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European Journal of Pharmacology 361 (1998) 165–173

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The behavioral effect of vasopressin in the ventral hippocampus is antagonized by an oxytocin receptor antagonist

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Received 3 August 1998; revised 23 September 1998; accepted 25 September 1998

Abstract

[Arg^8]vasopressin improved long-term retrieval processes and relearning in a go–no go visual discrimination task when bilaterally microinjected at a dose of 25 pg/animal into the ventral hippocampus of mice, 10 min prior to the retention session. We had shown that this enhancing effect is antagonized by pretreatment with equal or lower doses (25 pg or 1 ng) of the vasopressin V_1 receptor antagonist, (d(CH_2)$_5$Tyr(Me)-vasopressin). The present study was an attempt to determine whether the vasopressin V_2 receptor antagonist or oxytocin receptor antagonist is as effective as the vasopressin V_1 receptor antagonist to block the behavioral effect of vasopressin in the ventral hippocampus. We tested the effect of 25 pg of [d(CH_2)$_5$-D-Ile^2,Ile^4,Arg^8]vasopressin, a vasopressin V_2 receptor antagonist, and [d(CH_2)$_5$,Tyr(Me)^2,Thr^4,Tyr-NH_2^9]ornithine vasotocin, an oxytocin receptor antagonist, under the same experimental conditions as those used to test the effect of the vasopressin V_1 receptor antagonist. The results showed that the vasopressin V_2 receptor antagonist microinjected into the ventral hippocampus did not alter the enhancing effect of vasopressin on retrieval and relearning. In contrast, the oxytocin receptor antagonist blocked the vasopressin-enhancing effect on retention processes. We can conclude from the data that both vasopressin V_1 receptors and oxytocin receptors seem to be involved in the enhancing effect of vasopressin on memory retention. In contrast, the vasopressin V_2 receptors do not seem to be involved in the effect of the peptide.

Keywords: [Arg^8]vasopressin; Vasopressin V_2 receptor antagonist; Oxytocin receptor antagonist; Ventral hippocampus; Memory retrieval; Relearning

1. Introduction

In addition to having effects in peripheral target organs (Cowley and Liard, 1987; Valtin, 1987; Mohr and Richter, 1994), [Arg^8]vasopressin has a behavioral effect on several brain-controlled functions including grooming (Meisenberg, 1988), motor activities (Kruse et al., 1977; Kasting et al., 1980; Willcox et al., 1992), sexual behavior (Södersten et al., 1986), and flank marking (Ferris et al., 1984, 1988; Irvin et al., 1990). There is also substantial evidence that vasopressin affects learning and memory processes (De Wied et al., 1984; Dantzer et al., 1987; Le Moal et al., 1987; Ferris et al., 1988; Bunsey and Strupp, 1990; Engelmann et al., 1992; Alescio-Lautier et al., 1993; Kovacs and Versteeg, 1993; Kovacs and De Wied, 1994; Engelmann et al., 1996; Paban et al., 1997).

Limbic structures are highly involved in the effect of vasopressin on these processes. The hippocampus, the amygdala, and the septal area appear to be the structures where administration of the peptide is most effective on passive avoidance behavior (Kovacs et al., 1979, 1986). Dantzer et al. (1987) showed that the administration of vasopressin in the lateral septum improves social recognition in rats. We previously showed that, in mice, the hippocampus is involved in the enhancing effect of vasopressin on the retrieval and relearning of appetitive conditioning in a go–no go visual discrimination task (Alescio-Lautier et al., 1987, 1989), with more improvement when the peptide is injected into the ventral hippocampus than into the dorsal hippocampus (Metzger et al., 1989; Alescio-Lautier et al., 1993) as shown by Kovacs et al. (1986) for avoidance behavior.

Vasopressin acts on two classes of receptors, V_1 and V_2. Vasopressin V_1 receptors can be further classified into vasopressin V_{1A} (Howl and Wheatley, 1995) and V_{1B}

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0014-2999/98/$ - see front matter
PII: S0014-2999(98)00704-3

(Sugimoto et al., 1994; Saito et al., 1995) receptors. Vasopressin binding sites detected in the brain correspond to the vasopressin V_{1A} subtype receptors (Ostrowski et al., 1992, 1994; Szot et al., 1994; Dubois-Dauphin et al., 1996) and probably also to vasopressin V_2 type receptors (Cheng and North, 1989; Hirasawa et al., 1994; Kato et al., 1995). Behavioral studies using microinjection of a vasopressin V_1 receptor antagonist in the lateral ventricle of the brain, or in limbic structures such as the septum and the amygdala or the anterior hypothalamus, have shown that the central effects of vasopressin on avoidance conditioning (De Wied et al., 1984), social recognition (Dantzer and Bluthé, 1992; Everts and Koolhaas, 1997) and other behaviors (Ferris et al., 1988; Irvin et al., 1990; Willcox et al., 1992; Winslow et al., 1993) are mediated by vasopressin V_1 receptors. We have also reported that a vasopressin V_1 receptor antagonist given in the ventral hippocampus blocks the enhancing effect of vasopressin on retrieval and relearning (Alescio-Lautier et al., 1995).

