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5-HT receptor ligands differentially affect operant oral self-administration of ethanol in the rat

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Abstract

The present study evaluated the effects of the selective serotonin (5-hydroxyhyptamine; 5-HT) reuptake inhibitor, fluoxetine, the 5-HT_{1B} receptor agonist, tetrahydro-4-pyridyl[3,2-*b*]pyridine, CP-94,253 the preferential 5-HT_{2A} receptor agonist, 1-(2,5-dimethoxy-4 iodophenyl)-2-aminopropane, DOI and the mixed 5-$HT_{2C/1B}$ receptor agonist, 1-(3-chlorophenyl)piperazine, mCPP, on oral ethanol (10% v/v) self-administration in a two-lever, fixed-ratio:1, water vs. ethanol choice procedure in the rat. All compounds affected operant behavior, with varying degrees of specificity, that is, the extent to which a reduction of ethanol-reinforced lever pressing coincided with a reduction of ethanol preference, and selectivity, that is, the extent to which a reduction of ethanol-reinforced lever pressing could be dissociated from an effect on total responding on both levers. Fluoxetine (5–20 mg/kg, i.p.) and CP-94,253 (1–10 mg/kg, i.p.) induced a nonselective disruption of operant behavior; the profile being weakly specific for CP-94,253. DOI (0.1–0.3 mg/kg, i.p.) and mCPP (0.3–1 mg/kg, i.p.) induced a specific effect; the profile being more selective for DOI. These findings suggest that operant ethanol self-administration can be suppressed in a specific manner by activation of 5-HT_{2A} and, possibly, 5-HT_{2C} receptors, and in a nonselective manner by activation of 5-HT_{1B} receptors. As fluoxetine indirectly stimulates these receptors and its behavioral profile resembles more that of a 5-HT_{1B} receptor agonist, activation of 5-HT_{1B} receptors may underlie its effects on operant ethanol self-administration.

Keywords: Alcoholism; CP-94,253; DOI (2,5-dimethoxy-4 iodophenyl); Fluoxetine; mCPP (3-chlorophenyl); 5-HT_{1B} receptor; 5-HT_{2A} receptor; 5-HT_{2C} receptor

1. Introduction

Pharmacological manipulation of the brain serotonergic system has been demonstrated to affect consumption of ethanol; suggesting that serotonin (5-hydroxyhyptamine; 5-HT) is involved in alcohol abuse/dependence (Higgins et al., 1992; LeMarquand et al., 1994; De Vry et al., 1996). Thus, selective 5-HT reuptake inhibitors decrease ethanol intake in rodents (Gill et al., 1985; Naranjo et al., 1986; Gill and Amit, 1989; Maurel et al., 1998b), as well as in humans (e.g., Naranjo et al., 1986; Kranzler et al., 1995). However, it still remains unclear whether their effects on ethanol intake in a two-bottle choice procedure involve a serotonergic mechanism (Gill and Amit, 1989). Nevertheless, compounds which selectively activate particular subtypes of 5-HT receptors decrease ethanol consumption in animal models, with different degrees of specificity (that is, the extent to which a reduction of ethanol intake coincides with a reduction of ethanol preference in an ethanol vs. water choice situation), and selectivity (that is, the extent to which a reduction of ethanol intake can be dissociated from an effect on general consummatory behavior). Thus, 5-HT_{1A} receptor agonists, such as 8-hydroxy 2-(di-*N*-propylamino)tetralin, 8-OH-DPAT, and ipsapirone (De Vry, 1995), and the preferential 5-HT_{2A} receptor agonist, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane, DOI (McBride et al., 1990; Maurel et al., 1999a) have been shown to induce a relatively specific and selective reduction of ethanol intake in particular animal models of alcoholism; including the alcohol-preferring P rats, or the Alcohol-Addicted AA rats, or the Cologne Alcohol-Addicted cAA rats (a strain derived from the AA rats, Maurel et al., 1999a). On the other hand, the 5-HT_{1B}

