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Neuromodulation of memory in the hippocampus by vasopressin

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Abstract

The involvement of [Arg^8]vasopressin in memory processes was analyzed in the hippocampal structure, since we have reported that this is one of the main central target structures of the vasopressin-enhancing effect on memory. This structure is functionally differentiated along its dorsoventral axis, and the expression of the vasopressinergic system is dependent upon whether the dorsal or ventral part of the hippocampus is involved. For this reason, the effect of vasopressin injected into hippocampus was evaluated on the basis of the site of injection. We have shown, using a Go-No Go visual discrimination task with mice that both parts of the hippocampus are involved in the effect of endogenous or exogenous vasopressin, but with higher sensitivity for the ventral part. Based on the expression of Fos protein following intracerebroventricular injection of vasopressin in unconditioned or conditioned mice, we confirmed the greater involvement of the ventral hippocampus in the enhancing effect of vasopressin on memory processes. The effect of the peptide seems specific, since only a few of the hippocampal cells that expressed Fos protein in the unconditioned mice did so in the conditioned mice (cells in the dentate gyrus and the CA3 hippocampal field). Moreover, we have shown that in the ventral hippocampus, vasopressin generates different behavioral effects whether treatment is performed at the beginning or in the middle of the learning process, suggesting that the mnemonic context is an important factor for understanding the effect of vasopressin on memory in the ventral hippocampus.

Keywords: Vasopressin; Hippocampus; Memory process

1. Introduction

Memory is generally defined as the ability to acquire, store and retrieve information. For a long time, memory was considered as a single-unit system, but in the last two decades, extensive studies on humans as well as animals have shown that memory is actually a heterogeneous compound that includes different kinds of memory systems. In humans, different memory systems have been described (Tulving, 1985; Baddeley, 1994; Squire and Zola, 1998; Tulving and Markowitsch, 1998; Milner et al., 1998). Experimental studies on monkeys (Zola-Morgan et al., 1986; Rombouts et al., 1997; Mishkin et al., 1997; Fernandez et al., 1998) or rodents (Eichenbaum et al., 1992) with hippocampal lesion-induced memory deficits were based on the concept of hippocampal-dependent vs. hippocampal-independent memory systems. In spite of an abundant literature, while it is now widely accepted that there are several kinds of memory systems, the possible relationships between some or all of these remains an open question. In particular, can human memory systems be compared to those described in animals and vice versa?

Mnemonic systems must be distinguished from memory processes. The latter refer to defined operations used to achieve a given mnemonic performance. Processes like encoding, storage, and retrieval are components of memory systems but are not themselves systems. Moreover, there are good reasons for believing that a particular memory system could involve more than one memory process. The cellular mechanisms involved in these mnemonic processes have been the object of various hypotheses throughout the study of memory (Ungar, 1970; Verzeano, 1977; Miller, 1989). At present, the exact mechanisms underlying encoding, storage, and especially re-

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trieval are still unknown. The hypothesis now generally proposed is that the information in the brain is stored in a neural network. Strengthening of certain synapses allows for the establishment of a neural network specific to that information (Lynch et al., 1991; Laroche et al., 1997; Hampson and Deadwyler, 1997; Roman et al., 1999). According to the theory of Hebb (1949), learning involves simultaneous stimulation of the pre- and post-synaptic zones. This synaptic plasticity is thought to be based on the deeper modification of the synapses implicated in the corresponding memory trace. It is likely that some of these mechanisms are also involved in the reactivation of the neural network during information retrieval.

Information transmission processes are very complex. They involve the activation of different kinds of substances, which themselves generate different cellular mechanisms. These neuronal substances are usually divided into two categories: neurotransmitters and neuromodulators. It is generally agreed that the role of the neuromodulators is to alter the action of the neurotransmitters. Several neuromodulators, such as neuropeptides, have been shown to be involved in mnemonic processes. Following the pioneering work by De Wied, many studies have contributed to improving our understanding of the involvement of [Arg^8]vasopressin and its fragments or analogues in mnemonic processes. Their results from studies in rats, showing that vasopressin exerts long-term effects on the maintenance of learned responses by promoting memory consolidation, storage, and retrieval, led De Wied and his associates to develop the theory that vasopressin plays a major role in the modulation of these mnemonic processes (De Wied, 1971; De Wied et al., 1976; Van Wimersma Greidanus et al., 1983). Based on these studies, vasopressin is of great interest as one of the cellular signals that might be involved in neuronal communication in memory processes.