However, it seems that vasopressin V_1 receptors are not the only ones involved. Studies by De Wied et al. (1991) on passive avoidance behavior and by Popik et al. (1992) on social recognition showed the involvement of vasopressin V_2 receptors in the behavioral effect of vasopressin. De Wied et al. (1991) also reported the involvement of oxytocin receptors in the effect of the peptide. Oxytocinergic binding sites have been described in various regions of the brain (Freund-Mercier et al., 1987; Tribollet et al., 1988, 1992; Tribollet, 1992; Veinante and Freund-Mercier, 1997). While ventral hippocampus contains oxytocin receptors and they bind vasopressin, the effect of the peptide on retrieval and relearning, which is mediated via vasopressin V_1 receptors in the ventral hippocampus, could also be mediated in part by oxytocin receptors.

Thus, the present study was an attempt to determine whether or not the improvement of retrieval and relearning following vasopressin administration in the ventral hippocampus, in addition to being mediated by vasopressin V_1 receptors, is also mediated by vasopressin V_2 receptors and/or oxytocin receptors. We analyzed the ability of the vasopressin V_2 receptor antagonist, [d(CH_2)$_5$-D-Ile^2, Ile^4,Arg^8]vasopressin, and the oxytocin receptor antagonist, [d(CH_2)$_5$,Tyr(Me)^2,Thr^4,Tyr-NH_2^9]ornithine vasotocin, to block the enhancing effect of vasopressin.

2. Materials and methods

2.1. Animals

Sixty naive male BALB/c mice from Iffa Credo (St. Germain sur l'Arbresle, France) were used when 9 to 10 weeks old. Until the day of the experiment, all animals had free access to food and drinking water and were kept on a controlled illumination schedule with light on between 0700 and 1900 h.

2.2. Behavioral experiments

2.2.1. Visual discrimination task

The animals were trained in a successive visual discrimination test with food reinforcement. The device used had two separate alleys, one white and one black. Learning consisted of discriminating between the alley in which the animals were always reinforced and the alley in which they were never reinforced. After a habituation session, the mice were progressively food-deprived to 80–85% of their free-feeding weight and given unlimited access to water. Initial training consisted of one daily session for 3 days. A session included six reinforced trials (go trials) and six non-reinforced trials (no-go trials), in random order. Performance was measured in terms of the animals' running time in each alley. Learning was manifested by a decrease in running time for go trials and an increase in running time for no-go trials. The retention session consisted of an additional session under the same conditions but after a 24-day interval following the third learning session. Performance in the first go trial and first no-go trial was considered to reflect the level of retrieval, and performance in the subsequent go and no-go trials, to reflect the level of relearning. A detailed analysis of the learning and retention performance in this behavioral task has already been published (Alescio-Lautier and Soumireu-Mourat, 1986).

2.2.2. Locomotor activity

To test the hypothesis that a motor change might contribute to the observed behavioral effect of the treatment, locomotor activity was measured in a translucent, square, Plexiglas cage (22×22 cm^2) equipped with a photoelectric circuit. This circuit was connected to a microcomputer, automatically measuring crossing and rearing. A session lasting 10 min was held on 2 consecutive days.

2.3. Surgical procedure

Surgery took place 1 week after the end of the initial training in visual discrimination or 1 week before the beginning of the locomotor activity test. For intra-hippocampal cannulation, mice were implanted bilaterally with cannulae in the ventral hippocampus at the following coordinates: 3.0 mm posterior to the bregma, ± 3.1 mm lateral to the midline, and 3.3 mm below the surface of the skull. Cannulation was performed under Imalgen 500 (0.01%)/Rompun xylazine (0.1%) anesthesia (0.1 ml/10 g).

