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# Vasopressin opposes locomotor stimulation by ethanol, cocaine and amphetamine in mice

Joanne Chiu [a], Harold Kalant [a,b,*], Dzung Anh Lê [a,b]

[a] *Department of Pharmacology, University of Toronto, Toronto, Ontario, Canada, M5S 1A8*
[b] *Biobehavioral Research Department, Addiction Research Foundation, Toronto, Ontario, Canada*

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**Abstract**

The effects of arginine[8]-vasopressin on the stimulation of locomotor activity induced by ethanol, cocaine and amphetamine were examined in DBA/2N mice. Locomotor activity was measured by photocell beam interruption for a period of 45 min following ethanol, cocaine or amphetamine administration. Pretreatment with vasopressin alone in a dose of 2 (but not 1) μg/mouse s.c. reduced locomotor activity. The low dose of vasopressin did not modify the stimulation of locomotor activity induced by i.p. administration of ethanol in doses of either 1.5 or 2 g/kg. The high dose of vasopressin reduced locomotor activity induced by both doses of ethanol, in an apparently additive manner. Cocaine in doses of 15 and 20 mg/kg strongly stimulated locomotor activity, but this stimulation was completely antagonized by pretreatment with 1 μg of vasopressin. Similarly, the stimulation of locomotor activity induced by amphetamine (5 mg/kg) was also blocked by pretreatment with vasopressin. These findings raise the possibility that the effect of vasopressin varies with the extent and nature of dopaminergic involvement in the drug-induced stimulation of activity. For drugs like cocaine or amphetamine which stimulate locomotor activity primarily through the mesolimbic dopaminergic system, vasopressin can completely antagonize the stimulation. For ethanol, which stimulates locomotor activity through action on a number of other neurotransmitters as well as dopamine, vasopressin treatment only reduces its stimulation of locomotor activity in an additive manner. These results suggest a close interaction between vasopressin and dopamine action. 

*Keywords:* Vasopressin; Ethanol; Cocaine; Amphetamine; Dopamine; Locomotor activity

## 1. Introduction

The hypothalamic peptide and neurohypophyseal hormone [Arg[8]]vasopressin (vasopressin) can modify central nervous system (CNS) functions by modulating many neurotransmitter systems in the brain (for review, see De Wied et al., 1993). Its action on tolerance to the depressant effects of ethanol has been extensively studied. Administration of vasopressin in mice chronically treated with ethanol can maintain tolerance to the hypothermic and hypnotic effects of ethanol (Hoffman et al., 1978) after ethanol administration is discontinued. Similarly, Lê et al. (1982) and Speisky and Kalant (1985) reported that treatment with des-Gly[9]-[Arg[8]]vasopressin (DGAVP), an analog of vasopressin with very similar central actions but virtually devoid of peripheral effects, maintained tolerance to the hypothermic and motor-impairing effects of ethanol in rats after discontinuation of chronic ethanol administration.

When vasopressin was administered together with a single depressant dose of ethanol (1.8 g/kg) in the rat, it significantly enhanced the acute effects of that dose of ethanol (Wu et al., 1992), but it also produced a long-lasting tolerance to ethanol (Wu et al., 1996). These findings raise at least two different possible explanations: (1) vasopressin may have depressant effects of its own which are simply additive with those of ethanol and result in a stronger stimulus to the development of tolerance to the depressant effects of ethanol, or (2) vasopressin may in some as yet unexplained manner potentiate the acute effects of depressant doses of ethanol. No information was available concerning any acute interaction between vasopressin and a lower dose of ethanol that produces excitatory rather than depressant effects. However, coadministration of vasopressin with cocaine was reported to attenuate,

* Corresponding author. Tel.: +1-416-978-2730; Fax: +1-416-978-6395; E-mail: harold.kalant@utoronto.ca

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in a dose-dependent manner, the development of sensitization to locomotor stimulation by cocaine (Sarnyai et al., 1992).