2. Vasopressin

Vasopressin is a posterior hypophysis nonapeptide known to be an antidiuretic and pressor hormone (Cowley and Liard, 1987; Valtin, 1987). Its endocrine effects are mediated through receptors on target organs, including vasopressin receptors of the V_{1A} subtype located on the smooth muscle cells lining the blood vessels associated with the pressor response, and vasopressin V_2 receptors in the kidney, which are essential for the antidiuretic renal action of vasopressin. The vasopressin V_{1B} receptor subtype, which is detected in the pituitary gland, mediates vasopressin-stimulated adrenocorticotropin secretion by potentiating the action of corticotropin-releasing hormone (Mohr and Richter, 1994). In addition to the fibers which originate in the hypothalamic nuclei and make up the hypothalamus–neurohypophyseal pathway, there are vasopressinergic fibers in numerous cerebral regions ranging from the olfactory bulb to the spinal cord, in addition to vasopressinergic neuron groups in the septal region, the bed nucleus of the stria terminalis, and the medial amygdaloid nucleus (Buijs, 1978; Castel and Morris, 1988; Dubois-Dauphin et al., 1989; De Vries and Miller, 1998). The vasopressin receptors detected in the brain are type 1 receptors (De Kloet et al., 1985; Dubois-Dauphin et al., 1990; Krémarick et al., 1993; Szot et al., 1994; Tribollet et al., 1998). The cerebral binding sites of vasopressin V_1 receptors correspond in general to vasopressinergic projection sites. Stimulation of vasopressin V_1 receptors leads to G-protein-mediated phosphatidyl–inositol hydrolysis, which results in protein kinase C activation and cytosolic Ca^{2+} increases (Thibonnier et al., 1998). There is also evidence for the presence of vasopressin type 2 receptors in the central nervous system (CNS) (Hirasawa et al., 1994; Kato et al., 1995). These receptors are coupled with G protein and stimulate adenylate cyclase.

The central target structures as well as the receptors implicated in the behavioral and memory effects of the peptide have been studied extensively. It is well documented that the structures involved in the effects of vasopressin on learned behavior are those innervated by extrahypothalamic vasopressinergic pathways, in particular limbic structures such as the septum (Engelmann et al., 1992; Everts and Koolhaas, 1997), the hippocampus (Van Wimersma Greidanus and De Wied, 1976; Van Wimersma Greidanus and Maigret, 1996; Metzger et al., 1993), and the amygdala (Roozendaal et al., 1992; Koolhaas et al., 1998). The behavioral memory effect of vasopressin in all these structures is mediated not only by vasopressin V_1 receptors but also by oxytocin receptors (De Wied et al., 1991; Paban et al., 1998). The central involvement of the vasopressin V_2 receptors has also been suggested (De Wied et al., 1991; Popik et al., 1992; Croiset and De Wied, 1997).

In this review, by considering the hippocampal structure with which most of our studies were performed, we attempt to gain an insight into the effects of vasopressin on memory processes. It will be seen that, throughout, our results are consistent with De Wied's prediction, in the sense that vasopressin acts specifically on memory processes and may, in many cases, be considered as a neurotransmitter.

3. The hippocampus: one of the main central target structures of vasopressin enhancing-effects on memory

The hippocampus and related temporal-lobe areas have long been known to play a prominent role in memory formation (Jaffard and Meunier, 1993; Eichenbaum et al., 1992). The hippocampus seems to be one of the principal

central target structures for the memory-enhancing effect of vasopressin, whether the peptide is administered via a peripheral (subcutaneous, s.c.) or a central (intracerebroventricular, i.c.v.) route. Small lesions of the dorsal hippocampus were found to modify the behavioral effects of peripherally administered vasopressin on avoidance conditioning (Van Wimersma Greidanus and De Wied, 1976; Van Wimersma Greidanus et al., 1983). In experiments with an eight-arm radial maze, a hippocampal lesion blocked only the enhancing effects of s.c. injection of vasopressin-(4–9) on working memory but not its effects on reference memory (Dietrich and Allen, 1997b). Based on studies with visual discriminative learning in mice, we also reported the involvement of the dorsal hippocampus in the enhancing effect of vasopressin on memory retrieval, but, in this case, when the peptide was i.c.v. injected (Alescio-Lautier et al., 1987, 1989).

The relationship between the behavioral changes that follow the administration of vasopressin and the behavioral consequences of the release of endogenous vasopressin has been much studied (Van Wimersma Greidanus et al., 1979; Lebrun et al., 1987). Concerning the hippocampus, Laczi et al. (1983) detected a sharp drop in vasopressin during learning of avoidance conditioning when vasopressin was measured just after the electric shock. This reduction was temporary. When vasopressin was measured after the retention session, a drop in the vasopressin level was again observed eventhough no electric shock has been given, suggesting that hippocampal endogenous vasopressin acts during retrieval processes.

