage of memory) and retrieval processes (output stage of memory) (DE WIED *et al.*, 1976).

Abbreviations: AVP, arginine^8-vasopressin; 5-HT, 5-hydroxytryptamine; 5,6-DHT, 5,6-dihydroxytryptamine; NE, norepinephrine; DA, dopamine.

TABLE 5. FACILITATION OF MEMORY CONSOLIDATION BY LOCAL MICROINJECTION OF ARGININE[8]-VASOPRESSIN INTO THE NUCLEUS RAPHE DORSALIS: EFFECTS OF NEUROCHEMICAL LESIONING OF THE MIDBRAIN DORSAL RAPHE AREA

I. Microinjection*	II. Microinjection†	No. of rats	24 h Avoidance latency (median in seconds)
Saline	Saline	16	68
	AVP	10	280‡
5,6-dihydroxytryptamine	Saline	6	32
	AVP	7	34
6-OHDA	Saline	8	48
	AVP	7	40

* 5,6-dihydroxytryptamine or 6-OHDA was injected in a dose of 10 μg. 10 days prior to the behavioural testing.

† Arginine[8]-vasopressin (AVP) was microinjected in an amount of 50 pg, immediately after the learning trial and the passive avoidance behaviour was measured 24 h later.

‡ $P < 0.05$.

(Results are taken from the publication of KOVÁCS *et al.*, 1979*a*.)

raphe region by local microinjection of 6-OHDA (Table 5).

These data indicate that:

(1) serotoninergic neurotransmission is involved in the improvement of memory consolidation processes elicited by local, intracerebral administration of the neuropeptide;

(2) the most probable primary site of action, however, is not the serotoninergic cell bodies, but the noradrenergic nerve endings surrounding the serotoninergic cells.

According to this concept, vasopressin primarily affects noradrenergic neurotransmission in limbic midbrain terminals of the coeruleo-telencephalic pathway, and this system modulates the activities of other (e.g. serotoninergic) transmitter pathways in the brain. These complex changes in the neurotransmission of different pathways may lead to the improvement of memory consolidation processes following vasopressin treatment (Fig. 1).

PHYSIOLOGICAL IMPLICATIONS

Recent observations have led to the conclusion that vasopressin is involved physiologically in the control of learning and memory processes (DE WIED *et al.*, 1976). This conclusion was based on the observation that rats with a genetic failure to synthesize vasopressin (Brattleboro strain, VALTIN & SCHROEDER, 1964),

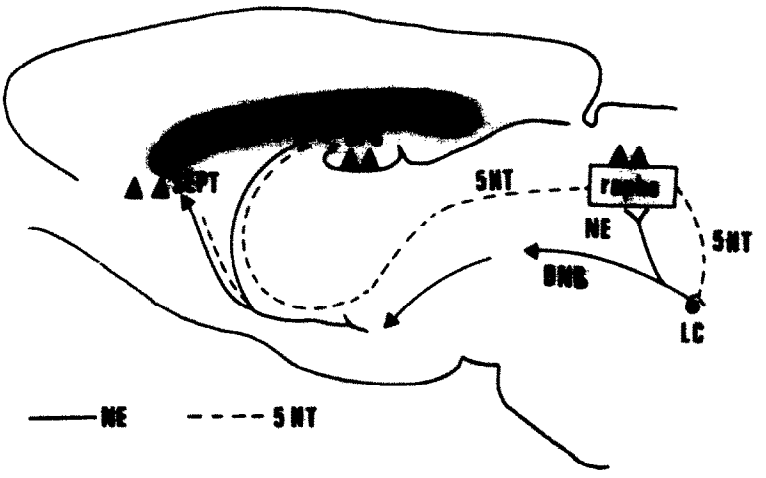

FIG. 1. Pathways in the brain that could be involved in the effect of vasopressin on memory consolidation processes.

Abbreviations: SEPT, dorsal septum; HPC, dentate gyrus hippocampi; raphe, dorsal raphe nucleus; LC, locus coeruleus; DNB, dorsal noradrenergic bundle; NE, norepinephrinergic pathway; 5-HT, serotoninergic pathway. The triangles indicate brain sites, where the local microinjection of the peptide facilitates memory consolidation and affects catecholamine disappearance (KOVÁCS *et al.*, 1979*a*).

as well as normal rats following the neutralization of central nervous vasopressin by specific antiserum, exhibited a severe memory deficit, which could be restored by substitution therapy with the neuropeptide (Bohus, Van Wimersma Greidanus & De Wied, 1975; Van Wimersma Greidanus *et al.*, 1975*b*). The normal presence of vasopressin in the cerebrospinal fluid (Heller, Hasan & Saifi, 1968; Vorherr, Bradbury, Hoghoughi & Kleeman, 1968; Dogterom, 1977) and in the brain tissue (Dogterom, Snijdewint & Buijs, 1978), together with the immunocytochemical evidence that vasopressin-containing nerve fibers innervate the hypothalamus and extrahypothalamic brain structures (Vandesande & Dierickx, 1976; Buijs, Swaab, Dogterom & Van Leeuwen, 1978) and make synaptic contacts to other neurons (Sofroniew & Weindl, 1978) provide a morphological–functional background for the physiological involvement of the neuropeptide in various CNS processes. Morphological evidence suggests the existence of specific vasopressin receptors, too, in the central nervous system (Castel, 1978); however, their functional characteristics need to be elucidated biochemically.

The biochemical and behavioral data (Kovács *et al.*, 1977; 1979*a*,*b*; Tanaka *et al.*, 1977*a*,*b*; Van Ree *et al.*, 1978; Telegdy & Kovács, 1979*a*) raised the possibility that the physiological modulatory role of vasopressin on memory processes is mediated by the cerebral catecholaminergic (noradrenergic) neurotransmission, as it is for the influence of the exogenously administered peptide. This hypothesis is strongly supported by the most recent data of Versteeg, Tanaka & De Kloet (1978), Szontágh, Kovács, Telegdy, Laczi & László (1978) and Telegdy & Kovács (1979*b*): they have shown that cerebral norepinephrine and dopamine levels and disappearance rates in homozygous Brattleboro rats are different from those in normal controls, and in many respects are the opposite of those observed in normal rats after vasopressin treatment. Intraventricular administration of vasopressin antiserum and of vasopressin itself also resulted in opposite changes in the rate of catecholamine disappearance (Tanaka *et al.*, 1977*b*; Versteeg, De Kloet, Van Wimersma Greidanus & De Wied, 1979).

Recent human data also indicate the importance of the dorsal noradrenergic bundle: McEntee & Mair (1978) concluded that the decreased activity in the ascending noradrenergic system might be the reason for the memory impairment characteristic of Korsakoff's psychosis. Oliveros *et al.* (1978), on the other hand, reported that vasopressin treatment alleviates the clinical symptoms of amnesia in Korsakoff's psychosis patients.

Conclusion

In conclusion, we have presented evidence that vasopressin treatment facilitates memory consolidation processes via modulation of the noradrenergic neurotransmission in limbic midbrain terminals of the dorsal noradrenergic bundle. It can be assumed that the physiological modulatory role of the neuropeptide involves the same (or a similar) mechanism.

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(*Accepted* 19 *June* 1979)