The neuronal mechanisms by which vasopressin produces these various effects are not fully known. Vasopressin interacts with a number of neurotransmitter systems in maintaining ethanol tolerance. Selective lesions of the mesolimbic serotoninergic (5-HT) pathway by 5,7-dihydroxytryptamine in rats, or depletion of central catecholamines by intracerebroventricular (i.c.v.) injection of 6-hydroxydopamine in mice, have been shown to prevent vasopressin maintenance of ethanol tolerance (Lê et al., 1982; Hoffman et al., 1983; Speisky and Kalant, 1985). In the 5,7-dihydroxytryptamine-lesioned animals, continuous i.c.v. infusion of a selective 5-$HT_2$ receptor agonist restored the ability of vasopressin to maintain ethanol tolerance (Wu et al., 1994).

Vasopressin has also been implicated in modulating the activity of mesolimbic dopaminergic neurons. Vasopressin has been shown to increase the release and turnover of dopamine in various brain structures (Kovács and Versteeg, 1993), including the nucleus accumbens of α-methyl-*p*-tyrosine treated rats (Kovács et al., 1977; Versteeg, 1983). The nucleus accumbens plays an important role in the stimulatory and reinforcing effects of cocaine (Pettit and Justice, 1991). The ability of vasopressin to modify behaviour by interacting with dopamine in this brain region is supported by the finding that the acquisition of self-administration of cocaine was inhibited by vasopressin and related peptides (Van Ree et al., 1988).

Ethanol stimulation of locomotor activity, like that produced by cocaine, has a dopaminergic basis. A number of studies have shown that ethanol-induced locomotor activity can be decreased by administration of dopamine receptor antagonists (Liljequist et al., 1981; Risinger et al., 1992; Shen et al., 1995; Lê et al., 1997). Ethanol doses that elicit behavioral stimulation have been reported to increase the release of dopamine and its metabolite 3,4-dihydroxyphenylacetic acid in the nucleus accumbens as measured by in vivo microdialysis (Imperato and Di Chiara, 1986; Yoshimoto et al., 1992).

If vasopressin exerts its behavioural actions, in part, by interacting with the mesolimbic dopaminergic system, pretreatment with vasopressin should modify the acute stimulation of locomotor activity by low-dose ethanol. It was not known whether vasopressin potentiates all actions of ethanol or selectively modulates depressant vs. stimulant effects of ethanol. This study was intended to examine these possibilities by examining the acute interaction of vasopressin with low-dose ethanol. The DBA/2N mouse was used for this study, because low doses of ethanol have been shown to cause pronounced hyperlocomotion in this strain (Crabbe et al., 1982; Tabakoff and Kiianmaa, 1982; Lê et al., 1997). For comparative purposes, the effects of vasopressin pretreatment on the stimulation of locomotor activity induced by cocaine and amphetamine, which exert their behavioural effects primarily through the dopaminergic system, were also examined.

## 2. Materials and methods

### 2.1. Subjects

Sixty adult, male DBA/2N mice, each weighing 14 to 24 g, were purchased from Charles River Canada (Montréal, Québec, Canada). Animals were allowed to acclimate to the environment for at least 1 week. They were housed in groups of five in plastic cages, in a vivarium at 21–23°C, 40% relative humidity and with lights on from 0700 to 1900 h. Water and standard Purina rodent chow were available ad libitum. Experiments were conducted during the light phase of the light/dark cycle.

### 2.2. Drugs

All drugs were dissolved in saline. Vasopressin was purchased from Bachem (Torrance, CA, USA) and was administered subcutaneously in a concentration of 1 μg/0.1 ml. Ethanol was administered intraperitoneally (i.p.) as a 12.5% w/v solution in water. Cocaine hydrochloride was prepared as 1.5 mg/ml and 2.0 mg/ml solutions, and amphetamine sulphate was prepared as 0.5 mg/ml and 0.75 mg/ml solutions; both drugs were given i.p.