2.4. Intra-hippocampal injection

[Arg^8]vasopressin was obtained from the Sigma. The antagonists [d(CH_2)$_5$-D-Ile^2,Ile^4,Arg^8]vasopressin, for the vasopressin V_2 receptor type, and [d(CH_2)$_5$,Tyr(Me)^2, Thr^4,Tyr-NH_2^9]ornithine vasotocin, for the oxytocin recep-

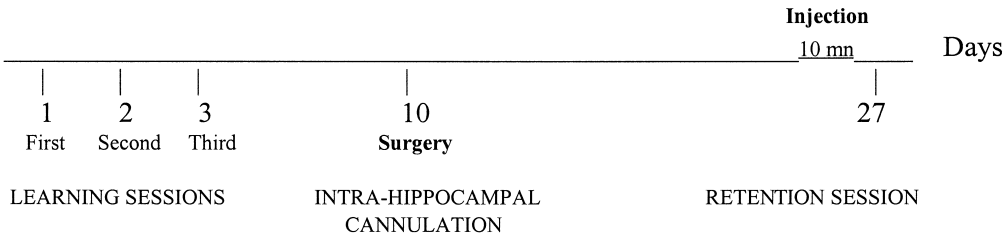

Fig. 1. General procedure.

tors, were obtained from Penninsula. The substances were dissolved in 0.9% NaCl immediately before use and injected into the ventral hippocampus in a volume of 0.3 μl. The dose for vasopressin was 25 pg/animal, which corresponds to the intra-hippocampal dose in mice behaviorally active for retention of the visual discrimination task (Metzger et al., 1993; Alescio-Lautier et al., 1995). The dose of the vasopressin V_2 receptor antagonist or oxytocin antagonist was 25 pg/animal, which corresponds to the same dose as that used to show that the vasopressin V_1