Direct involvement of the hippocampus in the effect of vasopressin was shown by using in situ microinjection. Microinjection of 8 or 25 pg vasopressin improved retention of the passive avoidance response (Kovács et al., 1986). Vasopressin injected in the dentate gyrus, after a learning trial improved passive avoidance behavior (Kovács et al., 1979), while vasopressin injected before the retention test improved passive avoidance behavior of rats made amnestic by pentylenetetrazol (Bohus et al., 1982). The anti-vasopressin antibody (1/50th) injected post-learning into the dorsal hippocampus and the dentate gyrus produced a marked passive-avoidance retention deficit (Kovács et al., 1982). Veldhuis et al. (1987) reported a similar result for the ventral hippocampus. Thus, anti-vasopressin in the hippocampus produces effects opposite to those obtained for vasopressin, thereby confirming the role of this structure in vasopressin's memory-enhancing effect on aversive conditioning. Van Wimersma Greidanus and Maigret (1996) showed that endogenous vasopressin in the hippocampus also plays a physiological role in social recognition.

Vasopressin has electrophysiological on the hippocampus (Chepkova et al., 1995; Urban, 1998) and the dentate gyrus (Chen et al., 1993), which supports the likelihood of a relationship between vasopressin and the hippocampus, and the mnemonic effects of the peptide in this structure.

3.1. Involvement of the dorsal vs. the ventral hippocampus in the memory-enhancing effect of vasopressin

Anatomical evidence suggests strongly that the hippocampus is functionally differentiated along its dorsoventral axis (Moser and Moser, 1998). Indeed, the cortical and subcortical connections of the dorsal and ventral hippocampus are different. The major cortical connections are channeled through the entorhinal cortex, which projects out onto distinct regions along the longitudinal axis of the dentate gyrus (Ruth et al., 1982; Dolorfo and Amaral, 1998). Information derived from the sensory cortices mainly enters into the dorsal two-thirds or three-quarters of the dentate gyrus (Burwell and Amaral, 1998). Only olfactory information seems to be distributed over the entire dentate gyrus. The afferent fractionation of the longitudinal axis is preserved on the efferent side. The rostral subcortical connections of the hippocampus are topographically organized along the septotemporal axis. The dorsal, intermediate, and ventral regions of the hippocampus project into cytoarchitectonically different sectors of the lateral septum (Risold and Swanson, 1997). The ventral hippocampal formation has strong efferent connections with several subcortical forebrain structures, including the rostral hypothalamus and the amygdala (Risold et al., 1997).

The vasopressinergic system is expressed differently in the dorsal and ventral parts of the hippocampus. In rodents, given the extensive extrahypothalamic pathways, the hippocampus receives only a scattered vasopressinergic input in its ventral part. Vasopressin immunoreactive fibers have been detected in the striata of the ventral hippocampal complex, including the paraventricular area, the claustrum, and the most ventral part of the dentate gyrus (Castel and Morris, 1988; De Vries and Miller, 1998). Most vasopressin fibers in the ventral hippocampus originate in the medial amygdaloid nucleus (Caffé et al., 1987). In contrast, the dorsal part of the hippocampus does not seem to be innervated by vasopressin fibers. Unlike vasopressinergic innervation, both the dorsal and ventral parts of the hippocampus contain vasopressin-binding sites corresponding essentially to the vasopressin V_{1A} receptor type. Some authors suggest that the hippocampus contains vasopressin V_2 receptors also (Hirasawa et al., 1994; Kato et al., 1995).

Considering these anatomical data, the behavioral effect of vasopressin injected into the hippocampus should be considered according to whether the site of the injection is dorsal or ventral. Results of studies focused on this point suggest that both parts of the hippocampus are involved in the effect of vasopressin, but with higher sensitivity in the ventral part. Kovács et al. (1986) found a greater improvement of passive avoidance responses in rats when vasopressin was injected into the ventral hippocampus. We also reported greater sensitivity of the ventral part of the hippocampus to the effect of vasopressin on memory retention in a visual discrimination task in mice (Metzger et al.,

1989; Alescio-Lautier et al., 1993). In those studies, we had examined the role of both exogenous and endogenous vasopressin in either the dorsal or the ventral hippocampus. The bilateral intrahippocampal administration of vasopressin (25 pg) or of an anti-vasopressin antibody (1/10 dilution) was carried out 10 min before the retention session performed 24 days after the end of the learning period. The results showed that vasopressin improved retrieval performance, whether the injection was into the dorsal or ventral hippocampus, but with a greater effect when the injection was ventral.