### 2.3. Apparatus—activity box

The activity boxes were made of stainless steel with Plexiglass lids, and had dimensions of $24 \times 12.5 \times 10$ cm ($L \times W \times H$). Two sets of infrared lamps and photocells were mounted on the long walls, 1.5 cm above the wire mesh floor, in such a manner that they divided the box into 3 equal compartments. Occlusions of the photobeams were recorded by an IBM computer and the interruption counts were used as a measure of horizontal locomotor activity.

### 2.4. Procedures

Prior to experimentation, all animals received four habituation sessions that were intended to reduce the novelty and stress associated with handling, injection, and exposure to the apparatus. During the habituation sessions, each mouse was given an i.p. injection of saline (0.2 ml) and immediately placed in the activity box. The horizontal locomotor activity was recorded for a 45-min period. The room was illuminated only by a 25 W red light bulb placed above the rack on which the activity boxes were located.

This study involved 4 experiments in which the same mice were used repeatedly. Experiments 1 and 2 assessed the effects of pretreatment with vasopressin in doses of 1 and 2 μg/mouse, respectively, on the locomotor stimula-

tory effect of ethanol. Experiments 3 and 4 assessed the effect of vasopressin (1 μg/mouse) on the locomotor stimulation induced by cocaine and amphetamine, respectively. The two alcohol experiments were performed two days apart, and the cocaine and amphetamine experiments were performed subsequently at one week intervals, to minimize the risk of possible interaction between the locomotor stimulatory effects of different drug treatments. On each experimental day, each animal was given a pretreatment (either saline or vasopressin) by subcutaneous injection 30 min prior to treatment with ethanol, cocaine or amphetamine.

In experiment 1, the mice were randomly assigned to one of the six treatment groups ($n = 10$ each): S-S (saline pretreatment and saline treatment), S-E1 (saline and 1.5 g/kg of ethanol), S-E2 (saline and 2 g/kg of ethanol), vasopressin-S (1 μg/mouse of vasopressin and saline), vasopressin-E1 (1 μg/mouse of vasopressin and 1.5 g/kg of ethanol), and vasopressin-E2 (1 μg/mouse of vasopressin and 2 g/kg of ethanol). Immediately after the second injection, the animals were placed in the activity boxes and their locomotor activity was monitored for a period of 45 min. In experiment 2, the procedure, drugs, and doses of ethanol were exactly the same as in experiment 1, except that the dose of vasopressin was increased to 2 μg/mouse. The design and procedures of experiments 3 and 4 were exactly the same as those of experiment 1, except that the treatment drugs employed were 15 and 20 mg/kg, respectively for cocaine, and 5 and 7.5 mg/kg for amphetamine. In experiments 2, 3 and 4 the animals were randomly reassigned each time to the various treatment groups, so that each group included animals from all of the previous treatments.

All procedures were approved by the Animal Care Committee, in keeping with the guidelines of the Canadian Council on Animal Care.

### 2.5. Statistical analyses

Locomotor activity is expressed as cumulative horizontal locomotor activity (mean ± S.E.M.) over a period of 45 min. Statistical analyses were performed using the NCSS® package (Kaysville, UT, USA). Data were analyzed by general linear model two-way analysis of variance (ANOVA) followed by post-hoc Newman–Keuls tests where appropriate. Level of significance was set at $P < 0.05$ for all analyses.