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receptor agonists, 1-(3-trifluoromethylphenyl) piperazine, TFMPP (McBride et al., 1990) and tetrahydro-4-pyridyl[3,2-b]pyridine, CP-94,253 (Maurel et al., 1998a), as well as the 5-$HT_{2C/1B}$ receptor agonist, *m*-chlorophenylpiperazine, mCPP (Buczek et al., 1994; Maurel et al., 1999a), were found to induce nonspecific and nonselective effects; possibly a consequence of a more general suppression of consummatory behavior. These results led to the hypothesis that stimulation of 5-HT_{1A} or 5-HT_{2A} receptors induces a specific and selective reduction of alcohol intake; whereas stimulation of 5-HT_{1B} or 5-HT_{2C} receptors induces a nonspecific and nonselective suppression of consummatory behavior (Schreiber et al., 1993; De Vry et al., 1996; Maurel et al., 1998a, 1999a). Comparison of the effects of several selective 5-HT reuptake inhibitors in alcohol-preferring cAA rats indicated that the reduction of alcohol intake of these compounds is moderately specific and relatively nonselective (Maurel et al., 1999b). With respect to the profile of selective serotonin reuptake inhibitors and 5-HT receptor agonists, it has been hypothesised that activation of 5-HT_{1A} and 5-HT_{2A} receptors underlies the effects of a selective 5-HT reuptake inhibitor on alcohol intake and preference, and that activation of 5-HT_{1B} and 5-HT_{2C} receptors underlies the effects of a selective 5-HT reuptake inhibitor on food- and total fluid intake (Maurel et al., 1999b).

The models generally employed for evaluation of the effects of selective 5-HT reuptake inhibitors and other serotonergic ligands on ethanol consumption allow only to a limited extent for an assessment of the mechanisms underlying possible alcohol intake-reducing effects. Such mechanisms may involve, amongst other, a drug-induced suppression of general consummatory behavior or an interaction of the drug with the discriminative- or reinforcing stimulus effects of ethanol. In view of the subtle differences in the degree of specificity and selectivity among different selective 5-HT reuptake inhibitors, as assessed in alcohol-preferring cAA rats, it has been concluded that it is unlikely that their reduction of ethanol intake is a mere consequence of a general suppressive effect on consummatory behavior (Maurel et al., 1999b). On the other hand, the recent finding that the selective 5-HT reuptake inhibitors fluoxetine and paroxetine, as well as the 5-HT_{1B} receptor agonists, TFMPP and CP-94,253, and the 5-$HT_{2C/1B}$ receptor agonist, mCPP, were able to generalize completely for the ethanol cue in rats trained to discriminate ethanol from saline, suggests that the alcohol intake-reducing effects of these compounds may be related to similarities between the discriminative stimulus effects of these drugs and ethanol (Grant et al., 1997; Maurel et al., 1997; Maurel et al., 1998b).

As excessive intake of ethanol could also be related to the reinforcing stimulus properties of ethanol, another conceivable mechanism may consist of an interaction of a particular compound with the reinforcing properties of ethanol. The involvement of the serotoninergic system in the modulation of operant oral ethanol self-administration is not well documented. Several studies demonstrated that fluoxetine reduced operant intravenous-, oral- and intragastric ethanol self-administration (Murphy et al., 1988; Haraguchi et al., 1990; Lyness and Smith, 1992; Wilson et al., 1996a), as well as nonoperant intake of ethanol in two-bottle drinking procedures. So far, results from studies employing 5-HT_{1A} receptor agonists suggest that activation of 5-HT_{1A} receptors may not lead to a specific and selective modulation of the reinforcing stimulus properties of ethanol, and therefore such a mechanism may not underlie the alcohol intake reducing effects of these compounds in nonoperant models (Roberts et al., 1998; Wilson et al., 1996b). In a recent study, it was shown that combined 5-HT_{1A} receptor agonist/5-HT_{2A} receptor antagonist activity provided a selective effect on ethanol reinforcement (Roberts et al., 1998). Still, it remains to be demonstrated, however, whether the ethanol intake reducing effects of 5-HT_{1B}, 5-HT_{2A} or 5-HT_{2C} receptor agonists, as obtained in nonoperant models, may involve an interaction of these compounds with the reinforcing stimulus properties of ethanol.