By measuring the expression of Fos protein following an i.c.v. injection of vasopressin in unconditioned and conditioned mice, we could also demonstrate the differential sensitivity of the hippocampus in the behavioral effect of vasopressin on memory consolidation (Paban et al., 1999). The unconditioned mice were injected with 2 ng of vasopressin in the lateral ventricle and were killed 120 min later. The conditioned mice learned the visual discrimination task, which consisted of three daily sessions. At the end of the third learning session, the mice were injected as above with 2 ng of vasopressin in the lateral ventricle (in this case vasopressin markedly improved memory consolidation) and were killed 120 min later. The unconditioned mice showed an increase in Fos protein expression in the dentate gyrus over the entire septotemporal area, the CA1 and CA3 hippocampal fields, also throughout the septotemporal extent, the lateral septum, the bed nucleus of the stria terminalis, and the basolateral and central amygdaloid nuclei (Fig. 1). In contrast, in the conditioned mice, the increase in Fos expression was only detected in the dentate gyrus along its septotemporal axis, the ventral CA3

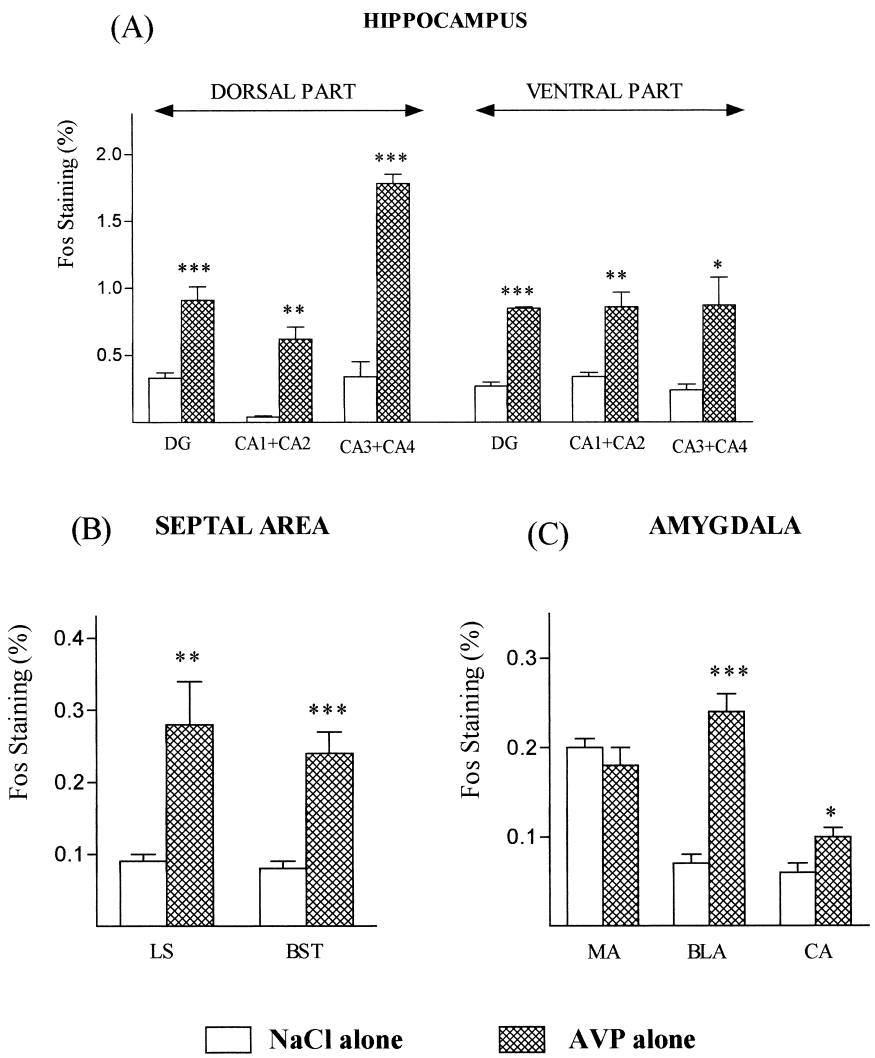


Fig. 1. Fos protein expression induced by i.c.v. injection of vasopressin in unconditioned mice. Effects of i.c.v. administration of vasopressin (2 ng/animal) on Fos expression in the mouse dorsal and ventral hippocampus (A), (DG: dentate gyrus, CA1 + CA2: hippocampal field, CA3–CA4: hippocampal field), the septal area (B), (LS: lateral septum, BST: bed nucleus of the stria terminalis), and amygdala (C), (MA: median amygdala, BLA: basolateral amygdala, CA: central amygdala). The data correspond to the mean values ± SD recorded in NaCl-injected mice (empty bars) and vasopressin-injected mice (hatched bars). The quantification of Fos-like immunoreactivity is plotted on the *y*-axis as the ratio of the stained area to the total area of interest. Fos-like immunoreactivity was measured at 120 min post-injection time intervals. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P \leq 0.001$.