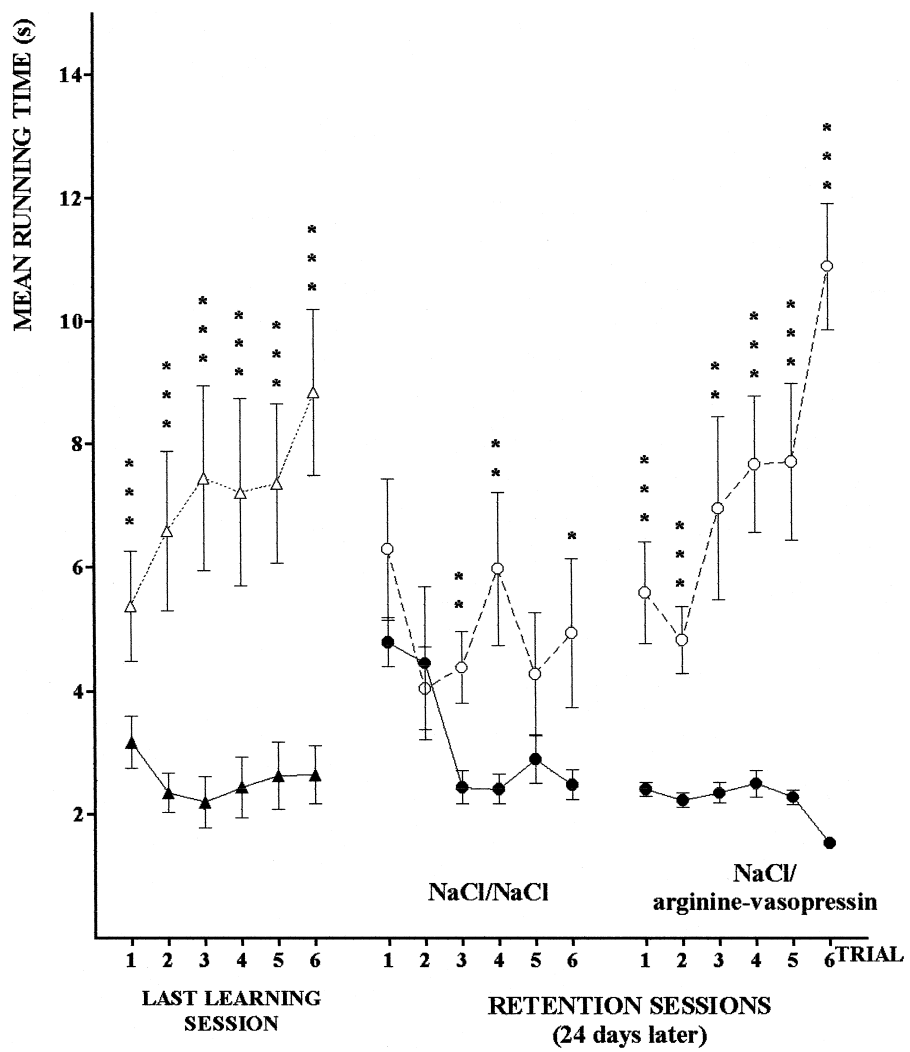

Fig. 2. Effects of bilateral microinjection of [Arg^8]vasopressin into the ventral hippocampus on the retention of a go–no go visual discrimination task. Left: trial-by-trial analysis of mean go (black triangles) and no go (white triangles) running times during the last learning session, for all six groups ($N = 60$), indicating the level of initial learning. Right: trial-by-trial analysis of mean go (black circles) and no go (white circles) running times during the retention session, with NaCl and vasopressin injected mice (NaCl/argininevasopressin) and corresponding controls: double volume injection of NaCl (NaCl/NaCl). Injections were given 10 min prior to the retention session. $* P < 0.05$, $** P < 0.01$, $*** P \leq 0.001$.

receptor antagonist, d(CH_2)$_5$,Tyr(Me)-vasopressin, injected into the ventral hippocampus blocks the enhancing effect of AVP on retrieval and relearning (Alescio-Lautier et al., 1995). The vasopressin V_2 receptor antagonist, oxytocin receptor antagonist, or NaCl was administered 10 min prior to the retention session of the visual discrimination task (or 10 min prior to the second session of the locomotor activity test) and was followed immediately by [Arg^8]vasopressin or NaCl (0.9%). The overall procedure is summarized in Fig. 1.

Six groups of 10 animals were set up for each test, corresponding to the following treatments: NaCl/NaCl, NaCl/[Arg^8]vasopressin, vasopressin V_2 receptor antagonist/NaCl, vasopressin V_2 receptor antagonist/[Arg^8]vasopressin, oxytocin receptor antagonist/NaCl, and oxytocin receptor antagonist/[Arg^8]vasopressin.

2.5. Histological control

The location of the cannula tip was determined at the end of the experiment. Each animal was deeply anesthetized with sodium pentobarbital and then perfused intracardially using 0.9% NaCl followed by 10% formol–NaCl solution, pH 7.0. The brains were removed and post-fixed in the same fixative for several days. Transverse sections of 40 μm were subsequently cut, mounted, and stained with Cresyl violet.