Therefore, the aim of the present study was to evaluate the effects of the 5-HT_{1B} receptor agonist CP-94,253, the preferential 5-HT_{2A} receptor agonist DOI, and the mixed 5-$HT_{2C/1B}$ receptor agonist mCPP, on operant self-administration of ethanol. Furthermore, the behavioral profile obtained by these selected 5-HT receptor agonists was compared with that of fluoxetine, thus allowing an indirect assessment of the relative contribution of these receptors to the effects of fluoxetine in the model. Drug effects were studied in a two-lever, water vs. 10% ethanol, oral self-administration paradigm employing a sucrose-fading procedure (Samson, 1986) and a fixed-ratio:1 (FR:1) schedule (Hyytiä and Koob, 1995). Four parameters were measured: (1) number of ethanol-reinforced lever presses, (2) number of water-reinforced lever presses, (3) total responding on both levers, and (4) ethanol preference, as defined by the quotient of measure (1) and (3). Effects of a compound were considered to be specific when reductions of ethanol-reinforced lever pressing coincided with reductions of ethanol preference, and considered to be selective when the former effect was obtained in the absence of an effect on total responding.

2. Materials and methods

2.1. Animals

Male Wistar rats (Winkelmann, Paderborn, Germany) weighing 160–180 g at the beginning of the experiment were used. The animals were housed under a reversed 12-h light/dark cycle (lights on at 7:00 PM) with free access to food and water. All training and testing sessions were

performed during the dark period. Temperature and humidity were kept constant at 22 ± 1°C and 55 ± 5%, respectively. Experimental protocols were approved by local government.

2.2. Apparatus

Conventional operant chambers (Model EW-10SF, Coulbourn Instruments, Lehigh Valley, USA) placed in lightproof, sound-attenuated and fan-ventilated cubicles were used. The liquid delivery system consisted of two levers mounted on the wall, one on each side, with a small cup on the front. Pressing the lever lifted the corresponding lever-arm out of a container, which was filled with fluid, resulting in the delivery of 0.06 ml of the fluid. A house light in each operant chamber was turned on for 10 s to indicate the beginning of the session. Recording of responses and fluid delivery were controlled by a microcomputer using the Med-PC programm (Med Associates, USA).

2.3. Training

Animals were trained to orally self-administer ethanol under a fixed-ratio:1 (FR:1) schedule, essentially as described by Hyytiä and Koob (1995). In short, on the first 3 days, rats were water deprived for 22 h prior to the sessions. During these 30 min daily sessions, responses on both levers were reinforced by delivery of 0.2% saccharin. On training day 4–9, water deprivation was discontinued and animals were trained to alternate responding at the left and right lever in a one-lever task to obtain a mixed solution of 5.0% ethanol (v/v) and 0.2% saccharin. From day 10 on, rats were introduced to a two-lever, choice task in which responding on one lever was reinforced by delivery of water, while responding on the other lever was reinforced by delivery of ethanol. The position of the ethanol-reinforced lever alternated daily. During days 10–19, the ethanol concentration was gradually increased from 5% to 8% and then to 10%, while the saccharin concentration was decreased on day 17 to 0.1% and on day 19 to 0.05%. From day 20 on, animals had to respond for 10% ethanol without addition of saccharin.

2.4. Drug testing

Following establishment of stable baseline responding (at least 50 responses per session on the ethanol-reinforced lever and an ethanol preference of 70% or higher), the effects of fluoxetine, CP-94,253, DOI and mCPP were assessed during 30 min free choice (ethanol vs. water) test sessions. Test sessions alternated with further baseline self-administration sessions. Animals showing stable baseline responding during two subsequent sessions were tested on the next day. Each animal received each dose of the compounds and the appropriate vehicle.

2.5. Drugs

Ethanol (ethanol absolute, 99.8% v/v) was purchased from Riedel-de Haën (Seelze, Germany). Saccharin was obtained from Sigma (St Louis, MO). Fluoxetine (synthesized by the Chemistry Department of Bayer, Wuppertal, Germany), DOI and mCPP (RBI, Natick, MA) and CP-94,253 (generous gift from Dr. Schwegler, Pfizer, Germany) were dissolved in distilled water and a few drops of lactic acid, if necessary. All drugs were injected i.p. in a volume of 1 ml/kg, 15 min (DOI, mCPP), 45 min (fluoxetine) or 60 min (CP-94,253) prior to the test session.