## 3. Results

The effect of pretreatment with 1.0 μg of vasopressin on ethanol-induced hyperactivity is shown in Fig. 1 (left panel). Ethanol itself caused a significant stimulation of locomotor activity; this was confirmed by the ANOVA, which showed a significant main effect of ethanol ($F(2,54) = 15.5$, $P < 0.001$). There was, however, no significant effect of vasopressin pretreatment ($F(1,54) = 1.8$, $P > 0.05$) or significant interaction between vasopressin

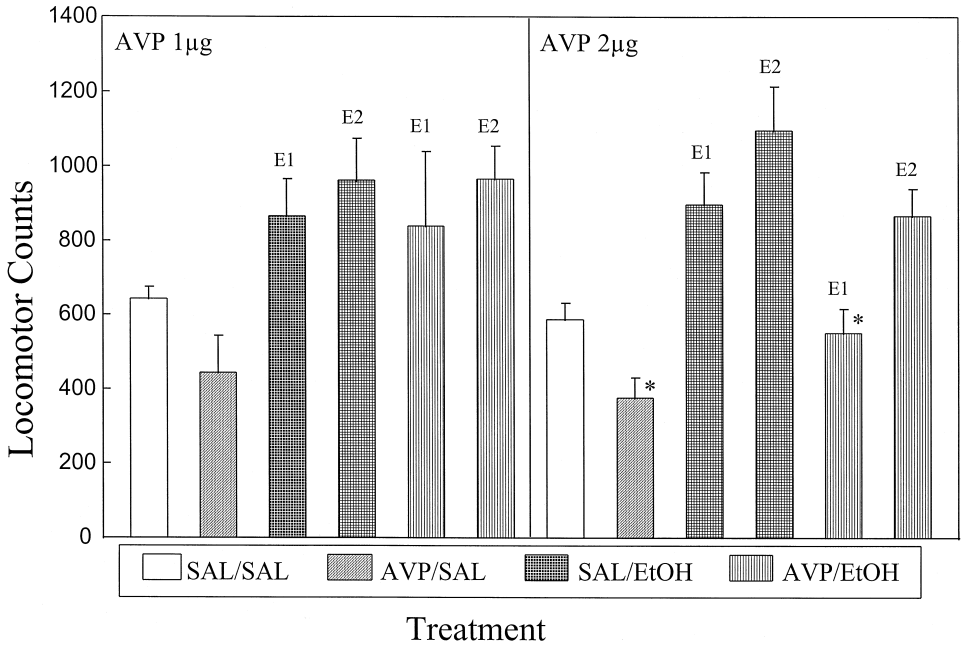


Fig. 1. Effect of pretreatment with vasopressin, 1 μg/mouse (left panel) and 2 μg/mouse (right panel), on the stimulation of locomotor activity (locomotor activity) induced by two different doses of ethanol. E1: 1.5 g/kg of ethanol; E2: 2.0 g/kg of ethanol; EtOH: ethanol, SAL: saline. Values presented are means ± S.E.M. $n = 9$–12 animals per group. Asterisks indicate vasopressin-pretreated groups that differed significantly from the corresponding saline-pretreated groups.

and ethanol ($F(2,54) = 0.9$, $P > 0.4$). The post hoc tests showed no significant difference between the saline–saline and the vasopressin–saline groups. Thus, vasopressin pretreatment did not affect the baseline activity and did not modify the stimulation of locomotor activity induced by ethanol.

Pretreatment with 2.0 μg of vasopressin (Fig. 1, right panel), however, had a significant main effect on locomotor activity ($F(2,54) = 15.7$, $P < 0.001$), and the post-hoc tests indicated that this dose of vasopressin significantly reduced the baseline locomotor activity. As in experiment 1, ethanol also significantly stimulated locomotor activity ($F(2,54) = 18.99$, $P < 0.001$). Preplanned comparisons showed that vasopressin pretreatment significantly blocked the stimulation of locomotor activity induced by 1.5 g/kg of ethanol ($P < 0.05$: saline–ethanol vs. vasopressin–ethanol) but not the stimulation induced by 2.0 g/kg of ethanol ($P > 0.05$).