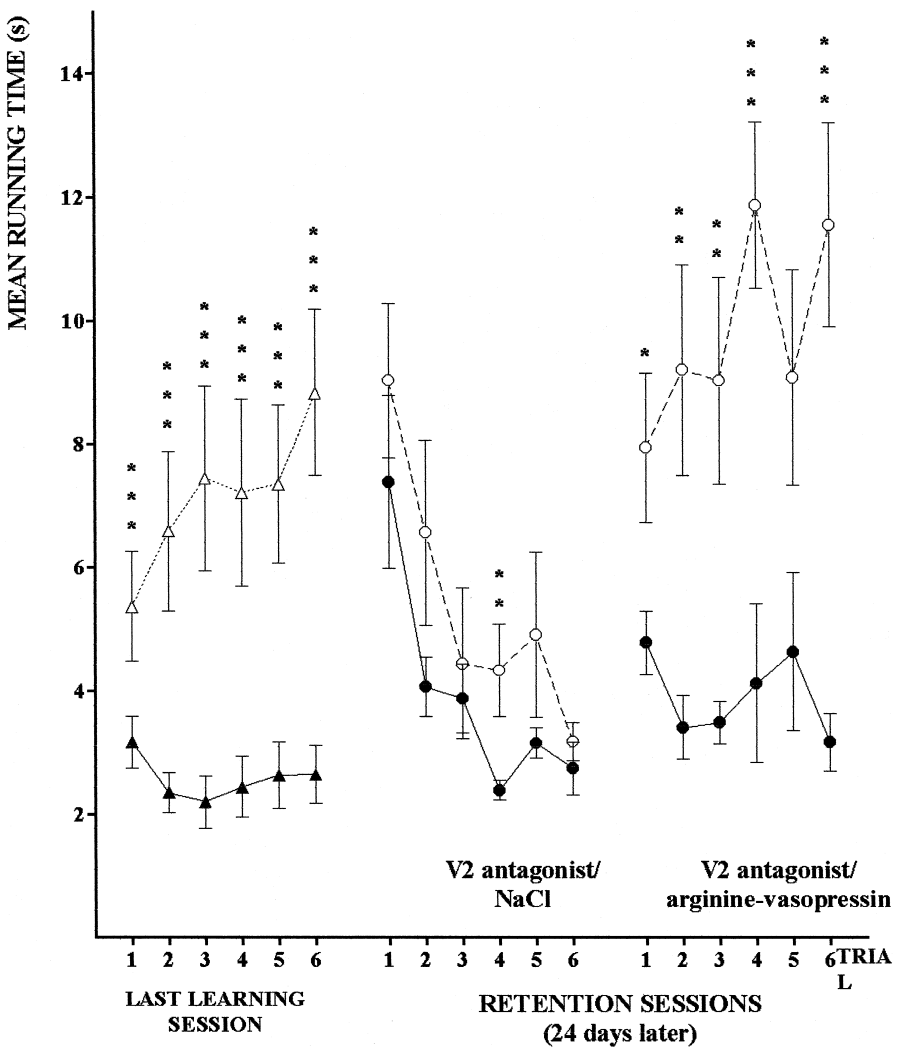

Fig. 3. Effects of bilateral microinjection of vasopressin V_2 receptor antagonist followed by bilateral microinjection of [Arg^8]vasopressin into the ventral hippocampus on the retention of a go–no go visual discrimination task. Left: trial-by-trial analysis of mean go (black triangles) and no go (white triangles) running times during the last learning session, for all six groups ($N = 60$), indicating the level of initial learning. Right: trial-by-trial analysis of mean go (black circles) and no go (white circles) running times during the retention session, with a vasopressin V_2 receptor antagonist ([d(CH_2)$_5$-D-Ile^2,Ile^4,Arg^8]vasopressin) and vasopressin-injected mice (vasopressin V_2 receptor antagonist/[Arg^8]vasopressin), and a vasopressin V_2 receptor antagonist and NaCl-injected mice (vasopressin V_2 receptor antagonist/NaCl) Injections were given 10 min prior to the retention session. $*\ P < 0.05$, $**\ P < 0.01$, $***\ P \leq 0.001$.

2.6. Statistical analysis

The data for the third learning session and retention test were analyzed using a repeated measurement, multivariate analysis of variance (MANOVA) for the trial-by-trial measure to determine the main effect of time (chronological series of trials) and its interaction effects with group and reinforcement (go and no-go trials). Analysis of variance (ANOVAs) for group × reinforcement was also done for each trial. Locomotor activity data were analyzed with Student's *t*-test. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Visual discrimination

A MANOVA performed on the third learning session for all groups showed that there was a main reinforcement × time interaction ($F(5,104) = 6.83$; $P < 0.0001$), indicating that all groups learned the task. There was no difference between the learning of these groups within the session (group × time interaction: $F(5,104) = 1.24$; $P = 0.19$) whatever the reinforcement (group × reinforcement × time interaction: $F(5,104) = 1.29$; $P = 0.15$). Thus, because the initial learning was similar in all groups, we can reasonably postulate that any change in the level of retrieval and relearning after the various treatments was an effect of the treatment itself. The performance of the six groups in the third learning session was averaged (Figs. 2–4).

In accordance with previous data, vasopressin injected 10 min before the retention session improved both retrieval and relearning compared to those of the NaCl/NaCl group (Fig. 2). The MANOVA for the retention session of these two groups revealed a reinforcement × time interaction