2.6. Statistics

Four parameters were measured: (1) responses on the ethanol-reinforced lever; (2) responses on the water-reinforced lever; (3) total responses on both levers; and (4) percentage of ethanol preference, that is, responses on the ethanol-reinforced lever divided by responses on both levers. Means and S.E.M.s were calculated for all groups. For ethanol preference, data from rats with a very low response rate (total responses on both levers ≤ 10) were excluded. A one-way analysis of variance (ANOVA) was employed for analysis of dose–response data. Following ANOVA, a Tukey post-hoc analysis was performed.

3. Results

Throughout the experiments, high and stable baselines for ethanol-reinforced lever responding (around 60 responses/session), ethanol lever preference (around 75%) and total responding (around 70 responses/session) were consistently obtained. Responses on the water-reinforced lever were consistently low, around 10 responses/session, except for DOI (see below).

Treatment with fluoxetine (5–20 mg/kg) significantly decreased ethanol-reinforced lever pressing and total responding [$F(3,28) = 4.81$, $P < 0.01$ and $F(3,28) = 4.81$, $P < 0.01$, respectively; Fig. 1]. Ethanol preference was not significantly affected. However, interpretation of the preference data at the highest dose of fluoxetine was hampered as only one animal out of six reached the criteria (total responding on both levers ≥ 10) to be included in the analysis. Ethanol preference for this rat was 41.7%. The effects on ethanol-reinforced lever pressing and total responding were observed at the highest dose tested. Neither fluoxetine nor the other drugs tested affected water-reinforced responding. Because effects on ethanol-reinforced lever responding coincided with effects on total responding, the profile of fluoxetine was considered to be nonselective. In addition, because the former effect was obtained in the absence of an effect on ethanol preference, the profile of fluoxetine was considered to be nonspecific.

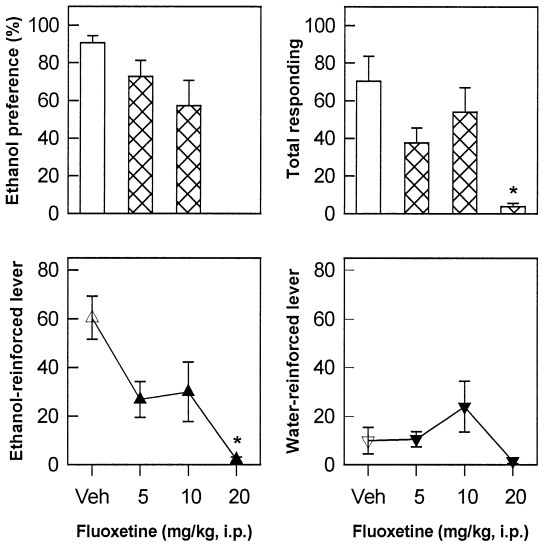

Fig. 1. Effects of fluoxetine on ethanol preference, total responding, ethanol-reinforced lever responding and water-reinforced lever responding in an oral ethanol (10%) vs. water self-administration paradigm. Data are shown as the mean ± S.E.M. of 6–10 rats per dose (preference data for the 20 mg/kg fluoxetine are not shown as only one rat reached the criteria to be included in the analysis, the preference for that rat was 41.7%). * $P < 0.05$, as compared with vehicle treatment.

Treatment with CP-94,253 (1–10 mg/kg) significantly affected ethanol preference, ethanol-reinforced lever pressing and total responding [$F(3,20) = 3.59$, $P < 0.05$; $F(3,24) = 11.54$, $P < 0.001$, and $F(3,24) = 6.18$, $P < 0.005$, respectively; Fig. 2]. Post-hoc analysis revealed that