The effect of vasopressin (1.0 μg/mouse) on cocaine-induced hyperactivity is shown in Fig. 2 (left). Cocaine treatment had a strong stimulatory effect. A two-way ANOVA ($F(2,53) = 12.24$, $P < 0.001$) followed by post-hoc Newman–Keuls tests of the saline-pretreated groups showed that both 15 and 20 mg/kg of cocaine significantly increased locomotor activity by more than 75% ($P < 0.05$). However, there was no difference in locomotor activity induced by these two doses of cocaine. Pretreatment with 1.0 μg/mouse of vasopressin had a significant main effect in the ANOVA ($F(1,53) = 52.39$, $P < 0.001$), and the post-hoc comparisons confirmed that vasopressin blocked the increase in locomotor activity produced by both doses of cocaine (15 and 20 mg/kg; $P < 0.05$ in both cases). However, as in experiment 1, the score of the vasopressin-S group did not differ from that of the S-S group. These results indicate that this dose of vasopressin alone had no effect on locomotor activity but it completely abolished the hyperlocomotion induced by these doses of cocaine. In contrast to experiment 2, there was a significant interaction between vasopressin pretreatment and cocaine dose ($F(2,53) = 6.34$, $P < 0.005$).

Fig. 2 (right) shows the effect of vasopressin (1.0 μg/mouse) on amphetamine-induced hyperactivity. A two-way ANOVA showed a significant main effect of amphetamine vs. saline ($F(2,53) = 23.84$, $P < 0.001$). Post-hoc Newman–Keuls tests demonstrated that 5 mg/kg of amphetamine, in the absence of vasopressin, increased locomotor activity by over 100% ($P < 0.05$). A higher dose of amphetamine (7.5 mg/kg), however, failed to produce any hyperlocomotion. Vasopressin pretreatment had a significant main effect ($F(1,53) = 23.97$, $P < 0.001$), and the locomotor activity of mice that received vasopressin prior to 5 mg/kg of amphetamine (A1) was significantly lower than that of the S-A1 treatment group ($P < 0.05$). After vasopressin pretreatment, neither dose of amphetamine caused a significant difference of locomotor activity compared to the S-S group, but the vasopressin-A2 group did differ from the vasopressin-S group ($P < 0.05$). As in experiments 1 and 3, vasopressin alone had no effect on locomotor activity as compared to the S-S treatment group. There was again a significant interaction between