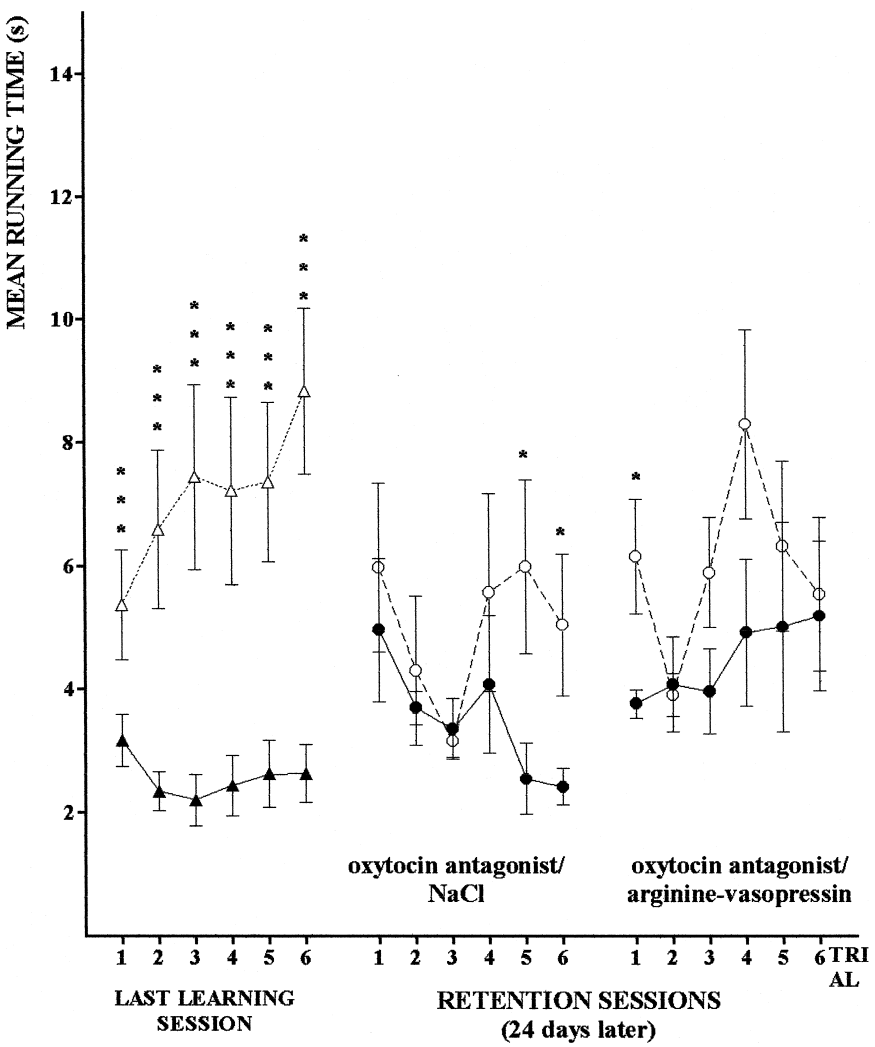

Fig. 4. Effects of bilateral microinjection of oxytocin receptor antagonist followed by bilateral microinjection of [Arg^8]vasopressin into the ventral hippocampus on the retention of a go–no go visual discrimination task. Left: trial-by-trial analysis of mean go (black triangles) and no go (white triangles) running times during the last learning session, for all six groups ($N = 60$), indicating the level of initial learning. Right: trial-by-trial analysis of mean go (black circles) and no go (white circles) running times during the retention session, with an oxytocin receptor antagonist [d(CH$_2$)$_5$,Tyr(Me)^2,Thr^4,Tyr-NH$_2^9$]ornithine vasotocin and vasopressin injected mice (OXT antagonist/[Arg^8]vasopressin), and an oxytocin receptor antagonist and NaCl-injected mice (OXT antagonist/NaCl). Injections were given 15 min prior to the retention session. $*\ P < 0.05$, $**\ P < 0.01$, $***\ P \leq 0.001$.

($F(5,32) = 5.79$; $P < 0.0007$), a group × time interaction ($F(5,32) = 2.86$; $P < 0.03$), but no reinforcement × group × time interaction ($F(5,32) = 1.38$; $P = 0.25$). Separate ANOVAs for each group revealed no reinforcement × time interaction ($F(5,14) = 1.90$; $P = 0.15$) for the NaCl/NaCl group, suggesting that these animals were not able to discriminate between go and no-go trials. In contrast, the same analysis applied to the performance of the Nacl/[Arg^8]vasopressin group showed a statistically significant difference between go and no-go trials, starting from the first trial of the session (reinforcement × time interaction, $F(5,14) \geq 9.49$, $P \leq 0.006$), indicating that [Arg^8]vasopressin-injected mice were able to discriminate between the two alleys.

Neither [d(CH$_2$)$_5$-D-Ile^2,Ile^4,Arg^8]vasopressin nor [d(CH$_2$)$_5$,Tyr(Me)^2,Thr^4,Tyr-NH$_2^9$]ornithine vasotocin at the dose used (25 pg) significantly affected performance (Figs. 3 and 4). MANOVA of the performance of both the NaCl/NaCl group and the vasopressin V$_2$ receptor antagonist/NaCl group revealed no interaction effect, whatever the factor considered, and subsequent ANOVAs for each trial showed that the group × reinforcement interaction did not reach statistical significance for any trial ($F(1,36) \leq 2.49$; $P \geq 0.11$). Thus, the vasopressin V$_2$ receptor antagonist did not affect retention performance. However, looking at behavioral performance, we can see that, compared to that of the NaCl/NaCl group (Fig. 2), the discrimination level of the vasopressin V$_2$ receptor antagonist/NaCl group (Fig. 3) seemed impaired. This impairment was reflected by a decrease in no-go running times as the session progressed.

Statistical analyses comparing the NaCl/NaCl group (Fig. 2) with the oxytocin antagonist/NaCl group (Fig. 4) ($F(5,32) = 1.68$; $P = 0.16$) as well as behavioral observation showed that these two groups performed in the same manner. Thus, the oxytocin receptor antagonist had no apparent intrinsic effect on retrieval and relearning performance.