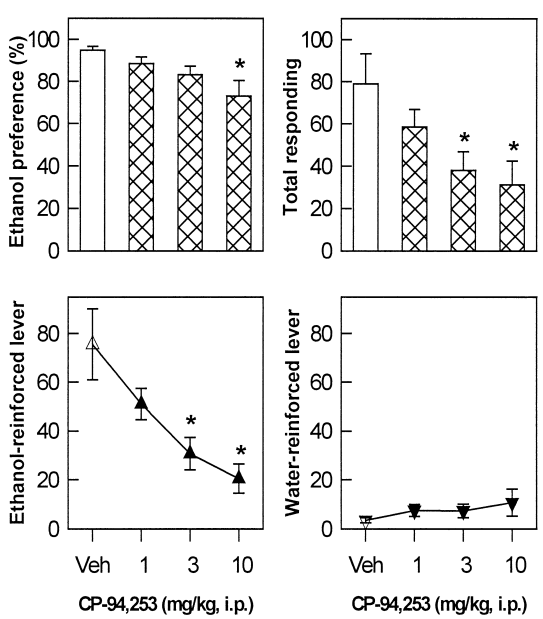

Fig. 2. Effects of CP-94,253 on ethanol preference, total responding, ethanol-reinforced lever responding and water-reinforced lever responding in an oral ethanol (10%) vs. water self-administration paradigm. Data are shown as the mean ± S.E.M. of 6–8 rats per dose. * $P < 0.05$, as compared with vehicle treatment.

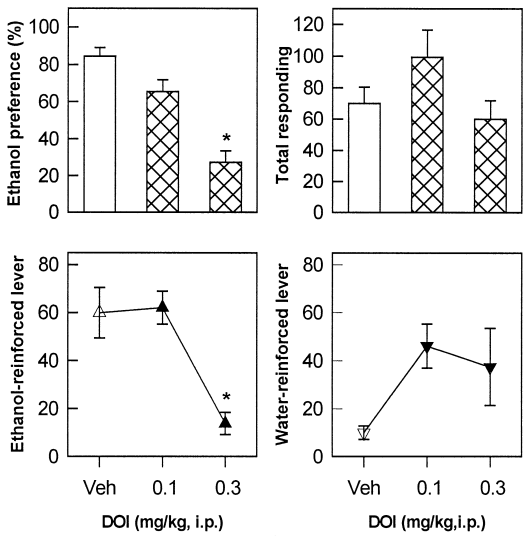

Fig. 3. Effects of DOI on ethanol preference, total responding, ethanol-reinforced lever responding and water-reinforced lever responding in an oral ethanol (10%) vs. water self-administration paradigm. Data are shown as the mean ± S.E.M. of 7 rats per dose. * $P < 0.05$, as compared with vehicle treatment.

CP-94,253 reduced ethanol-reinforced lever pressing and total responding at 3 and 10 mg/kg; whereas only the highest dose affected ethanol preference. Therefore, the profile of CP-94,253 was considered to be nonselective and weakly specific.

In contrast, treatment with DOI (0.1–0.3 mg/kg) resulted in a significant reduction of ethanol preference and ethanol-reinforced lever pressing [$F(2,18) = 23.53$, $P < 0.001$ and $F(2,20) = 12.96$, $P < 0.001$, respectively], in the absence of an effect on total responding (Fig. 3). It

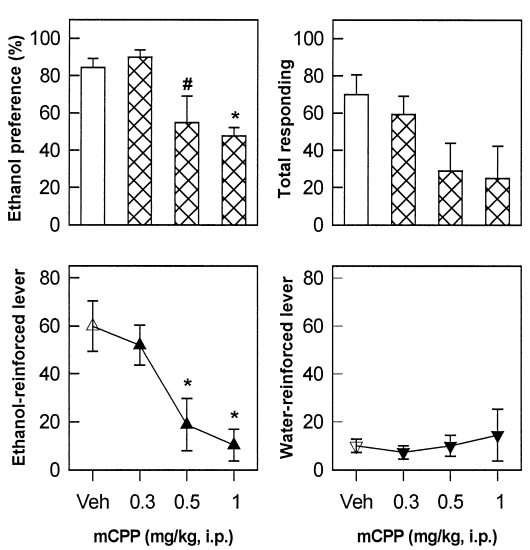

Fig. 4. Effects of mCPP on ethanol preference, total responding, ethanol-reinforced lever responding and water-reinforced lever responding in an oral ethanol (10%) vs. water self-administration paradigm. Data are shown as the mean ± S.E.M. of 7–8 rats per dose. * $P < 0.05$, as compared with vehicle treatment.