hippocampal field, and the lateral septum (Fig. 2). The pattern of Fos protein activation observed after post-training i.c.v. injection of vasopressin was not the same as that triggered by i.c.v. injection of vasopressin without training, since among the limbic structures activated following vasopressin alone, only certain areas (i.e., the septum and the hippocampus) seem to be involved in the enhancing effect of vasopressin on memory consolidation in visual discrimination learning. These data support the assumption that the hippocampus is one of the main central target structures for the effects of i.c.v.-injected vasopressin on memory processes. It is likely that the increase in Fos protein expression detected in the lateral septum is a consequence of hippocampal activation. Indeed, based on the neural connections between these two structures, we can expect that i.c.v.-injected vasopressin activates first the hippocampus, and in particular the CA3 field of its ventral part, then activates the lateral septum. However, further experiments are necessary to test this hypothesis. The fact that, in the hippocampus, only the ventral CA3 field exhibited an increase in Fos protein expression strongly supports the idea that the ventral part of the hippocampus is more sensitive than the dorsal part to vasopressin's effect on memory consolidation and retrieval of visual discriminative learning.

On the other hand, in our study of the behavioral effects of intra-hippocampal vasopressin injection, we showed that vasopressin micro-injected into the ventral part was unable to improve memory consolidation or retrieval in a Hebb–Williams test (Fig. 3). This study has been designed to examine the peptide's effects during memory processes in relation to the time of treatment. Mice were trained on

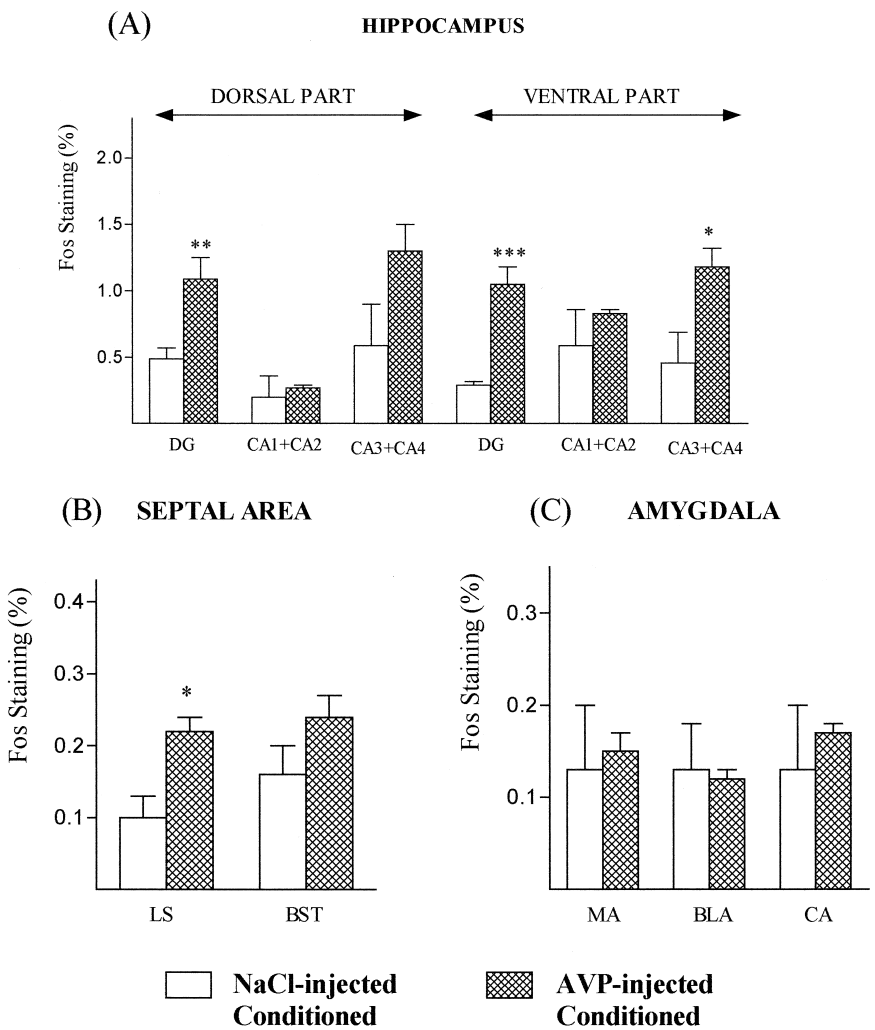
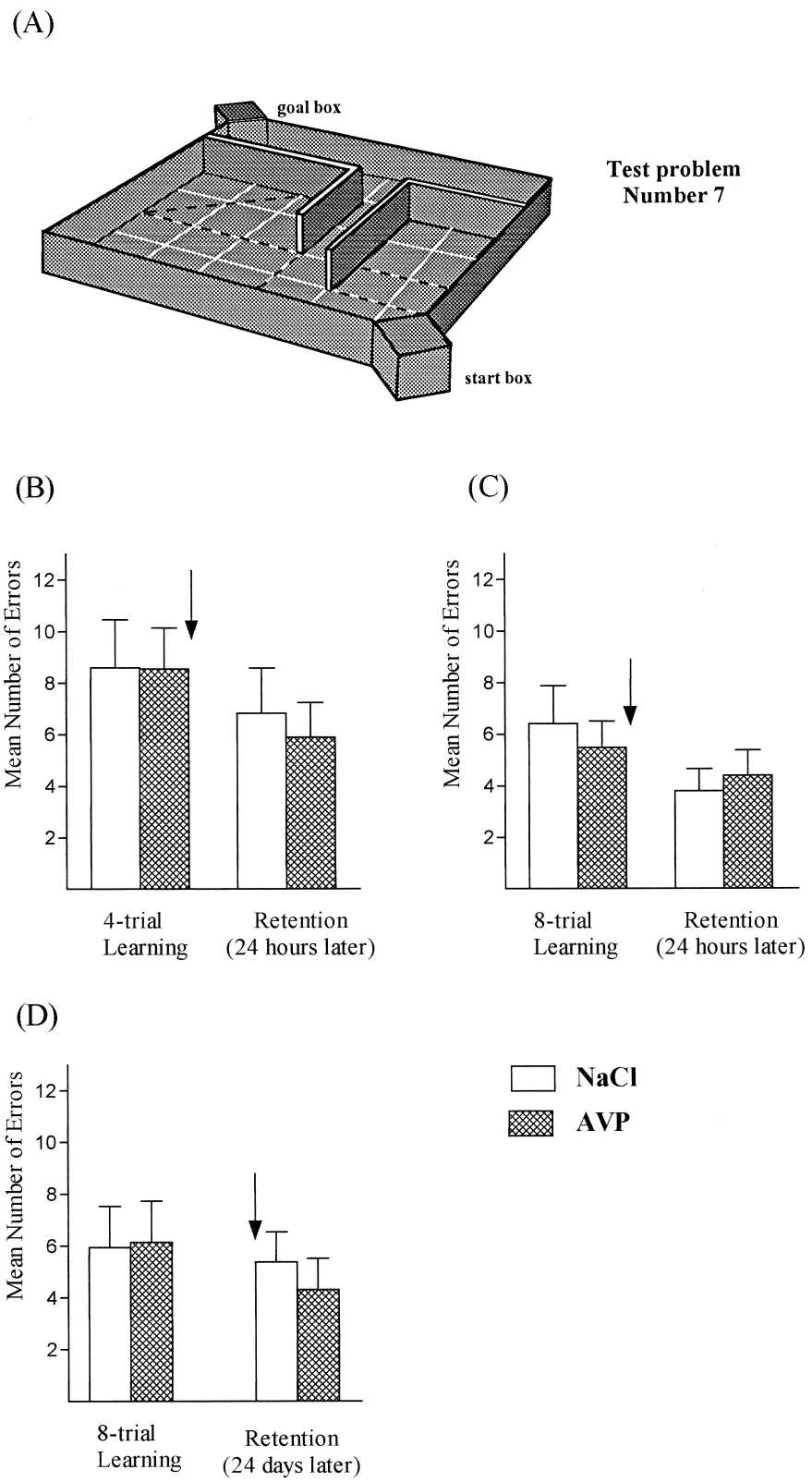