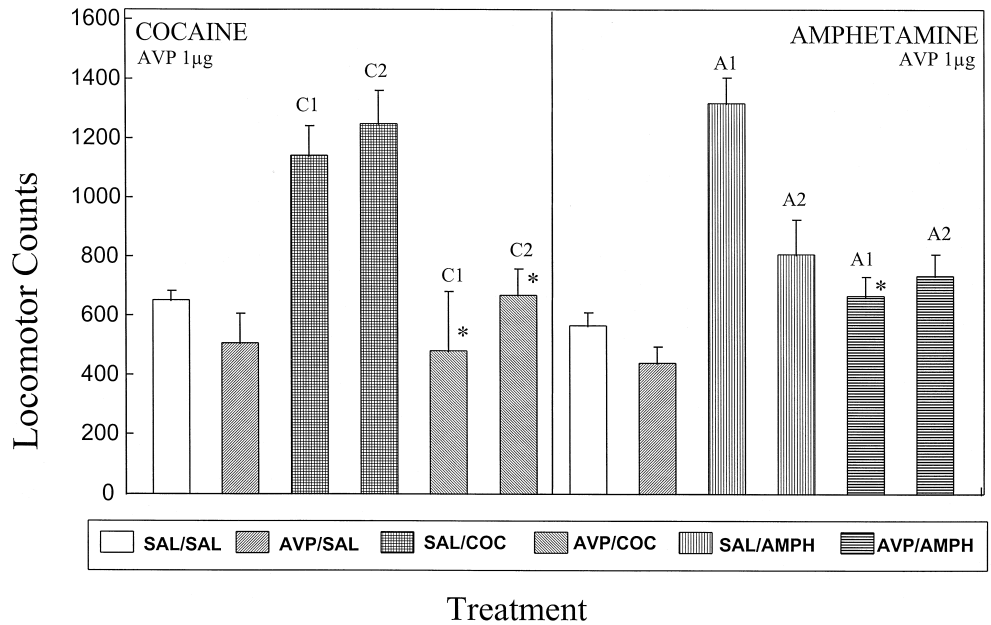


Fig. 2. Effect of pretreatment with vasopressin, 1.0 μg/mouse (s.c.), on the stimulation of locomotor activity induced by two different doses of cocaine (left panel) and two different doses of amphetamine (right panel). COC: cocaine; C1: 15 mg/kg of cocaine; C2: 20 mg/kg of cocaine; SAL: saline; AMPH: amphetamine; A1: 5 mg/kg of amphetamine; A2: 7.5 mg/kg of amphetamine. Values presented are means ± S.E.M. $N = 9–12$ animals per group. Asterisks indicate vasopressin-pretreated groups that differed significantly from the corresponding saline-pretreated groups.

vasopressin pretreatment and amphetamine dose ($F(2,53) = 9.97$, $P < 0.001$).

## 4. Discussion

The present study has again confirmed the well-known fact that ethanol (1.5 or 2 g/kg) and cocaine (15 and 20 mg/kg) produce marked enhancement of locomotor activity in DBA/2N mice. These results are comparable to those of previous studies using various strains of mice including the DBA/2N (Lê et al., 1997), BALB/c (Humeniuk et al., 1993), NMRI (Blomqvist et al., 1992) and CFLP (Sarnyai et al., 1992). Vasopressin pretreatment at a dose of 1 μg/mouse had no effect by itself on spontaneous locomotor activity and did not alter the ethanol-induced locomotor activity, but at a dose of 2 μg/mouse it reduced locomotor activity by itself and blocked the stimulation of locomotor activity induced by 1.5 g/kg ethanol, but not by 2 g/kg ethanol. The data are visually suggestive of an additive interaction (Fig. 1), but the statistical results do not permit a firm conclusion. It would be desirable to perform more detailed dose–response studies to settle the question, but this is difficult because the dose-effect curve for ethanol is biphasic within a very small dose range, and higher doses of vasopressin introduce confounding effects because of peripheral actions on blood pressure, gastrointestinal smooth muscle, and other systems.

In contrast, vasopressin at the dose which had no effect on ethanol-induced locomotor activity (1 μg/mouse) completely abolished locomotor activity induced by cocaine (Fig. 2, left) and by the lower dose of amphetamine (Fig. 2, right). A higher dose of amphetamine (7.5 mg/kg), not surprisingly, failed to induce locomotor activity. This finding was probably attributable to the stereotypic behaviour produced by high doses of amphetamine, which is characterized by grooming, sniffing, vertical bobbing and many repetitive body movements. As a result, animals showing stereotypic behaviour tend to have less horizontal locomotor activity. In order to verify this suggestion, more advanced detection apparatus such as video monitors and activity boxes with photobeam detectors more densely installed along different vertical and horizontal levels of the walls would be needed.

A potential source of concern in the present work is the possibility that some of the treatments might have relatively long-lasting effects that would confound the results when the same animals were used repeatedly. For example, a single treatment with a combination of vasopressin and ethanol was found to produce long-lasting tolerance to ethanol in the rat if the animal had to perform a learned task during the period of drug effect (Wu et al., 1996). It is by no means clear that in the present work a similar interaction would occur with respect to spontaneous unlearned behaviours in the mouse, but if it did, the effect would be to increase the dispersion of results in the later experiments in which each treatment group included animals with different previous treatment histories. The fact that no such increase in dispersion was seen (see Figs. 1 and 2) suggests that no appreciable long-term interactions had occurred. Moreover, if single-exposure tolerance had occurred, there should have been a smaller effect of ethanol on locomotor activity in experiment 2 than in experiment 1, and this was not the case. These facts do not prove conclusively that no long-term effects occurred, but they suggest that if there were any, they were not of sufficient magnitude to alter the conclusions.