should be noted that DOI is the only compound tested which tended to increase water-reinforced lever pressing. Post-hoc analysis revealed that DOI reduced ethanol preference and ethanol-reinforced lever pressing at 0.3 mg/kg. Therefore, the profile of DOI was considered to be selective and specific.

mCPP (0.3–1 mg/kg) significantly reduced ethanol preference and ethanol-reinforced lever pressing [$F(3,17) = 6.55$, $P < 0.01$ and $F(3,28) = 6.60$, $P < 0.01$, respectively]; whereas a tendency to decrease total responding was observed [$F(3,28) = 2.65$, $P < 0.1$; Fig. 4]. At 0.5 and 1 mg/kg, mCPP reduced ethanol-reinforced lever pressing; whereas only the highest dose tested affected significantly ethanol preference. Therefore, the profile of mCPP was considered to be relatively specific and selective.

4. Discussion

In the present study, drug-naive rats readily learned to orally self-administer a 10% ethanol solution in a two-lever ethanol vs. water FR:1 operant procedure (Samson, 1986; Weiss et al., 1993; Hyytiä and Koob, 1995). Throughout the experiment, relatively high and stable levels of responding for ethanol, as well as a high preference for the ethanol-reinforced lever was obtained, suggesting that the rats were responding for the positive reinforcing stimulus properties of ethanol. All compounds tested affected operant behavior, although with different degrees of specificity and selectivity. The selective 5-HT reuptake inhibitor, fluoxetine, and the 5-HT_{1B} receptor agonist, CP-94,253, both reduced ethanol-reinforced lever pressing. However, in the case of fluoxetine, this effect occurred in the absence of a significant reduction of ethanol preference; indicating that the effects were nonspecific. CP-94,253 induced only a weak reduction of ethanol preference, and therefore its effects were considered weakly specific. Since fluoxetine and CP-94,253 significantly reduced total responding (percent reduction of response rate, as compared with vehicle treatment: 90% and 65%, respectively), their effects were considered nonselective. On the other hand, the preferential 5-HT_{2A} receptor agonist, DOI, was found to induce a specific and selective effect on operant self-administration of ethanol, as the compound reduced both ethanol-reinforced lever pressing and ethanol preference at the same dose, in the absence of an effect on total responding. Although a somewhat similar profile was obtained with the mixed 5-$HT_{2C/1B}$ receptor agonist, mCPP, its effects were considered to be less selective as compared with DOI in view of the more marked reduction of total responding (percent reduction of response rate as compared with vehicle treatment: 65% and 20% at the highest dose tested, respectively). In addition, the profile of mCPP was also considered to be less specific as compared with DOI, as the minimal effective dose which reduced ethanol-reinforced responding was found to be lower than the minimal dose which affected ethanol preference.

The 5-HT ligands tested in the present study have also been reported to reduce ethanol intake with different degrees of specificity and selectivity in the alcohol-preferring cAA rats, employing a nonoperant, two-bottle, 10% ethanol vs. water standardized choice procedure (De Vry et al., 1996). In the cAA rat model, an effect on ethanol intake was considered to be specific when it coincided with an effect on ethanol preference; whereas it was considered to be selective if it occurred in the absence of an effect on total fluid- or food intake. Thus, in analogy to the pattern of action found with DOI in the present paradigm, DOI induced a specific and selective effect on alcohol intake in alcohol-preferring cAA rats (Maurel et al., 1999a); suggesting that the alcohol intake-reducing effects of DOI may involve interactions with the reinforcing stimulus effects of ethanol.

As mCPP showed a relatively specific and selective profile in the operant ethanol self-administration paradigm, it can also be suggested that its previously reported effects on alcohol intake may, to a certain degree, involve an interaction with the reinforcing stimulus effects of ethanol. However, it is likely that other mechanisms are (also) involved in the alcohol intake-reducing effects of mCPP. Indeed, in the light of the well-known hypophagic effects of mCPP (e.g., Kennett and Curzon, 1988) and the nonspecificity and nonselectivity of the profile of mCPP in alcohol-preferring cAA rats (Maurel et al., 1999a), it seems reasonable to assume that the effects on ethanol intake are predominantly a consequence of a general suppression of consummatory behavior (Maurel et al., 1999a).