Fig. 2. Fos protein expression induced by i.c.v. injection of vasopressin in conditioned mice. Effect of post-training i.c.v. injection of vasopressin (2 ng/animal) on Fos expression in the mouse dorsal and ventral hippocampus (A), (DG: dentate gyrus, CA1 + CA2: hippocampal field, CA3–CA4: hippocampal field), the septal area (B), (LS: lateral septum, BST: bed nucleus of the stria terminalis), and amygdala (C), (MA: median amygdala, BLA: basolateral amygdala, CA: central amygdala). The data correspond to the mean values ± SD recorded in NaCl-injected conditioned mice (empty bars) and vasopressin-injected conditioned mice (hatched bars). The quantification of Fos-like immunoreactivity is plotted on the *y*-axis as the ratio of the stained area to the total area of interest. Fos-like immunoreactivity was measured at 120 min post-injection time intervals. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P \leq 0.001$.

maze 7 of the original Hebb–Williams series (Rabinowitch and Rosvold, 1951). They performed either four or eight trials during the learning session. Vasopressin was administered (1) immediately after the last learning trial, in which case its effect was evaluated on the following day, or (2) immediately before the retention session, performed 24 days after the eight learning trial. Vasopressin had no effect, whether treatment was done during storage or during retrieval. Following the post-session injection of vasopressin, no effect was observed whether four or eight trials



were used indicating that whatever the level of performance at the time of treatment, vasopressin does not enhance consolidation processes in a Hebb–Williams maze.