The [d(CH$_2$)$_5$-D-Ile^2,Ile^4,Arg^8]vasopressin injection associated with [Arg^8]vasopressin injection did not block the enhancing effect of vasopressin on retrieval and relearning (Fig. 3). Indeed, MANOVA of the retention performance of both the vasopressin V$_2$ receptor antagonist/[Arg^8]vasopressin group (Fig. 3) and the NaCl/[Arg^8]vasopressin group (Fig. 2) yielded no group × reinforcement × time interaction ($F(5,32) = 1.19$; $P = 0.33$). Subsequent ANOVAs for each trial yielded no Group × Reinforcement interaction on any trial ($F(1,36) \leq 2.90$; $P \geq 0.09$), confirming that the performance of the vasopressin V$_2$ receptor antagonist/[Arg^8]vasopressin group was not different from that of the NaCl/[Arg^8]vasopressin group.

In contrast, MANOVA of the performance of the oxytocin antagonist/[Arg^8]vasopressin group (Fig. 4) and the NaCl/[Arg^8]vasopressin group (Fig. 2) revealed a group × reinforcement × time interaction ($F(5,32) = 2.94$; $P < 0.04$), indicating that retention performance was impaired when the oxytocin antagonist was injected prior to vasopressinergic treatment.

Table 1
Effects of the different treatments on locomotor activity

	Crossing	Rearing
NaCl/NaCl	220.05 ± 28.77	41.95 ± 6.88
NaCl/[Arg^8]vasopressin	322.40 ± 23.55	103.20 ± 13.30
Vasopressin V$_2$ receptor antagonist/NaCl	210.95 ± 30.40	37.65 ± 7.33
Vasopressin V$_2$ receptor antagonist/[Arg^8]vasopressin	329.85 ± 20.69	85.50 ± 7.30
Oxytocin receptor antagonist/NaCl	247.25 ± 38.30	53.20 ± 8.00
Oxytocin receptor antagonist/[Arg^8]vasopressin	368.90 ± 28.80	82.89 ± 10.48

3.2. Locomotor activity test

The results obtained in the second session are presented in Table 1. One-way ANOVA revealed statistical significance of the difference between groups for crossing ($F(1,54) = 5.14$; $P < 0.0007$) and rearing ($F(1,54) = 8.51$; $P < 0.0001$). The Newman–Keuls t-test ($P < 0.05$) showed that the NaCl/[Arg^8]vasopressin, vasopressin-V$_2$ receptor antagonist/[Arg^8]vasopressin and oxytocin receptor antagonist/[Arg^8]vasopressin groups had increased crossing and rearing, compared to those of the other three groups. Since the oxytocin receptor antagonist and the vasopressin V$_2$ receptor antagonist had no effect on crossing and rearing in other groups compared to those of the NaCl/NaCl group, the increase seen in [Arg^8]vasopressin groups pretreated with the two antagonists seems due to the effect of [Arg^8]vasopressin alone. Thus, [Arg^8]-vasopressin increases locomotor activity.

4. Discussion

We have shown in this study that an intra-hippocampal injection of the vasopressin V$_2$ receptor antagonist, [d(CH$_2$)$_5$-D-Ile^2,Ile^4,Arg^8]vasopressin, did not affect the enhancing effect of vasopressin on retention processes, whereas the oxytocin receptor antagonist, [d(CH$_2$)$_5$,Tyr(Me)^2,Thr^4,Tyr-NH$_2^9$]ornithine vasotocin, blocked the enhancing effect of the peptide.

It is consistent with earlier results (Alescio-Lautier et al., 1993, 1995; Metzger et al., 1993) that vasopressin injected into the ventral hippocampus improves memory retrieval and relearning. This is also in agreement with the report by Kovacs et al. (1986) of the involvement of the ventral part of the hippocampus in the improving effect of vasopressin on the retention of passive avoidance behavior in rats. While the increase in locomotor activity in vasopressin-treated animals can account for the decrease in go performance, it cannot explain the increase in no-go per-

formances across trials. Thus, the effect of vasopressin on retention performance is not linked to the effect of the peptide on locomotor activity. We assessed the effect of vasopressin in various locomotor activity tests and found that, surprisingly, for the same dose and the same site of injection, the effect of the peptide differed across tests. Hypo-activity (Alescio-Lautier et al., 1995), no effect (Metzger et al., 1993, 1994), and hyper-activity (the present study) were found. In other words, the effect of vasopressin is sensitive to the experimental context, so much so that it has opposite effects depending on the test used.