Fluoxetine showed a nonspecific and nonselective effect on ethanol-reinforced responding in the present study, whereas it induced a mildly specific and relatively nonselective profile in the cAA rats (De Vry et al., 1996; Maurel et al., 1998a, 1999b). Fluoxetine has been reported to reduce ethanol-reinforced lever pressing in other oral self-administration paradigms (Haraguchi et al., 1990; Wilson et al., 1996a). However, the degree of selectivity and specificity of the effects of fluoxetine in these studies remains to a certain extent unclear. As in the case of mCPP, it appears likely that the alcohol intake-reducing effects of selective 5-HT reuptake inhibitors are partly the result of an inhibitory effect on general consummatory behavior. However, as discussed elsewhere (Maurel et al., 1999b), the effects of selective 5-HT reuptake inhibitors on alcohol intake cannot entirely be explained by the latter mechanism, and it seems likely that other mechanisms, such as substitution for the stimulus effects of ethanol (Maurel et al., 1998b) are involved. Unfortunately, the pronounced effects on operant behavior as obtained in the present study preclude a definite conclusion with respect to possible interactions of fluoxetine with the reinforcing stimulus effects of ethanol.

The nonselective effects of CP-94,253 as obtained in the present procedure were largely reminiscent of the effects found with this compound in the cAA rat where

CP-94,253 strongly reduced ethanol intake in a dose range which also reduced total fluid- and food intake (Maurel et al., 1998a). In the cAA rats, the effects of CP-94,253 were also considered to be nonspecific as the compound did not affect ethanol preference; whereas in the present study CP-94,253 showed only a weak degree of specificity. As in the case of fluoxetine, the strong effects on operant behavior precluded a clear assessment of the compound's possible interaction with the reinforcing stimulus effects of ethanol. Nevertheless, in the light of its hypophagic effects (i.e, Lee and Simansky, 1997) and its particular profile in both operant and nonoperant models, it can be suggested that the alcohol intake-reducing effects of CP-94,253 are largely due to a general suppression of ingestive behavior (Maurel et al., 1998a).

The different specificity and selectivity profiles obtained with DOI, mCPP and CP-94,253 in the operant self-administration paradigm are supposed to reflect the different affinities of these compounds for particular receptor subtypes. Whereas DOI displays similar affinity for 5-HT_{2A} and 5-HT_{2C} receptors, behavioral effects of the compound are generally ascribed to its agonistic activity at 5-HT_{2A} receptors (e.g., Maurel et al., 1999a). In the case of the mixed 5-HT_{2C}/5-HT_{1B} receptor agonist, mCPP, behavioral effects may require stimulation of either 5-HT_{2C} or 5-HT_{1B} receptors, or even involve both receptor subtypes (e.g., Maurel et al., 1998a, 1999a). CP-94,253 has been reported to be a selective 5-HT_{1B} receptor agonist (Boess and Martin, 1994; Lee and Simansky, 1997) and it is highly likely that its behavioral effects are due to this property of the compound (e.g., Maurel et al., 1998a). Due to the lack of antagonism experiments with selective receptor antagonists in the present study, it is not known exactly which 5-HT receptor subtypes mediate the effects of DOI, mCPP and CP-94,253 on operant alcohol self-administration. However, based on the presumed receptor selectivity of the ligands used, it can tentatively be concluded that ethanol self-administration can be suppressed in a specific manner by activation of 5-HT_{2A} and, possibly, 5-HT_{2C} receptors; and in a nonselective manner by activation of 5-HT_{1B} receptors.

Blockade of the 5-HT transporter by fluoxetine leads to an increase of synaptic 5-HT levels, and therefore to the activation of different 5-HT receptor subtypes. As its behavioral profile in the present study resembles most that of the 5-HT_{1B} receptor agonist, CP-94,253, it is speculated that activation of 5-HT_{1B} receptors underlies the effects of fluoxetine on ethanol self-administration. However, this hypothesis needs to be confirmed by appropriate antagonism studies in which combined injections of fluoxetine and selective 5-HT receptor antagonists are tested. In addition, it must be verified to what extent stimulation of other 5-HT receptor subtypes, such as 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7 receptors, affect ethanol self-administration, and whether these receptors are involved in the behavioral effects of fluoxetine in this model.

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