The differential effects of vasopressin on ethanol- and cocaine-induced locomotor activity suggest that the stimulatory effects produced by these two drugs (which were of quite comparable magnitude at the doses used) are mediated, at least partially, by different pathways. The locomotor stimulatory effect of cocaine and amphetamine is known to be mediated primarily via the mesolimbic dopaminergic system (Asher and Aghajanian, 1974; Kelly et al., 1975). The ability of vasopressin to block locomotor activity induction by cocaine or by the low dose of amphetamine suggests that the dopaminergic system is a target site of vasopressin action in modifying locomotor activity. If this is the case, the more limited antagonistic effect of vasopressin on ethanol-induced locomotor activity would suggest that the dopaminergic system only partly mediates the locomotor stimulatory effect of ethanol. In the present study, the hyperlocomotion induced by the lower dose of ethanol (1.5 g/kg) was blocked by vasopressin pretreatment. This blocking effect of vasopressin was then overcome by a higher dose of ethanol (2.0 g/kg). These results are consistent with an algebraic summation of opposing effects on locomotor activity, and with the observation that vasopressin increased the depressant effects of a higher dose of ethanol that reduces locomotor function (Wu et al., 1992). It thus appears that vasopressin does not potentiate *all* effects of ethanol, i.e., it does not simply shift both the stimulation and depression portions of ethanol dose–response curves to the left. As vasopressin (1 μg/mouse) by itself did not affect locomotor activity, but attenuated the stimulation by ethanol, it appears to selectively potentiate the depressant effects of ethanol.

It has been reported that ethanol can induce locomotor activity in animals deprived of dopaminergic neurotransmission. In a study using monoamine-depleted mice as subjects, ethanol, in conjunction with $\alpha_2$-adrenoceptor stimulation, stimulated locomotion (Carlsson and Engberg, 1992). The dopaminergic system, therefore, is not the only pathway by which ethanol elicits its stimulatory effect. A number of studies show the involvement of neurotensinergic (Erwin et al., 1997), gamma-aminobutyratergic (Liljequist and Engel, 1982; Koechling et al., 1990; Humeniuk et al., 1993), α-adrenergic (Matchett and Erickson, 1977), serotonergic (Blomqvist et al., 1994), acetylcholinergic (Blomqvist et al., 1992) and glutaminergic systems

(for review, see Phillips and Shen, 1996) in mediating the locomotor stimulatory effect of ethanol. The roles of these neurotransmitter systems in ethanol-induced locomotor activity, and their possible interactions with vasopressin, remain to be elucidated.

Another possible explanation for the differential effects of vasopressin on ethanol- and cocaine-induced locomotor activity is the apparently distinct patterns of dopamine $D_1$ and $D_2$ receptor involvement in mediating the hyperlocomotion produced by these two drugs. Ushijima et al. (1995) and Lê et al. (1997) have reported that dopamine $D_1$, but not $D_2$, receptors play a significant role in cocaine-induced hyperactivity. In contrast, Lê et al. (1997) found that both dopamine $D_1$ and $D_2$ receptors are involved in the locomotor-activating effects of ethanol. Several antagonist studies have provided strong evidence for the involvement of dopamine $D_2$ receptors. For example, the dopamine $D_2$ receptor antagonists pimozide and raclopride have been found to decrease or completely block ethanol-stimulated activity at doses that did not themselves affect baseline locomotor activity (Liljequist et al., 1981; Koechling et al., 1990; Shen et al., 1995). The evidence for the involvement of dopamine $D_1$ receptors is not as clear. Shen et al. (1995) found that SCH 23390, a very selective $D_1$ receptor antagonist, decreased ethanol-induced stimulation in only one replicate of FAST mice; Koechling and her colleagues found that SCH 23390 had no effect on ethanol-induced locomotor activity in nonhabituated animals (1990), but did have an effect in habituated animals (Koechling and Amit, 1993). Furthermore, coadministration of SCH 23390 and raclopride produced a greater reduction of ethanol-stimulated activity than did either drug alone (Shen et al., 1995). These findings suggest that dopamine $D_1$ and $D_2$ receptors may interact in the mediation of ethanol-stimulated activity, but the $D_2$ receptor appears to have a more prominent effect, whereas the $D_1$ receptor is primarily involved in stimulation by cocaine.