These results are difficult to explain unless we take into account the suggestion that the dorsal and ventral parts of the hippocampus are responsible for different functions. In particular, it has been demonstrated that the dorsal, but not the ventral hippocampus is critical for spatial memory (Moser et al., 1993; Hock and Bunsey, 1998). This assumption is possibility made likely by electrophysiological data indicating a difference between the septotemporal regions of the hippocampus. Neurons with spatially restricted discharge patterns (place cells) have been reported to exist in both the dorsal and the ventral hippocampus (Jung et al., 1994; Poucet et al., 1994) but the proportion of cells with spatial correlates is lower in the ventral hippocampus and the place fields are generally wider and less selective than those in the dorsal region (Jung et al., 1994). In species such as primates, hippocampal information processing has been shown to depend on the part studied. Indeed, Colombo et al. (1998) reported that monkeys trained in a spatial delayed matching-to-sample task have a higher proportion of neurons with activity in the delay period in the posterior (dorsal) than in the anterior (ventral) part of the hippocampus. So, in general, since it has been shown that s.c.-injected vasopressin improves reference as well as working memory in an eight-arm radial maze (Dietrich and Allen, 1997a,b), one can hypothesize that the absence of an vasopressin effect in the Hebb–Williams maze, which contains spatial components, is linked, not to the task used (spatial vs. non-spatial), but to the site of injection.

The mnemonic role of the ventral hippocampus remains unclear, mainly because, curiously, this part has been less studied. The existence of relatively direct connections between both the rostral hypothalamus and amygdala and the ventral hippocampus suggests that the latter may interact with a variety of autonomic, endocrine, social, and emotional control systems. Input from the tuberomammillary nucleus in the posterior hypothalamus, which presumably carries information regarding internal states including hunger, suggests involvement of the ventral hippocampus in the internal state-conditional task. In this respect, Davidson and Jarrard (1993), who used a task in which the food-deprivation state was a contextual cue, and Hock and Bunsey (1998), who used an internal state-shock associated task, reported the involvement of the ventral hippocampus in the acquisition of information. However, it seems unlikely that the memory enhancing effect of vasopressin injected into the ventral hippocampus is solely due to an alteration of the «milieu intérieur». Further studies along these lines should provide more insight into the question.

3.2. The effect of vasopressin injected into the ventral hippocampus depends on the mnemonic context

Another interesting finding was that the mnemonic context is an important factor for understanding the effect of vasopressin on memory processes in the ventral hip-

Fig. 3. Effect of post-training or pre-retention intra-ventral hippocampal administration of vasopressin on retention of Hebb–Williams test. The Hebb–Williams close-field maze test consists of a square field (60 × 60 cm) with start and goal (20 × 10 cm) boxes located at diagonally opposite corners (A). The square field, which was covered with a clear Plexiglas top, was divided into 36 clearly marked squares. The squares defined error zones in blind alleys and served as markers for placing the barriers to create the maze problems. The maze used corresponded to test problem 7 of the Rabinowitch and Rosvold (1951) series. Procedure: Two weeks before the experiments, mice (40 naive male BALB/c) were implanted with intra-ventral hippocampal cannulae as described previously (Alescio-Lautier et al., 1989). Six days after surgery, the mice were reduced to 80–85% of normal body weight by dietary restrictions and handled for several days. Initially, the mice were given one adaptation session, which contained no barriers. During this session, the mice were allowed 30 min to explore freely and eat pellets in the goal box. On the next day, preliminary training was introduced in which mice were administered two practice problems. Each mouse received four trials per day in which it was placed in the start box and required to run to the goal box where it could eat for 10 s. A different practice problem was provided each day for a total of 2 days. The problems used (D and F) were those described by Rabinowitch and Rosvold. The behavioral effects of vasopressin on both memory consolidation and retrieval were examined to test the peptide's effects on memory consolidation, 2 days after preliminary training, the mice received one learning session which consisted of either four (B) or eight (C) trials on problem 7 of the original 12 Hebb–Williams mazes. Records were kept of the number of error zones that each mouse entered. Each error-zone entry was counted as one error. Learning was manifested by a decrease in the number of errors. Immediately after the last learning trial, either NaCl ($N = 10$) or vasopressin ($N = 10$) was given (arrow). The behavioral effects of the peptide were analyzed 24 hours later during the retention session, which consisted of eight trials. To test the peptide's effects on retrieval, learning consisted of eight trials on maze 7 (D). The mice were tested after a 24-day interval following the learning session. NaCl ($N = 8$) or vasopressin ($N = 8$) was administered (arrow) 10 min before the retention session. Results: Effects of AVP on memory consolidation: B and C show the mean number of errors made during the four (B) and the eight (C) learning trials, respectively. A MANOVA on the performance of the NaCl and vasopressin groups on either the four-or eight-trial learning session yielded no group × time interaction ($F(3,16) = 0.19$; $P = 0.89$ for the four-trial learning, $F(7,20) = 1.17$; $P = 0.36$ for the eight-trial learning), indicating that the NaCl and vasopressin groups in these two training conditions performed similarly. When vasopressin was injected after either the four trials of learning (B) or the eight trials of learning (C), no difference in retention was observed compared to the NaCl group. A MANOVA on the retention session of the NaCl and vasopressin groups revealed no group × time interaction ($F(3,16) = 2.77$; $P = 0.07$ for the four-trial learning, $F(7,20) = 1.37$; $P = 0.26$ for the eight-trial learning), indicating that vasopressin had no effect on memory consolidation whatever the level of performance at the time of treatment. Effects of AVP on retrieval: the results are presented in D. A MANOVA on the performance of the NaCl and vasopressin groups on the learning session which consisted of eight trials revealed no difference between the two groups (group × time interaction: $F(7,80) = 0.55$; $P = 0.77$). A MANOVA on the retention session yielded no group × time interaction ($F(7,80) = 1.45$; $P = 0.30$), showing that there was no difference between the groups, and consequently no effect of vasopressin on retrieval processes.