The lack of involvement of vasopressin V_2 receptors in retrieval and relearning is inconsistent with the results reported by De Wied et al. (1991) and Popik et al. (1992). These authors found, respectively, that an intracerebroventricular or an intra-septal injection of a vasopressin V_2 receptor antagonist before the injection of vasopressin blocks the enhancing effect of vasopressin on the retention of a passive avoidance task and on social recognition. However, these studies differed from ours in several respects. First, the effect of the peptide was tested on memory consolidation, whereas we tested it on retention. Indeed, De Wied et al. (1991) and Popik et al. (1992) injected the vasopressin V_2 receptor antagonist and vasopressin after the learning session of the passive avoidance and social recognition tests and evaluated the effect of the treatment in a later retention session. In our study, the two peptides were administered just before the retention session, and their effect was evaluated in this session. The difference between these experimental contexts could explain the discrepancy in results. If this is true, it would mean that vasopressin V_2 receptors may be involved in memory consolidation but not in retention processes. Second, the site of injection differed in the various studies, since De Wied et al. (1991) injected the peptide into the lateral ventricle and Popik et al. (1992), into the lateral septum. Thus, another explanation of the discrepant results (which does not rule out the one presented above) may be that the ventral hippocampus does not contain vasopressin V_2 receptors. Indeed, although they have been detected in the central nervous system (Ostrowski et al., 1992), their existence in the hippocampus remains to be confirmed. Hirasawa et al. (1994) demonstrated the existence of vasopressin V_2 receptor mRNA in the hippocampus, whereas Kato et al. (1995) reported that its expression in the hippocampus changes dynamically during the process of development in rats (its expression in the newborn decreases with age and could not be detected in rats more than 2 weeks old). Considering the known location of the vasopressin V_2 receptors, the results reported by Popik et al. are surprising since these receptors were not detected in the lateral septum. These authors offer one explanation, that the action of vasopressin on social recognition is mediated by a vasopressinergic receptor which does not discriminate between V_1 and vasopressin V_2 receptor antagonists. These peptides had been developed to block the peripheral rather than central effects of vasopressin. In our case, further studies, particularly dose–response experiments will be necessary to determine whether the vasopressin V_2 receptor is involved or not in retention processes in the ventral hippocampus.

In contrast to vasopressin V_2 receptors, oxytocin receptors in the ventral hippocampus are involved in the enhancing effect of vasopressin on retention performance. The involvement of the oxytocin receptors in the effect of vasopressin on memory was also reported by De Wied et al. (1991), and by Roozendaal et al. (1992, 1993) on other functions of the peptide. However, Popik et al. (1992) reported that the effect of vasopressin on social recognition in rats was not affected by the previous injection of an oxytocin receptor antagonist into the lateral septum. As a general rule, however, in structures such as the ventral hippocampus, amygdala, and septum, which contain both vasopressin V_1 and oxytocin receptors (Krémarik et al., 1993), the effect of vasopressin on memory processes depends on the activation of their own V_1 receptors (Winslow and Insel, 1993; Alescio-Lautier et al., 1995) but also on that of oxytocin receptors (De Wied et al., 1991; Roozendaal et al., 1992, 1993). The results obtained by Van Wimersma Greidanus and Maigret (1996), which showed that the presence or local release of AVP and oxytocin in the ventral hippocampus is of physiological importance for social recognition, support the idea that, in the ventral hippocampus, a some of the AVP effects may have an oxytocinergic component.

In addition, results of previous work (Alescio-Lautier et al., 1995) and of the present study suggest that the effect of vasopressin on retention processes is mediated by both vasopressin V_1 and oxytocin receptors. The involvement of two receptor types in these processes may appear redundant. Should this hold blocking of only one receptor type could not prevent the enhancing effect of vasopressin. Since blocking of only one receptor prevents the effect of AVP disagree with this assumption and suggests an undiscovered link between vasopressin V_1 and oxytocin receptors. Another explanation, as already hypothesized by De Wied et al. (1991) for the ventral hippocampus, would be that only one receptor type is involved in the effect of the peptide. This receptor would have the same affinity for vasopressin V_1, vasopressin V_2 receptor antagonists and for the oxytocin receptor antagonist. Thus, the receptors involved in the ventral hippocampus for the vasopressin memory enhancing effect remain to be determined. Further studies, particularly regarding the molecular characterization of the receptor sensitive to vasopressin in the ventral hippocampus would be useful for resolving this issue.

Acknowledgements

We are grateful to Michelle Bauget and Vivian Waltz for their technical assistance.

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