If vasopressin selectively modulates neurotransmission mediated by dopamine $D_1$, rather than $D_2$, receptors, it would have a more pronounced effect on cocaine-induced locomotor activity and a less significant effect on ethanol-induced locomotor activity. This explanation is not impossible. Vasopressin elicits its CNS effects via both vasopressin $V_1$ and $V_2$ receptors (Yamamura et al., 1983; Junig et al., 1985; Voorhuis et al., 1988) but only the $V_1$ receptor is involved in the maintenance of ethanol tolerance (Szabó et al., 1988). A similar selectivity of interaction with dopamine receptors is conceivable. The ability of vasopressin to modulate the turnover of dopamine in the mesolimbic area (Kovács et al., 1977; Versteeg, 1983) suggests the presence of vasopressin receptors on the presynaptic neurons. Vasopressin receptors can also exist on the postsynaptic neurons at dopaminergic synapses and modulate neurotransmission, as coexistence of pre- and postsynaptic vasopressin receptors has been reported (Ishizawa et al., 1990). Therefore, vasopressin receptors might be coexpressed with dopamine $D_1$ receptors on the neurons postsynaptic to dopaminergic terminals in the mesolimbic area, accounting for the preferential blocking effect of vasopressin on cocaine-induced locomotor activity. This possibility requires further investigation.

One further explanation of the present findings, that cannot yet be excluded, is that the dose ranges of cocaine and of amphetamine were not high enough to test adequately whether their interaction with vasopressin was truly different from that of ethanol. In Fig. 2, the locomotor activity scores of the vasopressin-C2 and vasopressin-A2 groups did appear to be higher than those of the corresponding vasopressin-S groups, though the difference was significant only for the vasopressin-A2 group. It is therefore worth noting that the dose ratio of high to low doses was 1.5:1 for amphetamine, but only 1.33:1 for cocaine, so that the risk of stereotypy may have been less with the high dose of cocaine than of amphetamine. Moreover, the effect of vasopressin alone appeared to be slightly less in experiments 3 and 4 than in experiments 1 and 2, possibly as a result of habituation. This combination of circumstances makes it difficult to exclude the possibility that with all three treatment drugs (ethanol, cocaine and amphetamine), the effect of vasopressin pretreatment was to cause a rightward shift of the dose–response curves for stimulation. If that were indeed the case, it would suggest an additive interaction of vasopressin depressant effect with the stimulatory effects of all three drugs.

In summary, ethanol (1.5 or 2.0 g/kg), cocaine (15 and 20 mg/kg), and a low dose of amphetamine (5 mg/kg) all increased locomotor activity. Vasopressin, at a dose which did not have any demonstrable effect on baseline activity, decreased the stimulatory effects of all three drugs. However, the modulatory actions of vasopressin on these drugs were not the same. At the doses used, vasopressin only partially antagonized the stimulation by ethanol, but completely blocked the stimulation by cocaine, consistent with the suggestion of a close interaction between vasopressin and dopamine. The differential effects of vasopressin on locomotor stimulation by these drugs may be related to the extent of mesolimbic dopaminergic involvement, or the involvement of dopamine $D_1$ and $D_2$ receptors, in mediating the stimulation of locomotor activity by different drugs. However, further experiments are needed to test these hypotheses specifically.

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