pocampus (Paban et al., 1997). The effect of a bilateral 25 pg microinjection of vasopressin into the ventral hippocampus depends upon when vasopressin is injected during visual discrimination learning. Following pre-session (pre-first or pre-second session) administration of vasopressin, no vasopressin effect was observed on the session prior to which it was administered. On the other hand, 48 h after the pre-first session treatment, it seems that vasopressin-treated animals had trouble learning the task. Following its post-session injection, vasopressin had no effect when the treatment was given after the first learning session, and there was a tendency to improvement of performance when the treatment was given after the second learning session, and while there was a clear enhancement of performance when the treatment was given after the third learning session. We have seen above that retention performance was clearly enhanced following a pre-long-term retention session (24 days after the end of learning). Thus, no matter when vasopressin was injected during memory processes, the effect differed. In other words, vasopressin in the ventral hippocampus does not affect the intake of information, but may contribute to its processing, storage, and retrieval. However, the involvement of vasopressin in memory consolidation and retrieval is significant when the animal has already extracted the stimuli needed for proper learning; otherwise, vasopressin delays acquisition. This means that the peptide contributes to information storage whenever that information has acquired a specific meaning in a given context. Interestingly, Sif et al. (1991) reported that both the dorsal and the ventral hippocampus displayed [^{14}C]glucose labelling patterns 5 min after training in a spatial discrimination task. The same labelling was found, no matter how well the behavioral task was learned. So, our results suggest that, even if the ventral hippocampus is mainly involved in memory consolidation whit visual associative tasks, vasopressin does not participate in the modulation of the early stages of these processes, while being involved in the modulation of the later stages of consolidation. This assumption may also mean that a molecule endogenous to a particular structure does not necessarily participate in all the steps of a given function of this structure (Alescio-Lautier and Soumireu-Mourat, 1998).

4. Conclusion

This review attempted to emphasize the idea that vasopressin in the hippocampus acts on memory in a specific manner. In particular, the increases in Fos protein expression following treatment with vasopressin suggest strongly that this peptide acts on specific cell groups inside certain central target structures (Paban et al., 1997). Wu et al. (1995) reported that peripherally injected vasopressin increases Fos in specific brain areas. Electrophysiological data also support this assumption, since they show that administration of vasopressin or vasopressin-(4–8) alone is associated with the long-lasting enhancement of the synaptic excitability of CA1/subiculum neurons in the ventral hippocampus (Chepkova et al., 1995). However, we showed that these same cell groups (CA1 hippocampal field) were no longer activated when the animals were placed in the learning context of a visual discrimination task. In general, irrespective of the experimental approach used to examine the behavioral effects of vasopressin, one can speculate that the action of this neuromodulatory substance is much more complex than has been expected several years ago. It is now clear that its effects depend on several kinds of factors, including the nature of the task used, the memory system studied, and the memory processes tested. Although these many factors make its study particularly confusing, they highlight vasopressin's specific involvement in memory. The use of Fos protein expression following vasopressinergic treatment seems to be a promising way to determine which cell groups are involved under the particular experimental conditions in which the peptidergic treatment is given. For instance, it would be interesting to compare Fos protein expression under each vasopressin memory-enhancing set of conditions, i.e., consolidation vs. retrieval, as well as under conditions where vasopressin has no effect, i.e., information intake or the early stages of memory consolidation.

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